Movement Disorders
Vol. 17, Suppl. 4, 2002, p. i

Published by Wiley-Liss, Inc.
DOI 10.1002/mds.5554

Editorial

Management of Parkinson's Disease: An Evidence-Based Review*

Although Parkinson's disease is still incurable, a large number of different treatments have become available to improve quality of life and physical and psychological morbidity. Numerous journal supplements have appeared in recent years highlighting one or more of these and disparate treatment algorithms have proliferated. Although these are often quite useful, this "mentor analysis" approach lacks the scientific rigor required by modern evidence-based medicine standards. The *Movement* Disorder Society, with generous but unrestricted support from representatives of industry, have, therefore, commissioned a systematic review of the literature dealing with the efficacy and safety of available treatments. The accompanying treatise is the result of a scrupulous evaluation of the literature aimed at identifying those treatments for which there is sound scientific support to justify their application (or avoidance) and to highlight where a lack of evidence points to the need for future clinical trials. The introductory chapter reviews the study methodology while subsequent chapters deal with specific interventions subdividing the evidence under the categories of: prevention of disease progression; symptomatic control of Parkinson's disease; prevention of motor complications; control of motor complications; and control of non-motor features. Based on a systematic review of the data, efficacy conclusions are provided. On the basis of a narrative non-systematic approach, statements on safety of the interventions are given and finally, a qualitative approach is used to summarize the implications for clinical practice and future research.

This mammoth task has taken two years to complete and the task force members, principal authors and contributors are to be congratulated for their outstanding work. Physicians, the Parkinson's disease research community and most of all patients themselves should welcome and embrace the salient findings of this report as an effort to improve clinical practice. It is hoped that this supplement will serve as a landmark in the treatment of Parkinson's disease, not only encouraging ongoing excellence in patient care but also providing guidance in the development of future research studies designed to fill the identified gaps in our current knowledge base.

Anthony E. Lang, MD, FRCPC
Andrew Lees, MD, FRCP
Co-Editors-in-Chief

*Produced by a task force commissioned by The *Movement* Disorder Society

Movement Disorders
Vol. 17, Suppl. 4, 2002, p. S1-S6

Published by Wiley-Liss, Inc.
DOI 10.1002/mds.5555

Introduction

Many therapeutic interventions are available for the management of Parkinson's disease including drugs, surgical interventions and physical treatments. They are not equally accessible and their real clinical value, as measured by their impact on clinically relevant outcomes, has not always been established through high quality, randomized, controlled clinical trials. In contrast, some therapeutic interventions have been well studied in controlled clinical studies and appear to be underused (as evidenced in other medical fields[1]). This underuse may actually be due to the lack of awareness of the supporting clinical evidence that is documented in the medical literature. Furthermore the research programs on specific therapeutic interventions or procedures are frequently established by industry as part of the drug development process and not necessarily to fill gaps in the available clinical evidence.

To identify areas that are understudied and/or where evidence is lacking, a clear understanding of what has been established through clinical research is required. The tools used in evidence-based medicine are useful in this context.

Evidence-based medicine[2] is a neologism. As such, many different meanings for the same concept may be intertwined in the reader's mind. To clarify this, we accept in this review the original definition proposed by Sackett and colleagues[3]:

"Evidence-based medicine (EBM) is the integration of best research evidence with clinical expertise and patients values; by best research evidence it is meant clinically-relevant research, often from the basic sciences of medicine, but especially from patient centered clinical research into the accuracy and precision of diagnostic tests (including the clinical examination), the power of prognostic markers, and the efficacy and safety of therapeutic, rehabilitative and preventive regiments."

The *Movement* Disorder Society (MDS) in order to contribute to the practice of EBM has commissioned an evidenced-based review of current pharmacological and selected non-pharmacological practices commonly used to manage patients with PD. To this end, a task force of clinical movement disorder experts and clinical pharmacologists was established. Members of this task force were the principal authors and co-authors of this document. The challenge lay in the fact that for many treatments currently available, effect sizes or risk-benefit relationships have not been systematically studied in well-designed controlled trials. A coordinated effort was undertaken to review the published information available to date, and determine the benefits and limitations of different pharmacotherapies and treatment strategies for managing patients with PD. To achieve this goal, a couple of strategic options were considered in order to limit the task to a realistic amount of work. In this chapter those strategic options and the methodology followed are described.

STRATEGIC OPTIONS

A systematic review is a research program organized around a clearly formulated and focused question. A systematic review is also characterized by the use of systematic and explicit methods to identify, select, and critically analyze the relevant studies. Furthermore, the systematic review analyzes and summarizes the data presented in the studies included in the review.[4]

Sometimes systematic reviews use meta-analyses to provide a summarized statistical analysis of the data available. However, meta-analyses are not a required component for a review to be systematic. The use of meta-analysis is considered optional and should be viewed as an available tool.

In this project, each chapter aims to be a systematic review of the efficacy of each of the therapeutic interventions identified. The safety discussion within these chapters uses a narrative, unsystematic approach due to the complexity of the literature published to date on safety of the different therapeutic interventions. This is an obvious limitation of the work.

The most relevant clinical questions addressed during a systematic review are questions centered around specific medical problems, symptoms or processes, and not necessarily on the efficacy of therapeutic interventions outside a specific context. However, there are some advantages in using therapeutic interventions as the organizational center of the review instead of the clinical problem. This approach reduces the complexity of the review allowing each chapter to focus on a simple topic, while meeting the generic aims of this project. Thus, single treatments are reviewed independently instead of management strategies that may involve a multitude of treatment options at the same time or in sequence.

Practices and treatments for management of Parkinson's disease vary worldwide, and are limited by individual treatment settings and resources. Therefore, this document does not provide practice guidelines because such guidelines are much more appropriately developed by local or regional institutions.[5]

This evidence-based review does not include quantitative summaries (no meta-analyses were conducted) of the different data sets. The main reason to avoid quantitative summaries was the overwhelming workload of such a task. The qualitative approach, such as the one undertaken here, is anyhow an important contribution to highlight the evidence available and it facilitates the inclusion of some subjectivity and expert opinion. This is explicitly limited to the two sections within each chapter entitled: (1) Implications for Clinical Practice, and (2) Implications for Future Research.

It is worth noting that in some instances the conclusions herein may differ from the available Cochrane reviews[6] on the same topic. When these conclusions differ, this review may be considered less conservative than The Cochrane Reviews. This reflects the differences in the methodology used. Cochrane reviews (1) are more comprehensive as based on a broader sources of data retrieved (with less publication and language selection bias; further described below), (2) use meta-analysis when possible, and (3) limit conclu-

sions to the boundaries of evidence reviewed, thereby avoiding subjectivity.[7]

The merit of both approaches is the transparency – defined as including full description of the methods, disclosure of the criteria for evidence retrieval, and a clear understanding on how conclusions are reached. This transparency makes it easier for the readers to spot differences between two approaches and allows their own interpretation of the data presented. Conclusions drawn from these reviews are aimed to provide generic guidance, as based on the evidence available to date.

This review suffers from some methodological limitations. Issues that might favor selection bias include exclusion of papers published in languages other than English. Specifically, selecting papers published only in English induces publication bias and language bias, both of which tend to inflate positive results.[8,9] Publication bias is reflected in the fact that the results from negative clinical trials often are unpublished or not published as full papers in English-language journals.[10]

Another limitation is that the primary source of evidence were electronic databases, which provides incomplete lists of papers.[11] For Level-II and III studies (defined below), the risk of missing relevant papers is greater than with Level-I studies because there is an increasing likelihood that studies of a more descriptive, nonrandomized, or uncontrolled designs are published outside of mainstream, peer-reviewed journals.

Despite these limitations, self-contained evidence-based reviews, such as this report, are still an important tool because they provide, within a single publication, a critical analysis of the extensive evidence available to physicians. Self-contained evidence-based literature reviews serve as a "guided tour" through the literature of the more "visible" papers published. Additionally, these evidence-based reviews often put the data into clinical practice perspective, as related to other evidence published in the field. In this light, evidence-based reviews allow a more comprehensive understanding of the scientific basis of clinical decisions as compared to a random assembly of studies that physicians access through independent efforts.

AIMS AND GOALS

The aim of this evidence-based review is to evaluate the evidence published to date and to provide assessments on the clinical efficacy, safety, and implications for clinical practice regarding the treatment of PD.

The specific goals are:

(1) Review the literature and identify the clinical evidence that supports specific treatments commonly used for treatment of PD;
(2) Determine which studies are scientifically sound so they can be used as evidence to support or condone specific treatments in clinical practice; and
(3) Identify where specific evidence is lacking so future research efforts may be directed toward addressing these specific areas of need.

Treatments identified for inclusion in this review were based on consensus among the authors and for each type of intervention the evidence was reviewed regarding aspects of symptomatic management and – where appropriate – also regarding prevention of disease progression (table 1):

Table 1 Specific Treatments Reviewed

Indication
• Prevention of disease progression • Symptomatic control of parkinsonism • Prevention of motor complications • Control of motor complications • Control of non-motor complications
Type of intervention

Drug treatment
• Amantadine
• Anticholinergics
• Levodopa
• MAO-B inhibitors
• COMT inhibitors
• DA agonists
  * Ergot-compounds
  - Bromocriptine
  - Cabergoline
  - Dihydroergocryptine
  - Lisuride
  - Pergolide
  * Non-ergot compounds
  - Apomorphine
  - Piripedil
  - Pramipexole
  - Ropinirole
• Drugs used to control autonomic dysfunction
  - Hypotension
  - Urinary dysfunction
  - Gastrointestinal dysfunction
• Drugs used to control neuropsychiatric dysfunction
  - Treatment of depression
  - Treatment of dementia and psychosis
Surgical treatment
• Deep brain surgery
• Neural transplantation
Physical and psychosocial treatment
• Physical therapy
• Psychosocial counseling
• Speech therapy

METHODS

IDENTIFICATION OF PUBLISHED MATERIAL

Literature searches were done using electronic databases including Medline (1966-20001), the central database in the Cochrane Library (1948-20002), and systematic checking of reference lists published in review articles and other clinical reports. Papers selected for review met the following inclusion/exclusion criteria with special exceptions noted in each of the respective chapters:

INCLUSION CRITERIA

· Randomized study

· Non-randomized controlled or non-controlled, prospective or retrospective study
· Patients with an established diagnosis of Parkinson's disease
· Established scales for measuring target symptoms
· Minimum of 20 patients
· Minimum of a 4-week treatment period
· Study report published in English
· Full paper citation

EXCLUSION CRITERIA

· Insufficient patient number
· Diagnosis not stated or not clear
· Duplicated patient series
· Technical information reports (reports describing the characteristics and the operational parameters of an intervention and where the evaluation of outcomes is non-existent or circumstantial)
· Use of non-validated or unconventional outcome measures
· Uncertain length of follow-up
· Incomplete follow-up
· Unable to track patient subgroups in the report (e.g., which patient had PD vs. other diagnosis; or which patients had unilateral vs. bilateral procedures)
· Non-English publication
· Abstract, review, or chapter

Further studies were also classified from a pragmatic clinical application perspective based on the putative clinical outcomes assessed in each study. Some studies had multiple endpoints and needed to be assessed independently for each of these clinical indications. The clinical indications considered include:
(1) Prevention of disease progression,
(2) Symptomatic control of Parkinson's disease,
(3) Prevention of motor complications,
(4) Control of motor complications, and
(5) Control of non-motor complications (autonomic dysfunction, depression, psychosis)

EFFICACY EVALUATION

CLASSIFICATION OF EVIDENCE

This review is based in a hierarchical organization of evidence.[12] Randomized controlled trials (RCT), if methodologically sound, are considered least biased and, thus, the most valid studies providing clinical evidence. The next level of evidence is supported by non-randomized, controlled clinical trials (CCT), followed by observational controlled studies (cohort and case-control studies). The lowest level of evidence considered was non-controlled case series. Clinical evidence was classified into three levels (Table 2). If sufficient RCTs were available (Level-I studies), studies with lower levels of evidence were only considered secondarily to amplify but not establish efficacy. In instances where RCTs did not exist, lower levels of evidence were used as the primary sources, but the conclusions were necessarily less firm.

Table 2 Level of Evidence

Level of Evidence	Definition
Level-I studies	Randomized, controlled trials
Level-II studies	Controlled clinical trials or observational controlled studies such as cohort or case-control studies
Level-III studies	Non-controlled studies like case series

RATING OF THE STUDY QUALITY SCORES

All Level-I studies were rated for study quality. The study quality score was derived from a list of key methodological topics, according to a published checklist[13], relevant for determining the methodological soundness of the trial (Table 3). A percentage score (not absolute values) was calculated for each study and is used as an indicator of the overall quality of the study. To assure consistency across studies, all the ratings were done by two of three committee members (OR, JF, CS). The differences in scores were reviewed and a consensus reached among the three reviewers.

A rating score, obtained as described above, was included for each Level-I study reviewed. This option deserves explanation because interpretation of a "quality score" might be tricky and useless if the reader is not familiar with the assessment used to create the score. In this review, the quality scores are descriptive variables, and they were not used to select the studies that were analyzed. As such, quality scores are useful. Particularly because when considering multiple Level-I studies, quality scores are helpful in stratifying the studies based on the strength of the evidence relative to the overall body of evidence being considered.

Table 3 Rating Scale for Quality of Evidence

	Yes	Unclear/ Possibly	No	N/A
RESULTS				
1. Is an estimate of the treatment effect given	2	1	0	N/A
2. Is it of clinical importance	2	1	0	N/A
3. Is the estimate of treatment effect sufficiently precise	2	1	0	N/A
VALIDITY: *SELECTION*				
4. Was the spectrum of patients well defined?	2	1	0	N/A
5. Was the diagnosis of the disease well defined?	2	1	0	N/A
6. If pragmatic, were suitably abroad eligible criteria used?	2	1	0	N/A
7. If explanatory, were eligibility criteria suitably narrow?	2	1	0	N/A
MEASUREMENT				
8. Was assignment to treatments stated to be random?	2	1	0	N/A
9. If yes, was the method of randomization explained?	2	1	0	N/A
10. Were all patients accounted for after randomization?	2	1	0	N/A
11. Were losses to follow-up low (<10)?	2	1	0	N/A
12. Were the treatment groups similar in important factors at the start of the trial?	2	1	0	N/A
13. Were all patients otherwise treated alike?	2	1	0	N/A
14. Were patients, health care workers and investigators “blind” to treatment?	2	1	0	N/A
15. Was assessment of outcome “blind”?	2	1	0	N/A
16. Was the occurrence of side effects explicitly looked for?	2	1	0	N/A
17. If yes, were estimates of their frequency/severity given?	2	1	0	N/A
STATISTICAL ANALYSIS				
18. Was the main analysis on “intention to treat”?	2	1	0	N/A
19. If no, was a sensitivity analysis performed?	2	1	0	N/A
20. Were additional clinically-relevant factors allowed for?	2	1	0	N/A
21. Were appropriate statistical methods used?	2	1	0	N/A
22. Were any “unusual” methods used?	2	1	0	N/A
23. If subgroup analyses were done, were they explicitly presented as such?	2	1	0	N/A
UTILITY				
24. Do the results help me choose treatment?	2	1	0	N/A
TOTAL (add ringed scores above):	(A)			
No. of questions which actually applied to this article (maximum=24):	(B)			
Maximum possible score (2 X B)	(C)			
OVERALL RATING (A/C expressed as a percentage)	%			

N/A=not applicable establishing conclusions

SAFETY EVALUATION[14]

As previously mentioned, safety profiles and tolerability of the interventions considered are described using a narrative, non-systematic approach[14]. The clinical information used to make an overall safety evaluation included:

· Adverse reactions reported in the trials analyzed in this review,
· Adverse reactions described in the product information documents, which differed among countries for some products,
· Regulatory measures taken by country or regional authorities based on safety and tolerability profiles of the treatment, and
· Literature reports based on non-systematically searched papers.

The safety descriptions are limited due to the paucity of data available in the literature, as well as limitations in our approach. Nevertheless, reviews of safety data were summarized as far as possible.

EVIDENCE-BASED CONCLUSIONS

Assessments of efficacy and safety for each therapeutic intervention were made followed by specific implications for use in clinical practice and for future clinical research. Where no evidence was available specifically relevant for patients with PD, this was clearly stated. A standardized wording was used to describe conclusions in order to avoid insurmountable subjectivity and inconsistencies across chapters. This wording is defined in Table 4.

Table 4. Definitions for specific recommendations

Efficacy Conclusions	Definition	Required Evidence
Efficacious	Evidence shows that the intervention has a positive effect on studied outcomes	Supported by data from at least one high-quality (score ≥ 75%) RCT without conflicting Level-I data
Likely efficacious	Evidence suggests, but is not sufficient to show, that the intervention has a positive effect on studied outcomes	Supported by data from any Level-I trial without conflicting Level-I data
Unlikely efficacious	Evidence suggests that the intervention does not have a positive effect on studied outcomes	Supported by data from any Level-I trial without conflicting Level-I data
Non-efficacious	Evidence shows that the intervention does not have a positive effect on studied outcomes	Supported by data from at least one high-quality (score ≥ 75%) RCT without conflicting Level I data
Insufficient evidence	There is not enough evidence either for or against efficacy of the intervention in treatment of Parkinson's disease	All the circumstances not covered by the previous statements
Safety		
Acceptable risk without specialized monitoring		
Acceptable risk, with specialized monitoring		
Unacceptable risk		
Insufficient evidence to make conclusions on the safety of the intervention		
Implications for Clinical Practice		
Clinically useful	For a given situation, evidence available is sufficient to conclude that the intervention provides clinical benefit	
Possibly useful	For a given situation, evidence available suggests, but insufficient to conclude that the intervention provides clinical benefit	
Investigational	Available evidence is insufficient to support the use of the intervention in clinical practice, but further study is warranted	
Not useful	For a given situation, available evidence is sufficient to say that the intervention provides no clinical benefit	
Efficacy unlikely	Evidence suggests that the intervention does not have a positive effect on studied outcomes. Supported by data from any Level-I trial without conflicting Level-I data	

WRITING PROCESS

A first meeting was held to discuss the principal format of the review and its methodology. Specific research tasks were assigned. For subsequent meetings, a smaller writing committee (principal authors) was formed and assigned the task of the primary preparation of the document with other participants taking on the role of co-authors. Additional contributors were recruited for specific focused tasks including internal quality control and quality ratings of Level-I trials. Following numerous face-to-face sessions and telephone conferences of the writing committee and prior to finalization, the document was peer-reviewed by the MDS Scientific Issues Committee and International Executive Committee. In addition, drug companies involved in the interventions reviewed were invited to check respective parts of the document for identification of published studies not identified by the committee. Comments received were addressed by the principal authors.

FINAL COMMENT

In the treatment of PD, there are many different decisions that health care providers make regarding symptomatic management, disease progression considerations, treatment of secondary conditions, and long-term quality-of-life implications. Consequently, efforts to better understand treatments that are proven effective and safe through systematic reviews will help influence clinical decisions for the optimal care for patients with PD disease.

Equally important, physicians and researchers need to have a clear understanding of those treatments that are: (a) not well studied specifically in patients with PD, (b) ineffective, or (c) unsafe. Furthermore, ongoing efforts to improve the quality of published evidence will only happen with critical reviews such as this that evaluate what studies are of sufficient quality to make treatment recommendations for patients with PD.

This review summarizes the published clinical evidence supporting the use of therapeutic interventions for PD. The evaluation panel recognised that its conclusions are constrained by some factors. Inclusion criteria to incorporate trials into the review process were chosen arbitrarily. Publication practices bias toward reports with favorable results. The database analysis was closed in January 2001 and it is expected that more recently published trials and future RCTs will permit modifications of conclusions in this ongoing effort.[1] This might be true for the most recent interventions, but is less likely to happen for older ones. The few RCTs identified with the older medications, like anticholinergics, amantadine and the first generation of dopamine agonists, were conducted in times when technical solutions to plan such trials were not yet developed.[2] Since then, those drugs went off patent, and there is no present financial interest in understanding them better. Consequently, conclusions on efficacy are sometimes more favorable for recently marketed drugs than for older ones, and this reflects historical factors rather than true clinical differences. Conversely, years of experience with an older agent offer greater reliability regarding safety than the short follow-up of recent agents. All along this review, conclusions were indeed more focused on proof of efficacy than safety. This problem is explained by the fact that reviewing RCTs is not the most adequate method to study an intervention's adverse reactions, especially the less frequent ones.

The level of evidence allowed to conclude that several interventions were "efficacious", but it should be clearly stated that when an intervention was not classified as efficacious, this only reflected the fact that there was not enough data from clinical trials to clearly support or refute its efficacy. One important finding of the project was to identify the numerous situations where data remained insufficient to conclude on efficacy. This was true for therapeutic strategies using simultaneous combinations or chronological associations as opposed to single interventions. This was also true for comparisons between single interventions. If choices among equivalent therapeutic options will always remain a matter of clinical expertise and individual preferences, a lot remains to be done to identify which options are equivalent. There are also insufficient data on long-term outcomes and mortality. The poverty of the evidence regarding routine interventions, like rehabilitation, and the treatment of depression, dementia or dysautonomia, is striking. It is expected that pointing out these insufficiencies will encourage the scientific community to conduct the appropriate investigations to correct such lacunas.

ACKNOWLEDGEMENTS

The MDS Evidence-based Assessment Project on interventions for the treatment of Parkinson's disease was supported by unrestricted educational grants to MDS from (alphabetical order): Dupont, Hoffman LaRoche, Medtronic, Novartis, Orion, Pharmacia, SmithKline Beecham (GlaxoSmithKline), and Watson Laboratories.

REFERENCES

1. Cohen N, Almoznino-Sarafian D, Alon I, et al. Warfarin for stroke prevention still underused in atrial fibrillation: patterns of omission. Stroke 2000;31(6):1217-22.
2. Evidence-Based Medicine Working Group. Evidence-based medicine. A new approach to teaching the practice of medicine. *JAMA* 1992;4:268(17):2420-5.
3. *Evidence-Based Medicine: How to Practice and Teach EBM* (2nd Edition). Sackett DL, Straus S, Richardson S, Rosenberg W, Haynes RB. London, eds. Churchill Livingstone. 2000; p. 1.
4. Cook DJ, Mulrow CD, Haynes B. Synthesis of best evidence for clinical decisions. In Systematic Reviews, Synthesis Of Best Evidence For Health Care Decisions. Mulrow CD, Cook DJ, eds. American College of Physicians, 1998.
5. SIGN Guidelines: An Introduction To SIGN Methodology For The Development Of Evidence-Based Clinical Guidelines. Edinburgh Scotland. Scottish Intercollegiate Guidelines Network (SIGN); 1999. 33(SIGN publications, 39).
6. Clarke CE, Sampaio C. Movement Disorders Cochrane Collaborative Review Group. Mov Disord 1997;12:477-482.
7. Jadad AR, Moher M, Browman GP, et al. Systematic reviews and meta-analyses on treatment of asthma: critical evaluation. BMJ 2000;320:537-540.
8. Stern JM, Simes RJ. Publication bias: evidence of delayed publication in a cohort study of clinical research projects. BMJ 1997;315:640-645.
9 Grégoire G, Derderian F, LeLorier J. Selecting the language of the publications included in a meta-analysis: is there a tower of Babel bias? J Clin Epidemiol 1995;48:159-63.
10. Egger M, Zellweger-Zahner T, Schneider M, Junker C, Lengeler C, Antes G. Language bias in randomized controlled trials published in English and German. Lancet 1997;350:326-329.
11. Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. BMJ 1994;309:1286-91.
12. Wolf SH, Battista RN, Anderson CM, Logan AG, Wang E and The Canadian Task Force on the periodic health examination. Assessing the clinical effectiveness of preventive manoeuvres: analytical principles and systematic methods in reviewing evidence and developing clinical practice recommendations. J Clin Epidemiology 43:891-905.
13. Dixon RA, Munro JF, Silcocks RP. Checklists for Critical Appraisal. The Evidence Based Medicine Workbook: Critical Appraisal for Clinical Problem Solving. Butterworth-Heinemann Medical 1997, Appendix I.
14. Kaufman DW, Shapiro S . Epidemiological assessment of drug-induced disease. Lancet 2000;356(9238):1339-43.

(FOOTNOTES)

1 Newly published high-quality RCTs were incorporated into the review as part of the writing and editing process up to October 2001.
2 The first RCT ever published dated from 1948. Central database is a collection of RCT and CCTs collected by the efforts of the Cochrane Collaboration through different means including hand searches. Therefore its inception date for RCTs is 1948 but other types of controlled studies are older (in the issue 1 of 2000 the older work entered in Central is from 1898).

Movement Disorders
Vol. 17, Suppl. 4, 2002, p. S7-S12

Published by Wiley-Liss, Inc.
DOI 10.1002/mds.5556

Anticholinergic Therapies in the Treatment of Parkinson's Disease

INTRODUCTION

BACKGROUND

Anticholinergics were the first widely accepted treatment for parkinsonism. Plants containing anticholinergic substances were already used in ancient Indian medicine for the treatment of a neurological condition, which appears to have been parkinsonism.[1] In 1867, Ordenstein first reported their antiparkinsonian effect, which Charcot had discovered fortuitously when administering tinctures of deadly nightshade (Atropa belladonna) for excessive salivation in parkinsonian patients.[2]

For almost a century, anticholinergics remained the only possible treatment for parkinsonism. At first, a variety of naturally occurring solanaceous alkaloids were used, often administered in the form of wine extracts (Bulgarian belladonna) or cigarettes. For a long time, the mechanism of action of the anticholinergics was believed to be due to peripheral muscarinic effects, and it was only in 1945 that acetylcholine was first proposed to be a central neurotransmitter.[3]

RATIONALE

In the 1940s and 1950s, the first clinical trials were carried out with newer synthetic anticholinergics. These early trials included many postencephalitic patients and generally are not considered well-designed trials by modern standards. However, they still constitute the majority of existing clinical trials concerning this class of drug. With the introduction of L-Dopa and increasing awareness of cognitive adverse reactions of anticholinergic drugs, interest in their use waned and the number of clinical trials declined.

The fact that anticholinergic therapy has remained in clinical use for well over a century, as well as the often remarkable clinical deterioration of parkinsonian symptoms after their abrupt discontinuation[4-6], suggests at least some beneficial effects. Pharmacological rationale for the use of anticholinergic drugs has been strengthened by the clear demonstration of dopaminergic-cholinergic antagonism in striatal function.

METHODS

KEY SEARCH ITEMS

Key search items included Parkinson and anticholinergic, or trihexyphenidyl, benzhexol, biperiden, orphenadrine, procyclidine, benztropine, bornaprine, ethopropazine, scopolamine, propantheline, benapryzine, cycrimine, elantrine, antihistamine, or diphenhydramine.

SPECIAL EXCEPTIONS TO INCLUSION/ EXCLUSION CRITERIA

· Because of the long history of the use of anticholinergics for treatment in Parkinson's disease (PD), the search period was extended to Cochrane Library 1948-1999; OldMedline 1960-1965; and Index Medicus from 1927.

· A homogeneous patient population with a diagnosis of idiopathic PD was not an absolute requirement. This would have excluded the vast majority of earlier articles in which postencephalitic patients usually constitute part of the patient population. A large number of the identified articles date back to the era before generally accepted criteria for the clinical diagnosis of idiopathic PD. Included were articles in which more than 50% of patients were classified as idiopathic. Also the minimum number of patients required was reduced to 15.

· Because of the paucity of high quality Level-I studies, Level-III studies were also included.

Articles dealing with the naturally occurring alkaloids are of historical interest in this context but were not included in the final evaluation. Early reports on substances that – to the best of our knowledge – either never came on the market or have not been licensed anywhere for as far as could be tracked back also were excluded.

BASIC PHARMACOLOGY

MECHANISM OF ACTION

The precise mechanism of action of the anticholinergics is still not clear, although it is generally believed that they work by correcting the disequilibria between striatal dopamine and acetylcholine activity. In 1967, Duvoisin[7] demonstrated that the centrally acting cholinesterase inhibitor, physostigmine, increased the severity of parkinsonian symptoms, and that these effects could be antagonized by anticholinergic drugs. Furthermore, it was shown by Nashold[8] that the direct injection during functional neurosurgery of acetylcholine into the globus pallidus of patients with PD resulted in increased tremor in the contralateral extremities, which was reduced by the subsequent injection of an anticholinergic drug.

Some of the anticholinergic drugs such as benztropine also have the ability to block dopamine uptake in central dopaminergic neurons. Some substances are predominantly used as antihistaminic (diphenhydramine) or have been developed as their derivatives (benztropine), but the antihistaminic properties of those substances do not contribute to their antiparkinsonian action.

There are two general types of acetylcholine receptors, the muscarinic and the nicotinic receptors. The muscarinic receptors are G proteins-linked receptors and the nicotinic receptors are ligand gated ion channels. The anticholinergics used in treatment of PD are specific for muscarinic receptors.

PHARMACOKINETICS

For some of these substances, which have been in clinical use for many years, formal pharmacokinetic studies in humans have not been performed, and therefore, some pharmacokinetic data are not published in the literature. Therefore the data available is limited, but all the anticholinergics reviewed below are reported as

being absorbed from gastrointestinal tract after oral administration, and all are lipophilic thereby allowing CNS penetration. Trihexyphenidyl reaches peak plasma concentrations in 2 to 3 hours after oral administration and has a duration of action of 1 to 12h. Benzotropine has a similar pharmacokinetic profile.

REVIEW OF CLINICAL STUDIES

The primary literature search, as described above, identified several hundred reports. Of these, 64 were reports on clinical trials of anticholinergics therapies reporting efficacy results, however, only 15 studies met the criteria for inclusion for this review.

PREVENTION OF DISEASE PROGRESSION

No qualified articles were identified.

SYMPTOMATIC CONTROL OF PARKINSONISM

All 15 identified reports meeting the criteria for inclusion addressed the use of anticholinergic drugs in the symptomatic management of parkinsonism. In all subcategories, the numbers of included articles were too small and patient populations usually were not homogeneous enough for a meaningful split among individual anticholinergic substances. For the same reason, no subdivisions were made for studies on monotherapy and combination therapy. The articles are discussed in chronological order in each subcategory.

Level-I Studies

Iivainen (1974)[9]: In a double-blind, cross-over study of bornaprine (8 mg/day) vs. placebo (six weeks for each treatment period) in 20 patients with mild to severe PD, the authors found a statistically significant reduction of resting tremor and postural tremor but no significant effect on rigidity and hypokinesia (this study used the author's own rating scales). Results are not presented in absolute figures. All but two patients were on combination therapy with other anticholinergics, L-dopa, or amantadine. The validity of this study is however weakened by the fact that (1) there was no washout period between the treatment and the placebo period thereby making interpretation more difficult due to the lack of detailed numerical results, and (2) there was a lack of detailed numerical outcome results reported. This study had an overall quality score of 63%.

Parkes et al. (1974)[10] did a randomized, double-blind, cross-over trial of benzhexol (8 mg), amantadine (200 mg), and their combination in 17 parkinsonian patients (including two post-encephalitic patients). Treatment duration was 4 weeks in each treatment arm and on combination therapy, followed by open-label administration of L-dopa alone, for 6 months. Both combination therapy and L-dopa therapy led to a statistically significant score reduction without a significant difference between the two strategies. Functional disability was reduced by 15% on benzhexol and on amantadine alone, by 40% on their combined use, and by 36% on L-dopa. Benzhexol lessened rigidity (by 9.4%) and improved posture (by 8%) but had little effect on akinesia (1.5%) and tremor (4.4%), while amantadine and L-dopa improved all symptoms. This is the only study available that compares an anticholinergic drug with amantadine. This study had an overall quality rating score of 60%.

Martin et al. (1974)[11] performed a randomized, double-blind study in 30 patients who were taking L-dopa (without decarboxylase inhibitor) either as monotherapy ("control" group) or in combination with trihexyphenidyl (mean dose not specified; "treatment" group). Treatment duration was 6 months. This study, despite being described as controlled, is difficult to interpret because the two patient groups appear different in their duration of disease (16.9 years in the control group vs. 7.9 years in the active treatment group) thereby preventing a meaningful comparison between treatments. The authors provide no explanation for this large difference in disease duration. Additionally, the study reports only limited numerical results on the rating scales, which were used to assess a number of motor functions; a statistical analysis was not reported, and the outcome data can partly be estimated from the graphs. The authors report no difference between groups in tremor and rigidity, and less improvement of speech in the "control" group. The mean required L-dopa dose was not changed by the addition of trihexyphenidyl. The authors conclude that the addition of trihexyphenidyl to L-dopa is "of no specific value". Although this study had an overall quality score of 75% there is an unexplained large difference in disease duration between the two groups at baseline, limiting efficacy conclusions.

Wallace et al. (1982)[12]: In a randomized, double-blind cross-over study over 30 weeks, Wallace[12] compared benztropine (mean dosage not specified) vs. placebo in addition to a stable dose of L-dopa in 29 mildly to moderately disabled patients with idiopathic PD. The authors found a small but statistically significant improvement in several motor measures such as tandem gait, strength and rigidity in upper extremities, and finger tapping as well as in selected activities of daily living. There is, however, an overall paucity of detail in the reported results, and tremor was not listed as an outcome variable. This study had an overall quality score of 59%.

Cantello et al. (1986)[13]: This study was a randomized, double-blind, cross-over study of bornaprine (mean dose 8.25 mg/day) vs. placebo (30 days on each treatment) in 27 patients with idiopathic PD. Disease severity ranged from Hoehn & Yahr (HY) scale 2 (14 patients) to 5 (1 patient), and patients were on stable antiparkinsonian therapy including L-dopa, bromocriptine, and other unspecified drugs. The objective outcome measure was the Webster Scale. The most marked improvement was reported for tremor (from 2.48 to 1.18 on bornaprine - $p<0.01$ – vs. 2.00 on placebo), but bradykinesia, rigidity, posture, facial expression, seborrhoea, and coping ability all were statistically significantly improved as well. The authors did not specifically state whether there was a statistically significant improvement of the total Webster Scale. Patients and physicians provided a subjective assessment, which was significantly in favor of bornaprine. No time was allowed for washout between the treatment and the placebo period. This study had an overall quality rating score of 60%.

Cooper et al. (1992)[14] conducted a randomized, controlled, single-blinded trial in 82 patients with early PD and 22 healthy controls. The aim of the study was to compare changes in motor function and in cognitive function in de-novo PD patients who had been started either on L-dopa (mean dose 415 mg/day), bromocriptine (mean dose 13.5 mg/day), or anticholinergics (21 patients on benzhexol, mean dose 5.9 mg daily; one patient on orphenadrine), or no treatment. These were compared to 22 healthy volunteers who were not on any treatment. There was no placebo group. The assessments were performed before treatment was started and after 4 months of therapy. As outcome measures for motor function, King´s College Rating Scale and Fine Finger Movements Test were used that showed a statistically significant

improvement in the L-dopa and anticholinergics group but not in the bromocriptine or in the untreated group. No differences in the effect on different parkinsonian symptoms were found. As the authors state, however, the low level of disease severity in these patients may have led to a relative insensitivity of symptom measurement. The authors' main endpoint was a detailed assessment of cognitive function in patients with PD and the impact of different treatments on this endpoint. A large number of neuropsychological tests were applied: Results that are relevant with respect to the anticholinergics include the Wechsler Memory Scale, which showed a significant improvement in the L-dopa and the untreated groups, whereas the anticholinergics group deteriorated. This latter result was not statistically significant. On some of the other tests, there was a specific deficit in the anticholinergics group. Looking at associations between results on motor and cognitive function tests, those patients on anticholinergics who had improved most in motor function were found to have deteriorated most on a number of neuropsychological tests. From the neuropsychological test results, the authors conclude that in PD, anticholinergics lead to an exacerbation of a pre-existing deficit in memory acquisition and immediate memory rather than accelerating the rate of forgetting. This study had an overall quality score of 55%.

Level-II Studies

Kaplan et al. (1954)[15] was the earliest published report an anticholinergic therapy that met inclusion criteria. In this nonrandomized, cross-over trial involving 35 patients (6 were considered post-encephalitic), benzhexol, panparnit, and hyoscine were compared to placebo over a 4-week treatment period for each treatment; there was a one-week, low-dose phase between treatment periods. Outcome measures were "over-all picture" on neurological examination, which showed 40.6% improvement on benzhexol, 31.4% on panparnit, 13.3% on hyoscine, and 6% on placebo; EMG-quantification of tremor (statistically significant improvement of amplitude on each drug compared to placebo but no improvement from baseline – deterioration of tremor after drug withdrawal was concluded from this); grip strength on dynamometer (no significant changes); and Purdue Pegboard (drugs slightly more effective than placebo, no difference between substances). Patients were blinded, but blinding of investigators is not specifically stated. The paper also does not report on any adverse reactions and lacks details on patient characteristics and reported results.

Strang (1965)[16] reported a trial of procyclidine, which appears to be methodologically complicated. The study combines a 2-month controlled, nonrandomized trial of procyclidine (unspecified dose) as adjunct to unspecified other antiparkinsonian drugs in 70 patients (15 were considered postencephalitic) with a 10-month, open-label observation period, in which the previous placebo patients as well as 15 additional patients were put on procyclidine as monotherapy. The quality of the study protocol is further limited by the fact that there were no numeric outcome measures reported for the first part of the trial and that statistical analysis is lacking. Efficacy measures were rating of each symptom on a 0% to 100% scale and timed performance tests, which were not further specified. At the end of the follow-up period, the author reports 40% improvement in tremor, 53% in rigidity, 42% in akinesia, 44% in gait, and 58% in sialorrhea.

Strang (1967)[17]: The same author as the previous study also conducted a nonrandomized, placebo-controlled, double-blind study of biperiden (mean dose not stated) in 80 patients with parkinsonism (of unspecified severity; 14 patients were considered postencephalitic) over a period of two months. This was followed by a 6-month, open-label follow-up period. Any other antiparkinsonian therapy was continued unchanged. As with patient characteristics, there is also a lack of details in the results reported. In fact, the only results that were given concerning the first, controlled part of the study were that 68% of patients had "significantly" improved, that 13 had discontinued the drug and that a "total ineffectiveness of placebo" had been noted. Numeric outcome results are only reported for the end of the open-label period, using the same rating scale of 0-100% for each symptom as in the other studies by the same author included here. He found an improvement of 53% in tremor (duration, frequency of occurrence, and amplitude), 40% in rigidity, 45% in bradykinesia, 38% in gait, and 54% in sialorrhea.

Friedman et al. (1997)[18]: In a nonrandomized, cross-over trial comparing benztropine (mean dose 3 mg/day) and the atypical neuroleptic clozapin (39 mg/day) in 19 patients, Friedman and colleagues showed a comparable and statistically significant tremor reduction of around 30% from baseline on both drugs. Primary variables were tremor scores in two scales and on video assessment.

Level-III Studies

Strang carried out two additional uncontrolled trials using a very similar methodology. Both studies involve large numbers of patients with a long follow-up:

Strang (1965)[19] followed 94 patients for one year who were on benztropine given either as monotherapy or in combination with other anticholinergics. The same rating scale was applied for parkinsonian symptoms and timed performance tests as in his other studies included in this review. These studies failed to describe details of the assessment methods used. Results were reported as percentage of improvement of each symptom in patients on monotherapy. Improvement in tremor (45%) and rigidity (40%) were similar, while akinesia was reported as improved by 33%. No detailed results are reported on the patients who were on combination therapy.

Strang (1965)[20]: In another noncontrolled trial, Strang reported on orphenadrine as monotherapy or in combination with benztropine in 150 patients (100 of whom were classified as idiopathic PD) treated over a 2-year period. Mean dosages were not stated. The same methodology as described above was used. At the end of the trial, only 83 patients were still taking the orphenadrine, with 60 patients still experiencing a clinical benefit. Response of tremor, rigidity, and akinesia were reported to be similar: 33% to 37% of patients obtained relief after 24 months.

Sancesario et al. (1984)[21] reported the results of a noncontrolled trial that assessed parkinsonian tremor, as measured using an accelerometer, on different doses (6 to 16 mg daily) of bornaprine. The report lacks details on specific results. The main result, according to the authors, was a statistically significant improvement of tremor amplitude and duration. Only 20% of the patients reported an improvement on self-assessment. The authors also state that bradykinesia "seemed to respond to higher doses in some patients", without reporting the relevant results.

Bassi et al. (1986)[22] carried out a noncontrolled trial of orphenadrine given over 6 months to a small number of patients: 9 patients (HY stage 1 to 2) were put on monotherapy (mean dose

not specified), and 11 patients (HY stage 3) received orphenadrine (150 mg daily) in addition to L-dopa (450 mg daily). Both groups showed a statistically significant improvement in disease severity (Webster Scale: from 10.2 to 5.2 on monotherapy and from 16.0 to 6.7 on combination), disability (Northwestern University Disability Scales: from 9.1 to 5.7 on monotherapy and from 19.0 to 5.8 on combination), and depression (Hamilton Rating Scale), with a trend for short-term memory to deteriorate in the patients on combination therapy.

PREVENTION OF MOTOR COMPLICATIONS

No qualified articles were identified.

CONTROL OF MOTOR COMPLICATIONS

No qualified articles were identified. The only report where anticholinergic was given for the management of motor symptoms was a single, open-label study in 9 patients with dysphasic dyskinesia on L-dopa therapy.[23]

REVIEW OF SAFETY

Among the drugs currently in use for the treatment of parkinsonism, anticholinergics give rise to a comparatively high number of safety concerns, which limit their clinical use. Due to their peripheral antimuscarinic action, anticholinergic therapy is contraindicated in narrow-angle glaucoma (one case of blindness caused by this has been reported in a parkinsonian patient)[24], tachycardia, hypertrophy of the prostate gland, gastrointestinal obstruction, and megacolon. They may cause blurred vision due to accommodation impairment, urinary retention, nausea, constipation (rarely leading to paralytic ileus)[25], and – frequently – dry mucous membranes. Gingivitis and caries due to this latter effect may occur and rarely lead to loss of teeth.[2] Reduced sweating may interfere with body temperature regulation, and fatal heat stroke has been reported (in psychotic patients who were on neuroleptic as well as anticholinergic treatment).[26,27]

Central anticholinergic activity may interfere with mental function and represent one of the most important limiting factors to their use. Impaired neuropsychiatric function has been demonstrated in patients who had not previously been demented.[28,29] In patients who had not shown any central side effects while on therapy, a significant improvement of mental functions after withdrawal of anticholinergics has been found.[30] Acute confusion, hallucinations, and sedation may occur. All these central adverse effects are more likely to occur with advanced age and in patients with previously impaired cognitive functions. The use of anticholinergics is contraindicated in demented patients.

Other central nervous adverse effects refer to the cholinergic impact on the motor system. There are a number of reports (usually involving small numbers of patients) on dyskinesias brought on[31] or increased[32] by the administration of anticholinergics, either as a monotherapy or in combination with L-dopa. In several articles, the onset occurs within days to weeks after initiation of treatment[33], and in some, dyskinesias were reported to be predominantly orobuccolingual with a tendency to spread to the limbs with higher doses.[34] These dyskinesias were reversible with withdrawal of the drugs. The abrupt withdrawal of anticholinergic drugs may lead to a rebound effect with marked deterioration of parkinsonism. Therefore, anticholinergics should be discontinued gradually and with caution.[4-6]

CONCLUSIONS

EFFICACY

PREVENTION OF DISEASE PROGRESSION

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of anticholinergics regarding the prevention of disease progression and in the prevention and control of motor complications.

SYMPTOMATIC CONTROL OF PARKINSONISM

Based on the evidence available to date, anticholinergic therapies are LIKELY EFFICACIOUS for the symptomatic control of PD. However, data is insufficient to establish the long-term efficacy of anticholinergic treatment and to distinguish between the clinical efficacy of monotherapy vs. adjunct therapy.

CONTROL OF MOTOR COMPLICATIONS

There is INSUFFICIENT EVIDENCE to conclude on differences between individual drugs within this class or clinical benefits relative to other antiparkinsonian agents.

CONTROL OF NON-MOTOR COMPLICATIONS

There is INSUFFICIENT EVIDENCE that the available data support the assumption that anticholinergic medications have different effects on different parkinsonian symptoms, such as a selective effect on parkinsonian tremor, or a lack of effect on bradykinesia.

SAFETY

The use of anticholinergics in the treatment of parkinsonism carries an ACCEPTABLE RISK WITHOUT SPECIALIZED MONITORING. Obvious requirements for clinical use of anticholinergic therapy are careful exclusion of the contraindications listed above, the titration of the lowest possible dosage for each patient, and regular follow-up clinic visits with an emphasis in detecting adverse reactions.

IMPLICATIONS FOR CLINICAL PRACTICE

From the evidence published to date, anticholinergic medications are CLINICALLY USEFUL in the symptomatic treatment of PD, both as monotherapy and when used in combination treatment strategies.

There are, however, considerable limitations to this usefulness: the antiparkinsonian effect of this class of drugs is usually only mild to moderate, and occurrence of adverse reactions – due both to peripheral and to central anticholinergic action – is not infrequent. Careful consideration of contraindications, individual dose adjustments, and active monitoring for adverse reactions are necessary. Abrupt withdrawal should be avoided.

In a number of controlled and uncontrolled studies, particularly dating from the earlier years of use of anticholinergics in PD, sialorrhea was used as an outcome variable, and response to anticholinergic therapy was usually reported in a range comparable to the response of other parkinsonian features.

IMPLICATIONS FOR CLINICAL RESEARCH

Further research may establish the role of anticholinergic agents in the prevention of motor complications, possibly as part of an early combination therapy aiming at delaying the initiation of L-dopa. A direct head-to-head comparison with dopamine agonists in de novo patients also would be of interest. In the literature published to date, there is anecdotal evidence of a possible beneficial

effect of anticholinergics in the management of motor complications. In light of a number of reports on dyskinesias induced or aggravated by anticholinergics, further studies seem warranted to establish their role in late-stage PD with motor complications.

REFERENCES

1. Manyam BV. Ayurvedic approach to neurologic illness. In: Weintraub MI, ed. *Alternative Medicine in Neurologic Illness*. Philadelphia, Mosby: 2000 (in press).
2. Lang AE, Blair RDG. Anitcholinergic drugs and amantadine in the treatment of Parkinson´s disease. In: Calne DB, ed. *Handbook of experimental pharmacology, Vol. 88: Drugs for the Treatment of Parkinson´s Disease*. Berlin Heidelberg: Springer-Verlag, 1989.
3. Feldburg W. Present views on the mode of action of acetylcholine in the central nervous system. Physiol Rev 1945;25:596-642.
4. Hughes RC, Polgar JG, Weightman D, Walton JN. Levodopa in parkinsonism: the effects of withdrawal of anticholinergic drugs. Brit Med J 1971;2:487-491.
5. Horrocks PM, Vicary DJ, Rees JE, Parkes JD, Marsden CD. Anticholinergic withdrawal and benzhexol treatment in Parkinson´s disease. J Neurol Neurosurg Psychiatry 1973;36:936-941.
6. Goetz CG, Nausiedad PA, Weines PH, Klawans HL: Practical guidelines for drug holidays in parkinsonian patients. Neurology 1981;31:641-642.
7. Duvoisin R. Cholinergic-anticholinergic antagonism in parkinsonism. Arch Neurol 1967;17:124-136.
8. Nashold BS. Cholinergic stimulation of globus pallidus in man. Proc Soc Exp Biol Med 1959;101:68.
9. Iivainen M. KR 339 in the treatment of parkinsonian tremor. Acta Neurol Scand 1974;50:469-470.
10. Parkes JD, Baxter RC, Marsden CD, Rees J. Comparative trial of benzhexol, amantadine, and levodopa in the treatment of Parkinson´s disease. J Neurol Neurosurg Psychiatry 1974;37:422-426.
11. Martin WE, Loewenson RB, Resch JA, Baker AB. A controlled study comparing trihexyphenidyl hydrochloride plus levodopa with placebo plus levodopa in patients with Parkinson´s disease. Neurology 1974;24:912-919.
12. Wallace W, Tourtelotte WW, Potvin AR, et al. Parkinson´s disease: Cogentin with sinemet, a better response. Prog Neuro-Psychopharmacol Biol Psychiat 1982;6:51-55.
13. Cantello R, Riccio A, Gilli M, et al. Bornaprine vs placebo in Parkinson disease: double-blind controlled cross-over trial in 30 patients. Ital J Neurol Sci 1986;7:139-143.
14. Cooper JA, Sagar HJ, Doherty SM, Jordan N, Tidswell P, Sullivan EV. Different effects of dopaminergic and anticholinergic therapies on cognitive and motor function in Parkinson´s disease. Brain 1992;115:1701-1725.
15. Kaplan HA, Machover S, Rabiner A. A study of the effectiveness of drug therapy in parkinsonism. J Nerv Dis 1954;119:398-411.
16. Strang RR. Experiences with cogentin in the treatment of parkinsonism. Acta Neurol Scand 1965;41:413-418.
17. Strang RR. Clinical evaluation of biperiden in Parkinson´s disease. Dis Nerv Syst 1967;28:191-193.
18. Friedman JH, Koller WC, Lannon MC, Busenbark K, Swanson-Hyland E. Benztropine versus clozapine for the treatment of tremor in Parkinson´s disease. Neurology 1997;48:1077-1081.
19. Strang RR. Kemadrin in the treatment of parkinsonism: a double blind and one-year follow-up study. Curr Med and Drugs 1965;5:27-32.
20. Strang RR. Orphenadrine ("disipal") in the treatment of parkinsonism: a two-year study of 150 patients. Med J Aust 1965;Sep11:448-450.
21. Sancesario G, Cicardi MC, Fiermonte G, Giacomini P, Stanzione P. Effectiveness of bornaprine on parkinsonian tremor. Ital J Neurol Sci 1984;V:289-293.
22. Bassi S, Albizzati MG, Calloni E, Sbacchi M. Treatment of Parkinson´s disease with orphenadrine alone and in combination with L-dopa. Brit J Clin Pract 1986;40:273-275.
23. Pourcher E, Bonnet A-M, Kefalos J Dubois B, Agid Y. Effects of etybenzatropine and diazepam on levodopa-induced diphasic dyskinesias in Parkinson´s disease. Mov Disord 1989;4:195-201.
24. Friedmann Z, Neumann E. Benzhexol-induced blindness in Parkinson´s disease. *Br* Med J 1972;1:605.
25. Wade LC, Ellenor GL. Combination mesoridazine- and benztropine mesylate induced paralytic ileus: two case reports. Drug Intell Clin Pharm 1980;14:17-22.
26. Stadnyk AN, Glezos JD. Drug-induced heat stroke. Can Med Assoc J 1983;128:957-959.
27. Tyndel F, Labont R. Drug-facilitated heat stroke. Can Med Ass J 1983;129:680.
28. Sadeh M, Braham J, Modan M. Effects of anticholinergic drugs on memory in Parkinson's disease. Arch Neurol 1982;39:666-667.
29. Syndulko K, Gilden ER, Hansch EC, Potvin AR, Tourtelotte WW, Potvin JH. Decreased verbal memory associated with anticholinergic treatment in Parkinson´s disease patients. Int J Neurosci 1981;14:61-66.
30. Lang AE. Treatment of Parkinson´s disease with agents other than levodopa and dopamine agonists: controversies and new approaches. Can J Neurol Sci 1984;11(Suppl):210-220.
31. Birket-Smith E. Abnormal involuntary movements induced by anticholinergic therapy. Acta Neurol Scand 1974;50:801-811.
32. Birket-Smith E. Abnormal involuntary movements in relation to anticholinergics and levodopa therapy. Acta Neurol Scand 1975;52:158-160.
33. Linazasoro G. Anticholinergics and dyskinesia. Mov Disord 1994;9(6):689.
34. Hauser RA, Olanow CW. Orobuccal dyskinesia associated with trihexyphenidyl therapy in a patient with Parkinson´s disease. Mov Disord 1993;8:512-514.

BIBLIOGRAPHY - EXCLUDED FROM ANALYSIS (REASON FOR EXCLUSION)

Berger FM. The treatment of paralysis agitans with theophorin. N Y State J Med 1949;49:1817-1820. (Type of parkinsonism not specified; no numeric outcome measure)

Berkowitz B, Alvermann E. Trihexyphenidyl (artane), stramonium, and nonchemotherapy of paralysis agitans. Arch Neurol Psychiatr 1952;67:462-472. (Type of parkinsonism not specified; limited numeric outcome measures)

Berris H. Parkinsonism: Preliminary report on two new antiparkinsonian agents. Lancet 1954;74:245-246. (Type of parkinsonism not specified; no numeric outcome measure)

Blonsky ER, Dale Ericsson A, McKinney AS, Rix A, Wang RIH, Rimm AA. Phase II multicenter study of elantrine in parkinsonism. Clin Pharmacol Therapeutics 1973;15:46-50. (Elantrine never marketed; no statistical analysis of numerical results)

Brown DM, Hughes BO, Marsden CD, Meadows JC, Spicer B. Some initial animal and human pharmacological studies with benapryzine. Br J Pharmacol 1973;47:476-486. (Six patients; treatment duration not specified)

Brumlik J, Canter G, De la Torre R, Mier M, Petrovick M, Boshes B. A critical analysis of the effects of trihexyphenidyl (artane) on the components of the parkinsonian syndrome. J Nerv Ment Dis 1964;138:424-431. (Treatment duration 2 weeks)

Budnitz J. The use of benadryl in Parkinson´s disease. New Engl J Med 1948;238:874-875. (Eight patients; no numeric outcome measures)

Canelis M, Farnell FJ, McGavack TH. Clinical experiences in parkinsonism with a new type of antispasmodic, 3-(1-piperidyl)-1-phenyl-1-cyclohexyl-1-propanol hydrochloride ("artane"). Am J M Sc 1949;218:655-659. (Sixteen out of 23 patients were postencephalic)

Corbin KB. Trihexyphenidyl: Evaluation of the new agent in the treatment of parkinsonism. JAMA 1949;141:377-382. (No numeric outcome measures)

Delisle Burns B, DeJong D, Solis-Quiroga OH. Effects of trihexyphenidyl hydrochloride (artane) on Parkinson's disease. Neurology 1964;14:12-23. (Treatment duration 3 weeks)

Doshay LJ. Five-year study of benztropine (cogentin) methanesulfonate. JAMA 1956;162(ii):1031-1034. (Less than 50% had idiopathic PD)

Doshay LJ, Constable K. Artane therapy for parkinsonism. JAMA 1949;140(17):1317-1322. (Only 41% of patients had idiopathic Parkinson's disease; no numeric outcome measure)

Doshay LJ, Constable K, Agate FJ. Ethopropazine (parsidol) hydrochloride in treatment of paralysis agitans. JAMA 1956;160(5):348-351. (Only 34% had idiopathic Parkinson's disease)

Doshay LJ, Constable K, Fromer S. Preliminary study of a new antiparkinson agent. Neurology 1952;2:233-243. (Six patients had idiopathic Parkinson's disease)

Doshay LJ, Constable K, Zier A. Major and minor tremor. Results in 544 treated cases. Neurology 1953;3:360-368. (Tested 11 substances including natural alkaloids; less than 50% with idiopathic Parkinson's disease)

Dow RS, Rosenbaum H. The treatment of parkinsonism with artane. Northwest Med 1949;48:699-701. (Ten patients; no numeric outcome)

Dow RS, Smith GN. Clinical evaluation of pagitane hydrochloride in parkinsonism. Neurology 1954;4:33-39. (Non-homogeneous patient population; 9 patients with idiopathic Parkinson's disease)

Effron AS, Denker PG. A clinical evaluation of certain antihistaminic and antispasmodic drugs in Parkinson´s disease. JAMA 1950;144(1):5-8. (No numeric outcome measure; eleven different subsubstances and combinations thereof)

Ellenbogen BK. Artane in the treatment of parkinsonism. Lancet 1950;Jun3:1034-1035. (Twelve patients; 7 postencephalic)

Gallagher DJA, Palmer H. A comparative study of the use of Artane and Lysivane in the treatment of parkinsonism. New Zealand Med J 1950;49:531-536. (Fourteen patients; no numeric outcome measure)

Garai O. Lysivane and artane in the treatment of parkinsonism. Lancet 1951;Feb 24:429-432. (Twenty-four out of 34 patients postencephalic; no numeric outcome measure)

Gillhespy RO, Hall Ratcliffe A. Treatment of parkinsonism with a new compound (B.S. 5930). Br Med J 1955;2:352-355. (No numeric outcome measure; treatment duration not specified)

Ghillespy RO, Mustard DM. The value of biperiden alone and in combination with bamipine in the treatment of Parkinson's disease. Brit J Clin Pract 1963;17(6):345-346. (Treatment duration not specified; no numeric outcome measure)

Hökendorf H. Combination therapy of extrapyramidal disease with trihexyphenidyl and L-dopa: An electromyographic study with specific reference to tremor. J Int Res 1979;7:19-28. (Non-homogeneous patient population; number of idiopathic Parkinson's disease and treatment duration not specified)

Koller WC. Pharmacologic treatment of parkinsonian tremor. Arch Neurol 1986;43:126-127. (Nine patients; treatment duration 2 weeks)

Lamid S, Jenkins RB. Crossover clinical trial of benapryzine and trihexyphenidyl in parkinsonian patients. J Clin Pharmacol 1975;15(8-9):622-626. (Ten patients)

Lerner PF. Kemadrin, a new drug for treatment of parkinsonian disease. J Nerv Ment Dis 1956;123:79-83. (Type of parkinsonism not specified)

McGavack TH, Elias H, Boyd LJ. Some pharmacological and clinical experiences with dimethylaminoethyl benzhydryl ether hydrochloride (benadryl). Am J Med Sci 1947;213:418-434. (Four Parkinson's disease patients; treatment duration not specified; no numeric outcome)

Muenter MD, Dinapoli RP, Sharpless NS, Tyce GM. 3-0-Methlydopa, L-dopa, and trihexyphenidyl in the treatment of Parkinson´s disease. Mayo Clin Proc 1973;48:173-183. (Six patients; three patients on trihexyphenidyl)

Norris JW, Vas CJ. Mexihene hydrochloride and parkinsonian tremor. Acta Neurol Scand 1967;43:535-538. (Treatment duration three weeks)

O´Doherty D, Forster FM. The use of benztropine sulfonate in the treatment of parkinsonism. Med Ann Distr Columb 1953;22(5):221-223. (Fourteen out of 24 patients postencephalic)

Phillips J, Montuschi E, Sharkey J. Artane in the treatment of parkinsonism. Lancet 1950;June 17:1131. (Type of parkinsonism not specified; no numeric outcome measure)

Poucher E, Bonnet A-M, Kefalos J, Dubois B, Agid Y. Effects of etybenzatropine and diazepam on levodopa-induced diphasic dyskinesias in Parkinson's disease. Mov Disord 1989;4:195-201. (Nine patients; acute challenge study)

Rix A. Evaluation of an experimental anticholinergic drug, elantrine, in treating the tremor of parkinsonism. Adv Exp Med Biol 1977;90:277-281. (Drug was never available for clinical use; no numeric results reported)

Rix A, Fisher R. Comparison of trihexyphenidyl and dihydromorphanthridine drivative in control of tremor of parkinsonism. South Med J 1972;65:1385-1389. (Type of parkinsonism not specified; treatment duration not specified; no numeric outcome measure)

Ryan GMS, Spurway Wood J. Benadryl in the treatment of parkinsonism. Lancet 1949;12:258-259. (Specifies two pts. only)

Salzer HM. Artane in the treatment of parkinsonism. Dis Nerv System 1950;11:77-78. (Twelve patients; no numeric outcome measure)

Schlezinger NS, Alpers BJ. The use of syntropan in parkinsonism. Am J M Sci 1941;201:374-379. (No numeric outcome measure)

Schrag A, Schelosky L, Scholz U, Poewe W. Reduction of parkinsonian signs in patients with Parkinson´s disease by dopaminergic versus anticholinergic single-dose challenges. Mov Disord 1999;14:252-255. (Acute challenge study)

Schwab RS, Chafetz ME. Kemadrin in the treatment of parkinsonism. Neurology 1955;5:273-277. (Type of parkinsonism not specified; no numeric outcome specified)

Schwab RS, Leigh D. Parpanit in the treatment of Parkinson's disease. JAMA 1949;139:629-634. (Thirty-eight of 50 patients postencephalic)

Schwab RS, Tillmann WR. Artane in the treatment of Parkinson´s disease. New Engl J Med 1949;241:483-485. (No numeric outcome specified; varying combinations with other anticholinergics)

Sciarra D, Carter S, Merritt HH. Caramiphen hydrochloride (panparnit) in the treatment of diseases of the basal ganglions. JAMA 1949;141:1226-1229. (Seventeen out of twenty eight patients postencephalic; no numeric outcome measure)

Strang RR. Double-blind clinical evaluation of UCB 1549 in treatment of Parkinson´s disease. Brit Med J 1966;2:1112-1113. (Drug never available for clinical use)

Timberlake WH. Double-blind comparison of levodopa and procyclidine in parkinsonism, with illustrations of levodopa-induced movement disorders. Neurology 1970;20:31-35. (Type of parkinsonism and treatment duration not specified)

Timberlake WH, Schwab RS. Experimental preparation W-483 in the treatment of Parkinson´s disease. N Engl J Med 1952;247:98-100. (Type of parkinsonism and treatment duration not specified)

Whyte RK, Hunter KR, Laurence DR, Stern GM, Armitage P. Levodopa and orphenadrine in parkinsonism. Eur J Clin Pharmacol 1971;4:18-21. (Treatment duration 2 weeks)

Ziegler DK, Torres F. Parsidol in the treatment of parkinsonism. Neurology 1955;5:197-200. (Treatment duration not specified; no numeric outcome measure)

Zier A, Doshay LJ. Treatment of parkinsonism with pagitane hydrochloride. Neurology 1954;4:682-689. (Only 35% had idiopathic Parkinson's disease; treatment duration "days to 15 months; no numeric outcome measure)

Zier A, Doshay LJ. Procyclidine hydrochloride (kemadrin) treatment of parkinsonism. Neurology 1957;7:485-489. (No numeric outcome measure)

Movement Disorders
Vol. 17, Suppl. 4, 2002, p. S13-S22

Published by Wiley-Liss, Inc.
DOI 10.1002/mds.5557

Amantadine and Other Antiglutamate Agents

INTRODUCTION

BACKGROUND

In 1969, Schwab et al.[1] first reported amantadine as being clinically useful in the treatment of Parkinson's disease (PD). Since that time, several clinical trials have investigated the efficacy of amantadine compared with anticholinergics and levodopa, given either alone or in combination with other antiparkinsonian medication. The majority of these trials were conducted between 1970 and 1975, and were controlled, double-blind, crossover studies. Subsequently, investigators' interest in amantadine waned and recent reviews on PD treatment and pharmacology placed amantadine as a secondary therapy for PD. Despite this varying clinical interest in amantadine, there remain several unresolved features of the drug, specifically, the clinical observation that discontinuation of amantadine in patients with PD may result in a dramatic worsening of clinical status.[2]

RATIONALE

More recently, interest in amantadine has reemerged, particularly due to the hypothesis of its possible role for the treatment of motor fluctuations and dyskinesias[3,4] in patients on chronic levodopa therapy. Consequently, a review of the published literature on amantadine is included, with the underlying objective of determining the efficacy and safety of amantadine and other antiglutamate agents in the treatment of PD.

METHODS

KEY SEARCH TERMS

The terms used for the search were: parkinsonism or Parkinson's disease, amantadine, memantine, ifenprodil, dextromethorphan, budipidine, and antiglutamate agents/drugs.

SPECIAL EXCEPTIONS

In the absence of randomized, controlled trials (RCT) meeting inclusion and exclusion criteria, other controlled clinical trials were included that: were nonrandomized, enrolled less than 20 patients, or had less than a 4-week evaluation period. Specifically, all studies specified a diagnosis of PD, used objective scales for target symptoms, had a minimum of 5 evaluated patients, used a standardized assessment of clinical efficacy, defined baseline and post-treatment time points, and defined an unequivocal grading of therapeutic effect (ie. no improvement, marked/moderate/complete improvement, or no modification of concomitant antiparkinsonian therapies during assay). Uncontrolled studies were only considered if no other type of studies were available.

AMANTADINE

BASIC PHARMACOLOGY

MECHANISM OF ACTION

Amantadine hydrochloride is 1-amino-adamantanamine, the salt of a symmetric 10-carbon primary amine that was originally introduced as an antiviral agent effective against A_2 Asian Influenza.[5] Originally, amantadine was fortuitously noted to be useful in relieving clinical symptoms in a single patient with PD.[1]

There are several proposed modes of action of amantadine in PD, but the exact mechanism remains unclear. Most of the behavioral and neurochemical studies indicate that amantadine interacts with catecholamines, specifically dopamine. Presynaptically, amantadine may exert its clinical effect by enhancing (through an amphetamine-like action) the release of stored catecholamines from intact dopaminergic terminals[6] and by inhibiting catecholamine reuptake processes at the presynaptic terminal. This later effect requires high concentrations of amantadine in vitro, and probably does not occur at therapeutic dosages.[7] Postsynaptically, amantadine exerts a direct effect on dopamine receptors[8] thereby introducing changes in the dopamine receptor affinity.[8] Amantadine's combined presynaptic and postsynaptic action causes simultaneous interference with reuptake, release and receptor interaction not necessarily in a direction favoring increased dopamine stimulation.[8]

In addition, nondopaminergic properties of amantadine are proposed, including an anticholinergic action[9] and a NMDA glutamate receptor blockade[10,11]

PHARMACOKINETICS

Amantadine hydrochloride is readily absorbed (blood levels peak 1-4 h after an oral dose of 2.5 mg/kg) with a clinical duration of up to 8 hours, and is poorly metabolized in humans (more than 90% of an ingested dose can be recovered unchanged in urine). Commercially available in most countries, amantadine hydrochloride is used clinically as 100-mg capsules or as syrup containing 50 mg/ml. The currently recommended dosage for us in PD is 200 to 300 mg given in 2 to 3 divided doses (ie. 100 mg BID to TID). Chronic administration results in amantadine accumulation in patients with impaired renal function, which can cause concomitant toxicity.[12] The drug is generally well tolerated; livedo reticularis and ankle edema are the most frequent adverse reactions.

REVIEW OF CLINICAL STUDIES

The results of the literature search process identified 56 published reports on amantadine. Of these, 23 articles were excluded because they did not meet the predefined inclusion criteria. Fifteen prospective randomized controlled trials were identified, which met the conditions established in method section. Furthermore, 15 reports were included based on special exceptions previ-

ously defined (non-randomized or uncontrolled studies).

In studies evaluating symptomatic control of parkinsonism amantadine was tested both as monotherapy as well as when given as adjunct to preexisting treatment with anticholinergics or Levodopa and these two types of studies will be reviewed separately.

PREVENTION OF DISEASE PROGRESSION

No qualified studies were identified.

SYMPTOMATIC CONTROL OF PARKINSONISM

MONOTHERAPY

Level-I Studies

Fahn et al. (1975)[13] reported the results of a randomized, crossover, placebo-controlled trial in 23 patients with PD. The study design was complex and included several successive crossover periods, which were separated by months of open therapy. Reviewing the first crossover period, the efficacy of amantadine versus placebo can be evaluated. Patients received either placebo or amantadine 200 mg/d for 2 weeks and the alternate drug was given for the next 2 weeks. The authors report improvement in 16 (70%) patients while treated with amantadine compared with placebo. During this first crossover period, several adverse reactions were reported including dizziness, nervousness, irritability, lightheadedness, depression, insomnia, anorexia, and sleepiness. No adverse reactions were evaluated as serious, and the two most frequents events were insomnia and anorexia. This study had a quality rating score of 46%.

Butzer et al. (1975)[14] studied 30 patients of whom 27 were analyzed while on monotherapy with amantadine, and 3 patients were co-medicated with anticholinergic or anti-histaminic therapy. This study was a double-blind, placebo-controlled, crossover study, and each period study had a duration of 2 weeks. Twenty-nine (out of the 30) patients were described as having idiopathic PD and 26 patients completed the study. Twenty patients preferred amantadine, 3 preferred placebo, and 3 were uncertain. Clinical assessments were based on evaluations of tremor, rigidity, all physical signs, daily activities, timed tests, repetitive motions and overall average. Amantadine produced an overall statistically significant improvement of 12%. After the end of the crossover phase 10 patients were followed for 10 to 12 months while on amantadine (open label). Forty-four independent adverse reactions were reported, some of which occurred in the same patients. The three most common reactions were oedema, livedo reticularis or rash, and light-headedness. This study had an overall quality rating score of 57%.

Parkes et al. (1974)[15] compared the effects of benzhexol (8 mg/d), amantadine (200 mg/d) and amantadine plus benzhexol, in 17 patients (15 with idiopathic PD) in a randomized, double-blind, crossover trial involving 4-week treatment periods. Fourteen patients completed the study. Administered as monotherapy, benzhexol and amantadine were associated with a 15% reduction in functional disability as assessed by a composite rating score including: akinesia, tremor, posture, and rigidity. Benzhexol lessened rigidity and improved posture, but had little or no effect on akinesia and tremor. amantadine had a minimal effect on akinesia but caused a moderate improvement in tremor and posture. The improvement in total disability induced by benzhexol and amantadine separately was not significantly different. The two drugs in combination produced a 40% reduction in total disability. Reported adverse reactions included dry mouth in 8 patients (and was more severe with benzhexol than with amantadine), mental confusion (benzhexol n=1; amantadine n=1), livedo reticularis (amantadine n=2). This study had a quality rating score of 60%.

Cox et al. (1973)[16] performed a double-blind, crossover trial of L-dopa versus amantadine in 27 patients treated for 6 weeks (with a 6-week interval between treatment periods). Patients demonstrated a marked improvement when given L-dopa first, but no clinical effect was observed in patients treated first with amantadine. However, L-dopa was less beneficial in patients who received amantadine, whereas amantadine became effective in patients who had previously taken L-dopa. The trial was not properly analysed to allow for a comparison of the effect size with L-dopa and amantadine. Only adverse reactions related with blood pressure and pulse rate were reported: amantadine did not affect pulse rate but, when given after L-dopa, both supine systolic and supine and erect diastolic blood pressure fell significantly. This study had a quality rating score of 48%.

Level-II Studies

Mawdsley et al. (1972)[17] reported the results of 42 patients enrolled in a double-blind, crossover trial that compared amantadine with placebo. The crossover methodology was unusual because after 2 weeks after the first treatment (amantadine or placebo), if the patient believed they had derived benefit from the medication, they were asked to continue treatment as issued. If the patient felt there had been no improvement, they were given the alternate treatment. After 4 weeks of treatment, if the patients expressed dissatisfaction with their progress, they were started on L-dopa. Patients who were satisfied with their treatment after 1 month continued on their current therapy regimen. Because of this methodology (where patients were allowed to switch therapy without a washout period between treatment regimens), this study is classified as Level II. Clinical improvements were assessed using the Webster scale. The proportion of patients who showed improvement of some degree after taking amantadine for 2 weeks (32 out of 42; 76%) was significantly greater than those who had taken placebo for a 2 weeks (12 out of 28; 43%). There was a marked decline in the improvement in patients who took amantadine for 4 weeks (4 out of 16; 25%), at which time the results showed a smaller number of patients producing an improvement than those observed in the group who had taken placebo for 2 weeks. Adverse reactions to amantadine were considered uncommon. The most common reaction was lethargy or drowsiness, which was reported in 6 patients; other adverse reactions were nausea (n=4), unpleasant dreams (n=4), dryness of the mouth (n=2), and severe hypotension (n=1). In the placebo group 5 patients reported nausea or lethargy.

Fieschi el al (1970)[18] performed an unblinded, study where amantadine was given to 31 patients for 2 weeks, followed by treatment with placebo for 1 week, after which L-dopa therapy was added. The optimal maintenance dosage for L-dopa was reached in 6 to 12 weeks. Improvement with amantadine was significantly lower (by a factor of 2) than the improvement associated with L-dopa treatment. Subsequently, 20 of these 30 patients were given L-dopa plus amantadine, and 11 patients preferred the new regimen to the previous one. No adverse reactions were reported.

Level-III Studies

There are no Level-I or II studies that address the long-term

efficacy of amantadine. Parkes et al. (1971)[19] evaluated the efficacy of long-term efficacy of amantadine in an open-label study where 66 patients were followed-up for one year receiving scheduled clinical evaluations comprising assessment of total disability, functional disability, akinesia, tremor, rigidity, posture and autonomic symptoms at baseline, 3, 6, 9, and 12 months. Twenty-six patients were treated with amantadine monotherapy (median dose 200mg/d, range 200mg-600mg/d), and they were reported as a separated subgroup. In this subgroup, amantadine induced a mean reduction of total disability of 17.3% at 3 months, and this improvement was maintained for up to one year. The individual symptoms (tremor, akinesia and rigidity) were considered improved. However, patients did not record a real improvement, despite lower scores in functional disability after a one-year treatment period. Furthermore, 40/66 patients received levodopa at 3 months due to lack of efficacy of amantadine. These 44 patients represent the second subgroup of this study. Adverse reactions were reported in reference to the global population (n=66), with the most common events including dry mouth, constipation and difficulty in focusing.

ADJUNCT THERAPY

Amantadine as Adjunct to Anticholinergic Therapy

Level-I Studies

Bauer et al. (1974)[20] compared the clinical efficacy of adjunct therapy with amantadine versus placebo in a randomized, double-blind, cross-over, placebo-controlled study with each period of treatment lasting 3 weeks. Forty-eight patients receiving anticholinergic therapy were included in the study, of whom 10% recorded improvement versus placebo in time tests. This improvement was greater (21%) in the group of patients that were given placebo during the first 3-week period and amantadine in the second 3-week period. No significant changes were found in the rigidity and tremor scores during amantadine treatment when compared with the placebo group. This study had a quality rating score of 55%.

Appleton et al. (1970)[21] reported amantadine superior to placebo in 20 patients receiving anticholinergics, as measured by (1) the patients' own assessments of their abilities to carry out activities of daily living and (2) the observers' assessment of rigidity, tremor, and akinesia. In time-performance tests, average performance was better while patients were taking amantadine than while taking placebo, but only in one-third of the measures assessed were the differences statistically significant. Adverse reactions were few and minor, and 19 of 20 patients studied preferred amantadine to placebo. This study had a quality rating score of 65%.

Jorgesen et al. (1971)[22] performed a multicenter, double-blind, crossover trial of 3 weeks duration to assess the effectiveness of amantadine in 149 patients taking anticholinergics as compared with placebo. Objective evidence of improvement was seen in 56% of patients (moderate to marked in 32%), and improvement was more prominent in severely affected patients. The most striking feature of this trial was the functional improvement reported by patients while on amantadine, and noteworthy gains were reported in rigidity and tremor. Bradykinesia was significantly improved but only when amantadine preceded placebo. Adverse reactions were generally mild. Motor deterioration was observed in some patients following abrupt discontinuation of amantadine. This study had a quality rating score of 57%.

Walker et al. (1972)[23] compared the effectiveness of amantadine versus placebo in a double-blind, crossover trial of 3 weeks duration. Forty-two patients participated in the trial. Other antiparkinsonian drugs were discontinued in 36 patients and 6 remained on anticholinergic therapy. The authors report that 64% of the patients on amantadine had some improvement, while 21% of patients treated with placebo reported improvement. Patients were evaluated using a comprehensive battery of tests that include evaluation of objective symptoms and subjective assessments. The results form this battery of tests, neurologists rated amantadine 74% superior to placebo. Patients performed as well or better on amantadine than on standard optimal anticholinergic therapy for most qualitative or quantitative measures assessed. However, very few comparisons reached statistical significance. This study had an overall quality rating score of 60%.

Barbeau et al. (1971)[24] administered add-on amantadine to 54 patients on anticholinergic therapy in a randomized, placebo-controlled, double-blind, crossover trial of 4 weeks duration for each treatment arm. Results were evaluated using several different parameters including patient's preferences, functional disability scores, physical impairment score, and quality of improvement. The authors found that 61% of patients preferred amantadine as compared to 18.5% preferred placebo. The degree of improvement in functional disability scores (amantadine = 32.98±3.53 vs. PL= 38.19±3.77) and in physical impairment scores (amantadine = 28.2 ±1.77 vs. PL=31.54±2.07) was highly significant compared to placebo. In 48% of patients that received amantadine, the quality of improvement was considered moderate to good. This study had a quality rating score of 57%.

Forssman et al. (1972)[25], in a crossover, double-blind study, compared the efficacy of amantadine versus placebo for treatment of PD. Twenty seven patients participated in the study, and remained on existing anticholinergic therapy. Clinical assessments were done by: grading akinesia, rigidity and tremor; assessing functional status and motor skill tests; and evaluating observed motor ability and the patients' subjective impression of treatment. Improvement in all clinical evaluations while on amantadine was statistically significant as compared with placebo. Adverse reactions were considered mild and were more frequent in the first week of treatment, with the most common reported reactions including: alertness, euphoria, insomnia, and dizziness. This study had a quality rating score of 55%.

Level-II Studies

Rinne et al. (1972)[26] performed a double-blind, non-randomized, placebo-controlled, crossover study of 4 weeks duration. The efficacy of amantadine versus placebo was compared in 38 patients with PD receiving anticholinergic therapy. Improvement associated with amantadine therapy was significant better as compared to placebo. Sixty percent of the patients showed moderate to minimal improvement. The total disability scores and the cardinal signs of PD were also statistically significantly improved versus placebo treatment. The most common reported adverse reactions included dizziness (n=24), sweating (n=17), anxiety (n=14), and insomnia (n=12).

Silver et al. (1971)[27], in a 20-week, double-blind trial, compared the effect of amantadine versus placebo in 50 patients (whose previous antiparkinsonian medication with anticholinergics was unchanged). The authors report that all scores experienced a significant improvement that peaked at 2 to 3 months, and there was a gradual tapering of the effect that was maintained for 7 months.

Forty-seven percent of patients mentioned an adverse reaction, with the two most common including livedo reticularis (9 out of 34) and oedema (4 out 34). Other adverse reactions reported were: dizziness, nausea, heartburn, confusion, hallucinations, increased tremor, weakness and ataxia.

Merry et al. (1974)[28], in a double-blind, placebo-controlled, non-randomized trial of 29 patients from which 3 dropped-out reported that patients classified as severely affected receiving amantadine improve 12.6 points or 47% compared with those on placebo that improved 2.3 points or 8%. This improvement was maintained over the 5-month study. The patient that dropped out due to an adverse event suffered a leg fracture. There were no other reported adverse reactions.

Amantadine as Adjunct to Levodopa

Level-I Studies

Fehling (1973)[29] studied the effect of amantadine versus placebo in a double-blind crossover study, of 1-month duration, in 21 patients receiving an optimal L-dopa dosage. Amantadine was significantly more effective than placebo in improving total PD scores, and postural and limb hypokinesia. From the functional point of view, this improvement was only marginal in most patients, and more noticeable in those receiving low doses of L-dopa. Abnormal involuntary movements did not change significantly during the study. The only adverse reaction reported was dry mouth. This study had a quality rating score of 43%.

Savery (1977)[30] enrolled 42 stable patients (on Levodopa/carbidopa medication) in a double-blind, randomized, crossover study where amantadine was added on to existing therapy. Each trial period had a duration of 9 weeks. Clinical evaluation was done scoring 10 symptoms of PD and 11 activities. The addition of amantadine to L-dopa/carbidopa provided significant improvement in symptoms and a decrease in impairment of activity. The amantadine benefit was apparent when compared with baseline (90% improvement) and with placebo (80% improvement). This benefit was also reflected in the global evaluations made by the investigator and the patients. Only 2 patients failed to demonstrate even minor improvement. Minor adverse reactions included nervousness, nausea and confusion; there was one report of livedo reticularis and 2 reports of mild blurred vision. This study has a quality rating score of 52%.

Level-II Studies

Millac et al. (1970)[31] performed a double-blind, non-randomized, placebo-controlled study where 32 patients with akinesia (as their principle disability) were divided into two groups (amantadine or placebo; groups were matched for age). After 3 treatment weeks, they were given L-dopa and the optimum dosage was established over a 3-month period. The degree of improvement measured by inquiry of the patients and their relatives, clinical examination, and other scales did not differ between treatment arms. Moreover, the authors found that the optimum dosage of L-dopa did not differ significantly between the two treatment arms (with or without amantadine). There was no difference in tolerability between the two groups

Webster et al. (1984)[32] reported the results from a double-blind, placebo-controlled crossover, non-randomized study, in which 26 individuals with middle-stage parkinsonism were given amantadine or placebo in addition to their existing L-dopa therapy. Efficacy was assessed by measuring activities of daily living, Webster's scale, and physicians' subjective assessment. The authors found that the addition of amantadine provided a symptomatic improvement in 50% of the patients in at least one of the efficacy measures. Adverse reactions were considered mild and rare.

Callagham et al. (1974)[33] subdivided 31 patients into 4 groups (open-label) to evaluate the effectiveness of amantadine and L-dopa as a single and combined treatment regimens. The authors found that L-dopa used as a single drug was much more effective as compared to all other treatment groups. The study does not confirm an increased benefit when amantadine is added to an optimal L-dopa dosage. The reported major adverse reactions occurred with both L-dopa and amantadine and were mainly gastrointestinal and dyskinetic symptoms with L-dopa, and hallucinations, oedema, and confusion with amantadine.

PREVENTION OF MOTOR COMPLICATIONS

No qualified studies were identified.

CONTROL OF MOTOR COMPLICATIONS

No qualified studies using assessment of motor fluctuations as primary outcome were identified. However, two studies assessing the antidyskinetic potential of amantadine also assessed motor fluctuations as secondary outcome.

Level-I Studies

Verhagen et al. (1998)[4] performed a crossover, double-blind, placebo-controlled study to evaluate the effects of amantadine on L-dopa-induced dyskinesias in 18 patients. Duration of daily "off" time and a "variance score" calculated from self-scoring diaries were used to assess effects of amantadine on motor fluctuations. All patients received amantadine or placebo during each 3-week treatment period. The maximum dose of amantadine was 400 mg. Scores for duration of daily "off" decreased significantly in the amantadine period over placebo (mean score of 1.0 vs. 1.5 on item 3a of hours; $p<0.01$) as did the variance of diary scores (1.3 vs. 3.3; $p<0.01$). This study had an overall quality score of 78%.

Luginger et al. (2000)[34] assessed the effect of amantadine (100 mg t.i.d.) on L-dopa-induced dyskinesia in a 5-week (treatment periods of 2 weeks separated by 1 week wash-out), double-blind, crossover trial in eleven patients with advanced PD complicated by motor fluctuations. Daily "on" and "off" times were recorded in diaries over the last 3 days of each 2-week period. Ten patients completed the study. There were no statistically significant differences in hours "on" or "off" in standard home diary recordings between amantadine and placebo. This study had an overall quality score of 72%.

Level-II Studies

No qualified studies were identified.

Level-III Studies

Shannon et al. (1987)[3] performed a 3-month study in which 20 patients with PD and motor fluctuations received amantadine (open-label) in addition to L-dopa and other antiparkinsonian medications. Moderate improvement in motor fluctuations (monitored in a four-point scale) occurred in 55% of the patients at 2 months and in 65% of patients at 3 months of treatment. There also was significant improvement in parkinsonian disability as measured by NYUPDS, NUDS and HY stage scores). Adverse reactions were considered mild and uncommon. Two patients reported confusion, one demonstrated an increase in chorea, and two demonstrated a

worsening of foot dystonia. One patient withdrew from the study due to dizziness.

CONTROL OF LEVODOPA-INDUCED DYSKINESIAS

Level-I Studies

Verhagen et al. (1998)[4] performed a crossover, double-blind, placebo-controlled study to evaluate the effects of amantadine on L-dopa-induced dyskinesias and motor fluctuations. This study used an intravenous acute challenge paradigm. All patients received amantadine or placebo during each 3-week treatment period. The maximum dose of amantadine was 400 mg. At the end of each study arm, patients were admitted to the treatment center and received an intravenous infusion of L-dopa for 7h at individually determined optimal rate (8 defined as the lowest rate producing a maximal anti-parkinsonian effect). The clinical evaluations done during the L-dopa infusion were the main outcome of the trial. At the end of each treatment arm, parkinsonian and dyskinesia scores were obtained in 18 patients (with advanced PD) during a steady-state intravenous L-dopa infusion. Fourteen patients completed the trial, all of who recorded that amantadine significantly reduced dyskinesia severity by 60% compared to placebo. Motor fluctuations also significantly improved according to UPDRS scores and patient-recorded diaries. Importantly, the primary outcome of this study was to assess the effect of an acute challenge with L-dopa instead of the usual longer-term treatment setting. Consequently, this diminishes the clinical relevance of these results for everyday practice. Four patients withdrew from the study due to adverse reactions (confusion 1, increasing hallucinations 1, recurrence of preexisting palpitations 1, and nausea 1). This study had a quality rating score of 78%.

Verhagen et al. (1999)[35] also published the results of a 1-year follow-up to the previous study[4], which included 13 of 17 patients that remained on amantadine. An additional 4 new patients also were included. Seven to 10 days prior to the follow-up assessment, amantadine that patients have already been taking was discontinued. Patients subsequently received either placebo or 100 mg amantadine. Patients who previously were taking amantadine received amantadine again but in a blind manner, and those not receiving amantadine previously received placebo. On the test day, patients received intravenous L-dopa followed by motor assessment. Results showed that amantadine-treated patients continued to have significantly reduced dyskinesias, with mean scores 50% lower as compared to the placebo group recorded at the start of the study.[4] Adverse reactions were not reported. This study had an overall quality rating score of 78%.

Snow et al. (2000)[36] performed a similar study to Verhagen and colleagues[4,33], where 24 patients with PD were enrolled in a double-blind, placebo-controlled, crossover trial, which compared amantadine 200 mg/d (titrated from the first week on 100mg/d) to placebo. After each treatment arm, the patients were exposed in the morning to an acute challenge of 1.5 times their usual L-dopa/DCI (decarboxylace inhibitor) dose of standard release L-dopa. Patients were evaluated clinically every 30 minutes. The primary endpoint of the study was the total dyskinesia score, which was the sum of all of the scores assigned for dyskinesia in the 3-hour period. The mean maximal dyskinesia score was the highest sum score at any time period. The subjective experience of dyskinesias was recorded with the use of UPDRS part IV questions 1 to 4. There was a significant reduction in the total dyskinesia from 29.0 with placebo to 22.0 with amantadine. The subjective experience of dyskinesia also was statistically significantly decreased. Safety profile during the study was not described. Two patients withdrew from the study, but neither was due to adverse reactions. This study had a quality rating score of 82%.

Luginger et al. (2000)[34] assessed the effect of amantadine on L-dopa-induced dyskinesia in a 5-week (treatment periods of 2 weeks separated by 1 week wash-out), double-blind, crossover trial. Eleven patients with advanced PD complicated by motor fluctuations and dyskinesias were studied. Amantadine was administered as 300 mg/d. Subjective dyskinesia intensity as well as daily "on" and "off" times were recorded in diaries over the last 3 days of each 2-week period. In addition, oral L-dopa challenges were performed before the first and on the last day of each treatment period. Ten patients completed the study. Dyskinesia severity following oral L-dopa challenges was significantly reduced by 52% after amantadine treatment, scores changed from 14.5±9.4 (before treatment) to 7.0 ± 8.2 (after treatment), whereas there was no change after placebo treatment (the score before treatment was 16.6±11.4 and after 15.5±12.1). Analysis of the diary data also showed a significant reduction in the cumulative dyskinesia score by 53%. The magnitude of L-dopa response, as measured by percent reduction of the UPDRS Part III, was unchanged by amantadine or placebo treatment compared with baseline. One patient withdrew from the study due to dizziness while on placebo. One patient that completed the study experienced reversible oedema of both feet during treatment with amantadine. This study had a quality rating score of 72%.

Level-II Studies

No qualified studies were identified.

REVIEW OF SAFETY

Adverse reactions associated with amantadine are primarily classified as central nervous system (CNS) effects. Those CNS reactions occurring in more then 5% of patients receiving amantadine include dizziness, anxiety, impaired coordination, insomnia and nervousness. Additionally, nausea and vomiting can occur in 5% to 10%. Effects can appear after a few hours, or following several days of therapy, or after an increase in dosage. The adverse reactions are generally mild but may be severe, particularly in elderly patients. In 1% to 5% of the patients reported adverse reactions include: headaches, irritability, nightmares, depression, ataxia, confusion, somnolence/drowsiness, agitation, fatigue, hallucinations, diarrhea, constipation, anorexia, xerostomia, and livedo reticularis. In less than 1% of patients, adverse reactions reported include: psychosis, abnormal thinking, weakness, amnesia, slurred speech, hyperkinesias, hypertension, urinary retention, decreased libido, dyspnea, and rash.[37] Orthostatic hypotension and possible congestive heart failure can occur during chronic amantadine administration.

CONCLUSIONS

EFFICACY

PREVENTION OF DISEASE PROGRESSION

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of amantadine regarding prevention of progression of Parkinson's disease.

SYMPTOMATIC CONTROL OF PARKINSONISM

All level I studies assessing symptomatic efficacy of amantadine have been of low to moderate methodological quality thus limiting efficacy conclusions. Based on 3 positive Level-I studies comparing amantadine monotherapy to placebo and 6 such studies comparing an adjunct amantadine versus placebo amantadine is considered LIKELY EFFICACIOUS in improving symptomatic control of parkinsonism – both when given as monotherapy or when added to preexisting therapy with anticholinergics or levodopa. However, the effect size and duration of benefit are uncertain.

PREVENTION OF MOTOR COMPLICATIONS

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of amantadine regarding the prevention of motor complications in Parkinson's disease.

CONTROL OF MOTOR COMPLICATIONS

Based on 3 Level-I placebo-controlled studies, amantadine is considered EFFICACIOUS in reducing levodopa-induced dyskinesias in the short term. Data are inadequate to conclude on the long-term efficacy of this approach.

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of amantadine in reducing motor fluctuations in Parkinson's disease.

SAFETY

Amantadine has an ACCEPTABLE RISK, WITHOUT SPECIALIZED MONITORING.

IMPLICATIONS FOR CLINICAL PRACTICE

Amantadine monotherapy is USEFUL for symptomatic control of parkinsonism – both when given as monotherapy or as add-on treatment in patients previously receiving anticholinergics or levodopa. However the duration of clinical benefit is not established. Amantadine is USEFUL in the control of dyskinesias, but the long-term clinical benefits are not known. Amantadine is INVESTIGATIONAL for treatment of motor fluctuations. Currently, there is no evidence to support a neuroprotective effect of amantadine in PD.

IMPLICATIONS FOR CLINICAL RESEARCH

One of the more pressing areas to address in future clinical trials is to evaluate the effect of amantadine on motor fluctuations, and in particular, long-term effect on dyskinesias. The duration of effect of amantadine is not well understood, and research in this area will be clinically valuable, particularly if it helps identify a subpopulation of long-responders. Similarly, further characterisation of the effects of acute motor deterioration in patients treated over the long-term with amantadine is needed. Additional studies are also needed on the clinical effects of withdrawing amantadine treatment.

OTHER ANTIGLUTAMATE AGENTS

A number of agents believed to act primarily through central antiglutamate properties have been clinically studied in Parkinson's disease. Numbers of available trials are very small and only one level I trial was identified for the entire group. With the exception of dextromethorphane these agents have only been studied regarding their effect on symptomatic control of parkinsonism.

MEMANTINE

BASIC PHARMACOLOGY

MECHANISM OF ACTION

Memantine (1-amino-3,5-dimethyladamantane) is a compound that has been proposed to be beneficial in PD.[38] The mode of action of the drug, which belongs to the 1-amino-admantanes, has not been completely clarified. Memantine binds to the MK-801 binding site of the NMDA receptor at therapeutic concentrations[39], and reduces NMDA-induced membrane currents.[40] The mechanism of action postulated for memantine is similar to amantadine normalising the activity of the glutamatergic cortico-striatal and subthalamicopallidal pathways, which may be overactive in PD.

PHARMACOKINETICS

Memantine is readily absorbed (blood levels peak 20 to 30 min after an oral dose of 5 mg/kg), has a mean life up to 100 hours, and is poorly metabolised in humans. The currently recommended dosage for patients with PD is 30 mg given in three divided doses (ie. 10 mg TID).

REVIEW OF CLINICAL STUDIES

No studies assessing the efficacy of memantine regarding prevention of disease progression, prevention of motor complications or control of motor complications have been identified.

SYMPTOMATIC CONTROL OF PARKINSONISM

Level-I Studies

No qualified studies were identified.

Level-II Studies

No qualified studies were identified.

Level-III Studies

Rabey et al. (1992)[41] performed an open study with blind assessment in order to test the efficacy of memantine for treatment of PD. Ten of the 14 patients enrolled in the study completed the trial. In 5 patients, the main parkinsonian features (rigidity, bradykinesia, tremor, gait, and postural reflexes) improved significantly, and the "off" episodes improved in 60% of patients; 5 patients remained unaltered. Dyskinesia did not change substantially during the trial. Memantine was generally well tolerated, with confusion, dizziness, abdominal pain, and psychomotor agitation as reported adverse reactions.

CONCLUSIONS

EFFICACY

There is INSUFFICIENT EVIDENCE to conclude about the efficacy of memantine in any of the indications in Parkinson's disease reviewed in this report.

SAFETY

There is INSUFFICIENT EVIDENCE to conclude on the safety of memantine in the treatment of PD.

IMPLICATIONS FOR CLINICAL PRACTICE

Memantine is considered INVESTIGATIONAL for use in any indications in Parkinson's disease.

IMPLICATIONS FOR CLINICAL RESEARCH

The efficacy and tolerability of memantine for the treatment of PD is not well studied, and additional well-designed clinical trials are warranted based on an improved understanding of the pharmacological characteristics of memantine.

IFENPRODIL

BASIC PHARMACOLOGY

MECHANISM OF ACTION

Ifenprodil is a non-competitive NMDA receptor antagonist, which inhibits antagonism of MK 801 binding in medial pallidum. Moreover ifenprodil also possesses alpha-adrenoreceptor blocking properties.

PHARMACOKINETICS

The pharmacokinetic profile of the drug is poorly known. No published data are available about his plasma half life and brain distribution.

REVIEW OF CLINICAL STUDIES

No studies assessing ifenprodil regarding prevention of disease progression or prevention of motor complications have been identified.

SYMPTOMATIC CONTROL OF PARKINSONISM

Level-I Studies

No qualified studies were identified.

Level-II Studies

No qualified studies were identified

Level-III Studies

Montastruc et al. (1992)[42] in an uncontrolled, non-randomized study analyzed the effect of add-on therapy with ifenprodil. Two groups of patients with idiopathic PD were studied: one group included nine non-fluctuating patients, and the other group included 11 patients with peak-dose dyskinesia. (Efficacy was evaluated using a blinded assessment.). Add-on therapy with ifenprodil 60 mg/d did not modify the parkinsonian symptoms in either group as assessed by the UPDRS motor subscore (Part III). In the dyskinesias group, there was no change in the dyskinesia score. Reported adverse reactions were palpitations and sedation in 1 patient and a feeling of nasal congestion in another.

CONCLUSIONS

EFFICACY

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of ifenprodil in any indication in PD.

SAFETY

There is INSUFFICIENT EVIDENCE to conclude on the safety of ifenprodil.

IMPLICATIONS FOR CLINICAL PRACTICE

Use of ifenprodil for any indication in Parkinson's disease is considered INVESTIGATIONAL.

IMPLICATIONS FOR CLINICAL RESEARCH

The only way to establish efficacy and tolerability of ifenprodil in PD is to conduct the appropriate clinical trials. However before any attempts are made to pursue this task, the pharmacological characteristics of ifenprodil, particularly as compared to other antiglutamatergic agents, should be further studied in appropriate experimental models.

DEXTROMETHORPHAN

BASIC PHARMACOLOGY

MECHANISM OF ACTION

Dextromethorphan, a widely used and well tolerated antitussive agent, is a relatively low-affinity, non-competitive antagonist of NMDA receptors[43], and also binds to sigma receptors, whose role in the basal ganglia is not well defined but may include modulation of glutamatergic and dopaminergic neurotransmission.[44]

PHARMACOKINETICS

Dextromethorphan is readily absorbed (blood levels peak 1 to 4 h after an oral dose of 2.5 mg/kg) with a medial elimination half-life of 2 hours. The dose varies between 100 to 200 mg. Its major metabolite is dextrorphan, a product of oxidative O-demetilation in the liver by the cytochrome P450 enzyme debrisoquin hydroxylase (CYP2D6). Quinidine inhibits O-demetilation of dextromethorphan, and then the half-life of dextromethorphan is 16 h.

Genetic polymorphism has been demonstrated for dextromethorphan oxidative O-demetilation with both extensive metabolizers and poor metabolizers that can be easily identified by determining the dextromethorphan/dextrorphan metabolic ratio in urine. The half-life of the drug is extremely prolonged in poor metabolizers (up to 45 hours).[45] The drug is generally well tolerated, but side effects such as light-headedness, slurred speech, fatigue, depression and hallucinations have been reported.

REVIEW OF CLINICAL STUDIES

No studies assessing dextromethorphane regarding prevention of disease progression or of motor complications have been identified.

SYMPTOMATIC CONTROL OF PARKINSONISM

Level-I Studies

No qualified studies were identified.

Level-II Studies

No qualified studies were identified.

Level-III Studies

Bonuccelli et al. (1992)[46] tested dextromethorphan in 6 "de novo" patients and in 6 patients where dextromethorphan was added to existing therapy. This was an open-label study with increasing dosage of 45, 90, 120 and 180 mg/d. The authors observed a significant improvement on UPDRS over baseline for tremor, rigidity and finger tapping (the indices with the greatest improvement) with the dose of 180 mg/d. One week after drug withdrawal, motor performance returned to baseline. One patient withdrew at 90 mg/d dose because of light-headedness, drowsiness, and mild ataxia.

Montastruc et al.[47] investigated the effects of an add-on therapy with dextromethorphan in patients with PD. An initial study was performed using a daily dose of 90 mg in 13 nondemented patients with PD. Clinical assessments were done in a blind fashion using the UPDRS motor score at baseline and after 1 month of treatment. Ten patients completed the study. UPDRS scores did not reveal any change. Three patients dropped out of the study due to adverse reactions: major sedation with urinary incontinence (n=1), pruritus with nausea (n=1) and nausea (n=1). A second study with the same design was conducted in 8 nondemented patients with PD treated with dextromethorphan 180 mg. Similarly, no differences in the UPDRS motor scores were detected. Four patients dropped out due to adverse reactions, which included sedation, dizziness, and severe cutaneous dysesthesia. Three of the remaining four suffered from severe constipation.

CONTROL OF MOTOR COMPLICATIONS

Level-I Studies

No qualified studies were identified.

Level-II Studies

Verhagen et al. (1998)[48] performed a double-blind, crossover, study to test the efficacy of dextromethorphan in six patients with dyskinesias and motor fluctuations (2 to 3 week treatment period). With dextromethorphan, the average and maximum dyskinesia scores improved by >50%, without compromising the antiparkinsonian response of L-dopa.

REVIEW OF SAFETY

Dextromethorphan is well tolerated in general populations for treatment of cough and is considered safe, however it has not been specifically tested in patients with PD.

CONCLUSIONS

EFFICACY

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of dextromethorphan in any indication in Parkinson's disease.

SAFETY

Published data on dextromethorphan treatment cover less than 40 patients and treatment duration was in the order of 1 month. Therefore, there is INSUFFICIENT EVIDENCE to conclude on the safety of dextromethorphan in patients with Parkinson's disease.

IMPLICATIONS FOR CLINICAL PRACTICE

Use of dextromethorphan for treatment of PD is considered INVESTIGATIONAL.

IMPLICATIONS FOR CLINICAL RESEARCH

The efficacy and tolerability of dextromethorphan for treatment of PD warrants further investigation.

BUDIPINE

BASIC PHARMACOLOGY

MECHANISM OF ACTION

The lipophilic t-butyl analogue of 1-alkyl-4,4-diphenyl piperidine, budipine, possesses a polyvalent spectrum of mechanisms of action. Budipine experimentally increased the brain content of norepinephrine, serotonin, dopamine, and histamine in reserpine-treated rats. Budipine did not alter the receptor affinity of these neurotransmitters but antagonizes the effect of NMDA at its receptor binding site in vitro.

PHARMACOKINETICS

Budipine has a large volume of distribution. Its half-life is approximately 31 h with little plasma fluctuations. Of the administered dose 50% to 60% is recovered in urine, 20% as parent compound and 30% as a hydroxylated non-conjugated metabolite.

REVIEW OF CLINICAL STUDIES

No studies assessing the efficacy of budipine regarding prevention of disease progression or motor complication have been identified.

SYMPTOMATIC CONTROL OF PARKINSONISM

Level-I Studies

Spieker et al. (1999)[49] conducted a randomized, double-blind, parallel-group study comparing budipine versus placebo in 84 patients. Study medication was either budipine 60 mg or placebo, which were as add-on therapy to patients with PD who had a Columbia University Rating Scale (CURS) score between 24 and 50. The study included a 4-month treatment period and the primary end-point was the tremor subscore calculated from the tremor-related items of the CURS. The treatment scores decreased from 6.4±3.4 (baseline) to 5.3±3.9 in the placebo group and from 6.1±2.5 (baseline) to 3.5±2.6 in the budipine group (this difference was statistically significant). Adverse reactions were reported but are not described in the publication. This study had a quality rating score of 50%.

Level-II Studies

Jellinger et al. (1987)[50], evaluated budipine as an adjuvant treatment for patients with PD. This was a placebo-controlled trial that was reported as being double-blind in design, but distribution between treatment groups was not clearly stated. An overall assessment of efficacy and adverse reactions were made by the investigator and by each patient (n=31). Improvement in budipine group was 22% compared to the placebo group (4%) as measured on the CURS. The improvements were greatest for tremor, followed by diadochocinesia. Two patients on budipine discontinued treatment due to severe mental confusion. Other adverse reactions reported were occasional dryness of the mouth.

CONTROL OF MOTOR COMPLICATIONS

Level-I Studies

No qualified studies were identified.

Level-II Studies

No qualified studies were identified.

Level-III Studies

Spieker et al. (1999)[51], performed an open-label study in 7 patients with PD with motor fluctuations. Budipine given as an add-on therapy (final dose of 40 mg/d) decreased the time "off" in 5 of the 7 patients (average decrease in all patients 2.8 ± 3.9 h) and improved motor scales as assessed by on-off diaries and the

UPDRS score motor section. Four patients experienced slight dryness of the mouth and one patient dropped out due to dizziness.

REVIEW OF SAFETY

Budipidine was available in a small number of European countries and its safety profile was considered similar to that of amantadine, although the specific side-effects of amantadine like livedo reticularis and oedema were not a feature. Recently (July 2000) the German regulatory authorities, after analysing the pharmacovigilance data on cardiac arrhythmias, decided that budipine was associated with an excess of severe cardiac arrhythmias. This was seen as a significant risk that the uncertain clinical benefits did not outweigh. Therefore budipidine is no longer available in the European Union.

CONCLUSIONS

EFFICACY

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of budipine in any indication in Parkinson's disease.

SAFETY

Budipine has an UNACCEPTABLE RISK for cardiac arrhythmias.

IMPLICATIONS FOR CLINICAL PRACTICE

The risk benefit ratio of budipine is unfavourable (based on increased risk of cardiac arrhythmias) and therefore the use of budipine for treatment of PD is UNACCEPTABLE.

IMPLICATIONS FOR CLINICAL RESEARCH

Clinical use of budipine, at this time, carries a significant risk of cardiac arrhythmias. Congeners of this agent that lack cardiac toxicity could potentially be developed.

REFERENCES

1. Schwab RS, England AC Jr, Poskancer DC, Young RR. Amantadine in the treatment of Parkinson's disease. JAMA 1969;208:1168-1170.
2. Berguer JR, Weiner WJ. Exacerbation of Parkinson's disease following the withdrawal of amantadine. Neurology 1985;35(Suppl 1):200.
3. Shannon KM, Goetz CG, Carroll VS, Tanner CM, Klawans HL. Amantadine and motor fluctuations in chronic Parkinson's disease. Clin Neuropharmacol 1987;10:522-526.
4. Verhagen Metman L, Del Dotto P, van den Munckhof P, et al. Amantadine as treatment for dyskinesias and motor fluctuations in Parkinson's disease. Neurology 1998;50:1323-1326.
5. Davies WL, Grunert RR, Haff RF, et al. Antiviral activity of 1-adamantamine (amantadine). Science 1964;144:862-863.
6. Von Voigtlander PF, Moore KE. Dopamine: release from the brain in vivo by amantadine. Science 1971;174:408-410.
7. Heimans RL, Rand MJ, Fennesy MR. Effects of amantadine on uptake and release of dopamine by a particulate fraction of rat basal ganglia. J Pharm Pharmacol 1972;24:875-879.
8. Gianutsos G, Chute S, Dunn JP. Pharmacological changes in dopaminergic systems induced by long-term administration of amantadine. Eur J Pharmacol 1985;110:357-361.
9. Nastuck WC, Su PC, Doubilet P. Anticholinergic and membrane activities of amantadine in neuromuscular transmission. Nature 1976;264:76-79.
10. Stoof JC, Booij J, Drukarch B. Amantadine as N-methil-D-aspartic acid receptor antagonist. New possibilities for therapeutic application? Clin Neurol Neurosurg 1992;94(suppl):S4-S6.
11. Greenamyre JT, O'Brien CF. N-methyl-D-aspartate antagonists in the treatment of Parkinson's disease. Arch Neurol 1991;48:977-981.
12. Ing TS, Daugirdas JT, Soung LS, et al. Toxic effects of amantadine in patients with renal failure. Can Med Assoc J 1979;120:695-698.
13. Fahn S, Isgreen WP. Long-term evaluation of amantadine and levodopa combination in parkinsonism by double-blind crossover analyses. Neurology 1975;25:695-700.
14. Butzer JF, Silver DE, Sans AL. Amantadine in Parkinson's disease. A double-blind, placebo-controlled, crossover study with long-term follow-up. Neurology 1975;25:603-606.
15. Parkes JD, Baxter RC, Marsden CD, Rees JE. Comparative trial of benzhexol, amantadine, and levodopa in the treatment of Parkinson's disease. J Neurol Neurosurg Psychiatry 1974;37:422-426.
16. Cox B, Danta G, Schnieden H, Yuill GM. Interactions of L-dopa and amantadine in patients with Parkinsonism. J Neurol Neurosurg Psychiatry 1973;36:354-361.
17. Mawdsley C, Williams IR, Pullar IA, Davidson DL, Kinlock NE. Treatment of parkinsonism by amantadine and levodopa. Clin Pharmacol Ther 1972;13:575-583.
18. Fieschi C, Nardini M, Casacchia M, Tedone ME. Amantadine versus L-2 dopa and amantadine plus L-dopa. Lancet 1970;2:154-155.
19. Parkes JD, Baxter RC, Curzon G, et al. Treatment of Parkinson's disease with amantadine and levodopa. A one-year study. Lancet 1971;1:1083-1086.
20. Bauer RB, McHenry JT. Comparison of amantadine, placebo, and levodopa in Parkinson's disease. Neurology 1974;24:715-720.
21. Appleton DB, Eadie MJ, Sutherland JM. Amantadine hydrochloride in the treatment of Parkinsonism. A controlled trial. Med J Aust 1970;2:626-629.
22. Jorgensen PB, Bergin JD, Haas L, et al. Controlled trial of amantadine hydrochloride in Parkinson's disease. N Z Med J 1971;73:263-267.
23. Walker JE, Albers JW, Tourtellotte WW, Henderson WG, Potvin AR, Smith A. A qualitative and quantitative evaluation of amantadine in the treatment of Parkinson's disease. J Chronic Dis 1972;25:149-182.
24. Barbeau A, Mars H, Botez MI, et al. Amantadine-HCl (Symmetrel) in the management of Parkinson's disease: a double-blind cross-over study. Can Med Assoc J 1971;105:42-47.
25. Forssman B, Kihlstrand S, Larsson LE. Amantadine therapy in parkinsonism. Acta Neurol Scand 1972;48:1-18.
26. Rinne UK, Sonninen V, Siirtola T. Treatment of Parkinson's disease with amantadine and L-Dopa. Europ Neurol 1972;7:228-240.
27. Silver DE, Sahs AL. Double blind study using amantadine hydrochloride in the therapy of Parkinson's disease. Trans Am Neurol Assoc 1971;96:307-308.
28. Merry RTG, Galbraith AW. A double-blind study of Symmetrel (amantadine hydrochloride) in Parkinson's disease. J Int Med Res 1974;2:137-141.
29. Fehling C. The effect of adding amantadine to optimum L-dopa dosage in Parkinson's syndrome. Acta Neurol Scand 1973;49:245-251.
30. Savery F. Amandadine and a fixed combination of levodopa and carbidopa in the treatment of Parkinsons disease. Dis Nerv Syst 1977;38:605-608.
31. Millac P, Hasan I, Espir ML, Slyfield DG. Treatment of Parkinsonism with L-dopa and amantadine. Lancet 1970;2:720.
32. Webster DD, Sawyer GT. The combined use of amantadine HCl and levodopa/carbidopa in Parkinson's disease. Curr Ther Res 1984;35:1010-1013.
33. Callagham N, Mcllroy M, O'Connor M. Treatment of Parkinson's disease with levodopa and amantadine used as a single drugs and in combined therapy. Ir J Med Sci 1974;143:67-78.
34. Luginger E, Wenning GK, Bosch S, Poewe W. Beneficial effects of amantadine on L-dopa-induced dyskinesias in Parkinson's disease. Mov Disord 2000;15:873-878.
35. Verhagen Metman LV, Del Dotto P, LePoole K, Konitsiotis S, Fang J, Chase TN. Amantadine for levodopa-induced dyskinesias. A 1-year follow-up study. Arch Neurol 1999;56:1383-1386.
36. Snow BJ, Macdonald L, Mcauley D; Wallis W. The effect of amantadine on levodopa-induced dyskinesias in Parkinson's disease: a double-blind, placebo-controlled study. Clin Neuropharmacol 2000;23:82-85.
37. Clinical Pharmacology 2000 web site. http://cp.gsm.com/apps. Consulted in December 28, 2000.
38. Schneider E, Fischer PA, Clemens R, et al. Effects of oral memantine on symptoms of Parkinson's disease. Dtsch Med Wochenschr 1984;109:987-990.
39. Kornhuber J, Bormann J, Retz W, Hübers M, Riederer P. Memantine displaces (^{3}H) MK-801 at therapeutic concentrations in postmortem human frontal cortex. Eur J Pharmacol 1989;166:589-590.
40. Bormann J. Memantine is a potent blocker of N-methyl-D-aspartate (NMDA) receptor channels. Eur J Pharmacol 1989;166:591-592.
41. Rabey JM, Nissipeanu P, Korczyn AD. Efficacy of memantine, an NMDA receptor antagonist, in the treatment of Parkinson's disease. J Neural Transm Park Dis Dement Sect 1992;4:277-282.
42. Montastruc JL, Rascol O, Senard JM, et al. A pilot study of N-Metyl-D-Aspartate (NMDA) antagonist in Parkinson's disease. J Neurol Neurosurg Psychiatry 1992;55:630-631.
43. Wong BY, Cuolter DA, Choi DW, Price DA. Dextrorphan and dextromethorphan, common antitussives, are antiepileptic and antagonize N-methyl-D-aspartate in brain slices. Neurosci Let 1988;85:261-266.
44. Debonnel G, de Montigny C. Modulation of NMDA and dopaminergic neurotransmissions by sigma ligands: possible implications for the treatment of psychiatric dissorders. Life Sci 1996;58:721-734.

45.Hollander D, Pradas J, Kaplan R, McLeod HL, Evans WE, Munsat TL. High-dose dextromethorphan in amyotrophic lateral sclerosis: phase I safety and pharmacokinetic studies. Ann Neurol 1994;36:920-924.
46.Bonuccelli U, Del Dotto P, Piccini P, Behgé F, Corsini GU, Muratorio A. Dextromethorphan and parkinsonism. Lancet 1992;340:53.
47.Montastruc JL, Fabre N, Rascol O, Senard JM, Blin O. N-methyl-Aspartate (NMDA) antagonist and Parkinson's disease: a pilot study with dextromethorphan. Mov Disord 1994;9:242-243.
48.Verhagen Metman L, Del Dotto P, Natté R, van den Munckhof P, Chase TN. Dextromethorphan improves levodopa-induced dyskinesias in Parkinson's disease. Neurology 1998;51:203-206.
49.Spieker S, Breit S, Klockgether T, Dichgans J. Tremorlytic activity of budipine in Parkinson's disease. J Neural Transm 1999;56(suppl):165-172.
50.Jellinger K, Bliesath H. Adjuvant treatment of Parkinson's disease with budipine: a double-blind trial versus placebo. J Neurol 1987;234:280-282.
51.Spieker S, Löschmann PA, Klockgether T. The NMDA antagonist budipine can alleviate levodopa-induced motor fluctuations. Mov Disord 1999;14:517-519.

BIBLIOGRAPHY OF CLINICAL ARTICLES EXCLUDED (REASON FOR EXCLUSION)

Dallos V, Heathfield K, Stone P,Allen FA. Use of amantadine in Parkinson's disease. Br Med J 1970;4:24-26. (Results cases)
Fieschi C, Nardini M, Casacchia M, Tedone ME. Amantadine for Parkinson's disease. Lancet 1970;1:945-946.
Freedman BE, Getz E, MacGregor JM, Ames FR. Amantadine hydrochloride in the treatment of parkinsonism: a placebo-controlled double-blind study. S Afr Med J 1971;45:435-437. (High prevalence of "cerebral atherosclerosis")
Gilligan BS, Veale J, Wodak J. Amantadine hydrochloride in the treatment of Parkinson's disease. Med J Aust 1970;2(14):634-637. (High proportion of non-PD patients)
Godwin-Austen RB, Frears CC, Bergmann S, Parkes JD, Knill-Jones RP. Combined treatment of parkinsonism with L-dopa and amantadine. Lancet 1970;2:383-385. (Unknown proportion of non-IPD cases)
Griffiths AV, Parker WN, Palmer RM. Experiences with amantadine hydrochloride in Parkinson's disease. Practitioner 1971;207(241):679-680. (Only 4 patients)
Hunter KR, Stern GM, Laurence DR, Armitage P. Amantadine in Parkinsonism. Lancet 1970;1(7657):1127-1129. (Number of patients: 17)
Koller WC. Pharmacologic treatment of parkinsonian tremor. Arch Neurol 1986;43:126-127. (Number of patients: 9)
MacFadyen DJ, Picton TW, Zeldowicz L, McGeer PL. Amantadine –HCI in the treatment of Parkinson's disease: a controlled trial. J Clin Pharmacol New Drugs 1972;12:274-279. (High proportion of non-PD patients)
Mann DC, Pearce LA, Waterbury D. Amantadine for Parkinson's disease. Neurology 1971;21:958-962. (Duration study: 4 days)
Merrick EM, Schmitt PP. A controlled study of the clinical effects of amantadine hydrochloride (Symmetrel). Curr Ther Res Clin Exp 1973;15:552-558. (Patients studied are not IPD cases)
Parkes JD. Clinical pharmacology of amantadine and derivatives. In: Przuntek H, Riederer P (eds) *Early Diagnoses And Preventive Therapy In Parkinson's Disea*se. Springer. Wien New York, 1989, p. 335-341. (Book Chapter)
Pollock M, Jorgesen B. Combined L-Dopa and amantadine in Parkinson's disease. Aust N Z Med 1972;3:252-255. (Unknown number of non-IDP patients)
Rao NS, Pearce J. Amantadine in parkinsonism. An extended prospective trial. Practicioner 1971;206:241-245. (High proportion of non-IPD cases)
Sandyk R, Iacono RP, Snyder SR. Amantadine for levodopa resitant parkinsonism. Int J Neurosci 1987;32:715-717. (Only 1 patient)
Schwab RS, England AC, Poskanzer DC, Young RR. Amantadine in the treatment of Parkinson's disease. JAMA 1969;208:1168-1170. (Not placebo open)
Schwieger AC, Jenkins AC. Observations on the effect of amantadine hydrochloride in the treatment of Parkinsonism. Med J Aust 1970;3:630-632.
Spieker S, Breit S, Klockgether T, Dichgans J. Tremolytic activity of budipina in Parkinson's disease. J Neural Transm Suppl 1999;56:165-172. (Number of patients: 11 and 14)
Timberlake WH, Vance MA. Four-year treatment of patients with parkinsonism using amantadine alone or with levodopa. Ann Neurol 1978;3:119-128. (Clinical profile not defined)
Uitti RJ, Rajput AH, Ahslkog JE, et al. Amantadine treatment is an independent predictor of improved survival in Parkinson's disease. Neurology 1996;46:1551-1556. (Unknown proportion of non-IPD cases)
Walker JE, Potvin A, TourtellotteW, et al. Amantadine and levodopa in the treatment of Parkinson's disease. Clin Pharmacol Ther 1972;13:28-36. (Clinical profile not defined)
Wheatley D. Combined treatment in Parkinson's disease. Practitioner 1983;227:446-447. (Number of patients: 16)
Zeldowicz LR, Hubermann J. Long-term therapy of Parkinson's disease with amantadine, pa alone and combined with levodopa. Can Med Assoc J 1973;109(7):588-593. (Clinical profile not defined)

Movement Disorders
Vol. 17, Suppl. 4, 2002, p. S23-S37

Published by Wiley-Liss, Inc.
DOI 10.1002/mds.5558

Levodopa

INTRODUCTION

BACKGROUND

The loss of dopamine-generating neurons in the substantia nigra pars compacta (SNpc) is the major pathological change in Parkinson's disease (PD). Although other neurochemical changes develop in the striatum and elsewhere, the deficiency of dopamine in the striatal projections from SNpc accounts for the cardinal motor features of parkinsonism.[1,2] Consequently, augmenting striatal dopaminergic transmission by Levodopa substitution was shown to induce marked clinical improvement.[3,4]

RATIONALE

Levodopa (L-dopa) has an established role as one of the most efficacious antiparkinsonian agents documented by decades of clinical use. The effect size of Levodopa in PD is large and robust and argues against possible bias that usually effect uncontrolled studies. Therefore, it now seems irrelevant to discuss the evidence basis of Levodopa's well-established efficacy. However, the effect size and benefit risk ratio of Levodopa versus other antiparkinsonian agents as well as between different formulations of Levodopa has remained one of the prevailing controversial issues concerning optimal management of PD.

STANDARD LEVODOPA

METHODS

One of the differences in this chapter, as compared to other chapters in this review, is the abundant literature on Levodopa in PD and the established role of the drug in the treatment of PD. As a result, this section is based exclusively on Level-I studies where there was a Levodopa active comparator arm. (Studies employing standard Levodopa and sustained release formulations of Levodopa are reviewed separately.)

KEY SEARCH TERMS

These are detailed in each of the corresponding chapter for the respective active comparator studies (see Amantadine, Anticholinergics, DA-Agonists, MAO-B-Inhibitors, and COMT-Inhibitors).

SPECIAL EXCEPTIONS TO INCLUSION/ EXCLUSION CRITERIA

Only Level-I trials are included. No systematic attempts were made to identify studies on Levodopa without dopa decarboxylase inhibitors.

BASIC PHARMACOLOGY

MECHANISM OF ACTION

Levo-3,4-dihydroxyphenylalanine (Levodopa) is an amino acid naturally occurring as an L-stereoisomer in the bean pods of certain legumes. In the mammalian brain, Levodopa is a transient metabolic intermediate in the pathway producing dopamine. The enzymatic reaction generating Levodopa is L-tyrosine hydroxylation, the rate-limiting step regulating dopamine synthesis. Once produced, Levodopa does not accumulate because it is rapidly decarboxylated (both systemically and in the brain) to dopamine by L-amino acid decarboxylase (L-AAD). Synthetic Levodopa administered orally is transferred rapidly into the brain from the circulation by means of a large neutral amino acid (LNAA)-specific carrier system.[5] Its facilitated transport through the blood-brain barrier is similar to the uptake mechanisms in the duodenum and jejunum, although the gut transporter has a higher capacity for LNAA's. Levodopa exerts its antiparkinsonian efficacy through conversion into dopamine, which occurs intraneuronally and at other sites where LNAA decarboxylase activity is present, such as in glia.[6] Dopamine produced endogenously is packaged intraneuronally into vesicles; whether this occurs for dopamine synthesis from Levodopa in the PD patient, however, is not known.

The pulsatile nature of dopamine production from Levodopa administration does not duplicate the physiological pattern of neurotransmitter secretion.[6] Normally, there is a low but continuous release of dopamine with superimposed bursts of increased release. Considerable experimental evidence in animal studies suggests that chronic intermittent dopaminergic stimulation may be responsible for dyskinesia and motor fluctuations, which occurs after prolonged Levodopa use such as dyskinesias and motor fluctuations.[8]

PHARMACOKINETICS AND METABOLISM

Once absorbed from the gastrointestinal tract, Levodopa is distributed widely throughout the body and has several metabolic dispositions, including metabolism via several enzymatic pathways, auto-oxidation, and renal clearance.[9]

Levodopa administered by mouth is almost completely absorbed from the gut. Much of the dopamine produced from Levodopa is metabolized to homovanillic acid and, to lesser extent, to dopamine sulfate and dihydroxyphenylacetic acid. Levodopa is also a substrate for catechol-O-methyltransferase (COMT), and enzyme forming 3-O-methyldopa. A large fraction of each orally administered Levodopa dose is irreversibly converted to 3-O-methyldopa, which cannot be utilized in dopamine synthesis. Less than 5% of an oral dose of Levodopa is delivered to the brain.[9] If Levodopa is not administered with an inhibitor of L-AAAD or COMT, a large proportion of each oral dose of Levodopa will be diverted to the products of these enzymes. Use of the decarboxylase inhibitors carbidopa or benserazide will permit an approximately four-fold reduction of Levodopa doses needed for optimal symptom control.[10,11] Immediate-release formulations of Levodopa typically achieve a C_{max} between 15 and 45 minutes after oral intake of the drug.[9] L-AAAD inhibitors increase the magnitude of the Levodopa

C_{max}.[12] The plasma half-life of Levodopa, influenced mostly by distribution in tissues such as skeletal muscle and by extensive hepatic first-pass metabolism, usually ranges from 1-2 hours.

REVIEW OF CLINICAL STUDIES

PREVENTION OF DISEASE PROGRESSION

The only possibility to thoroughly assess the impact of Levodopa on the progression of PD is by means of placebo-controlled, long-term trials. To date, none have been published in the literature, but there is presently one ongoing clinical trial (ELLDOPA) specifically designed to address this question.[13] The ELLDOPA study is a placebo-controlled, 40-week, double-blind, randomized trial that seeks to determine Levodopa's effect on the natural history of PD. The primary outcome measure of this trial will be the changes in UPDRS at the end of the follow-up, after a 14-day wash-out period of all antiparkinsonian medications. Neuroimaging techniques (beta-CIT-SPECT) will also be used as a surrogate marker for disease progression.

Comparative prospective randomized trials comparing Levodopa with different dopamine agonists (ropinirole, pergolide, pramipexole) using functional imaging criteria as surrogate markers of disease progression are ongoing (ropinirole), will soon be published (pergolide) or have recently been published (pramipexole). These studies do not contain placebo treatment arms. While they may be able to show relative differences between the active treatments, they will not allow conclusions about the impact of treatments relative to the natural course of untreated PD disease. This is also true for a Level I study assessing the effect of deprenyl, Levodopa, and bromocriptine on the progression of PD.

Olanow and colleagues (1995[14]) randomized 101 untreated PD patients (mean age = 66 years) to one of the following four treatment groups (Deprenyl® plus Sinemet®; placebo-Deprenyl® plus Sinemet®; Deprenyl® plus bromocriptine; placebo-Deprenyl® plus bromocriptine). The final visit was performed at 14 months, 2 months after withdrawal of Deprenyl (or its placebo) and 7 days after withdrawal of Sinemet or bromocriptine. Deterioration of UPDRS total score between baseline and final visit was used as an index of PD progression. While this study was designed to assess the impact of Deprenyl on the progression of PD it also showed that deterioration in UPDRS score was not significantly different in patients randomized to treatment with Sinemet (1.7 ±1.6) or bromocriptine (4.5±1.2). This study therefore suggests that Levodopa and bromocriptine have the same impact on progression of motor impairment in PD, however, no conclusion is possible about the magnitude or direction of this impact relative to untreated disease. This study had an overall quality score of 76%.

Parkinson Study Group (2000[15]): This was a randomized, double-blind, controlled, two year prospective study including 301 patients randomly assigned to pramipexole monotherapy (N=151) or Levodopa (N=150) (see also section "Symptomatic Control of Parkinsonism" for further details). Open label supplementation with Levodopa was permitted from week 11 until the end of the trial according to clinical need. The primary outcome measure was the time of first occurrence of pre-specified motor complications. This trial included a subset of 82 patients who underwent b-CIT-SPECT imaging before baseline and immediately before the final study visit to detect possible differences in the decline of b-CIT uptake as a surrogate marker for disease progression with the two treatments. Patients treated initially with pramipexole (N=39) showed a mean decline of 20% (standard deviation 14.2%) in striatal b-CIT uptake compared with a 24.8% decline (standard deviation 14.4%) decline in patients treated initially with Levodopa (N=39). Four patients were lost to b-CIT follow-up. The observed differences between the two groups were not statistically significant.[15]

There are a number of Level-II studies assessing the impact of Levodopa on mortality in PD (see section on Levodopa safety). While mortality is a robust endpoint and certainly meaningful from a public health perspective, it only partially reflects disease progression in PD. Confounding variables include comorbidity, general changes in PD management, changes in life expectancy and co-treatment invalidating the available Level-II studies using retrospective historical controls. Ideally, studies assessing the impact of Levodopa on mortality require untreated controls, who are followed until death, which is clearly effectively impossible.

SYMPTOMATIC CONTROL OF PARKINSONISM

MONOTHERAPY

In this section all Level-I comparative trials using Levodopa as monotherapy versus monotherapy with an active comparator (as identified in all chapters on antiparkinsonian drugs of this review) have been included. Specific details on search methods, inclusion and exclusion criteria appear and comprehensive descriptions of study details can be found in the corresponding sections of this review.

Levodopa versus Dopamine Agonists

Bromocriptine versus Levodopa

Six Level-I studies with Levodopa as an active comparator have been included (also see chapter on DA agonists).

Libman et al. (1987[16]) studied 51 de novo patients for a mean duration of 19.5 weeks. Efficacy was assessed using Hoehn and Yahr scale, Columbia University Scale and the Northwestern University Disability Scale (NUDS). Bromocriptine (24 mg/d) and Levodopa (252 mg/d) were reported to induce similar improvements on all efficacy parameters. Hoehn and Yahr score improved by at least one unit in 42% of the bromocriptine-treated patients, and in 32% of the Levodopa-treated ones. The mean Columbia score improved by 62% in the bromocriptine (from 18.9 at baseline to 7.3 at week 21) and by 55% in the Levodopa group by 55% (from 16.4 at baseline to 7.4 at week 21). This improvement was not statistically different between both groups. This study had an overall quality score of 69%.

Riopelle et al. (1987[17]) treated 81 de novo patients for a mean of 5.5 months. Main efficacy parameter was the CURS, Hoehn and Yahr stage and NUDS scores. At the mean dose of 26 mg/d, bromocriptine was reported to improve parkinsonian symptoms to a similar degree as Levodopa (262 mg/d): the Columbia score improved by 61% with bromocriptine and 55% with Levodopa and NUDS score improvements were also similar (38% with bromocriptine and 37% with Levodopa). Unfortunately, the raw data scores are not provided in the text. This study had an overall quality score of 75%.

Cooper and colleagues (1992[18]) performed an open, randomized, 4-month study in 67 patients receiving Levodopa monotherapy (415 mg/d), bromocriptine (13.5 mg/d), or anticholinergics (21 patients on benzhexol 5.9 mg/d; 1 patient on orphenadrine). The study was mainly designed to assess different effects of dopaminergic and anticholinergic therapies on a number of cognitive outcomes but motor response was also assessed,

using the King's College Rating Scale (KCRS) and unimanual and bimanual fine finger movements. No head to head comparisons between the different treatment arms were made. At 4 months, motor status improved in the Levodopa (KCRS: baseline = 22.9 vs. 4-month = 12.0, p<0.01) and anticholinergics (KCRS: baseline = 22.3 vs. 4-month = 17.2, p<0.05) groups, while bromocriptine did not induce any significant change (KCRS: baseline = 23.0 vs. 4-month = 21.0, NS). This study had an overall quality score of 55%.

The UK Parkinson's Disease Research Group (1993[19]) performed a randomized open study in 782 de novo PD patients using 3 treatment arms: Levodopa monotherapy, Levodopa combined with selegiline, and bromocriptine monotherapy. Outcome criteria for motor function (secondary endpoints) were a modified version of the Webster scale and the NUDS. After one year of follow-up, Levodopa alone (420 mg/d) or in combination with selegiline (352 mg/d plus 10 mg/d) was found to be significantly more potent than bromocriptine (36 mg/d) (Webster adjusted improvement in score: Levodopa = 3.1, Levodopa+selegiline = 3.4, bromocriptine: 2.1; adjusted difference (95% CI) in favor of Levodopa vs. bromocriptine: 0.93 (0.27-1.5), p=0.006; and in favor of Levodopa+selegiline vs. bromocriptine: 1.25 (0.61-1.89), p= 0.0002). More patients withdrew from the study because of adverse events in the bromocriptine group during the study (mainly because of gastrointestinal and psychiatric adverse reactions). At 3 years only 33% of patients initially randomized to bromocriptine were still receiving agonist monotherapy compared to 68% in the Levodopa monotherapy arm. This study had an overall quality score of 63%.

Montastruc and colleagues (1994[20]) performed a randomized open study in 60 de novo patients (mean age = approximately 61 years) followed up for 5 years. While patients were initially randomized to monotherapy with either Levodopa or bromocriptine, Levodopa could be added later to the bromocriptine arm. At baseline, disease severity was reported to be comparable in both groups according to the Hoehn and Yahr stage. The primary objective of this trial was to compare the occurrence of long-term motor complications, but motor function was also assessed twice a year, using the Columbia University scale until 1985, and the UPDRS thereafter. At 5 years only 4 of 31 patients were still receiving bromocriptine monotherapy (mean delay to the adjunction of Levodopa: 2.7 years). The authors found similar efficacy of Levodopa monotherapy (569 mg/d) and combined Levodopa plus bromocriptine treatment (471 mg/d plus 52 mg/d) as assessed by the UPDRS at the endpoint or at the last visit of follow-up (bromocriptine/Levodopa group: 10.6; Levodopa group: 11.0). However, no direct comparisons between the respective monotherapies are possible in this trial. Hallucinations were more frequent in the bromocriptine group (5 in the bromocriptine/Levodopa group versus 2 in the Levodopa group). Long-term motor complications were less frequent in the bromocriptine group (see "Prevention of Motor Complications").This study had an overall quality score of 69%.

Olanow et al. (1995[14]) performed a 14-month, double-blind, randomized four-arm trial comparing Levodopa plus placebo versus Levodopa plus deprenyl versus bromocriptine plus placebo versus bromocriptine plus deprenyl. The study was primarily designed to assess the impact of deprenyl and Levodopa on the progression of PD. However, before washout it was possible to compare the symptomatic effects of Levodopa (L-dopa: 400 mg/d) versus bromocriptine (28 mg/d) using the total UPDRS scores. Levodopa-treated patients were slightly more improved (UPDRS at baseline = 23.4 vs. 12 month = 18.3) than those on bromocriptine (~ 28 mg/d) (UPDRS at baseline = 22.7 vs. 12 month = 21.5), but the difference was not significant. There were no reported significant differences in the incidence of side effects in both groups. This study had an overall quality score of 76%.

In addition two studies were identified where Levodopa monotherapy and bromocriptine monotherapy were used as separate arms in three arm trials also including "early combination" of both drugs.

Herskovits and colleagues (1988[21]) randomized 86 de novo PD patients to one of three arms over a follow-up of 31 months: Levodopa monotherapy versus bromocriptine monotherapy versus combined Levodopa plus bromocriptine treatment. However, secondary Levodopa supplementation was possible in the bromocriptine group and at the end of the trial half of the patients in that group had combined treatment. Doses were 12.6 mg/d for bromocriptine monotherapy, to which a mean of 401.8 mg/d Levodopa was added in the course of the study in 50% (14/28) of patients. The Levodopa monotherapy group received 556 mg/d and the initially combined group received 572 mg/d plus 7.5 mg/d of bromocriptine. Motor outcome was assessed using the Webster Rating. Antiparkinsonian improvement was reported to be about 50% in all 3 groups, with no significant difference between treatments. These results appear on a figure of the article, but, unfortunately, no exact quantitative raw data are provided in the text or in a table. This study had an overall quality score of 63%.

Hely et al. (1994[22]) conducted a 5-year randomized open study of 149 de novo PD patients (mean age = 62 years) allocated to low doses of either Levodopa (64 patients) or bromocriptine (62 patients) monotherapy. The study was designed to be double-blind in the titration phase only, and to assess primarily if the incidence of late motor complications was lower in the bromocriptine group. Interim results on the first 3 years have also been reported but are not summarized here. Efficacy was assessed with a modified Columbia scale. ADL was also measured using the NUDS. Subsequent addition of Levodopa to bromocriptine or bromocriptine to Levodopa was allowed, thus creating subsequently new combination groups. Analyses were performed on the 2 monotherapy treatment groups as originally randomized (bromocriptine and Levodopa), and also on the main treatment subgroups subsequently formed. The mean daily dose of bromocriptine was 32 mg/d. Less than 10% of patients were still on bromocriptine monotherapy after 3 years and none after 5 years. Median times on bromocriptine monotherapy were 12 months and 52.3 months on Levodopa alone. Doses at year one were 18 mg/d for bromocriptine and 344 mg/d for Levodopa alone. In the bromocriptine group, the main reason to stop monotherapy and switch to combination was lack of efficacy. Mean change from baseline in modified Columbia score on bromocriptine alone showed improvement at 6 months (-2.41, p<0.01), but not thereafter. Mean change from baseline in modified Columbia score on Levodopa alone also showed improvement at 6 months (-3.69, p<0.001), one year (-3.96, p<0.001), and 2 year (-3.19, p<0.001). Levodopa was significantly better than bromocriptine alone at 1 year. Conversely, the patients who switched from bromocriptine alone to a combination of Levodopa and bromocriptine showed significantly more improvement than the Levodopa monotherapy group at one year (mean change in modified Columbia score : -5.75, p=0.002). However, no head-to-head comparisons between the two arms were performed. This

study had an overall quality score of 57%.

Lisuride versus Levodopa

Rinne et al. (1989[23]) randomized 90 de novo parkinsonian patients to open treatment with Levodopa monotherapy, monotherapy with lisuride or initial combined treatment with both drugs. Total follow-up was 4 years and motor response was assessed using the Columbia University Rating Scale. Patients also recorded the occurrence and severity of fluctuations in disability in a daily diary. At three months and one year improvements were significantly greater in the Levodopa monotherapy arm compared to the lisuride arm (CURS improvement: Levodopa 56% vs. lisuride 32%, $p<0.01$; daily doses not given, doses at one year were 718 mg/d for Levodopa and 1.9 mg/d for lisuride). After two years of treatment only 33% of patients (N=6) still remained on lisuride monotherapy so that efficacy comparisons between the monotherapy arms no longer seem meaningful due to small numbers. This study had an overall quality score of 44%.

Pergolide versus Levodopa

Kulisevsky et al. (1998[24]) included 20 de novo patients in a 6 month open label randomized trial comparing pergolide and Levodopa. Motor effects were assessed using the UPDRS. At 6 months pergolide (2.8 mg/d) and Levodopa (435 mg/d) showed similar decreases in UPDRS subscores II and III. The numerical effect of Levodopa was larger than that of pergolide, however, the study was clearly not powered to detect statistically significant differences between the two treatments (improvement of UPDRS II was from a mean of 8.7 at baseline to 6.1 at month 6 in the pergolide arm and from 11.8 to 5.8 in the Levodopa arm. Decreases for UPDRS III were from 22.9 to 15.7 in the pergolide versus from 24.8 to 14.0 in the Levodopa arm.)

Oertel et al. (2000[25]): A large randomized, double-blind, prospective long-term trial comparing pergolide and Levodopa monotherapy has included 294 drug-naive patients and its main results have been presented in abstract form.[25] Once fully published this study is expected to provide high quality data on the relative symptomatic efficacy of pergolide versus Levodopa.

Pramipexole versus Levodopa

Parkinson Study Group (2000[15]): This is a randomized Levodopa controlled two-year prospective study of pramipexole monotherapy. One hundred fifty-one patients were randomized to pramipexole monotherapy while 150 patients received Levodopa. The trial consisted of a 10-week dosage escalation period followed by a 21-month maintenance period. Open-label supplementation with Levodopa was permitted from week 11 until the end of the trial according to clinical need. The primary outcome variable was defined as time from randomization until the first occurrence of any of three pre-specified motor complications: wearing-off, dyskinesias, or "on"/"off" fluctuations (see "Prevention of Motor Complications" section). Secondary outcome variables included changes in scores of the UPDRS, a PD quality of life scale, the EuroQol, and the need for Levodopa/Carbidopa supplementation.

A subset of 82 patients underwent SPECT imaging with b-CIT before baseline and immediately before the final study visit (see above "neuroprotection").

At the end of the trial subjects allocated to pramipexole were on an average dose of 2.78 mg/d and those allocated to Levodopa took an average of 406 mg/d. Fifty-three percent of subjects in the pramipexole group required supplemental Levodopa compared with 39% in the Levodopa group ($P = 0.02$). The dose of open-label supplemental Levodopa was almost identical in the two arms (264 versus 252 mg/d), the average total daily dose of experimental plus supplemental Levodopa in the Levodopa arm was 509 mg/d.

The mean improvement in total UPDRS as well as the motor and ADL subscores from baseline to the end of the study was significantly greater in the Levodopa group compared with patients on pramipexole. Total UPDRS scores decreased by 4.5 points with pramipexole compared to 9.2 points with Levodopa ($P < 0.001$). Similarly motor scores decreased by 3.4 versus 7.3 points ($P < 0.001$) and ADL scores decreased by 1.1 versus 2.2 points in the pramipexole versus Levodopa arm ($P = 0.001$).

Ropinirole versus Levodopa

Rascol et al. (1998)[26] conducted a randomized controlled trial including 268 de novo patients randomized to ropinirole or Levodopa in a two-to-one ratio. Open Levodopa supplementation was allowed in both arms and results are available after 6 months[26] and 5 years[27] of follow-up. Primary efficacy endpoint for the planned 6-months interim analysis was the percentage improvement in UPDRS motor score. Secondary efficacy variables included the proportion of patients with a 30% reduction in UPDRS motor score ("responders"), patients with scores of 1 (very much improved) or 2 (much improved) on a CGI score and the proportion of patients requiring Levodopa supplementation. At 6 months Levodopa (464 mg/d) induced significantly greater improvement in UPDRS motor scores compared to ropinirole (9.7 mg/d): UPDRS motor score improved by -32% with ropinirole (from 21.5 at baseline to 15.7 at endpoint) and by -44% with Levodopa (from 21.7 at baseline to 13.3 at endpoint) ($p<0.05$). However, at this time point there was no significant difference in the number of responders (ropinirole: 48%; Levodopa: 58%) At six months, CGI analysis did not reveal intergroup differences for patients with Hoehn and Yahr stages I-II, but there was a significant difference in favor of Levodopa in the patients with Hoehn and Yahr Stages II.5 and III at baseline (OR 0.11; 95%CI (0.04-0.35)). By the end of the first 6 months, 4% of the ropinirole-treated patients required Levodopa supplement versus 1% of the Levodopa-treated ones (NS). This study had an overall quality score of 90%.

The primary outcome for the final analysis at 5 years was the occurrence of dyskinesia; but antiparkinsonian efficacy was also recorded using UPDRS II (ADL) and III (motor examination). At 5 years patients on Levodopa (mean dose 753 mg/d including open label supplement in 36% of the patients) had a mean decrease from baseline in UPDRS motor scores of 4.8 points compared to 0.8 points in the ropinirole group (mean dose 16.5 mg/d plus 427 mg/d of open-label complementary Levodopa in 66% of the patients). This difference in mean score (4.48, 95%CI 1.25-7.72) was significant in favor of Levodopa ($P = 0.008$). UPDRS ADL scores increased by 1.6 points in the ropinirole group while mean scores did not change in patients on Levodopa. This difference in favor of Levodopa was not significant. Classical dopaminergic adverse reactions were reported in both treatment groups, including nausea, somnolence, insomnia, dizziness, hallucination, vomiting, postural hypotension. Hallucinations were more frequent with ropinirole than Levodopa (17% vs. 6%, respectively), but severe hallucinations leading to withdrawal from the trial were infrequent in both groups (4% vs. 2%, respectively). This study had an overall quality score of 90%.

Cabergoline versus Levodopa

Rinne et al. (1997[28], 1998[29]) performed a controlled prospective trial including 413 de novo patients (mean age approximately 61 years) randomized to cabergoline or Levodopa in a one-to-one ratio. Cabergoline could be titrated up to 4 mg/d on a once a day regimen, and Levodopa up to 600 mg/d tid. Open Levodopa supplementation was allowed in both arms according to clinical need. Motor effects were assessed using the UPDRS. The proportion of patients experiencing a 30% decrease in parkinsonian disability and the proportion of patients requiring the addition of Levodopa were also analyzed. At one year mean UPDRS motor scores decreased more in the Levodopa group (468 mg/d) compared to the cabergoline group (2.8 mg/d) (16.4 versus 12.6). It is not stated in the paper if this difference was statistically significant. By this time 38% in the cabergoline group versus 18% in the Levodopa group required open Levodopa supplementation.

Patients were subsequently followed up for a total of 3 to 5 years. The primary end-point was the onset of motor complications but antiparkinsonian efficacy was also monitored using the UPDRS part II and III. After 4 years Levodopa treated patients are reported to have an "average 30% improvement" in motor disability (UPDRS III) compared to 22 to 23% versus baseline in the cabergoline group. No statistical analysis are reported and 65% of cabergoline patients required Levodopa supplementation at the time of final analysis. Adverse events were quite similar in both groups, including among the most frequent ones nausea and vomiting, dizziness and hypotension, sleep problems. Edema was more frequent on the cabergoline group. This study had an overall quality score of 75%.

Levodopa versus Anticholinergics

Cooper et al. (1992[18]): The only available study where Levodopa monotherapy was compared to monotherapy with anticholinergics was performed by Cooper and colleagues (1992).[18] However, this was a study designed to assess differential effects on neuropsychological functions in de novo patients with idiopathic PD, and direct statistical comparisons of numerical results in the Levodopa versus anticholinergic arm were not performed.

Motor assessments were based on the King's College Rating Scale and a Finger Motility Scale and there was significant improvement over baseline in both the Levodopa and the anticholinergics arm. This study had an overall quality score of 55% (see above).

Levodopa versus Amantadine

A single randomized trial of Levodopa versus amantadine monotherapy was identified. Cox et al. (1973[30]) enrolled 27 patients to a double-blind, crossover study where patients had two six-week courses of monotherapy with either drug, separated by a period of six weeks without treatment. Motor effects were assessed on a modified Webster scale and by means of timed tests of writing, walking and lighting a match. In addition, mechanical recordings of tremor and rigidity were also performed (two assessments at three-weekly intervals before and during each treatment period). The Webster scores, time to write a standard sentence or light a match all significantly improved over baseline in patients receiving Levodopa (mean daily dose 2.9 to 3.3 g without DC-inhibitor) before Amantadine ("Levodopa starters") while there was no significant improvement in any of the assessments in patients receiving Amantadine first (mean daily dose 303 to 323 mg). Levodopa induced improvements were less impressive in patients receiving the drug in the second double-blind period ("Amantadine starters") but still significant for some Webster score items and timed tests. This was also the case for Amantadine when given in the second treatment period ("Levodopa starters"). Although this study was not designed to directly compare effect sizes of Levodopa and Amantadine monotherapy the results suggest that Levodopa is more effective. This study had an overall quality score of 48%.

ADJUNCT THERAPY

Although supplementation of Levodopa to dopamine agonists or other antiparkinsonian medications in stable PD is common clinical practice in order to improve symptomatic control no Level-I studies specifically assessing the effectiveness of this strategy have been identified.

PREVENTION OF MOTOR COMPLICATIONS

Although the use of Levodopa specifically aimed at preventing motor complications seems contradictory a number of randomized controlled prospective trials are available to assess the incidence of such complications during long-term Levodopa treatment. These will be reviewed here. Results between these studies are difficult to compare because of differences in Levodopa dose, length follow-up, definition and assessment methods for motor complications.

Ten long-term, prospective, randomized, controlled trials in de novo patients provide incidence data on the development of motor fluctuations and/or drug-induced dyskinesias with Levodopa monotherapy. Five were trials comparing LD with bromocriptine, one each with lisuride, cabergoline, ropinirole and pramipexole, and one compared two pharmakokinetic formulations of Levodopa.

The UK Parkinson's Disease Research Group (1993[19]) included 782 de novo patients randomly allocated to Levodopa alone, Levodopa plus selegiline or bromocriptine. Involuntary movements, oscillations in motor performance and early morning dystonia were recorded at follow-up visits but no special definitions are reported. At three years the incidence of motor response oscillations was 33 and 35% in the two Levodopa arms. Twenty-seven percent of patients in the Levodopa monotherapy arm had developed dyskinesias. Levodopa-induced dystonia was observed in 25% of patients after three years. These percentages are reported to be "higher" in patients on Levodopa or on combination than in those on bromocriptine, but p values are not reported. Mean daily doses are given at one year only and were 420 mg/d. The mean length of time to develop drug-induced dyskinesias and motor oscillations was 24.5 months. This study had an overall quality score of 63%.

Montastruc and colleagues (1994[20]) randomized 60 de novo patients to monotherapy with Levodopa or bromocriptine (to which Levodopa could be added later). At 5 years patients in the Levodopa arm received a mean daily dose of 569 mg/d. Motor complications were defined either as involuntary abnormal movements (peak dose or biphasic dyskinesia or dystonia), or as motor fluctuations, i.e. wearing-off effects or on/off phenomena. Motor complications of any type were observed in 90% of patients with a mean delay of 2.7 years. Fourteen of 29 patients had developed drug-induced dyskinesias and 10 of 29 patients showed wearing-off phenomena. Mean delays from first treatment to appearance of wearing-off fluctuations were 2.9 years. This study had an overall quality score of 69%.

Przuntek et al. (1996[31]) randomly allocated 674 newly diagnosed patients with PD (who could have received Levodopa for less than 6-months) to monotherapy with Levodopa or combined treatment with Levodopa and bromocriptine. Patients were followed up for 42 months on these two types of treatment and the occurrence of motor side-effects was assessed clinically by evaluating fluctuations in mobility, on/off phenomena and drug-induced dyskinesias that included chorea, dystonia, and other dyskinetic movements. The primary endpoint of this study was the time of onset of the first manifestation of any of these motor side-effects. A complex system of scoring according to severity and body distribution was adopted. Twenty-nine percent (87/302) patients developed motor side-effects with Levodopa monotherapy at a final dose of 439 mg/d. Motor response oscillations were observed in 15% and at least one type of drug-induced dyskinesia in 20% of patients. Mean delays until the first occurrence of any motor side-effects were 3.2 years. This study had an overall quality score of 65%.

Gimenez-Roldan and colleagues (1997[32]) enrolled 50 patients with previous treatment of Levodopa for a maximum of 6 months to a randomized parallel group long-term study comparing Levodopa monotherapy with adjunct treatment with bromocriptine. Total follow-up period was 44 months in an open label design. The frequency of motor response oscillations and choreatic dyskinesias was compared between the two groups. Motor fluctuations were defined as daily episodes of exacerbation in parkinsonian symptoms; isolated freezing of gait was not included in this definition. Dyskinesias were defined as presence of abnormal involuntary movements of choreic nature in one or more body parts as observed during follow-up visits. At month 44 47% of the patients on Levodopa monotherapy had developed response oscillations of the wearing-off type and dyskinesias were present in 37% of patients (mean dose of Levodopa was 725.6 mg/d at last follow-up). This study had an overall quality score of 68%.

Hely and colleagues (1994[22]) enrolled 149 previously untreated PD patients into a randomized trial comparing low dose Levodopa monotherapy (defined as less than 600 mg/d) with low dose bromocriptine monotherapy (defined as 30 mg/d). Fluctuations were defined as end of dose failure which was recorded present if patients reported early morning akinesia, wearing-off effect or increase of dose frequency to more than 3 times daily at any of the follow-up visits. The term *on/off fluctuation* was reserved for sudden severe and at times unpredictable changes in mobility. Involuntary movements were recorded as dyskinesias when movements were rapid, irregular and painless or as dystonia when sustained abnormalities of posture - sometimes painful - had occurred. The time of onset of any of these motor complications was taken as the first visit at which patients reported them or the investigator identified them. After 5 years of treatment the mean dose and the Levodopa monotherapy arm was 471 mg/d, 35 of 64 evaluable patients on Levodopa monotherapy had developed drug-induced dyskinesias. Twenty-three patients on Levodopa monotherapy developed drug-induced painful dystonia which consisted in early morning foot dystonia in all but two. The average incidence of newly arising dyskinesias was 7.4% for each 6 months period of treatment on Levodopa. End of dose fluctuations were not observed in the first year of treatment but their incidence increased over time reaching 18% in the last 6 months. Wearing-off occurred in 41% of the patients randomized to Levodopa. This study had an overall quality score of 57%.

Rinne et al. (1989[23]) included 90 de novo patients in a randomized 4 year trial comparing Levodopa monotherapy versus lisuride monotherapy versus the combination of the two. Patients are reported to have recorded the occurrence and severity of fluctuations in disability and clinical side-effects in a daily diary. At four years and a mean daily dose of 668 mg of Levodopa end of dose failure occurred in 52% of patients and peak-dose dyskinesias were observed in 44%.

Rascol and colleagues (1998[26]) evaluated the incidence of dyskinesias and motor fluctuations in a cohort of 268 patients randomized to monotherapy with Levodopa in a prospective controlled trial of ropinirole monotherapy. Motor complications were assessed according to the UPDRS part IV definition. The primary outcome was the occurrence of dyskinesia assessed using item 32 ("duration: what proportion of the waking day are dyskinesia present?") of the UPDRS part IV. Other outcome measurements were "disabling dyskinesia" defined as a score of 1 or more on item 33 ("how disabling are the dyskinesia") of the UPDRS IV. Wearing-off and freezing were also monitored using the corresponding items of the UPDRS. At five years mean daily Levodopa dose was 753 mg/d. Forty-five percent of patients on Levodopa monotherapy had developed dyskinesias and 34% had developed wearing-off fluctuations. This study had an overall quality score of 90%.

Rinne and colleagues (1997[28]) followed up 412 de novo patients for 3 to 5 years who had been randomized to monotherapy with either cabergoline (N=208) or Levodopa (N=204). The primary endpoint of this study was the onset of motor complications confirmed at two subsequent visits and defined on the basis of a checklist comprising ten different categories (daily wearing off, nocturnal akinesia, early morning akinesia, off period freezing, peak dose dyskinesia, early morning dystonia, dose related off period dystonia, dose related on period dystonia, random-freezing, other) and were scored positive if at least one of these was present on two subsequent visits. Based on this definition motor complications had developed in 34% of Levodopa treated patients at final follow-up (on average 4 years). Peak dose dyskinesias were present in 28 and daily wearing-off was recorded in 38 of Levodopa treated 204 patients. This study had an overall quality score of 75%.

The Parkinson Study Group (2000[15]) enrolled 301 patients with idiopathic PD with no or less than 2 months prior exposure to Levodopa or a dopamine agonist into a prospective multicenter double-blind randomized controlled trial. Patients were followed for two years (23.5 months) and the primary endpoint was the time from randomization until the first occurrence of any of three prespecified dopaminergic complications: wearing-off, dyskinesias or "on"/"off" fluctuations. Dyskinesias had been defined as abnormal involuntary movements excluding early morning dystonia or other "off"-period dystonic phenomena. Wearing-off was defined as a perception of decreased mobility or dexterity usually bearing close relationship to the timing of antiparkinsonian medications, while "on"/"off" effects were defined as unpredictable and generally sudden shifts between mobility and immobility not apparently related to the timing of antiparkinsonian medications.

By the end of the study, 51% of subjects randomized to Levodopa had reached the primary endpoint. Drug-induced dyskinesias were observed in 31% on Levodopa, wearing-off phenomena were recorded in 38% while "on"/"off" fluctuations affected 5.3% Levodopa treated patients.

Block and colleagues (1997[33], also reported by Koller and colleagues, 1999[34]) enrolled 618 patients with PD without prior exposure to Levodopa into randomized trial comparing standard ver-

sus sustained release Levodopa and followed patients up for 5 years. Primary endpoint in this trial was defined as the presence of motor fluctuations defined in three different ways: based on 24 hour diaries filled in on two consecutive days per week for a total of 8 days over a one month period after each quarterly visit patients had to exhibit a minimum of 10% on-time with dyskinesias or 20% of off-time during the waking day to reach endpoint. Alternatively, 5 of 10 questions in a motor fluctuation questionnaire specially designed for the trial had to be scored positive by the investigator. A third definition of endpoint was that both the diary and the questionnaire criterion were met. All three criteria had to be met on at least two consecutive visits for an "event" to be coded for the survival analysis. After 5 years of treatment the mean daily dose of standard Levodopa in this trial was 426 mg. 21% of patients had fluctuations or dyskinesias by the diary criterion while only 16% had reached the event by questionnaire definition. The paper does not quote percentages of patients meeting both criteria. This study had an overall quality score of 80%.

CONTROL OF MOTOR COMPLICATIONS

It is common practice to modify dose size and dose frequency of standard Levodopa preparations to improve motor response oscillations and/or dyskinesias but no Level-I trials assessing such strategies were identified. Studies assessing alternative pharmacokinetic formulations of delivery routes of Levodopa will be reviewed below.

REVIEW OF SAFETY

Treatment of PD with standard Levodopa causes a number of typical dopaminergic adverse events including nausea, vomiting, and hypotension. Central dopaminergic adverse reactions include hallucinosis and paranoid psychosis as well as drug-induced dyskinesias. From the available Level-I studies the risk of drug-induced psychosis with Levodopa monotherapy appears low with less than 5% of de novo patients being affected after 3 to 5 years. The incidence of Levodopa-induced dyskinesias in prospective randomized long-term trials varies between less than 20% to more than 50% at 5 years.

There have been a number of retrospective and prospective cohort studies assessing mortality in Levodopa treated patients with PD. All but one have found excess mortality over the general population by factors between 1.5 and 2.5.[35-39] However, the impact of Levodopa treatment itself on the mortality of PD has only been inferred from comparisons with historical controls and this approach is obviously flawed by confounding changes in life expectancy, levels of general medical care, uncontrolled factors of comorbidity and co-medication. Given these limitations a number of such studies have demonstrated associations of improved survival after initiation of Levodopa treatment in PD.[35,40-44] While it is commonly accepted that Levodopa treatment by virtue of its symptomatic efficacy improves disability and survival early in the disease advancing disability in later stages along with age associated comorbidity still accounts for excess mortality.

Because of the role of oxidative stress as a pathogenetic factor of nigral cell death in PD and the theoretical possibility that the oxidative metabolism of Levodopa itself might accelerate this process there has been an intense debate of possible nigral toxicity induced by Levodopa treatment.[45] Although a number of in vitro experiments in neuronal and non-neuronal cell cultures have indeed demonstrated toxic effects of Levodopa results from in vivo studies are controversial.[46] In addition to the conflicting evidence from experimental studies there is currently no clinical indication of detrimental effects of Levodopa in terms of accelerating disease progression.[47] However, the mechanisms leading to potentially irreversible dyskinesias following prolonged Levodopa exposure may be viewed as a type of drug-related "toxicity".

CONCLUSIONS

EFFICACY

PREVENTION OF DISEASE PROGRESSION

There is INSUFFICIENT EVIDENCE to conclude on the effects of Levodopa on the progression of PD. Evidence from a single Level-I trial designed to assess the effects of deprenyl on disease progression when added to bromocriptine or Levodopa for a period of 12 months suggests that Levodopa and bromocriptine are not different regarding impact on progression of motor impairment as assessed after appropriate washout periods following 12 months of treatment. Recently concluded studies have employed surrogate markers (18FD-PET/Beta-CIT-SPECT) to assess the relative impact of Levodopa versus dopamine agonists but such studies do not allow conclusions on the impact of Levodopa treatment on disease progression in relation to untreated PD. Again the only available Level-I trial showed similar outcomes regarding decline of striatal b-CIT binding as assessed by SPECT after two years of treatment with Levodopa or pramipexole.

SYMPTOMATIC CONTROL OF PARKINSONISM

Although there are no Level-I placebo-controlled trials available, the efficacy of Levodopa regarding symptomatic control of parkinsonism is clearly established. Levodopa monotherapy is LIKELY MORE EFFICACIOUS than monotherapy with anticholinergics or amantadine, but the two Level-I studies identified in this review are insufficient for methodological reasons to unequivocally prove superiority of Levodopa.

Similarly, based on 8 Level-I studies, Levodopa monotherapy is LIKELY MORE EFFICACIOUS than monotherapy with bromocriptine, but methodological quality, designs (Levodopa supplementation to bromocriptine in case of clinical need in several trials) and reported study results are too heterogeneous to make this a firm conclusion.

There is INSUFFICIENT EVIDENCE to conclude on the relative efficacy of Levodopa versus lisuride monotherapy since a single Level-I trial eventually lost power for meaningful comparisons between Levodopa and lisuride monotherapy due to Levodopa add-on in the majority of lisuride patients.

A single trial assessing pergolide versus Levodopa monotherapy only included 20 de novo patients and provides INSUFFICIENT EVIDENCE to conclude on the relative efficacy of these two types of treatment, but a larger long-term randomized controlled trial has been completed and awaits full publication.

Based on one high quality long-term prospective double-blind trial each there is sufficient evidence to conclude that Levodopa monotherapy is MORE EFFICACIOUS than monotherapy with ropinirole, pramipexole or cabergoline in improving symptomatic control in de novo patients with PD.

PREVENTION OF MOTOR COMPLICATIONS

Efficacy conclusions related to the prevention of motor complications are not applicable to standard Levodopa therapy.

CONTROL OF MOTOR COMPLICATIONS

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of strategies modifying standard Levodopa dosage and/or timing to control motor fluctuations or dyskinesias.

SAFETY

Numerous Level-I trials with Levodopa as active comparator confirm the established clinical view that Levodopa treatment is SAFE WITHOUT SPECIALIZED MONITORING. The incidence of Levodopa related motor complications with long-term monotherapy as assessed in Level-I studies varies between less than 20% and more than 50% after 3 to 5 years of treatment. Furthermore, Level-I trials comparing Levodopa monotherapy with dopamine agonist monotherapy in de novo patients uniformly show lesser incidences of neuropsychiatric adverse reactions with Levodopa compared to dopamine agonists. So far there is no indication that Levodopa monotherapy has adverse effects on the progression of PD. Furthermore, a number of retrospective and prospective studies indicate that Levodopa therapy is associated with a reduction in early excess mortality from PD.

IMPLICATIONS FOR CLINICAL PRACTICE

Levodopa monotherapy is CLINICALLY USEFUL in improving motor symptoms of PD. Although the evidence from comparative randomized prospective trials is sparse and partially contradictory Levodopa must still be considered the gold standard of symptomatic efficacy in the drug treatment of PD. However, its long-term use is associated with motor complications affecting between 20% and 50% of patients after 2 to 5 years. Among these, Levodopa induced dyskinesias can be particularly disabling and difficult to control such that the initiation of Levodopa treatment must be based on clear clinical need. In many instances starting treatment with alternative dopamine replacement strategies like dopamine agonists will be sufficient for some time and there is convincing evidence from adequate clinical trials that early agonist monotherapy with later Levodopa supplementation significantly reduces the risk for Levodopa long-term motor complications.

IMPLICATIONS FOR CLINICAL RESEARCH

Placebo-controlled trials in de novo patients are needed to assess Levodopa's possible impact on rates of progression of PD and on surrogate markers of nigrostriatal dopaminergic integrity. Such studies could also help to settle the question of potential Levodopa-associated toxicity. Ideally these should be performed as three arm trials including a dopamine agonist arm.

Given Levodopa's high level of symptomatic efficacy in controlling motor symptoms of PD long-term trials assessing the outcome of alternative pharmacokinetic profiles of Levodopa administration, like combined treatment with COMT inhibitors, in de novo patients of PD are needed to identify ways to improve the rate of motor complications associated with standard Levodopa long-term treatment.

In addition longer-term prospective trials comparing such modified Levodopa regimes with dopamine agonists for more than 10 years have to be performed and should include quality of life and pharmaco-economic assessments.

SLOW RELEASE LEVODOPA

RATIONALE

Standard Levodopa has a short half-life of less than 2 hours eventually leading to short lived ("short duration") responses. Multiple oral doses of standard Levodopa thus produce pulsatile peaks of Levodopa plasma levels and presumably striatal dopamine levels. Such pulsatile dopamine receptor stimulation in the striatum has been incriminated as possible mechanism for the development of late motor complications due to sensitization of dopamine receptor response.

Levodopa slow release formulations have been developed to smooth out Levodopa plasma levels prolonging clinical effects from a single dose and also the providing more continuous dopamine receptor stimulation during the day.

METHODS

KEY SEARCH TERMS

Levodopa slow release, Madopar HBS, Sinemet CR and PD.

BASIC PHARMACOLOGY

MECHANISM OF ACTION

This is not different from standard Levodopa.

PHARMACOKINETICS

The slow release of the drug in the GI tract from these controlled release forms results in a substantial extension of plasma LD levels. The two available products delay the peak LD concentration beyond that of the immediate-release preparation by 45 to 90 minutes.[36] Both products have decreased bioavailability (AUC) resulting in a 30% reduction in a dose equivalence. With each of the sustained release LD-decarboxylase inhibitor preparations, the plasma half-life of LD is also extended by up to two hours beyond the pharmacokinetic profile of the immediate-release product. Other formulations are under development to produce more continuous release of LD, such as a product combining LD in two drug retention materials for a more sustained pharmacokinetic profile.[37]

REVIEW OF CLINICAL STUDIES

PREVENTION OF DISEASE PROGRESSION

No studies specifically assessing the effect of Levodopa slow release preparations on progression of PD have been identified.

SYMPTOMATIC CONTROL OF PARKINSONISM

No placebo controlled trials assessing symptomatic efficacy of slow release Levodopa preparations were identified. Two Level-I studies providing data on the symptomatic efficacy of monotherapy with Levodopa sustained release preparations have been identified and are included in this review.

Dupont and colleagues (1996)[38] included 134 de novo patients with PD into a randomized double-blind parallel group multicenter study comparing the therapeutic responses of slow release Levodopa/benserazide (Madopar HBS) to standard Levodopa/benserazide (Madopar). Patients were followed up for 5 years and efficacy parameters included the Webster Scores, Unified Parkinson's Disease Rating Scores as well as North Western University Disability Scale Scores. Webster Scores improved from a baseline mean of 10.9 (standard) and 10.4 (slow release) to 5.2 and 4.1 at year 1 and were again similar at year 5 (11.2 vs. 9.3).

Similarly there were no differences in NUDS Scores between the two groups at any time point or in UPDRS Scores (18.9 vs. 15.8 at year 2 and 29.9 vs. 26.0 at year 5). Reportedly there were no differences with respect to the incidence or types of side-effects but details are not reported in the paper.

Mean daily Levodopa dose at year 1 was 564 mg for the standard Levodopa arm and 516 mg for the slow release arm. This rose to 719 versus 638 mg/d by year 5. Number of doses were similar and around four in both arms over the total study duration.This study suggests that slow release Levodopa/benserazide has similar symptomatic efficacy as monotherapy in de novo PD as standard Levodopa/benserazide. This study had an overall quality score of 71%.

Block and colleagues (1997[33], amplified by Koller et al. in 1999[34]) reported a similar 5-year trial comparing immediate released and controlled released carbidopa in 618 patients with PD never exposed to Levodopa. The primary endpoint of this study was the occurrence of motor complications but evaluations of PD symptoms severity were also performed. These included the New York University Parkinson's Disease Scale, the North Western University Disability Scale, a global assessment by the patient, each on a quarterly basis. In addition UPDRS scores and Hoehn and Yahr stages as well as Schwab and England activities of daily living scores were obtained annually. NYUPDS scores were significantly improved over each year of follow-up but progressed towards baseline by year 5 (shown as a bar graph, but no numerical values given in the text). No differences between the two treatment groups were identified in any of the efficacy assessments. The only exception relates to UPDRS ADL scores, which were significantly more reduced over baseline in the slow-release compared to the immediate-release arm. However, the actual numerical differences between mean ADL scores and the groups were small (less than one point) at all times. Doses after 5 years were 426 mg/d in the immediate release group and 728 mg/d in the controlled release group. Numbers of doses averaged 4.3 tablets per day at year 5 in the immediate release group compared to 3.6 in the controlled release group. Approximately 30% of patients in each group were maintained on the initial twice a day dosing regimen throughout the study.

The overall incidence of withdrawals due to adverse events was 11% for the immediate release and 8% for the CR group. Nausea was seen in 29% of patients altogether and the incidence of withdrawal due to nausea was significantly higher in the immediate release group compared to the CR group (7 patients versus none). Otherwise adverse events occurred with similar frequency in both arms including dizziness, orthostatic effects, hallucinations, and dyskinesias. This study had an overall quality score of 80%.

In addition to these two large monotherapy trials in de novo patients Goetz and colleagues[48] have compared symptomatic efficacy of CR vs. standard levodopa in a small randomized double-blind crossover study involving 20 patients with more advanced PD (mean duration of PD 9.8 years) but without motor fluctuations. Patients had been on levodopa for a mean of 8.2 years and some were receiving concomitant antiparkinsonian medication (amantadine in 9 cases, anticholinergics in 5, and bromocriptine in 2).

Levodopa was given in four divided doses during the standard-formulation phase and two divided doses on the morning and afternoon in the CR phase while the noon and evening doses were replaced by matching placebo. Crossover periods had a 6 weeks duration, assessments using a modified New York University Parkinson's Disease Scale (NYUPDS), the Northwestern University Disability Scale (NUDS) and the Hoehn and Yahr stage were performed every two weeks and scores of the last visit of each phase were used for final analysis. There were no significant differences in either mean daily levodopa dose (600 mg for standard vs. 650 mg for CR levodopa) or any of the PD symptom severity measures (NYUPDS scores 5.4 vs. 5.6 / NUDS 7.5 vs. 7.7 / Hoehn and Yahr stage 2.5 vs. 2.4, each for standard vs. CR formulation).

PREVENTION OF MOTOR COMPLICATIONS

Dupont and colleagues (1996[38]) in their randomized controlled comparative trial of standard Madopar versus Madopar HBS in previously untreated patients with idiopathic PD assessed the relative numbers of patients developing motor fluctuations and Levodopa-induced dyskinesias by year 5 using UPDRS subsection IV ratings. In their trial open label Bromocriptine could be added in order to control motor fluctuations if clinically necessary. This was eventually the case in 28.6% of patients receiving standard Madopar and 34.3% of those on Madopar HBS and the mean daily dose of Bromocriptine averaged 11.3 mg. There was no statistically significant difference in percentages of patients developing fluctuations either of the wearing-off or on-off type (59% with Madopar standard versus 57% with Madopar HBS). The number of patients still in the trial by year 5 was relatively low (29 in the Madopar standard arm versus 35 in the Madopar HBS arm). Twelve patients in each arm had developed Levodopa-induced dyskinesias by the end of the trial corresponding to 41% of standard Levodopa patients versus 34% of slow release Levodopa patients.

This trial, therefore, provided no evidence that initial treatment with sustained release Levodopa might influence the occurrence of Levodopa related motor complications over 5 years of treatment. The quality score of this trial is 71%.

In the 5-year comparative trial of sustained release versus immediate release Sinemet reported by Block and colleagues[33] and later by Koller and colleagues[34], the primary endpoint was the occurrence of motor fluctuations. The onset of motor fluctuations was defined either by a diary or investigator questionnaire criterion. For the diary criterion patients had to complete a total of eight 24-hour diary recordings over one month following each quarterly visit. They were defined as having reached the endpoint when the diary sums at two consecutive visits revealed either more than 20% of the waking day as spent in the "off" or more than 10% of the waking day spent in "on" with dyskinesia. The earlier of those two consecutive visits was defined as the onset of motor fluctuations. Similarly patients were defined as having reached the endpoint at the earlier of two consecutive visits where the motor fluctuation questionnaire scored positive on 50% or more of the 10 questions (see section "Standard Levodopa").

Using these definitions there were no significant differences between the two treatment groups for the occurrence of motor fluctuations either by diary or by questionnaire data. After 5 years 20.6% of the immediate release group versus 21.8% of the slow-release group had fluctuations or dyskinesias by the diary criterion. Only 16% of each group had developed motor fluctuations by the questionnaire definition. This study has a quality score of 80%.

CONTROL OF MOTOR COMPLICATIONS

Ten randomized controlled trials using Levodopa slow-release preparations to control motor fluctuations in advanced PD were identified. Nine trials were comparative studies of standard Sinemet versus Sinemet CR, one trial compared Madopar slow-release versus standard Madopar specifically in the treatment of nocturnal and early morning disabilities.

Controlled-release carbidopa/Levodopa versus standard carbidopa/Levodopa

Sage and Mark (1988[39]) included 25 patients with fluctuating PD following chronic standard carbidopa/Levodopa therapy in a double-blind crossover study comparing carbidopa/Levodopa CR (50 mg/200 mg) with standard carbidopa/Levodopa (25 mg/100 mg). Patients were suffering from motor fluctuations for 5 years on average, had at least four standard carbidopa/Levodopa doses per day and wearing-off type fluctuations. In addition 20 patients experienced random on/off oscillations, 18 also had Levodopa-induced dyskinesias. Prior treatment with dopamine agonists had to be discontinued at least two weeks prior to study entry. The trial period was 24 weeks: an initial 8 week open label dose finding phase was followed by a 16-week double-blind crossover period. During the first four weeks of the open label phase patients were retitrated to an "optimal" dose schedule of standard carbidopa/Levodopa and were then switched to carbidopa/Levodopa CR in an open label fashion which was again titrated to an optimal response schedule over four weeks. The double-blind period was divided into two 8-week crossover sections during which patients either took their pre-determined "optimal" carbidopa/Levodopa CR dose plus placebo or optimal standard carbidopa/Levodopa dose plus placebo in random order. Further dose adjustments during the double-blind period were allowed as clinically necessary. Clinical assessments were made at weeks 1, 2, 4, 6, and 8 of each crossover period using the UPDRS, Hoehn and Yahr staging, Schwab and England Scales for both the on and off condition. In addition, patients were asked to record 24-hour self-scoring diaries twice a week – presumably preceding study visits. At the end of each crossover period patients underwent a 6-hour continuous observation of motor effects and dyskinesias.

The report does not detail the actual numerical outcomes of the various assessments but rather numbers of patients showing "improvement" in those parameters. With this type of evaluation significantly more patients had increased hours "on" without dyskinesias when on carbidopa/Levodopa CR compared to the standard carbidopa/Levodopa period (58% versus 29%). Duration of dyskinesias, on the other hand, was less in 25% of patients during the standard Levodopa phase compared to the CR period. Seventy-nine percent of patients took fewer doses per day in the CR period compared to 4% in the standard carbidopa/Levodopa period corresponding to means of 5.3/d versus 7.8/d. Mean total Levodopa dose was 1544 mg/d in the CR period compared to 1303 mg/d in the standard carbidopa/Levodopa period.

This study seems to indicate improvement of motor fluctuations with carbidopa/Levodopa CR compared to standard carbidopa/Levodopa but statistical analysis of numerical on- or off-time values are not reported. This study had an overall quality score of 60%.

Ahlskog and colleagues (1988[40]) included 23 patients with fluctuating PD into a similar trial with an identical 8-week, double-blind, double-dummy randomized trial preceded by two 4-week open label dose titration phases for each LD-preparation. Comparisons were made between assessments at final visits of each double-blind period including UPDRS scores on and off, Schwab and England scores, diary data from the last two weeks of each double-blind period, dosing frequency and total daily dose, as well as patient ratings of overall response and investigator ratings of improvement or worsening on a 7 point scale.

Mean number of doses at the end of each double-blind period was significantly lower in the slow-release versus standard Levodopa group (7.0 versus 9.8) and daily Levodopa dose was significantly greater in the slow release versus standard Levodopa period (2000 mg/d versus 1800 mg/d). Diary recordings of off-time showed a trend towards lesser hours "off" in the slow-release phase over standard Levodopa (3.2 versus 3.7) but this was not statistically significant. Likewise there were no significant differences in Schwab and England scores during either period or in physician's ratings of efficacy. Subjective ratings of the severity of clinical fluctuations by patients did not show significant differences in rating scores for either period, however, more patients rated their fluctuations as improved in the CR period over the standard carbidopa/Levodopa phase. Patient ratings of the duration of dyskinesias and dyskinesia-related disability were not significantly different between the slow release versus standard Levodopa periods. Numbers of hours "on" with dyskinesias recorded in the diary cards also did not differ between the two crossover periods. More patients developed confusion or hallucinations and dyskinesias or dystonia during the combined open label and double-blind controlled release Levodopa periods. One patient each dropped out of the study while receiving slow-release carbidopa/Levodopa because of an erratic antiparkinsonian response, increased dyskinesia or confusion. This study had an overall quality score of 65%.

Feldman and colleagues (1989[41]) included 41 patients with idiopathic PD into a double-blind crossover study comparing standard and CR carbidopa/Levodopa during two 6-week double-blind periods. The average duration of PD was 7 years and 40% had wearing-off motor fluctuations. Efficacy regarding wearing-off oscillations was assessed by subjective patient ratings on a 5 point scale from one ("extremely helpful" to "worse than no medication at all"). In addition, patients preference for medication was also evaluated. At the end of the study there were no significant differences between mean scores of patient ratings for efficacy concerning wearing-off phenomena (3.3 on standard Levodopa versus 3.0 on CR Levodopa) or in medication preference by the patients.

Efficacy ratings on the NYUPDS and NUDS Rating Scales were also similar between the two periods. Levodopa total doses were higher in the CR periods than with standard Levodopa (590 mg versus 493 mg).

The report does not mention dyskinesias as an adverse event and it is stated that there was no difference in the overall number of side-effects between the two crossover periods. This study had an overall quality score of 67%.

Hutton and colleagues (1989[42]) reported a multicentre study of carbidopa/Levodopa CR versus standard carbidopa/Levodopa in fluctuating PD including 202 patients with motor fluctuations of an average duration of more than three years. Concomitant treatment with amantadine, MAOB-inhibitors or dopamine agonists was discontinued at least two weeks prior to the study.

The trial design of this 24-week crossover study was identical

to the one used by Sage and Mark (1988[39]) or Ahlskog and colleagues (1988[40], see above). Motor fluctuations were assessed by self-scoring diaries and in addition UPDRS total scores were obtained at the end of weeks 2, 4, 6, and 8 of each double-blind period. Patients were asked to rate their global improvement with respect to clinical fluctuations at the end of each double-blind period. Total daily doses and dosing frequency were also recorded.

There were a total of 44 withdrawals, 35 during the dose titration period, most often due to insufficient therapeutic response (11 in the carbidopa/Levodopa standard titration period and 8 in the CR dose titration period).

Analysis of diary data showed a trend for lower average percentages in time "off" when patients were receiving carbidopa/Levodopa CR over standard Levodopa. Although this difference was numerically small and in the range between 3% and 4% less "off" time it was statistically significant at weeks 4 and 6 in analyses of variance. The reduction in "off" time with slow-release treatment over standard Levodopa treatment was in the order of 30 to 40 minutes per day and the relative percentage decrease was 10%. Analysis of item 38 of the UPDRS also yielded a significant difference in duration of daily "off" in favor of carbidopa/Levodopa CR.

There was a median 33% decrease in the average frequency of daily dosing between standard carbidopa/Levodopa (mean 6.8 doses/day) and carbidopa/Levodopa CR (mean 4.5 doses/day). Daily Levodopa intake increased from a mean of 975 mg/d to 1238 mg/d comparing standard carbidopa/Levodopa to carbidopa/Levodopa CR.

During double-blind treatment 15% of patients on standard carbidopa/Levodopa versus 20% on carbidopa/Levodopa CR had adverse events. Frequencies of the most common adverse events were similar during standard carbidopa/Levodopa and carbidopa/Levodopa CR double-blind periods: dyskinesias (6 versus 9%), hallucinations (4 versus 5%), nausea (3 versus 2%), vomiting (3 versus 1%), and confusion (1 versus 3%). This study had an overall quality score of 75%.

Jankovic and colleagues (1989[45]) included 20 patients with wearing-off fluctuations into a double-blind comparative crossover trial of carbidopa/Levodopa CR versus standard carbidopa/Levodopa using the same 24-week trial design as described above (two open label dose finding periods of 4-week to 8-week double-blind crossover phases). Efficacy was assessed through Schwab and England ADL scores "on" and "off", UPDRS scores "on" and "off" (presumably part III, but this is not specified in the report), as well as diary data (two 24-hour periods per double-blind trial week). Daily number of doses as well as total daily dose were also recorded.

Eighteen patients elected to enter an open label follow-up protocol with carbidopa/Levodopa CR treatment for a total of 12 months. At the end of the double-blind study "on"-time without dyskinesias had actually significantly decreased in the slow-release Levodopa phase compared to standard carbidopa/Levodopa and there was a non significant trend for increased hours "off". "On"-time with dyskinesias, however, was not different between the two double-blind periods. Daily Levodopa dose had increased from a mean of 685 mg/d to 815 mg/d comparing standard versus slow-release periods. Daily number of doses was significantly lower with carbidopa/Levodopa CR (5.7 versus 3.8). There were no significant differences in UPDRS motor scores "on" or "off" or Schwab and England ADL scores "on" and "off" between the two double-blind phases.

In the open-label extension phase of 18 patients treated with carbidopa/Levodopa CR on-time with dyskinesias significantly increased compared to the end of the double blind period on standard sinemet, but total "on"-time or "off"-time were not significantly different. The increase in total Levodopa daily dose and decrease in dosing frequency persisted throughout the open label follow-up on slow-release Levodopa.

Contrary to what is concluded in the report this study fails to show beneficial effect of sinemet CR in reducing wearing-off motor-fluctuations but rather indicates increases in Levodopa-induced dyskinesias compared to standard Sinemet. This study had an overall quality score of 70%.

Lieberman and colleagues (1990[46]) reported results of a randomized double-blind crossover study of controlled release versus standard Sinemet in 24 patients with wearing-off oscillations again using the same 24 weeks trial design described above. Assessments again included UPDRS ratings "on" and "off" for parts II and III as well as part IV. In addition patients kept 24 hour "on/off" diaries for two days per double-blind trial week and patient and physician global assessments were obtained at each visit.

During slow-release phases of the double-blind study patients needed higher total Levodopa doses and took significantly fewer doses per day (5.0 versus 6.2). There were no significant differences between the mean scores in any of the UPDRS ratings or the number of hours "on" or "off" recorded in the diaries. However, it is stated in the report that the number of patients whose dyskinesia and fluctuation scores on UPDRS part IV improved was significantly greater during the Sinemet CR phase than the standard phase of the double-blind crossover trial. The same was true for numbers of patients showing improvements in hours on or off as assessed by home-diaries.

Of 35 patients entering the open part of the study 9 dropped out during open label titration of standard Sinemet (4 because of increased dyskinesias, 5 because of increased parkinsonism) and two more dropped out during open label Sinemet CR titration because of insufficient motor effect.

Wolters and colleagues (1992[47]) entered 84 patients with fluctuating PD into a Dutch multicenter trial of Sinemet CR versus standard Sinemet. After an open-label 8 week dose finding period (weeks 1 - 4 on standard Sinemet and weeks 5 – 8 on Sinemet CR) patients entered a parallel group double-blind, double dummy period of 24 weeks. Assessments included NYUPDS and NUDS scores as well as "on/off" diaries. Unfortunately, the report does not include statistical comparisons between the two arms in the double-blind period but rather compares data obtained at week 32 to assessments at week 8, i.e. the end of the open-label titration period for both arms. Therefore, this report does not contain Level-I data on the comparative efficacy of slow-release versus standard Levodopa on motor fluctuations in PD.

Wolters and Tesselaar (1996[49]) report results of a Dutch-British multicenter trial of sinemet CR versus standard Sinemet in 170 patients with fluctuating PD. The design is identical to that reported by Wolters et al.[47] "On"-time as assessed by self-scoring diaries averaged 68% of the waking day at the end of the open-label Sinemet standard titration period at week 4 and this did not significantly change after 24 weeks of double-blind treatment with standard Sinemet (64% at week 24). In the Sinemet CR group the mean proportion of "on-time" increased significantly to 73% at week 4 and 74% at week 8 but went back to 69% by the end of the study. Direct comparisons between the two treatment arms revealed

statistically significantly increased "on-times" in favor of Sinemet CR only at week 4. The mean daily number of "off"-periods was significantly less in the slow release arm over the entire double-blind period, however, percentages of daily "off"-time or hours off are not reported. There was also a significantly greater decline in NYUPDS scores in the slow-release versus standard arm during the double-blind treatment period. While the patient's global evaluation between treatment groups favored Sinemet CR both at weeks 12 and 24 physicians global evaluation was not significantly different between the two arms at any time. The mean number of doses per day during the double-blind period was 5.1 for carbidopa/Levodopa standard and 4.9 for carbidopa/Levodopa CR.

A total of 18 patients of this trial withdrew because of clinical adverse events, 15 of these withdrew during Sinemet CR treatment (10 during open label titration, 5 in the double blind treatment period). Adverse events leading to withdrawal are not detailed in the report but it is stated that these were "mainly" related to dyskinesia, dystonia, hallucinations, nausea, and vomiting. This study had an overall quality score of 63%.

Controlled-Release Benserazide/Levodopa vs. Standard Benserazide/Levodopa

The UK Madopar CR Study Group (1989[50]) performed a double-blind crossover study of bedtime doses of either standard or controlled-release Madopar in 103 patients with PD and a variety of nocturnal and early morning motor disabilities. While only 42 of 103 patients experienced daytime motor fluctuations all had various combinations of difficulties turning in bed or getting out of bed, nocturnal / early morning pain and cramping or foot spasms and about one third additionally complained of sleep problems. Patients were randomized to receive either 125 mg of standard or slow-release Madopar immediately before going to bed in addition to an otherwise unchanged antiparkinsonian regimen. Weekly dose titration was allowed up to a maximum of four times 125 mg of either preparation and the individual optimum dose was maintained for a two-week observation period after which subjects were crossed over to the alternative preparation starting at 125 mg and following the same titration and maintenance schedule.

Assessments were based on patient's diaries and patient and investigator assessment scores of nocturnal motor disabilities, time of onset of clinical benefit from the first morning dose, hours of sleep, and overall condition and mobility.

Eighty-two patients completed the study; mean optimum dosages were similar between the two treatments (2.4 capsule CR versus 2.2 capsule standard). Nocturnal or early morning disability scores did not differ between the two optimum treatment periods. There was no difference in the percentages of patients reporting improvement after Madopar CR or standard Madopar (61% versus 59%); patients wishing to continue each treatment were also similar (64% on Madopar CR and 55% on standard Madopar). In the overall investigator assessment Madopar CR was more frequently preferred over standard Madopar. Withdrawal rates due to lack of effect or adverse events (14 cases in total) were similar between the two treatments. Overall the results of this study seem to show equivalent efficacy of standard and slow-release Madopar in improving nocturnal and early morning disabilities but assessments were largely based on subjective criteria. This study had an overall quality score of 68%.

REVIEW OF SAFETY

Slow-release Levodopa preparations have a very similar safety profile compared to standard Levodopa. A number of reports have found increased rates of dopaminergic side-effects during slow-release treatment periods in crossover trials or in slow-release Levodopa arms of parallel group comparisons relating to dyskinesias and confusion and hallucinosis. However, this was usually associated with increases in total daily dose compared to standard Levodopa. The pharmacokinetic profile of slow-release preparations may also induce prolonged periods of biphasic dyskinesias due to slower rises and falls of Levodopa plasma concentrations and increases in dyskinesia's severity have been related to overlap phenomena following delayed gastric emptying of Madopar HBS.[51]

CONCLUSIONS

EFFICACY

PREVENTION OF DISEASE PROGRESSION

There is INSUFFICIENT EVIDENCE to conclude on the effects of slow-release levodopa on the progression of Parkinson's disease.

SYMPTOMATIC CONTROL OF PARKINSONISM

There are no placebo-controlled trials assessing the symptomatic efficacy of slow-release Levodopa preparations in PD. Based on two good quality Level-I comparative trials showing equivalent efficacy between slow-release and standard formulation of Levodopa, there is sufficient evidence to conclude that slow-release Levodopa is EQUALLY EFFICACIOUS as standard Levodopa in improving motor symptoms.

PREVENTION OF MOTOR COMPLICATIONS

Based on two Level-I studies available slow-release Levodopa preparations are NOT EFFICACIOUS in reducing the incidence of motor fluctuations and/or Levodopa-induced dyskinesias.

CONTROL OF MOTOR COMPLICATIONS

All studies addressing the control motor fluctuations have compared controlled-release to standard Levodopa therapy and do not include a placebo-arm. Results of multiple Level-I active comparator trials are conflicting and overall data provide INSUFFICIENT EVIDENCE to conclude on the efficacy of slow-release Levodopa in controlling response oscillations in fluctuating PD. Even in studies reporting positive results improvements are generally of transient duration (less than 6 months) and the effect size is small (less than one hour increase in on-time compared to standard Levodopa).

SAFETY

Treatment with Levodopa slow-release preparations is safe without specialized monitoring. Due to higher dosing requirements, slow-release Levodopa treatment may increase preexisting dopaminergic side-effects in particular dyskinesias and hallucinosis.

IMPLICATIONS FOR CLINICAL PRACTICE

Monotherapy with Levodopa slow-release preparations is CLINICALLY USEFUL and induces symptomatic benefit of the same magnitude as standard Levodopa. Dose infrequency is less than with standard Levodopa and up to one third of patients may gain sufficient control from twice daily regimens over up to five years.

Initial monotherapy with Levodopa slow-release preparations is considered NOT CLINICALLY USEFUL in preventing the development of Levodopa-induced dyskinesias and/or motor fluctuations.

Although efficacy results from controlled clinical trials are largely negative or inconsistent small benefits in total daily on-time can be obtained when switching patients with wearing-off fluctuations from standard to slow-release Levodopa. Such effects are usually in the order of less than one hour gained per day and transient. Slow-release Levodopa treatment is thus considered POSSIBLY USEFUL in this clinical situation, particularly when combined regimens of standard plus slow-release Levodopa are used. Delayed-"on" phenomena following single morning doses of slow-release Levodopa usually require combinations of the two pharmacokinetic principles.

Single bedtime doses of slow-release Levodopa are also clinically useful in improving nocturnal and early morning disability of patients with PD but it appears doubtful if this is really more effective than adding bedtime doses of standard Levodopa in the same situation.

IMPLICATIONS FOR CLINICAL RESEARCH

· Combined treatment of slow-release Levodopa with other strategies modifying Levodopa pharmacokinetics deserve study both with respect to prevention and control of motor complications. This includes studies of combined treatment with slow-release Levodopa plus MAOB-inhibitors or slow-release Levodopa plus COMT-inhibitors compared to standard Levodopa.

· It is also unclear if add-on treatment with slow-release Levodopa following initial agonist monotherapy might be associated with lesser long-term risks for dyskinesias compared to add-on of standard Levodopa.

ALTERNATIVE PHARMACOKINETIC FORMULATIONS AND DELIVERY ROUTES OF LEVODOPA

Although the exact mechanisms underlying the development of Levodopa related motor complications are incompletely understood the pharmacokinetics of Levodopa and its gastrointestinal absorption mechanisms are important contributing factors to erratic absorption of Levodopa and fluctuating plasma levels. While Levodopa slow-release preparations and add-on treatment with COMT inhibitors are aimed at increasing half-life and bioavailability of Levodopa a number of strategies have been used to improve gastrointestinal absorption of Levodopa. These modifications are aiming at improvement of delayed "on" or "no on" phenomena due to absorption failure as well as at providing more constant gastrointestinal delivery. Such formulations and delivery routes include dispersible Levodopa preparations or Levodopa prodrugs with high water solubility like Levodopa-methyl-ester and Levodopa-ethyl-ester[52-56], all aimed at achieving faster peak plasma levels after oral ingestion as well as dual release formulations of Levodopa designed to overcome the delay in C_{max} of sustained released preparations.[57]

Enteral infusions of Levodopa bypass the stomach and thus avoid gastric emptying as a factor for delayed and erratic Levodopa absorption. Using infusion pumps they also provide a means of constant Levodopa delivery with similar plasma level profiles to i.v. Levodopa infusions.[58]

REVIEW OF CLINICAL STUDIES

No Level-I trials assessing the effects of any of these new delivery routes or formulations of Levodopa on any of the indications analyzed in this review have been identified. However, there were three randomized clinical-pharmacokinetic studies assessing plasma Levodopa levels and motor response on individual test days.

Verhagen-Metman et al. (1994)[59] studied plasma levels and motor responses in five patients with fluctuating PD comparing liquid Levodopa/carbidopa with Levodopa/carbidopa tablets on two randomly selected days in a double-blind protocol and failed to detect significant differences regarding plasma Levodopa level oscillations and motor response fluctuations.

Kurth et al. (1993)[60] compared duodenal infusions of Levodopa/carbidopa versus standard oral dosing by exposing 10 patients with motor fluctuations to either regimen over two days in random sequence. Plasma levels were markedly more constant with duodenal infusions and functional "on" hours were also statistically significantly increased on the infusion days.

Several open-label observations in small numbers of patients including one report with a 10-year follow-up suggest sustained clinical benefit from enteral Levodopa infusions in PD patients with motor fluctuations and some reports also report improvements in preexisting Levodopa-induced dyskinesias (see Syed et al. 1998[61]).

Contin et al. (1999)[62] studied pharmacokinetics and time to onset of the clinical response as assessed by a finger tapping test in a randomized cross-over single dose study comparing standard versus dispersible levodopa/benserazide in 8 patients. Time to peak plasma levels (t_{max}) was significantly shorter after ingestion of the dispersible versus the standard formulation (median of 37 min. vs. 82 min., $p < 0.02$). Clinical response parameters, however, were not different, except for a trend of shorter latencies to onset of a motor response, which failed to reach statistical significance, after the dispersible dose.

Descombes and colleagues (2001)[63] recently reported results of a randomized, double-blind single dose study comparing 200 mg of levodopa plus 50 mg of benserazide given either as a slow-release or novel dual-release preparation consisting of a three layer tablet combining immediate - and slow-release properties. Sixteen patients with idiopathic Parkinson's disease and motor fluctuations were studied regarding time to switch "on", duration of "on", degree of UPDRS improvement and dyskinesia severity. In addition, pharmacokinetic parameters were compared. The dual-release formulation resulted in significantly shorter times to switch "on" (43 vs. 81 minutes, $p = 0.0009$) compared to the slow-release formulation and there was a trend to longer "on" duration (114 vs. 80 minutes, $p = 0.07$). UPDRS improvement and dyskinesias scores were similar following either preparation and C_{max} and AUC were significantly greater with the dual-release tablet and t_{max} was significantly shorter. There were no differences in tolerability.

Presently two large double-blind randomized controlled trials assessing the efficacy of Levodopa ethylester in improving "time-to-on" after oral ingestion and in reducing total daily "on" time compared to standard Levodopa have been initiated.

CONCLUSIONS

EFFICACY AND SAFETY

There is INSUFFICIENT EVIDENCE to conclude on efficacy

or safety of dual-release preparations of Levodopa, Levodopa-ethyl-ester or enteral infusions of Levodopa in any of the indication addressed in this review.

IMPLICATIONS FOR CLINICAL PRACTICE

The use of dispersible tablets of levodopa/benserazide is considered a POSSIBLY USEFUL pragmatic approach for patients experiencing delayed on phenomena in response to standard levodopa preparations. This may eventually apply even more to levodopa-ethylester should this drug become available on the basis of positive outcomes of ongoing Level-I trials.

Although enteral infusions of levodopa have been shown to produce relatively constant plasma levels and reduce motor fluctuations the clinical usefulness of this approach is severely limited by aspects of the practicability, particularly in the long-term.

Dual-release preparations are of interest but their use is considered INVESTIGATIONAL.

IMPLICATIONS FOR CLINICAL RESEARCH

Modifying the pharmacokinetics of levodopa preparations to achieve faster t_{max}, more reliable absorption into the systemic circulation and sustained blood levels is an area of pharmacological research with potentially great clinical impact for long-term efficacy of levodopa treatment. Combinations of levodopa preparations with fast absorption and extended release (dual release systems) must be tested in clinical trials against standard levodopa preparations. There is also a need for the development of constant enteral infusion systems with improved practicability as well as a need to study those in controlled long-term clinical trials regarding their potential to smooth out motor fluctuations and reverse preexisting dyskinesias.

REFERENCES

1. Ehringer H, Hornykiewicz O. Verteilung von Noradrenalin und Dopamin (3-Hydroxatyramin) im Gehirn des Menschen und ihr Verhalten bei Erkrankungen des extrapyramidalen Systems. Klin Wochenschr 1960;38:1236-1239.
2. Hornykiewicz O. Imbalance of brain monoamines and clinical disorders. Prog Brain Res 1982;55:419-429.
3. Birkmayer W, Hornykiewicz O. Der L-3,4-Dioxyphenylalanin (=DOPA)-Effekt bei der Parkinson-Akinese. Wien Klin Wochenschr 1961;73:787-788.
4. Cotzias GC, Papavasiliou PS, Gellene R. Modification of parkinsonism – chronic treatment with L-dopa. New Engl J Med 1969;280:337-345.
5. Wade LA, Mearrick PT, Morris J. Active transport of levodopa in the intestine. Nature 1973;242:463-465.
6. Hefti F, Melamed E, Wurtman RJ. The site of dopamine formation in rat striatum after L-dopa administration. J Pharmacol Exp Ther 1981;217:189-197.
7. Spencer SE, Wooten GF. Altered pharmacokinetics of L-dopa metabolism in rat striatum deprived of dopaminergic innervation. Neurology 1984;34:1105-1108.
8. Chase TN. Levodopa therapy: consequences of the nonphysiologic replacement of dopamine. Neurology 1998;50(suppl 5):S17-S25.
9. Nutt JG, Fellman JH. Pharmacokinetics of levodopa. Clin Neuropharmacol 1984;7:35-49.
10. Cedarbaum JM, Kutt H, Dhar AK, Watkins S, McDowell FH. Effect of supplemental carbidopa on bioavailability of l-dopa. Clin Neuropharmacol 1986;9:153-159.
11. Nelson MV, Berchou RC, LeWitt PA, et al. Pharmacokinetic and pharmacodynamic modeling of levodopa plasma concentrations, and clinical effects in Parkinson's disease after Sinemet. Clin Neuropharmacol 1989;12:91-97.
12. Nutt JG, Woodward WR, Anderson JL. Effect of carbidopa on pharmacokinetics of intravenously administered levodopa: implications for mechanism of action of carbidopa in the treatment of parkinsonism. Ann Neurol 1985;13:537-544.
13. Fahn S. Parkinson disease, the effect of levodopa, and the ELLDOPA trial. Arch Neurol 1999;56:529-535.
14. Olanow CW, Hauser A, Gauger L, Malapira T, et al. The effect of deprenyl and levodopa on the progression of Parkinson's disease. Ann Neurol 1995;38:771-777.
15. Parkinson Study Group. Pramipexole vs. Levodopa as initial treatment for Parkinson's disease. JAMA 2000;284:1931-1938.
16. Libman I, Gawel MJ, Riopelle RJ et al. A comparison of bromocriptine (Parlodel) and levodopa-carbidopa (Sinemet) for treatment of "de novo" Parkinson's disease patients. Can J Neurol Sci 1987;14(suppl):455-459.
17. Riopelle RJ. Bromocriptine and the clinical spectrum of Parkinson's disease. Can J Neurol Sci. 1987;14(3 suppl):455-459.
18. Cooper JA, Sagar HJ, Doherty SM, Jordan N, et al. Different effects of dopaminergic and anticholinergic therapies on cognitive and motor fluctuation in Parkinson's disease. A follow-up study of untreated patients. Brain 1992;115:1701-1725.
19. Parkinson's Disease Research Group in the United Kingdom. Comparisons of therapeutic effects of levodopa, levodopa and selegiline, and bromocriptine in patients with mild, early Parkinson's disease: three year interim report. Br Med J 1993;307:469-472.
20. Montastruc JL, Rascol O, Senard J, Rascol A. A randomized controlled study comparing bromocriptine to which levodopa was later added, with levodopa alone in previously untreated patients with Parkinson's disease: a five year follow up. J Neurol Neurosurg Psychiatry 1994;57:1034-1038.
21. Herskovits E, Yorio A, Leston J. Long term bromocriptine treatment in de novo parkinsonian patients. Medicina 1988;48:345-350.
22. Hely MA, Morris JG, Reid WG, et al. The Sydney Multicentre Study of Parkinson's disease: a randomized, prospective five year study comparing low dose bromocriptine with low dose levodopa-carbidopa. J Neurol Neurosurg Psychiatry 1994;57:803-910.
23. Rinne UK. Lisuride, a dopamine agonist, in the treatment of early Parkinson's disease. Neurology 1989;39:336-339.
24. Kulisevsky J, Lopez-Villegas D, Garcia-Sanchez C, Barbanoj M, et al. A six-month study of pergolide and levodopa in de novo Parkinson's disease patients. Clin Neuropharmacol 1998;21:358-362.
25. Oertel WH. Pergolide versus L-Dopa (PELMOPET). Mov Disord 2000;15(suppl 3):4.
26. Rascol O, Brooks DJ, Brunt ER et al. Ropinirole in the treatment of early Parkinson's disease: a 6-month interim report of a 5-year levodopa-controlled study. Mov Disord 1998;13:39-45.
27. Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, et al. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levdodopa. N Engl J Med 2000;342:1484-1491.
28. Rinne UK, Bracco F, Chouza C et al. Cabergoline in the treatment of early Parkinson's disease: results of the first year of treatment in a double-blind comparison of cabergoline and levodopa. Neurology 1997;48:363-368.
29. Rinne UK, Bracco F, Chouza C et al. Early treatment of Parkinson's disease with cabergoline delays the onset of motor complications. Results of a double-blind levodopa controlled trial. Drugs 1998;55(suppl):23-30.
30. Cox B, Danta G, Schnieden H, Yuill GM. Interactions of L-Dopa and Amantadine in patients with parkinsonism. J Neurol Neurosurg Psychiatry 1973;36:354-361.
31. Przuntek H, Welzel D, Gerlach M, et al. Early institution of bromocriptine in Parkinson's disease inhibits the emergence of levodopa-associated motor side effects. Long-term results of the PRADO study. J Neural Transm Gen Sect 1996;103:699-715.
32. Gimenez-Roldan S, Tolosa E, Burguera JA, et al. Early combination of bromocriptine and levodopa in Parkinson's disease: a prospective randomized study of two parallel grups over a total follow-up period of 44 months including an initial 8-month double blind stage. Clin Neuropharmacol 1997;20:67-76.
33. Block G, Liss C, Scott R, Irr J, Nibbelink D. Comparison of immediate-release and controlled release carbidopa/levodopa in Parkinson's disease. A multicenter 5-year study. Eur Neurol 1997;37:23-27.
34 Koller WC, Hutton JT, Tolosa E, Capildeo R, Carbidopa/Levodopa Study Group. Immediate-release and controlled-release carbidopa/levodopa in PD: a 5-year randomized multicenter study. Neurology 1999;53:1012-1019.
35. Agid Y. Levodopa: is toxicity a myth? Neurology 1998;50:858-863.
36. LeWitt PA. Extending the action of levodopa's effects. In: LeWitt PA, Oertel WH (eds). *Parkinson's Disease: The Treatment Options*. London: Martin Dunitz Publishers, 1999, chap 10, pp. 141-158.
37. Ghika J, Gachoud JP, Gasser U, the L-Dopa Dual-release Study Group. Clinical efficacy and tolerability of a new levodopa-benserazide dual-release formulation in parkinsonian patients. Clin Neuropharmacol 1997;20:130-139.
38. Dupont E, Anderson A, Boqs J, et al. Sustained-release Madopar HBS compared with standard Madopar in the long-term treatment of de novo parkinsonian patients. Acta Neurol Scand 1996;93:14-20.
39. Sage J, Mark M. Comparison of controlled-release Sinemet (CR4) and Standard Sinemet (25 mg/100 mg) in advanced Parkinson's disease: a double-blind, crossover study. Clin Neuropharmacol 1988;11:174-179.
40. Ahlskog JE, Muenter MD, McManis P, Bell GN, Bailey PA. Controlled-release Sinemet (CR-4): a double-blind crossover study in patients with fluctuating Parkinson's disease. Mayo Clin Proc 1988;63:876-886.
41. Feldman RG, Mosbach PA, Kelly MR, Thomas CA, Saint Hilaire MH. Double-blind comparison of standard Sinemet and Sinemet CR in patients with mild-to-moderate Parkinson's disease. Neurology 1989;39:96-101.

42.Hutton JT, Morris JL, Bush DF, Smith ME, Liss CL, Reines S. Multicenter controlled study of Sinemet CR vs Sinemet (25/100) in advanced Parkinson's disease. Neurology 1989;39:67-72.
43.Rajput AH, Uitti RJ, Rajput AH, Offord KP. Timely levodopa (LD) administration prolongs survival in Parkinson's disease. Parkinsonism & Related Disorders 1997;3:159-165.
44.Jenner PG, Brin MF. Levodopa neurotoxicity: experimental studies versus clinical relevance. Neurology 1998;50(suppl 6):S39-S43.
45.Jankovic J, Schwartz K, Vander Linden C. Comparison of Sinemet CR4 and standard Sinemet: Double-blind and long-term open trial in parkinsonian patients with fluctuations. Mov Disord 1989;4:303-309.
46.Lieberman A, Gopinathan G, Miller E, Neophytides A, Baumann G, Chin L. Randomized double-blind cross-over study of Sinemet-Controlled Release (CR4 50/200) versus Sinemet 25/100 in Parkinson's disease. Eur Neurol 1990;30:75-78.
47.Wolters EC, Horstink MW, Roos RA, Jansen EN and the Dutch Sinemet CR Study Group. Clinical efficacy of Sinemet CR 50/200 versus Sinemet 25/100 in patients with fluctuating Parkinson's disease. An open, and a double-blind, double-dummy, multicenter treatment evaluation. Clin Neurol Neurosurg 1992;94:205-211.
48.Goetz CG, Tanner CM, Shannon KM, Carroll VS, Klawans HL, Carvey PM, Gilley D. Controlled-release carbidopa/levodopa (CR4-Sinemet) in Parkinson's disease patients with and without motor fluctuations. Neurology 1988;38:1143-1146.
49.Wolters EC, Tesselaar HJM, International (NL & UK) Sinemet CR Study Group. International (NL-UK) double-blind study of Sinemet CR and standard Sinemet (25/100) in 170 patients with fluctuating Parkinson's disease. J Neurol 1996;243:235-240.
50.UK Madopar CR Study Group. A comparison of Madopar CR and Standard Madopar in the treatment of nocturnal and early-morning disability in Parkinson's disease. Clin Neuropharmacol 1989;12:498-505.
51.Poewe WH, Lees AJ, Stern GM. Low-dose L-dopa therapy in Parkinson's disease: a six-year follow-up study. Neurology 1986;36:1528-1530.
52.Cooper DR, Marrel C. van der Waterbeemd H, et al. L-dopa esters as potential prodrugs: behavioural activity in animal models of Parkinson's disease. J Pharm Pharmacol 1987;39:627-635.
53.Bayer AJ, Day JJ, Finucane P, Pathy MS. Bioavailability and acceptability of a dispersible formulation of levodopa-benserazide in parkinsonian patients with and without dysphagia. J Clin Pharm Ther 1988;13:191-194.
54.Juncos JL, Mouradian MM, Fabbrini G, et al. Levodopa methyl ester treatment of Parkinson's disease. Neurology 1987;37:1242-1245.
55.Ruggieri S, Stocchi F, Carta A, et al. Jejunal delivery of levodopa methyl ester. Lancet 1989;2:45-46.
56.Djaldetti R, Atlas D, Melamed E. Effect of subcutaneous administration of levodopa ethyl ester, a soluble prodrug of levodopa, on dopamine metabolism in rodent striatum: implication for treatment of Parkinson's disease. Clin Neuropharmacol 1996;19:65-71.
57.Dingemanse J, Kleinbloesem CH, Crevoisier C, Lankhaar G, Gasser UE. Pharmacokinetic studies with a dual-release formulation of levodopa, a novel principle in the treatment of Parkinson's disease. Eur Neurol 1998;39:119-124.
58.Nilsson D, Hansson LE, Johansson K, Nystrom C, Paalzow L, Aquilonius SM. Long-term intraduodenal infusion of a water based levodopa-carbidopa dispersion in very advanced Parkinson's disease. Acta Neurol Scand 1998;97:175-183.
59.Verhagen-Metman L, Hoff J, Mouradian MM, Chase TN. Fluctuations in plasma levodopa and motor responses with liquid and tablet levodopa/carbidopa. Mov Disord 1994;9:463-465.
60.Kurth MC, Tetrud JW, Tanner CM, et al. Double-blind, placebo-controlled, crossover study of duodenal infusion of levodopa/carbidopa in Parkinson's disease patients with "on-off" fluctuations. Neurology 1993;43:1698-1703.
61.Syed N, Murphy J, Zimmerman Th (jr.), Mark MH, Sage JI. Ten Years' experience with enteral levodopa infusions for motor fluctuations in Parkinson's disease. Mov Disord 1998;13:336-338.
62.Contin M, Riva R, Martinelli P, Cortelli P, Albani F, Baruzzi A. Concentration-effect relationship of levodopa-benserazide dispersible formulation versus standard form in the treatment of complicated motor response fluctuations in Parkinson's disease. Clin Neuropharmacol 1999;22:351-355.
63.Descombes S, Bonnet AM, Gasser UE, Thalamas C, Dingemanse J, et al. Dual-release formulation, a novel principle in L-dopa treatment of Parkinson's disease. Neurology 2001;56:1239-1242.

BIBLIOGRAPHY - EXCLUDED FROM ANALYSIS (REASON FOR EXCLUSION)

Bayer AJ, Day JJ, Finucane P, Pathy MS. Bioavailability and acceptability of a dispersible formulation of levodopa-benserazide in parkinsonian patients with and without dysphagia. J Clin Pharm Ther 1988;13:191-194. (Pharmacokinetic study, less than 29 pts.)

Bredberg E, Nilsson D, Johansson K, Aquilonius SM, Johnels B, Nyström C, Paalzow L. Intraduodenal infusion of a water-based levodopa dispersion for optimisation of the therapeutic effect in severe Parkinson's disease. Eur J Clin Pharmacol 1993;45:117-122. (Single-dose study, less than 20 pts.)

Cedarbaum JM, Silvestri M, Clark M, et al. Results of long-term treatment with controlled-release levodopa/carbidopa (Sinemet CR). J Neural Transm 1990;2:205-213. (Less than 20 pts. in Level I part of study)

Cedarbaum JM, Silvestri M, Kutt H. Sustained enteral administration of levodopa increases and interrupted infusion decreases levodopa dose requirements. Neurology 1990;40:995-997. (Single case)

Deleu D, Ebinger G, Michotte Y. Clinical and pharmakokinetic comparison of oral and duodenal delivery of levodopa/carbidopa in patients with Parkinson's disease with a fluctuating response to levodopa. Eur J Clin Pharmacol 1991;41:453-458. (Single-dose study in 4 pts.)

Dessibourg CA, Gachoud JP. Benefits of a new galenic form of levodopa and benserazide in the treatment of patients with Parkinson's disease. Schweiz Rundsch Med Prax 1995;84:1235-1238. (Article in German)

Dingemanse J, Kleinbloesem CH, Crevoisier Ch, Lankhaar G, Gasser UE. Pharmacokinetic studies with a dual-release formulation of levodopa, a novel principle in the treatment of Parkinson's disease. Eur Neurol 1998;39:119-124. (Pharmacokinetic study in healthy controls)

Grandas F, Martinez-Martin P, Linazasoro G, on behalf of the STAR Multicenter Study Group. Quality of life in patients with Parkinson's disease who transfer from standard levodopa to Sinemet CR: the STAR study. J Neurol 1998;245:31-33. (Not Level I)

Hutton JT, Albrecht JW, Roman GC, Kopetzky MT. Prolonged serum levodopa levels with controlled-release Carbidopa-Levodopa in the treatment of Parkinson's disease. Arch Neurol 1988;45:55-57. (Study duration less than 4 weeks)

Kleedorfer B, Poewe W. Comparative efficacy of two oral sustained-release preparations of L-dopa in fluctuating Parkinson's disease. Preliminary findings in 20 patients. J Neural Transm 1992;4:173-178. (Less than 20 pts. per treatment arm)

Kurlan R, Rubin AJ, Miller Ch, Rivera-Calimlim L, Clarke A, Shoulson I. Duodenal delivery of levodopa for on-off fluctuations in parkinsonism: preliminary observations. Ann Neurol 1986;20:262-265. (Not Level-I, less than 20 pts.)

Kurlan R, Nutt JG, Woodward WR, et al. Duodenal and gastric delivery of levodopa in parkinsonism. Ann Neurol 1988;23:589-595. (Single-dose protocol, less than 20 pts.)

Kurth MC, Tetrud JW, Tanner CM, et al. Double-blind, placebo-controlled, crossover study of duodenal infusion of levodopa/carbidopa in Parkinson's disease patients with "on-off" fluctuations. Neurology 1993;43:1698-1703. (Less than 20 pts., less than 4 weeks duration)

Linazasoro G, Grandas F, Martinez Martin P, Bravo JL, for the STAR study group. Controlled release levodopa in Parkinson's disease: influence of selection criteria and conversion recommendations in the clinical outcome of 450 patients. Clin Neuropharmacol 1999;22:74-79. (Not Level-I)

MacMahon DG, Sachdev D, Boddie HG, Ellis CJK, Kendal BR, Blackburn NA. A comparison of the effects of controlled-release levodopa (Madopar CR) with conventional levodopa in late Parkinson's disease. J Neurol Neurosurg Psychiatry 1990;53:220-223. (Not Level I)

Pakkenberg H, Birket-Smith E, Dupont E, Hansen E, Mikkelsen B, Presthus J, Rautakorpi I, Riman E, Rinne UK. Parkinson's disease treated with sinemet or madopar. A controlled multicenter trial. Acta Neurol Scandinav 1976;53:376-385. (No comparator)

Rondot P, Ziegler M, Aymard N, Holzer J. Clinical trial of Madopar HBS in parkinsonian patients with fluctuating drug response after long-term levodopa therapy. Eur Neurol 1987;27:114-119. (Not Level-I)

Sage JI, Trooskin S, Sonsalla PK, Heikkila R, Duvoisin RC. Long-term duodenal infusion of levodopa for motor fluctuations in Parkinsonism. Ann Neurol 1988;24:87-89. (Not Level-I, less than 20 pts.)

Sage JI, Schuh L, Heikkila RE, Duvoisin RC. Continuous duodenal infusions of levodopa: plasma concentrations and motor fluctuations in Parkinson's disease. Clin Neuropharmcol 1988;11:36-44. (Not Level-I, less than 20 pts.)

Sage JI, Trooskin S, Sonsalla PK, Heikkila RE. Experience with continuous enteral levodopa infusions in the treatment of 9 patients with advanced Parkinson's disease. Neurology 1989;39:60-63. (Not Level-I, less than 20 pts.)

Stocchi F, Quinn NP, Barbato L, Patsalos PN, O'Connel MTO, Ruggieri S, Marsden CD. Comparison between a fast and a slow release preparation of levodopa and a combination of the two: a clinical and pharmacokinetic study. Clin Neuropharmacol 1994;17:38-44. (Single-dose study, less than 20 pts.)

Verhagen-Metman L, Hoff J, Mouradian MM, Chase TN. Fluctuations in plasma levodopa and motor responses with liquid and tablet levodopa/carbidopa. Mov Disord 1994;9:463-465. (Single-dose study, less than 20 pts.)

Movement Disorders
Vol. 17, Suppl. 4, 2002, p. S38-S44

Published by Wiley-Liss, Inc.
DOI 10.1002/mds.5559

MAO-B Inhibitors for the Treatment of Parkinson's Disease

INTRODUCTION

BACKGROUND

Early attempts to enhance dopaminergic neurotransmission through inhibition of one of dopamine's major metabolizing enzyme - monoamine oxidase (MAO) - were made soon after the discovery of the striatal dopaminergic deficit and the efficacy of L-dopa.[1] However, side-effects ("cheese effect") associated with the non-selective type A plus B MAO inhibitors used in those days prevented further use. The development of selective MAO-B inhibitors through the work of Knoll et al.[2] on Selegiline, however, re-introduced the concept of MAO-inhibition into the therapy of Parkinson's disease.[3]

RATIONALE

MAO-B inhibition blocks the metabolism of dopamine and therefore could enhance both endogenous dopamine and dopamine produced from exogenously administrated Levodopa. Furthermore, MAO-B inhibitors block the conversion of MPTP to its active metabolic MPP^+, which is a selective substantia nigra neurotoxin suggesting that this class of agents could have neuroprotective properties.

METHODS

KEY SEARCH TERMS

Parkinson's disease, selegiline, MAO-B inhibitors, parkinsonism, neuroprotection, motor fluctuations.

SPECIAL EXCEPTIONS TO INCLUSION/ EXCLUSION CRITERIA

This review of reported studies was limited to Level-I evidence provided by one or more well designed, randomized, controlled studies and there were multiple such studies available to draw evidence-based conclusions on the efficacy of this class of agent.

SELEGILINE

BASIC PHARMACOLOGY

MECHANISM OF ACTION

Selegiline causes irreversible inhibition of MAO-B. MAO catalyzes the oxidative deamination of neuroactive amines such as dopamine. The drug is an irreversible or suicide inhibitor forming a covalent bond with the flavin adenine dinucleotide co-factor of MAO. Selegiline is a relatively selective MAO-B inhibitor. However, the MAO-B selectivity is lost at higher doses of the drug.

Selegiline may enhance the activity of catecholaminergic neurons by other mechanisms besides MAO-B inhibition. Other effects reported include[4]:

1. Inhibition of the uptake of catecholamines.
2. Inhibition of presynaptic catecholamine autoreceptors.
3. Stimulation of action potential transmission release coupling.
4. Release of catecholamine by amphetamine metabolites.

Furthermore, selegiline possess other pharmacologic activity that could be important for its putative neuroprotective mechanism of action.[4] These include:

1. An effect on mitochondrial membrane potential activity.
2. An anti-apoptosis effect.
3. Reduction of oxidative stress.
4. A neurotrophic effect.
5. An ability to decrease excitotoxicity.

PHARMACOKINETICS

Selegiline is rapidly absorbed from the gastrointestinal tract.[5] The main metabolites of selegiline are desmethylselegiline, methamphetamine and amphetamine. These compounds are less pharmacologically active L-isomers. Selegiline is metabolized mainly in the liver and disappears rapidly from the serum with a half-life of 0.15 hours. Peak metabolite levels are seen 0.5 to 2.0 hours after an oral dose. The majority of the drug is bound to plasma protein. PET scans show that selegiline binds to brain regions with a high content of MAO-B. Selegiline is an irreversible inhibitor, and therefore, the effect on MAO-B is significantly longer than the drug elimination half-life, and depends on the resynthesis of enzyme protein, and is likely to be longer than one month. The long-lasting affect is a problem for planning the duration of "washout" for studies designed to assess neuroprotection.

REVIEW OF CLINICAL STUDIES

PREVENTION OF DISEASE PROGRESSION

Most of the published studies measured "time to initiate levodopa therapy" as the primary outcome variable. This outcome can be influenced by the symptomatic effect of the drug, therefore making the analysis of the results inconclusive regarding the neuroprotective properties.

Tetrud & Langston (1989)[6]: Tetrud and Langston[4] were the first to study the effect of selegiline (10 mg/day) as putative neuroprotective therapy. They evaluated 54 patients (average age 61.0 years). Forty-four completed the trial for the duration of 36 months. The authors reported that, for the primary outcome, selegiline significantly delayed the need for Levodopa therapy. Analysis of Kaplan-Meier survival curves for each group showed that selegiline delayed the need for Levodopa therapy; the average time until Levodopa needed was 312.1 days for patients in the placebo group and 548.9 days for patients in the selegiline group. Disease progression, as monitored by assessment scales e.g., UPDRS, Hoehn-Yahr, and Schwab and England, was slowed (by 40% to 83% per year) in the selegiline group compared to placebo. The authors suggested the drug may have neuroprotective properties but they did not directly consider potential confounding symptomatic effects of selegiline. Insomnia was the only side

effect that occurred significantly more often with selegiline. This study had an overall quality rating score of 78%.

DATATOP study (1989)[7]: In this study, both selegiline (10 mg/day) and alpha tocopherol, 2000 units, [vitamin E] were studied in 800 untreated patients (average age 61.1 years) with mild disease (2 x 2 factorial study design). The authors found that selegiline significantly delayed the development of disability requiring levodopa therapy, (primary endpoint). Only 97 subjects who received selegiline reached the end point during an average 12-month follow-up, as compared with 176 subjects who did not receive selegiline. The risk of reaching the end point was significantly reduced by 57% for the subjects who received selegiline. The subjects who received selegiline also had a significant reduction in their risk of having to give up full-time employment. However, the improvement in motor scores after initiation of selegiline and the worsening after drug withdrawal suggested that the beneficial effects of selegiline may be related, in part, to a symptomatic amelioration of Parkinson's disease. However, there was a statistically significant reduction in disability as compared to placebo even among selegiline-treated subjects who initially had no improvement in motor scores. This suggests that the results may not be entirely explained by the symptomatic effects of selegiline. Symptomatic deterioration may have been observed in all patients if a "wash-out" period was preformed prior to reaching the end point. Symptomatic deterioration also may have been observed over a longer period of time. Adverse experiences reported included 311 events (136 in those without selegiline, 175 in those with selegiline). One hundred and fourteen events were considered as possible health risks (63 without selegiline, 51 with selegiline), and 11 events were considered to pose definite health risks (6 without selegiline, 5 with selegiline). The adverse effects reported most commonly, regardless of the perceived seriousness, were lightheadedness (32 subjects), trouble falling asleep (28), nausea (23), skin rash (22), headache (21), dry mouth (19), and constipation (16). Neither the rate of occurrence of these adverse experiences nor that of coexisting conditions differed significantly between treatment groups except for dryness of the mouth (5 without selegiline, 14 with selegiline, $p = 0.047$). This study had an overall quality rating score of 95%.

Parkinson Study Group (1996)[8] : An additional study done by the Parkinson Study Group (1996)[8] reported the results of 310 patients that did not reach endpoint. These patients all received selegiline, but the blindness of the original assessment was maintained. If selegiline had a neuroprotective effect, the subjects who had originally received selegiline would have shown superior and sustained benefits after reinitiation of selegiline treatment as compared to subjects not previously treated with selegiline. However, during the extended trial, 108 subjects assigned previously to selegiline reached the endpoint of disability faster than 121 subjects not assigned selegiline. This suggests that initial advantages of selegiline were not sustained. However, firm conclusions from this study are difficult because the selegiline patients had more severe impairment at baseline, there was a 2-month interruption of therapy, and there were variations in interpretations of open label assignments.

Myllyla et al. (1992)[9]: In this Finnish trial, the authors reported long-term effects of selegiline, (10 mg/day) in previously untreated patients with early disease. They followed 47 selegiline-treated patients for 2 years. The median duration of time before initiation of levodopa was 545 ± 90 days with selegiline and 372 ± 28 days with placebo, $p = 0.03$. Disability was significantly less in the selegiline group than in the placebo group for up to 12 months (e.g., CURS, NUDS, WRS). A reduction in the need for long-term levodopa therapy was noted. The authors concluded that the drug may have neuroprotective properties and that it may slow down the rate of progression of Parkinson's disease. However, this study includes the same confounding issues as reviewed in the DATATOP study previously described. The only reported side effect (in selegiline-treated patients) not mentioned by patients in the placebo group was insomnia, of which four patients in the selegiline group complained. Three patients complained of dry mouth and three had nausea in the placebo group. There were no significant changes in blood pressure during the treatment. The heart rates of the patients in the selegiline group were slightly higher than those of the patients in the placebo group, but no clinical symptoms were associated with this adverse reaction. Liver function tests remained normal in both groups. This study had an overall quality rating score of 83%.

Olanow et al. (1995)[10]: Olanow and coworkers[8] used a different study design to address the issue of neuroprotection with selegiline (10 mg/day). This 14-month trial was aimed at minimizing confounding symptomatic effects by including a 2-month "wash-out" of selegiline before assessing the final outcome. One hundred and one patients (average age 66.2 years) were evaluated at baseline (untreated) and again after the final visit following withdrawal of anti-parkinsonian medication. Deterioration of parkinsonian scores (motor UPDRS) between the two visits [baseline and 14 months] were used as the index of disease progression. Selegiline was withdrawn two months prior and levodopa 7-14 prior to the final visit. Placebo-treated patients deteriorated by 5.8 ± 1.4 points on the UPDRS, while selegiline-treated patients changed only 0.4 ± 1.3 points ($p<0.001$). This investigation shows that selegiline prevents deterioration of clinical scores in patients with early Parkinson's disease. The observed effects are more readily explained by a neuroprotective rather than a symptomatic action of the drug. However, in spite of the 2-month "wash-out", this time period still may not have been long enough to eliminate all symptomatic effects of the drug. No clinically significant adverse effects were encountered during the study, and there were no statistically significant differences in the incidence of side effects between any of the treatment groups. This study had an overall quality rating score of 76%.

Palhagen et al. (1995)[11]: In a similar design to the DATATOP clinical trial, Palhagen and colleagues studied 157 patients (average age 63.8 years) over a 12-month period with a two-month "wash-out" prior to the initiation of levodopa therapy. The primary endpoint was "time to disability sufficient to require levodopa therapy". Analysis of Kaplan-Meier survival curves for each group showed that selegiline significantly delayed the need for levodopa therapy. The semiannual rate of disability progression was slowed significantly in the selegiline group as analyzed with the UPDRS (total and motor scores). Selegiline had a "wash-in" effect (i.e., an initial symptomatic amelioration of Parkinson's disease at 6 weeks and 3 months). However, after the 8-week "wash-out" period, no significant differences in the deterioration of disability between the groups was revealed in any of the scales. Similarly, the progression of symptoms from baseline to the end of the "wash-out" period was significantly slower in the selegiline group when the progression was adjusted by the time to reach the endpoint. Selegiline significantly delayed the need to start levodopa in early Parkinson's disease. Additionally, after a 2-month "wash-out" period, there was no significant symptomatic effect of selegiline. The

authors concluded that this data supported the concept of neuroprotective properties of the drug. The most common adverse reactions were gastrointestinal, psychiatric/neurological and urogenital. Mild gastrointestinal adverse reactions (cholecystitis, flatulence, gastrointestinal discomfort, nausea, and diarrhea) occurred significantly more in the selegiline group (12 versus 3). Otherwise there were no significant differences in the type or frequency of the adverse reactions during the study. This study had an overall quality rating score of 76%.

SYMPTOMATIC CONTROL OF PARKINSONISM

MONOTHERAPY

DATATOP study (1989)[7]: In the DATATOP study mentioned above, a small but statistically significant clinical effect was observed with selegiline monotherapy in de novo Parkinson's disease patients at doses of 10 mg/day.[6] At one and three months after treatment ("wash-in"), selegiline was significantly better than placebo in all components of the UPDRS (UPDRS motor scores at one and three months for selegiline were 15.7 and 15.8 compared to 16.8 and 17.5 for placebo). The authors considered these changes not to be clinically relevant. However, statistically significant deterioration was noted upon selegiline withdrawal at one and two months ("wash-out"). (Adverse reactions are discussed above.) This study had an overall quality rating of 95%.

Teravainen (1990)[12]: In a randomized, double-blind, placebo controlled crossover study of 20 de novo Parkinson's disease patients, Teravainen evaluated doses of selegiline 5 to 30 mg/day. Duration of treatment with selegiline was eight weeks and treatment with placebo was four weeks. Subjects were clinically evaluated weekly (UPDRS, CURS). Clinically significant changes were not observed in any patient nor was subjective benefit reported. The mean scores on the 30 mg/day dose were approximately 10% less than placebo (not statistically significant). The study was problematic because of the crossover design where there was no "wash-out" period between treatment phases. One patient reported insomnia and one patient reported headache while treated with selegiline. In the placebo group, one patient reported back pain. This study had an overall quality rating score of 58%.

Myllyla et al. (1992)[9]: The study of Myllyla and colleagues (as described above) reported that 27 Parkinson's disease patients treated with selegiline improved compared to 25 placebo controls. Scores for CURS, WRS and NUDS were significantly lower for selegiline. This effect was observed for up to one year. The sum of scores for tremor, rigidity, and bradyskinesia also were significantly better at one year in the selegiline group compared to placebo. The most pronounced differences were found in rigidity and bradykinesia. However, the mean CURS scores in the selegiline group reached the baseline score after four months. The initial improvement time was about three months. (Adverse reactions are discussed above.) This study had an overall quality rating score of 83%.

Allain et al. (1993)[13]: This study tested selegiline (10 mg/day) for treatment in 93 Parkinson's disease patients (average age 64.9 years) who were from 13 centers in France. Patients were followed for three months and evaluated by the UPDRS, Hoehn-Yahr, Schwab-England, and Hamilton Depression Scale. Selegiline (n=48) was significantly better than placebo (n=47) for the motor UPDRS score and for depression scores. There was no difference between selegiline and placebo in global scores, scores of activities of daily living and Hoehn-Yahr stage. No differences in adverse reactions were reported between selegiline and placebo. This study had an overall quality rating score of 83%.

Mally et al. (1995)[14]: Mally and coworkers evaluated 20 de novo Parkinson's disease patients (Hoehn-Yahr I to III, average age 62.5 years, average disease duration, 2.1 years), in a randomized, placebo controlled, parallel study design. Significant changes were observed in motor behavior and daily activity (UPDRS) after three weeks of treatment with selegiline at 10mg/day. The total scores of the UPDRS and NUDS were significantly changed after four weeks, $p<0.01$. Hypokinesia and walking improved the greatest. Rigidity was not changed. The authors conclude that hypokinesias can be significantly improved with selegiline. No adverse reactions were reported. This study had an overall quality rating score of 55%.

Palhagen et al. (1998)[11] : In this study, the authors randomized 157 de novo Parkinson's disease patients to selegiline or placebo. Selegiline had an "on-off" effect (initial symptomatic improvement) at six weeks and three months. The change in the total UPDRS was -2.0 ± 5.3 and 1.7 ± 5.4 compared to placebo, 0.4 ± 5.0 and 1.0 ± 5.3 ($p<0.01$). Changes on the visual analog scales for motor dysfunction were -3.0 ± 21.3 for selegiline at three months compared to placebo, 6.8 ± 19.6 ($p<0.05$). (Adverse reactions are discussed above.) This study had an overall quality rating score of 85%.

ADJUNCT THERAPY

Five randomized controlled trials were identified where selegiline was given as adjunct to other antiparkinsonian therapies, four studies were in Levodopa -treated patients, one in lisuride-treated patients.

Przuntek & Kuhn (1987)[15]: These authors studied the efficacy of selegiline in 28 patients (21 with Parkinson's disease) in a placebo-controlled, double-blind, six-week trial in patients on Levodopa treatment. Both the Columbia University Rating Scale and the SCHOPPE Motor Performance Series showed improvements when patients on optimum levadopa therapy were additionally given selegiline. During the first withdrawal period the patients experienced a significant deterioration. When selegiline was again added, a significant improvement was seen, which deteriorated again during the second withdrawal period. The worsening of symptoms was, however, not as pronounced as in the first withdrawal period. This may be due to the shorter duration of the second withdrawal period or the possibility of having residual selegiline effects in this withdrawal period. Both the Columbia University Rating Scale and the SCHOPPE Motor Performance Series showed marked improvements, particularly in the akinesia-rigidity syndrome. Zung's Scale failed to reveal an additional antidepressant effect in the patients on individualized levodopa therapy. The tolerability was good in 26 cases and fair in four cases. Ten patients experienced adverse reactions: There were two cases of alopecia and one report each of pruritus, exanthem, psoriasis, dryness of the mouth, thirst, dizziness, giddiness, difficulty in sleeping, internal trembling, spasmodic state, queasiness, abdominal discomfort, and anginal attack. A relationship between these adverse reactions and selegiline cannot be excluded in eight of these cases. This study had an overall quality rating score of 21%.

Sivertsen et al. (1989)[16]: Sivertsen and colleagues studied 42 patients in a 4-month crossover study as well as in a 16-month parallel design of selegiline (10 mg/day) and placebo added to Levodopa treatment. There was a 4-week "wash-out" in the crossover study (short-term study). After this, patients continued treatment in two parallel groups. The majority of patients had no motor

fluctuations. Addition of selegiline, as well as placebo, to the levodopa medication allowed equal (28% and 27% respectively) significant reduction of daily levodopa doses without clinical deterioration during the first 8-week period, but this was not so marked during the second treatment period. Thus, there was a significant period effect. When the reduction of the daily mean Levodopa dose was compared for the selegiline and placebo treatment periods, analysis of variance showed that the daily levodopa dose was reduced significantly more during selegiline treatment in the long-term study. The number of daily levodopa doses decreased with both treatments – more so during selegiline treatment (from 4.4 $\pm$ 1.0 to 3.8 $\pm$ 1.0) – but there was no statistically significant difference between selegiline and placebo. Addition of selegiline caused improvement of tremor in the short-term study. No significant difference was observed in the scores for rigidity, functional performance or total CUDS score. Adverse reactions were few except for dizziness in eight patients on selegiline and three patients on placebo. All side effects disappeared after levodopa reduction. This study had an overall quality rating score of 52%.

Lees et al. (1995)[17]: This study compared the effectiveness of levodopa and levodopa combined with selegiline in treating early, mild Parkinson's disease in an open-label, three-arm (selegeline plus Levodopa, bromocriptine, levodopa) prospective, randomized trial. Five hundred and twenty patients with early disease who were not being treated with dopaminergic drugs were studied in 93 hospitals throughout the United Kingdom. Patients on Levodopa alone had slightly more disability than those on Levodopa plus selegiline, but the differences were not significant on the Webster or Northwestern University disability scales at four years. The dose of Levodopa required to produce optimum motor control increased in the Levodopa group, median dose 375 mg/day at one year and 625 mg/day at four years compared to the median dose of the Levodopa and selegiline group 375 mg/day, which did not change over time. The authors reported that the mortality in previously untreated Parkinson's disease patients was significantly higher for those treated with Levodopa plus selegiline than for those treated with Levodopa alone (28% v.18%; adjusted for age, sex, and other baseline factors). This study had an overall quality rating score of 75%.

Larsen et al. (1997)[18]: This study investigated the effects of selegiline (10 mg/day) or placebo added to Levodopa therapy in early Parkinson's disease in 163 patients (average age 64.3 years, mean duration of disease 2.0 years, Hoehn-Yahr I to III) in a double-blind, placebo-controlled, parallel-group design. Patients were followed until termination point or five years. The primary outcome variables were the UPDRS scales and the time to develop "wearing off" fluctuations. The results reported were based on an interim analysis where 80% of the 163 randomized patients had been followed up to three years. After three months of Levodopa therapy, both treatment groups showed a marked and comparable improvement in the total UPDRS score and subscores, and the daily Levodopa dosage were nearly identical. The daily Levodopa dose and the UPDRS score after three month drug adjustments were considered the baseline values for statistical analyses of possible changes with time in these variables during the later disease development. The parkinsonian disability, as measured by the total and motor UPDRS scores showed a gradual decline from one year of treatment and during the rest of the observation period. Although this decline in function was more pronounced in the placebo group, the differences in increase of the total and motor UPDRS scores over time were not significantly different between the two groups. During the same period (from month 3 until month 54), there was almost no change in daily Levodopa dose in the selegiline group, whereas the Levodopa dose in the placebo group showed a constant increase during the observation period. After 24 months of treatment, the difference in daily Levodopa dose was significant between patients taking selegiline as compared to placebo. The difference in the increase of daily Levodopa dose over time in the two treatment groups until three years of treatment was also statistically significant. The supportive analysis of all available observations until 4.5 years showed a corresponding level of significance for an increasingly higher need for Levodopa with time in the placebo group compared with the daily dose in the selegiline group. The authors reported that of the patients dropping out because of adverse reactions, 16 were in the selegiline group and 11 in the placebo group. More adverse effects were observed in the selegiline group (117 reactions) versus the placebo group (105 reactions). Slightly more patients in the selegiline group reported orthostatic hypotension and other effects related to the central nervous system. This study had an overall quality rating score of 70%.

Nappi et al. (1991)[19]: Nappi and colleagues studied selegiline (10 mg/day) vs. placebo after 1 month of lisuride treatment in 20 de novo parkinsonian patients followed for 3 months using CURS and NUDS. Lisuride dosage was reduced by 22.8% without change in clinical status. The mean dose of lisuride in combination with selegiline was 1.41$\pm$0.34 mg compared to placebo treatment, 1.93$\pm$0.37 mg, $p<0.05$. This study included an endpoint of "dose for lisuride." The clinical relevance of this endpoint in unclear. There were no reported adverse reactions of selegiline in combination with lisuride. This study had an overall quality rating score of 86%.

PREVENTION OF MOTOR COMPLICATIONS

No qualified studies were identified.

CONTROL OF MOTOR COMPLICATIONS

Lees et al. (1977)[20]: Lees et al. evaluated 41 Parkinson's disease patients (average age 62.5 years) with an average disease duration of 8.0 years in a double-blind, placebo-controlled study of selegiline (10 mg/day) added to Levodopa in both mild and severe fluctuating patients. Although "on-off" diary data were collected, the study does not report treatment effects on this parameter. It is stated that selegiline improved "wearing-off" disabilities in approximately 65% of patients. No statistically significant improvement occurred in diurnal akinesia, and there was no improvement in patients with severe "on-off" disabilities with freezing and rapid oscillation (yo-yo effect). Depression was unchanged. There was no significant change in CUDS and NUDS. The authors reported the following adverse reactions with selegiline: dyskinesia (14), nausea (9), dry mouth (6), dizziness (3), postural hypotension (2), syncope (1), paresthesia (1), hallucinations (1) and unpleasant taste (1). This study had an overall quality rating score of 50%.

Lieberman et al. (1987)[21]: This was a randomized, double-blind placebo controlled parallel study of selegiline (10 mg/day) added to Levodopa studied 33 Parkinson's disease patients (average age 63.3 years) for 8 weeks. Seventeen patients were randomly assigned to the selegiline group and 16 to the placebo group. All patients completed the 8-week trial. Both groups of patients were comparable in age, sex, duration of Parkinson's disease, Levodopa dose, duration of Levodopa treatment, disease severity, and prior treatment with bromocriptine or other dopamine agonists. Although the patients given selegiline were younger, this difference was not

significant. The 17 patients who were randomly assigned to the selegiline group experienced a significant 22% decrease in their parkinsonian symptoms; a significant 17.4% decrease in their parkinsonian signs; and a significant 21% decrease in their Levodopa dose. The 17 patients did not, as a group, experience an improvement in the number of hours that they were "on". Overall, the conditions of 12 of the 17 patients (71%) were judged to have improved. Although there was no increase in number of hours "on" patients reported that their dose of Levodopa lasted longer, that the transitions between their "on" and "off" periods were less abrupt, that the "on" periods were better and that the "off" periods less severe. Although these subjective responses could not be quantified, the authors said they were useful in arriving at the global assessment. However, this approach is very subjective and seriously compromises the conclusions of the studies. There was no difference between selegiline and placebo groups in adverse reactions. At completion, 3 of 17 on selegiline discontinued the drug: two patients had no benefit and one had adverse reactions. (This patient had mild dementia, and during the course of treatment with selegiline became more confused. On discontinuation of treatment, the patient returned to the baseline state.) This study had an overall quality rating score of 73%.

Golbe et al. (1988)[22]: Golbe and coworkers investigated selegiline (10 mg/day) and placebo added to Levodopa in 99 Parkinson's disease (average age 62.4 years, Hoehn-Yahr Stage II to IV) in a randomized, double-blind, placebo-controlled, multicenter, parallel study (6 week study period). Using diary forms, patients recorded disability hourly at home, three days a week, during a 2-week baseline, and during a 6-week treatment period. Drug response was recorded as follows: 0= bad or not working, 1=intermittent effect, 2=working, good time. Mean hourly self-assessment of gait significantly improved in 28 of 50 patients (56%) receiving selegiline (mean 0.25 points on a 0-2 scale) and in 14 of 46 (30.4%) taking placebo (mean 0.15). Mean hourly overall symptom control significantly improved in 29 (58%) taking selegiline (mean 0.34) and in 12 (26.1%) taking placebo (mean 0.15). Patient's mean pre-treatment baseline hourly self assessment scores for "drug working" in selegeline and placebo group was 1.29 and 1.28, respectively. Mean scores (measured hourly) over the 6 weeks of treatment were 1.41 and 1.11 for selegeline vs. placebo, respectively ($p<0.001$). No significant improvement occurred in the objective quality of the "on" state with selegiline. Mean daily Levodopa dosage decreases were 17% in the selegiline group and 7% in the placebo group. Adverse reactions included: nausea (selegiline 20%, placebo 6.5%), lightheadedness (selegiline 12%, placebo 2.2%), dyskinesias and hallucinations which all abated after the Levodopa dose was reduced. Additional side effects included abdominal pain (selegiline 8%, placebo 4.3%), and confusion (selegiline 6%, placebo 0%). This study had an overall quality rating score of 83%.

REVIEW OF SAFETY

Selegeline, in general is a well-tolerated drug. When used as monotherapy, infrequently reported side effects include: insomnia (especially if the drug is given late in the day), headache, nausea, loss of balance, dry mouth, and gastrointestinal symptoms (flatulence, discomfort, and constipation). No significant changes in blood pressure have been reported. Many studies find no difference in the incidence of reported adverse reactions between selegiline and placebo. Dopaminergic adverse reactions (such as hallucination and dykinesia) can occur when selegiline is added to levodopa therapy. These adverse reactions usually subside when the dose of levodopa is reduced.

Lees et al. (1995)[17] reported that the mortality in previously untreated Parkinson's disease patients (n=520 patients in 93 British hospitals) was higher for those treated with levodopa plus levodopa/selegiline than for those treated with levodopa alone (28% v.18%; adjusted for age, sex, and other baseline factors, hazard ratio = 1.57, 95% confidence interval (CI) = 1.07, - 2.31). This study had an overall quality rating score of .75. In a follow-up to this study, whereby the patient number was increased to 624, an increased mortality for the combined treatment group was still detected, but the hazard ratio was lower than in the previous report, and no longer statistically significant (adjusted hazard ratio = 1.30 (95% CI 0.99, 1.72).[23] The increased mortality appeared to be associated with the 2nd to 4th years of treatment. The authors could not explain the increased mortality, but suggested that the combined therapy be avoided in patients with postural hypotension, frequent falls, confusion or dementia.

Overall, these studies showing increased mortality have been extensively discussed and criticized and a number of objections have been raised including problem of design and statistics.[24,25]

CONCLUSIONS

EFFICACY

PREVENTION OF DISEASE PROGRESSION

Due to a variety of methodological problems of available studies – including lack of validated endpoints, conformating symptomatic efficacy and uncertainty about appropriate duration of wash-out periods – there is INSUFFICIENT EVIDENCE to conclude on the neuroprotection effect of selegiline in patients with Parkinson's disease.

SYMPTOMATIC CONTROL OF PARKINSONISM

Monotherapy

Five of the six identified studies reported to date demonstrated a modest benefit of selegiline as initial monotherapy in Parkinson's disease. The one study failing to detect differences between selegiline and placebo was methodologically inadequate. Therefore, selegiline is considered EFFICACIOUS as symptomatic monotherapy in Parkinson's disease. However the effect size was small and there is insufficient evidence to conclude on the relative efficacy to other treatments.

Adjunct Therapy

Results of four Level-I studies in patients without motor fluctuations are inconsistent and overall there is INSUFFICIENT EVIDENCE to conclude on the efficacy of selegeline in this indication. Where Levodopa dose reductions were reported this was not associated with enhanced symptomatic control. The clinical significance of this Levodopa-sparing effect is unknown. In fluctuating patients data are likewise INSUFFICIENT to conclude on the efficacy of adjunct selegeline in improving "on" motor function.

PREVENTION OF MOTOR COMPLICATIONS

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of selegiline in preventing motor complications in Parkinson's disease.

CONTROL OF MOTOR COMPLICATIONS

Three short-term, Level-I studies are inconsistent in study design and results. Overall data are INSUFFICIENT to conclude on the efficacy of selegeline in the short term short-term management of motor fluctuations in patients with Parkinson's disease.

SAFETY

Selegiline in Parkinson's disease has an ACCEPTABLE RISK WITHOUT SPECIALIZED MONITORING, when used as monotherapy or when added to dopaminergic drugs both in fluctuating and nonfluctuating patients. A prior study reporting enhanced mortality and cardiovascular events when selegiline was combined with levodopa has not been reproduced.

IMPLICATIONS FOR CLINICAL PRACTICE

Selegiline is considered INVESTIGATIONAL as a neuroprotective agent.

Selegiline as initial monotherapy for the symptomatic control of Parkinson's disease is CLINICALLY USEFUL. However, the clinical effects of selegiline may be minimal.

As adjunct therapy in Levodopa-treated patients selegeline is POSSIBLY USEFUL in improving parkinsonism.

Likewise selegiline is considered POSSIBLY USEFUL for the treatment of motor fluctuations in Parkinson's disease. Despite its wide clinical usage for this indication, the evidence supporting this is modest.

No recommendations can be made regarding the relative efficacy of selegiline to other antiparkinson medication because no level-I direct comparison studies have been conducted.

IMPLICATIONS FOR CLINICAL RESEARCH

There are two major areas of research for selegiline. First, it is important to define the mechanism of action of the drug because selegiline is complex with actions other than MAO-B inhibition. More selective MAO-B inhibitors will help define the specific role of this enzyme in the pathophysiology of Parkinson's disease. The role of the amphetamine metabolite of selegine remains to be investigated. Second, it is important to define further its clinical role in neuroprotection, monotherapy, motor fluctuation, and adjunct therapy, by performing active comparator trials. This will help define its place in these indications. Studies using more sensitive measures (possibly including neuroimaging surrogate markers) of neuroprotection may help to distinguish between symptomatic and neuroprotective mechanisms.

It is also possible that other MAO-B inhibitors besides selegiline could be more efficacious as symptomatic monotherapy in Parkinson's disease. However, a study of another MAO-B inhibitor, lazabemide, found this drug to have only a minimal antiparkinsonian effect.[26] However, other properties of these drugs besides MAO-B inhibition could potentially be important for its therapeutic usefulness.

Future research should answer the question of whether reducing levodopa dosage early in the course of Parkinson's disease is beneficial. The ability of levodopa either to protect or damage neurons of the substantia nigra needs to be clarified, since MAO-B inhibitors have the ability to spare levodopa dosage and reduce dopamine metabolism.

It also may be possible that other MAO-B inhibitors may be more beneficial as adjuvant therapy to Levodopa in the treatment of motor fluctuations. If such drugs are developed, they should be studied for their potential in prolonging the responsiveness to Levodopa therapy.

RASAGILINE

Recently rasagiline mesylate has entered a clinical development program. Similar to selegiline rasagiline mesylate is an irreversible MAO inhibitor with high selectivity for the B form of the enzyme. It is more potent than selegiline on a weight basis such that 0.5 - 1 mg/day causes total inhibition of platelet MAO-B in humans.[27] Unlike selegiline it is devoid of amphetamine-like metabolites.

So far a single double-blind randomized placebo-controlled study of rasagiline mesylate as adjunct to levodopa has been published.[28] Seventy patients were randomized into four parallel groups (0.5 mg, 1 mg, 2 mg rasagiline mesylate, and placebo). Treatment over 12 weeks resulted in greater improvements of UPDRS total scores for all rasagiline groups compared to placebo but differences were not statistically significant. Further Level-I trials, both in de novo and fluctuating patients with Parkinson's disease are underway and no conclusions on the efficacy and safety of rasagiline mesylate in any indication in Parkinson's disease can be made at this time.

REFERENCES

1. Gerstenbrand F, Prosenz P. Über die Behandlung des Parkinson Syndroms mit Monoaminoxydasehemmern allein und in Kombination mit L-Dopa. Praxis 1965;54:1373-1377.
2. Knoll J. Deprenyl [selegiline]: the history of its development and pharmacological action. Acta Neurol Scand 1983;95:57-80.
3. Birkmayer W, Riederer P, Ambrozi L, Youdim MBH. Implications of continued treatment with Madopar and L-deprenyl in Parkinson's disease. Lancet 1987;i:439-443.
4. Olanow CW, Riederer P. Selegiline and neuroprotection in Parkinson's disease. Neurology 1996;47C(suppl 3):51.
5. Riederer P, Youdim MB, Rausch WD, Birkmayer W, Jellinger K, Seemann D. On the mode of action of L-deprenyl in the human central nervous system. J Neural Transm 1978;43:217-226.
6. Tetrud JW, Langston JW. The effect of deprenyl (selegiline) in the natural history of Parkinson's disease. Science 1989;245:519-522.
7. Parkinson's Study Group. Effect of deprenyl on the progression of disability in early Parkinson's disease. N Engl J Med 1989;321:1364-1371.
8. Parkinson Study Group. Impact of deprenyl and tocopherol treatment on Parkinson's disease in DATATOP subjects not requiring levodopa. Ann Neurol 1996;39:29-36.
9. Myllyla VV, Sotaniemic KA, Vuorinen JA, Heinonen EA. Selegiline as initial treatment in de novo parkinsonian patients: Neurology 1992;42:339-343.
10. Olanow CW, Hauser RA, Gauger L, et al. The effect of deprenyl and levodopa on the progression of Parkinson's disease. Ann Neurol 1995;38:771-777.
11. Palhagen S, Heinonan EH, Hagglund J, et al. Selegiline delays the onset of disability in de novo parkinsonian patients. Swedish Parkinson Study Group. Neurology 1998;51:520-525.
12. Teravainen H. Selegiline in Parkinson's disease. Acta Neurol Scand 1990;81:333-336.
13. Allain H, Pollak P, Neukirch HC. Symptomatic effect of selegiline in de novo parkinsonian patients. The French Selegiline Multicenter Trial. Mov Disord 1993;8(suppl 1):S36-S40.
14. Mally J, Kovacs AB, Slone TW. Delayed development of symptomatic improvement by (—)-deprenyl in Parkinson's disease. J Neurol Sci 1995;134:143-145.
15. Przuntek H, Kuhn W. The effect of R-(-)-deprenyl in de novo Parkinson patients on combination therapy with levodopa and decarboxylase inhibitor. J Neural Transm Suppl 1987;25:97-104.
16. Sivertsen B, Dupont E, Mikkelsen B, et al. Selegiline and levodopa in early or moderately advanced Parkinson's disease: a double-blind controlled short- and long-term study. Acta Neurol Scand Suppl 1989;126:147-152.
17. Lees A. Comparison f therapeutic effects and mortality data of levodopa and levodopa combined with selegiline in patients with early, mild Parkinson's disease. Parkinson's Disease Research Group of the United Kingdom. BMJ 1995;311:1602-1607.

18.Larsen JP, Boas J. The effects of early selegiline therapy on long-term levodopa treatment and parkinsonian disability: an interim analysis of the Norwegian—Danish 5- year study. Norwegian-Danish Study Group. Mov Disord 1997;12:173-182.
19.Nappi G, Martignoni E, Horowski R, et al. Lisuride plus selegiline in the treatment of early Parkinson's disease. Acta Neurol Scand 1991;83:407-410.
20.Lees AJ, Shaw KM, Kohout LJ, et al. Deprenyl in Parkinson's disease. Lancet 1977;2:791-795.
21.Lieberman AN, Gopinathan G, Neophytides A, Foo SH. Deprenyl versus placebo in Parkinson's disease. A double-blind study. N Y State J Med 1987;87:646-649.
22.Golbe LI., Lieberman AN, Muenter MD, et al. Deprenyl in the treatment of symptom fluctuations in advanced Parkinson's disease. Clin. Neuropharmacol 1988;11:45-55.
23.Ben-Shlomo Y, Churchyard A, Head J, et al. Investigation by Parkinson's disease Research Group of United Kingdom into excess mortality seen with combined levodopa and selegiline treatment in patients with early, mild Parkinson's disease: further results of randomized trial and confidential inquiry. BMJ 1998;316:1191-1196.
24.Olanow CW, Myllyla VV, Sotaniemi KA, et al. Effect of selegiline on mortality in patients with Parkinson's disease: a meta-analysis. Neurology 1998;51:825-830.
25.Foley P, Gerlash M, Youdim MBH, Riederer P. MAO-B inhibitors: multiple roles in the therapy of neurodegenerative disorders? Parkinsonism & Related Disorders 2000;6:25-27.
26.Parkinson Study Group: A controlled trial of lazabemide (R019-6327) in untreated Parkinson's disease. Ann Neurol 1993;33:350-356.
27.Sterling J, Veinberg A, Lerner D, et al. R (+) N-propargyl-l-aminoindan (rasagiline) and derivatives: highly selective and potent inhibitors of monoamine-oxidase B. J Neural Transm Suppl 1998;52:301-305.
28.Rabey JM, Sagi I, Huberman M, et al. Rasagiline mesylate, a new MAO-B inhibitor for the treatment of Parkinson's disease: a double-blind study as adjunctive therapy to levodopa. Clin Neuropharmacol 2000;23:324-330.

BIBLIOGRAPHY - EXCLUDED FROM ANALYSIS (REASON FOR EXCLUSION)

Alder CH, Sethi K, Hauser RA, et al. Ropinirole for the treatment of early Parkinson's disease. The Ropinirole Study 'Group. Neurology 1997;49:393-399. (Did not evaluate selegiline as primary treatment)
Birkmayer W. Implications of combined treatment with 'Madopar" and L-deprenil in Parkinson's disease. A long-term study. Lancet 1977;1(8009):439-443. (Not randomized study)
Birkmayer W. The potentiation of the anti akinetic effect after L-dopa treatment by an inhibitor of MAO-B, Deprenil. J Neural Transm 1975;36:303-326. (Not randomized study)
Brannan T, Yahr MD. Comparative study of selegiline plus L-dopa-carbidopa versus L-dopa-carbidopa alone in the treatment of Parkinson's disease. Ann Neurol 1995;37:95-98. (Not randomized study)
Brodersen P, Philbert A, Gulliksen G, Stigard A. The effect of L-Deprenyl as on-off phenomena in Parkinson's disease. Acta Neurol Scand 1985;71:494-497. (Less than 20 patients)
Calzetti S, Negrotti A, Cassio A.. L-Deprenyl as an adjuvant to low-dose bromocriptine in early Parkinson's disease: a short-term, double-blind, and prospective follow-up study. Clin Neuropharmacol 1995;18:250-257. (Not randomized study)
Chouza C, Aljanati R, Scaramelli A, et al. Combination of selegiline and controlled release levodopa in the treatment of fluctuations of clinical disability in parkinsonian patients. Acta Neurol Scand Suppl 1989;80:127-137. (Not randomized study)
Csanda E, Tarczy M. Clinical evaluation of deprenyl (selegiline) in the treatment of Parkinson's disease. Acta Neurol Scand Suppl 1983;95:117-122. (Not randomized study)
Csanda E, Tarczy, Takats A. (-)Deprenyl in the treatment of decompensated Parkinson's disease. J Neural Transm Suppl 1986;22:248-252. (Not randomized study)
Csanda E, Tarczy M. Selegiline in the early and late phases of Parkinson's disease. J Neural Transm Suppl 1987;2583:105-113. (Not randomized study)
Elizan TS, Yahr MD, Moros DA, Mendoza MR, Prang S, Bodian CA. Selegiline as an adjunct to conventional levodopa therapy in Parkinson's disease. Experience with this type B monoamine oxidase inhibitor in 200 patients. Arch Neurol 1989;46:1280-1283. (Not randomized study)
Elizan TS, Moros DA, Yahr MD. Early combination of selegiline and low-dose levodopa as initial symptomatic therapy in Parkinson's disease. Experience in 26 patients receiving combined therapy for 26 months. Arch Neurol 1991;48:31-34. (Not randomized study)
Fischer PA, Baas H. Therapeutic efficacy of R-(-)-deprenyl as adjuvant therapy in advanced parkinsonism. J Neural Transm Suppl 1987;25:137-147. (Not randomized study)
Fornadi F, Ulm G. Early combination with deprenyl: a retrospective analysis. Adv Neurology 1990;53:437-440. (Not randomized study)
Gerstenbrand F, Ransmayr G, Poewe W. Deprenyl (selegiline) in combination treatment of Parkinson's disease. Acta Neurol Scand Suppl 1983;95:123-126. (Not randomized study)
Giovannini P. Deprenyl in Parkinson's disease: personal experience. Ital J Neurol Sci 1985;6:207-212. (Not randomized study)
Giovannini P, Martignoni E, Piccolo I, et al. (-)Deprenyl in Parkinson's disease: a two-year study in the different evolutive stages. J Neural Transm Suppl 1986;22:235-246. (Not randomized study)
Golbe LI. Long term efficacy and safety of deprenyl (selegiline) in advanced Parkinson's disease. Neurology 1989;39:1109-1111. (Not randomized study)
Hassan MN. Experience with selegiline in the treatment of de novo Parkinson's disease. Today's Ther Trends 1993;10:203-214. (Not randomized study)
Heinonen EH, Rinne UK, Tuominen J. Selegiline in the treatment of daily fluctuations is disability of parkinsonian patients with long term levodopa treatment. Acta Neurol Scand Suppl 1989;126:113-118. (Less than 20 patients)
Hubble JP, Koller WC, Waters C. Effects of selegiline dosing on motor fluctuations in Parkinson's disease. Clin Neuropharmacol 1993;16:83-87. (Less than 20 patients)
Lander CM, Lees A, Stern G. Oscillations in performance in levodopa-treated parkinsonians: treatment with bromocriptine and L-deprenyl. Clin Exp Neurol 1979;16:197-203. (Not randomized study)
LeWitt PA, Segal SA, Mistura KL, Schork MA. Symptomatic anti-parkinsonian effect of monamine oxidase-B inhibitors: comparison of selegiline and lazabamide. Clin Neuropharmacol 1993;16:332-337. (Not randomized study)
Lieberman AN, Gopinathan G, Neophytides A, et al. Deprenyl in the treatment of Parkinson's disease. A specific type B monoamine oxidase inhibitor. N Y State J Med 1984;84:13-16. (Not randomized study)
Lieberman AN. Long-term experience with selegiline and levodopa in Parkinson's disease. Neurology 1992;42(suppl 4):32-36. (Not randomized study)
Poewe W, Gerstenbrand F, Ransmayr G.. Experience with selegiline in the treatment of Parkinson's disease. J Neural Transm Suppl 1987;25:131-135. (Not randomized study)
Poungvarin N, Viriyavejakul A. L-deprenyl therapy in Thai patients with Parkinson's disease: before and after, clinical trial of 50 patients. J Med Assoc Thai 1990;73:381-386. (Not randomized study)
Presthus J, Berstad J, Lien K. Selegiline (L-deprenyl) and low dose levodopa treatment of Parkinson's disease. A double-blind crossover trial. Acta Neurol Scand 1987;76:200-203. (Less than 20 patients)
Rascol O, Montastruc JL, Senard JM, Demonet JF, Simonetta M, Rascol A. Two weeks of treatment with deprenyl (selegiline) does not prolong L-dopa effect in parkinsonian patients: a double-blind crossover placebo controlled trial. Neurology 1988;38:1387-1391. (Less than 4-week study duration)
Rinne UK, Siirtola T, Sonninen V. L-deprenyl treatment of on-off phenomena in Parkinson's disease. J Neural Transm 1978;43:253-263. (Not randomized study)
Rinne UK. Deprenyl (selegiline) in the treatment of Parkinson's disease. Acta Neurol Scand Suppl 1983;95:107-111. (Not randomized study)
Ruggieri S, Denaro A, Meco G, Carta A, Stocchi F, Agnoli A. Multicenter trial of L-Deprenyl in Parkinson's disease. Ital J Neurol Sci 1986;7:133-137. (Not randomized study)
Schachter M, Marsden CD, Parkes JD, Jenner P, Testa B. Deprenyl in the management of response fluctuations in patients with Parkinson's disease on levodopa. J Neurol Neurosurg Psychiatry 1980;43:1016-1021. (Less than 20 patients)
Streifler M, Rabey M. Long-term effects of L-deprenyl in chronic levodopa treated parkinsonian patients. J Neural Transm Suppl 1983;19:265-272. (Not randomized study)
Streifler M. Beta-type monamine oxidase [MAO] inhibitors in long term levodopa treated parkinsonism: a combined clinical trial with L-deprenyl. Curr Ther Res Clin Exp 1980;27:643-648. (Not randomized study)
Trebini F, Daniele D, Gillio S, Scarzella L. Clinical evaluation of selegiline (L-deprenyl) in the long-term L-dopa treatment syndrome. Acta Neurol 1985;7:432-439. (Not randomized study)
Ulm G, Fornadi F. R-(-)deprenyl in the treatment of end-of-dose akinesia. J Neural Transm Suppl 1987;25:163-172. (Not randomized study)
Wajsbort J. The clinical and biochemical investigation of L-deprenyl in Parkinson's disease with special reference to the "on-off" effect. J Neural Transm 1982;55:201-215. (Not randomized study)
Yahr MD, Mendoza MR, Moros D, BergmannKJ. Treatment of Parkinson's disease in early and late phases: use of pharmacological agents with special reference to deprenyl (selegiline). Acta Neurol Scand Suppl 1983;95:95-102. (Not randomized study)
Ziv I, Achiron A, Djaldetti R, Dressler R, Melamed E. Short-term beneficial effect of deprenyl monotherapy in early Parkinson's disease: a quantitative assessment. Clin Neuropharmacol. 1993;16:54-60. (Not randomized study)

Movement Disorders
Vol. 17, Suppl. 4, 2002, p. S45-S51

Published by Wiley-Liss, Inc.
DOI 10.1002/mds.5560

COMT Inhibitors

INTRODUCTION

BACKGROUND

Straightforward therapeutic strategies are available for early treatment of "uncomplicated" Parkinson's disease (PD). Specifically, since its introduction in 1961, levodopa (the precursor of dopamine) has been considered the gold standard in PD treatment. Efforts to optimize levodopa therapy are a common therapeutic goal. Although many patients are able to function when receiving levodopa, clinical response to levodopa therapy declines as the disease progresses. After five years, many patients suffer from "motor complications" that present due to the decline in therapeutic response to levodopa therapy. These complications include motor fluctuations (commonly referred to as the "on" and "off" state) and dyskinesia.

RATIONALE

The rationale for treating fluctuations is to provide a continuous dopaminergic input to the striatum. This can be achieved by giving smaller dosing intervals of levodopa, controlled-release formulations, additional dopamine agonists, or continuous subcutaneous infusions of apomorphine. Inhibition of catechol-O-methyltransferase (COMT), an enzyme that catalyzes the metabolization of levodopa to 3-O-methyldopa, provides another approach. Inhibition of this enzyme results in a prolonged maintenance of serum levodopa levels, and hence a longer clinical levodopa response.

Presently, there are two COMT-inhibitors used in clinical practice: tolcapone, and entacapone, which differ somewhat in their basic pharmacology. Both substances have been available since the mid-90s (they have been available for phase III clinical studies since that, tolcapone was approved in 1997 and entacapone in 1998).

METHODS

KEY SEARCH TERMS

Entacapone, tolcapone, COMT, and COMT-inhibition.

SPECIAL EXCEPTIONS TO INCLUSION/ EXCLUSION CRITERIA

Only randomized, controlled trials (Level-I studies) were included in this review.

BASIC PHARMACOLOGY

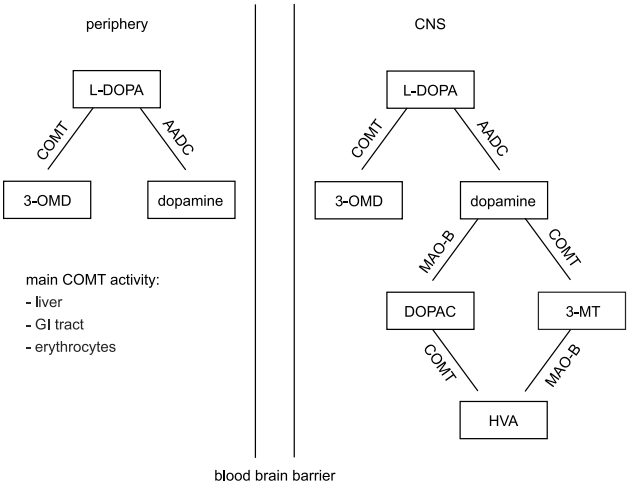
MECHANISM OF ACTION/ PHARMACODYNAMICS

COMT-inhibitors reduce the metabolism of levodopa resulting in prolonged availability of levodopa in the gastrointestinal tract and a longer half-life of levodopa in plasma. Consequently, COMT-inhibition increases the amount of time available for levodopa to pass the blood brain barrier and enter the brain where it is directly converted to dopamine or is stored. The co-administration of a COMT-inhibitor with levodopa therapy prolongs the action of an individual dose of levodopa.

Levodopa is metabolized in the periphery (in addition to other metabolic pathways) by the enzymes aromatic amino acid decarboxylase (AADC) and COMT (Figure 1). When AADC is inhibited, as in the case of the available levodopa/AADC-inhibitor preparations, the *O*-methylation pathway becomes prominent. Therefore, inhibiting COMT in the periphery results in a longer plasma half-life of levodopa. Specifically, both entacapone and tolcapone are specific and reversible inhibitors of COMT. They approximately double the bioavailability of levodopa, giving rise to an increase of the area under the levodopa plasma concentration/time curve (AUC). However, the average levodopa maximum plasma concentration (C_{max}) and the time to C_{max} (t_{max}) are generally unaffected.

One difference between these two agents is that therapeutic doses of entacapone only act peripherally (i.e., gastrointestinal tract, the liver, and erythrocytes) and do not alter cerebral COMT activity. High doses of tolcapone may pass the blood brain barrier in humans and block central nervous COMT.

Figure 1: Metabolic pathways of levodopa in the periphery and the brain *(adapted from Kurth and Adler[1])*



L-DOPA:	Levodopa
3-OMD:	3-*O*-methyldopa
COMT:	Catechol-*O*-methyltransferase
AADC:	Aromatic amino acid decarboxylase
MAO-B:	Monoaminooxidase-B
DOPAC:	Dihydroxyphenylic acid
3-MT:	3-methyl-tyramine
HVA:	Homovanillic acid

PHARMACOKINETICS

TOLCAPONE

Tolcapone is rapidly absorbed after oral administration with a t_{max} of 1.4 h to 1.8 h. C_{max} and AUC increase roughly dose-proportionally and are independent of multiple-dose treatment up to 400 mg tolcapone three times daily (t.i.d). Food seems to have an impact on the absorption of tolcapone: tolcapone intake 45 minutes after a standard breakfast leads to a delay in absorption and a decrease in C_{max} of about 50%. Around 65% of an oral dose of tolcapone enters the general circulation. Less than 20% of the drug is lost in a first-pass metabolism. The volume of distribution of tolcapone is small due to its high plasma protein binding (>99.8%). Tolcapone is almost completely metabolized prior to excretion. Only about 0.5% of the ingested dose are found unchanged in urine. The predominant metabolic pathway is conjugation to the inactive glucuronide. Furthermore, the agent is methylated by COMT and metabolized by cytochrome P450 to a primary alcohol that is subsequently oxidized to the carboxylic acid. When given to healthy male subjects, 60% of ^{14}C-tolcapone metabolites are found in urine and 40% in feces. Tolcapone is a low-extraction-ratio drug with a moderate systemic clearance of 7 L/h. The half-life is 1 to 4 hours.

ENTACAPONE

Entacapone is rapidly absorbed with t_{max} values between 0.4 and 0.9 h. Increases in both C_{max} and AUC are directly proportional to the dose of entacapone administered. Food does not affect the absorption of entacapone to any significant extent (this corrected text is taken directly from the Comtess / Comtan SmPC, also same message is in the Comtess EPAR, 16.9.1998, KR). Bioavailability of entacapone is approximately 36% and increases linearly with increasing doses. Entacapone is administered as the (E)-isomer, and an isomerization to the (Z)-isomer occurs in the circulation. Plasma protein binding (in vitro) is 98%. Entacapone is predominantly metabolized in the liver. The main metabolites of entacapone are glucuronide conjugates of the unchanged drug and its (Z)-isomer. Only 0.1% to 0.2% of an oral dose is excreted in the urine as unchanged entacapone. An estimated 80% to 90% of the dose is excreted in the feces, and 10% to 20% in the urine (as derived from animal data studies). Elimination half-life of entacapone extends between 1 h and 2.2 h. Mean total plasma clearance values of 800 ml/min (48 L/h) have been reported.

Table 1 Pharmacology of entacapone and tolcapone

	Entacapone	Tolcapone
t_{max}	0.4 - 0.9 h	1.4 - 1.8 h
Bioavailability	36 %	65 %
Metabolization	Isomerization from (E) to (Z)-isomer Conjugation to inactive glucuronide	Conjugation to inactive glucuronide Methylation by COMT Oxidation by cytochrome P450
Unchanged in urine	0.1 - 0.2 %	0.5 %
Metabolite excretion - feces - urine	 80 - 90 % 10 - 20 %	 40 % 60 %
T1/2	1 - 2.2 h	1 - 4 h (might be slightly longer in PD)
Plasma clearance	48 L/h	7 L/h
Plasma protein binding	98 %	99.8 %

REVIEW OF CLINICAL STUDIES

TOLCAPONE

Seventeen studies were identified; eight met inclusion criteria and nine were excluded. A list of the excluded trials is given below (Bibliography) with the reason for exclusion described.

PREVENTION OF DISEASE PROGRESSION

No qualified studies were identified.

SYMPTOMATIC CONTROL OF PARKINSONISM

MONOTHERAPY

No qualified studies were identified.

ADJUNCT THERAPY

Waters et al. (1997)[2]: In a double-blind, placebo-controlled, parallel-group, multicenter trial, Watters and coworkers tested the efficacy of tolcapone (100 mg or 200 mg, t.i.d.) as adjunct therapy to levodopa in 298 PD patients without major motor fluctuations. The goal of the study was to investigate "stable" patients, but patients with "mild" fluctuations also were included. The primary efficacy measure was the UPDRS II scale (ADL). At 6 months, both dosages of tolcapone produced small, but significant reductions in the UPDRS II (tolcapone 100 mg: 1.4; tolcapone 200 mg: 1.6), also in the part III (motor part) and in the total UPDRS. Both tolcapone groups showed a slight, but significant reduction in levodopa dosage (tolcapone 100 mg: 20.8 mg; tolcapone 200 mg: 32.3 mg), whereas the placebo group had a mean increase (46.6 mg). There were 11 drop-outs due to adverse reactions in the placebo, 20 (100 mg), and 18 in the (200 mg). Diarrhea was the most frequent nondopaminergic adverse reaction, often leading to withdrawal. Other adverse reactions were nausea, dyskinesia, anorexia, and sleep disorder. Liver enzyme increases were observed in 8 of the tolcapone patients, causing withdrawal in four cases. This study had an overall quality rating score of 83%.

Dupont et al. (1997)[3]: This study tested the efficacy tolcapone (200 mg or 400 mg t.i.d.) in 97 patients with PD. At the time of inclusion into the double-blind, placebo-controlled, parallel-group, multicenter trial, patients were classified as nonfluctuators. However, at the time of preselection and recruitment, patients had progressed and some were classified as fluctuators. The "wearing-off" phenomenon was controlled with more frequent levodopa dosage prior to inclusion in the study. Levodopa was decreased by 35% on day 1 of the study and subsequently retitrated as required. The primary efficacy parameter was the change of levodopa dosage after retitration under study medication, while patients remained in a non-fluctuating state. After titration, both tolcapone groups

had greater reductions in levodopa dosage compared to baseline (tolcapone 200 mg: 182.0 mg; tolcapone 400 mg: 180.6 mg) than the placebo group (113.9 mg). However, this effect was not significantly different from placebo. The UPDRS II (ADL) changed significantly (by 1.1) over placebo, but only in the 200 mg group, and none of the other secondary endpoints showed statistical differences compared to placebo. Although this relative short study (6 weeks) had a negative outcome concerning the primary efficacy variable, it confirms the results of Waters et al.[1] regarding the UPDRS II (ADL). The primary outcome measure of this trial is complex and has not been validated clinically. Considering the substantial reduction of levodopa in the placebo group, it is possible that patients had received doses greater than necessary for symptomatic control prior to inclusion. Three drop-outs due to adverse reactions occurred in each of the verum groups, none in the placebo group. The most frequent adverse reactions were nausea, dyskinesia, and diarrhea (in the latter two, however, no significant difference to placebo). There was no specific comment on liver enzymes. This study had an overall quality rating score of 73%.

PREVENTION OF MOTOR COMPLICATIONS

No qualified studies were identified.

CONTROL OF MOTOR COMPLICATIONS

Rajput et al. (1997)[4]: Rajput studied 202 patients with PD who had "wearing-off" phenomenon. This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter trial receiving either tolcapone, 100 mg or 200 mg, three times daily or placebo. The primary efficacy parameter was the daily "on" and "off" time, determined on the basis of patient diaries (self-rating). After 3 months, patients treated with tolcapone 200 mg t.i.d. had significantly reduced "off" time from baseline by 3.25 h; the reduction of 2.3 h seen with tolcapone 100 mg was not statistically significant. Changes in "on" time were not stated. Patients receiving tolcapone had a significant decrease in mean daily levodopa dose (tolcapone 100 mg: 166.3 mg; tolcapone 200 mg: 207.1 mg), and in the number of doses. UPDRS scores did not change with tolcapone. There were 17% and 22% of drop-outs due to adverse reactions in each of the verum groups, and 15% in the placebo group. The most frequently reported adverse reactions were nausea, dyskinesia, sleep disorder, insomnia, anorexia, and diarrhea. Five patients in the verum groups developed elevated liver enzymes, one of who withdrew from the trial. This study had an overall quality rating score of 80%.

Kurth et al. (1997)[5]: This study tested the efficacy of tolcapone in 161 PD patients experiencing "wearing-off" motor fluctuations. This was a dose-finding, randomized, multicenter, double-blind, placebo-controlled, parallel-group trial that tested three doses of tolcapone (50, 200, and 400 mg t.i.d.). At baseline and on day 42, patients were evaluated every 30 minutes for a period of 10 hours. The primary outcome measures were: (1) the "off" time during 10 h (investigator's rating), and (2) the integrated UPDRS motor score over 10 h (area under the curve, AUC). Ten patients did not complete the study. The results show that tolcapone significantly reduced "off" time by 16% to 18% (absolute changes) in all verum arms, which is stated to correspond to a reduction of 1.5 h or a relative reduction of approximately 40% compared to baseline. The integrated UPDRS motor score over 10 h (area under the curve, AUC) was significantly reduced by 49%. Levodopa dosage and frequency were significantly reduced by 200 mg. There were five drop-outs, which were not specified according to treatment group; one of the patients in the tolcapone group had a serious adverse reaction. The most frequent adverse reactions were dyskinesias, nausea, and urine discoloration. This study had an overall quality rating score of 83%.

Myllyla et al. (1997)[6]: Myllyla studied the efficacy of three different doses of tolcapone (50, 200, or 400 mg t.i.d., 6 weeks) in 154 PD patients with ''wearing-off'' symptoms. This was a multicenter, double-blind, randomized, placebo-controlled, parallel-group trial, and the primary efficacy parameters were the daily "on" and "off" times as assessed from the patients' diaries. Tolcapone was more effective than placebo in reducing the ''wearing-off'' phenomenon between baseline and week 6, at all three dosages. The most effective dose reported was 200 mg t.i.d, which increased ''on''-time significantly from 37.9% of the waking day to 50.8%, and reduced ''off''-time significantly from 26.7% of the waking day to 16.4%. (Changes from baseline were not given in hours [i.e. absolute time]). Levodopa dose was significantly decreased by 79.1 mg. Whereas a global assessment improved significantly with all doses, UPDRS scores did not improve. There were three drop-outs due to adverse reactions in the placebo group, and two in the 40 mg group, one in the 200 mg group, and three in 400 mg treatment group. The most frequent adverse reactions in the verum groups were dyskinesia and nausea. Laboratory abnormalities did not occur. This study had an overall quality rating score of 80%.

Baas et al. (1997)[7]: This study tested the efficacy of tolcapone (100 mg, or 200 mg of tolcapone t.i.d.) in patients (n=177) with signs of "wearing off". This study was a multi-center, randomized, double-blind, placebo-controlled, parallel-group trial, and the primary efficacy parameters were the daily "on" and "off" times as assessed by the patients' diary. After 3 months, "off" time decreased significantly by 31.5% (tolcapone 100 mg), and 26.2% (tolcapone 200 mg) of the baseline value. "On" time increased significantly by 21.3% (tolcapone 100 mg) and 20.6% (tolcapone 200 mg) over baseline values. (Changes are not given in hours [i.e. absolute time].) The mean total daily levodopa dose decreased significantly by 109 mg (tolcapone 100 mg), and 122 mg (tolcapone 200 mg). With 200 mg tolcapone t.i.d., only the motor part of the UPDRS was significantly reduced. Twenty-seven patients dropped out due to adverse reactions: 7% from the placebo group; 23% in tolcapone 100 mg group and 15% in the tolcapone 200 mg group. Dyskinesia and nausea were the most frequent levodopa induced adverse reactions. Diarrhea was the most often reported non-dopaminergic adverse reaction and the most frequent reason for withdrawal from the study. Specifically, four patients in the 100 mg tolcapone t.i.d group and six patients in the 200 mg t.i.d group withdrew because of diarrhea. There were abnormal liver enzymes (aspartate aminotransferase AST; alanine aminotransferase ALT) in three tolcapone-treated patients, leading to withdrawal from the study in one patient (see above). This study had an overall quality rating score of 85%.

Adler et al. (1998)[8]: Adler and colleagues enrolled 215 PD patients with predictable end-of-dose motor fluctuations in a multicenter, randomized, double-blind, placebo-controlled, parallel-group study that tested the efficacy of tolcapone, 100 or 200 mg, t.i.d., orally for 6 weeks. The primary efficacy parameter was the change in daily "on" and "off" time as documented in patients' diaries. Both tolcapone regimens significantly reduced "off" time

by 2.0 h/day and 2.5 h/day, respectively, and increased "on" time by 2.1 h/day and 2.3 h/day, respectively. Investigators' global measures of disease severity indicated that significantly more tolcapone-treated patients had reduced wearing off and symptom severity than placebo-treated patients. No significant change in quality-of-life measures occurred. Clinical improvements occurred despite a significant reduction in total daily levodopa dose of 185.5 mg (23%) in the 100 mg t.i.d. group, and 251.5-mg (29%) in the 200-mg t.i.d. group. Adverse reactions lead to discontinuation in 7% of placebo patients and 3% and 5% in the tolcapone groups. Principal adverse reactions were dyskinesia, anorexia, and nausea. Liver abnormalities were not reported. This study had an overall quality rating score of 95%.

The Tolcapone Study Group (1999)[9]: This is the only active comparator study published to date, and it was an open-label, randomized, parallel-group, multi-center trial, comparing bromocriptine (maximal dose 30 mg) to tolcapone (200 mg) in 146 patients with end-of-dose fluctuations. The study was primarily a safety and tolerability study. Therefore no primary efficacy variable was defined, but daily "on" and "off" times were recorded in diaries, UPDRS subscores I to IV were calculated, and the levodopa dose was recorded. After 8 weeks, there was no significant difference between the two treatment groups in terms of "on/off" times and UPDRS scores, but the levodopa dose was decreased by 124 mg (16.5%) in the tolcapone group compared with a reduction of 30 mg (4%) in the bromocriptine group. This difference was statistically significant. There were eight dropouts in each group. The incidence of nausea, orthostatic hypertension, hallucinations, and peripheral edema was greater in the bromocriptine arm, while xerostomia, dystonia, and muscle cramps occurred more often in the tolcapone group. This study had an overall quality rating score of 75%.

REVIEW OF SAFETY

The majority of adverse reactions with administration of tolcapone is due to an increase in levodopa bioavailability and, thus, is dopaminergic in nature. Dyskinesia (about 50%) and nausea (about 20% to 30%) are the most common dopaminergic adverse reactions, although other adverse reactions include hallucinations, insomnia, anorexia, and orthostatic dysregulation. However, the adverse reactions are usually transient and relieved by reducing the levodopa dose. Dropouts because of dyskinesia (only 1.7% in a single study), nausea or vomiting (1% to 3%) or because of hallucinations (1% to 3%) were rare. Marked diarrhea was the most commonly reported nondopaminergic adverse reaction (about 20%). Diarrhea began between two and four months after initiation of therapy and was not frequently reported in studies of only 6-weeks duration. In approximately half of the cases, diarrhea subsided spontaneously or could be controlled. However, diarrhea was a main reason for withdrawal of tolcapone. Withdrawal rates were approximately 3% to 10% without a clear dose relationship. The underlying mechanism of the diarrhea is unknown at this time. Urine discoloration occurred in about 10% of subjects, but never lead to withdrawal from the study. Laboratory analysis showed only a few test abnormalities in parkinsonian patients receiving tolcapone. Three of the eight studies report elevated liver transaminases, and the occurrence was 3% to 4%. Of these patients, 37.5% withdrew from the study. Reports on the recovery rate after withdrawal are scarce. Four of the ten patients remaining on treatment were followed and all recovered. However, three fatal cases of liver injury following treatment with tolcapone have been reported during the post-marketing period (as described elsewhere[10,11]). Consequently, tolcapone was suspended within the European Union (EU)[12]; in the USA the labeling was changed. Specifically, The Food and Drug Administration recommends serum ALT and AST to be determined at baseline, biweekly in the first year, every four weeks in the next six months, and every eight weeks afterwards. Tolcapone should be discontinued if either enzyme exceeds the upper limit of normal. The mechanism of liver toxicity is not clear.

CONCLUSIONS

EFFICACY

PREVENTION OF DISEASE PROGRESSION

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of tolcapone regarding prevention of progression of Parkinson's disease.

SYMPTOMATIC CONTROL OF PARKINSONISM

Based on one Level-I study and additional data from a second trial, when used with levodopa, tolcapone is EFFICACIOUS in improving symptomatic control in patients with PD without or with minor motor fluctuations. This conclusion is restricted to these groups and does not extend to patients with motor fluctuations. The evidence from five Level-I studies is contradictory and available data are INSUFFICIENT to conclude on the efficacy of tolcapone regarding improvement of "on" motor function in this group of patients.

PREVENTION OF MOTOR COMPLICATIONS

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of tolcapone regarding prevention of motor complications of Parkinson's disease.

CONTROL OF MOTOR COMPLICATIONS

Based on five Level-I trials, tolcapone is EFFICACIOUS for management of motor fluctuations. Tolcapone increases "on" and decreases "off" time by about 1 to 2 hours per day. The longest duration of study has been six months, and long-term benefits have not been studied. There is INSUFFICIENT EVIDENCE to conclude on the relative efficacy of tolcapone to other drugs used for this indication.

SAFETY

In non-fluctuating and in fluctuating patients who can be adequately treated with other drugs, tolcapone carries an UNACCEPTABLE RISK. In fluctuating patients who have failed other therapies, tolcapone has an ACCEPTABLE RISK, BUT REQUIRES SPECIALIZED MONITORING as defined by regulatory authorities in different countries where available (e.g., liver function).

IMPLICATIONS FOR CLINICAL PRACTICE

Because of an unacceptable risk and the modest effect size among non fluctuating patients with Parkinson's disease tolcapone is NOT USEFUL in this patient group. Tolcapone is POSSIBLY USEFUL for the management of motor complications ("wearing-off") in patients who have failed alternative medications, but requires regular liver function monitoring.

IMPLICATIONS FOR CLINICAL RESEARCH

· Studies are needed to further study the mechanism of hepatotoxicity, risk factors for hepatotoxicity, as well as the mechanism of tolcapone-induced diarrhea.

· Controlled clinical trials should be done in the population of patients that has current access to tolcapone (i.e. those with motor fluctuation resistant to other medications).

ENTACAPONE

Ten studies were identified through the literature search, and three studies met inclusion/exclusion criteria. A list of the seven trials that were excluded is given below (Bibliography); the reason for exclusion is also described.

PREVENTION OF DISEASE PROGRESSION

No qualified trials were identified.

SYMPTOMATIC CONTROL OF PARKINSONISM

MONOTHERAPY

No qualified trials were identified.

ADJUNCT THERAPY IN STABLE (NON-FLUCTUATING) PARKINSON'S DISEASE

No qualified trials were identified. Two Level-I-trials including patients without motor fluctuations have been recently completed but results have not been published as a full paper.[13]

PREVENTION OF MOTOR COMPLICATIONS

No qualified trials were identified.

CONTROL OF MOTOR COMPLICATIONS

Ruottinen & Rinne (1996)[14]: In this 1-month, double-blind, randomized, cross-over study in 26 fluctuating PD patients, the authors tested the efficacy of entacapone (200 mg) or placebo as add-on therapy to levodopa (doses given 4 to 10 times daily). The primary clinical outcome was the duration of the motor response to an individual levodopa/DDC inhibitor dose. The results show that the duration of motor response was prolonged by 34 minutes (24%) over the placebo response rate. Entacapone treatment resulted in a significant reduction of 140 mg (16%) in the mean total daily levodopa dose, which became necessary because of newly observed or increased intensity of dyskinesia. Also, according to the home diaries, the mean daily "on" time increased significantly by 2.5 h (placebo: 0.4 h), despite the lowered mean levodopa intake. Furthermore, plasma levodopa and its metabolites were measured. Entacapone significantly prolonged the availability of levodopa in the plasma (measured as the increase in the area under the curve [AUC] by 35%) without affecting the maximum plasma levodopa concentration (C_{max}) or the time to maximum concentration (t_{max})**.** There were 58 newly occurring adverse reactions in the entacapone and 39 in the placebo group. The most frequent adverse reactions in the verum groups were diarrhea, abdominal pain, and increase of dyskinesia. One patient in the placebo group and two in the verum group dropped out because of adverse reactions. This study had an overall quality rating score of 71%.

The Parkinson Study Group (1997)[15]: The investigators studied 205 patients with PD who had motor fluctuations. This was a placebo-controlled, double-blind, parallel-group, multi-center trial, and patients were followed for 24 weeks. Upon entry into the trial, patients were randomized to receive either entacapone 200 mg or placebo with each dose of levodopa. The primary measure of efficacy was the change in percentage of "on" time as recorded by subjects with 24-hour home diaries. Entacapone treatment significantly increased the (absolute) percent "on" time by 5.0 percentage points (equal to about 1h) when compared to placebo. The effect of entacapone was more prominent in patients with a smaller percent "on" time (<55%) at baseline, and increased as the day progressed. Total UPDRS and the motor and ADL subscores improved significantly with entacapone, and the total daily levodopa intake was 12% lower than in the placebo group (statistically significant). Ninety five percent of patients in the placebo group and 97% in the verum group experienced adverse reactions, the most frequent (in the verum group) being dyskinesia, urine discoloration, nausea, and constipation. In both groups seven patients discontinued the trial because of adverse reactions. This study had an overall quality rating score of 86%.

Nomecomt Study (1998)[16]: This study looked at a total of 171 PD patients who had wearing-off type motor fluctuations were studied in a six-month, randomized, placebo-controlled, double-blind, parallel-group, multi-center trial. The patients received either 200 mg entacapone or placebo with each daily levodopa dose. The primary efficacy measures were (1) the mean daily "on" time as indicated by the patients' home diaries and (2) the benefit (duration of "on" time) derived from the first levodopa dose in the morning. Home diaries indicated that entacapone significantly increased the mean "on" time by 1.4 h and correspondingly decreased the "off" time by 1.1 h. The average benefit derived from the (first) morning levodopa dose as related by the patients was increased significantly by 0.24 h. The daily levodopa dose was reduced significantly in the entacapone group by 113 mg (12%). Diarrhea was the most common nondopaminergic adverse reaction. Further frequent adverse reactions were nausea, urine discoloration, and worsening of dyskinesia. Due to adverse reactions there were five drop-outs in the placebo group and 6 in the verum group. This study had an overall quality rating score of 83%.

REVIEW OF SAFETY

The majority of adverse reactions with administration of entacapone is due to an increase in levodopa bioavailability and, thus, is dopaminergic in nature. Dyskinesia (20-50%) and nausea (about 20%) are the most common dopaminergic adverse reactions. The adverse reactions are usually transient and relieved by reducing the levodopa dose. Dropouts because of dyskinesia (only 1.9% in one study), nausea or vomiting (1.2% in one study), or hallucinations (1% in one study) were rare. Marked diarrhea was the most commonly reported nondopaminergic adverse reaction (15% to 20%). In contrast to tolcapone, there are no observations reported concerning the time course of diarrhea. Diarrhea was the cause of withdrawal in only one of the studies (3.4%). Urine discoloration occurred in 10% to 40% but was never the primary reason for withdrawal from these three studies.

No laboratory abnormalities were seen in parkinsonian patients receiving entacapone. Rises in liver enzymes were occasionally seen in clinical studies with entacapone, but at similar rates compared to placebo-arms. To date, there have been no cases of clinical hepatotoxicity associated with entacapone and monitoring of liver enzymes is not required. According to the EMEA, patients

with a history of neuroleptic malignant syndrome or non-traumatic rhabdomyolysis should not be treated with entacapone although there have been no instances of NMS like syndromes in patients receiving entacapone.

CONCLUSIONS

EFFICACY

PREVENTION OF DISEASE PROGRESSION

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of entacapone regarding the prevention of progression of Parkinson's disease.

SYMPTOMATIC CONTROL OF PARKINSONISM

Based on several Level-I-studies entacapone is EFFICACIOUS in improving "ON" motor function in patients with fluctuating Parkinson's disease. No data are presently available to conclude on its efficacy as adjunct to levodopa in patients without motor fluctuations ("stable responders").

PREVENTION OF MOTOR COMPLICATIONS

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of entacapone regarding prevention of motor complications of Parkinson's disease.

CONTROL OF MOTOR COMPLICATIONS

Based on three positive Level-I-trials entacapone is EFFICACIOUS for the management of motor fluctuations given at a dose of 200 mg with each levodopa intake. The longest duration of study has been six months, and long-term effects are undetermined. No recommendation can be made regarding the relative efficacy of entacapone versus other treatments used for this indication (MAO-B inhibitors, DA agonists, and other levodopa formulations).

SAFETY

Treatment of patients with PD with motor fluctuations with entacapone has an ACCEPTABLE RISK WITHOUT SPECIALIZED MONITORING. Post-marketing surveillance did not reveal evidence for hepatic toxicity, but time of follow-up was limited.

IMPLICATIONS FOR CLINICAL PRACTICE

Entacapone is CLINICALLY USEFUL in the management of motor fluctuations ("wearing-off") in levodopa-treated patients with Parkinson's disease. There are no reported serious safety hazards although up to 3% of patients may develop severe diarrhea requiring drug discontinuation. Patients taking entacapone may need to reduce their daily levodopa intake if dyskinesia appears or is exacerbated. No data are available on patients without fluctuations; therefore, no recommendation is possible at this point.

IMPLICATIONS FOR CLINICAL RESEARCH

· The role of early adjunct therapy with entacapone to levodopa therapy as a strategy to prevent or postpone the emergence of motor complications needs to be studied in randomized controlled long-term trials.

· As all studies available to date have been in fluctuating patients with mild-to-moderate wearing-off fluctuations, the role of entacapone in the management of unpredictable fluctuations phenomenon needs to be defined.

· Further research should focus on the relative efficacy of entacapone versus other treatments used for this indication (MAO-B inhibitors, DA agonists, levodopa formulations, and other COMT inhibitors).

· Studies on the long-term clinical benefit regarding efficacy, safety, quality of life, survival, and the cost-effectiveness of the different approaches are necessary.

· The mechanism underlying entacapone-induced diarrhea also needs to be studied.

REFERENCES

1. Kurth MC, Adler CH. COMT inhibition: A new treatment strategy for Parkinson's disease. Neurology 1998;50(suppl 5):S3-14.
2. Waters CH, Kurth M, Bailey P, et al. Tolcapone in stable Parkinson's disease: efficacy and safety of long-term treatment. The Tolcapone Stable Study Group. Neurology 1997;49:665-671.
3. Dupont E, Burgunder JM, Findley LJ, Olsson JE, Dorflinger E. Tolcapone added to levodopa in stable parkinsonian patients: a double-blind placebo-controlled study. Tolcapone in Parkinson's Disease Study Group II (TIPS II). Mov Disord 1997;12:928-934.
4. Rajput AH, Martin W, Saint-Hilaire MH, Dorflinger E, Pedder S. Tolcapone improves motor function in parkinsonian patients with the "wearing-off" phenomenon: a double-blind, placebo-controlled, multicenter trial. Neurology 1997;49:1066-1071.
5. Kurth MC, Adler CH, Hilaire MS, et al. Tolcapone improves motor function and reduces levodopa requirement in patients with Parkinson's disease experiencing motor fluctuations: a multicenter, double-blind, randomized, placebo-controlled trial. Tolcapone Fluctuator Study Group I. Neurology 1997;48:81-87.
6. Myllyla VV, Jackson M, Larsen JP, Baas H. Efficacy and safety of tolcapone in levodopa-treated Parkinson's disease patients with ''wearing-off'' phenomenon: a multicenter, double-blind, randomized, placebo-controlled trial. Eur J Neurol 1997;(4):333-341.
7. Baas H, Beiske AG, Ghika J, et al. Catechol-O-methyltransferase inhibition with tolcapone reduces the "wearing off" phenomenon and levodopa requirements in fluctuating parkinsonian patients. J Neurol Neurosurg Psych 1997;63:421-428.
8. Adler CH, Singer C, O'Brien C, et al. Randomized, placebo-controlled study of tolcapone in patients with fluctuating Parkinson disease treated with levodopa-carbidopa. Tolcapone Fluctuator Study Group III. Arch Neurol 1998;55:1089-1095.
9. Tolcapone Study Group. Efficacy and tolerability of tolcapone compared with bromocriptine in levodopa-treated parkinsonian patients. Tolcapone Study Group. Mov Disord 1999;14:38-44.
10. Colosimo C. The rise and fall of tolcapone. J Neurol 1999;246(10):880-882.
11. Assal F, Spahr L, Hadengue A, Rubbici-Brandt L, Burkhard PR. Tolcapone and fulminant hepatitis. Lancet 1998;352:958.
12. The European Agency for the Evaluation of Medicinal Products (EMEA) Entacapone: CPMP/2178/98 (22 September 1998); Tolcapone: CPMP/343/97 (27 August 1997).
13. Brooks D, Poewe W, Deuschl G, Leinonen M, Kultalahti ER, Reinikeinen K, Gordin A. and the UK-Irish Entacapone Study Group and the Celomen Study Group. Effect of entacapone on activities of daily living and daily levodopa dosage in patients with early Parkinson's disease without motor fluctuations. Parkinsonism & Related Disorders 2001;7:S53
14. Ruottinen HM, Rinne UK. Entacapone prolongs levodopa response in a one month double blind study in parkinsonian patients with levodopa related fluctuations. J Neurol Neurosurg Psychiatry 1996;60:36-40.
15. Parkinson Study Group. Entacapone improves motor fluctuations in levodopa-treated Parkinson's disease patients. Ann Neurol 1997;42:747-755.
16. Rinne UK, Larsen JP, Siden A, Worm Petersen J, and the Nomecomt Study Group. Entacapone enhances the response to levodopa in parkinsonian patients with motor fluctuations. Neurology 1998;51:1309-1314.

BIBLIOGRAPHY - EXCLUDED FROM ANALYSIS (REASON FOR EXCLUSION)

Agid Y, Destee A, Durif F, Montastruc JL, Pollack P. Tolcapone, bromocriptine, and Parkinson's disease. Lancet 1997;350:712-713. (Letter; only preliminary results from Tolcapone Study Group 1999)

Baas H, Beiske AG, Ghika J, et al. Catechol-O-methyltransferase inhibition with tolcapone reduces the "wearing off" phenomenon and levodopa requirements in fluctuating parkinsonian patients. Neurology 1998;50:S46-53. (Duplicate publication from Baas et al., 1997)

Davis TL, Roznoski M, Burns RS. Effects of tolcapone in Parkinson's patients taking L-dihydroxyphenylalanine/carbidopa and selegiline. Mov Disord 1995;10:349-351. (Included less than 20 patients)

Deuschl G, Poewe W, Poepping M, and the Celomen Study Group. Efficacy and safety of entacapone as an adjunct to levodopa treatment in Parkinson's disease (PD): Experience from the Austrian-German six months study. Parkinsonism & Related Disorders 1999;5:S75. (Abstract)

Hauser RA, Molho E, Shale H, Pedder S, Dorflinger EE. A pilot evaluation of the tolerability, safety, and efficacy of tolcapone alone and in combination with oral selegiline in untreated Parkinson's disease patients. Tolcapone De Novo Study Group. Mov Disord 1998;13:643-647. (Patients without levodopa medication, only useful as a safety study)

Kaakkola S, Teravainen H, Ahtila S, et al. Entacapone in combination with standard or controlled-release levodop/carbidopa: a clinical and pharmacokinetic study in patients with Parkinson's disease. Eur J Neurol 1994;2:341-347. (Included less than 20 patients)

Kaakkola S, Teravainen H, Ahtila S, Rita H, Gordin A. Effect of entacapone, a COMT inhibitor, on clinical disability and levodopa metabolism in parkinsonian patients. Neurology 1994;44:77-80. (Included less than 20 patients)

Limousin P, Pollak P, Pfefen JP, Tournier-Gervason CL, Dubuis R, Perret JE. Acute administration of levodopa-benserazide and tolcapone, a COMT inhibitor, Parkinson's disease. Clin Neuropharmacol 1995;18:258-265. (Included less than 20 patients)

Lyytinen J, Kaakkola S, Ahtila S, Tuomainen P, Teravainen H. Simultaneous MAO-B and COMT inhibition in L-Dopa-treated patients with Parkinson's disease. Mov Disord 1997;12:497-505. (Included less than 20 patients)

Merello M, Lees AJ, Webster R, Bovingdon M, Gordin A. Effect of entacapone, a peripherally acting catechol-O-methyltransferase inhibitor, on the motor response to acute treatment with levodopa in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 1994;57:186-189. (Included less than 20 patients)

Rajput AH, Martin W, Saint-Hilaire MH, Dorflinger E, Pedder S. Tolcapone improves motor function in parkinsonian patients with the "wearing-off" phenomenon: a double-blind, placebo-controlled, multicenter trial. Neurology 1998;50:S54-S59. (Duplicate publication from Rajput et al., 1997)

Roberts JW, Cora-Locatelli G, Bravi D, Amantea MA, Mouradian MM, Chase TN. Catechol-O-methyltransferase inhibitor tolcapone prolongs levodopa/carbidopa action in parkinsonian patients. Neurology 1993;43:2685-2688. (Open-label, non-controlled study that included less than 20 patients)

Ruottinen HM, Rinne UK. Effect of one month's treatment with peripherally acting catechol-O-methyltransferase inhibitor, entacapone, on pharmacokinetics and motor response to levodopa in advanced parkinsonian patients. Clin Neuropharmacol 1996;19:222-233. (Included less than 20 patients, open study)

Ruottinen HM, Rinne UK (1996). A double-blind pharmacokinetic and clinical dose-response study of entacapone as an adjuvant to levodopa therapy in advanced Parkinson's disease. Clin Neuropharmacol 1996;19:283-296. (No long-term follow-up; this was mainly a dose-response study)

Waters CH, Kurth M, Bailey P, et al. Tolcapone in stable Parkinson's disease: efficacy and safety of long-term treatment. Tolcapone Stable Study Group. Neurology 1998;50:S39-S45. (Duplicate publication of Waters et al., 1997)

Yamamoto M, Yokochi M, Kuno S, et al. Effects of tolcapone, a catechol-O-methyltransferase inhibitor, on motor symptoms and pharmacokinetics of levodopa in patients with Parkinson's disease. J Neural Transm 1997;104:229-236. (Open-label, non-controlled study in less than 20 patients)

Movement Disorders
Vol. 17, Suppl. 4, 2002, p. S52

Published by Wiley-Liss, Inc.
DOI 10.1002/mds.5561

DA Agonists - Overview

INTRODUCTION

BACKGROUND

Levodopa (L-dopa) is the most widely used therapy for symptomatic management in Parkinson's disease (PD). However, L-dopa is not effective for treating all parkinsonian symptoms, it exerts no known effect on slowing disease progression, and it induces a number of adverse reactions classified as either "peripheral" (eg. nausea, vomiting, hypotension) or "central" (eg. psychosis and motor complications such as fluctuations and dyskinesias). As a result, many patients require alternative therapies.

Dopamine (DA) agonists are some of these commonly used alternative treatments for PD. The initial discovery of the antiparkinsonian effects of a DA agonist, namely bromocriptine, was first reported by Calne and colleagues, in the early seventies.[1,2] Since this time, several dopamine agonists have been approved and marketed for use in patients with PD. In spite of this relatively long period of clinical use, the role of DA agonists in the management of PD remains controversial. Some experts debate that DA agonists should be used later in the course of the disease, specifically at the end of the L-dopa "honeymoon" period. This strategy is recommended to improve the patient's condition once faced with motor complications associated with long-term L-dopa therapy. Others argue that DA agonists should be used earlier in the course of disease, and even as first-line treatment, in order to delay or reduce the need for levodopa and therefore reduce the risk of L-dopa-induced long-term motor complications.

RATIONALE

Dopamine agonists may indeed have several potential advantages over L-dopa.[3] For example, in contrast to L-dopa, dopamine agonists are supposed to act directly at the level of the dopamine (DA) receptors. Stimulating postsynaptic dopamine receptors, therefore, directly offers the theoretical possibility to by-pass the degenerating nigrostriatal dopaminergic pathway. Moreover, dopamine agonists do not depend on a pool of decarboxylase enzymes for conversion into active neurotransmitter, like L-dopa, which needs to be decarboxylated into dopamine.

All DA agonists have complex pharmacodynamic properties, which differ among agents in this class, but they are all acting on D2-like DA receptors. It is generally accepted that the D2-like receptor activity of dopamine agonists explains the antiparkinsonian effect. Their putative selectivity on some DA or non-DA receptor subtypes could also be related to potential specific clinical profiles, such as a reduced risk for some adverse reactions associated with the stimulation (or nonstimulation) of specific receptors.

Some authors suggest that DA agonists may have neuroprotective properties.[4] Unlike L-dopa, which is transformed into DA, DA agonists do not produce potentially toxic metabolites and free radicals, which have been implicated in the pathophysiology of PD. Conversely, acting on dopamine presynaptic receptors, dopamine agonists can reduce dopamine turnover, and therefore, further reduce the generation of dopamine-derived toxic free radicals. Finally, dopamine agonists can allow the concomitant use of lower doses of L-dopa (L-dopa dose sparing effect), thus reducing generation of L-dopa- and DA-derived toxic metabolites.

Most dopamine agonists have a longer elimination half-life than L-dopa. It is possible that an abnormal pulsatile dopaminergic stimulation, as induced by daily oral L-dopa administration, deregulates dopaminergic and non-dopaminergic receptors at the level of the basal ganglia, leading to the occurrence of abnormal motor responses like fluctuations and dyskinesias.[5] The use of longer-acting compounds like DA agonists may help reduce the risk of occurrence of such adverse drug reactions. However, these remain speculative.

Most mechanism(s) of action of DA agonists in PD are still undetermined including an understanding of possible neuroprotective effects of DA agonists, differences in the role of D1-like vs. D2-like receptors, and clinical effects of some DA agonists on non-DA receptors (eg. noradrenergic, serotonergic). It also is unclear if all DA agonists are equivalent or if they have different specific pharmacological properties, which might differentiate one DA agonist from another regarding efficacy or safety. Possible differences among subpopulations of patients with PD and their clinical response to DA agonists is unclear (eg. greater clinical benefits in younger vs. older patients). Studies need to be done to assess: (1) if there is any difference on long-term follow-up when combining a DA agonist with L-dopa; (2) when to initiate DA therapy in a patient; or (3) when to initiate one drug first, and supplement with other medications at later time points.

The different DA agonists specifically discussed in this chapter include (alphabetical order) apomorphine, bromocriptine, cabergoline, dihydroergocryptine, lisuride, pergolide, piribedil, pramipexole, and ropinirole. These agonists will be discussed in two sections, ergot-based and non-ergot-based.

METHODS

KEY SEARCH TERMS

The terms used for the search included "Parkinson's disease" and "dopaminergic agonists", or "dopamine agonists", or "bromocriptine", or "pergolide", or "lisuride", or "ropinirole", or "apomorphine", or "pramipexole", or "cabergoline", or "piribedil" or "dihydroergocryptine".

SPECIAL EXCEPTIONS TO INCLUSION/ EXCLUSION CRITERIA

In addition to the previously reviewed general inclusion/exclusion criteria, this chapter specifically excludes studies including less than 20 patients per treatment group, and interim analysis reports, unless such analysis had been explicitly planned in advance in the protocol and the study powered for such analysis.

In the case of the absence of Level-I data fulfilling such inclusion/ exclusion criteria, smaller (less than 20 patients per treatment group), shorter (less than 4 weeks), randomized (Level-I) data, and/or non-randomized but controlled (Level-II) and uncontrolled (Level-III) trials have been incorporated. The reasons for these special exceptions are specified within each of the corresponding DA agonists subsections.

Movement Disorders
Vol. 17, Suppl. 4, 2002, p. S53-S67

Published by Wiley-Liss, Inc.
DOI 10.1002/mds.5562

DA Agonists - Ergot derivatives: Bromocriptine

BASIC PHARMACOLOGY

MECHANISM OF ACTION

Bromocriptine is a tetracyclic ergoline compound derived from plant alkaloids.[6] It is the first DA agonist marketed for the treatment of PD. Bromocriptine is a D2-like receptor agonist and a partial D1-like receptor agonist (which means that it has some weak D1 antagonistic effects on normosensitive receptors). Like most ergot derivatives, bromocriptine has also 5-HT2 antagonist effects and mild adrenergic effects.

Bromocriptine improves the symptoms of all available rodent and primate models of PD. Bromocriptine lowers prolactine plasma levels, induces nausea and lowers blood pressure. Some authors speculate that bromocriptine might have neuroprotective properties because it can act in vitro as a free radical scavenger, and it can reduce DA turnover in vivo and therefore, may minimize damage caused by oxidative stress.[7,8]

PHARMACOKINETICS

After oral administration, bromocriptine is not completely absorbed (in humans), and maximal plasma levels are reached after 70 to 100 minutes with high variations among individuals.[9,10] The absolute oral bioavailability is less than 10 % since 90% of it undergoes first-pass hepatic metabolism. Bromocriptine plasma elimination half-life is about 6-8 hours. Ninety percent is bound to plasma proteins. Only a small amount is excreted unchanged in the urine (5%). The high level of metabolism that occurs increases the risk of drug interaction. Macrolides, acting as enzyme inhibitors and displacing bromocriptine from the binding protein, may lead to increased plasma bromocriptine concentrations and toxicity.

REVIEW OF CLINICAL STUDIES

This paragraph is limited to clinical trials involving standard formulations of bromocriptine. A slow release formulation of bromocriptine has also been developed, but is excluded from this review because it has not been marketed in most countries.[11,12]

PREVENTION OF DISEASE PROGRESSION

Level-I Studies

Olanow et al. (1995)[13]: Olanow and colleagues performed a randomized, parallel groups, double-blind, placebo-controlled study (also known as the SINDEPAR trial), which assessed the effect of selegiline and bromocriptine on the progression of PD. In this study, 101 untreated patients with PD (mean age = 66 years) were randomly assigned to one of the following four treatment groups (Deprenyl(r) plus Sinemet(r); placebo-Deprenyl(r) plus Sinemet(r); Deprenyl(r) plus bromocriptine; placebo-Deprenyl(r) plus bromocriptine). The final visit was performed at 14 months, 2 months after withdrawal of Deprenyl (or its placebo) and 7 days after withdrawal of Sinemet or bromocriptine. Deterioration of UPDRS total score between baseline and final visit was used as an index of PD progression. Deterioration in UPDRS score was not significantly different in patients randomized to treatment with Sinemet (1.7 ±1.6) or bromocriptine (4.5±1.2), suggesting that the disease probably progressed at the same rate in the L-dopa- and bromocriptine-treated patients. This result does not support a "neuroprotective" effect of bromocriptine. However, in the absence of placebo only-treated patients, it is not possible to conclude if both drugs had no effect or had similar effects on disease progression. Moreover, it is unclear if a one-week L-dopa and bromocriptine wash-out period was sufficient to eliminate the long-duration of symptomatic response associated with both drugs. If not, assessing UPDRS scores after a "short" wash-out period may not be a reliable outcome to measure disease progression. No "clinically significant" adverse reactions were reported during this study. The authors reported that there were no statistically significant differences in the incidence of adverse reactions among treatment groups. The study had an overall quality score of 76%.

SYMPTOMATIC CONTROL OF PARKINSONISM

Sixteen randomized (Level-I) studies were identified and reviewed below. Additionally, one small (less than 20 patients per treatment group), randomized, placebo-controlled trial is included because of the lack of other identified larger Level-I placebo-controlled information.[14] One study by Rinne[15], which is frequently cited in the literature and had a strong impact on many physicians' clinical practice, is excluded from this review because it is not randomized and uses a retrospective historical L-dopa-treated group of patients in the comparator arm (Level II).

MONOTHERAPY LEVEL-I STUDIES

Placebo-controlled Studies

Staal-Schreinemachers et al. (1986)[14]: This was a 6-month, double-blind, parallel-group study conducted in 24 de novo patients with PD (12 patients per group) randomized to bromocriptine (up to 15 mg/day) or placebo. Twenty-one patients (placebo: n=11, bromocriptine: n=10) completed the study. Efficacy was assessed using a 0-3 rating scale for separate parts of the body (as proposed by the Research Group on Extrapyramidal Disorders of the World Federation of Neurology) and the Northwestern University Disability Scale. Compared with the placebo group, improvement in parkinsonian symptoms (combined scores for bradykinesia, rigidity, and tremor) and independence in daily living were reported to be statistically significantly better in the bromocriptine group (15 mg/d). (The main assessment criteria used in this study has not been clearly validated, and the magnitude of the clinical effect is not explicitly given [scores appearing in figures only with no raw values reported in the text]). Adverse reactions were observed in 5

out of the 10 patients receiving bromocriptine and were consistent with known dopaminergic adverse reactions (eg. nausea, anorexia, vomiting, dizziness, vasospasm, cramps in the legs, and postural hypotension). After a 1-year follow-up, bromocriptine was still used as monotherapy (daily dose increased to 30 mg/d) in 6 out of 10 patients, and L-dopa was adjuncted in another 4 patients. This study had an overall quality score of 64%.

Active Comparator Studies

L-dopa-controlled Studies

Libman et al. (1986)[16]: Fifty-one de novo patients with PD were enrolled in this double-blind, L-dopa-controlled, parallel arm study. Forty-nine patients completed the double-blind part of the trial, and were assessed after a mean duration of treatment of 19.5 weeks. Efficacy was assessed using Hoehn and Yahr Scale, Columbia University Rating Scale (CURS), and the Northwestern University Disability Scale (NUDS). Bromocriptine (24 mg/d) and L-dopa (252 mg/d) induced similar improvements on all efficacy parameters. Hoehn and Yahr score improved by at least one unit in 42% of the bromocriptine-treated patients, and in 32% of the L-dopa-treated patients. The mean CURS significantly improved in the bromocriptine group by 62% (from 18.9 at baseline to 7.3 at week 21) and in the L-dopa group by 55 % (from 16.4 at baseline to 7.1 at week 21). This improvement was not statistically different between groups and was reported to have occurred at the cost of comparable adverse reactions in both groups with the most frequent event reported being nausea. This study had an overall quality score of 69%.

Riopelle et al. (1987)[17]: This was a randomized, double-blind, parallel group L-dopa-controlled study conducted in 81 de novo patients with PD (mean age=66 years). Seventy-seven patients completed the trial and were followed for 5.5 months. Parameters used to assess efficacy were the clinical status of the Hoehn and Yahr Scale, the CURS, and the NUDS. At the mean dose of 26 mg/d, bromocriptine was reported to improve parkinsonian symptoms with the same efficacy than L-dopa (262 mg/d): Hoehn and Yahr score improved by 20% with bromocriptine and by 16% with L-dopa. Similarly, the CURS score improved by 61% with bromocriptine and 55% with L-dopa. The NUDS score also improved by 38% with bromocriptine and by 37% with L-dopa (the raw data scores are not reported in the text). This improvement was reported to occur with comparable amount of adverse reactions (not specifically reported in the text). This study had an overall quality scale of 75%.

Cooper et al. (1992)[18]: This was an open-label, randomized, parallel group, 4-month study designed to assess different effects of dopaminergic and anticholinergic therapies on a number of cognitive outcomes (eg. Weschler Memory Scale) in newly diagnosed, de novo patients with PD. Motor response was also assessed using the King's College Rating Scale (KCRS) and the unimanual and bimanual fine finger movement tasks. Sixty-seven patients (mean age approximately 60 years) were randomized to one of 3 monotherapy regimen: L-dopa, bromocriptine or anticholinergics. A fourth group of patients elected not to be treated and were retested in an untreated state thereby creating a "non-randomized," untreated comparative control group. At 4 months, motor status significantly improved in the L-dopa (415 mg/d, KCRS: baseline=22.9 vs. 4 months=12.0) and anticholinergics groups (KCRS: baseline=22.3 vs. 4 months=17.2). In contrast, bromocriptine, used at a low dose which might not be clinically adequate (13.5 mg/d) did not induce any significant change (KCRS: baseline=23.0 vs. 4 months=21.0). The L-dopa group reported significantly improved working memory (Wechsler Memory Scale), while bromocriptine resulted in no significant memory improvements and anticholinergic treatment showed a trend toward deterioration. No details are provided about adverse reactions. This study had an overall quality score of 55%.

Parkinson's Disease Research Group in the UK (1993)[19]: This was a randomized, open-label study in 782 de novo PD patients and compared the efficacy and safety of three parallel arm treatment groups: L-dopa monotherapy, L-dopa combined with selegiline and bromocriptine monotherapy. Patients' mean age at entry was about 62 years. This was a 3-year planned interim analysis report. The study was powered for differences in mortality following 10 years of follow-up. Outcome measurement indices of motor function (secondary endpoints) were a modified version of the Webster Scale and the NUDS. In the clinical report, both 1-year and the 3-year data are reported together. After a 1-year follow-up, L-dopa alone (420 mg/d) or in combination with selegiline (352 mg/d plus 10 mg/d) was found to be significantly more potent than bromocriptine (36 mg/d) (Webster adjusted improvement score: L-dopa=3.1, L-dopa+selegiline=3.4, bromocriptine:2.1; adjusted difference [95% CI] in favor of L-dopa vs. bromocriptine:0.93 [0.27-1.5], p=0.006;and in favor of L-dopa+selegiline vs. bromocriptine 1.25 [0.61-1.89], p=0.0002). However, regarding the small intergroup differences and the strong power of the study due to the large numbers of patients, the authors concluded that the difference on functional improvement was "not considered marked enough to suggest that the choice of treatment at this early stage of the disease was critical". More patients withdrew from the study because of adverse reactions in the bromocriptine group (mainly because of gastrointestinal and psychiatric adverse reactions). After 3 years, 32% of the patients were still treated with bromocriptine monotherapy. Motor complications were less frequent in the bromocriptine patients compared with the two other treatment groups (see paragraph on Prevention of Motor Complications). This study had an overall quality score of 63%.

Montastruc et al. (1994)[20]: This was a randomized, parallel group, open-label study conducted in 60 de novo patients with PD (mean age=approximately 61 years) with a 5-year follow-up. This study tested the effects of an initial bromocriptine monotherapy to which L-dopa could be added during the course of the study in case of waning efficacy or dose-limiting side-effects. The primary objective of this trial was to compare the occurrence of long-term motor complications, but motor function was also assessed twice a year, using the CURS until 1985, and the UPDRS thereafter. At baseline, disease severity was reported to be comparable in both groups according to the Hoehn and Yahr stage. After 5 years, bromocriptine (52 mg/d) combined with L-dopa in 27/31 patients (471 mg/d, after a mean delay of 2.7 years) and L-dopa monotherapy (569 mg/d) were reported to induce the same control on parkinsonian symptoms. UPDRS motor scores at the endpoint or at the last visit of follow-up were 10.6 in the bromocriptine/L-dopa group and 11.0 in the L-dopa group. Four of the 31 patients in the bromocriptine group did not require L-dopa addition. No data are available on digestive or cardiovascular adverse reactions. Hallucinations were more frequent in the bromocriptine group (5 in the bromocriptine/L-dopa group vs. 2 in the L-dopa group). Long-term motor complications were less frequent in the bromocriptine group (see section on Prevention of Motor Complications). The overall quality score was 69%.

Olanow et al. (1995)[12]: This was a 14-month, double-blind, randomized, placebo-controlled study, (also see section on Prevention of Disease Progression) designed to evaluate the effects of deprenyl, L-dopa, and bromocriptine on PD progression (n=101 de novo patients with PD). Before the wash-out period, it was possible to compare the symptomatic effects of L-dopa and bromocriptine using the total UPDRS scores. Sinemet-treated patients (~ 400 mg/d) demonstrated a trend toward improvement (UPDRS at baseline=23.4 vs. 12 month=18.3) compared to the bromocriptine-treated group (~ 28 mg/d) (UPDRS at baseline=22.7 vs. 12 month=21.5), but the difference was not significant. There were no reported difference in the incidence of adverse reactions in both groups, but no details are provided. This study had an overall quality score of 76%.

Pergolide-controlled Studies

Mizuno et al. (1995)[21] (also see section on Pergolide): This short-term (8-week), double-blind, pergolide-controlled study reported results on the clinical differences in treatment of two different subtypes of patients with PD: newly diagnosed and advanced disease. Results were reported separately in these two subpopulations of patients. Forty-nine de novo patients with PD were randomized to pergolide (maximum dose 2.25 mg/d) and 49 others were randomized to bromocriptine (maximum dose 22.5 mg/d). Efficacy was evaluated using a simplified rating scale consisting of five-grade rating scores (from normal to marked improvement) similar to the UPDRS but with the number of criteria evaluated reduced to 21. Global improvement was also assessed by the investigator using a 5-point, semiquantitative scale (from marked improvement to worsening). Pergolide (mean dose 1.43 mg/d) and bromocriptine (mean dose 15.1 mg/d) improved most of the variables studied (ie. tremor, rigidity, akinesia, retropulsion, short-step gait, masked face, freezing, hygiene, feeding, and dressing; many variables were analyzed and therefore, mean data is not provided in the body of this review. No data was reported on changes in total score). The magnitude of the improvement was reported to be similar in both treatment groups with no between-treatment differences observed in the global improvement rating scale (marked improvement: pergolide 4.1% vs. bromocriptine 10.4%, moderate improvement: pergolide 36.7% vs. bromocriptine 31.3%, mild improvement: pergolide 49.0% vs. bromocriptine 45.8%). Adverse reactions were comparable in both groups (pergolide 32.8%, bromocriptine 25.5%); the most common reactions including nausea (pergolide 29.5%, bromocriptine 30.4%) and hallucinations (pergolide 6.6%, bromocriptine 5.4%). This study had an overall quality score of 53%.

Ropinirole-controlled Studies

There are two published Level-I studies identified that compared bromocriptine and ropinirole in de novo patients with PD[22,23] (also see section on Ropinirole). Both reports correspond to the same parallel, double-blind study, conducted in 335 de novo patients with PD, but analyzed at two different time points.

Korczyn et al. (1998)[22]: This was a planned interim analysis at 6 months following initiation of treatment. The study was stratified for selegiline concomitant use, and L-dopa (open label) supplementation was allowed if study medication was insufficient to control parkinsonian symptoms at the highest tolerated dose. The primary efficacy end-point at 6-months was the percentage improvement in UPDRS motor score. Secondary efficacy variables included the proportion of patients with a 30% reduction in UPDRS motor score (responders), patients with scores of 1 (very much improved) or 2 (much improved) on a CGI score, and the proportion of patients requiring L-dopa supplementation. At a mean dose of 8.3 mg/d, ropinirole was found to be slightly, but significantly, more potent on parkinsonian disability than bromocriptine (16.8 mg/d) (UPDRS% reduction: ropinirole=-35% vs. bromocriptine=-27%, $p<0.05$). Stratification for selegiline showed that there was a significant treatment-interaction with selegiline; the difference in UPDRS improvement was only present in patients who were not receiving selegiline. Secondary motor efficacy variables showed a similar trend in favor of ropinirole. Overall, regardless of selegiline stratification, 58% of patients were considered as responders with ropinirole and 43% with bromocriptine (OR 0.93; 95% CI (1.29 -2.89)). Overall, CGI responder analysis showed the same trend (48% vs. 40%), but the difference was statistically significant only in the non-selegiline-treated patients. By the end of the study, 7% of the ropinirole-treated patients required L-dopa supplement vs. 11% of the bromocriptine-treated patients. Regarding the small amplitude of these differences, it seems reasonable to question their clinical relevancy from a practical clinical viewpoint. Adverse reactions caused premature withdrawal in 5% of the ropinirole-treated patients and in 10% of the bromocriptine-treated ones. The list of adverse reactions reported with both drugs was consistent with other reactions reported with dopaminergic agents (nausea: ropinirole 36%, bromocriptine 20%; vomiting: ropinirole 10%, bromocriptine 5%; postural hypotension: ropinirole 7%, bromocriptine 9%; psychiatric symptoms: ropinirole 7%, bromocriptine 5%; somnolence:ropinirole 6%, and bromocriptine 7%). The overall quality score for this study was 89%.

Korczyn et al. (1999)23: This was the final analysis of the previous report comparing bromocriptine to ropinirole.[22] After 3 years of treatment, comparable differences favoring ropinirole were also observed in the patients who completed the trial (ropinirole 12mg/d, bromocriptine 24 mg/d). UPDRS II scores (Activity Daily Living) were: ropinirole=5.83 vs. bromocriptine=7.28 ($p<0.01$) and UPDRS III percentage changes were: ropinirole=-31% vs. bromocriptine=-22% (non-significant). A 1.46 point difference in a self-rated daily living activities (ADL) was reported between treatment groups, and the differences were statistically significant between treatments. However, the magnitude of the difference between groups was small and the clinical relevancy of this difference remains uncertain. After a 3-year treatment period, approximately one third of the patients remaining in the trial maintained a monotherapy treatment regimen without the need of L-dopa supplementation. Adverse reactions were similar in both groups including nausea, vomiting, dizziness, hypotension and psychiatric symptoms. Approximately one third of the patients withdrew from the trial at 3 years. Long-term motor complications were similar and remarkably infrequent in both treatment groups (also see section on Prevention of motor complications). The overall quality score for this study was 76%.

Other Level-I Studies

UK Bromocriptine Research Group (1989)[24]: This was a randomized, double-blind, parallel arm, controlled study comparing the benefit/risk ratio of two different introductory dosage regimens of bromocriptine in 134 de novo patients with PD. Dose titration regimens for bromocriptine were either a "low/slow" regimen (up to a maximum of 25 mg/d) or a "high/fast" regimen (up to a maximum of 100 mg/d). A patient's ability to achieve a 33% improvement in clinical rating scores was recorded using a combined score of func-

tional disability (Webster) and self-rated daily living activities (ADL). Fifty percent of the patients had reached the improvement criteria in 26 weeks, 49% from the "low/slow" (mean bromocriptine dose=22 mg/d) and 53% from the "high/fast" (mean bromocriptine dose=55 mg/d) group, which was not significantly different between treatment regimens. Adverse reactions leading to withdrawal from the study (eg. psychiatric disturbances, gastro-intestinal, and postural hypotension) occured in 36% of the patients in the "high/fast" group vs. 20% in the "low/slow" group ($p<0.05$). The "high/fast" regimen was less well tolerated than the "low/slow" regimen, but the latter had the disadvantage of a longer delay before patients reached an effective dose. The authors recommend an intermediate dosing strategy. This study had an overall quality score of 63%.

ADJUNCT THERAPY (L-DOPA-TREATED PD PATIENTS)

There are two populations where bromocriptine was added to L-dopa therapy: early combination or late combination. Early combination is defined as adding bromocriptine to L-dopa treatment within the first month in stable, nonfluctuating patients. Late combination is defined as adding bromocriptine after patients have received several years of L-dopa therapy in patients with motor fluctuations.

Early Combination

Herskovits et al. (1988)[25]: This was a randomized, open-label study conducted over a 31-month period in 86 de novo patients with PD patients (mean age 68 years). The study was unusual in that patients were randomized to one of three different treatment arms: L-dopa monotherapy, bromocriptine monotherapy, and early combination. L-dopa could subsequently be added, if needed, in the bromocriptine initial monotherapy arm. Efficacy was assessed using the Webster Scale and the Hoehn and Yahr Scale. At the end of the trial, 50 % of the patients received secondary L-dopa supplementation in the bromocriptine group. Bromocriptine initial monotherapy mean dose was 12.6 mg/d (plus 401 mg/d additional L-dopa in 14/28 patients), L-dopa monotherapy mean dose was 556 mg/d, and in the combination group, mean L-dopa dose was 572 mg/d plus 7.5 mg/d of bromocriptine (not L-dopa sparing in practice). Antiparkinsonian treatment effect (as assessed with the Hoehn and Yahr rating scale and the Webster disability scale) was reported to be about 50% in all 3 groups (no numerical data available in the manuscript), with no significant difference among treatments. Adverse reactions were observed in the bromocriptine initial monotherapy group (3 patients, 2 dropouts because of vomiting or allergic nodular vasculitis, the third patient reporting dyskinesia) and in the levodopa-treated group (8 patients, no drop-out, 3 with nausea-vomiting, 3 hallucinations, 2 dystonia and one akathesia - more than one adverse reaction in 3 patients). This study had an overall quality score of 63%.

Nakanishi et al. (1992)[26]: This was a large three-arm study conducted in 702 de novo patients with PD. The results of this study have been published annually over a 10-year follow-up period. The planned duration of this study was 5 years, and therefore the summary is limited to the planned 5-year report. The bromocriptine initial monotherapy arm reported in this trial cannot be considered in this chapter (which is limited to Level-I randomized data), because all de novo patients with PD were allocated to bromocriptine without a comparative treatment group. Therefore, this review is limited to the other two treatment groups, which correspond to patients who had been already treated with L-dopa for less than 5 years and in whom further increments of L-dopa had been considered. These patients were randomly allocated in an open fashion to receive bromocriptine (combination therapy group) or to continue on L-dopa as monotherapy. Efficacy was assessed using unconventional scales for primary parkinsonian symptoms (eg. tremor, rigidity, akinesia, frozen gait) and ADL was assessed using a semiquantitative scoring scale (0-4). 216 patients entered the early combination group and 200 the L-dopa monotherapy group. Fifty-four percent in the early combination group and 62% in the L-dopa monotherapy group were followed for up to 5 years. The average dose of bromocriptine was low (11 mg/d at 5 years), while the maintenance dose of L-dopa was 387 mg/d in the combination group and 407 mg/d in the L-dopa group (bromocriptine was not L-dopa sparing in practice). The overall clinical efficacy was reported as comparable in both the combination and the L-dopa groups with regard to cardinal parkinsonian features, while ADL was reported to be significantly worse than the initial score in the L-dopa group but not in the combination group. (Data were presented in complex figures and efficacy was difficult to evaluate accordingly). Classical gastro-intestinal, cardiovascular, and neuropsychiatric adverse reactions were reported in both groups, and did not seem to be more frequent in either group. Review of the long-term follow-up results showed that a wearing-off effect and dyskinesia were less frequent in the combination treatment group than in the L-dopa treatment group (also see section on Prevention of Motor Complications). This study had an overall quality score of 40%.

Hely et al. (1994)[27]: This was a 5-year, open-label study conducted in 149 de novo patients with PD (mean age=62 years) randomly allocated to low-dose of L-dopa or bromocriptine therapy. The study was designed to be double-blind in the titration phase only, and to assess if the incidence of late motor complications was lower in the bromocriptine group. Efficacy was assessed with a modified CURS. ADL was also measured using the NUDS. Subsequent addition of L-dopa to bromocriptine or bromocriptine to L-dopa was allowed, thus creating new combination groups. Analyses were performed on the two monotherapy treatment groups as originally randomized (bromocriptine and L-dopa), and also on the main treatment subgroups subsequently formed. One hundred and twenty-six patients did not show any atypical features of parkinsonism and completed the titration phase. Sixty-two patients were randomized to bromocriptine and 64 to L-dopa. The mean daily dose of bromocriptine was 32 mg/d. Less than 10% of the patients could be managed on bromocriptine monotherapy after 3 years, and none after 5 years. The median treatment period with bromocriptine monotherapy was 12 months. In contrast, median treatment period for L-dopa monotherapy was 52 months. In the bromocriptine group, the main reason to stop monotherapy and switch to combination was lack of efficacy. Mean change from baseline in the modified CURS score on bromocriptine alone showed improvement at 6 months (-2.41, $p<0.01$), but no improvement was reported thereafter. Mean change from baseline in the modified CURS score for L-dopa monotherapy also showed improvement at 6 months (-3.69, $p<0.001$), and also after 1 year (-3.96, $p<0.001$) and 2 years (-3.19, $p<0.001$). L-dopa was significantly better than bromocriptine alone at 1 year. Conversely, the patients who switched from bromocriptine alone to a combination of L-dopa and bromocriptine showed significantly more improvement than the L-dopa monotherapy group at 1 year (mean change in modified CURS: -5.75, $p=0.002$). Reasons for withdrawing from

the bromocriptine group were confusion and hallucinations (n = 10), postural hypotension (n = 4), and nausea (n = 4). The 10 patients who became confused on bromocriptine were switched to L-dopa. Of these, 7 reported confusion with L-dopa treatment. In the L-dopa monotherapy group, 6 patients experienced confusion and hallucinations leading to withdrawal, and 4 experienced nausea. Regarding motor complications, no patient treated with bromocriptine monotherapy developed dyskinesia or "on-off" phenomenon. When L-dopa was secondarily added to bromocriptine, the prevalence of dyskinesia remained reduced when compared with the group randomized to L-dopa monotherapy (also see section on Prevention of Motor Complications). The 10-year follow-up report presents mortality data on these patients.[28] This study had an overall quality score of 57%.

Przuntek et al. (1996)[29]: This was a randomized, parallel-group, controlled study designed to assess the benefits (specifically on long-term motor complications) of adding bromocriptine as early combination to L-dopa. This study was prematurely terminated due to an increase in mortality risk[30] (also see section on Safety). The long-term effects on motor complications are reported below (see section on Prevention of Motor Complications). A total of 674 newly diagnosed patients with PD (mean age 53 years) were randomly allocated to monotherapy with L-dopa or a combination therapy based upon a 40% replacement of L-dopa by bromocriptine within 6 months. Pretreatment with L-dopa for up to 6 months was allowed. Combination therapy was started in all the bromocriptine patients within the first year of treatment. Parkinsonian symptoms were assessed by means of the Webster Rating Scale and the Hoehn and Yahr Scale. Patients were followed for up to 42 months of treatment. In the early combination group, treatment with bromocriptine was associated with a 31% reduction of the daily dose of L-dopa (bromocriptine 13.8 mg/d plus L-dopa 308 mg/d; L-dopa monotherapy daily dose 439 mg/d). Overall motor improvements were similar in both groups (raw numbers were not reported). These data suggest that a mean dose of about 14 mg/d of bromocriptine had a L-dopa-sparing effect averaging 130 mg/d without significant deterioration in motor status. There were no major differences observed between the two treatment groups in terms of non-motor adverse reactions, which included those events commonly associated with dopaminergic therapy including drowsiness, dizziness, sleep disturbances, dryness of mouth, constipation, palpitation, headache, nausea, vomiting, hallucinations and confusion. Conversely, long-term motor complications were less frequent in the combination group (see section on Prevention of Motor Complications). This study had an overall quality score of 65%.

Gimenez-Roldan et al. (1997)[31]: This was an 8-month, double-blind, parallel-group, placebo-controlled study conducted in 50 patients (mean age = 60 years) who had responded favorably to L-dopa and had been treated for less than 6 months. The primary outcome measure of the study was a surrogate endpoint: to assess if the association of bromocriptine allowed a significant reduction in L-dopa use. Stability of motor status was assessed using the UPDRS. Following this initial 8-month treatment period, patients were allowed to continue in two parallel, open-label treatment groups for up to 44 months and long-term motor complications were monitored. Bromocriptine was introduced at a fixed dose of 15 mg/d. After 8 months of treatment, this dose did not allow a significant reduction in L-dopa daily dose as compared to placebo (L-dopa + bromocriptine group: 465 mg/d vs. L-dopa + placebo group: 507 mg/d). At the conclusion of the 44-month follow-up phase, the bromocriptine dose was increased to 24 mg/d and the L-dopa daily dose was significantly reduced (L-dopa + bromocriptine: 515 mg/d vs. L-dopa + placebo:726 mg/d, $p<0.01$). The incidence of motor complications was also significantly reduced in the early combination group (see section on Prevention of Motor Complications). No data are reported on non-motor adverse reactions. This study had an overall quality score of 68%.

Late Combination Studies

The majority of studies referring to late combination therapy with bromocriptine in L-dopa-treated patients with PD were performed in patients with motor fluctuations. In this population, the effect of bromocriptine in "on/off" periods is reviewed in the section entitled Control of Motor Complications (see below). In this section, the analysis of the clinical data is limited to the symptomatic control of parkinsonism (eg. assessed using recognized scales such as the UPDRS parts II or III) which was usually measured as a secondary endpoint at a given time of the day (while the patients where "on", or when "off" before the first morning dose of levodopa, for example). The results of the literature search identified 13 Level-I studies meeting predefined inclusion criteria (eg. enrolling more than 20 L-dopa-treated evaluable patients per treatment group with a followed-up period of at least 4 weeks duration). Four studies were placebo-controlled, 7 were active comparator trials using other dopamine agonist: cabergoline (n=1), pergolide (n=4), lisuride (n=2). One study compared two different regimens of bromocriptine titration and one study compared bromocriptine to the COMT-inhibitor, tolcapone.

Placebo-controlled Studies

Kartzinel et al. (1976)[32]: Thirty-two patients with PD were included in this 6-month, randomized, double-blind, placebo-controlled study. Twenty patients (mean age 61 years) completed the trial. The patient population was heterogeneous in that 6 had undergone thalamotomy, 6 had dementia, 14 received L-dopa plus carbidopa, and 6 received L-dopa alone. Eight were subject to "on-off" phenomenon. Bromocriptine was introduced progressively up to a maximum tolerated dose (up to 100 mg/d) and L-dopa was reduced progressively as much as possible over time. Efficacy was assessed using an 11-item rating scale (tremor, gait, arising from chair, posture, balance, rigidity, drooling, finger dexterity, writing, speech, and facial expression) scored from 0 (normal) to 4 (maximal disability). Over the course of the trial, mean daily dose of Sinemet and L-dopa was reduced by 74% ($p<0.01$) in patients receiving bromocriptine. Treatment with bromocriptine (79 mg/d) was associated with a significantly improved "total disability score" (mean improvement of 19%). Little information is available on the response to placebo treatment. Adverse reactions included fatigue, dyskinesia, gastrointestinal symptoms, and confusion. This study is the first randomized, double-blind, placebo-controlled trial that reported benefits of adding a dopamine agonist in the treatment of PD. At the time this study was performed (1976), many of the currently accepted standard outcome measures used for assessing improvement of therapies in PD were not in place. This study had an overall quality score of 43%.

Hoehn and Elton (1985)[33]: Thirty six patients with PD who were on a stable dose of L-dopa for 3 months were included in a randomized, double-blind, placebo-controlled, parallel-group, 10-month study. Thirty-three patients had wearing-off problems. Twenty-six patients reported peak-dose dyskinesia. By randomization, 27 patients received bromocriptine, and 9 received pla-

cebo, but both groups received placebo during the first (baseline) and last 4 weeks (washout) of the study. Efficacy was assessed using a modified CURS. Efficacy was assessed by the percent improvement over baseline. Neurological scores of the bromocriptine-treated (daily dosages of 10 and 20 mg/d) group were significantly improved over the placebo-treated group. Improvement with bromocriptine was reported to be first noticeable with a 10 mg/d dose and increased effectiveness was observed with increasing doses. By the end of the trial, bromocriptine treatment was increased to 20 mg/d and was associated with a significant mean improvement of 37% over baseline; the average improvement in the placebo-treated group reached 21% (not significantly different from baseline measures). Adverse reactions were reported to be similar in placebo and bromocriptine treatment groups (ie. orthostatic dizziness and hypotension, dyskinesia, insomnia, and mental changes). Nausea and orthostatic hypotension were more frequent with bromocriptine vs. placebo. Six patients had mental disturbances on bromocriptine, and 6 on placebo. This study had an overall quality score of 55%.

Toyokura et al. (1985)[34]: This was a randomized, placebo-controlled, parallel group, 2-month study conducted in 222 L-dopa-treated patients with more than one year of L-dopa therapy (mean age=63 years) who reported at least one adverse event to L-dopa (ie. wearing-off, on/off, frozen gait, dyskinesia, gastrointestinal symptoms). Major parkinsonian symptoms (akinesia, tremor, rigidity, pulsion, and gait disturbance) were evaluated using a semiquantitative scale from 0 to 4. Activities in daily living (hygiene, feeding, and toilet care) were also evaluated using the same scale. Improvement was judged as marked, moderate, mild, or none for each of these endpoints. Late motor side effects (fluctuations, dyskinesia) were also evaluated. Twenty-seven out of the 114 bromocriptine-treated patients and 17 of 108 placebo-treated patients dropped out of the study early. At the mean dose of 16.7 mg/d, changes in the disability scores of tremor, rigidity, akinesia, and gait disturbances were reported to be significantly improved by at least one time point during bromocriptine therapy, and similar improvements were reported in the placebo group. The improvements were said to be significantly better in the bromocriptine group, at least in one of the measures evaluated. The percentage of improvement was significantly better in the bromocriptine group in akinesia (27% vs. placebo 20%) and gait disturbance (27% vs. 21%). A very large number of statistical comparisons were performed, at different time points, which may impact the level of their clinical meaning. Nausea was the most frequent adverse reaction and dyskinesia was significantly more frequent with bromocriptine. This study had an overall quality score of 63%.

Guttman et al. (1997)[35]: The primary outcome of this study was to compare the efficacy and safety of pramipexole to placebo in fluctuating L-dopa-treated patients with PD (see section on Pramipexole). However, a third arm was added as an active comparator and included treatment with bromocriptine. The study was powered to compare both active treatments to placebo, but not to each other. The study was a randomized, parallel group, double-blind, 36-week trial. A total of 247 patients were included in the trial (mean age=62 years) and 79 received pramipexole, 84 bromocriptine, and 83 placebo. The primary efficacy endpoints were the UPDRS Part II and III. Other endpoints were the Schwab and England Scale, a timed walking test, and quality of life scales. Compared with placebo, bromocriptine (22.6 mg/d) significantly improved UPDRS II (bromocriptine -14% vs. placebo -5%, $p<0.02$) and UPDRS III (bromocriptine - 24% vs. placebo -6%, $p<0.01$). Treatment with bromocriptine also was associated with an improvement in quality-of-life scales. When pramipexole was compared with bromocriptine, there was a trend in favor of pramipexole being more potent than bromocriptine, but the difference were not statistically significant for any of the outcome measures (see section on pramipexole). Reported adverse reactions were quite similar for both agonists, including dizziness, postural hypotension, headache, insomnia, hallucinations, and confusion. Nausea and dyskinesia were more common in both active groups than in the placebo group (nausea: pramipexole 36%; bromocriptine 37%, placebo 25%; dyskinesia:pramipexole 40%; bromocriptine 45%, placebo 27%). This study had an overall quality score of 85%.

Active Comparator Studies

Bromocriptine titration regimens studies

MacMahon et al. (1991)[36]: This was a double-blind, randomized, parallel group study conducted in 173 L-dopa-treated patients with PD. Patients were randomized to two different treatment regimens (8-week titration periods each): 7-step standard titration with bromocriptine increasing up to 15 mg/d vs. a 3-step similar treatment regimen. This study is interesting in that it compared two different bromocriptine titrations in a relatively aged population of patients with PD (mean age 75 years). Efficacy was assessed with the Webster scale and the CAPE ADL. One hundred and fifty-nine patients entered the active treatment phase of the trial. The mean age of the patients was 75 years (range 59-88). Both regimens significantly improved motor symptoms (Webster score improved by 29% in each group and the CAPE ADL by 32% in both groups). The authors reported no between-group differences in term of side effects (data not reported), withdrawals or deaths between the standard and simplified regimens: drug-related withdrawals occurred in 16 patients of each group; four deaths occurred in the 7-step titration regimen and 2 in the 3-step titration group. The results look rather similar to previous reports in younger patients, especially in terms of safety; although, little details are given in this report regarding individual adverse reactions.

Bromocriptine vs. Cabergoline

Inzelberg et al. (1996)[37] (see also section Cabergoline): This was a double-blind, parallel group, randomized study performed in 44 patients who had increasing disability and motor fluctuations (mean age = 72 years, mean disease duration = 10 years). Dosage was titrated up to a maximum daily dose of 6 mg once a day (mean daily dose reached was 3.18 mg/d) of cabergoline or 40 mg/d of bromocriptine (mean daily dose reached was 22 mg/d) administered tid. The mean follow-up duration was 9 months. Efficacy was measured using ADL scores, Schwab and England motor disability score, and UPDRS Part III. Cabergoline and bromocriptine induced a comparable improvement of most assessment criteria including ADL scores (cabergoline: from 11 at baseline to 9 at completion; bromocriptine: from 11 at baseline to 9 at completion, $p<0.01$ for both treatments comparisons to baseline), UPDRS III (cabergoline: from 35 at baseline to 28 at completion; bromocriptine: from 38 at baseline to 29 at completion, $p<0.0001$ for both treatments vs. baseline assessments). There were no significant differences between the two treatments. Adverse reactions were typical of dopaminergic side effects, including dyskinesias, orthostatic hypotension, confusion, hallucinations, insomnia, nausea, and edema. The frequency of such adverse reactions was similar for both drugs. Twelve cases (out of 44) withdrew from the

trial. This study had an overall quality score of 52%

Bromocriptine vs. Pergolide

LeWitt et al. (1983)[38] (see also section on Pergolide): This was a double-blind, two-period, cross-over study conducted in 27 patients with PD (mean age = 59 years, mean duration of disease = 11 years). The periods of treatment lasted 7-10 weeks. No wash-out period was performed between the two active treatment periods. The studied population was heterogeneous, including 9 patients with mild parkinsonism that responded well to L-dopa, 15 patients with more advanced disease and late motor complications, and 3 patients who did not receive L-dopa at the time of the study. Agonists were titrated to a maximal optimal daily dose. Clinical evaluations were carried out for tremor, rigidity, akinesia, facial expression, speech, dyskinesia, and handwriting. A blinded clinical observer rated each element of performance from 0 to 4, (modified from a Duvoisin scale). Objective evaluations of gait and upper limb reaction time were also performed. Twenty-four of the 27 patients completed the study. The mean optimal daily dose of pergolide was 3.3 mg/d and that of bromocriptine was 42 mg/d. With both drugs adjusted to an optimal dose, similar control of parkinsonism was reported, although the exact amplitude of the mean improvements and raw values are not specifically detailed in the report. Similar incidence of adverse reactions was reported in each treatment group. The most frequent reactions were nausea and orthostatic hypotension. Sedation and hallucinations were reported to be less frequent. One patient presented with a symptomatic unilateral pleural fibrosis, which resolved with cessation of the drugs. This study had an overall quality score of 50%.

Mizuno et al. (1995)[21] (see section on Pergolide): In this short-term (8-week), double-blind, parallel group study, 93 PD patients with "unsatisfactory results on L-dopa therapy" were randomized to pergolide (maximum permitted dose 2.25 mg/d) and 99 others to bromocriptine (maximal permitted dose 22.5 mg/d). Patients with early PD were also studied in this report, but these results were analyzed separately (see section on Monotherapy). Efficacy was evaluated using a simplified rating scale consisting of a five-grade rating score (from normal to marked improvement) similar to the UPDRS, but with the number of criteria evaluated reduced to 21. A global improvement was also assessed by the investigator using a 5-point semi-quantitative scale (from "marked improvement" to "worsening". Pergolide (mean daily dose 1.24 mg) and bromocriptine (mean daily dose 14.6 mg) both improved most of the items studied). Unfortunately, no data on a total score are available. The authors reported that there was a tendency for a greater improvement in the rating scale scores for pergolide, but the difference did not reach statistical significance. There was no difference between the two treatments regarding the global improvement rating scale (marked improvement: pergolide 8.6% vs. bromocriptine 6.1%, moderate improvement: pergolide 40.9% vs. bromocriptine 33.7%, mild improvement: pergolide 39.8% vs. bromocriptine 40.8%). The incidence of adverse reactions were comparable in both groups (pergolide 29.4%, bromocriptine 27.6%), and the most common being nausea (pergolide 20.1%, bromocriptine 11.2%), and hallucinations (pergolide 7.3%, bromocriptine 5.2%). This study had an overall quality score of 53%.

Pezzoli et al. (1995)[39] (see also section on Pergolide): This was a single-blind cross-over study carried out in 68 PD patients who showed a declining response to L-dopa therapy. Both drugs were administered for 12 weeks. No wash-out interval was planned between the two active treatment periods. Fifty-seven patients (mean age 61 years) completed the study and were evaluated. Efficacy was evaluated using the New York University Parkinson's Disease Scale (NYUPDS) and a Clinical Global Impressions score (from 1= very much better to 7=very much worse). Authors used a 10:1 bromocriptine: pergolide dose ratio. The optimal daily dosages were 24.2 mg of bromocriptine and 2.3 mg of pergolide. Significant improvements vs. baseline occurred during both bromocriptine and pergolide therapy. Direct comparison of the two drugs showed pergolide to be significantly more effective than bromocriptine in 4 of 5 daily living scores of the NYUPDS and in the total aggregate score ($p<0.05$). Pergolide was also reported to be more effective on the NYUPDS physical examination total aggregated score and several subscores ($p<0.05$; results reported in figures only, and no raw data provided). Both pergolide and bromocriptine significantly improved CGI, with a significant improvement for pergolide compared with bromocriptine (actual severity of the disease was improved in 49% of the pergolide-treated patients and in 39% of the bromocriptine-treated patients, $p<0.01$). Although statistically significant, these differences appear rather small, and the clinical relevancy of these findings is unclear. Moreover, a 1:10 ratio between pergolide and bromocriptine was chosen arbitrarily and may be biased in favor of pergolide. Adverse reactions were comparable with both treatments (nausea, hypotension). This study had an overall quality score of 57%.

Boas et al. (1996)[40] (see section on Pergolide): This was a 24-week (12 weeks per period) open-label, cross-over study conducted in 33 L-dopa-treated patients with PD who had sub-optimal control of fluctuations (mean age 63 years). The authors used a 10:1 bromocriptine:pergolide dose ratio. No wash-out period was performed between the two active treatment periods. Efficacy was assessed using UPDRS (motor examination and complication of therapy sections). Twenty-seven patients completed the study. The mean doses of bromocriptine and pergolide at the end of the titration phase were 21.7 mg/d and 3.6 mg/d, respectively. The improvement vs. baseline in UPDRS motor examination scores was significant with both treatments ($p<0.05$), and the improvement was reported to be significantly greater with pergolide than with bromocriptine ($p<0.01$). Similar to the previous report, the dose selection based on a 1:10 treatment ratio may be biased in favor of pergolide and the differences between treatments is modest with the clinical relevancy of these differences unclear. The daily dose of L-dopa was significantly lower with pergolide (-26%) than with bromocriptine (-10%), showing a greater L-dopa-sparing effect in favor of pergolide ($p<0.01$). Adverse reactions were comparable with both drugs. The most commonly reported reactions included nausea (4 in each group);dyskinesia worsened with both drugs. No data were reported concerning psychosis. The overall quality score for this study was 60%.

Bromocriptine vs. Lisuride

LeWitt et al. (1982)[41] (see section on Lisuride): This was a double-blind randomized cross-over (7-10 week per period of treatment) trial conducted in 28 patients with PD (mean age 55 years). No wash-out period was performed between active treatment periods. The population of patients was heterogeneous, with several patients having mild parkinsonism "responding well to levodopa", more than half of the patients having late motor complications, and 4 patients not receiving L-dopa at the onset of the study. Clini-

cal evaluation was carried out for tremor, rigidity, posture, gait, balance, finger dexterity, facial expression, speech, writing and arising from sitting. Each endpoint was rated from 0 (normal) to 4 (maximal abnormality), modified from the CURS score. Objective measurements of gait and upper limbs movements were also measured (reaction time and movement time). Twenty-six patients completed the trial. Optimal doses were 4.5 mg/d for lisuride and 56.5 mg/d for bromocriptine. The "clinical" and "objective" ratings of parkinsonian features were reported to be similar at the optimal doses of each drug (no raw data were reported in the article). A clinical aggregate score for akinesia (finger dexterity, facial expression, gait, posture, balance, speech and arising from sitting) showed a small, but significant difference in favor of bromocriptine (p=0.018). The clinical differences appeared small in amplitude and the clinical relevancy of this difference is unclear. Adverse reactions were reported to be quite similar with both drugs. Effects on mental state were prominent in several patients. Hallucinations were present in 7 lisuride-treated patients and 1 bromocriptine-treated patient. Vivid dreaming was reported in 8 lisuride and 8 bromocriptine-treated patients. Gastrointestinal discomfort was reported in 8 lisuride and 8 bromocriptine-treated patients. Light-headedness related to hypotension was reported in 13 lisuride and 13 bromocriptine-treated patients. Somnolence occurred in 9 lisuride and 7 bromocriptine-treated patients. This study had an overall quality score of 41%.

Laihinen et al. (1992)[42] (see section on Lisuride): This was a double-blind, randomized cross-over (8-weeks per period with a 2-week wash-out in between) trial performed in 20 patients with PD (mean age 62 years) suffering from deteriorating response to L-dopa and motor fluctuations. Efficacy was assessed using the CURS. Mean optimal daily dose of lisuride was 1.3 mg/d and bromocriptine was 15 mg/d. The total CURS improved by 30% with lisuride and 29% with bromocriptine after 8 weeks of treatment. Adverse reactions typical of dopamine agonists were reported for both drugs (nausea, orthostatic hypotension, hallucinations, and dyskinesia) and were very similar with both drugs. This study had an overall quality score of 69%.

Bromocriptine vs. Tolcapone

The Tolcapone Study Group (1999)[43] performed an 8-week, randomized, open-label, parallel group study conducted in 146 L-dopa-treated patients with end-of-dose deterioration of efficacy. Tolcapone was given at 200 mg three times a day. Bromocriptine was titrated up to optimal dosage (maximal daily dose of 30 mg/d). L-dopa dose could be adjusted according to the need to manage L-dopa-induced adverse effects like dyskinesia. The primary objective of this trial was safety, but efficacy endpoints were also assessed including UPDRS scores. The mean bromocriptine optimal daily dose was 22.4 mg/d. Sixteen patients in each group withdrew because of adverse reactions or intercurrent illness. By the end of the 8-week treatment period, a surrogate endpoint like the L-dopa daily dose decreased by 124 mg (16.5%) in the tolcapone group and by 30 mg (4%) in the bromocriptine group (p<0.01). However, no significant difference was seen between the 2 groups in UPDRS scores (UPDRS II: -0.1 units with bromocriptine and -0.9 unit with tolcapone; UPDRS III: -3.3 units with bromocriptine and -3.1 unit with tolcapone). Bromocriptine was associated with more hallucinations (10% vs. 1%), orthostatic hypotension (23% vs. 6%) and nausea (37% vs. 17%) as compared to tolcapone. Conversely, more patients with tolcapone had muscle cramps (21% vs. 7%) and dystonia (14% vs. 1%) as compared to bromocriptine. Dyskinesias were frequent with both drugs (bromocriptine: 38%, tolcapone: 51%). This study had an overall quality score of 75%.

PREVENTION OF MOTOR COMPLICATIONS

Several long-term studies have specifically looked at the impact of early treatment with bromocriptine on the occurrence of long-term motor complications (fluctuations and dyskinesias) related to L-dopa therapy, in de novo PD patients who have not previously been exposed to levodopa (or only for no more than a few weeks). Seven Level-I trials corresponding to the predefined inclusion/exclusion criteria have been identified.[19,20,23,26,27,29] These studies have been described above (see section on Symptomatic Control of Parkinsonism: Monotherapy); therefore the outcomes regarding long-term motor complications will only be summarized below.

Bromocriptine as initial monotherapy, and L-dopa adjuncted later if needed

Parkinson Study Group in the UK (1993):[19] 782 patients with PD were allocated to 3 arms (L-dopa, L-dopa plus selegiline, or bromocriptine) and followed for 3 years. The occurrence of involuntary movements, oscillations in performance, and early morning dystonia were recorded (no definition for these parameters was reported). At the end of the follow-up period, 181 of the 263 patients randomized to bromocriptine completed the study. Dyskinesia occurred in 2% of these patients and disabling "on-off"" phenomena in 5%. In the L-dopa group, there were 27% of patients with dyskinesia and 33% had disabling "on-off" phenomena. In the L-dopa plus selegiline group, these values were 34% and 35% respectively. These percentages were reported to be "higher" in patients on L-dopa or on combination therapy than in those on bromocriptine monotherapy (p values were not reported). This study had an overall quality score of 63%.

Hely et al. (1994)[27]: 149 patients with PD were randomized to low-dose bromocriptine or L-dopa and followed for 5 years. Patients received subsequently L-dopa supplementation, if needed, in the bromocriptine group and bromocriptine in the L-dopa group, which makes assessments more complex. Fluctuations (end-of dose failure) were recorded as being present if (1) the patients reported this in response to questioning or (2) seen by the investigator (identified as early morning akinesia, wearing-off of the effect of each dose before the next dose was due based on a 3 times a day dosage, or dosage frequency was more than 3 times daily). The term "on-off" was defined as sudden, severe, and at times unpredictable changes in mobility. Involuntary movements were separated into two types: dyskinesia and dystonia. No patient developed dyskinesia while on bromocriptine monotherapy. Fifty-two patients developed dyskinesias by 5 years: 35 patients in the L-dopa treatment group, and 17 in the bromocriptine with L-dopa supplementation (p=0.002). The incidence of dyskinesia in the L-dopa group was higher for women than men (p<0.05), for younger than older patients (p<0.05), and for patients with more severe initial disease (p<0.05). Dystonia was observed in 21 L-dopa-treated patients and in 10 bromocriptine-treated patients, of whom 9 had received levodopa before the dystonia developed (p<0.05). Wearing-off occurred in 41% of the patients randomized to L-dopa and in 37% of patients randomized to bromocriptine. This study had an overall quality score of 57%.

Montastruc et al. (1994)[20]: Sixty patients with PD were random-

ized to bromocriptine or L-dopa as initial treatment. Bromocriptine-treated patients could receive L-dopa supplementation during the course of the disease, if needed. Two types of motor complications were evaluated: involuntary abnormal movements (including peak-dose and dysphasic dyskinesia and dystonia) and motor fluctuations (including wearing-off and "on/off" phenomena). After 5 years of follow-up, 4/31 bromocriptine-treated patients did not require L-dopa supplementation. None of these 4 patients presented motor complications. In the remaining patients, motor complications were observed in 56% of the bromocriptine-treated patients and in 90% of the L-dopa treated patients ($p<0.01$). Dyskinesias were seen in fewer patients on bromocriptine (3/25) vs. 14/29 in patients treated with L-dopa. Wearing-off occurred in 10/25 bromocriptine-treated patients and in 10/29 L-dopa-treated patients (no difference between treatments), but the mean time to develop such motor fluctuations was longer with bromocriptine (4.5 years) than with L-dopa (2.9 years; $p<0.05$). This study had an overall quality score of 69%.

Korczyn et al. (1999)[23]: 335 patients with PD were randomized to receive initial bromocriptine or ropinirole treatment and followed-up for 3 years. L-dopa supplementation was possible in both groups during the study if needed. The results showed a low incidence of dyskinesias in both groups regardless of L-dopa supplementation (ropinirole: 7.7%, bromocriptine: 7.2%, NS). This study had an overall quality score of 76%.

Bromocriptine as early combination to L-dopa therapy

Nakanishi et al. (1992)[26]: 216 patients with PD (who received L-dopa for less than 5 years) were randomized to receive bromocriptine/L-dopa combination or to stay on L-dopa monotherapy. They were followed for 5 years. The results reported that 49% remained on combination therapy after 5 year and 46 % remained on L-dopa monotherapy. It is not clear from the text which population data were analyzed and no details were provided on how motor fluctuations were recorded. Forty patients of the combination group were said to have wearing-off phenomenon when entering into the trial. Five years later, there were still 40 patients reporting a wearing-off phenomenon. In the L-dopa monotherapy group, 20 (baseline) and 40 (5 years) reported wearing-off phenomenon, and the difference was reported to be significant (p value not given). The "on/off" phenomenon was present at baseline in 21 patients of the combination group and in 24 after 5 years. In the L-dopa group, 10 and 14 patients reported "on/off", respectively, at baseline and after 5 years. Dyskinesias were present at baseline in 24 patients of the combination group and in 14 patients after 5 years. In the L-dopa group, there were 15 and 12 patients reporting dyskinesias, respectively, at baseline and after 5 years. It is difficult to understand how dyskinesia was less frequent after 5 years of follow-up than at baseline in both groups. This study had an overall quality score of 40%.

Przuntek et al. (1996)[29]: 674 PD patients (who received L-dopa for less than 6-months) were randomized to receive an adjunct treatment with placebo or bromocriptine. Adjunct treatment was titrated in order to try to reduce the dose of L-dopa by 40%. Motor adverse reactions were monitored, looking specifically at changes in fluctuations in mobility, "on/off" phenomena, and dyskinesias (including chorea, dystonia, and other dyskinesia movements). A complex system of scoring based on severity and body distribution was used. Motor complications as a whole were reported to be less frequent in the combination group (20%) than in the L-dopa group (28.8%) ($p= 0.008$). This study had an overall quality score of 67%.

Gimenez-Roldan et al. (1997)[31]: 50 patients with PD who had received L-dopa for less than 6 months were randomized to receive bromocriptine or placebo and followed for up to 44 months. At the end of follow-up, dyskinesias were present in 9.5% of the combination group as compared with 36.8% of the L-dopa-treated group ($p<0.05$). Similarly, wearing-off, severe enough to require change in treatment, was reported to be less frequent in patients in the combination group (14.2%) than in those treated with L-dopa (47.3%, $p<0.05$). This study had an overall quality score of 68%.

CONTROL OF MOTOR COMPLICATIONS

This section focuses on the efficacy of bromocriptine in controlling motor complications (most frequently the « wearing-off » type) in fluctuating patients with PD who were also on L-dopa therapy. These data are usually based on diaries fulfilled by the patients themselves. Data related to motor examination outcomes reported in the same trials have been reviewed previously in the section on Control of Parkinsonism.

Placebo-controlled Studies

Hoehn and Elton (1985)[33]: Thirty-six patients with PD on a stable dose of L-dopa for 3 months were included in a randomized, double-blind, placebo-controlled, parallel-group, 10-month study. Thirty-three patients had wearing-off effects. Twenty-six had peak-dose dyskinesia. Wearing-off effect (assessed at each clinic visit) was reported to be improved in 18/25 patients in the bromocriptine group, and 0/8 placebo-treated patients. Off-dose dystonia and leg pain were also improved in 9/13 patients in the bromocriptine treatment group and 0/2 placebo-treated patients. Improvement was reported to be noticeable in doses greater than bromocriptine 10 mg/d, with increased effectiveness associated with increasing doses. This study had an overall quality score of 55%.

Toyokura et al. (1985)[34] performed a randomized, placebo-controlled, parallel-group, 2-month study conducted in 222 L-dopa-treated patients that manifested at least one adverse reaction to L-dopa (eg. wearing-off, "on/off", frozen gait, dyskinesia, or gastrointestinal symptoms). Wearing-off phenomena and "on/off" phenomena were assessed (among other variables), and rated as severe, moderate, or mild when present. No diaries were used but patients were asked careful questions such as: How long did the effects of L-dopa last? How often did the effects occur? and How many hours in a day did the patients have difficulty moving around? The severity of fluctuations and length of off-periods were taken into account in the comprehensive judgment of assessing fluctuations. Wearing-off was reported to be improved by 26.7% in the bromocriptine treatment group and by 7.1% in the placebo-treatment group. "On/off" was improved by 28.6% with bromocriptine and by 0% with placebo. The difference was not significant. This study had an overall quality score of 63%.

Guttman et al. (1997)[35] (see also section on Pramipexole): The study was a randomized, parallel-group, double-blind, 36-week trial. A total of 247 patients were included in the trial in which motor fluctuations were assessed using diary cards. Bromocriptine did not significantly reduce the amount of time spent "off", while pramipexole was reported as significantly reducing amount of time spent "off." (specific data endpoints not reported). This study had an overall quality score of 85%.

Active Comparator Studies

Bromocriptine vs. Cabergoline

Inzelberg et al. (1996)[37] (see section on Cabergoline): This was a double-blind, parallel group, randomized study performed in 44 patients who had increasing disability and motor fluctuations The mean follow-up duration was 9 months. Dyskinesias were assessed using item 32 of UPDRS (% of awake hours spent with dyskinesia) and "off" periods were measured using diaries. Percentages of "off" hours for cabergoline changed from 34% at baseline to 17% at completion ($p<0.0001$). The percentages of "off" hours for bromocriptine were 32% at baseline to 26% at completion ($p<0.0001$). This effect was not significantly different between the two treatment groups. This study had an overall quality score of 52%.

Bromocriptine vs. Pergolide

Mizuno et al. (1995)[21] (see section on Pergolide): This was an 8-week, double-blind, parallel-group study conducted in 93 patients with PD who had "unsatisfactory results on L-dopa therapy." Patients were randomized to pergolide (maximum daily dose 2.25 mg) and 99 were randomized to bromocriptine (maximum daily dose 22.5 mg). Efficacy was assessed using a simplified rating scale consisting of a 5-grade rating scores, one of which concerned the severity of the wearing-off phenomenon. Improvement in wearing-off phenomenon was similar in the two treatments (bromocriptine mean score reduction from 3.6 at baseline to 3.2, $p<0.01$; and pergolide mean score reduction from 3.6 at baseline to 3.1, $p<0.001$). This study had an overall quality score of 53%.

Bromocriptine vs. Lisuride

Laihinen et al. (1992)[42] (see section on lisuride): This was a double-blind, randomized, cross-over (8-weeks per period with a 2-week wash-out in between) trial performed in 20 PD patients suffering from deteriorating response to L-dopa and different kinds of fluctuations. Fluctuations in disability were reported (method of assessment is not described). Similar responses to therapy were reported in both treatments. At week 8 of treatment, 2 patients did not improve, 4 patients had a minimal improvement, 8 patients had a moderate improvement, and 5 patients reported a marked improvement with lisuride. With bromocriptine, 1 reported no improvement, 4 reported minimal improvement, 8 reported moderate improvement, and 6 reported marked improvement. This study had an overall quality score of 69%.

Bromocriptine vs. Tolcapone

Tolcapone Study Group (1999)[43]: This was an 8-week, randomized, open-label, parallel group study conducted in 146 L-dopa-treated patients with end-of-dose deterioration of efficacy. "On/off" periods were assessed using diaries. No significant differences were seen between the two treatment groups for changes in "on/off" time ("off" time was reduced by 15% with bromocriptine and 19% with tolcapone). This study had an overall quality score of 75%.

REVIEW OF SAFETY

The adverse reactions reported with bromocriptine are consistent with other dopamine agonists adverse reactions reported in de novo and advanced disease patients and include nausea-vomiting, orthostatic hypotension, and psychosis. Leg edema also is frequently reported in patients treated with bromocriptine. The incidence of the gastrointestinal and cardiovascular adverse reactions are reportedly reduced by co-prescribing domperidone.[44,45] A gradual increasing dose of bromocriptine reduces the frequency and severity of adverse reactions.[24]

The incidence of adverse reactions (eg, psychosis, confusion, and hallucinations) varies markedly from one study to the other depending on how the reactions are recorded, which patients were treated (eg, patients with early disease or late disease), and how long patients were followed (eg, from a few weeks to several years). Hallucinations appear to be more frequently reported with bromocriptine treatment than with L-dopa treatment. This clinical observation is not always clearly noted in published L-dopa-controlled trials.

In dyskinetic, L-dopa-treated patients, bromocriptine exacerbates dyskinesias. Conversely, when prescribed in L-dopa-naïve (de novo) patients with PD, the early use of bromocriptine monotherapy induces fewer motor complications than L-dopa. Early bromocriptine combination with L-dopa, or early bromocriptine monotherapy to which L-dopa is subsequently added, also seems to reduce the risk of motor complications compared with an initial L-dopa treatment maintained as monotherapy over the long term (see section on Prevention of Motor Complications).

A rare and potentially severe adverse reaction that has been reported in patients treated with bromocriptine is pleuropulmonary and/or peritoneal fibrosis[46], which is associated with ergot derivatives in general. Somnolence is observed in patients treated with bromocriptine. Few case-reports of "sleep attacks" have also been reported with bromocriptine.[47] Increased risk of bromocriptine-induced adverse reactions have been reported due to drug-drug interactions with metabolic inhibitors, like the macrolides.[48]

Few studies have looked at the impact of bromocriptine therapy on life expectancy in patients with PD. We have identified two prospective, Level-I trials. Przuntek et al (1992)[30] performed a planned interim analysis that led to premature discontinuation of the randomized, parallel, open label study published by the same authors[29], which has been summarized above (see section Symptomatic Control of Parkinsonism: Monotherapy). This study was designed to compare the long-term motor effects of an early bromocriptine combination with L-dopa. Specifically, bromocriptine was added in an attempt to reduce L-dopa dose (L-dopa sparing effect of 40%) within the first year of treatment. Five hundred and eighty-seven patients were enrolled. The trial was prematurely interrupted because mortality rate was significantly greater in the L-dopa monotherapy group (18/302 patients) as compared to the combination group (8/285 patients; $p=0.02$). The authors concluded that the mortality risk associated with L-dopa was reduced by more than 50% by its combination with bromocriptine. The reason for this difference in mortality rate remains unclear, and patients mainly died from cardiovascular complications. Moreover, about 50% of the patients included in the trial had discontinued study medication by the time of analysis, and the life status was unknown in 48% of these individuals.

Hely et al. (1999)[28] assessed a cohort of patients after 10 years of follow-up (original report described above[27]). Fifty patients (38 %) of the 130 available participants in the follow-up cohort died during the first 10 years. The authors concluded that bromocriptine did not reduce mortality or slow down progression of disease. In fact, by 10 years, there were 29 deaths among the 63 patients randomized to bromocriptine and 33 at last follow-up. There were 21 deaths among the 67 patients randomized to L-dopa and 30 at last follow-up. Multivariate analysis showed that, among other factors

like older age at onset and rapid pre-study disease progression, randomization to bromocriptine was predictive of increased mortality (p=0.048). However, if patients were able to remain on bromocriptine for more than 1 year after randomization, no increased mortality was found. The authors suggested that this difference was probably due to a recruitment bias in that slightly more severe patients with PD (even if not statistically significant) were randomized to bromocriptine at baseline. Mortality rate was increased in patient with PD when compared to the general population (standardized mortality ratio = 1.58 for all patients, regardless of bromocriptine or L-dopa initial treatment, p<0.001), and no additional benefit was gained from early use of bromocriptine.

CONCLUSIONS

Throughout the literature, there are several randomized (Level-I) studies evaluating the effects of bromocriptine in several hundred patients with PD who were followed for up to 10 years. However, many of these trials were performed several decades ago, prior to the use of standard clinical study criteria (variable inclusion criteria, differences in outcome criteria, variable titration and final daily dose, statistical analysis, among others). This is illustrated by the studies' low to moderate quality scores, which reduces the impact of their results and prevents definite positive conclusions on the efficacy of bromocriptine. However, more recent studies comparing bromocriptine to ropinirole, pramipexole and tolcapone also have been done and show only marginal differences among these treatments and the clinical relevance of these differences is not clear.

EFFICACY

PREVENTION OF DISEASE PROGRESSION

There is INSUFFICIENT EVIDENCE to conclude whether there are neuroprotective effects of bromocriptine (only one small and short-term Level-I negative study was identified).[13]

SYMPTOMATIC CONTROL OF PARKINSONISM

Monotherapy

Because of the lack of definitive placebo-controlled trials and because of the low quality scores of most published active comparator trials using levodopa or other dopamine agonists (non-validated outcome measurements or insufficient statistical power), bromocriptine monotherapy is considered as LIKELY EFFICACIOUS to control parkinsonian symptoms during the first months of treatment. Based on large randomized controlled studies[19, 27], bromocriptine is less efficacious than levodopa in this indication. There is INSUFFICENT EVIDENCE to conclude on the relative ranking of the efficacy of bromocriptine compared to other DA agonists. There is only one Level-I study that compares bromocriptine to ropinirole showing bromocriptine to be marginally less efficacious than ropinirole.[22,23]

Early combination in L-dopa-treated patients

Because of the lack of placebo-controlled trial, because of the low quality scores of available levodopa-controlled trials, and because of conflicting results on levodopa sparing effect[29, 31], there is INSUFFICIENT EVIDENCE to conclude on bromocriptine efficacy on parkinsonism when adjuncted early in stable non-fluctuating levodopa-treated patients

Late combination in L-dopa-treated patients

Based on one recent placebo-controlled trial incorporating a bromocriptine-treatment arm[35], and several lower quality Level-I studies, bromocriptine is considered EFFICACIOUS as adjunct therapy to levodopa in advanced patients with PD and motor fluctuations. Bromocriptine has been compared in this indication to several other dopamine agonists (lisuride, pergolide, cabergoline) and to a COMT-inhibitor (tolcapone). Only pergolide was reported to be marginally, but significantly, superior to bromocriptine.[39]

PREVENTION OF MOTOR COMPLICATIONS

Based on several Level-I L-dopa-controlled trials with moderate quality scores[19,20,27,29], as well as one Level-I ropinirole study[23], bromocriptine is considered LIKELY EFFICACIOUS in reducing the risk of long-term motor complications.

CONTROL OF MOTOR COMPLICATIONS

In the literature, there are several older, low quality, Level-I studies suggesting beneficial effects of bromocriptine in controlling motor complications.[32,33,34] However, these results are in conflict with a single, more recent, higher quality, Level-I study that failed to support efficacy of bromocriptine in controlling motor complications.[35] Given the conflicting results, bromocriptine is considered as LIKELY EFFICACIOUS in controlling motor fluctuations in L-dopa-treated patients with PD.

SAFETY

The use of bromocriptine has an ACCEPTABLE RISK WITHOUT SPECIALIZED MONITORING. However, it is important to consider that bromocriptine is associated with all the adverse reactions typical of this class of medication including gastrointestinal, cardiovascular, and neuropsychiatric effects. High doses and rapid titration are associated with more frequent adverse reactions. Like most ergot derivatives, fibrosis has been reported with bromocriptine. Edema is also commonly observed. The effect of early intervention with bromocriptine on life expectancy remains controversial mostly due to the limited number and conflicting Level-I studies.[28,30]

IMPLICATIONS FOR CLINICAL PRACTICE

Bromocriptine is the oldest dopamine agonist marketed for the treatment of Parkinson's disease. It has been evaluated in a large number of clinical trials and in a number of different clinical situations. However, most of these trials have been conducted in times when the methods to assess efficacy were not standardized and well validated, and this explains why most of the level I trials reviewed here have only low or moderate quality scores. Nevertheless, the follow-up of PD patients on bromocriptine is longer than that of any of the other dopamine agonists. Therefore, bromocriptine is considered CLINICALLY USEFUL in the treatment of both early and advanced PD. In the early stages of disease if bromocriptine is used as initial monotherapy, within a year of follow-up, the efficacy of bromocriptine wanes: on average only 50% of the patients (40% to 75% according to the clinical reports) remain adequately managed with bromocriptine monotherapy after one year; 30% (10% to 50 %) after 3 years; and 10% (0% to 20 %) after 5 years. The variability in response may be related to different dosages of bromocriptine (10 mg/d to 70 mg/d) with higher doses being more efficacious than lower doses. The early combination of low doses of L-dopa plus bromocriptine, or the second-

ary supplementation of an initial bromocriptine monotherapy with low doses of L-dopa, allow some compensation for the loss in efficacy and to achieve the same symptomatic efficacy on long-term than L-dopa used alone at higher doses.

Patients who have not been previously treated with L-dopa may be maintained on bromocriptine monotherapy, and late motor complications (fluctuations and dyskinesia) normally associated with L-dopa therapy appear to be very infrequent. When low doses of L-dopa are combined, the risk for motor complications increases, but is still reduced (especially the risk of of dyskinesia) as compared to treatment with L-dopa alone.

In more advanced fluctuating L-dopa-treated patients with PD, bromocriptine may improve motor scores and disability. The efficacy of bromocriptine in treating motor complications is less well documented.

The dose necessary to achieve clinical improvements is usually above 10 mg/d, ranging from 20 to 40 mg/d. Some authors recommend even higher doses; however, lower doses (<30 mg/d) are better tolerated than higher ones (>50 mg/d).

From a practical perspective, there is little evidence demonstrating that other either dopamine agonists or tolcapone show clinically relevant superior efficacy over bromocriptine, although some statistically significant differences have been reported in a small number of clinical trials, as reported with pergolide[39] and ropinirole.[22,23]

IMPLICATIONS FOR CLINICAL RESEARCH

- Since bromocriptine has been available clinically for a long time, most of the reported studies to date were done prior to current standards used for clinical research. Consequently, quality scores are lower than what is normally seen with more recent studies conducted with newer compounds, like pramipexole and ropinirole. Because bromocriptine is less expensive (generic formulations are available in many countries), and there is little evidence that bromocriptine is markedly less effective or less potent than other newer dopamine agonists, modern comparative trials and pharmacoeconomic trials are needed to compare these agents to verify or negate clinical similarities or differences among these agents.
- Bromocriptine is empirically recommended in younger rather than older patients due to the risk of associated adverse reactions. Well designed trials should be conducted to confirm this practice and to define what is the optimal dose range.
- There is a need to assess if initial bromocriptine monotherapy, with late levodopa supplementation is equivalent regarding long-term efficacy (10 years), safety, and costs as compared to combined early L-dopa and bromocriptine treatment in de novo patients with PD (early combination strategy).
- Additional studies are also needed to assess if patients should be started on initial bromocriptine monotherapy (in an effort to delay the start of L-dopa therapy), or if patients should be started with L-dopa and supplemented with bromocriptine once motor complications appear.
- Further long-term studies are necessary to assess the impact of bromocriptine on quality of life and mortality.

REFERENCES

1. Calne DB, Teychenne PF, Claveria LE, Eastman R, Greenacre JK, Petrie A. Bromocriptine in parkinsonism. Br Med J 1974;4:442-444.
2. Calne DB, Teychenne PF, Leigh PN, Bamji AN, Greenacre JK. Treatment of parkinsonism with bromocriptine. Lancet 1974;2(7893):1355-1356.
3. Montastruc JL, Rascol O, Senard JM. Treatment of Parkinson's disease should begin with a dopamine agonist. Mov Disord 1999;14:725-730.
4. Olanow CW, Jenner P, Brooks D. Dopamine agonists and neuroprotection in Parkinson's disease. Ann Neurol 1998;44:(suppl 1):S167-174.
5. Chase TN, Oh JD. Striatal mechanisms and pathogenesis of parkinsonian signs and motor complications. Ann Neurol 2000;47(suppl 1):S122-130.
6. Montastruc JL, Rascol O, Senard JM. Current status of dopamine agonists in Parkinson's disease management. Drugs 1993;46:384-393.
7. Yoshikawa T, Minamiyama Y, Naito Y, Kondo M. Antioxidant properties of bromocriptine, a dopamine agonist. J Neurochem 1994;62:1034-1038.
8. Yamamoto M. Do dopamine agonists provide neuroprotection ? Neurology 1998;51(suppl 2):S10-12.
9. Friis ML, Gron U, Larsen NE, Pakkenberg H, Hvidberg EF. Pharmacokinetics of bromocriptine during continuous oral treatment of Parkinson's disease. Eur J Clin Pharmacol 1979;15:275-280.
10. Schran HF, Bhuta SI, Schwarz HJ, Thorner MO. The pharmacokinetics of bromocriptine in man. Adv Biochem Psychopharmacol 1980;23:125-139.
11. Mannen T, Mizuno Y, Iwata M, et al. A multi-center double-blind study on slow-release bromocriptine in the treatment of Parkinson's disease. Neurology 1991;41:1598-1602.
12. Jansen EN, Staal-Schreinemachers A, van der Sande JJ, Haas JA, Lakke JP. Parlodel SRO in Parkinson's disease:a double-blind randomized comparison of Parlodel Standard and Parlodel SRO. Eur Neurol 1992;32:318-320.
13. Olanow CW, Hauser RA, Gauger L, et al. The effect of deprenyl and levodopa on the progression of Parkinson's disease. Ann Neurol 1995;38:771-777.
14. Staal-Schreinemachers AL, Wesseling H, Kamphuis DJ, Burg WVD, Lakke JPWF. Low-dose bromocriptine therapy in Parkinson's disease: double-blind, placebo-controlled study. Neurology 1986;36:291-293.
15. Rinne UK. Early combination of bromocriptine and levodopa in the treatment of Parkinson's disease:a 5-year follow-up. Neurology 1987;37:826-828.
16. Libman I, Gawel MJ, Riopelle RJ, Bouchard S. A comparison of bromocriptine (Parlodel¨) and levodopa-carbidopa (Sinemet) for treatment of "de novo" Parkinson's disease patients. Can J Neurol Sci 1987;14:576-580.
17. Riopelle RJ. Bromocriptine and the clinical spectrum of Parkinson's disease. Can J Neurol Sci 1987;14:455-459.
18. Cooper JA, Sagar HJ, Doherty M, Jordan N, Tidswell P, Sullivan EV. Different effects of dopaminergic and anticholinergic therapies on cognitive and motor function in Parkinson's disease. Brain 1992;115:1701-1725.
19. Parkinson's Disease Research Group in the United Kingdom. Comparisons of therapeutic effects of levodopa, levodopa and selegiline, and bromocriptine in patients with early, mild Parkinson's disease:three year interim report. BMJ 1993;307:469-472.
20. Montastruc JL, Rascol O, Senard JM, Rascol A. A randomized controlled study comparing bromocriptine to which levodopa was later added, with levodopa alone in previously untreated patients with Parkinson's disease: a five year follow-up. J Neurol Neurosurg Psychiatry 1994;57:1034-1038.
21. Mizuno Y, Kondo T, Narabayashi H. Pergolide in the treatment of Parkinson's disease. Neurology 1995;45(Suppl 31):S13-S21.
22. Korczyn AD, Brooks DJ, Brunt ER, Poewe WH, Rascol O, Stocchi F. Ropinirole versus bromocriptine in the treatment of early Parkinson's disease:a 6-month interim report of a 3-year study. 053 Study Group. Mov Disord 1998:13:46-51.
23. Korczyn AD, Brunt ER, Larsen JP, Nagy Z, Poewe WH, Ruggieri S. A 3-year randomized trial of ropinirole and bromocriptine in early Parkinson's disease. The 053 Study Group. Neurology 1999;53:364-370.
24. UK Bromocriptine Research Group. Bromocriptine in Parkinson's disease:a double-blind study comparing "low-slow" and "high-fast" introductory dosage regimens in de novo patients. J Neurol Neurosurg Psychiatry 1989;52:77-82.
25. Herskovits E, Yorio A, Leston J. Long-term bromocriptine treatment in de novo parkinsonian patients. Medicina 1988;48:345-350.
26. Nakanishi T, Iwata M, Goto I, Kanazawa I, Kowa H, Mannen T, Mizuno Y, Nishitani H, Ogawa N, Takahashi A, Tashiro K, Tohgi H, Yanagisawa N. Nationwide collaborative study on the long-term effects of bromocriptine in the treatment of parkinsonian patients. Final Report. Eur Neurol 1992;32(suppl 1):9-22.
27. Hely MA, Morris JGL, Reid WGJ. The Sydney multicentre study of Parkinson's disease:a randomized, prospective five year study comparing low dose bromocriptine with low dose levodopa-carbidopa. J Neurol Neurosurg Psychiatry 1994;57:903-910.
28. Hely MA, Morris JGL, Traficante R, Reid WGJ, O' Sullivan DJ, Williamson PM. The Sydney multicentre study of Parkinson's disease:progression and mortality at 10 years. J Neurol Neurosurg Psychiatry 1999;67:300-307.
29. Przuntek H, Welzel D, Gerlach M, et al. Early institution of bromocriptine in Parkinson's disease inhibits the emergence of levodopa-associated motor side effects. Long-term results of the PRADO study. J Neural Transm 1996;103:699-715.
30. Przuntek H, Welzel D, Blÿmmer E, et al. Bromocriptine lessens the incidence of mortality in L-dopa-treated parkinsonian patients:PRADO-study discontinued. Eur J Clin Pharmacol 1992;43:357-363.

31.Gimenez-Roldan S, Tolosa E, Burguera JA, Chacon J, Liano H, Forcadell F. Early combination of bromocriptine and levodopa in Parkinson's disease:a prospective randomized study of two parallel groups over a total follow-up period of 44 months including an initial 8-month double-blind stage. Clin Neuropharmacol 1997;20:67-76.
32.Kartzinel R, Teychenne P, Gillespie MM. Bromocriptine and levodopa (with or without carbidopa) in parkinsonism. Lancet 1976;2:272-275.
33.Hoehn MMM, Elton RL. Low dosages of bromocriptine added to levodopa in Parkinson's disease. Neurology 1985;35:199-206.
34.Toyokura Y, Mizuno Y, Kase M, et al. Effects of bromocriptine on parkinsonism. A nation-wide collaborative double-blind study. Acta Neurol Scand 1985;72:157-170.
35.Guttman M, International Pramipexole-Bromocriptine Study Group. Double-Blind randomized, placebo controlled study to compare safety, tolerance and efficacy of Pramipexole and Bromocriptine in advanced Parkinson's disease. Neurology 1997;49:1060-1065.
36.MacMahon DG, Overstall PW, Marshall T. Simplification of the initiation of bromocriptine in elderly patients with advanced Parkinson's disease. Age Ageing 1991;20:146-151.
37.Inzelberg R, Nisipeaunu P, Rabey JM, et al. Double-blind comparison of cabergoline and bromocriptine in Parkinson's disease patients with motor fluctuations. Neurology 1996;47:785-788.
38.LeWitt PA, Ward CD, Larsen TA, et al. Comparison of pergolide and bromocriptine therapy in parkinsonism. Neurology 1983;33:1009-1014.
39.Pezzoli G, Martignoni E, Pacchetti C, et al. A cross-over, controlled study comparing pergolide with bromocriptine as an adjunct to levodopa for the treatment of Parkinson's disease. Neurology 1995;45(suppl 3):S22-27.
40.Boas J, Worm-Petersen J, Dupont E, Mikkelsen B, Wermuth L. The levodopa dose-sparing of pergolide compared with that of bromocriptine in an open-label, cross-over study. Eur J Neurol 1996;3:44-49.\
41.LeWitt PA, Gopinathan G,Ward CT. Lisuride versus bromocriptine treatment in Parkinson's disease:a double-blind study. Neurology 1982;32:69-72.
42.Laihinen A, Rinne UK, Suchy I. Comparison of lisuride and bromocriptine in the treatment of advanced Parkinson's disease. Acta Neurol Scand 1992;86:593-595.
43.The Tolcapone Study Group. Efficacy and tolerability of tolcapone compared with bromocriptine in levo-dopa-treated parkinsonian patients. Mov Disorders 1999;14:38-44.
44.Agid Y, Pollak P, Bonnet AM, Signoret JL, Lhermitte F. Bromocriptine associated with a peripheral dopamine blocking agent in treatment of Parkinson's disease. Lancet 1979;1(8116):570-572.
45.Quinn N, Illas A, Lhermitte F, Agid Y. Bromocriptine and domperidone in the treatment of Parkinson's disease. Neurology 1981;31:662-667.
46.Ben-Noun L. Drug-induced respiratory disorders: incidence, prevention and management. Drug Saf 2000;23:143-164.
47.Ferreira JJ, Galitzky M, Montastruc JL, Rascol O. Sleep attacks and Parkinson's disease treatment. Lancet 2000;355:1333-1334.
48.Periti P, Mazzei T, Mini E, Novelli A. Pharmacokinetic drug interactions of macrolides. Clin Pharmacokinet 1992;23:106-131.

BIBLIOGRAPHY - Excluded from Analysis (REASON FOR EXCLUSION)

Agid Y, Pollak P, Bonnet AM, Signoret JL, Lhermitte F. Bromocriptine associated with a peripheral dopamine blocking agent in treatment of Parkinson's disease. Lancet 1979;1:570-572. (Study on domperidone)
Allain H, Le-Coz F, Goulley F, et al. Comparison of three regiments of Parlodel-SRO in levodopa-treated parkinsonians: a randomized double-blind cross-over study. Int J Clin Pharmacol Ther Toxicol 1991;29:314-322. (Study on Parlodel SRO)
Andreu N, Damase-Michel C, Senard JM, Rascol O, Montastruc JL. A dose-ranging study of selegiline in patients with Parkinson's disease: effect on platelet monoamine oxidase activity. Mov Disord 1997;12:293-296. (Focus on selegiline effects on platelet MAO-B)
Baas H, Schneider E, Fischer PA, Japp G. Mesulergine and bromocriptine in long-term treatment of advanced parkinsonism. J Neural Transm 1985;64:45-54. (< 20 patients per treatment group)
Bakheit AM, Henderson LM, Moore AP, Simpson JA, Thomas M. Long-term double masked trial of early treatment with L-dopa plus bromocriptine versus L-dopa alone in Parkinson's disease. Interim results. Eur Neurol 1990;30:108-111. (< 20 patients per treatment groups)
Bateman DN, Kahn C, Legg NJ, Reid JL. Metoclopramide in Parkinson's disease. Clin Pharmacol Ther 1978;24:459-464. (Study on metoclopramide)
Bateman DN, Coxon A, Legg NJ, Reid JL. Treatment of the on-off syndrome in parkinsonism with low dose bromocriptine in combination with levodopa. J Neurol Neurosurg Psychiatry 1978;41:1109-1113. (< 20 patients per treatment group)
Ben-Shlomo Y, Churchyard A, Head J, et al. Investigation by Parkinson's Disease Research Group of United Kingdom into excess mortality seen with combined levodopa and selegiline treatment inpatients with early, mild Parkinson's disease: further results of randomized trial and confidential inquiry. BMJ 1998;316:1191-1196. (Date focusing on selegiline and not bromocriptine)
Bergamasco B, Benna T, Scarzella L. Long-term bromocriptine treatment of de novo patients with Parkinson's disease. A seven-year follow-up. Acta Neurol Scand 1990;81:383-387. (Level III)
Bonnet AM, Serre I, Marconi R, Agid Y, Dubois B. A "combined" levodopa test as a useful method for evaluating the efficacy of dopamine agonists: application to pergolide and bromocriptine. Mov Disord 1995;10:668-671. (< 20 patients per treatment group)
Bromocriptine Multicentre Trial Group. Bromocriptine as initial theray in elderly parkinsonian patients. Age-Ageing 1990;19:62-67. (Data reviewed in another paper)
Brunt E, Aitken C. A double-blind comparative study of ropinirole versus bromocriptine in the treatment of parkinsonian patients not optimally controlled on L-dopa. J Neurol 1996;243:S38. (Abstract)
Burton K, Larsen TA, Robinson RG, Bratty PJ, Martin WR, Schulzer, Calne DB. Parkinson's disease: a comparison of mesulergine and bromocriptine. Neurology 1985;35:1205-1208. (Study on mesulergine)
Calne DB, Teychenne PF, Claveria LE, Eastman R, Greenacre JK, Petrie A. Bromocriptine in parkinsonism. Br Med J 1974;4:442-444. (Level III)
Cantello R, Riccio A, Gilli M, Delsedime M, Scarzella L, Aguggia M, Bergamasco B. Ital J Neurol Sci 1986;7:139-143. (Study on bornaprine)
Caraceni T, Musicco M, Gasparini M, et al. A multicenter Italian randomized study on early treatment of Parkinson disease: comparison of 1-dopa, 1-deprenyl and dopamine agonists. Study design and short term results. Ital J Neurol Sci 1992;13:735-739. (Non-English literature)
Caraceni T. A case for early levodopa treatment of Parkinson's disease. Clin Neuropharmacol 1995;18(suppl 3):S38-S42. (Insufficient description of methods)
de Yebenes JG, et al. A comparative study of the effect of bromocriptine and pergolide on Parkinson disease. Rev Neurol 1997;25:1343-1345. (Non-English literature)
Debono AG, Donaldson I, Marsden CD, Parkes JD. Letter:bromocriptine in parkinsonism. Lancet 1975;2:987-988. (Letter)
Devathasan G, Chong PN, Puvanendran K, Lun KC, Wong PK. Low-dose bromocriptine therapy in severe Parkinson's disease. Clin Neuropharmacol 1984;7:231-237. (< 20 patients per treatment group)
Dupont E, Andersen A, Boas J, et al. Sustained-release Madopar HBS compared with standard Madopar in the long-term treatment of de novo parkinsonian patients. Acta Neurol Scand 1996;93:14-20. (Focus on Madopar HBS)
Dupont E, Boas J, Mikkelsen B, Wermuth L, Worm PJ. The levodopa dose-sparing capacity of pergolide compared with that of bromocriptine. Eur J Neurol 1996;3(suppl 1):9-12. (Data reviewed in another paper)
Eisler T, Thorner MO, MacLeod RM, et al. Prolactin secretion in Parkinson disease. Neurology 1981;31:1356-1359. (Non clinical endpoint)
Factor SA, Sanchez-Ramos JR, Weiner WJ. Parkinson's disease: an open label trial of pergolide in patients failing bromocriptine therapy. J Neurol Neurosurg Psychiatry 1988;51:529-533. (Data on pergolide)
Factor SA, Weiner WJ. Early combination therapy with bromocriptine and levodopa in Parkinson's disease. Mov Disord 1993;8:257-262. (Level III; review)
Fischer PA, Przuntek H, Majer M, Welzel D. Combined treatment of the early stages of Parkinson's syndrome with bromocriptine and levodopa. The results of a multicenter study. Dtsch Med Wochenschr 1984;109:1279-1283. (Non-English literature)
Foster NL, Newmann RP, LeWitt PA, et al. Peripheral beta-adrenergic blockade treatment of parkinsonian tremor. Ann Neurol 1984;16:505-508. (Study on nadolol)
Gawel M, Riopelle R, Libman I, Bouchard S. Bromocriptine in the treatment of Parkinson's disease:a double-blind study against L-dopa/carbidopa. Adv Neurol 1986;45:535-538. (Same data analysed in another paper)
Gerlach J. Effect of CB 154 (2-bromo-alpha-ergocryptine) on paralysis agitans compared with Madopar in a double-blind, cross-over trial. Acta Neurol Scand 1976;53:189-200. (< 20 patients per treatment group)
Godwin-Austen RB, Smith NJ. Comparison of the effects of bromocriptine and levodopa in Parkinson'' disease. J Neurol Neurosurg Psychiatry 1977;40:479-482. (< 20 patients per treatment group)
Goetz CG, Tanner CM, Glantz RH, Klawans HL. Chronic agonist therapy for Parkinson's disease: a 5-year study of bromocriptine and pergolide. Neurology 1985;35:749-751. (< 20 patients per treatment group)
Goulley F, Wolmark Y, Bourdeix I, Chaumet-Riffaud PD. Parlodel in early combination with levodopa in the treatment of Parkinson disease. Comparison of 2 dosage forms. Therapie 1993;48:233-238. (Non-English literature)
Grimes JD, Delgado MR. Bromocriptine:problems with low-dose de novo therapy in Parkinson's disease. Clin Neuropharmacol 1985;8:73-77. (Level III)

Gron U. Bromocriptine versus placebo in levodopa treated patients with Parkinson's disease. Acta Neurol Scand 1977;56:269-273. (< 20 patients per treatment group)

Hely MA, Morris JG, Rail D, et al. The Sydney multicentre study of Parkinson's disease:a report on the first 3 years. J Neurol Neurosurg Psychiatry 1989;52:324-328. (Interim analysis - final data analysed in another article)

Inzelberg R, Nisipeanu P, Rabey JM, et al. Comparison of cabergoline (CBG) and bromocriptine (BCR) in Parkinson's disease (PD) patients with motor fluctuations. Neurology 1995;45:A292. (Abstract)

Jacobides GB, Audibert A. Treatment of Parkinson disease with bromocriptine (CB 154 Sandoz). Ther Umsch 1975;32:469-471. (Non-English literature)

Jansen EN. Bromocryptine in levodopa response-losing parkinsonism. A double-blind study. Eur Neurol 1978;17:92-99. (< 20 patients per treatment group)

Jansen EN, Staal-Schreinemachers A, van-der-Sande JJ, Haas JA, Lakke JP. Parlodel SRO in Parkinson's disease: a double-blind randomized comparison of Parlodel standard and SRO. Eur Neurol 1992;32:318-320. (Study on Parlodel SRO)

Jungmann E, Haak T, Althoff PH, Fassbinder W, Schoffling K. Dopaminergic ef fects on kidney function and responsiveness of aldosterone, plasma renin activity, prolactin catecholamines, and blood pressure to stimulation in patients with prolactinoma. Comparison of the efficacy of pergolide and bromocriptine therapy. Arzneimittelforschung 1988;38:296-300. (Non-clinical endpoints)

Kartzinel R, Shoulson I, Calne DB. Studies with bromocriptine. Part 2. Double-blind comparison with levodopa in idiopathic parkinsonism. Neurology 1976;26:511-513. (< 20 patients per treatment group)

Kartzinel R, Shoulson I, Calne DB. Studies with bromocriptine:III. Concomitant administration of caffeine to patients with idiopathic parkinsonism. Neurology 1976;26:741-743. (Study on caffeine)

Kowa H, Kanazawa I, Goto I, Kuno S, Mizuno Y, Ogawa N, Tashiro K, Yanagisawa N. Nine-year follow-up study of bromocriptine monotherapy for Parkinson's disease. Eur Neurol 1997;38(suppl 1):23-28. (Data analysed in another paper)

Korchounov A, Braune HJ, Huffmann G, Schipper HI. Cardiovascular side effects of levodopa compared to additional treatment with bromocriptine in Parkinson's disease. J Neurol Sci 1997;150(suppl.):S181-S181. (Abstract)

Kristensen O, Hansen E. Bromocriptine in the treatment of advanced parkinsonism. Acta Neurol Scand 1977;56:274-276. (< 20 patients per treatment group)

Lambert SWJ, Klyn JGM, Oosterom R. Mechanism of action and tolerance of mesulergine. Clin Pharmacol Ther 1984;36:620-627. (Study on mesulergine)

Lees AJ on behalf of the Parkinson's Disease Research Group of the United Kingdom. Comparison of therapeutic effects and mortality data of levodopa and levodopa combined with selegiline in patients with early, mild Parkinson's disease. BMJ 1995;311:1602-1607. (No data provided on bromocriptine)

Lees AJ, Haddad S, Shaw KM, Kohout LJ, Stern GM. Bromocriptine in parkinsonism. Arch Neurol 1978;35:503-505. (Level II)

Libman I, Gawel M, Riopelle RJ, Bouchard S. A double-blind study evaluating the use of bromocriptine (Parlodel) vs L-dopa/carbidopa (Sinemet) in "de novo" parkinsonians. J Neurol 1985;232:184. (Abstract)

Libman I, Gawel MJ, Riopelle RJ, Bouchard S. A comparison of bromocriptine (Parlodel) and levodopa-carbidopa (Sinemet) for treatment of "de novo" Parkinson's disease patients. Can J Neurol Sci 1987;14:576-580. (Data reviewed in another paper)

Lieberman J, Pollak S, Lesser M, Kane J. Pharmacologic characterization of tardive dyskinesia. J Clin Psychopharmacol 1988;8:254-260. (Non-Parkinson's disease patients)

Lieberman AN, Neophytides A, Leibowitz M, et al. Comparative efficacy of pergolide and bromocriptine in patients with advanced Parkinson's disease. Adv Neurol 1983;37:95-108. (Chapter in a book)

Lieberman A, Goldstein M, Neophytides A, et al. Lisuride in Parkinson's disease: efficacy of lisuride compared to levodopa. Neurology 1981;31:961-965. (Study on lisuride)

Limousin P, Pollak P, Pfefen JP, Tournier GCL, Dubuis R, Perret JE. Acute administration of levodopa-benserazide and tolcapone, a COMT inhibitor, in Parkinson's disease. Clin Neuropharmacol 1995;18:258-265. (Study on tolcapone)

Ludwig CL, Weinberger DR, Bruno G, et al. Buspirone, Parkinson's disease, and the locus ceruleus. Clin Neuropharmacol 1986;9:373-378. (Study on buspirone)

Mackenzie RA, Lance JW. A double-blind trial of bromocriptine in Parkinson's disease. Med J Aust 1978;2(suppl 3):27-28. (< 20 patients per treatment group)

Mackenzie RA, Lance JW. An evaluation of bromocriptine in the treatment of Parkinson's disease. Clin Exp Neurol 1978;15:228-236. (< 20 patients per treatment group)

Maier Hoehn MM, Elton RL. Low dosages of bromocriptine added to levodopa in Parkinson's disease. Neurology 1985;35:199-206. (Abstract)

Mannen T, Mizuno Y, Iwata M, Goto I, Kanazawa I, Kowa H, Nishitani H, Ogawa N, Takahashi A, Tashiro K, et al. A multi-center, double-blind study on slow-release bromocriptine in the treatment of Parkinson's disease. Neurology 1991;41:1598-1602. (Study on Parlodel SRO)

Martins R, Simoes F, Garret C, et al. Selegiline and/or bromocriptine in the early stages of Parkinson's disease: PARJUPAR Study. Rev Portug Neurol 1993;2:199-204. (Non-English literature)

Milon D, Allain H, Reyman JM, Morel G, Sabouraud O, Van-den-Driessche J. Randomized double-blind trial of injectable heptaminol for controlling spontaneous or bromocriptine-induced orthostatic hypotension in parkinsonians. Fundam Clin Pharmacol 1990;4:695-705. (Study on heptaminol)

Micieli G, Martignoni E, Cavallini A, Pacchetti C, Rossi F, Horowski R, Nappi G. Lisuride and bromocriptine in L-dopa stable-responder parkinsonian patients:a comparative, double-blind evaluation of cardiopressor and neurochemical effects. Funct Neurol 1996;11:317-325. (< 20 patients per treatment group)

Montastruc JL, Rascol O, Rascol A. Early treatment of Parkinson's disease with bromocriptine versus levodopa: first results after a 2 years follow-up. Therapie 1988;43:461-463. (Non-English literature)

Montastruc JL, Rascol O, Rascol A. A randomized controlled study of bromocriptine versus levodopa in previously untreated parkinsonian patients: a 3 year follow-up. J Neurol Neurosurg Psychiatry 1989;52:773-775. (Data appear in another article)

Montastruc JL, Rascol O, Rascol A. Comparison of bromocriptine and levodopa as first line treatment of Parkinson's disease: results of a 3-year prospective randomized study. Rev Neurol Paris 1990;146:144-147. (Non-English literature)

Nadeau SE, Malloy PF, Andrew ME. A cross-over trial of bromocriptine in the treatment of vascular dementia. Ann Neurol 1988;24:270-272. (Non-Parkinson's disease patients)

Nakanishi T, Mizuno Y, Goto I, et al. A nation-wide collaborative study on the long-term effects of bromocriptine in patients with Parkinson's disease. First interim report in Japan. Eur Neurol 1988;28(suppl 1):3-8. (Unplanned interim analysis)

Nakanishi T, Iwata M, Goto I, et al.. Second interim report of the nation-wide collaborative study on the long-term effects of bromocriptine in the treatment of parkinsonian patients. Eur Neurol 1989;29:(suppl 1):3-8. (Unplanned interim analysis)

Nakanishi T, Kanazawa I, Goto I, et al. Third interim report of the nation-wide collaborative study on the long-term effects of bromocriptine in the treatment of parkinsonian patients. Eur Neurol 1990;30(suppl 1):3-8. (Unplanned interim analysis)

Nakanishi T, Kanazawa I, Iwata M, et al. Nation-wide collaborative study on the long-term effects of bromocriptine in the treatment of parkinsonian patients:analysis on the maintenance and the change of the original mode of treatment. Eur Neurol 1992;32(suppl 1):23-29. (Same data analysed in another paper)

Nakanishi T, Mizuno Y, Goto I, et al. A nationwide collaborative study on the long-term effects of bromocriptine in patients with Parkinson's disease. The fourth interim report. Eur Neurol 1991;31(suppl 1):3-16. (Unplanned interim analysis)

Newmann RP, LeWitt PA, Shults C, et al. Dystonia: treatment with bromocriptine. Clin Neuropharmacol 1985;8:328-333. (Non-Parkinson's disease patients)

Ogawa N. Levodopa and dopamine agonists in the treatment of Parkinson's disease: advantages and disadvantages. Eur Neurol 1994;34(suppl 3):20-28. (Level III)

Ogawa N, Kanazawa I, Kowa H, et al. Nationwide multicenter prospective study on the long-term effects of bromocriptine for Parkinson's disease. Final report of a ten-year follow-up. Eur Neurol 1997;38(suppl 2):37-49. (Data reviewed in another paper)

Ogawa N. Early introduction of dopamine agonists in the long-term treatment of Parkinson's disease. Neurology 1998;51(suppl 2):S13-S20. (Level III)

Olanow CW, Alberts MJ, Stajich J, Burch G. A randomized blinded study of low-dose bromocriptine versus low-dose carbidopa/levodopa in untreated Parkinson's patients. In: Recent Developments in Parkinson's disease; Volume II. 1987. Florham Park: New Jersey, 201-208. (Chapter in a book)

Olsson JE, Rascol A, Korten JJ, Dupont E, Gauthier G. Early treatment with a combination of bromocriptine and levodopa compared with levodopa monotherapy in the treatment of Parkinson's disease. Current Therapeutic Research 1989;46:1002-1014. (Chapter in a book)

Olsson JE, Duchek M, Ekberg R, et al. L-dopa and bromocriptine in Parkinson disease. Early combination therapy has better effect. Lakartidningen 1993;90:1545-1548. (Non-English literature)

Olsson JE. Bromocriptine and levodopa in early combination in Parkinson's disease: first results of the Collaborative European Multicentric Trial. Adv Neurol 1990;53:421-423. (Chapter in a book)

Parkes JD, Marsden CD, Donaldson I, et al. Bromocriptine treatment in Parkinson's disease. J Neurol Neurosurg Psychiatry 1976;39:184-193. (< 20 patients per treatment group)

Pezzoli G, et al. Pergolide compared with bromocriptine in Parkinson's disease:a multicenter, cross-over, controlled study. Mov Disord 1994;9:431-436. (Data reviewed in another paper)

Pfeiffer RF, Wilken K, Glaeske C, Lorenzo AS. Low-dose bromocriptine therapy in Parkinson's disease. Arch Neurol 1985;42:586-588. (< 20 patients per treatment group)

Piccini P, Del-Dotto P, Pardini C, D'Antonio P, Rossi G, Bonuccelli U. Diurnal worsening in Parkinson patients treated with levodopa. Rev Neurol 1991;61:219-224. (Non-English literature)

Pollak P. Tolcapone versus bromocriptine as an adjunct to L-dopa therapy in the treatment of Parkinson's disease patients exhibiting motor fluctuations. J Neurol 1996;243:S9. (Abstract)
Pollak P, Gaio JM, Hommel M, Pellat J, Château R. Acute study of the association of bromocriptine and domperidone in parkinsonism. Therapie 1981;36:671-676. (Non-English literature).
Przuntek H, Welzel D, Schwarzmann D, Letzel H, Kraus PH. Primary combination therapy of early Parkinson's disease. A long-term comparison between the combined regimen bromocriptine/levodopa and levodopa monotherapy-first interim report. Eur Neurol 1992;32(suppl 1):36-45. (Unplanned interim analysis)
Quinn N, Illas A, Lhermitte F, Agid Y. Bromocriptine and domperidone in the treatment of Parkinson disease. Neurology 1981;31:662-667. (Study on domperidone)
Rascol A, Olsson JE, Worm-Petersen J, Korten JJ, Foreman MI. Early combination of bromocriptine with levodopa in the treatment of Parkinson's disease: a five-year multicentric study. Mov Disord 1994;9:102. (Abstract)
Reid WG. The evolution of dementia in idiopathic Parkinson's disease: Neuropsychological and clinical evidence in support of subtypes. Special Issue: 1991 IPA Research Awards in Psychogeriatrics: Winning papers and selected outstanding submissions. Intern Psychogeriat 1992; 4(suppl 2):147-160. (Not focusing on bromocriptine)
Rinne UK. Combined bromocriptine-levodopa therapy early in Parkinson's disease. Neurology 1985;35:1196-1198. (Level III)
Riopelle RJ, Gawel MJ, Libman I, et al. A double-blind study of bromocriptine and L-dopa in de novo Parkinson's disease. Eur Neurol 1988;28(suppl 1):11-14. (Data reviewed in another paper)
Sampaio C, Branco MC, Rosa MM, Passarinho M, Castro CA. A pharmacokinetic interaction between subcutaneous apomorphine and levodopa/carbidopa (Sinemet registered trade mark). Clin Drug Invest 1995;9:363-366. (Study on apomorphine)
Scarzella L, Cantello R, Delsedime M, et al. Clinical trial on the therapeutic activity of dihydroergokryptine in parkinsonism: preliminary results. Curr Ther Res Clin Exp 1985;38:432-440. (Study on dihydroergokryptine)
Schrag AE, Brooks DJ, Brunt E, et al. The safety of ropinirole, a selective nonergoline dopamine agonist, in patients with Parkinson's disease. Clin Neuropharmacol 1998;21:169-175. (Study on ropinirole)
Schneider E, Fischer PA. Bromocriptine in the treatment of progressive stages of Parkinson's disease. Dtsch Med Wochenschr 1982;107:175-179. (Non-English literature)
Shan DE, Yeh SI. An add-on-study of selegiline to Madopar in the treatment of parkinsonian patients with dose-related fluctuations:comparison between Jumexal and Parkryl. Chinese Med J 1996;58:264-268. (Non-English literature)
Stern G, Lees A. Long-term effects of bromocriptine given to de novo patients with idiopathic Parkinson's disease. Adv Neuro 1987;45:525-527. (Chapter in a book)
Stocchi F, Keens J, The 053 Study Group. The efficacy at six months of ropinirole vs bromocriptine as early therapy in Parkinson's disease. Eur J Neurol 1996;3:S179. (Abstract)
Stocchi F, Keens J. The efficacy at 6 months of ropinirole versus bromocriptine as early therapy in parkinsonian patients. J Neurol 1996;243:S38. (Abstract)
Tashiro K, Goto I, Kanazawa I, et al. Eight-year follow-up study of bromocriptine monotherapy for Parkinson's disease. Eur Neurol 1996;36(suppl 1):32-37. (Data analysed in another paper)
Teychenne PD, Rosin AJ, Plotkin CN, Calne DB. Cross tolerance between two dopaminergic ergot derivatives —bromocriptine and lergotrile. Br J Clin Pharmacol 1980;9:47-50. (Study on lergotrile)
Teychenne PF, Bergsrud D, Racy A, et al. Bromocriptine: low-dose therapy in Parkinson disease. Neurology 1982;32:577-583. (< 20 patients per treatment group)
Teychenne PF, Bergsrud D, Elton RL, Racy A. Bromocriptine:long-term low-dose therapy in Parkinson's disease. Clin Neuropharmacol 1986;9:138-145. (Level III)
Teychenne PF, Leigh PN, Reid JL, et al. Idiopathic parkinsonism treated with bromocriptine. Lancet 1975;2:473-476. (Level III)
Thorner MO, Ryan SM, Wass JA, et al. Effect of the dopamine agonist, lergotrile mesylate, on circulating anterior pituitary hormones in man. J Clin Endocrinol Metab 1978;47:372-378. (Non-Clinical endpoint)
Tolosa E, Blesa R, Bayes A, Forcadell F. Low dose bromocriptine in the early phases of Parkinson's disease. Clin Neuropharmacol 1987;10:168-174. (< 20 patients per treatment group)
Tourtellotte WW, Potvin AR, Costanza AM, et al. Cyclobenzaprine:a new type of anti-parkinsonian drug. Prog Neuro-Psychopharmacol 1978;2:553-578. (Study on cyclobenzaprine)
Tsui JK, Ross S, Poulin K, Douglas J, et al. The effect of dietary protein on the efficacy of L-dopa:a double-blind study. Neurology 1989;39:549-552. (Study not focusing on bromocriptine)
Ulm G, Fornadi F. R-(-)-deprenyl in the treatment of end-of-dose akinesia. J Neural Transm 1987;25:163-172. (Study on deprenyl)
Wallis WE. A progress report on the New Zealand multicentre Parkinson's disease trial. A comparison of low-dose treatment with bromocriptine or L-dopa. Eur Neurol 1988;28(suppl 1):9-10. (Level III)
Weiner WJ, Factor SA, Sanchez-Ramos JR, et al. A. Early combination therapy (bromocriptine and levodopa) does not prevent motor fluctuations in Parkinson's disease. Neurology 1993;43:21-27. (< 20 patients per treatment group)
Yanagisawa N, Kanazawa I, Goto I, et al. Seven-year follow-up study of bromocriptine therapy for Parkinson's disease. Eur Neurol 1994;34(suppl 3):29-35. (Data analysed in another paper)

Movement Disorders
Vol. 17, Suppl. 4, 2002, p. S68-S71

Published by Wiley-Liss, Inc.
DOI 10.1002/mds.5563

DA Agonists - Ergot derivatives: Cabergoline

BASIC PHARMACOLOGY

MECHANISM OF ACTION

Cabergoline is an orally administered synthetic tetracyclic ergoline derivative that acts in vitro and in vivo as a selective D2 receptor agonist with no substantial affinity for D1 receptors. As with other ergotamine derivatives, it has also some affinity for non-dopamine receptors (noradrenergic and serotonergic).[1]

Cabergoline improves the symptoms of the primate model of Parkinson's disease (PD) after MPTP intoxication. Cabergoline lowers prolactin secretion, and like all effective D2-agonists, induces nausea, vomiting and orthostatic hypotension in healthy volunteers.[1]

PHARMACOKINETICS

One major characteristic of cabergoline is its long duration of effect with oral administration, probably because its elimination half-life is approximately 65 hours. For example, cabergoline is highly effective in suppressing prolactin levels with a duration of action up to 21 days after a single 1 mg oral dose. Such a pharmacokinetic profile allows a once-daily dosing treatment regimen. The cabergoline Tmax is observed at 2.5 hours, and it is metabolized into several metabolites excreted mainly by the fecal route.[1]

REVIEW OF CLINICAL STUDIES

PREVENTION OF DISEASE PROGRESSION

No qualified studies were identified.

SYMPTOMATIC CONTROL OF PARKINSONISM

MONOTHERAPY

To date, there are no Level-I, placebo-controlled studies that have investigated the efficacy of cabergoline as monotherapy. Two clinical reports were identified, but correspond to the same L-dopa-controlled study that performed two different analyses: one planned interim analysis at 1 year[2], and a final analysis at 3 to 5 years.[3] In this study, cabergoline was initiated as monotherapy, and L-dopa supplementation was added in patients if required (i.e. based on dose limiting adverse reactions and if they reached maximal dose of cabergoline).

Rinne et al. (1997)[2]: This is the only available study assessing the effects of cabergoline monotherapy (with secondary open L-dopa supplementation if needed) at one-year. It is a randomized, L-dopa-controlled (Level I), double-blind study conducted in 413 de novo patients with PD (mean age approximately 61 years). Cabergoline could be titrated up to 4 mg/d on a once a day regimen, and L-dopa up to 600 mg/d tid. Open label L-dopa supplementation was allowed during the course of the study. PD disability was evaluated using mean UPDRS (Unified Parkinson's Disease Rating Scale) scores and the CGI (Clinical Global Impression) scale. The proportion of patients experiencing a 30% decrease in parkinsonian disability and the proportion requiring the addition of L-dopa were also analysed. Thirty-seven (9%) patients withdrew from the study by 1 year. At this 1-year interim analysis, mean cabergoline daily dose was 2.8 mg/d and that of L-dopa was 468 mg/d. Thirty-eight percent of the patients received L-dopa supplementation in the cabergoline group (mean daily dose 305 mg/d). At baseline, UPDRS was 29.1 in the L-dopa and 27.5 in the cabergoline group. After 1-year of treatment, the decrease in scores was higher in the L-dopa (16.5) than in the cabergoline group (13.7). The difference between the two treatments groups was reported to be small (< 2.8 points) and there is no clear statistical comparison. Irrespective of L-dopa supplementation, 81% of the cabergoline patients and 88% of the L-dopa ones were clinically improved (30% reduction in UPDRS). CGI was rated similarly in both groups (61% of the patients being much improved with cabergoline and 67% with levodopa). The proportion of patients requiring L-dopa supplementation was greater in the cabergoline group (38%) than in the L-dopa group (18%, $p<0.01$). Both drugs had quite similar adverse event profiles, typical of dopaminergic side effects. Peripheral edema, gastric upset (nausea, vomiting, dyspepsia, gastritis) and dizziness were more frequent with cabergoline than L-dopa therapy. Sleep disorders, postural hypotension, confusion, and hallucinations were reported with the same frequency in both groups. This study had an overall quality rating score of 75%.

Rinne et al. (1998)[3]: In the long-term extension of the study reported above[2], over 400 subjects were followed for a minimum of 3 years. The primary end-point was the onset of motor complications, but antiparkinsonian efficacy was also monitored using the UPDRS Parts II and III. The withdrawal rate was 16% in cabergoline-treated patients and 13% in the L-dopa-treated patients. After 3 to 5 years of treatment (study endpoint), the mean daily dose of cabergoline was 3 mg/d and that of L-dopa 500 mg/d. 35 % of the patients still in the trial who were on cabergoline did not require L-dopa supplementation, compared with 52% in the L-dopa group. The authors reported that both treatments had comparable improved motor disability after 4 years, in the patients who completed the study; L-dopa recipients still showed on average 30% improvement in motor disability (UPDRS III), while treatment with cabergoline was associated with a 22% to 23% improvement versus baseline. However, no statistical analysis was provided. Adverse reactions were quite similar in both groups, with the most frequent reactions including nausea and vomiting, dizziness and hypotension, and sleep problems. Edema was more frequent in patients treated with cabergoline. This study had an overall quality rating score of 75%.

ADJUNCT THERAPY

Early Combination

No qualified studies were identified.

Late Combination

Two Level-I studies qualified for this analysis. One is a placebo-controlled trial and the other is a bromocriptine-controlled.

Hutton et al. (1996)[4]: This was the only large (188 patients with suboptimally controlled PD and end-of-dose deterioration or motor complications, mean age 63 years), 6-month, randomized, parallel group, placebo-controlled study identified in the search. The primary efficacy endpoint was change in UPDRS Part II and III, and changes in daily dose of L-dopa were also assessed. At the end of the study, cabergoline ADL (activities in daily living) scores were significantly better than those of placebo (12.3 [-19% from baseline] vs. 14.3 [-4% from baseline], p=0.032). The same difference in favor of cabergoline was also reported for UPDRS III (13.7 [-16% from baseline]) vs. 16.3 [-6% from baseline]; p=0.014). In the cabergoline group, the mean L-dopa dose was reduced by 175 mg/d as compared to placebo, where it was reduced by 25.5 mg/d. Adverse reactions were consistent with other drugs in the class and included those related to autonomic nerve system effects (more frequent with cabergoline than placebo), cardiovascular effects, and neuropsychiatric effects. This study had an overall quality score of 80%.

Inzelberg et al. (1996)[5] (This study was previously reviewed in the Bromocriptine section.): This was a 9-month, double-blind, parallel-group, randomized study performed in 44 patients showing increasing disability and motor fluctuations. Cabergoline (3.18 mg/d) and bromocriptine (22 mg/d) induced comparable improvement of most assessment criteria including ADL scores (cabergoline: from 11 at baseline to 9 at completion; bromocriptine: from 11 at baseline to 9 at completion, p<0.01 for both treatments), UPDRS III (cabergoline: from 35 at baseline to 28 at completion; bromocriptine: from 38 at baseline to 29 at completion, p<0.0001 for both treatments). None of these effects were significantly different between the 2 groups. The frequency of adverse reactions (typical of dopaminergic adverse reactions) was similar for both drugs. This study had an overall quality rating score of 52%.

PREVENTION OF MOTOR COMPLICATIONS

The only study identified that met the inclusion criteria was the final analysis (after 3 to 5 years of follow-up) of a larger randomized, L-dopa-controlled, Level-I study previously described (see Symptomatic Control of Parkinsonism). Below the data relevant to the effects of cabergoline in the prevention of motor complication are reviewed.

Rinne et al. (1998)[3]: 412 patients were randomized to treatment with cabergoline or L-dopa and followed for 3 to 5 years. The primary end-point was the onset of motor complications, which was confirmed at two subsequent clinic visits, and assessed on the basis of a complex and heterogeneous checklist in which fluctuations were classified into different categories (daily "wearing-off", nocturnal akinesia, early morning akinesia, "off" period freezing, peak-dose dyskinesia, early morning dystonia, dose-related "off" period dystonia, dose-related "on" dystonia, and random freezing, among others). At final analysis (3 to 5 year), the mean daily dose of cabergoline was 3 mg/d and L-dopa dose was 500 mg/d. Thirty-five percent of the patients that remained in the trial and who were treated with cabergoline did not require L-dopa supplementation as compared to 52% in the L-dopa group. Motor complications were statistically less frequent in the cabergoline arm (22 %) than in the L-dopa arm (34 %) (p<0.02). This study had an overall quality rating score of 75%.

CONTROL OF MOTOR COMPLICATIONS

The two Level-I studies already reviewed above in the section Control of Parkinsonism also qualified for review in this section. Therefore, only relevant data for control of motor complications will be reviewed here.

Hutton et al. (1996)[4]: This was 6-month, randomized, parallel, placebo-controlled study conducted in 188 patients with suboptimally controlled PD who had end-of-dose deterioration or other motor complications. Motor fluctuations were assessed as a secondary endpoint using item 39 of UPDRS Part IV (Complications of Therapy). Patients also kept diaries for "on" and "off" assessment. The cabergoline group at endpoint had significantly less "off" time compared with the placebo group (p=0.01), but no raw data were reported in the text. The amount of time spent "on", according to diaries, also increased significantly with cabergoline compared with the placebo group (p<0.05), but no actual data were reported in the text.

Inzelberg et al. (1996)[5]: This was a double-blind, parallel-group, randomized study performed in 44 patients showing increasing disability and motor fluctuations. "Off" periods were measured using diaries. Percentage "off" hours decreased with cabergoline (from 34% at baseline to 17% at completion) and bromocriptine (from 32% at baseline to 26% at completion, p<0.0001 for both treatments), and the differences between treatments was not statistically significant.

REVIEW OF SAFETY

Cabergoline has been associated with adverse reactions consistent with other dopaminergic agonists including gastrointestinal, cardiovascular and neuropsychiatric effects. There is no evidence that cabergoline has a safety profile different from other ergotamine derivatives like bromocriptine.

Similar to other dopamine agonists, it is likely that cabergoline aggravates dyskinesia in already dyskinetic, L-dopa-treated, patients although little data are reported in the literature that specifically address this issue. Conversely, when used as an initial therapy (before L-dopa) and regardless of subsequent L-dopa supplementation, there is some indication that cabergoline reduces the long-term risk of the occurrence of motor complications, especially dyskinesia.[3]

Few cases of fibrosis have been reported with cabergoline, as with other ergot compounds.[6,7]

Little data are available on "sleep attacks", and in selected clinical studies, sleep problems were reported without further details. One patient on cabergoline (and other antiparkinsonian and non-antiparkinsonian medications) was recently reported to have episodes that might correspond to "sleep-attack" episodes.[8]

In one study, edema was reported to be more frequent with cabergoline than with L-dopa.[3]

No data are available related to cabergoline and mortality.

CONCLUSIONS

Overall, less than 400 patients treated with cabergoline who were followed for a minimum of 6 months and up to 4 years were identified for inclusion in this review.

EFFICACY

PREVENTION OF DISEASE PROGRESSION

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of cabergoline regarding neuroprotection in patients with PD.

SYMPTOMATIC CONTROL OF PARKINSONISM

Monotherapy

No placebo-controlled studies have been done to assess the symptomatic efficacy of cabergoline as monotherapy in PD. There is only one identified L-dopa-controlled Level-I study.[2,3] In this study, patients received open-label levodopa supplementation to keep control of parkinsonian symptoms in both treatment arms, and therefore, there is INSUFFICIENT EVIDENCE to conclude on cabergoline efficacy for symptomatic control in PD.

Adjunct therapy in L-dopa-treated patients

Based on one large level-I placebo-controlled study[4] conducted in L-dopa-treated patients with motor fluctuations, cabergoline is considered as EFFICACIOUS in improving control of parkinsonian motor symptoms in advanced L-dopa-treated patients with PD. There is INSUFFICIENT EVIDENCE to conclude on cabergoline efficacy as an early combination therapy with levodopa in PD patients without motor fluctuations.

PREVENTION OF MOTOR COMPLICATIONS

Based on one 4-year L-dopa-controlled trial[3], initial treatment with cabergoline monotherapy with subsequent L-dopa supplementation is EFFICACIOUS in reducing the risk of occurrence of long-term L-dopa-induced motor complications.

CONTROL OF MOTOR COMPLICATIONS

Based on one Level-I, placebo-controlled trial[4] (which failed to include all the raw data on the "off" period), cabergoline is LIKELY EFFICACIOUS in controlling motor fluctuations in advanced L-dopa-treated patients with PD.

SAFETY

The clinical data available to date suggest that using and prescribing cabergoline in patients with PD carries an ACCEPTABLE RISK WITHOUT SPECIALIZED MONITORING. There is no indication that its safety profile differs from that of the other available dopamine agonists.

No data are available for use long-term (10 years) or on mortality.

IMPLICATIONS FOR CLINICAL PRACTICE

Cabergoline used initially as monotherapy in de novo patients with PD and later used with L-dopa supplementation is CLINICALLY USEFUL for reducing the risk of occurrence of long-term motor complications. The actual effect of cabergoline to control parkinsonism in early PD patients however remains INVESTIGATIONAL. After 3 to 5 years of treatment, only 20% of the patients can remain on cabergoline monotherapy and most patients need L-dopa.

As adjunct treatment in L-dopa-treated patients with motor fluctuations, cabergoline is CLINICALLY USEFUL in enhancing symptomatic control. The effect of cabergoline in controlling motor fluctuations is not fully documented.

In the studies reported herein, cabergoline was used at doses ranging from 2 to 5 mg/d. The clinical interest of cabergoline is the possibility to use it once daily, which is preferable for many patients; none of the other drugs in this class have a once-daily dosing regimen. Randomized, active comparator trials using other antiparkinsonian medications (e.g. dopamine agonists, MAO-B and COMT inhibitors) have not been done.

IMPLICATIONS FOR CLINICAL RESEARCH

In the literature there are few reports on the efficacy and safety of cabergoline. Additional studies are needed including:

- Well-designed, short-term, placebo-controlled study in L-dopa naïve PD patients to properly assess the magnitude of the effect of cabergoline on parkinsonian symptoms.
- Appropriate comparisons with other antiparkinsonian agents (other dopamine agonists, MAO-B and COMT-inhibitors).
- Studies comparing the risk of fluctuations and dyskinesias in patients treated with cabergoline versus treatment with other shorter-acting dopamine agonists (e.g. lisuride). The prolonged elimination half-life of cabergoline offers an advantage of once-daily dosing, but possible disadvantages with this treatment regimen are not well understood. For example, the prolonged elimination half-life might be a handicap in terms of wash-out of adverse events (like psychosis). These benefits vs. risks need to be further evaluated in prospective, controlled trials.
- Studies on the long-term quality of life impact of cabergoline, effects on mortality, and pharmacoeconomic benefits.

REFERENCES

1. Fariello RG. Pharmacodynamic and pharmacokinetic features of cabergoline. Rationale for use in Parkinson's disease. Drugs 1998;55(suppl 1):10-16.
2. Rinne UK, Bracco F, Chouza C, et al. Cabergoline in the treatment of early Parkinson's disease: results of the first year of treatment in a double-blind comparison of cabergoline and levodopa. The PKDS009 Collaborative Study Group. Neurology 1997;48:363-368.
3. Rinne UK, Bracco F, Chouza C, et al. and the PKDS009 Study Group. Early treatment of Parkinson's disease with cabergoline delays the onset of motor complications. Drugs 1998;55(suppl 1):23-30.
4. Hutton JT, Koller WC, Ahlskog JE, et al. Multicenter, placebo-controlled trial of cabergoline taken once daily in the treatment of Parkinson's disease. Neurology 1996;46:1062-1065.
5. Inzelberg R, Nisipeanu P, Rabey JM, et al. Double-blind comparison of cabergoline and bromocriptine in Parkinson's disease patients with motor fluctuations. Neurology 1996;47:785-788.
6. Geminiani G, Fetoni V, Genitrini S, Giovannini P, Tamma F, Caraceni T. Cabergoline in Parkinson's disease complicated by motor fluctuations. Mov Disord 1996;11:495-500.
7. Ling LH, Ahlskog JE, Munger TM, Limper AH, Oh JK. Constrictive pericarditis and pleuropulmonary disease linked to ergot dopamine agonist therapy (cabergoline) for Parkinson's disease. Mayo Clin Proc 1999;74:371-375.
8 Ebersbach G, Norden J, Tracik F. Sleep attacks in Parkinson's disease: polysomnographic recordings. Mov Disord 2000;15(Suppl 3):89.

BIBLIOGRAPHY - EXCLUDED FROM ANALYSIS (REASON FOR EXCLUSION)

Ahlskog EJ, Muenter MD, Maraganore DM, et al. Fluctuating Parkinson's disease. Arch Neurol 1994;51:1236-1241. (Level III)

Ahlskog JE, Wright KF, Muenter MD, Adler CH. Adjunctive cabergoline therapy of Parkinson's disease: comparison with placebo and assessment of dose responses and duration of effect. Clin Neuropharmacol 1996;19:202-212. (< 20 patients per treatment group)

Del Dotto P, Colzi A, Pardini C, et al. Cabergoline improves motor disability without modifying L-dopa plasma levels in fluctuating Parkinson's disease patients. J Neural Transm 1995;45(suppl):259-265. (< 20 patients per treatment group)

Del Dotto P, Colzi A, Musatti E, et al. Clinical and pharmacokinetic evaluation of L-dopa and cabergoline cotreatment in Parkinson's disease. Clin Neuropharmacol 1997;20:455-465. (< 20 patients per treatment group)

Geminiani G, Fetoni V, Genitrini S, Giovannini P, Tamma F, Caraceni T. Cabergoline in Parkinson's disease complicated by motor fluctuations. Mov Disord 1996;11:495-500. (Level III)

Guttman M. on behalf of the international pramipexole/bromocriptine study group. Double-blind comparison of pramipexole and bromocriptine treatment with placebo in advanced Parkinson's disease. Neurology 1997;49:1060-1065. (Study on pramipexole)

Hutton JT, Morris JL, Brewer MA. Controlled study of the antiparkinsonian activity and tolerability of cabergoline. Neurology 1993;43:613-616. (No comparator)

Hutton JT, Hurtig H, Hiner B, et al. Multicenter placebo controlled study of cabergoline taken once daily in the treatment of Parkinson's disease. Neurology 1995;45:203. (Abstract)

Hutton JT. Multicenter, placebo-controlled trial of cabergoline (CBG) taken once daily in the treatment of Parkinson's disease. Eur J Neurol 1995;2(suppl):44. (Abstract)

Inzelberg R, Nisipeanu P, Rabey MJ, Korczyn AD. Long-term tolerability and efficacy of cabergoline, a new long-acting dopamine agonist, in Parkinson's disease. Mov Disord 1995;10:604-607. (Level III)

Inzelberg R, Nisipeanu P, Rabey JM, et al. Comparison of cabergoline (CBG) and bromocriptine (BCR) in Parkinson's disease (PD) patients with motor fluctuations. Neurology 1995;45:292. (Abstract)

Jori MC, Franceschi M, Gyusty MC, et al. Clinical experience with cabergoline, a new ergoline derivative, in the treatment of Parkinson's disease. Adv Neurol 1990;53:539-543. (Chapter in a book)

Lieberman A, Imke S, Muenter M, et al. Multicenter study of cabergoline, a long-acting dopamine receptor agonist, in Parkinson's disease patients with fluctuating responses to levodopa/carbidopa. Neurology 1993;43:1981-1984. (No comparator)

Lera G, Vaamonde J, Rodriguez M, Obeso JA. Cabergoline in Parkinson's disease: long-term follow-up. Neurology 1993;43:2587-2590. (Level III)

Marsden CD. Clinical experience with cabergoline in patients with advanced Parkinson's disease treated with levodopa. Drugs 1998;55(suppl 1):17-22. (Level III)

Rabey JM, Nissipeanu P, Inzelberg R, Korczyn AD. Beneficial effect of cabergoline, new long-lasting D2 agonist in the treatment of Parkinson's disease. Clin Neuropharmacol 1994;17:286-293. (Level III)

Rinne UK, Bracco F, Chouza C, et al. Cabergoline delays the onset of motor complications in early Parkinson's disease. J Neurol Sci 1997;150:S114 (Abstract)

Steiger MJ, El-Debas T, Anderson T, Findley LJ, Marsden CD. Double-blind study of the activity and tolerability of cabergoline versus placebo in parkinsonians with motor fluctuations. J Neurol 1996;243:68-72. (< 20 patients per treatment group)

Movement Disorders
Vol. 17, Suppl. 4, 2002, p. S72-S73

Published by Wiley-Liss, Inc.
DOI 10.1002/mds.5564

DA Agonists - Ergot derivatives: Dihydroergocryptine (DHEC)

BASIC PHARMACOLOGY

MECHANISM OF ACTION

DHEC is a dihydro-derivative of ergocryptine acting as a D2 agonist and a partial D1 agonist. Therefore, DHEC has a pharmacodynamic profile quite comparable to that of bromocriptine. Like all ergotamine derivatives, DHEC has effects on serotonergic and adrenergic receptors.[1,2] DHEC improves the symptoms of the MPTP-treated monkey model of Parkinson's disease (PD). In healthy volunteers, its effects on D2 receptors reduce prolactin plasma levels, and induce nausea and hypotension. Preclinical data suggest that DHEC may have neuroprotective properties.[3,4]

PHARMACOKINETICS

DHEC, like other ergot derivatives, has linear kinetics. Its oral bioavailability after first pass effect is low (below 5%). It has linear metabolism with generation of active metabolites, is eliminated through feces, and has no interference with L-dopa kinetics.

REVIEW OF CLINICAL STUDIES

PREVENTION OF DISEASE PROGRESSION

No qualified studies were identified.

SYMPTOMATIC CONTROL OF PARKINSONISM

MONOTHERAPY

Two Level-I studies qualified: (1) one is a parallel group, placebo-controlled study in "de novo" patients with PD[5] and (2) the second is a cross-over, L-dopa-controlled trial conducted in L-dopa-treated patients in whom L-dopa given previously was withdrawn two days before the commencement of the investigation and randomization to DHEC or Madopar.[6]

Bergamasco et al. (2000)[5]: This was a prospective, 3-month interim analysis of an 18-month, randomized double-blind placebo-controlled parallel group study conducted in 123 de novo patients with PD (mean age 63 years). Efficacy was measured using the total score of the UPDRS as the primary end-point (first 3 parts). Eight patients (6 on DHEC and 2 on placebo) were considered as withdrawals and were not included in the analysis. At 3-month analysis, DHEC was superior to placebo ($p = 0.019$) as measured by the total UPDRS scores, which decreased from 31 at baseline to 27 at 3 month (-14%) with DHEC, and increased from 29 to 30 (+3%) with placebo. Due to this positive response, the trial was terminated early as planned a priori in the protocol. At the time of termination, 73 patients had reached the 6-month observation visit, and the analysis performed in this subset of patients confirmed the efficacy of DHEC (UPDRS improvement on DHEC of 17% vs. 11% decline with placebo, $p<0.001$). The incidence of adverse reactions did not differ between DHEC (13%) and placebo (10%) treatment, and gastrointestinal complaints were the most common. This study had an overall quality score of 93%.

Gerlach (1976)[6]: This was a randomized, cross-over, double-blind, L-dopa-controlled study (8 weeks per period) conducted in 20 L-dopa-treated patients with PD and a Webster total score higher than 6. L-dopa given previously was withdrawn 2 days before the start of the study when they were randomization to either DHEC or Madopar. Efficacy was evaluated using the Webster Rating Scale. Madopar (800 mg/d) was significantly more effective than DHEC (30mg/d) on the parkinsonian median Webster scores (7.5 vs. 11.5 respectively, $p<0.01$). More patients had dyskinesias with L-dopa ($n = 13$) than with DHEC ($n = 4$). Two patients complained of nausea under DHEC vs. one in the Madopar treatment group. Psychosis was reported in three Madopar-treated patients and in no DHEC-treated ones. Dizziness was reported in one Madopar-treated patient. This study had an overall quality score of 70%.

ADJUNCT THERAPY TO L-DOPA-TREATED PATIENTS WITH PD

Early Combination in Stable Patients with PD

No Level-I study meeting the predefined inclusion criteria qualified for review. However, one smaller (less than 20 patients per treatment-group), placebo-controlled trial was identified[7] and included because of the lack of other Level-I data.

Martignoni et al. (1991)[7]: This is a 6-month randomized double-blind, parallel placebo-controlled study conducted in 20 L-dopa-treated patients with PD (stable responders; mean age approximately 61 years; mean disease duration approximately 3 yrs.). Ten patients were randomized to DHEC and 10 to placebo. Efficacy was assessed using the Columbia University Rating Scale (CURS) and the NWUDRS. All patients completed the study. The mean daily dose of DHEC was 57 mg/d after 6 months of treatment. At 6 months, inter-group comparisons reported a significant difference between the two groups in favor of DHEC for CURS ($p<0.002$) and NWUDRS ($p<0.002$) scores. (No raw data are given in the published report for the placebo-treated group.) The 10 DHEC-treated patients reported that the CURS score improved from 33.6 at baseline to 26.8 at 6 months ($P<0.009$), and that the NWUDRS improved from 43.3 at baseline to 44.6 at 6 months (not statistically significantly different). Adverse reactions reported in DHEC-treated patients were related to the gastro-enteric system (nausea) and cardiovascular system (dizziness).

Late Combination

No Level-I studies conducted in advanced L-dopa treated patients that qualified for inclusion were identified.

PREVENTION OF MOTOR COMPLICATIONS

No qualified studies were identified.

CONTROL OF MOTOR COMPLICATIONS

The search identified only one Level-I trial meeting inclusion

criteria, which is a lisuride-controlled study[8] that is also reviewed in the Lisuride section (no placebo-controlled studies were identified) and is briefly reviewed below.

Battistin et al. (1999)[8]: This is a randomized, double-blind, parallel-group, lisuride-controlled study conducted in 68 L-dopa-treated patients with PD who qualified as having "inadequate therapeutic responsiveness." Only 3-month follow-up data are reported. DHEC (60mg/d) was reported to induce a significantly greater reduction in UPDRS Part IV (complications of therapy) than lisuride (1.2 mg/d) (2.5 vs. 4.3 respectively, $p<0.05$). This study had an overall quality score of 80%.

REVIEW OF SAFETY

There is limited information published to date on the safety of DHEC for treatment in patients with PD. DHEC has been associated with other typical dopaminergic adverse reactions including gastrointestinal, cardiovascular, and neuropsychiatric effects. In one study8, such adverse reactions were significantly less frequent than in a group of patients receiving lisuride, but the incidence of adverse reactions was unexpectedly high in this trial.

Similar to other ergotamine derivatives, fibrosis has been associated with DHEC.[9]

No data are available on the effects of DHEC on mortality.

CONCLUSIONS

EFFICACY

In controlled clinical studies to date, only about 200 PD patients have been treated with DHEC and followed for several months post-treatment. Therefore, conclusions listed below are based on a small population base.

PREVENTION OF DISEASE PROGRESSION

There are no studies available to date, therefore, there is INSUFFICIENT EVIDENCE to conclude about neuroprotective effects of DHEC in patients with PD.

SYMPTOMATIC CONTROL OF PARKINSONISM

Monotherapy

Based on one Level-I, placebo-controlled trial[5], DHEC is EFFICACIOUS in the management of de novo patients with PD. However, efficacy beyond 3 months is not established at this time.

Adjunct Therapy in L-dopa treated patients

There is only one small, short-term Level-I, lisuride-controlled study[7]; therefore, there is INSUFFICIENT EVIDENCE to conclude on the efficacy of DHEC in controlling parkinsonism as an adjunct treatment in L-dopa-treated patients.

PREVENTION OF MOTOR COMPLICATIONS

There is INSUFFICIENT EVIDENCE to conclude on the potential efficacy of the early use of DHEC in reducing the risk of occurrence of long-term motor complications in de novo patients with PD.

CONTROL OF MOTOR COMPLICATIONS

There is only one small, short-term Level-I, lisuride-controlled study[7], therefore, there is INSUFFICIENT EVIDENCE to conclude on the efficacy of DHEC in controlling motor fluctuations in advanced L-dopa-treated patients with PD.

SAFETY

Based on limited data available, the use of DHEC is ACCEPTABLE WITHOUT SPECIALIZED MONITORING in the management of patients with PD.

IMPLICATIONS FOR CLINICAL PRACTICE

Because of the limited clinical studies, DHEC is considered POSSIBLY USEFUL in the treatment of early PD, but remains INVESTIGATIONAL in most clinical situations. DHEC may not be a first-line choice because other dopamine agonists have been more rigorously tested in clinical studies. However, it can be considered a treatment option in the management of PD. Therapeutic doses reported in clinical trials range between 30 mg/day to 60 mg/day. DHEC is only available in selected countries.

IMPLICATIONS FOR CLINICAL RESEARCH

There is no evidence available on the relative efficacy of DHEC compared to other dopamine agonists. Additional studies are needed including:

- Well-designed (large studies), long-term, placebo-controlled trials to assess the efficacy of DHEC in patients with early and late PD.
- Long-term, L-dopa-controlled studies in de novo patients to assess the impact of early DHEC treatment on long-term motor complications.
- Long-term studies to assess DHEC on disease progression.
- Comparative trials to assess the relative efficacy of DHEC vs. other antiparkinsonian medication (e.g. other dopamine agonists, MAOB, and cox-2 inhibitors).
- Well-designed studies to assess the effects of DHEC on pharmacoeconomic cost/benefits, quality of life changes, and effects on mortality in patients with PD.

REFERENCES

1. Davis JN, Strittmater WJ, Hoyler E, Leefkowitz RJ. [3H]dihydroergocryptine binding in rat brain. Brain Res 1977;132:327-336.
2. Kemp DM, George SE, Bungay PJ, Naylor LH. Partial agonism at serotonin 5-HT1B and dopamine D2L receptors using a luciferase reporter gene assay. Eur J Pharmacol 1999;373:215-222.
3. Bernocchi G, Gerzeli G, Scherini E, Vignola C. Neuroprotective effects of alpha-dihydroergocryptine against damages in the substantia nigra caused by severe treatment with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Acta Neuropathol 1993;85:404-413.
4. Battino M, Littarru GP, Gorini A, Villa RF. Coenzyme Q, peroxidation and cytochrome oxidase features after parkinson's-like disease by MPTP toxicity in intra-synaptic and no-synaptic mitochondria from Macaca fascicularis cerebral cortex and hippocampus: action of dihydroergocriptine. Neurochem Res 1996;21:1505-1514.
5. Bergamasco B, Frattola L, Muratorio A, Piccoli F, Mailland F, Parnetti L. Alpha-dihydroergocryptine in the treatment of de novo parkinsonian patients: results of a multicentre, randomized, double-blind, placebo-controlled study. Acta Neurol Scand 2000;101:372-380.
6. Gerlach J. Effect of CB 154 (2-bromo-alpha-ergocryptine) on paralysis agitans compared with Madopar in a double-blind, cross-over trial. Acta Neurol Scand 1976;53:189-200.
7. Martignoni E, Pacchetti C, Sibilla L, Bruggi P, Pedevilla M, Nappi G. Dihydroergocryptine in the treatment of Parkinson's disease: a six month's double-blind clinical trial. Clin Neuropharmacol 1991;14:78-83.
8. Battistin L, Bardin PG, Ferro-Milone F, Ravenna C, Toso V, Reboldi G. Alpha-dihydroergocriptine in Parkinson's disease: a multicentre randomized double-blind parallel group study. Acta Neurol Scand 1999;99:36-42.
9. Oechsner M, Groenke L, Mueller D. Pleural fibrosis associated with dihydroergocryptine treatment. Acta Neurol Scand 2000;101:283-285.

BIBLIOGRAPHY - Excluded from Analysis (REASON FOR EXCLUSION)

Foster NL, Newman RP, LeWitt PA, Gillespie MM, Larsen TA, Chase TN. Peripheral beta-adrenergic blockade treatment of parkinsonian tremor. Ann Neurol 1984;16:505-508. (Study on nadolol)

Movement Disorders
Vol. 17, Suppl. 4, 2002, p. S74-S78

Published by Wiley-Liss, Inc.
DOI 10.1002/mds.5565

DA Agonists - Ergot derivatives: Lisuride

BASIC PHARMACOLOGY

MECHANISM OF ACTION

Lisuride is an alpha-amino-ergoline with D2 receptor agonist properties and has no apparent D1 receptor effects. Similar to most ergotamine derivatives, lisuride also has 5-HT2 activity. In animal models of Parkinson's disease (PD), lisuride antagonizes reserpine-induced akinesia and induces rotation in the unilaterally 6-OHDA-lesioned rat. Lisuride lowers serum prolactin levels, induces nausea, and lowers blood pressure in healthy volunteers.[1]

PHARMACOKINETICS

After oral administration, lisuride is absorbed completely from the gastrointestinal tract. Peak plasma levels are obtained between 60 to 80 minutes, with high individual variation. Terminal half-life for elimination of lisuride from the plasma is around 2 hours, which is shorter than most other dopamine agonists. Similar to other ergotamine derivatives, absolute oral bioavailability of lisuride is low due to first pass metabolism ranging between 10 to 20%. 60 to 70% of lisuride is bound to human plasma proteins. Lisuride is extensively metabolised with more than 15 metabolites identified.

Lisuride has solubility properties similar to apomorphine and therefore can be given subcutaneously and intravenously.

REVIEW OF CLINICAL STUDIES

PREVENTION OF DISEASE PROGRESSION

No qualified studies were identified.

SYMPTOMATIC CONTROL OF PARKINSONISM

MONOTHERAPY

Only one randomized (Level-I) study assessing the effect of lisuride in L-dopa-naïve de novo PD patients was identified, according to the inclusion criteria.

Rinne (1989)[2]: This was an open-label, parallel-group, L-dopa-controlled study including 90 patients (mean age 62 years) randomized into 3 different arms: lisuride alone, L-dopa alone, and lisuride plus L-dopa as early combination. If the therapeutic response in the lisuride arm was insufficient after 3 months of treatment, L-dopa could be added to form a second early combination group. Efficacy was assessed using the CURS (Columbia University Rating Scale). Patients recorded, in a daily diary, the occurrence and severity of fluctuations in disability, and were followed for 4 years. After 3 months of follow-up, lisuride monotherapy was less effective than L-dopa (daily doses not given) (CURS percent improvement: L-dopa 56% vs. lisuride 32%, $p<0.01$). After 4 years of treatment, only 17% of the patients were maintained on lisuride monotherapy. In the other patients L-dopa supplementation was required. After 4 years of follow-up, early combination of lisuride (1.1 mg/d) and low-dose of L-dopa (484 mg/d) resulted in an antiparkinsonian response equal to that achieved with higher doses of L-dopa monotherapy (668 mg/d) (% improvement CURS: combination regimen 28% vs. L-dopa 25%). A similar improvement was reported in the group of lisuride-treated patients who received early L-dopa supplementation after 3 months of treatment (lisuride daily dose = 0.8 combined with 630 mg/d of L-dopa, % improvement CURS: 29%). For both groups that received combination therapy, there were significantly fewer end-of-dose failures and dyskinesias (see "Prevention of Motor Complications" below). Dopaminergic adverse reactions (digestive, cardiovascular, psychiatric) were quite similar among the three groups. The main reason for withdrawal from lisuride treatment was insufficient therapeutic response. Psychiatric adverse reactions leading to withdrawal occurred in one patient receiving lisuride monotherapy and 4 patients receiving combination therapy. Severe nausea, requiring domperidone treatment, was observed in 7 lisuride-treated, 3 combination-treated, and no L-dopa-treated patients. This study had an overall quality rating score of 44%.

ADJUNCT THERAPY

Lisuride can be added to L-dopa therapy as either an early combination or late combination treatment approach. In this review, early combination is defined as adding lisuride to L-dopa treatment within the first months in stable, nonfluctuating patients. Late combination is defined as adding lisuride after patients with motor fluctuations received several years of L-dopa therapy.

Early Combination Level-I Studies in Stable L-dopa-treated Patients

Allain et al. (2000)[3]: This was a randomized, controlled trial that included 82 recently diagnosed L-dopa-treated patients with PD (mean duration of L-dopa therapy was 5 months, disease duration was less than 3 years, Hoehn and Yahr Score less than 3; and the mean age was 59 years). Patients were randomized to L-dopa alone (monotherapy; n=41) or L-dopa plus lisuride (early combination; n=41). The first year of follow-up was double-blind, while the four consecutive years were open-label. The primary outcome measures were the change of L-dopa dosage and total UPDRS score during the "On" period. Long-term motor complications also were monitored (and described in more detail below: "Prevention of Motor Complications"). 52 % of patients completed the 5-year study. The mean daily L-dopa dose escalated to 446.7 mg/day at month 60 in the monotherapy group compared with 387.5 mg/day in the early combination group ($p<0.001$). The total UPDRS score showed progressive deterioration in the L-dopa group (38.37 at baseline vs. 48.95 at 60 months) compared with the early combination group in which the score remained unchanged through 60 months. The number of adverse reactions was greater in the early combination group than in the L-dopa monotherapy group and included classical dopaminergic reactions (i.e. psychiatric events,

insomnia, and gastrointestinal disorders [p<0.02]). This study had an overall quality rating score of 73%.

Late Combination in Fluctuating Patients

Level-II Studies (Placebo Controlled Studies)

No truly randomized placebo-controlled study met all the inclusion criteria. However, one placebo-controlled, double-blind, within-group comparison study was identified on a small group (n<20) of heterogenous patients.[4] Because of the lack of other Level-I, placebo-controlled studies, a summary of this trial is included in this review.

Gopinathan et al. (1981)[4]: Eighteen patients with PD were studied in this trial. The population of the trial was rather heterogeneous, as two postencephalitic parkinsonian patients were included in the study and there were L-dopa-treated and non-treated patients among those with PD. Most patients reported motor fluctuations in response to therapy. The study was not truly randomized because it was double-blind, within-patient comparison of lisuride and placebo. All patients received increasing doses of lisuride until the maximal tolerated dose or 5 mg/d. After 30 days, lisuride was withdrawn and patients received placebo for a final 10-day phase of observation. A blind observer scored parkinsonian symptoms using a modified CURS. Objective evaluations also included reaction and movement times. Two of the patients withdrew because of confusion. Mean improvement in clinical scores (difference between scores on lisuride and placebo) was reported to be significantly different in favor of lisuride (total score difference = 4.37, p<0.01). Adverse reactions included psychiatric reactions (n = 6), drowsiness (n = 9), gastrointestinal symptoms (n = 8), and light-headedness (n = 11).

Level-I Studies (Active Comparator Studies)

LeWitt et al. (1982)[5]: As this study is previously reviewed in the Bromocriptine section, only a brief review is included here. The study was a double-blind, randomized, cross-over (7-10 weeks per period of treatment) trial conducted in 28 patients with PD. Optimal doses were 4.5 mg/d for lisuride and 56.5 mg/d for bromocriptine. Clinical evaluation was carried out from a modified CURS. The ratings of parkinsonian features were reported to be similar at the optimal doses for lisuride and for bromocriptine, but no raw data are presented in the article. A clinical aggregate score for akinesia (finger dexterity, facial expression, gait, posture, balance, speech, and arising from sitting) showed a small but significant difference in favor of bromocriptine (p=0.018; no raw data are available and the clinical relevance of this small difference is unclear). Adverse reactions were reported to be similar between the two treatments. This study had an overall quality rating score of 59%.

Laihinen et al. (1992)[6] (also summarized in the section on Bromocriptine): This was a double-blind, randomized, cross-over trial (8-weeks per treatment period with a 2-week wash-out in between treatments) performed in 20 patients with PD suffering from deteriorating response to L-dopa and different kinds of fluctuations. Efficacy was assessed using the CURS. Mean optimal daily dose of lisuride was 1.3 mg/d and bromocriptine was 15 mg/d. The total CURS improved by 30% with lisuride and 29% with bromocriptine after 8 weeks of treatment. Adverse reactions were similar to other dopamine agonists therapy and did not differ between treatments. This study had an overall quality rating score of 69%.

Battistin et al. (1999)[7] (Also described in the section on dihydroergocryptine): This was a randomized, double-blind, parallel group, dihydroergocryptine (DHEC)-controlled study conducted in 68 L-dopa-treated patients PD who were reported as having an inadequate therapeutic response (mean age approximately 63 years). The study prematurely discontinued after 1 year of treatment because there was a high drop-out rate due to adverse reactions; only 3-month follow-up data are reported. Efficacy was assessed using the UPDRS score Part IV (dyskinesia + clinical fluctuations) as the primary outcome (also described below: Control of Motor Complications). The symptom pattern of the disease was evaluated using the CURS and the NWUDRS. Eleven patients (2 DHEC and 9 lisuride) were excluded from analysis because they dropped out before 1 month of treatment. Intention-to-treat (ITT) analysis was performed in 57 patients. Lisuride (1.2 mg/d) and DHEC (60 mg/d) both improved parkinsonian disability scales (CURS and NWUDRS) and the data presented were limited to the results of the ITT analysis (no raw values were reported in the text). In the per protocol analysis, CURS total score improved from 37 at baseline to 26.4 after 3 months with lisuride and form 36.7 to 26.7 with DHEC (no difference between the 2 groups). NWUDRS total score improved from 38/9 at baseline to 41.5 at 3 months with lisuride and from 38.7 to 40.9 with DHEC. Adverse reactions were considerably more frequent with lisuride (67% of the patients treated with lisuride vs. 25% of those receiving DHEC). Twenty-three patients discontinued treatment because of adverse reactions as compared to three in the DHEC group. Specific adverse reactions included hallucinations, gastrointestinal effects, and hypotension. This study had an overall quality rating score of 80%.

PREVENTION OF MOTOR COMPLICATIONS LEVEL-I STUDIES

Rinne (1989)[2]: This study (see also Symptomatic Control of Parkinsonism) looked at 90 de novo patients with PD who were openly randomized to 1 of 3 different arms: lisuride alone, L-dopa alone, or lisuride plus L-dopa as early combination. If the therapeutic response in the lisuride arm was insufficient after 3 months of treatment, L-dopa could be added to form a second early combination group. In this study, no wearing-off and no dyskinesia were observed after 4 years of treatment in the small subgroup of patients who could be maintained with lisuride monotherapy (5 patients). In patients that received lisuride plus L-dopa as combination (in the third month), the risk to develop dyskinesias and wearing-off was significantly reduced when compared with L-dopa used at initial monotherapy at higher doses (L-dopa monotherapy group: 52% end-of-dose failure and 64% peak-dose dyskinesia vs. both combination groups: 13% end-of-dose failure and 19% peak-dose dyskinesia; p<0.01 for both complications). This study had an overall quality rating score of 44%.

Allain et al. (2000)[3]: As described previously (Symptomatic Control of Parkinsonism) 82 patients were randomized to receive L-dopa or early combination of L-dopa plus lisuride. This was an open-label, parallel group, 5-year study in patients who were recently diagnosed PD and receiving L-dopa for less than 6 months. Incidence of treatment-related complications were evaluated using the UPDRS Part IV subscore, which remained low in both treatment groups: scores increased from 0.49 to 0.96 in the L-dopa treated group and from 0.32 to 0.73 in the combination group. The difference was not significant between both treatment groups. This study had an overall quality rating score of 73%.

CONTROL OF MOTOR COMPLICATIONS

ORAL FORMULATION LEVEL-I STUDIES

Laihinen et al. (1992)[6]: This study is reviewed in detailed in the bromocriptine section. Briefly, this was a double-blind, randomized, cross-over (8-weeks per period with a 2-week wash-out in between) trial performed in patients with PD suffering from a deteriorating response to L-dopa and different kinds of fluctuations. Fluctuations in disability were evaluated, but the method of assessment is not described. There was the same number of patients reporting beneficial effects on motor fluctuations with both drugs. In the lisuride treatment group after 8 weeks: 2 patients did not improve, 4 patients had a minimal improvement, 8 patients reported a moderate improvement, and 5 patients had a marked improvement. With bromocriptine treatment these numbers were: 1, 4, 8 and 6 for no, minimal, moderate and marked improvement, respectively. This study had an overall quality rating score of 69%.

Battistin et al. (1999)[7]: This study is also summarized previously (see Symptomatic Control of Parkinsonism). Briefly, this was a randomized, double-blind, parallel group dihydroergocryptine (DHEC)-controlled study conducted in 68 L-dopa-treated patients PD who were reported as having inadequate therapeutic responsiveness. The study was prematurely stopped at 1 year due to the high drop-out rate caused by adverse reactions; only the 3-month data are reported. Efficacy was assessed using the UPDRS score Part IV (dyskinesia + clinical fluctuations) as the primary outcome. DHEC (60mg/d) was reported to induce a significantly greater reduction in UPDRS Part IV than lisuride (1.2 mg/d, 2.5 vs. 4.3 respectively, $p<0.05$). This study had an overall quality rating score of 80%.

INTRAVENOUS/SUBCUTANEOUS FORMULATIONS

The relatively short duration of action and its water solubility characteristics have led to the clinical testing of lisuride by prolonged IV infusion. However, lisuride is no longer available in this formulation, and there were no qualified Level-I studies identified for inclusion in this review. Several Level-III studies have been reported in the literature[8-13], but are not included in this review.

REVIEW OF SAFETY

According to the literature published to date, lisuride is associated with the typical dopaminergic adverse drug reactions, including gastrointestinal effects, exacerbation of pre-existing dyskinesia, cardiovascular effects, and neuropsychiatric reactions. In two studies, psychiatric adverse reactions were reported more frequently in the lisuride treatment-group than in patients receiving bromocriptine[5] or DHEC.[7] However, these short-term studies are limited and do not permit conclusions on the safety of long-term use of lisuride. Case-reports of pleuropulmonary fibrosis have been reported with lisuride similar to adverse reactions associated with other ergotamine derivative dopamine agonists.[14] Episodes of "sleep attacks" have also been reported in selected patients treated with lisuride.[15]

CONCLUSIONS

Level-I studies available to assess the risk/benefit ratio of lisuride in the treatment of PD are limited (less than 150 patients have been followed-up from 4 weeks to 5 years), and the quality of these studies is often moderate. Moreover, in the absence of placebo-controlled data, a number of important practical issues can only be addressed based on available Level II or Level III studies.

EFFICACY

PREVENTION OF DISEASE PROGRESSION

There are no studies available that report on the neuroprotective role of lisuride in PD, therefore, there is INSUFFICIENT EVIDENCE to conclude about the efficacy of lisuride regarding neuroprotection.

SYMPTOMATIC CONTROL OF PARKINSONISM

Monotherapy

Based on one Level-I study[2], lisuride is LIKELY EFFICACIOUS as monotherapy when given early in the course of the PD (this study had a large dropout group). Lisuride monotherapy is less efficacious than L-dopa after a few months of treatment, and 50% of the patients require L-dopa supplementation after 1 year.

Adjunct therapy

Based on one Level-I, placebo-controlled study in patients with early PD, lisuride is LIKELY EFFICACIOUS as early combination therapy to L-dopa.[3] Based on three small, short-term, low-quality, active comparator trials[5-7], there is INSUFFICIENT EVIDENCE to conclude about the efficacy of lisuride as adjunct therapy in advanced L-dopa-treated patients.

PREVENTION OF MOTOR COMPLICATIONS

Based on conflicting Level-I study results (one positive[2] and one negative[3]), there is INSUFFICIENT EVIDENCE to conclude about the efficacy of lisuride in the prevention of motor complications in patients with PD.

CONTROL OF MOTOR COMPLICATIONS

In the absence of Level-I placebo-controlled studies, and conflicting study results of active comparator trials with low quality ratings[6,7], there is INSUFFICIENT EVIDENCE to conclude about the efficacy of oral lisuride in the management of motor fluctuations.

SAFETY

Oral lisuride treatment carries an ACCEPTABLE RISK WITHOUT SPECIALIZED MONITORING. It appears to have a similar safety profile to other dopamine agonists, although some trials have reported a greater incidence of adverse events with lisuride.

IMPLICATIONS FOR CLINICAL PRACTICE

In early management and treatment of Parkinson's disease, lisuride is POSSIBLY USEFUL as monotherapy or as an adjunct to levodopa. Its use in advanced Parkinson's disease patients with motor fluctuations is INVESTIGATIONAL. (In several European countries, the drug is marketed as monotherapy and as a levodopa adjunct.) In most published reports, lisuride is given t.i.d. at a dose ranging from 1.5 to 4.5 mg/d. The clinical effects of lisuride are less well documented as compared to other several other DA agonists.

IMPLICATIONS FOR CLINICAL RESEARCH

Lisuride appears to be an agonist with a similar profile to that of the other ergotamine derivative DA agonists. To assess the clinical efficacy of lisuride, placebo-controlled, randomized studies and comparative trials with other antiparkinsonian agents are needed.

REFERENCES

1. Lange KW. Clinical pharmacology of dopamine agonists in Parkinson's disease. Drugs Aging 1998;1:381-389.
2. Rinne UK. Lisuride, a dopamine agonist in the treatment of early Parkinson's disease. Neurology 1989;39:336-339.
3. Allain H, Destée A, Petit H, et al. Five-year follow-up of early lisuride and levodopa combination therapy versus levodopa monotherapy in de novo Parkinson's disease. The French Lisuride Study Group. Eur Neurol 2000;44:22-30.
4. Gopinathan G, Teravainen H, JM Dambrosia, et al. Lisuride in parkinsonism. Neurology 1981;31:371-376.
5. LeWitt PA, Gopinathan G, Ward CD, et al. Lisuride versus bromocriptine treatment in Parkinson disease: a double-blind study. Neurology 1982;32:69-72.
6. Laihinen A, Rinne UK, Suchy I. Comparison of lisuride and bromocriptine in the treatment of advanced Parkinson's disease. Acta Neurol Scand 1992;86:593-595.
7. Battistin L, Bardin PG, Ferro-Milone F, Ravenna C, Toso V, Reboldi G. Alpha-dihydroergocryptine in Parkinson's disease: a multicentre randomized double blind parallel group study. Acta Neurol Scand 1999;99:36-42.
8. Obeso JA, Luquin MR, Martinez-Lage JM. Lisuride infusion pump: a device for the treatment of motor fluctuations in Parkinson's disease. Lancet 1986;1(8479):467-470.
9. Vaamonde J, Luquin MR, Obeso JA. Subcutaneous lisuride infusion in Parkinson's disease. Response to chronic administration in 34 patients. Brain 1991;114:601-617.
10. Heinz A, Wohrle J, Schols L, Klotz P, Kuhn W, Pruzuntek H. Continuous subcutaneous lisuride infusion in OPCA. J Neural Transm Park Dis Dement Sect 1992;90(1):145-150.
11. Stocchi F, Ruggieri S, Antonin A, et al. A subcutaneous lisuride infusion in Parkinson's disease: clinical results using different modes of administration. J Neural Transm 1998;27(Suppl):27-33.
12. Stocchi F, Bramante L, Monge A, et al. Apomorphine and lisuride infusion: a comparative chronic study. Adv Neurol 1993;60:653-655.
13. Obeso JA, Luquin MR, Vaamonde J, Martinez-Lage JM. Subcutaneous administration of lisuride in the treatment of complete motor fluctuations in Parkinson's disease. J Neural Transm Supppl 1988;27:17-25.
14. Bhatt MH, Keenan SP, Fleetham JA, Calne DB. Pleuropulmonary disease associated with dopamine agonist therapy. Ann Neurol 1991;30:613-616.
15. Ferreira JJ, Galitzky M, Montastruc JL, Rascol O. Sleep attacks and Parkinson's disease treatment. Lancet 2000;355:1333-1334.

BIBLIOGRAPHY - EXCLUDED FROM ANALYSIS (REASON FOR EXCLUSION)

A multicenter Italian randomized study on early treatment of Parkinson disease: comparison of L-dopa, 1-deprenyl and dopaminoagonists. Study design and short term results. The Italian Parkinson Study Group. Ital J Neurol Sci 1992;13:735-739. (Not in English)

Bayulkem K, ErisirK, Tuncel A, Bayulkem B. A study on the effect and tolerance of lisuride on Parkinson's disease. Adv Neurol 1996;69:519-530. (Book chapter)

Capria A, Attanasio A, Quatrana M, et al. Cardiovascular effects of lisuride continuous intravenous infusion in fluctuating Parkinson's disease. Clin Neuropharmacol 1989;12:331-338. (Non-parkinsonian endpoint)

Caraceni T. A case for early levodopa treatment of Parkinson's disease. Clin Neuropharmacol 1994;18:S38-S42. (Insufficient description of methods)

Casacchia M, Meco G, Castellana F, Bedini L, Cusimano G, Agnoli A. Therapeutic use of a selective cAMP phosphodiesterase inhibitor (Rolipram) in Parkinson's disease. Pharmacol Res Commun 1983;15:329-334. (Study on rolipram)

Chouza C, Caamano JL, de Medina O, Aljanati R, Scaramelli A, Romero S. A combined regimen of subcutaneous lisuride and oral Madopar HBS in Parkinson's disease. J Neural Transm Suppl 1988;27:61-70. (< 20 patients)

Critchley PH, Grandas Perez F, Quinn NP, Parkes JD, Marsden CD. Continuous subcutaneous lisuride infusions in Parkinson's disease. J Neural Transm 1988;27:55-60. (< 20 patients).

De Yebenes JG, Fahn S, Lovelle S, et al. Continuous intracerebroventricular infusion of dopamine and dopamine agonists through a totally implanted drug delivery system in animal models of Parkinson's disease. Mov Disord 1987;2:143-158. (Animal data)

Destée A, Defebvre L, Fondarai J, Patay M. Early combination of lisuride and levodopa in the treatment of Parkinson's disease. Comparison with levodopa alone during a double-blind then open trial: a 3-year follow-up. J Neurol 1996;243:S79. (Abstract)

Djaldetti R, Melamed E. Management of response fluctuations: practical guidelines. Neurology 1998;51:S36-40. (Review)

Fernandez Pardal M, Micheli F, Gatto M, Perez y Gonzalez N. Treatment of Parkinson's disease with subcutaneous lisuride infusions. J Neural Transm Suppl 1988;27:75-84. (< 20 patients)

Foster NL, Newman RP, Le Witt WPA, Gillespie MM, Chase TN. Treatment of resting tremor by beta-adrenergic blockade. Am Heart J 1984;108:1173-1177. (Study on nadolol)

Gershanik OS, Scipioni O, Garcia S. Lisuride infusion pump in Parkinson's disease. A report of two cases. J Neural Trans Suppl 1988;27:85-90. (< 20 patients)

Giovannini P, Scigliano G, Grassi MP, Carella F, Parti E, Caraceni T. Bromocriptine-lisuride cross tolerance. Ital J Neurol Sci 1983;4:129-130. (Non-English literature)

Giovannini P, Scigliano G, Piccolo I, Soliveri P, Suchy I, Caraceni T. Lisuride in de novo parkinsonian patients: a four-year follow-up. Acta Neurol Scand 1988;77:322-327. (Level III; less than 20 patients per treatment group)

Giovannini P, Scigliano G, Piccolo I, Soliveri P, Suchy I, Caraceni T. Lisuride in Parkinson's disease. 4-year follow-up. Clin Neuropharmacol 1988;11:201-211. (Less than 20 patients per treatment group)

Guttman M. Double-blind comparison of pramipexole and bromocriptine treatment with placebo in advanced Parkinson's disease. International Pramipexole-Bromocriptine Study Group. Neurology 1997;49:1060-1065. (Study on pramipexole and bromocriptine)

Hardie RJ, Lees AJ, Stern GM. On-off fluctuations in Parkinson's disease. A clinical and neuropharmacological study. Brain 1984;107:487-506. (Level III)

Hayashi R, Tako K, Makishita H, Koyama J, Yanagisawa N. Efficacy of a low-dose subcutaneous lisuride infusion in Parkinson's disease. Intern Med 1998;37:444-448. (< 20 patients)

Krause W, Nieuweboer B, Ruggieri S, Stocchi F, Suchy I. Pharmacokinetics of lisuride after subcutaneous infusion. J Neural Transm Suppl 1988;27:71-74. (< 20 patients)

Lees AJ, Stern GM. Pergolide and lisuride for levodopa-induced oscillations. Lancet 1981;2(8246):577. (Level III)

Lestingi L, Bonifati V, Stocchi F, Antonozzi I, Meco G. TRH test and the continuous dopaminergic stimulation in complicated Parkinson's disease. Eur Neurol 1992;32:65-69. (Non-parkinsonian endpoints; < 20 patients)

LeWitt PA, Burns RS, Calne DB. et al. Lisuride treatment in Parkinson's disease: clinical and pharmacokinetic studies. Adv Neurol 1983;37:131-140. (Book chapter)

LeWitt PA, Ward CD, Larsen TA, et al. Comparison of pergolide and bromocriptine therapy in parkinsonism. Neurology 1983;33:1009-1014. (Study on pergolide and bromocriptine)

Lieberman A, Goldstein M, Neophytides A, et al. Lisuride in Parkinson disease: efficacy of lisuride compared to levodopa. Neurology 1981;31:961-965. (Level III; less than 20 patients per treatment group)

Lieberman AN, Goldstein M, Leibowitz M, et al. Lisuride combined with levodopa in advanced Parkinson disease. Neurology 1981;31:1466-1469. (Level III)

Ludwig CL, Weinberger DR, Bruno G, et al. Buspirone, Parkinson's disease, and the locus ceruleus. Clin Neuropharmacol 1986;9:373-378. (Study on buspirone)

Luquin MR, Obeso JA, Vaamonde J, Martinez Lage JM. Orally administered lisuride in the treatment of complex fluctuations of motion in Parkinson disease. Neurologia 1989;4:229-232. (Non-English literature; Spanish)

Luquin MR, Scipioni O, Vaamonde J, Gershanik O, Obeso JA. Levodopa-induced dyskinesias in Parkinson's disease: clinical and pharmacological classification. Mov Disord 1992;7:117-124. (Review)

Marti Masso JF, Urtasun M. Citicoline in the treatment of Parkinson's disease. Clin Ther 1991;13:239-242. (Study on citicoline)

Martignoni E, Horowski R, Liuzzi A, et al. Effects of terguride on anterior pituitary function in parkinsonian patients treated with L-dopa: a double-blind study versus placebo. Clin Neuropharmacol 1996;19:72-80. (Study on terguride)

Martignoni E, Pacchetti C, Aufdembrinke B, et al. Terguride in stable Parkinson's disease. Funct Neurol 1995;10:143-146. (Study on terguride)

Meneghetti G, Bracco F, Giometto B, Ferla S, Schergna E. Therapeutic effect of lisuride in advanced Parkinson's disease. Eur Neurol 1986;25:74-80. (Level III; < 20 patients per treatment group)

Micieli G, Martignoni E, Bono G, et al. A study of the cardiopressor effects of lisuride in the treatment of parkinsonism and pathological aging brain. Clin Neuropharmacol 1989;12:404-415. (Non-parkinsonian endpoint)

Micieli G, Martignoni E, Cavallini A, et al. Lisuride and bromocriptine in L-dopa stable-responder parkinsonian patients: a comparative, double-blind evaluation of cardiopressor and neurochemical effects. Funct Neurol 1996;11:317-325. (Non-parkinsonian endpoints)

Nappi G, Martignoni E, Horowski R, et al. Lisuride plus selegiline in the treatment of early Parkinon's disease. Acta Neurol Scand 1991;83:407-410. (Study on selegiline)

Obeso JA, Luquin MR, Martinez-Lage JM. Lisuride infusion pump: a device for the treatment of motor fluctuations in Parkinson's disease. Lancet 1986;1(8479):467-470. (< 20 patients)

Obseso JA, Luquin MR, Vaamonde J, Grandas F, Martinez Lage JM. Continuous dopaminergic stimulation in Parkinson's disease. Can J Neurol Sci 1987;14:488-492. (Review)

Pacchetti C, Martignoni E, Bruggi P, et al. Terguride in fluctuating parkinsonian patients: a double-blind study versus placebo. Mov Disord 1993;8:463-465. (Study on terguride)

Pochlau D, Baier JE, Kovaes S, et al. Is dopaminergic therapy immunologically rejuvinating? Increased interferon-gamma production with the dopaminergic agent lisuride. Fortschr Med 1994;112:174-176. (Non-English literature)

Poungvarin N, Prayoonwiwat N, Devahasatin V, Viriyavejakul A. An open label trial of pergolide in Thai patients in Parkinson's disease. J Med Assoc Thai 1996;79:205-209. (Study on pergolide)

Ruggieri S, Stocchi F, Carta A, et al. One year treatment with lisuride delivery pump in Parkinson's disease. Prog Neuropsychopharmacol Biol Psychiatry 1989;13:173-183. (< 20 patients)

Stibe C, Lees A, Stern G. Subcutaneous infusion of apomorphine and lisuride in the treatment of parkinsonian on-off fluctuations. Lancet 1987;1(8537):871. (< 20 patients)

Stibe CM, Lees AJ, Kempster PA, Stern GM. Subcutaneous apomorphine in parkinsonian on-off oscillations. Lancet 1988;1:403-406. (Study on apomorphine)

Stocchi F, Nordera G, Marsden CD. Strategies for treating patients with advanced Parkinson's disease with disastrous fluctuations and dyskinesias. Clin Neuropharmacol 1997;20:95-115. (Review)

Stocchi F, Patsalos PN, Berardelli A, et al. Clinical implications of sustained dopaminergic stimulation. Clin Neuropharmacol 1994;17:S7-13. (< 20 patients)

Stocchi F, Ruggieri S, Antonini A, et al. Subcutaneous lisuride infusion in Parkinson's disease: clinical results using different modes of administration. J Neural Transm Suppl 1988;27:27-33. (< 20 patients)

Todes CJ. At the receiving end of the lisuride pump. Lancet 1986;2(8497):36-37. (< 20 patients)

Vaamonde J, Luquin MR, Obeso JA. Dopaminergic responsiveness to apomorphine after chronic treatment with subcutaneous lisuride infusion in Parkinson's disease. Mov Disord 1990;5:260-262. (Study on apomorphine)

Vermersch P, Fondarai J, Petit H. [Randomized study during a year of early combination of L-dopa/lisuride in Parkinson disease]. Therapie 1991;46:481-486. (Non-English literature; French)

Wachtel H, Rettig KJ, Loschmann PA. Effect of chronic subcutaneous minipump infusion of lisuride upon locomotor activity of rats. J Neural Trans Suppl 1988;27:177-183. (Animal study).

Movement Disorders
Vol. 17, Suppl. 4, 2002, p. S79-S82

Published by Wiley-Liss, Inc.
DOI 10.1002/mds.5566

DA Agonists - Ergot derivatives: Pergolide

BASIC PHARMACOLOGY

MECHANISM OF ACTION

Pergolide is a synthetic ergoline dopamine (DA) agonist that acts at both D1-like and D2-like receptors.[1,2] Although pergolide has mixed D1/D2 receptor activity, it has high intrinsic activity at D2-like receptors, where its effects predominate. Unlike other ergoline DA agonists (eg. bromocriptine), which has partial D1 effects and thus partially antagonizes D1 receptors (and thereby reduces cAMP production), pergolide stimulates adenylate cyclase activity (although only at high concentrations). Pergolide, like most ergot derivatives, also acts on non-DA receptors.

In vivo, pergolide reduces prolactin plasma levels, reduces blood pressure and induces contralateral rotation in the rat PD model with unilateral 6-hydroxydopamine substantia nigra lesion. Putative neuroprotective properties have been reported in vitro (free radical scavenger) and in vivo (aged rat) (for review see Yamamoto [1998][3]; Lange et al. [1994][4]).

PHARMACOKINETICS

Pergolide pharmacokinetic properties are poorly understood. Pergolide is rapidly absorbed from the gastrointestinal tract, reaching peak-plasma concentrations within 1 to 2 hours.[5] Complete elimination of a single radiolabelled dose from the body is achieved within 4-5 days, with a mean elimination half-life of about 24 hours. Many metabolites (at least 10 different ones) can be detected, which do not appear to be produced by glucuronidation or sulfate conjugation.

REVIEW OF CLINICAL STUDIES

All studies included in this review on pergolide were classified as Level I (Level II and III studies were excluded).

PREVENTION OF DISEASE PROGRESSION

No studies were identified on the neuroprotective effect of pergolide in PD. There are two on-going randomized (Level-I), long-term clinical studies on this topic. One is an English trial, assessing the clinical effects of low-dose of pergolide. The other one is a European 3-year study, using PET neuroimaging endpoints, known as the PELMO-PET study. The preliminary results were presented at the VIth International Symposium of the Movement Disorders Society (Barcelona, 2000) and should be published in the near future. Both trials are not indeed designed to truly assess neuroprotection, but rather compare relative rates of disease progression in L-dopa and pergolide groups.

SYMPTOMATIC CONTROL OF PARKINSONISM

MONOTHERAPY OR EARLY COMBINATION IN DE NOVO PATIENTS

Barone et al. (1999)[7]: This was the only large, randomized (Level I), parallel-group, double-blind, placebo-controlled, 3-month study conducted in 105 de novo patients with PD (mean age approximately 62 years). Efficacy assessments included UPDRS, a CGI score and the Schwab and England ADL score. The primary outcome measure for comparison was the number of "responders," defined as those patients with a 30% or greater improvement on the UPDRS motor scale (Part III). At the mean dose of 2 mg/d, pergolide was more effective than placebo, as demonstrated by the greater proportion of responders (57% with pergolide vs. 17% with placebo, $p<0.001$). All other endpoints (UPDRS overall score, UPDRS II, Schwab & England ADL score, and CGI) also favored pergolide. Typical dopaminergic adverse reactions were reported in this study, and were more frequent with pergolide than placebo (eg. anorexia, dizziness, nausea, vomiting; $p<0.05$). Somnolence was reported in 15% of the pergolide-treated patients and in 6% of the placebo-treated patients. This study had an overall quality score of 95%.

Mizuno et al. (1995)[7]: This study is reviewed in detail in the bromocriptine section and, therefore, will only be briefly reviewed below. This short-term (8-week), double-blind study reported results on the efficacy of pergolide on different types of patients with PD (newly diagnosed as well as advanced disease). Forty-nine de novo patients with PD were randomized to pergolide and 49 to bromocriptine. Pergolide (mean dose 1.43 mg/d) and bromocriptine (mean dose 15.1 mg/d) both improved most of the outcomes studied (ie. tremor, rigidity, akinesia, retropulsion, short-step gait, masked face, freezing, hygiene, feeding, and dressing). There were too many items assessed to report all endpoints in this summary, and total score is available. Many patients were excluded from analysis, and the improvement was said to be similar in both groups. Adverse reactions were also comparable in both groups. This study had a total quality score of 53%.

The available information about the long-term efficacy of pergolide when used as monotherapy in early PD patients is even more limited. The only available information is reported in an open (Level-III), 2- to 4-year uncontrolled study (Mizuno et al, 1995). Among 62 de novo patients that received pergolide as initial antiparkinsonian treatment, L-dopa was added to pergolide in 28 patients at some point during follow-up because of disease progression with an unsatisfactory response to pergolide. Additional Level-I data is underway and should be available when the next 3-year L-dopa-controlled results of the PELMO-PET study are published.

ADJUNCT THERAPY IN L-DOPA-TREATED PATIENTS

Early Combination

No qualified Level-I studies were identified.

Late Combination

Most studies reporting the results from adjunct treatment with

pergolide in L-dopa-treated patients with PD have been performed in patients with motor fluctuations. Several of these studies are further described in the section Control of Motor Complications. Only 5 randomized, (Level-I) studies met our inclusion/exclusion criteria and are described below. One is placebo-controlled, and four are bromocriptine-controlled.

Placebo-controlled Trials

Olanow et al. (1994)[8]: This was the only large, Level-I, randomized, parallel group, placebo-controlled study assessing the effects of pergolide as adjunct to levodopa/carbidopa in 376 patients with moderately severe dyskinesia or end-of-dose deterioration (mean age = 63 years). The study assessed efficacy over a 6-month period using a new parkinsonian disability score including a variety of weighted items including depression, speech, facial expression, sialorrhea, tremor, rigidity, bradykinesia, finger taps, rapid alternating hand patting, foot tapping, rising from a chair, axial posture, stability and gait (maximal score = 356). Other assessment criteria were a weighted assessment of ADL (maximum score = 100), an assessment of dyskinesia (0-4) and a quantitative estimate of number of "off" hours. At the study endpoint, pergolide (mean dose 2.94 mg/d) induced a greater decrease in L-dopa daily dose than placebo (-25% vs. -5%, respectively, $p<0.001$). There was a significant improvement vs. placebo in most assessment criteria. This was true for total Parkinsonian score: 88 in the pergolide treatment group vs. 120 in the placebo treatment group ($p<0.001$) with an improvement of parkinsonian score of >25% occuring in 56% of pergolide-treated vs. 25% of placebo-treated patients ($p<0.001$). ADL improved significantly more with pergolide (22.1) than placebo (30.8; $p<0.001$). Adverse reactions included dyskinesia, nausea, hallucinations, drowsiness, insomnia, and were more frequent with pergolide than placebo. Adverse reactions led to withdrawal in 9.5% pergolide-treated patients and 4.3% of the placebo-treated patients. This study had an overall quality score of 83%.

Bromocriptine-controlled Trials

There were four bromocriptine-controlled Level-I trials reported to date, and they have only moderate quality scores and are briefly summarized below (see also section on Bromocriptine).

LeWitt et al. (1983)[9]: This was a double-blind, two-period, cross-over study conducted in 27 patients with PD. The periods of treatment ranged from 7 to 10 weeks. The mean optimal dose of pergolide was 3.3 mg/d and that of bromocriptine was 42 mg/d. With both drugs adjusted to an optimal dose, similar control of parkinsonism was reported. Adverse reactions were similar in spectrum and frequency for each treatment. This study had an overall quality score of 50%.

Mizuno et al. (1995)[7]: This short-term, (8-week), double-blind, parallel group study enrolled 93 PD patients that had "unsatisfactory results on L-dopa therapy" to pergolide (maximum permitted dose 2.25 mg/d) and 99 patients to bromocriptine (maximum permitted dose 22.5 mg/d). Pergolide (mean dose 1.24 mg/d) and bromocriptine (mean dose 14.6 mg/d) both improved most of the endpoints studied. There was no statistical difference between the treatments. Adverse reactions were comparable in both groups. This study had an overall quality score of 53%.

Pezzoli et al. (1995)[10]: This was a single-blinded, 12 weeks, cross-over study carried out in 68 patients PD who showed a declining response to L-dopa therapy. The optimal daily dosages were 24.2 mg for bromocriptine and 2.3 mg for pergolide. Significant improvements vs. baseline occurred during both bromocriptine and pergolide therapy. Direct comparison of the two treatments showed pergolide to be significantly more effective than bromocriptine in 4 of 5 daily living scores of the NYUPDS, the physical examination total aggregated score, and several subscores ($p<0.05$). These differences were small, and their clinical relevancy is unclear. Adverse reactions were quite comparable with both treatments. This study had an overall quality rating score of 57%.

Boas et al. (1996)[11]: This is a 24-week (12 week per period), open-label, cross-over study conducted in 33 L-dopa-treated patients with PD that had suboptimal control of motor fluctuations. The mean doses of bromocriptine and pergolide at the end of the titration phase were 21.7 mg/d and 3.6 mg/d, respectively. The improvement in UPDRS motor examination scores was significant over baseline scores with both agents ($p<0.05$), and the improvement was reported to be significantly greater with pergolide than with bromocriptine ($p<0.01$). The daily dose of levodopa was significantly lower with pergolide (-26%) than with bromocriptine (-10%, $p<0.01$). The difference of effect between treatments was however modest and, therefore, the clinical relevance of this difference in not clear. Adverse reactions were comparable with both drugs. This study had an overall quality score of 60%.

PREVENTION OF MOTOR COMPLICATIONS

At the time of this report, there is limited published evidence on the use of pergolide in the prevention of motor complications. No Level- I trial was identified, and the 3-year data of the L-dopa-controlled PELMO-PET study has not been published yet. Until now, the only available data identified comes from the 62 patients followed-up in an open-label, uncontrolled study (Level III) in 2 to 4 years follow-up period reported by Mizuno and colleagues (1995)[7] (and is described previously in the Section on Symptomatic Control of Parkinsonism: Monotherapy). The incidence of the "wearing-off" phenomenon was reported to be 8.8% in patients that could be continued on pergolide monotherapy while it reached 42.9% in those who received L-dopa supplementation but it is possible that the group of patients on pergolide monotherapy might have had a milder disease. Similarly, dyskinesias were rare during pergolide monotherapy (14.7%), increasing to 21.5% in patients who received pergolide plus L-dopa.

CONTROL OF MOTOR COMPLICATIONS

Only two randomized, (Level-I) studies met inclusion/exclusion criteria. One is placebo-controlled and the other is a bromocriptine-controlled trial.

Olanow et al. (1994)[8]: As summarized previously, this was a Level-I, randomized, parallel-group, placebo-controlled study (see section on Control of Parkinsonism). Quantitative estimate of the number of "off" hours per day during the week preceding each visit was assessed using a diary card. At study endpoint, pergolide (2.94 mg/d) induced a greater decrease in hours "off" than placebo (pergolide: from 5.6 hours at baseline to 3.8 hours at final visit vs. placebo: from 5.2 hours at baseline to 5.0 hours at final visit, $p<0.001$).

Mizuno et al. (1995)[7] (also see section on Bromocriptine): This study is reviewed in the Bromocriptine section and therefore only summarized briefly. This was an 8-week, double-blind, parallel-group study conducted in with PD who had an "unsatisfactory results on L-dopa therapy." 93 patients were randomized to

pergolide (maximum permitted dose 2.25 mg/d) and 99 were randomized to bromocriptine (maximal permitted dose 22.5 mg/d). Efficacy was assessed using a simplified rating scale consisting of a 5-grade rating score, one of which assessed the severity of the wearing-off phenomenon. The wearing-off phenomenon with bromocriptine treatment (mean score reduction from 3.6 at baseline to 3.2, $p<0.01$) was similar to pergolide treatment (mean score reduction from 3.6 at baseline to 3.1, $p<0.001$).

REVIEW OF SAFETY

Pergolide is associated with adverse reactions similar to those reported with other dopaminergic agonists (eg. nausea, vomiting, hypotension, and psychosis). Dyskinesia is exacerbated when pergolide is added to L-dopa therapy. There is a lack of evidence that the early use of pergolide can delay or reduce the risk of occurrence of motor complications (eg. dyskinesia or wearing-off). The results from the PELMO-PET study should help address these clinical issues.

As with other ergot derivatives, case-reports of pleural pulmonary fibrosis have been published in patients receiving pergolide.[12-14]

Several cases of "sleep attacks" have been reported with pergolide.[15,16] There is some debate if "sleep attacks" are less frequent with pergolide than with other dopamine agonists, like pramipexole and ropinirole, but in the absence of well-conducted epidemiological data, this remains uncertain.

Pergolide does not seem to have an effect on life expectancy, but data on mortality is limited. There is one open-label, retrospective, uncontrolled analysis of mortality data from clinical trials involving 1330 patients with PD that received pergolide as an adjunct to L-dopa.[17] When compared to the general population of the same gender, age and race, the ratio of observed to expected deaths (over the same period of observation) was 2.3.

CONCLUSIONS

In spite of its long and wide use in many countries, the amount of available Level-I evidence supporting the efficacy and safety of pergolide remains limited (less than 200 patients followed-up for less than 6 months). Specifically, there are only two large, placebo-controlled studies (one in de novo and one in L-dopa-treated patients).

EFFICACY

PREVENTION OF DISEASE PROGRESSION

There are INSUFFICIENT EVIDENCE to determine the efficacy of pergolide in the prevention of disease progression in patients with PD.

SYMPTOMATIC CONTROL OF PARKINSONISM

Monotherapy

On the basis of one recent randomized, placebo-controlled study[6], pergolide is considered EFFICACIOUS in the treatment of de novo patients with PD. However, efficacy beyond 3 months is not established at this time (but, studies are underway).

Adjunct Therapy

On the basis of one placebo-controlled study[8], pergolide is considered EFFICACIOUS for the treatment of parkinsonism as an adjunct therapy to L-dopa in patients with PD and motor fluctuations. There is INSUFFICIENT EVIDENCE to conclude on the efficacy of the early combination of pergolide to levodopa in stable PD patients. Efficacy for long-term management beyond 6 months has not been established in randomized, controlled trials. Like other agonists, pergolide allows reduction of the daily dose of L-dopa.

PREVENTION OF MOTOR COMPLICATIONS

There is INSUFFICIENT EVIDENCE to determine the efficacy of pergolide regarding prevention of motor complications in patients with PD.

CONTROL OF MOTOR COMPLICATIONS OR OTHER COMPLICATIONS

Based on one placebo-controlled, Level-I study[8], pergolide is EFFICACIOUS in controlling motor fluctuations.

SAFETY

Studies reviewed above show that the use of pergolide has an ACCEPTABLE RISK WITHOUT SPECIALIZED MONITORING. There is no evidence that this risk is different from that of the other available dopamine agonists (see section on Bromocriptine).

IMPLICATIONS FOR CLINICAL PRACTICE

Pergolide has been available in clinical practices longer than many of the newer DA agonists providing good clinical experience with this drug, but it has been less rigorously studied in clinical trials. Based on the evidence available to date, pergolide is CLINICALLY USEFUL as initial, short-term (3 months), monotherapy in de novo patients with PD for the treatment of parkinsonism, and as adjunct therapy in L-dopa-treated patients with PD.

In most published clinical trials, pergolide was used at a mean daily dose between 1.5 mg/day and 3.5 mg/d, with a t.i.d. regimen.

There are no studies demonstrating unequivocal superiority of pergolide over bromocriptine. Regarding patient management, an equivalency ratio has been proposed of 1:10 with appropriate titration around this dosage. To date, no other comparative studies are available comparing pergolide to other dopamine agonists.

IMPLICATIONS FOR CLINICAL RESEARCH

- Pergolide effects on long-term clinical outcomes and disease progression are needed (ie. The PELMO-PET study is ongoing).
- Active comparator trials evaluating the relative efficacy of pergolide to other DA agonists and other antiparkinsonian agents, like MAO-B and COMT inhibitors are needed.
- Pharmacoeconomic studies are needed to compare the cost benefits between the different DA agonists.
- Long-term data on the impact of pergolide on quality of life and mortality are needed.

REFERENCES

1. Langtry HD, Clissold SP. Pergolide. A review of its pharmacological properties and therapeutic potential in Parkinson's disease. Drugs 1990;39:491-506.
2. Goetz CG, Diederich NJ. Dopaminergic agonists in the treatment of Parkinson's disease. Neurol Clin 1992;10:527-540.
3. Yamamoto M. Do dopamine agonists provide neuroprotection ? Neurology 1998;51(suppl2):S10-12.
4. Lange KW, Rausch WD, Gsell W, Naumann M, Oestreicher E, Riederer P. Neuroprotection by dopamine agonists. J Neural Trans 1994;43(suppl):183-201.
5. Wachtel H. Antiparkinsonian dopamine agonists: a review of the pharmacokinetics and neuropharmacology in animals and humans. J Neural Trans Park Dis Dement Sect 1991;3:151-201.
6. Barone P, Bravi D, Bermejo-Pareja F, Marconi R, Kulisevsky J, Malagù S, Weiser R, Rost N, and the Pergolide Monotherapy Study Group. Pergolide monotherapy in the treatment of early PD. A randomized controlled study. Neurology 1999;53:573-579.

7. Mizuno Y;Kondo T, Narabayashi H. Pergolide in the treatment of Parkinson's disease. Neurology 1995;45(suppl 3):S13-21.
8. Olanow CW, Fahn S, Muenter M, Klawans H, Hurtig H, Stern M, Shoulson I, Kurlan R, Grimes JD, Jankovic J, Hoehn M, Markham CH, Duvoisin R, Reinmuth O, Leonard HA, Ahlskog E, Feldman R, Hershey L, Yahr MD. A multicenter double-blind placebo-controlled trial of pergolide as an adjunct to Sinemet in Parkinson's disease. Mov Disord 1994;9:40-47.
9. Le Witt PA, Ward CD, Larsen TA, Rapharlson MI, Newman RP, Foster N, Dambrosia JM, Calne DB. Comparison of pergolide and bromocriptine therapy in parkinsonism. Neurology 1983;33:1009-1014.
10. Pezzoli G, Martignoni E, Pacchetti C, et al. Pergolide compared with bromocriptine in Parkinson's disease: a multicenter, cross-over, controlled study. Mov Disord 1994;9:431-436.
11. Boas J, Worm-Petersen J, Dupont E, Mikkelsen B, Wermuth L. The levodopa dose-sparing capacity of pergolide compared with that of bromocriptine in an open-label, cross-over study. Eur J Neurol 1996;3:44-49.
12. Kunkler RB, Osborn DE, Abbott RJ. Retroperitoneal fibrosis caused by treatment with pergolide in a patient with Parkinson's disease. Br J Urol 1998;82:147.
13. Lund BC, Neiman RF, Perry PJ. Treatment of Parkinson's disease with ropinirole after pergolide-induced retroperitoneal fibrosis. Pharmacotherapy 1999;19:1437-1438.
14. Shaunak S, Wilkins A, Pilling JB, Dick DJ. Pericardial, retroperitoneal, and pleural fibrosis induced by pergolide. J Neurol Neurosurg Psychiatry 1999;66:79-81.
15. Schapira AHV. Sleep attacks (sleep episodes) with pergolide. Lancet 2000;355:1332-1333.
16. Ferreira JJ, Galitzky M, Montastruc JL, Rascol O. Sleep attacks and Parkinson's disease treatment. Lancet 2000;355:1333-1334.
17. Sayler ME, Street JS, Bosomworth JC, Potvin JH, Kotsanos JG. Analysis of mortality in pergolide-treated patients with Parkinson's disease. Neuroepidemiology 1996;15:26-32.

BIBLIOGRAPHY - Excluded from Analysis (REASON FOR EXCLUSION)

Ahlskog JE, et al. Pergolide: long-term use in Parkinson's disease. Mayo Clin Proc 1988;63:979-987. (Level III)

Ahlskog JE, Muenter MD. Treatment of Parkinson's disease with pergolide: a double-blind study. Mayo Clin Proc 1988;63:969-978. (Data reviewed in another paper)

Bonnet AM, Serre I, Marconi R, Agid Y, Dubois B. A "combined" levodopa test as a useful method for evaluating the efficacy of dopamine agonists: application to pergolide and bromocriptine. Mov Disord 1995;10:668-671. (< 20 patients per treatment group)

de Yebenes JG, Garcia-Ruiz PJ, Sanchez -Pernaute R. A comparative study of the effect of bromocriptine and pergolide on Parkinson disease. Rev Neurol 1997;25:1343-1345. (Not in English)

Diamond SG, et al. One-year trial of pergolide as an adjunct to Sinemet in treatment of Parkinson's disease. Adv Neurol 1984;40:537-539. (Book chapter)

Diamond SG, Markham CH, Treciokas LJ. Double-blind trial of pergolide for Parkinson's disease. Neurology 1985;35:291-295. (Data reviewed in another paper)

Dupont E, Boas J, Mikkelsen B, Wermuth L, Worm PJ. The levodopa dose-sparing capacity of pergolide compared with that of bromocriptine. Eur J Neurol 1996;3:9-12. (Data reviewed in another paper)

Facca A et al. High-dose pergolide monotherapy in the treatment of severe levodopa-induced dyskinesias. Mov Disord 1996;11:327-329. (< 20 patients)

Factor SA, et al. Parkinson's disease: an open label trial of pergolide in patients failing bromocriptine therapy. J Neurol Neurosurg Psychiatry 1988;51:529-533. (Level III)

Goetz CG, Tanner CM, Glantz R, Klawans HL. Pergolide in Parkinson's disease. Arch Neurol 1983;40:785-787. (Level III)

Goetz CG, Tanner CM, Glantz RH, Klawans HL. Chronic agonist therapy for Parkinson's disease: a 5-year study of bromocriptine and pergolide. Neurology 1985;35:749-751. (< 20 patients)

Jankovic J. Controlled trial of pergolide mesylate in Parkinson's disease and progressive supranuclear palsy. Neurology 1983;33:505-507. (Less than 4 weeks follow-up)

Jankovic J, Orman J. Parallel double-blind study of pergolide in Parkinson's disease. Adv Neurol 1986; 45:551-553. (Data already reviewed in another paper)

Jankovic J. Long-term study of pergolide in Parkinson's disease. Neurology 1985;35:296-299. (Level III)

Jungmann E, Haak T, Althoff Ph, Fassbinder W, Schoffing K. Dopaminergic effects on kidney function and responsiveness of aldosterone plasma renin activity, prolactin, catecholamines, and blood pressure to stimulation in patients with prolactinoma. Comparison of the efficacy of pergolide and bromocriptine therapy. Arzneimittelforschung 1988;38:296-300. (Non-clinical endpoint)

Klawans HL, et al. A 6-month trial of pergolide mesylate in the treatment of idiopathic Parkinson's disease. Adv Neurol 1983;37:75-83. (Book chapter)

Klawans HL, et al. Dystonia-Parkinson syndrome: differential effects of levodopa and dopamine agonists. Clin Neuropharmacol 1986;9:298-302. (Level III)

Kulisevsky J, Garcia C, Lopez-Villegas D, Avila A, Barbanoj M. A six-month prospective study of levodopa versus pergolide in de novo Parkinson's disease patients. J Neurol 1997;244:S121. (Abstract)

Kulisevsky J, Lopez-Villegas D, Garcia-Sanchez C, Barbanoj M, Gironell A, Pascal-Sedano B. A six-month study of pergolide and levodopa in de novo Parkinson's disease patients. Clin Neuropharmacol 1998;21:358-362. (< 20 patients per treatment group)

Kurlan R, Miller C, Levy R, Macik B, Hamill R, Shoulson I. Long-term experience with pergolide therapy of advanced parkinsonism. Neurology 1985;35:738-742. (Level III)

Kurlan R, Miller C, Knapp R, Murphy G, Shoulson I. Double-blind assessment of potential pergolide-induced cardiotoxicity. Neurology 1986;36:993-995. (Level III)

Lees AJ, et al. Pergolide and lisuride for levodopa-induced oscillations. Lancet 1981;12(8246):577. (Level III)

Lang AE, et al. Lisuride and pergolide in Parkinson's disease. Adv Neurol 1983;37:109-120. (Book chapter)

Leibowitz M, et al. The effects of pergolide on the cardiovascular system of 40 patients with Parkinson's disease. Adv Neurol 1983;37:121-130. (Book chapter)

Lieberman AN, et al. Pergolide and lisuride for Parkinson's disease. Lancet 1979;2(8152):1129-1130. (Level III)

Lieberman A, Goldstein M, Leibowitz M, et al. Treatment of advanced Parkinson disease with pergolide. Neurology 1981;31:675-682. (Level III)

Lieberman AN, Goldstein M, Gopinathan G, et al. Further studies with pergolide in Parkinson's disease. Neurology 1982;32:1181-1184. (Level III)

Lieberman AN, et al. Comparative efficacy of pergolide and bromocriptine in patients with advanced Parkinson's disease. Adv Neurol 1983;37:95-108. (Book chapter)

Lieberman AN, et al. Long-term treatment with pergolide:decreased efficacy with time. Neurology 1984;34:223-226. (Level III)

Lieberman AN, et al. Pergolide and lisuride in advanced Parkinson's disease. Adv Neurol 1984;40:503-507. (Book chapter)

Lieberman AN, Gopinathan G, Neophytides A. Efficacy of pergolide and mesulergine. Eur Neurol 1986;25:86-90. (Study on mesulergine; < 20 patients per treatment group)

Lierberman AN, Leibowitz M, Gopinathan G, et al. The use of pergolide and lisuride two experimental dopamine agonists, in patients with advanced Parkinson disease. Am J Med Sci 1985;290:102-106. (Data already reviewed in another paper)

Lieberman AN, et al. Comparative efficacy of two dopamine agonists, pergolide and lergotrile, in Parkinson disease. N Y State J Med 1988;88:420-422. (Study on lergotrile)

Login IS. Pergolide versus bromocriptine. Neurology 1984;34:258. (Abstract)

Olanow CW, Alberts MJ. Double-blind controlled study of pergolide mesylate in treatment of Parkinson's disease. Clin Neuropharmacol 1987;10:178-185. (Data reviewed in another paper)

Olanow CW, Alberts MJ. Double-blind controlled study of pergolide mesylate as an adjunct to Sinemet in the treatment of Parkinson's disease. Adv Neurol 1987;45:555-560. (Data reviewed in another paper)

Poungvarin N et al. An open label trial of pergolide in Thai patients with Parkinson's disease. J Med Assoc Thai 1996;79:205-209. (Level III)

Pezzoli G, Martignoni E, Pacchetti C, et al. A cross-over, controlled study comparing pergolide with bromocriptine as an adjunct to levodopa for the treatment of Parkinson's disease. Neurology 1995;45(suppl 3):S22-27. (Data already reviewed in another paper)

Pezzoli G, et al. Pergolide mesylate in the treatment of Parkinson's disease resistant to other treatments. First Italian experience. Clin Ther 1991;136:39-45. (Non-English literature)

Schwarz J, et al. Improvement of motor fluctuations in patients with Parkinson's disease following treatment with high doses of pergolide and cessation of levodopa. Eur Neurol 1997;37:236-238. (Less than 20 patients per treatment group)

Sage JI, Duvoisin RC. Pergolide therapy in Parkinson's disease: a double-blind, placebo-controlled study. Clin Neuropharmacol 1985;8:260-265. (Less than 20 patients per treatment group)

Sage JI, Duvoisin RC. Long-term efficacy of pergolide in patients with Parkinson's disease. Clin Neuropharmacol 1986;9:160-164. (Level III)

Tanner CM, et al. Pergolide mesylate: four years experience in Parkinson's disease. Adv Neurol 1987;45:547-549. (Level III)

Zimmerman T, Sage JI. Comparison of combination pergolide and levodopa to levodopa alone after 63 months of treatment. Clin Neuropharmacol 1991;14:165-169. (Less than 20 patients per treatment group)

Movement Disorders
Vol. 17, Suppl. 4, 2002, p. S83-S89

Published by Wiley-Liss, Inc.
DOI 10.1002/mds.5567

DA Agonists - Non-Ergot derivatives: Apomorphine

BASIC PHARMACOLOGY

MECHANISM OF ACTION

Apomorphine is a dihydro-aporphine synthesized by reducing morphine with hydrochloric acid to a chlorhydrate, which is rapidly oxidized when in contact with air.[1] Apomorphine is a mixed D1 and D2 agonist, and is ten times more potent than dopamine. It has the same affinity for D1 and D2-like receptors and has a high affinity for D3 receptors.[1]

In healthy volunteers, apomorphine induces typical dopaminergic effects (eg. hypersalivation, hypotension, nausea, vomiting) and has marked sedative effects.

Recently, apomorphine has been shown to have antioxidant and potentially neuroprotective properties in in vitro and in vivo models of Parkinson's disease (PD).[2,3] In patients with PD, subcutaneous apomorphine induces an "on" state within 10 to 15 minutes, comparable in amplitude to the L-dopa-induced "on" response.

PHARMACOKINETICS

After oral administration, apomorphine is completely absorbed from the gastrointestinal tract but, due to pronounced metabolic inactivation of the compound on first passage by the liver (first pass effect), orally administered apomorphine is, for the most part, not bioavailable. Due to this pharmacokinetic profile, apomorphine in not efficacious when administered orally. Therefore, this route of administration is not used in clinical practice.

There are no pharmacokinetic investigations with apomorphine in healthy volunteers, and the only available data were obtained in patients with PD. After subcutaneous injection, the maximal apomorphine plasma level (Tmax) is obtained within 10 minutes and shows large variations among individuals. The plasma elimination half-life is approximately 35 minutes. Apomorphine is 95% bound to plasma proteins. The most important mechanism of apomorphine inactivation in vivo is glucuronidation and subsequent excretion of conjugates via the kidney. Methylation as well as demethylation is another catabolic route, with theoretical potential interactions with COMT inhibitors.

Apomorphine is generally used subcutaneously in clinical practice. This route of administration is associated with rapid onset of antiparkinsonian effects and circumvents difficulties with erratic gastric emptying and intestinal absorption. An injectable pen for apomorphine, similar to those used with insulin, is available in some countries. Chronic infusion with an ambulatory mini-pump is possible as well.

Apomorphine has also been tested for sublingual, intranasal, and rectal administration in an attempt to circumvent the problem of first pass metabolism through the liver.

REVIEW OF CLINICAL STUDIES WITH SUBCUTANEOUS APOMORPHINE

PREVENTION OF DISEASE PROGRESSION

No qualified studies were identified.

SYMPTOMATIC CONTROL OF PARKINSONISM

MONOTHERAPY OR EARLY COMBINATION IN DE NOVO PATIENTS

In de novo patients with early parkinsonism, acute subcutaneous challenges with apomorphine monotherapy have been proposed to test the dopaminergic responsiveness of the motor symptoms in order to help clinicians in differential diagnosis between "idiopathic" Parkinson's disease and other parkinsonian syndromes[4]. However, in early PD the sensitivity and specificity of this test is low and remains debated. There is no long-term, randomized controlled trial for subcutaneous apomorphine in PD, and the only present therapeutic indication for subcutaneous apomorphine is to help control severe "on/off" oscillations in L-dopa-treated patients who have received other oral treatments (eg. DA agonists, MAO-B inhibitors, COMT inhibitors) without sufficient improvement. Consequently no study qualifying for this indication was identified.

ADJUNCT THERAPY IN L-DOPA-TREATED PATIENTS

Early Combination

No qualified studies were identified.

Late Combination

Level-II Studies

No Level-I studies qualifying for inclusion in this review were identified. One short (less than 4 weeks of follow-up) controlled trial was identified. It is not clear from the text if this study was truly randomized or not and, therefore, it is considered a Level-II trial. It is incorporated in this review in the absence of randomized Level-I information.

Duby et al. (1972)[5]: Thirty-one patients with parkinsonism were studied in three different treatment regimens: 17 received subcutaneous acute challenges with apomorphine without concomitant L-dopa treatment; 20 received apomorphine with oral L-dopa; and 6 with and without L-dopa. Some patients participated in more than one treatment regimen. This review summarises the results from patients "off" L-dopa therapy. In a double-blind, placebo-controlled comparison, each patient received 2 to 5 single injections of apomorphine or sodium chloride solution 60 to 90 minutes after a standard breakfast. Tests were initiated with 0.5 or 1.0 mg of apomorphine, and increased as tolerated. No domperidone pre-treatment was administrated. Efficacy was assessed with a

"non-validated" method using "grading of parkinsonian signs and of choreoathetoid involuntary movements". The report does not specify the order of the injections as truly random, but assessments were made in a double-blind fashion. Placebo treatment in 11 patients (15 tests) reduced scores by no more than 10% (mean effect = 1.2±1.2%). Maximum benefit with apomorphine was reported between 40 to 60 minutes after injection. Six of 11 patients "off" L-dopa showed improvement in overall parkinsonian score by more than 23%. Similar trends were reported in the other arms of the trial performed in patients receiving L-dopa therapy. Reported adverse drug reactions included nausea, vomiting, orthostatic hypotension, pallor, sweating, and dizziness, among others.

Level-III Studies

Because of the paucity of Level-I and Level-II information, Level-III studies with more than 20 patients followed up for more than 4 weeks assessing quantitatively the effects of apomorphine on parkinsonian symptoms were also considered. Only two studies qualified for inclusion in this review.

Ostergaard et al. (1995)[6]: This is a short-term (4-day) randomized, placebo-controlled, double-blind, cross-over trial, assessing the duration of "off"periods when apomorphine was given as subcutaneous injections by a single use pen (see section on Control of Motor Complications). However, this 4-day randomized trial was (1) preceded by an open evaluation of the dopaminergic response of various parkinsonian symptoms to apomorphine through an acute apomorphine test, and (2) followed by an 8-week open-label extension when UPDRS scores were recorded. Twenty-two patients with PD and severe "on-off" phenomenon entered the study (mean age = 59 years, mean PD duration = 10 years, mean duration of L-dopa therapy = 8 years).

Results from the apomorphine test: 21 out of 22 patients were evaluated, and four variables were assessed immediately and 30-45 minutes after each injection (rigidity, tremor, time to make 20 hand turnings and time to walk 7 meters and back). A positive test was defined as a significant effect in at least two of the four tests (minimum 25% reduction for tremor or rigidity and minimum 33% reduction in hand turnings or walking). 20 out of 22 patients fulfilled the criteria for a positive response. The optimal dose of apomorphine was 3.4 (0.8-6.0) mg.

During the 8-week extension period, Activity of Daily Living (part II) was assessed for "off" period only and Motor Examination (part III) was assessed during an "on" period only, at baseline and at endpoint. This allowed, in theory, assessment of the response of parkinsonian symptoms to apomorphine in L-dopa-treated patients (screening versus 8-week). Fourteen out of the 22 patients terminated the 8-week follow-up. There were only modest changes in UPDRS scores. UPDRS part II (off) was 18.3 (7.0-27.0) at screening and 13.2 (5.0-22.0) at week 8. UPDRS part III (on) was 9.8 (1.5-22.2) at screening and 6.7 (1.0-14.4) at week 8. No statistical comparisons were provided. One explanation why no major UPDRS differences were reported in this part of the trial is because of the short duration of action of subcutaneous injections of apomorphine. This pharmacological feature suggests that the drug may be useful to reduce the duration of "off" periods (see section on "Control of Motor Complications"). It is unlikely that any residual effect of apomorphine is observed once the patient has switched back to "off". Similarly, when "on", it is difficult to achieve an additive effect of apomorphine to L-dopa if the timing of assessment relative to dosing is not carefully monitored. The situation is markedly different for continuous apomorphine infusion (see below[7]).

Pietz et al.1998[7]: This study is also reviewed below in greater details (see section "Control of Motor Complications"). Briefly, out of 60 patients with advanced Parkinson's disease, (age range 42-80 years), 49 were treated for 3 to 66 months with intermittent subcutaneous injections or continuous infusions of apomorphine. The principle assessment outcome measure was "time spent off" as assessed with diaries, but the Hoehn and Yahr and Schwab and England scales were also recorded, allowing an estimate of the effects of apomorphine on the parkinsonian syndrome itself. No UPDRS assessment was performed.

25 patients were treated with continuous infusion (median 44 months follow-up) . The median Hoehn and Yahr stages significantly improved in both "on" (before apomorphine 3.0; on apomorphine 2.5; p=0.02) and "off" condition" (before apomorphine 4.5; on apomorphine 4.0; p<0.01) while the levodopa treatment could be reduced in most patients (24 out of 25 in the continuous infusion group). The baseline dose of L-dopa was 900 mg/d and dropped to 450 mg/d and 8 patients stopped L-dopa completely. The total daily dose of apomorphine at the end of follow-up was 116 mg. The Schwab and England scale also improved in the "on" condition " (before apomorphine 70%; on apomorphine 80%; p<0.01) as well as in the "off" condition " (before apomorphine 40%; on apomorphine 50%; p<0.01).

In the same study, 24 patients were also treated with non-continuous subcutaneous injections of apomorphine for more than 2 months (median 22 months). The Hoehn and Yahr staging in the "on" and "off" condition did not show any significant change. For the Schwab and England score there was a significant improvement in "off" but not in "on" (before treatment 60%; on apomorphine 70%; p=0.027)

PREVENTION OF MOTOR COMPLICATIONS

No qualified studies were identified for the use of apomorphine in prevention of motor complications.

CONTROL OF MOTOR COMPLICATIONS

No Level-I studies qualified according to our inclusion criteria. However, one smaller and shorter randomized (Level-I) and few non-randomized, uncontrolled (Level-III) trials enrolling more than 20 patients with a 4 week follow-up period were identified and have therefore been incorporated in this section for review.

Level-I Studies

Ostergaard et al. (1995)[6]: (see also section on "Symptomatic Control of Parkinsonism" as an adjunct in L-dopa-treated patients). This is a randomized, placebo-controlled, double-blind, cross-over trial, with a short scheduled 4-day period of apomorphine treatment and 4-day period of placebo. Domperidone pretreatment was used (60mg/d). Apomorphine was given as subcutaneous injections by a single use pen. Apomorphine dose was optimized for each patient before the study, and the maximum single dose allowed was 12 mg. 22 patients with PD and severe "on-off" phenomenon entered the study (mean age = 59 years, mean PD duration = 10 years, mean duration of L-dopa therapy = 8 years). Seventeen patients participated in the cross-over design. Number, duration and severity of "off" periods were recorded by a staff member who monitored patients for 8 hours a day, for 2 days during each cross-over phase. Changes of oral antiparkinsonian medica-

tions were "discouraged". Apomorphine, at the mean dose of 3.9 mg (1 to 8 mg), had a significant and superior effect versus placebo in reducing both severity and duration of "off" periods: apomorphine caused a 58% reduction in the mean daily duration of "off" periods compared with placebo (apomorphine: 2 hours "off" vs. placebo: 4.8 hours "off" during 8-hours of observation, p<0.0001). The severity of the "off" periods also improved with apomorphine, while the number of "off" periods increased possibly due to a fragmentation of otherwise longer "off" periods. Apomorphine increased the patients' feeling of freedom. The study was extended to include an open label, 8-week follow-up period. After this follow-up period, the clinical effects were unchanged. Eight patients dropped out due to hypotension, unsatisfactory effect or lack of motivation. The main adverse reactions were involuntary movements, nausea, orthostatic hypotension and subcutaneous nodules.

Level-III Studies

Frankel et al. (1990)[8] included 57 L-dopa-treated patients with PD who had refractory "off" period disabilities. Patients received subcutaneous apomorphine for 16 months. Thirty patients (mean age = 59 years, mean PD duration = 15 years, mean duration of L-dopa therapy = 13 years) were given intermittent suprathreshold injections for 13.5 months. The time spent "off" fell from 6.9 to 2.9 hours (diary records, p<002). Similarly, 21 patients (mean age = 59 years, mean PD duration = 18 years, mean duration of L-dopa therapy = 16 years) received continuous apomorphine infusion for 22 months and the time spent "off" decreased from 9.9 to 4.5 hours (p<0.01). Six patients were reported as failures (severe disability during "on" periods). The incidence of neuropsychiatric side effects was 7%. All patients on continuous infusions developed nodules at the needle sites. Most patients initially reported mild drowsiness and nausea.

Hughes et al. (1993)[9]: This study reports the results of 71 patients treated with subcutaneous apomorphine who received continuous waking-day infusion with boluses or repeated intermittent injections for 1 to 5 years. It is not clear if this study includes patients reported in the previous clinical report.[8] The reduction in daily "off" period time was approximately 50% (diary records), but increasingly severe on-phase dyskinesia and postural instability marred the long-term therapeutic response in many patients. No significant tolerance or loss of therapeutic effect was reported.

Colzi et al.(1998)[10] This study reports the long-term follow-up (minimum duration of 2.7 years) of 19 PD patients with unpredictable "on-off" and severe dyskinesia treated with continuous subcutaneous apomorphine. L-dopa was slowly, but steadily, reduced with a concomitant increase in apomorphine dosage. Nine patients stopped L-dopa therapy, while the others continued to take an early morning dose and/or a nocturnal controlled release dose. A mean 65% reduction in dyskinetic severity and a mean 85% reduction in frequency and duration occurred. On discontinuation of L-dopa, a concomitant reduction in "off" period time was also seen (35% to 10% of waking day "off"). Most patients experienced abdominal cutaneous nodules at the needle site and four developed abdominal wall scaring with ulcerations. Neuropsychiatric effects were seen in three patients.

Pietz et al. (1998)[7] (see also above section "Control of Parkinsonian Symptoms in patients already treated with L-dopa): 60 patients with advanced Parkinson's disease were included in this study, of whom 49 (age range 42-80 years) were treated for 3 to 66 months with intermittent subcutaneous injections or continuous infusions of apomorphine. The 11 other patients dropped out after a test period of 2 months due to psychiatric side effects (n=3), insufficient effect (n=3), technical difficulties in handling the equipment (n=2), hemolytic anaemia (n=1), death from unrelated reason (n=1) and participation in another trial (n=1). Efficacy was assessed by a specialized nurse who recorded "off" and "on" and "on with dyskinesia" every 30 minutes during the awake part of the day for at least 2 days before treatment, and for 4-8 hours at every evaluation visit. Dyskinesias were also estimated according to the Obeso scale. The patients completed "on-off" diaries for at least 1 week before each follow-up visit.

Twenty-five patients were treated with continuous infusion (median 44 months follow-up). The daily time in "off" was reduced from 50% (baseline) to 25% (p<0.001). Other outcome measures (Hoehn and Yahr, Schwab and England) were also improved. The L-dopa treatment was reduced in most patients (24 out of 25 in the continuous infusion group). Baseline dose was 900 mg/d and dropped to 450 mg/d, and 8 patients stopped L-dopa completely. The total daily dose of apomorphine at the end of follow-up was 116 mg. Five patients stopped treatment because of psychiatric side effects (n=3) and insufficient effect (n=2). Time spent "off" was reduced from 50% at baseline to 25%. Overall dyskinesias were reported unchanged (severity improved in 7 patients, unchanged in 9 patients and worse in 9 patients; duration decreased in 5 patients, unchanged in 12 and increased in 8 patients). The Obeso dyskinesia scale had an intensity score of 2.2 (range 0-4) and a duration score of 1.7 (0-3) before treatment and of 1.9 (0-4) and 1.5 (0-3) respectively on apomorphine. Local irritations (nodules) were reported in all patients, with abscess in one case and necrotic areas in other patient. Other adverse events were orthostatic hypotension, urinary urge, diarrhea, nausea, hyperlibido. Psychiatric changes were seen in 11 patients (psychosis, hallucinations, illusion, and confusion).

Twenty-four patients were treated with subcutaneous injections of apomorphine for more than two months (median 22 months). Time spent "off" was reduced from 50% at baseline to 30% on apomorphine (p<0.001). Changes in other outcome measures (Hoehn and Yahr and Schwab and England scores) were less conclusive. The mean L-dopa daily dose remained unchanged, but the number of doses a day increased from 7 to 10. Dyskinesia intensity and duration were reported to be inconsistently influenced by apomorphine (intensity improved in 2 patients, worse in 3 and unchanged in 19; duration decreased in 2 patients, unchanged in 19 and increased in 3). The mean Obeso score in "on" with and without apomorphine was unchanged (intensity score 1.7 (0-4) before apomorphine and 1.6 (0-4) after apomorphine; duration score 1.3 (0-3) before apomorphine and 1.4 (0-3) after apomorphine). The most frequent side effects were nausea (n=8) and orthostatic hypotension (n=4). Two patients developed hallucinations and one reported confusion.

REVIEW OF CLINICAL STUDIES WITH OTHER ROUTES OF ADMINISTRATION OF APOMORPHINE

INTRANASAL APOMORPHINE

No Level-I studies were identified that fulfilled all the inclusion criteria needed for this review. However, one small (less than 20

patients per treatment group) and short (less than 4 weeks of follow-up) randomized, double-blind, placebo-controlled, cross-over trial studied the clinical efficacy of intranasal apomorphine as rescue therapy for PD in the "off" states. [11]

Dewey et al. (1998)[11]: This study was a 2-week trial (2-week study period separated by a 1-week wash-out period) done in 9 patients with PD (mean age = 61 years; mean disease duration = 12.6 years). Patient diary records revealed that intranasal apomorphine (4.1mg / administration) had a latency to onset effect of 11 minutes and a duration of action of 50 minutes. Intranasal apomorphine adverse reactions included nasal irritation (n = 3), dyskinesia (n = 4), nausea (n = 2), and yawning (n = 2).

Few other small and short-term Level-III trials (involving less than 20 patients) have also been published with intranasal apomorphine[12-14] and are available in the literature for further review.

SUBLINGUAL APOMORPHINE

No Level-I study fulfilling our inclusion criteria qualified for review, however one small study is included (performed in less than 20 patients) that reported the results of sublingual apomorphine as rescue therapy for PD off-states (Ondo et al.1999).[15]

Ondo et al. (1999)[15]: This is a double-blind, placebo-controlled study that enrolled ten patients with PD who had motor fluctuations. After having a defined optimal acute dose of sublingual apomorphine, patients underwent efficacy assessment using timed motor tasks (finger tapping, walking). At the dose of 40 mg, apomorphine improved tapping speed (31% over placebo) and ambulation speed (45% over placebo) ($p<0.05$). Onset of effect occurred within 20 minutes in 7 patients and within 40 minutes in the remaining 3 patients. Eight of 10 patients found the taste disagreeable. One had nausea and another patient presented with orthostatic hypotension.

There are also in the literature other small (less than 20 patients), short-term (less than 4 weeks), open-label studies (Level III) assessing the pharmacokinetics and clinical effects of apomorphine when administered via sublingual administration.[16-20]

OTHER ROUTES OF ADMINISTRATION

There are a few additional studies reporting efficacy and tolerability of other routes of administration of apomorphine, but none qualified for inclusion in this review.[21,22]

REVIEW OF SAFETY

Similar to other DA agonists, apomorphine can induce nausea and vomiting, hypotension, psychosis and sexual dysfunction (ie. hypersexuality; frequent erections). The use of domperidone coadministration reduces the severity of the "peripheral" digestive and cardiovascular dopaminergic adverse reactions. Subcutaneous nodules at the injection site are frequent and sometimes painful and may become infected. It is likely that this adverse reaction is related to the intrinsic physical properties of the compound, since problems of local toxicity have been reported at any site of apomorphine administration (subcutaneous, sublingual, and intranasal). The reports of hypersexuality due to apomorphine have led to its expanded clinical use to treat sexual dysfunction and impotency.

Although apomorphine is a derivative of an opiate component, there is no evidence associating apomorphine with addiction.

Rare Combs-positive haemolytic anemia, especially in patients receiving continuous subcutaneous infusions, have been reported, and the usefulness of blood count monitoring for this purpose remains uncertain.[23,24]

CONCLUSIONS

The evidence related to the use of apomorphine in the treatment of Parkinson's disease is based on a limited number of open-label, Level- III studies, enrolling small numbers of patients. Some of these patients have been followed-up for several years.

EFFICACY

PREVENTION OF DISEASE PROGRESSION

There is INSUFFIENCT EVIDENCE to conclude on the efficacy of apomorphine in the prevention of disease progression.

SYMPTOMATIC CONTROL OF PARKINSONISM

Monotherapy or early combination in de novo patients

For diagnostic purposes, apomorphine has been proposed as a way to test the dopaminergic responsiveness of parkinsonian symptoms in patients with early parkinsonism[9] but has low sensitivity and specificity. In the absence of controlled studies and long-term follow-up data, there is INSUFFICIENT EVIDENCE to conclude on the efficacy of apomorphine in de novo patients with Parkinson's disease.

Adjunct therapy in L-dopa-treated patients

Continuous subcutaneous infusion of apomorphine is considered LIKELY EFFICACIOUS for controlling parkinsonian symptoms in patients with advanced PD who are already on L-dopa therapy. This conclusion is based on open-label, Level-III trials reporting that L-dopa therapy can be substantially reduced, or even stopped (without deterioration of symptoms in some patients, and improvement in other patients) when patients are treated with apomorphine pumps. There is INSUFFICIENT EVIDENCE to conclude on apomorphine efficacy as an adjunct to levodopa for early treatment of PD in patients without motor fluctuations.

PREVENTION OF MOTOR COMPLICATIONS

There is INSUFFIENCT EVIDENCE to conclude on the efficacy of apomorphine in the prevention of motor complications.

CONTROL OF MOTOR COMPLICATIONS

Subcutaneous apomorphine (continuous infusion or pen jet injections) is considered LIKELY EFFICACIOUS in the control of motor fluctuations in patients with advanced PD who have severe "on-off" problems. This conclusion is based on one small, short-term, placebo-controlled study[6] and several Level-III trials reporting that subcutaneous apomorphine can (1) switch patients with PD from the "off" to the "on" condition with an amplitude of the response comparable with that of L-dopa and (2) reduce the duration of "off" periods.

In spite of one encouraging small long-term level III study[10], there is INSUFFICIENT EVIDENCE to conclude about the efficacy of apomorphine (continuous infusion) on the long-term management of L-dopa-induced dyskinesias.

Although similar response rates are observed for the sublingual and intranasal administrations compared to subcutaneous administration, strong Level-I evidence is lacking, and therefore, alternative routes of administration of apomorphine (eg. sublingual, intranasal) are LIKELY EFFICACIOUS in controlling motor fluc-

tuations but poorly tolerated in practice. Pharmacokinetic parameters must permit plasma concentrations to reach adequate levels to achieve this therapeutic goal.

SAFETY

The use of apomorphine has an ACCEPTABLE RISK, WITHOUT SPECIAL MONITORING, if accompanied by domperidone administration in order to reduce the severity of "peripheral" digestive and cardiovascular dopaminergic adverse events. However, the complex use of the subcutaneous route of administration, specially that of continuous pumps, requires a trained referring center to adequately manage the patients.

IMPLICATIONS FOR CLINICAL PRACTICE

As "rescue therapy" for patients with sudden, unexpected and resistant "off" periods, the evidence available (mainly restricted to Level III consistently reporting improved parkinsonism scores to a degree comparable to levodopa) is considered sufficient to conclude that subcutaneous apomorphine is POSSIBLY USEFUL. Because of the alternate route of administration and complexity of treatment paradigms, apomorphine is often restricted to complex and difficult to manage patients. Apomorphine should be administered by physicians experienced with the drug and managing these complex patients. Dose ranges vary and single injections range between 2-6 mg. This is consistent with a 0.5 to 4 mg/h for continuous infusion. A caregiver is needed who will be able and willing to administer treatment, which may be difficult to do when patients are in the "off" periods.

Until additional studies are done, the use of apomorphine given through other routes of administration (other than the subcutaneous) remains INVESTIGATIONAL.

IMPLICATIONS FOR CLINICAL RESEARCH

- Randomized controlled studies are needed to assess the usefulness of subcutaneous apomorphine vs. other treatments (like deep brain stimulation and other forms of surgery usually recommended to improve severe motor fluctuations).
- Further controlled studies are needed to establish the potential long-term benefit of apomorphine continuous subcutaneous infusion on dyskinesia.
- Interaction between apomorphine and COMT inhibitors should be studied in patients with PD.
- Additional trials are needed to assess the efficacy and safety of routes of apomorphine administration that are more practical (eg. sublingual formulations) than subcutaneous injections.
- Studies should be done to assess the usefulness of monitoring changes of blood cells during chronic treatment with apomorphine.

REFERENCES

1. Neef C, van Laar T. Pharmacokinetic-pharmacodynamic relationships of apomorphine in patients with Parkinson's disease. Clin Pharmacokinet 1999;37:257-271.
2. Gassen M, Glinka Y, Pinchasi B, Youdim MB. Apomorphine is a highly potent free radical scavenger in rat brain mitochondrial fraction. Eur J Pharmacol 1996;308:219-225.
3. Grumblatt E, Mandel S, Berkuzki T, Youdim MB. Apomorphine protects against MPTP-induced neurotoxicity in mice. Mov Disord 1999;14:612-618.
4. Hughes AJ, Lees AJ, Stern GM. Challenge tests to predict the dopaminergic response in untreated Parkinson's disease. Neurology 1991;41:1723-1725.
5. Duby SE, Cotzias GC, Papavasiliou PS, Laurence WH. Injected apomorphine and orally administered levodopa in parkinsonism. Arch Neurol 1972;27:474-480.
6. Ostergaard L, Werdelin L, Odin P, et al. Pen injected apomorphine against off phenomena in late Parkinson's disease: a double blind, placebo controlled study. J Neurol Neurosurg Psychiatry 1995;58:681-687.
7. Pietz K, Hagell P, Odin P. Subcutaneous apomorphine in late state Parkinson's disease: a long term follow up. J Neurol Neurosurg Psychiatry 1998;65:709-716.
8. Frankel JP, Lees AJ, Kempster PA, Stern GM. Subcutaneous apomorphine in the treatment of Parkinson's disease. J Neurol Neurosurg Psychiatry 1990;53:96-101.
9. Hughes AJ, Bishop S, Kleedorfer B, et al. Subcutaneous apomorphine in Parkinson's disease: response to chronic administration for up to five years. Mov Disord 1993;8:165-170.
10. Colzi A, Turner K, Lees AJ. Continuous subcutaneous waking day apomorphine in the long term treatment of levodopa induced interdose dyskinesias in Parkinson's disease. J Neurol Neurosurg Psychiatry 1998;64:573-576.
11. Dewey RB, Maraganore DM, Ahlskog E, Matsumoto JY. A double-blind, placebo-controlled study of intranasal apomorphine spray as a rescue agent for off-states in Parkinson's disease. Mov Disord 1998;13:782-787.
12. Kapoor R, Turjanski N, Frankel J, et al. Intranasal apomorphine: a new treatment in Parkinson's disease. J Neurol Neurosurg Psychiatry 1990;53:1015.
13. Kleedorfer B, Turjanski N, Ryan R, Lees AJ, Milroy C, Stern GM. Intranasal apomorphine in Parkinson's disease. Neurology 1991;41:761-762.
14. Dewey RB, Maraganore DM, Ahlskog JE, Matsumoto JY. Intranasal apomorphine rescue therapy for parkinsonian "off" periods. Clin Neuropharmacol 1996;19:193-201.
15. Ondo W, Hunter Ch, Almaguer M, Gancher S, Jankovic J. Efficacy and tolerability of a novel sublingual apomorphine preparation in patients with fluctuating Parkinson's disease. Clin Neuropharmacol 1999;22:1-4.
16. Lees AJ, Montastruc JL, Turjanski N, et al. Sublingual apomorphine and Parkinson's disease. J Neurol Neurosurg Psychiatry 1989;52:1440.
17. Durif F, Deffond D, Tournilhac M et al. Efficacy of sublingual apomorphine in Parkinson's disease. J Neurol Neurosurg Psychiatry 1990;53:1105.
18. Montastruc JL, Rascol O, Senard JM, et al. Sublingual apomorphine in Parkinson's disease: a clinical and pharmacokinetic study. Clin Neuropharmacol 1991;14:432-437.
19. Hughes AJ, Webster R, Bovingdon M, Lees AJ, Stern GM. Sublingual apomorphine in the treatment of Parkinson's disease complicated by motor fluctuations. Clin Neuropharmacol 1991;14:556-561.
20. van Laar T, Neef C, Danhof M, Roon KI, Roos RAC. A new sublingual formulation of apomorphine in the treatment of patients with Parkinson's disease. Mov Disord 1996;11:633-638.
21. Hughes AJ, Bishop S, Lees AJ, Stern GM, Webster R, Bovingdon M. Rectal apomorphine in Parkinson's disease. Lancet 1991;337:118.
22. van Laar T, Jansen EN, Neef C, Danhof M, Roos RA. Pharmacokinetics and clinical efficacy of rectal apomorphine in patients with Parkinson's disease: a study of five different suppositories. Mov Disord 1995;10:433-439.
23. Pinter MM, Helscher RJ, Mundsperger N, Binder H. Transient increase of pancreatic enzymes evoked by apomorphine in Parkinson's disease. J Neural Transm 1998;105:1237-1244.
24. Poewe WP, Kleedorfer B, Wagner M, et al. Continuous subcutaneous apomorphine infusions for fluctuating Parkinson's disease. Long-term follow-up in 18 patients. Adv Neurol 1993;60:656-659.

BIBLIOGRAPHY - EXCLUDED FROM ANALYSIS (REASON FOR EXCLUSION)

Baas H, Harder S, Burklin F, Demisch L, Fischer PA. Pharmacodynamics of levodopa coadministered with apomorphine in parkinsonian patients with end-of-dose motor fluctuations. Clin Neuropharmacol 1998;21:86-92. (Less than 20 patients)

Baas H, Harder S, Demisch L, Burklin F, Stecker K, Fischer PA. Fluctuations in Parkinson's disease. Pathogenetic significance of levodopa's cerebral pharmacokinetics and pharmacodynamics. J Neural Transm Suppl 1995;46:367-379. (Review)

Barclay CL, Duff J, Sandor P, Lang AE. Limited usefulness of electroconvulsive therapy in progressive supranuclear palsy. Neurology 1996;46:1284-1286. (Non-apomorphine trial)

Bonuccelli U, Piccini P, Del Dotto P, Rossi G, Corsini GU, Muratorio A. Apomorphine test for dopaminergic responsiveness: a dose assessment study. Mov Disord 1993;8:158-164. (Acute challenge)

Bonuccelli U, Piccini P, Del Dottto P, Rossi G, Corsini GU, Muratorio A. Naloxone partly counteracts apomorphine side effects. Clin Neuropharmacol 1991;14:442-449. (Less than 20 patients)

Buttner T, Muller T, Kuhn W. Effects of apomorphine on visual functions in Parkinson's disease. J Neural Transm 2000;107:87-94. (Non-motor outcome)

Casa M, Guardia J, Prat G, Trujols J. The apomorphine test in heroin addicts. Addiction 1995;90:831-835. (Non-PD patients)

Castaigne P, Laplane D, Dordain G. Clinical experimentation with apomorphine in Parkinson's disease. Res Commun Chem Pathol Pharmacol 1971;2:154-158. (Less than 20 patients)

Corsini GU, Del Zompo M, Gessa GL, Mangoni A. Therapeutic efficacy of apomorphine combined with an extracerebral inhibitor of dopamine receptors in Parkinson's disease. Lancet 1979;1:954-956. (Less than 20 patients)

Cotzias GC, Papavasiliou PS, Fehling C, Kaufman B, Mena I. Similarities between neurologic effects of L-dopa and of apomorphine. N Engl J Med 1970;282:31-33. (Less than 20 patients)

Cotzias GC, Papavasiliou PS, Tolosa ES, Mendez JS, Bell-Midura M. Treatment of Parkinson's disease with aporphines. Possible role of growth hormone. N Engl J Med 1976;294:567-572. (Less than 20 patients)

Dewey RB Jr, Maraganore DM, Ahlskog JE, Matsumoto JY. Intranasal apomorphine rescue therapy for parkinsonian "off" periods. Clin Neuropharmacol 1996;19:193-201. (Less than 20 patients)

Duby SE, Cotzias GC, Papavasiliou PS, Lawrence WH. Injected apomorphine and orally administered levodopa in Parkinsonism. Arch Neurol 1972;27:474-480. (Less than 20 patients)

Durif F, Deffond D, Tournilhac M. Efficacy of sublingual apomorphine in Parkinson's disease. J Neurol Neurosurg Psychiatry 1990;53:1105. (Less than 20 patients)

Esteban-Munoz J, Marti MJ, Marin C, Tolosa E. Long-term treatment with intermittent intranasal or subcutaneous apomorphine in patients with levodopa-related motor fluctuations. Clin Neuropharmacol 1997;20:245-52. (Less than 20 patients)

Frattola L, Albizzati MG, Bassi S, Ferrarese C, Trabucchi M. On-Off phenomena, dyskinesias and dystonias comparison of lisuride versus apomorphine acute treatment. Acta Neurol Scand 1982;66:227-236. (Heterogeneous population)

Gancher ST, Woodward WR, Nutt JG. Apomorphine tolerance in Parkinson's disease: lack of a dose effect. Clin Neuropharmacol 1996;19:59-64. (Less than 20 patients)

Gervason CL, Pollak PR, Limousin P, Perret JE. Reproducibility of motor effects induced by successive subcutaneous apomorphine injections in Parkinson's disease. Clin Neuropharmacol 1993;16:113-119. (Less than 20 patients)

Gilhus NE. Apomorphine in Parkinson's disease. Tidsskr Nor Laegeforen 1991;111:3166-3169. (Not English)

Harder S, Baas H, Demisch L, Simon E. Dose response and concentration response relationship of apomorphine in patients with Parkinson's disease and end-of-dose akinesia. Int J Cin Pharmacol Ther 1998;36:355-362. (Less than 20 patients)

Hutchinson WD, Levy R, Dostrovsky JO, Lozano AM, Lang AE. Effects of apomorphine on globus pallidus neurons in parkinsonian patients. Ann Neurol 1997;42:767-775. (Non-clinical endpoint)

Kompoliti K, Wang QE, Goetz CG, Leurgans S, Raman R. Effects of central dopaminergic stimulation by apomorphine on speech in Parkinson's disease. Neurology 2000;54:458-462. (Less than 20 patients)

Krack P, Pollak P, Limousin P, et al. Opposite motor effects of pallidal stimulation in Parkinson's disease. Ann Neurol 1998;43:180-192. (Study on surgery)

Kreczy-Kleedorfer B, Wagner M, Bösch S, Poewe W. Langzeitergebnisse kontinuierlicher sbkutaner Apomorphinpumpentherapie bei Patienten mit fortgeschrittener Parkinson-Krankeit. Nervenarzt 1993;64:221-225. (Article in German, less than 20 patients)

Linazasoro G. The apomorphine test in gait disorders associated with parkinsonism. Clin Neuropharmacol 1996;19:171-176. (<20 patients)

Llau ME, Durrieu G, Tran MA, Senard JM, Rascol O, Montastruc JL. A study of dopaminergic sensitivity in Parkinson's disease: comparison in «de novo» and levodopa-treated patients. Clin Neuropharmacol 1996;19:420-427. (Non-clinical endpoint)

MacMahon DG. Use of apomorphine in clinical practice. Adv Neurol 1999;80:529-533. (Chapter in a book)

Manfredi L, Garavaglia P, Beretta S, Pellegrini G. Increased cortical inhibition induced by apomorphine in patients with Parkinson's disease. Neurophysiol Clin 1998;28:31-38. (Non-clinical endpoint)

McDowell FH, Sweet R. Actions of dopaminergic agonists in parkinsonism. Adv Neurol 1975;9:367-371. (Chapter in a book)

McRae A, Dahlstrom A. Transmitter-loaded polymeric microspheres induce regrowth of dopaminergic nerve terminals in striata of rats with 6-OH-DA induced parkinsonism. Neurochem Int 1994;25:27-33. (Less than 20 patients)

Merello M, Leiguarda R. Treatment of motor fluctuations in Parkinson's disease with subcutaneous injections of apomorphine. Medicina (B Aires) 1995;55:5-10. (Not English)

Merello M, Pikielny R, Cammarota A, Leiguarda R. Comparison of subcutaneous apomorphine versus dispersible Madopar latency and effect duration in Parkinson's disease patients: a double-blind single-dose study. Clin Neuropharmacol 1997;20:165-167. (Less than 20 patients)

Merello M, Starkstein S, Petracca G, Cataneo EA, Manes F, Leiguarda R. Drug-induced parkinsonism in schizophrenic patients: motor response and psychiatric changes after acute challenge with L-dopa and apomorphine. Clin Neuropharmacol 1996;19:439-443. (Non PD patients)

Miranda M, Saez D. Apomorphine test: evaluation of dopaminergic response in patients with Parkinson disease. Rev Med Chil 1995;123:326-329. (Not English)

Montastruc JL. Recent advances in the clinical pharmacology of Parkinson's disease. Therapie 1991;46:293-303. (Not English)

Moro E, Albanese A. Apomorphine and levodopa challenge in patients with a focal midbrain lesion. Mov Disord 1999;14:269-275. (Non-PD patients)

Nardini M, Sciannandrome R, Fieschi C, De Simone G. Piribedil in the treatment of Parkinson's disease. Riv Patol Nerv Ment 1975;96:103-110. (Not English)

Nutt JG, Carter JH. Apomorphine can sustain the long-duration response to L-DOPA in fluctuating PD. Neurology 2000;54:247-250. (Less than 20 patients)

Odin P, Mangalanayagam L, Nilson B, Lindvall O. Subcutaneous apomorphine-a valuable therapeutic alternative in Parkinson's disease. Lakartidningen 1991;88:3811-3814. (Not English)

Panegyres PK, Graham SJ, Willliams BK, Higgins BM, Morris JG. Sublingual apomorphine solution in Parkinson's disease. Med J Aust 1991;155:371-374. (Less than 20 patients)

Papavasiliou PS, Cotzias GC, Rosal VL, Miller ST. Treatment of parkinsonism with N-n-propyl norapomorphine and levodopa (with or without carbidopa). Arch Neurol 1978;35:787-791. (Less than 20 patients)

Piccini P, Del Dotto P, Napolitano A, Pardini C, Bonuccelli U. The apomorphine test for diagnosis of parkinsonian syndrome. Riv Neurol 1990;60:221-223. (Not English)

Pinter MM, Alesch F, Murg M, Helscher RJ, Binder H. Apomorphine test: a predictor for motor responsiveness to deep brain stimulation of the subthalamic nucleus. J Neurol 1999;246:907-913. (Less than 20 patients)

Pirtosek Z, Merello M, Carlsson A, Stern G. Preclamol and parkinsonian fluctuations. Clin Neuropharmacol 1993;16:550-554. (Study on preclamol effects)

Pollak P, Benabid AL, Limousin P, Gervason CL, Jeanneau-Nicolle E. External and implanted pumps for apomorphine infusion in parkinsonism. Acta Neurochir 1993;58:48-52. (Less than 20 patients)

Pollak P, Mallaret M, Gaio JM, Hommel M, Perret J. Blood pressure effects of apomorphine and domperidone in parkinsonism. Adv Neurol 1987;45:263-266. (Chapter in a book)

Reuter I, Ellis CM, Ray Chaudhuri K. Nocturnal subcutaneous apomorphine infusion in Parkinson's disease and restless legs syndrome. Acta Neurol Scand 1999;100:163-167. (Less than 20 patients)

Rossi P, Colosimo C, Moro E, Tonali P, Albanese A. Acute challenge with apomorphine and levodopa in Parkinsonism. Eur Neurol 2000;43:95-101. (<4 weeks)

Ruzicka E, Roth J, Spackova N, Mecir P, Jech R. Apomorphine induced cognitive changes in Parkinson's disease. J Neurol Neurosurg Psychiatry 1994;57:998-1001. (Less than 20 patients)

Sam E, Jeanjean AP, Maloteaux JM, Verbeke N. Apomorphine pharmacokinetics in parkinsonism after intranasal and subcutaneous application. Eur J Drug Metab Pharmacokinet 1995;20:27-33. (Less than 20 patients)

Schrag A, Schelosky L, Scholz U, Poewe W. Reduction of Parkinsonian signs in patients with Parkinson's disease by dopaminergic versus anticholinergic single-dose challenges. Mov Disord 1999;14:252-255. (<4 weeks)

Schwarz J, Tatsch K, Gasser T, Arnold G, Oertel WH. [123]IBZM binding predicts dopaminergic responsiveness in patients with parkinsonism and previous dopaminomimetic therapy. Mov Disord 1997;12:898-902. (Non-therapeutic trial)

Schwarz J, Tatsch K, Gasser T, Arnold G, Pogarell O, Kunig G, Oertel WH. 1231-IBZM binding compared with long-term clinical follow up in patients with de novo parkinsonism. Mov Disord 1998;13:16-9. (Non-clinical endpoint)

Stefani A, Mazzone P, Bassi A, et al. Electrophysiological and clinical desensitisation to apomorphine administration in parkinsonian patients undergoing stereotaxic neurosurgery. Exp Neurol 1999;156:209-213. (Less than 20 patients)

Stibe CM, Lees AJ, Kempster PA, Stern GM. Subcutaneous apomorphine in parkinsonian on-off oscillations. Lancet 1988;20:403-406. (Less than 20 patients)

Stibe C, Lees A, Stern G. Subcutaneous infusion of apomorphine and lisuride in the treatment of parkinsonian on-off fluctuations. Lancet 1987;1(8537):871. (Less than 20 patients)

Stocchi F, Bramante L, Monge A, et al. Apomorphine and lisuride infusion. A comparative chronic study. Adv Neurol 1993;60:653-655. (Chapter in a book)

Stocchi F, Vacca L, De Pandis MF, Torti M, Nordera G, Cattoni M, Ruggieri S. Evaluation of the efficacy and tolerability of apomorphine (Apofin vial) administered in continuous subcutaneous infusion by timed minipump in patientn with severe Parkinson's disease complicated by multiple daily motor fluctuations. Revista Neurologia 1999;9:217-223. (Article in Italian)

Truelle JL, Chanelet J, Bastard J, Emile J. Polygraphic recording of tremor and of hypertonic phenomena. Application to the action of various drugs. Rev Neurol 1975;131:29-42. (Not English)

van der Geest R, van Laar T, Gubbens-Stibbe JM, Bodde HE, Danhor M. Iontophoretic delivery of apomorphine. II: An in vivo study in patients with Parkinson's disease. Pharm Res 1997;14:1804-1810. (Non-clinical endpoint)

van der Geest R, van Laar T, Kruger PP, et al. Pharmacokinetics, enantiomer interconversion, and metabolism of R-apomorphine in patients with idiopathic Parkinson's disease. Clin Neuropharmacol 1998;21:159-168. (Less than 20 patients)

van Hilten JJ, Wagemans EA, Ghafoerkhan SF, van Laar T. Movement characteristics in Parkinson's disease: determination of dopaminergic responsiveness and threshold. Clin Neuropharmacol 1997;20:402-408. (Less than 20 patients)

van Laar T, Jansen EN, Essink AW, Neef C, Oosterloo S, Roos RA. A double-blind study of the efficacy of apomorphine and its assessment in "off"-periods in Parkinson's disease. Clin Neurol Neurosurg 1993;95:231-235. (Non-PD patients)

van Laar T, Neef C, Danhof M, Roon KL, Roos RA. A new sublingual formulation of apomorphine in the treatment of patients with Parkinson's disease. Mov Disord 1996;11:633-638. (Less than 20 patients)

van Laar T, van der Geest R, Danhof M, Bodde HE, Goossens PH, Roos RA. Stepwise intravenous infusion of apomorphine to determine the therapeutic window in patients with Parkinson's disease. Clin Neuropharmacol 1998;21:152-158. (Less than 20 patients)

van Laar T. Jansen ENH, Essink AWG, Neef C, Oosterloo S, Roos RAC. A double-blind study of the efficacy of apomorphine and its assessment in "off"-periods in Parkinson's disease. Clin Neurol Neurosurg 1993;95:231-235. (Less than 20 patients)

Verhagen Metman L, Locatelli ER, Bravi D, Mouradian MM, Chase TN. Apomorphine responses in Parkinson's disease and the pathogenesis of motor complications. Neurology 1997;48:369-372. (Non-therapeutic trial)

Zaleska B, Domzal T. Apomorphine in treatment of Parkinson's disease with fluctuations. Neurol Neurochir Pol 1999;33:1297-1303. (Not English)

Zoldan J, Merims D, Kuritzky A, Ziv I, Melamed E. Apomorphine for treatment of "off-periods" in Parkinson's disease. Harefuah 1999;137:444-446. (Not English)

Movement Disorders
Vol. 17, Suppl. 4, 2002, p. S90-S92

Published by Wiley-Liss, Inc.
DOI 10.1002/mds.5568

DA Agonists - Non-Ergot derivatives: Piribedil

BASIC PHARMACOLOGY

MECHANISM OF ACTION

Piribedil is a non-ergot derivative D2/D-3 agonist[1] with alpha-2 antagonistic effects[2]. Piribedil is effective in reversing parkinsonian symptoms in the MPTP-treated primate[3]. The clinical effects of piribedil cause lower prolactin plasma levels and blood pressure, and induces nausea. There is also some evidence that piribedil has neuroprotective effects in experimental models[4].

PHARMACOKINETICS

Piribedil is administered orally, Tmax is reached within 1 hour, and it has a relatively long plasma elimination half-life (20 hours). Piribedil solubility allows it to be used intravenously for experimental purposes or acute challenge tests.

REVIEW OF CLINICAL STUDIES

PREVENTION OF DISEASE PROGRESSION

No qualified Level-I studies were identified.

SYMPTOMATIC CONTROL OF PARKINSONISM

MONOTHERAPY

No Level-I clinical trial was identified, as based on the predefined inclusion criteria. There is a large randomized placebo-controlled study presently on-going. However, at the moment, only one uncontrolled, Level-III trial was identified[5]. It will briefly be reviewed here in the absence of other available published evidence.

Rondot et al. (1992)[5]: This is an open-label, 3-month study assessing the efficacy of piribedil in 113 de novo patients with PD. The Webster scale was used to assess efficacy. Twenty-tree patients dropped-out prematurely, and analysis was performed in the 90 patients who completed the study. In these patients, piribedil, at a mean dose of 207 mg/d, improved the Webster scale by 41% ($p<0.001$). Adverse reactions were consistent with those of any D2 agonist (eg. digestive, cardiovascular, psychiatric).

ADJUNCT THERAPY

No qualified studies were identified. The publication of a recently conducted randomized placebo-controlled study in stable levodopa-treated PD patients is expected.

PREVENTION OF MOTOR COMPLICATIONS

No qualified studies were identified. There is an on-going 2-year levodopa-controlled extension of the placebo-controlled study mentioned in the section on Control of Parkinsonism as Monotherapy.

CONTROL OF MOTOR COMPLICATIONS

No qualified studies were identified.

REVIEW OF SAFETY

Based on the limited amount of available data and its long use in clinical practice in several countries, it appears that adverse reactions associated with piribedil are similar to other dopamine agonists in this class of drug including gastrointestinal cardiovascular and neuropsychiatric events. One case report of possible "sleep attacks" in a patient on piribedil has recently been reported.[6]

CONCLUSIONS

EFFICACY, SAFETY AND IMPLICATIONS FOR CLINICAL PRACTICE

According to the paucity of Level-I data and the lack of studies published that met inclusion criteria, there is INSUFFICIENT EVIDENCE to conclude about the efficacy, safety and implications for clinical practice of piribedil. Level-I studies are ongoing, and future recommendations will be based on these forthcoming reports.

IMPLICATIONS FOR CLINICAL RESEARCH

- There is a clear need to conduct modern, randomized, controlled, well-designed trials to assess the benefit/risk ratio of piribedil in the treatment of PD.
- Pharmacoeconomic studies are needed to compare the cost benefits of piribedil to other treatments in this class of drug and also to other medications used to treat PD.
- Studies that specifically assess the impact of piribedil on quality of life and the effect on mortality are also needed.

REFERENCES

1. Millan MJ, Peglion JL, Vian J, Rivet JM, Brocco M, Gobert A, Newman-Trancredi A, Daquet C, Bervoets K, Girardon S, Jacques V, Chaput C, Audinot V. Functional correlates of dopamine D3 receptor activation in the rat in vivo and their modulation by the selective antagonist (+)-S 14297.I.Activation of postsynaptic D3 receptors mediates hypothermia, whereas blockade of D2 receptors elicits prolactin secretion and catalepsy. J Pharmacol Exp Ther 1995;275:885-898.
2. Millan MJ, Cusac D, Milligam G, Carr C, Audinot V, Gobert A, Lejeunde F, Rivet JM, Brocco M, Duquiroix D, Nicolas JP, Boutin JA, Newman-Trancredi A. Antiparkinsonian agent piribedil displays antagonist properties at native rat and cloned human alpha-2adrenoceptors: cellular and functional characterization. J Pharmacol Exp Ther 2001;297:876-887.
3. Smith L, De Salvia M, Jenner P, Marsden CD. An appraisal of the antiparkinsonian activity of piribedil in MPTP-treated common marmosets. Mov Disord 1996;11:125-135.
4. Calzi F, Bellasio R, Guiso G, Caccia S, Tacconi MT. Effect of piribedil and its metabolite S584 oh brain lipid peroxidation in vitro and in vivo. Eur J Pharmacol 1997;338:185-190.
5. Rondot P, Ziegler M. Activity and acceptability of piribedil in Parkinson's disease:a multicentre study. J Neurol 1992;239(Suppl 1):28-34.
6. Ferreira JJ, Galitzky M, Montastruc JL, Rascol O. Sleep attacks and Parkinson's disease treatment. Lancet 2000;355:1333-1334.

BIBLIOGRAPHY - EXCLUDED FROM ANALYSIS (REASON FOR EXCLUSION)

Agid Y, Barroche G, Bonnet AM, et al. Dopamine receptor stimulating agonists in the treatment of Parkinson's disease. Biomedicine 1979;30:67-71. (Level III)

Allain H, Van den Driessche J, Menault F, Pape D, Reymann JM, Bentue-Ferrer D. Drugs and indications for medical treatment in Parkinson's disease. Sem Hop 1980;56:277-282. (Non-English literature)

Arbuthnott GW, Murray LG. Dopamine receptor agonists in psychiatric disease. Adv Neurol 1975;9:345-348. (Chapter in a book)

Barbeau A. Progress in understanding and treating Parkinson's disease. Can J Neurol Sci 1976;3:81-84. (Level III)

Bathien N, Rondot P, Koutlidis RM. Electrophysiological and pharmacological analysis of L-dopa-induced dyskinesia and tardive dyskinesia. J Physiol 1981;77:131-141. (Non-English literature)

Bathien N, Koutlidis RM, Rondot P. EMG patterns in abnormal involuntary movements induced by neuroleptics. J Neurol Neurosurg Psychiatry 1984;47:1002-1028. (Non-Parkinson's disease subjects)

Burton K, Calne DB. Dopamine agonists and Parkinson's disease. Clin Neurol Neurosurg 1984;86:172-177. (Level III)

Callaghan N, Fitzpatrick E, O'Mahony JB. Piribedil (ET 495) in the treatment of Parkinson's disease combined with amantadine or levodopa. Acta Neurol Scand 1975;52:179-186. (< 20 patients per treatment group)

Cane DB. Piribedil in parkinsonism. Adv Neurol 1974;5:325. (Chapter in a book)

Casacchia M, Carolei A, Zamponi A, Agnoli A, Fazio C.. Therapy of Parkinson's disease. Practical criteria of treatment. Recenti Prog Med 1976;60:567-584. (Non-English literature)

Chase TN, Shoulson I. Dopaminergic mechanisms in patients with extrapyramidal disease. Adv Neurol 1975;9:359-366. (Chapter in a book)

Corsini GU, Del Zompo M, Spissu A, Mangoni A, Gessa GL. Parkinsonism by haloperidol and piribedil. Psychopharmacology 1978;59:139-141. (Non-Parkinson's disease patients)

Coward DM, Doggett NS. The production of an alternative laboratory model of the Parkinson syndrome using a new benzylimidoylurea derivative LON 954. Psychopharmacology 1977;52:165-71. (Non-human experimental work)

Dourish CT. Piribedil:behavioural, neurochemical and clinical profile of a dopamine agonist. Prog Neuropsychopharmacol Biol Psychiatry 1983;7:3-27. (Level III)

Dubois B, Agid Y. Dopaminergic agonists in Parkinson disease. Rev Prat 1986;36:207-214. (Level III; non-English literature)

Emile J, Chanelet, J, Truelle JL, Bastard J. Action of piribedil in Parkinson's disease: I.V. test and oral treatment. Adv Neurol 1975;9:409-413. (Chapter in a book)

Feigenson JS, Sweet RD, McDowell FH. Piribedil:its synergistic effect in multidrug regimens for parkinsonism. Neurology 1976;26:430-433. (Level III)

Filion M. Effects of interruption of the nigrostriatal pathway and of dopaminergic agents on the spontaneous activity of globus pallidus neurons in the awake monkey. Brain Res 1979;178:425-441. (NonParkinson's disease patients)

Goldstein M, Lieberman A, Battista AF, Lew JY, Hata F. Bromocriptine, lergotrile:the antiparkinsonian efficacy and the interaction with monoaminergic receptors. Pharmacology 1978;16:143-149. (Level III)

Hungerbuhler JP, Regli F. Considerations in the drug treatment of parkinsonism. Schweiz Rundsch Med Prax 1978;67:1648-1657. (Non-English literature)

Iversen LL, Horn AS, Miller RJ. Actions of dopaminergic agonists on cyclic AMP production in rat brain homogenates. Adv Neurol 1975;9:197-212. (Chapter in a book)

Jenner P. Parkinson's disease: pathological mechanisms and actions of piribedil. J Neurol 1992;239:S2-8. (Level III)

Kapfhammer HP, Ruther E. Dopamine agonists in the therapy of Parkinson syndrome. Nervenarzt 1985;56:69-81. (Non-English literature)

Lieberman A, Le Brun Y, Zolfaghari M. Proceedings: effects of piribedil (ET-495) - a dopaminergic receptor stimulating agent in Parkinson's disease. Psychopharmacol Bul 1974;10:42-43. (Level III)

Lieberman AN, Shopsin B, Brun YL, Boal D, Zolfaghari M. Studies on piribedil in parkinsonism. Adv Neurol 1975;9:399-407. (Chapter in a book)

McDowell FH, et al. Actions of dopaminergic agonists in parkinsonism. Adv Neurol 1975;9:367-371. (Chapter in a book)

McLellan DL, Chalmers RJ, Johnson RH. Clinical and pharmacological evaluation of the effects of piribedil in patients with parkinsonism. Acta Neurol Scand 1975;51:74-82. (< 20 patients per treatment group)

Meltzer HY. Dopamine autoreceptor stimulation:clinical significance. Pharmacol Biochem Behav 1982;17:1-10. (Level III)

Mentenopoulos G, Katsarou Z, Bostantjopoulou S, Logothetis J. Piribedil therapy in Parkinson's disease. Use of the drug in the retard form. Clin Neuropharmacol 1989;12:23-8. (< 20 patients per treatment group)

Milon D, Allain H, Bentue-Ferrer D, Martinet JP, Lemaitre MH, Decombe R. Cardiac beta-adrenoceptor sensitivity and Parkinson's disease. Fundam Clin Pharmacol 1991;5:539-548. (Study on beta-blocker)

Mindham RH, Lamb P, Bradley R. A comparison of piribedil procyclidine and placebo in the control of phenothiazine-induced parkinsonism. Br J Psychiatry 1977;130:581-585. (Non-Parkinson's disease patients)

Mindham RHS. Assessment of drugs in schizophrenia. Assessment of drug-induced extrapyramidal reactions and of drugs given for their control. Br J Clin Pharmacol 1976;3(suppl 2):395-400. (Non-Parkinson's disease patients)

Montastruc JL, Ziegler M, Rascol O, Malbezin M. A randomized, double-blind study of a skin patch of a dopaminergic agonist, piribedil, in Parkinson's disease. Mov Disord 1999;14:336-341. (< 20 patients per treatment group)

Montastruc JL, Rascol O, Senard JM. Current status of dopamine agonists in Parkinson's disease management. Drugs 1993;46:384-393. (Level III)

Moreaud O, Fournet N, Roulin JL, Naegele B, Pellat J. The phonological loop in medicated patients with Parkinson's disease:presence of phonological similarity and word length effects. J Neurol Neurosurg Psychiatry 1997;62:609-611. (Level III)

Nardini M, Sciannandrone R, Fieschi C, De-Simone G. Piribedil in the treatment of Parkinson's disease. Riv Patol Nerv Ment 1975;96:103-110. (Non-English literature)

Ohmoto T, Miyamoto T, Baba Y. Experimental and clinical study on the dopaminergic receptor stimulating agents. No To Shinkei 1977;29:31-40. (Non-English literature)

Oules MJ, Boscredon J. Cerebral dopaminergic mechanisms. Present status of the problem. Ann Med Psychol 1979;137:925-929. (Non-English literature)

Parkes JD. Bromocriptine in the treatment of parkinsonism. Drugs 1979;17:365-382. (Level III)

Patat A, Gandon J, Rochat C, Trocherie S, Allain H. Effect of piribedil on psychomotor and cognitive functions in healthy young subjects. 8th ECNP Congresss 1995; Venice, Italy. (Non-Parkinson's disease subjects)

Poirier LJ. Dopaminergic agonists in animal models of parkinsonism. Adv Neurol 1975;9:327-335. (Book chapter)

Pycock C, Dawbarn D, O'Shaughnessy C. Behavioural and biochemical changes following chronic administration of L-dopa to rats. Eur J Pharmacol 1982;79:201-215. (Non-Parkinson's disease subjects)

Rinne UK Sonninen V, Marttila R. Dopaminergic agonist effects on Parkinsonian clinical features and brain monoamine metabolism. Adv Neurol 1975;9:383-392. (< 20 patients per treatment group; book chapter)

Rinne UK, Marttila R, Sonninen V. Brain dopamine turnover and the relief of parkinsonism. Arch Neurol 1977;34:626-629. (< 20 patients per treatment group)

Rinne UK, Sonninen V, Marttila R. Brain dopamine turnover and the relief of parkinsonism. Adv Exp Med Biol 1977;90:267-275. (< 20 patients per treatment group)

Rondot P, Bathien N, Dumas JL. Indications of piribedil in L-dopa-treated parkinsonian patients: physiopathologic implications. Adv Neurol 1975;9:373-381. (Book chapter)

Schechter MD. Amphetamine discrimination as a test for anti-parkinsonism drugs. Eur J Pharmacol 1977;44:51-56. (Study on amphetamine; < 4 weeks follow-up)

Schmitt H, Laubie M, Poignant JC, et al. New therapeutic indications for a dopamine agonist. Piribedil. Sem Hop 1978; 54:325-334. (Non-English literature)

Shoulson I, Chase T. Caffeine and the antiparkinsonian response to levodopa or piribedil. Neurology 1975;25:722-724. (< 4 weeks of follow-up)

Shoulson I, Chase TN. Clonidine and the antiparkinsonian response to L-dopa or piribedil. Neuropharmacol 1976;15:25-27. (< 4 weeks of follow-up)

Smith L, De Salvia M, Jenner P, Marsden CD. An appraisal of the antiparkinsonian activity of piribedil in 1-methyl1-4-phenyl-1,2,3,6-tetrahydropyridine-treated common marmosets. Mov Disord 1996;11:125-135. (Non-Parkinson's disease subjects)

Sweet RD, Wasterlain C, McDowell FH. Piribedil-an oral dopamine agonist for treatment of Parkinson's disease. Trans Am Neurol Assoc 1974;99:258-260. (Data reviewed in another article)

Sweet RD, Wasterlain CG, McDowell FH. Piribedil, a dopamine agonist, in Parkinson's disease. Clin Pharmacol Ther 1974;16:1077-1082. (Data reviewed in another article)

Sweet RD, Wasterlain CG, McDowell FH. Piribedil, a dopamine agonist, in Parkinson's disease. Clin Pharmacol Ther 1974;16:1077-1082. (Heterogeneous population)

Truelle JL, Chanelet J, Bastard J, Emile J. Polygraphic recording of tremor and increased tone in Parkinson's disease. Application to evaluation of drug actions. Rev Neurol 1975;131:29-42. (Non-English literature)

Truelle JL, Chanelet J, Bastard J, Six P, Emile J. Long-term clinical and electrophysiological study of a new dopaminergic agonist in 54 patients with parkinsonism. Sem Hop Ther 1977;53:453-456. (Non-English literature)

Truelle JL, Chanelet J, Bastard J, Six P, Emile J. Piribedil, dopaminergic agonist. Prolonged clinical and electrophysiological study in 60 parkinsonian patients. Nouv Presse Med 1977;6:2987-2990. (Non-English literature)
van Praag HM. Central monoamine metabolism in depressions. II. Catecholamines and related compounds. Compr Psychiatry 1980;21:44-54. (Level III)
Velasco M, Luchsinger A. Dopamine: pharmacologic and therapeutic aspects. Am J Ther 1998;5:37-43. (Level III)
Vermersch P, Petit H. Long-term selegiline tolerance in the treatment of Parkinson's disease. Therapie 1992;47:75-78. (Non-English literature)
Willner P. Dopamine and depression: a review of recent evidence. I Empirical studies. Brain Res 1983;287:211-224. (Level III)
Ziegler M, Georgiadis G, Elghozi JL. Acute hypotensive effect of a central dopaminergic agonist, piribedil, administered intravenously in the normotensive human. Arch Mal Cœur Vaiss 1984;77:1186-1190. (< 4 weeks follow-up; non-English literature)

Movement Disorders
Vol. 17, Suppl. 4, 2002, p. S93-S97

Published by Wiley-Liss, Inc.
DOI 10.1002/mds.5569

DA Agonists - Non-Ergot derivatives: Pramipexole

BASIC PHARMACOLOGY

MECHANISM OF ACTION

Pramipexole is an orally active, non-ergoline, dopamine agonist.[1] In vitro and in vivo studies have shown that it is a full agonist for the D2 receptor subfamily, with preferential affinity for the D3 receptor subtype.[2] Pramipexole also has some D2 affinity, but has a very low affinity for other non-DA receptors, except some effects on alpha-2 receptors. Pramipexole produces an improvement in Parkinson-like signs in MPTP-treated primates. Like other D2 agonists, pramipexole decreases prolactin secretion and induces nausea and hypotension in healthy volunteers. Pramipexole has been shown to have potential neuroprotective effects in vitro and in vivo.[3] Putative antidepressant properties also have been considered for pramipexole.[4]

PHARMACOKINETICS

Pramipexole is rapidly and completely absorbed after oral administration. Its bioavailability is greater than 90%. Maximal plasma concentration (Tmax) is reached within 1 to 3 hours. Pramipexole does not bind significantly to plasma protein. The plasma elimination half-life of pramipexole (T1/2) is about 10 hours. Only 10% of the drug is metabolized, and the main route of elimination is renal, with potential clinical consequences in cases of renal failure. This mode of elimination may account for some pharmacokinetic differences related to age, gender, and potential interaction with drugs like cimetidine.[5]

REVIEW OF CLINICAL STUDIES

PREVENTION OF DISEASE PROGRESSION

One Level-I, L-dopa controlled study was identified that met inclusion criteria.[6]

Parkinson's Disease Study Group (2000)[6]: This study was a randomized, L-dopa controlled, two-year, prospective study of pramipexole monotherapy. One hundred and fifty-one patients were randomized to pramipexole monotherapy and 150 patients received L-dopa. The trial consisted of a 10-week dosage escalation period followed by a 21-month maintenance period. Open-label supplementation with L-dopa was permitted from week 11 until the end of the trial, according to clinical need. The primary outcome variable was defined as time to motor complications (see section on Prevention of Motor Complications). A subset of 82 patients underwent SPECT imaging with Beta-CIT before baseline and immediately before the final study visit. At the end of the trial, subjects allocated to pramipexole were on an average dose of 2.78 mg/d and patients randomized to L-dopa took an average of 406 mg/d. Fifty-three percent of subjects in the pramipexole group required supplemental L-dopa compared with 39% in the L-dopa group (P = 0.02). The dose of open-label supplemental L-dopa was similar in the two treatment groups (264 vs. 252 mg/d), and the average total daily dose of experimental plus supplemental L-dopa in the L-dopa arm was 509 mg/d. The mean (standard deviation) decline in Beta CIT striatal uptake over the 23.5 months did not differ significantly between the two treatment groups and was 20.0% (14.2%) in the pramipexole group compared with 24.8% (14.4%) in the L-dopa group. Caudate and putamen-specific Beta-CIT uptake during the 23.5-month observation period also did not differ between the two treatment groups. These results do not support a neuroprotective role for pramipexole, and therefore the authors conferred that further study was warranted. The rate of decline of Beta-CIT uptake was not different between the two groups at 2 years, but it was 20% less in the pramipexole group than the L-dopa group. The authors are continuing to follow this cohort of patients to observe the course of neuroimaging outcomes at 4 years. This study had a quality score of 95%.

SYMPTOMATIC CONTROL OF PARKINSONISM

MONOTHERAPY

Three Level-I, placebo-controlled studies and one L-dopa controlled study met the selection criteria.

Hubble et al. (1995)[7]: This was a randomized, 9-week, parallel-group, placebo-controlled study conducted in 55 de novo patients with PD (mean age 63 years). Pramipexole was progressively titrated up to 4.5 mg/d. Efficacy was assessed using UPDRS Parts II and III. Results showed that pramipexole induced a greater antiparkinsonian improvement than placebo (mean UPDRS II change from baseline with pramipexole = 5.19 vs. 2.16 with placebo, $p<0.002$; mean UPDRS III change from baseline with pramipexole = 11.97 vs. 8.31 with placebo, NS). Pramipexole was associated with adverse reactions consistent with other DA agonists in this class of drug, including orthostatic hypotension, dizziness, nausea, insomnia, and hallucinations. This study had a quality rating score of 83%.

The Parkinson Study Group (1997)[8]: The effects of four different doses of pramipexole (1.5, 3, 4.5 and 6 mg) vs. placebo were tested in a randomized parallel-group design in 264 de novo patients with PD (mean age approximately 62 years) divided into 5 parallel groups. This study used a 6-week dose-titration period followed by a 4-week maintenance period. The primary outcome variable used to assess efficacy was the change in the total UPDRS score between baseline and week 10. After 10 weeks of treatment, the combined group of pramipexole-treated subjects showed a 20% improvement in motor outcome measurements, which was significantly different compared to placebo (mean changes in total UPDRS: placebo = -0.9, pramipexole 1.5 mg/d = -6.3, pramipexole 3.0 mg/d = -5.9 , pramipexole 4.5 mg/D = -6.5 , pramipexole 6.0 mg/d = -7.0). The same pattern of treatment effects was apparent for the UPDRS motor score and ADL score. An increase in adverse reactions was associated with higher doses of pramipexole

and included nausea, hallucinations, and somnolence, among others. This study had an quality rating score of 95%.

Shannon et al. (1997)[9]: This was a randomized, placebo-controlled, parallel-group study in 335 patients with early PD (mean age 63 years). Pramipexole or placebo was given during a 7-week dose-titration period (up to a maximum dose of 4.5mg/d), followed by a 24-week period of maintenance therapy. The primary endpoints were changes in UPDRS Parts II and III between baseline and the end of the maintenance period. Pramipexole (mean dose 3.8 mg/d) significantly reduced the severity and signs of all PD assessment criteria compared with placebo. The UPDRS ADL decreased with pramipexole from 8.2 at baseline to 6.4 at completion, while it increased with placebo from 8.3 at baseline to 8.7 at completion ($p<0.0001$). Similarly, the UPDRS motor score decreased with pramipexole from 18.8 at baseline to 14.1 at completion, while it increased with placebo from 18.8 at baseline to 20.1 at completion ($p<0.0001$). No clear data are available about the need for L-dopa supplementation, although only one patient in the pramipexole group discontinued treatment for "unsatisfactory therapeutic effect" vs. seven patients in the placebo group. Nausea, insomnia, somnolence, constipation and visual hallucinations were the most frequently observed adverse reactions and were more frequent with pramipexole than with placebo. Visual hallucinations occurred in 10% of the pramipexole-treated patients and in 2% of the placebo-treated patients. Sedation occurred in 18% of the pramipexole-treated patients and in 9% of the placebo-treated patients. This study had an quality rating score of 75%.

Parkinson's Disease Study Group (2000)[6]. This study is described previously (see the section on Prevention of Disease Progression) and will be briefly summarized below. One hundred and fifty-one patients were randomized to pramipexole monotherapy while 150 patients received levodopa. Patients were followed for 21 months and open-label supplementation with L-dopa was permitted. The primary outcome variable was defined as time to motor complications. Among secondary outcome variables, changes in UPDRS scores allow assessment of control of parkinsonism. At the end of the trial, subjects allocated to pramipexole were on an average dose of 2.78 mg/d, and those allocated to L-dopa took an average of 406 mg/d. Fifly-three percent of subjects in the pramipexole group required supplemental L-dopa compared with 39% in the L-dopa group ($P = 0.02$). The dose of open-label supplemental L-dopa was similar in the two treatment groups (264 versus 252 mg/d), the average total daily dose of experimental plus supplemental L-dopa in the L-dopa arm was 509 mg/d. The mean improvement in total UPDRS as well as the motor and ADL subscores from baseline to the end of the study was significantly greater in the L-dopa group compared with patients on pramipexole. Total UPDRS scores decreased by 4.5 points with pramipexole compared to 9.2 points with L-dopa ($P < 0.001$). Similarly motor scores decreased by 3.4 vs. 7.3 points ($P < 0.001$), and ADL scores decreased by 1.1 vs. 2.2 points in the pramipexole vs. L-dopa treatment group ($P = 0.001$). More patients in the pramipexole group reported somnolence, hallucinations, edema as adverse reactions compared with patients in the L-dopa treatment group. Three patients reported falling asleep while driving a car (two in the pramipexole group and one in the L-dopa). Two additional subjects complained of abrupt or sudden onset of drowsiness unrelated to driving (both in the pramipexole treatment group). This study had a quality rating of 95%.

ADJUNCT THERAPY IN L-DOPA-TREATED PATIENTS WITH PD

Early addition in Stable L-dopa-treated Patients with PD

No qualified studies were identified.

Late addition in L-dopa-treated Patients with Motor Fluctuations

Four randomized, double-blind, (Level-I) studies qualified for inclusion in this review. All studies included patients with advanced PD that were treated with L-dopa and complained of motor fluctuations. All four studies were placebo-controlled studies, but one included a bromocriptine arm as well.

Lieberman et al. (1997)[10]: This large, randomized, parallel-group, placebo-controlled trial enrolled 360 patients with PD and motor fluctuations. There was a 7-week increasing-dose phase (up to 4-5 mg/d), and a maintenance phase that lasted up to 6 months. The two primary endpoints for efficacy were the change from baseline to final maintenance visit of "on/off" ratings of UPDRS II and III. With pramipexole, the mean improvement of UPDRS II average of "on" and "off" was 20% vs. 4% with placebo ($p<0.0001$) with a concomitant reduction in L-dopa dosage of 27% vs. 5% with placebo ($p<0.0001$), respectively. Major adverse reactions were reported more common in the pramipexole than in the placebo group and included dyskinesia, orthostatic hypotension, dizziness, insomnia, hallucinations, and nausea. This study had an overall quality rating score of 86%.

Guttman et al. (1998)[11] (see also section on Bromocriptine): This was a large, parallel-group, 9-month study enrolling 247 patients with PD with motor fluctuations. Participants were randomized into 3 groups: placebo, pramipexole (up to 4-5 mg/d), and bromocriptine (up to 30 mg/d). The primary endpoints were the UPDRS II (average "on" and "off" scores) and UPDRS III. Secondary endpoints included quality of life scales among others. The median percent change in UPDRS II from baseline was -27% with pramipexole, -14% with bromocriptine, and -5% with placebo. Both pramipexole and bromocriptine were significantly more effective than placebo (pramipexole vs. placebo, $p<0.0002$; bromocriptine vs. placebo, $p<0.02$). The median percent change in UPDRS III from baseline was -35% with pramipexole, -24% with bromocriptine and -6% with placebo. Both pramipexole and bromocriptine were significantly more effective than placebo ($p<0.001$ and $p<0.01$, respectively). Although there was a trend for pramipexole to be more potent than bromocriptine, this difference did not reach significance (this study was not powered for between-group comparisons for active treatments). Both DA agonists improved significantly several dimensions of quality of life scales. Most common adverse reactions included dyskinesia, dizziness, orthostatic hypotension, nausea, insomnia, hallucinations, and headache. Adverse reactions were more frequent in the active groups than in the placebo groups, with no differences between pramipexole and bromocriptine. This study had an overall quality score of 98%.

Wermuth et al. (1998)[12]: This was an 11-week, randomized, parallel-group, double-blind, placebo-controlled study conducted in 69 patients complaining of dyskinesia, "on/off" fluctuations, dystonia, akinesia or end-of-dose deterioration (mean age 62 years). Patients were evaluated using UPDRS. The primary outcome was the absolute change in total score from baseline to the end of the

maintenance period, but no specific indications were given regarding assessment time vs. drug intake time. Pramipexole was more effective than placebo, with a significant reduction in the total score of the UPDRS at the end of the study (-16.9 vs. -9.0 respectively, p<0.02). Dyskinesia scores were not reported to be exacerbated. L-dopa dose was reduced by -151 mg/d with pramipexole and -11 mg/d with placebo (NS). The most common adverse reactions were dizziness, insomnia, nausea, somnolence, and postural hypotension. This study had an overall quality rating score of 88%.

Pinter et al. (1999)[13]: This study reported the effects of pramipexole in an 11-week, randomized, parallel, double-blind, placebo-controlled trial conducted in 78 patients with motor fluctuations (mean age = 60 years). The primary endpoint was the change in the UPDRS total score at the end of the maintenance interval compared with baseline. Secondary endpoints were changes in UPDRS subscores (among others). The mean UPDRS total score (2 hours after drug in take) improved significantly more with pramipexole, than with placebo (-20.1 [i.e.-37,3%] versus -5.9 [i.e. -13.1%]; p<0.0002). Most other endpoints also favored pramipexole vs. placebo. Main adverse reactions were usually more frequent with pramipexole than placebo and included fatigue, dyskinesia, agitation, vivid dreams, postural hypotension, and nausea. Somnolence was reported in more placebo-treated patients (9%) than in pramipexole-treated patients (6%). This study had an overall quality score of 90%.

PREVENTION OF MOTOR COMPLICATIONS

One Level-I L-dopa-controlled study was identified.

Parkinson's Disease Study Group (2000)[6]: This was a randomized, L-dopa-controlled, 2-year, prospective study of pramipexole monotherapy (previously reviewed in the section on Prevention of Disease Progression, and also in Control of Parkinsonism-Monotherapy). Briefly, 151 patients were randomized to pramipexole monotherapy and 150 patients received L-dopa. Open-label supplementation with L-dopa was permitted. The primary outcome variable was defined as time from randomization until the first occurrence of any of the three pre-specified motor complications: wearing-off, dyskinesias, or "on/off" fluctuations. At the end of the trial, patients randomized to pramipexole treatment were on an average dose of 2.78 mg/d and patients randomized to L-dopa took an average of 406 mg/d. Fifty three percent of subjects in the pramipexole group required supplemental L-dopa compared with 39% in the L-dopa group (P = 0.02). The dose of open-label supplemental L-dopa was almost identical in the two arms (264 vs. 252 mg/d), the average total daily dose of experimental plus supplemental L-dopa in the L-dopa arm was 509 mg/d. There was a highly statistically significant difference (P < 0.001) in the percentages of patients reaching the primary endpoint by the end of the study (23.5 months): 51% in the L-dopa group vs. 28% of subjects in the pramipexole group (former on 100 mg more L-dopa per day with greater efficacy on parkinsonism). Wearing off was observed in 36/151 pramipexole-treated patients and 57/150 L-dopa treated patients. Dyskinesias were observed in 15/151 pramipexole-treated patients and 45/150 L-dopa treated patients. This study had a quality score of 95%.

CONTROL OF MOTOR COMPLICATIONS

Four randomized double-blind, (Level I) studies met the inclusion criteria for review. These four trials are the same as those reviewed previously (see section on Symptomatic Control of Parkinsonism: Adjunct to L-dopa), and therefore, only the relevant endpoints regarding specific control of motor complications is reviewed below.

Lieberman et al. (1997)[10]: This 6- month, randomized, parallel-group, placebo-controlled trial enrolled 360 patients with motor fluctuations. Secondary endpoints included percentage of "off" period (as measured using patient diaries). Time spent "off" decreased by 31% with pramipexole vs. 7% with placebo (p<0.001) with a concomitant reduction in L-dopa dosage of 27% vs. 5% with placebo (p<0.0001), respectively. This study had an overall quality score of 86%.

Guttman et al. (1998)[11] (see also section on Bromocriptine): This was a parallel group, 9-month study enrolling 247 patients with PD with motor fluctuations. Patients were randomized into one of three treatment arms: placebo, pramipexole (up to 4-5 mg/d), and bromocriptine (up to 30 mg/d). Secondary endpoints included the frequency of "on" and "off" times on patient's diary records (among others). Both agonists reduced time spent "off", but the difference reached statistical significance vs. placebo for pramipexole (-15%, p<0.007) but not for bromocriptine vs. placebo. This study had an overall quality score of 98%.

Wermuth et al. (1998)[12]: This was an 11-week, randomized, parallel-group, double-blind, placebo-controlled study conducted in 69 patients complaining of dyskinesia, "on-off" fluctuations, dystonia, akinesia, or end-of-dose deterioration. Patients were provided with diaries to record "off" and "on" periods. The percentage of "off" time during waking hours decreased in the pramipexole group from 36% to 26% and in the placebo group from 43% to 40% (no statistics provided). Dyskinesia scores were not reported to be exacerbated. This study had an overall quality score of 88%.

Pinter et al. (1999)[13]: This study reported the effects of pramipexole in an 11-week, randomized, parallel-group, double-blind, placebo-controlled trial conducted in 78 patients with motor fluctuations. Secondary endpoints were, among others, changes in dyskinesia scores and patients diaries. With pramipexole, time spent "off" decreased from 33% to 21% during the waking hours, whereas this change was smaller in the placebo group (33% to 35%). No significant effect on dyskinesia was observed. This study had an overall quality score of 90%.

REVIEW OF SAFETY

According to published clinical trials, the use of pramipexole is associated with the characteristic adverse reactions of DA agonists, as a class, including gastrointestinal, cardiovascular, and neuropsychiatric effects. Pramipexole has been reported to induce leg edema (similar to other dopamine agonists).[14] When compared with bromocriptine[11] , both pramipexole and bromocriptine were found to have similar safety profiles. In this study, psychosis did not appear to be less frequent in pramipexole-treated patients (although theoretically, this could have been expected due to the relative selectivity of this compound on dopamine receptors and its lack of effect on 5HT receptors).[11] Switching from another DA agonist to pramipexole on a rapid schedule seems well tolerated, with no special adverse reactions observed.[15]

When used as an adjunct therapy to L-dopa, pramipexole increases abnormal movements, which can be addressed clinically by a concomitant partial decrease of L-dopa dosing. When used early, pramipexole reduces the risk of long-term motor complication, as compared with levodopa early monotherapy.[6]

Recent post-marketing case-reports of sudden and irresistible

"sleep attacks" have led some drug agencies/authorities to reconsider the benefit/risk ratio of this pramipexole.[16,17] In some countries, the risk of falling asleep while driving have prompted the authorities to advise patients that they should not drive while taking pramipexole. In other countries (eg. England), this risk is considered as acceptable by the Driving Agency, and doctors are simply asked to inform their patients of the risk of such sleep episodes. Similar cases also have been reported with other dopamine agonists, including ropinirole, pergolide, bromocriptine, piribedil.[16,18-20] Similar episodes also have been reported in patients with PD taking L-dopa monotherapy.[21] Further studies evaluating the main risk factors for such episodes are required before definite conclusions can be drawn.

The occurrence of fibrosis has not yet been reported with pramipexole, which is in agreement with its non-ergot profile. However, it is too early to conclude on the incidence of this adverse reaction, and such a rare adverse event can only be detected and studied in large, long-term term studies and in post-marketing surveys.

Pramipexole has been available commercially for a short time; therefore, information on mortality is not available.

CONCLUSIONS

About 800 patients with PD have been treated with pramipexole in a number of Level-I trials, with a maximum duration of follow-up, under controlled conditions, of 2 years. Most of the studies were done recently and have a high quality rating.

EFFICACY

PREVENTION OF DISEASE PROGRESSION

Because the only published report failed to show statistical significance (as measured using a surrogate marker, in a small study, resulting in an insignificant trend[6]), there is INSUFFICIENT EVIDENCE to conclude on the efficacy of pramipexole regarding the prevention of disease progression in PD. Data on longer follow-up are expected.

SYMPTOMATIC CONTROL OF PARKINSONISM

Monotherapy or Early Combination

Based on multiple placebo-controlled, Level-I trials, pramipexole used as monotherapy in de novo patients with PD is EFFICACIOUS in controlling motor symptoms over the first 2 years of treatment[6-9]. Longer, controlled, follow-up studies (over two years) are not yet available.

Adjunct Therapy in L-dopa-treated Patients with PD

In advanced L-dopa-treated PD patients suffering from motor fluctuations, pramipexole has been studied extensively and is EFFICACIOUS as adjunct therapy in patients with Parkinson's disease receiving L-dopa therapy. Pramipexole was superior to placebo in a number of Level-I studies[10-13]. It improved motor disability in "on" and "off" conditions and reduced L-dopa daily dose by an average of one third. In the single active comparator trial, pramipexole was only marginally (not statistically significant) more effective than bromocriptine, and the clinical relevance of this minimal difference is not known.[11]

PREVENTION OF MOTOR COMPLICATIONS

Based on one, large (2-year), L-dopa controlled study[6], pramipexole is EFFICACIOUS in reducing the risk of motor complications in patients with PD though with lower efficacy than seen in the L-dopa arm to control parkinsonism (a 2-year extension study is ongoing).

CONTROL OF MOTOR COMPLICATIONS

Based on several placebo-controlled trials[10-13], pramipexole is EFFICACIOUS in patients with advanced PD with motor complications. Pramipexole reduces time spent "off" by 1 to 2 hours.

SAFETY

The risk of using pramipexole is considered ACCEPTABLE, WITHOUT SPECIALIZED MONITORING. However, due to concerns about hypersomnolence and inappropriate episodes of daytime somnolence ("sleep attacks"), clinical monitoring of daytime somnolence is warranted.

Pramipexole induces the usual dopamine adverse reactions that are reported with other dopamine agonists (including nausea, vomiting, hypotension, dyskinesia, and hallucinations). From the available published clinical trials, there is no evidence that the incidence of adverse events associated with pramipexole is either higher or lower as compared to other dopamine agonist treatments, but concerns about hypersomnolence require further investigation.

IMPLICATIONS FOR CLINICAL PRACTICE

There is sufficient evidence to conclude that pramipexole is CLINICALLY USEFUL for the treatment of early and advanced PD, although long-term benefit of its use in early de novo patients remains to be determined. It has not proved to be significantly more effective or to induce fewer adverse events than bromocriptine. The usual daily dose prescribed in PD patient is 2 to 4.5 mg/d. Compared with other agonists, pramipexole dose titration is relatively simple and rapid (3 doses are proposed: 1.5, 3 and 4.5 mg/d, with a t.i.d. regimen).

In some countries, concerns about the incidence of "sleep attacks" have been raised. Importantly, there are different regulations worldwide, with each country carrying individual recommended warnings for treatment. In the USA and England, for example, patients must simply be informed of the risk of somnolence. In other countries, like France, patients on pramipexole have to be advised not to drive because of the risk of hypersomnolence.

IMPLICATIONS FOR CLINICAL RESEARCH

- Randomized, controlled trials testing the efficacy and tolerability of pramipexole should be done including comparative trials to other dopamine agonists and to other antiparkinsonian agents such as MAO-B and COMT inhibitors.
- Additional studies are needed concerning the incidence of sleep attacks in patients taking pramipexole. The relative frequency of this adverse reaction needs to be compared to other treatments in this class of medication.
- Long-term studies that specifically investigate the low propensity of pramipexole for inducing dyskinesia in L-dopa-naïve (non-primed) patients with PD are needed.
- The role of pramipexole on prevention of disease progression (or neuroprotective effects) needs to be further studied.
- Future long-term, follow-up studies (10 years) are necessary to clearly assess the usefulness of the early use of pramipexole on patient's functioning, life expectancy, and quality of life.
- Pharmacoeconomic studies are needed to assess the benefits of this relatively expensive drug compared with less expensive DA

agonists (eg, older medications like bromocriptine).

• The effects of pramipexole on non-motor symptoms, like depression, should be tested in clinical trials.

REFERENCES

1. Dooley M, Markham A. Pramipexole. A review of its use in the management of early and advanced Parkinson's disease. Drugs & Aging 1998;12:495-514.
2. Piercey MF. Pharmacology of pramipexole, a dopamine D3-preferring agonist useful in treating Parkinson's disease. Clin Neuropharmacol 1998;21:141-151.
3. Sethy VH, Wu H, Oostveen JA, Hall ED. Neuroprotective effects of the dopamine agonists pramipexole and bromocriptine in 3-acetylpyridine-treated rats. Brain Research 1997;754:181-186.
4. Szegedi A, Hillert A, Wetzel H, Klieser E, Gaebel W, Benkert O. Pramipexole, a dopamine agonist, in major depression: antidepressant effects and tolerability in an open-label study with multiple doses. Clin Neuropharmacol 1997;20(suppl 1):S36-S45.
5. Wright CE, Sisson TL, Ichhpurani AK, Peters GR. Steady-state pharmacokinetic properties of pramipexole in healthy volunteers. J Clin Pharmacol 1997;37:520-525.
6. Parkinson Study Group. Pramipexole vs. levodopa as initial treatment for Parkinson's disease: A randomized controlled trial. JAMA 2000;284:1931-1938.
7. Hubble JP, Koller WC, Cutler NR, et al. Pramipexole in patients with early Parkinson's disease. Clin Neuropharmacol 1995;18:338-347.
8. Parkinson Study Group. Safety and efficacy of pramipexole in early Parkinson disease. A randomized dose-ranging study. JAMA 1997;278:125-30
9. Shannon KM, Bennett JP, Friedman JH, for the Pramipexole Study Group. Efficacy of pramipexole, a novel dopamine agonist, as monotherapy in mild to moderate Parkinson's disease. Neurology 1997;49:724-728.
10. Lieberman A, Ranhosky A, Korts D. Clinical evaluation of pramipexole in advanced Parkinson's disease : results of a double-blind, placebo-controlled, parallel-group study. Neurology 1997;49:162-168.
11. Guttman M, and the International Pramipexole-Bromocriptine Study Group. Double-blind comparison of pramipexole and bromocriptine treatment with placebo in advanced Parkinson's disease. Neurology 1997;49:1060-1065.
12. Wermuth L, and The Danish Pramipexole Study Group. A double-blind, placebo-controlled, randomized, multi-center study of pramipexole in advanced Parkinson's disease. Eur J Neurol 1998;5:235-242.
13. Pinter MM, Pogarell O, Oertel WH. Efficacy, safety, and tolerance of the non-ergoline dopamine agonist pramipexole in the treatment of advanced Parkinson's disease: a double-blind, placebo controlled, randomized, multicentre study. J Neurol Neurosurg Psychiatry 1999;66:436-441.
14. Tan EK, Ondo W. Clinical characteristics of pramipexole-induced peripheral edema. Arch Neurol 2000;57:729-732.
15. Goetz CG, Blasucci L, Stebbins GT. Switching dopamine agonist in advanced Parkinson's disease. Is rapid titration preferable to slow ? Neurology 1999;52:1227-1229.
16. Frucht S, Rogers JD, Greene PE, Gordon MS, Fahn S. Falling asleep at the wheel motor vehible mishaps in persons taking pramipexole and ropinirole. Neurology 1999;52:1908-1910.
17. Hauser RA, Gauger L, Anderson WM, Zesiewicz TA. Pramipexole-induced somnolence and episodes of daytime sleep. Mov Disord 2000;15:658-663.
18. Ferreira JJ, Desboeuf K, Galitzky M, Thalamas C, Brefel-Courbon C, Fabre N, Senard JM, Montastruc JL, et al. "Sleep attacks" and Parkinson's disease : results of a questionnaire survey in a movement disorders outpatient clinic. Mov Disord 2000;15(suppl 3):P897.
19. Ferreira JJ, Galitzky M, Montastruc JL, Rascol O. Sleep attacks and Parkinson's disease treatment. Lancet 2000;355:1333-1334.
20. Schapira AH. Sleep attack (sleep episodes) with pergolide. Lancet 2000;355:1332-1333.
21. Ferreira JJ, Galitzky M, Brefel-Courbon C, Senard JM, Montastruc JL, Castro-Caldas A, Rascol O, et al. "Sleep attacks" as an adverse drug reaction of levodopa monotherapy. Mov Disord 2000;15(suppl 3):P661.

BIBLIOGRAPHY - EXCLUDED FROM ANALYSIS (REASON FOR EXCLUSION)

Guttan M, International Pramipexole-Bromocriptine Study Group. Double-blind, randomized, placebo-controlled study to compare safety, tolerance and efficacy of Pramipexole and Bromocriptine in advanced Parkinson's disease. Neurology 1997;48:A269. (Abstract)

Hubble J, Cutler N, Friedman J, Goetz C, Ranhosky A, Korts D. Pramipexole in early Parkinson's disease: a single-blind, placebo-controlled, randomized multicenter safety and efficacy study. Can J Neurological Sci 1993;20S:S152. (Abstract)

Künig G, Pogarell O, Mšller C, Delf M, Oertel WH. Pramipexole, a nonergot dopamine agonist, is effective against rest tremor intermediate to advanced Parkinson's disease. Clin Neuropharmacol 1999;22:301-305. (< 20 patients per treatment group)

Molho ES, Factor SA, Weiner WJ, et al. The use of pramipexole, a novel dopamine (DA) agonist, in advanced Parkinson's disease. J Neural Transm 1995;45(suppl):225-230. (< 20 patients per treatment group)

Pinter MM, Arnold G, Albani L, et al. Pramipexole in advanced Parkinson's disease: a double blind, placebo controlled, randomized multicentre trial. Can J Neurological Sci 1993;20S:S234. (Abstract)

Sethy VH, Ellerbroock BR, Wu H. U-95666E: a potential anti-parkinsonian drug with anxiolytic activity. Prog Neuropsychopharmacol Biol Psychiatry 1997;21:873-883. (Non-antiparkinsonian endpoint)

Wermuth L. Pramipexole - a new dopamine agonist: a double blind placebo controlled randomized study in advanced Parkinson's disease. Can J Neurological Sci 1993;20S:S238. (Abstract)

Willingham DB, Bennett JP, Greenberg NJ, Rost-Ruffner E. The effect of a D2-specific dopamine agonist (Pramipexole) on response time in early Parkinson's disease patients. Psychobiology 1997;25:321-326. (< 20 patients per treatment group)

Movement Disorders
Vol. 17, Suppl. 4, 2002, p. S98-S102

Published by Wiley-Liss, Inc.
DOI 10.1002/mds.5570

DA Agonists - Non-Ergot derivatives: Ropinirole

BASIC PHARMACOLOGY

MECHANISM OF ACTION

Ropinirole is a selective dopamine (DA) agonist with non-ergoline structure.[1,2] It interacts with D2-like receptors in vitro and in vivo, showing greatest affinity for the D3 subtype, with little or no interaction with other neurotransmitter receptors. Ropinirole produces alterations in motor behavior indicative of antiparkinsonian activity, including contralateral rotation in 6-hydroxydopamine-lesioned rats and reversal of disability on MPTP-treated primates. The administration of ropinirole over a 4-week period in L-dopa-naive MPTP-treated marmosets induces significantly less dyskinesia than observed with L-dopa treatment over the same period of time with comparable efficacy.[3] As expected from any effective D2 agonist, clinical pharmacology studies have shown ropinirole to lower serum prolactin levels, and to induce symptomatic postural hypotension, nausea and vomiting. In vitro, ropinirole illustrates some potential neuroprotective properties.[4]

PHARMACOKINETICS

After oral administration, ropinirole is rapidly absorbed, and has a median Tmax of about 1.4 hours after dosing. It has a bioavailability of 46 % and a mean elimination half-life of about 6 hours. Ropinirole is recommended as a t.i.d. dosing regimen. Plasma protein binding is low and concentration independent. Ropinirole is metabolized predominantly by the liver. The drug is oxidized, mainly through the cytochrome P450 1A2 pathway. Drug interactions (macrolides, theophilline) and hepatic insufficiency are, therefore, theoretically possible, although no such events have been reported in the clinical literature.

REVIEW OF CLINICAL STUDIES

PREVENTION OF DISEASE PROGRESSION

No qualified studies were identified that assessed the efficacy of ropinirole in the prevention of disease progression. A large, 2-year, L-dopa-controlled study in de novo patients with PD, is ongoing and is assessing the effect of ropinirole on disease progression relative to L-dopa, as measured using both 18F-dopa PET and clinical ratings as endpoints.

SYMPTOMATIC CONTROL OF PARKINSONISM

MONOTHERAPY

Six randomized (Level-I), double-blind studies have been reported that qualified for this review. These included two placebo-controlled parallel trials[5,6], one L-dopa-controlled study with a 6-month planned interim analysis[7] and a 5-year final report[8], and one bromocriptine-controlled study with a 6-month planned interim analysis[9] and a 3-year final report.[10]

Adler et al. (1997)[5]: This randomized, double-blind, placebo-controlled, parallel-group, 6-month study included 241 patients with early PD and limited or no prior dopaminergic therapy (mean age 63 years). This study was stratified for concomitant use of selegiline. L-dopa open-label supplementation was allowed if study medication was insufficient to control parkinsonian symptoms at the highest tolerated dose. Primary efficacy endpoint was the percentage improvement in the UPDRS motor score. Secondary efficacy variables included the proportion of patients with a 30% reduction in UPDRS motor score ("responders"), patients with scores of 1 (very much improved) or 2 (much improved) on a CGI score, and the proportion of patients requiring L-dopa supplementation. Ropinirole (16 mg/d) was superior to placebo on all different efficacy assessment endpoints. UPDRS motor score improved by -24% with ropinirole (from 17.9 at baseline to 13.4 at endpoint) and deteriorated by +3% with placebo (from 17.7 at baseline to 17.9 at endpoint). There were 47% responders with ropinirole and 20% with placebo (OR =4.45 [95%CI : 2.26-8.78]). Thirty-three percent vs. 12% of patients were "very much" or "much improved" on CGI (OR =4.06 [95%CI : 2.00-8.22]). By the end of the study, 11% of the ropinirole-treated patients required L-dopa supplement vs. 29% of the placebo-treated patients (OR =0.30 [95%CI : 0.14-0.61]). Adverse reactions common to other DA agonists were reported in this trial and included nausea, dizziness, somnolence, and headache, which were generally more frequent with ropinirole than placebo. The subjects who completed this study were included in a 6-month, double-blind, extension study[11] that showed superiority of ropinirole was maintained over placebo during this period. Forty four percent of the patients completed the 1-year study without the need for L-dopa. This study had a quality score of 88%.

Brooks et al. (1998)[6]: This was a randomized, parallel-group, placebo-controlled, 3-month study conducted in 63 de novo patients with PD requiring dopaminergic treatment (no previous dopaminergic treatment lasting for more than 6 months was allowed and had to be withdrawn before entering into the trial). Randomization ratio was 2:1 for ropinirole:placebo. Clinical status was assessed using the UPDRS III (motor examination part used as the primary endpoint), a CGE, and a finger-tapping score. At endpoint, UPDRS III improved by 43% in the ropinirole group and by 21% in the placebo group (p = 0.018). Other outcome measures were also in favor of ropinirole. Adverse reactions were similar to those reported for other DA agonists and included nausea, somnolence and dizziness. This study had an overall quality score of 90%.

Rascol et al. (1998)[7] : This was a 6-month planned analysis of a 5-year, randomized (ratio 2:1), L-dopa-controlled study conducted in 268 patients with early PD requiring dopaminergic treatment (no previous dopaminergic treatment lasting more than 6 weeks was allowed and had to be withdrawn 2 weeks before entering

into the trial). As it was anticipated that ropinirole monotherapy might progressively exhibit a waning effect, investigators were allowed add-on L-dopa therapy (as an open-label treatment) in both treatment groups, if the maximum allowed dose (24 mg/d) or maximum tolerated of ropinirole dose did not achieve sufficient control of symptoms. Investigators were instructed to try to maintain monotherapy by a progressive up-titration of the study drugs as much as possible. Efficacy parameters were the same as those previously described.[5] The mean daily dose of ropinirole was 10mg/d in the ropinirole arm while that of L-dopa was 460 mg/d in the L-dopa arm. The results showed that L-dopa was significantly more efficacious than ropinirole: after 6 months, UPDRS motor score improved by -32% with ropinirole (from 21.5 at baseline to 15.7 at endpoint) and by -44% with L-dopa (from 21.7 at baseline to 13.3 at endpoint) ($p<0.05$). The responder prevalence was 48% with ropinirole and 58% with levodopa (NS). CGI analysis did not reveal between-group differences for patients with Hoehn and Yahr stages I-II, but there was a significant difference in favor of L-dopa in the patients with Hoehn and Yahr Stages II.5 and III at baseline (OR 0.11; 95%CI [0.04-0.35]). However, the amplitude of these differences is small. By the end of the 6-month study, 4% of the ropinirole-treated patients required L-dopa supplement vs.1% of the L-dopa-treated patients (NS). Both treatments had the same adverse reaction profile (nausea, insomnia, somnolence, dizziness, dyspepsia, headache, vomiting). Psychiatric symptoms were seen in 8% of the ropinirole-treated patients and in 5% of L-dopa-treated patients. This study had an overall quality score of 90%.

Korczyn et al. (1998)[8]: This was a planned interim analysis at 6-months from a 3-year study. Three hundred and thirty-five patients with early PD were enrolled in this double-blind, bromocriptine-controlled, parallel-group trial. As in the previous trial[7], open-label L-dopa supplementation was allowed if needed. Efficacy endpoints were the same as those previously described.[5,7] At 6 months, the mean dose of ropinirole was 8.3 mg/d, which was slightly, but significantly, more effective on reducing parkinsonian disability as compared to bromocriptine (16.8 mg/d) (UPDRS% reduction: ropinirole = -35% vs. bromocriptine = -27%, $p<0.05$). Stratification for selegiline showed that there was a significant treatment-interaction with selegiline, and the difference in favor of ropinirole was present in the patients who were not on selegiline. Secondary motor efficacy variables showed a similar trend in favor of ropinirole: overall, regardless of selegiline stratification, there were 58% responders with ropinirole and 43% with bromocriptine (OR 0.93; 95%CI [1.29 -2.89]). Overall, CGI responder analysis showed the same trend (48% vs. 40%), but the difference was statistically significant only in the non-selegiline-treated patients. However, the amplitude of these differences was small. By the end of the 6-month study, 7% of the ropinirole-treated patients required L-dopa supplement vs. 11% of the bromocriptine-treated patients (NS). Adverse reactions caused premature withdrawal in 5% of the ropinirole-treated patients and in 10% of the bromocriptine-treated patients. The list of adverse reactions reported with both drugs is very typical of all dopaminergic agents (nausea: ropinirole 36%, bromocriptine 20%; vomiting: ropinirole 10%, bromocriptine 5%; postural hypotension: ropinirole 7%, bromocriptine 9%; psychiatric symptoms: ropinirole 7%, bromocriptine 5%; and somnolence: ropinirole 6%, bromocriptine 7%). This study had a quality rating score of 89%.

Korzyn et al. (1999)[9]: This was the final 3-year analysis of the previously reported study (see above).[8] Approximately one third of the patients withdrew from the trial at 3 years. Comparable differences between treatments were also observed at the final endpoint assessments in the patients who completed the trial (mean doses: ropinirole 12mg/d, bromocriptine 24 mg/d). Specifically, UPDRS II (ADL; ropinirole = 5.83 vs. bromocriptine = 7.28, $p<0.01$) and UPDRS III (motor examination [percentage change]: ropinirole = -31% vs. bromocriptine = -22%, NS). Although statistically significant, the difference between both groups remained small (treatment difference 1.46 points for ADL; the clinical relevance of this difference is not clear). After 3 years of treatment, about one third of the patients still in the trial received either agonist as monotherapy without the need for L-dopa supplementation. Adverse reactions were quite similar in both groups, including: nausea, vomiting, dizziness, hypotension and psychiatric symptoms. Long-term motor complications were similarly and remarkably infrequent in both treatment groups (see section below on Prevention of Motor Complications). This study had an overall quality rating score of 76%.

Rascol et al. (2000)[10]: This was the final analysis of a 5-year, randomized, double-blind, parallel-group, L-dopa-controlled study conducted in 268 de novo patients with PD (see above for the 6-month interim analysis)[7]. The primary outcome was the occurrence of dyskinesia, but antiparkinsonian efficacy was also recorded using UPDRS II (ADL) and III (motor examination). At the end of the study, the mean dose of ropinirole was 16.5 mg/d (plus 427 mg/d of complementary L-dopa in 66% of the patients) and 753 mg/d of L-dopa (including open-label supplement in 36% of the patients). There was no significant difference between the 2 groups in the mean changes from baseline in ADL scores among the patients who completed the study (1.6 worsening with ropinirole treatment vs. 0.0 worsening with L-dopa therapy; NS). However, there was a slight, but significant difference in favor of L-dopa for the motor examination scores (0.8 with ropinirole vs. 4.8 with L-dopa, [4.48; 95%CI, 1.25-7.72, $p<0,01$]). Considering the small amplitude of the observed difference in motor score, the absence of significant difference in ADL, and the strong power of the trial due to large number of patients, the antiparkinsonian efficacy of L-dopa monotherapy and that of ropinirole (supplemented when needed by low doses of L-dopa) the difference on motor examination scores was not regarded as clinically relevant. Classical dopaminergic adverse reactions were reported in both treatment groups, including nausea, somnolence, insomnia, dizziness, hallucination, vomiting, and postural hypotension. Hallucinations were more frequent with ropinirole than L-dopa (17% vs. 6%, respectively), but severe hallucinations leading to withdrawal from the trial were infrequent in both groups (4% vs. 2%, respectively). This study had an overall quality score of 90%.

ADJUNCT THERAPY IN L-DOPA-TREATED PATIENTS WITH PD

No Level-I study qualified for this review since the two published trials conducted in advanced L-dopa-treated patients only assessed time spent "off" and/or reduction in L-dopa daily dose.[12,13]

PREVENTION OF MOTOR COMPLICATIONS

Two Level-I, long-term studies reported on the occurrence of motor complications in de novo patients with PD. These studies[9,10] have already been previously described in the section "Control of motor symptoms: Monotherapy". Therefore, only relevant data for

prevention of motor complications will be summarized in this section.

Rascol et al. (2000)[10]: This was a 5-year, randomized, double-blind, parallel-group, L-dopa-controlled study conducted in 268 de novo PD patients. The primary outcome was the occurrence of dyskinesia assessed using item 32 ("duration: what proportion of the waking day are dyskinesia present ?") of the UPDRS Part IV. Other outcome measurements were "disabling dyskinesia" defined as a score of 1 or more on items 32 and 33 ("how disabling are the dyskinesia") of the UPDRS IV. Wearing-off and freezing were also monitored using the corresponding items of the UPDRS. The analysis of time to dyskinesia showed a significant difference in favor of ropinirole (hazard ratio for remaining free of dyskinesia, 2.82; 95% CI, 1.78-4.44, p<0.001). At 5 year, the cumulative incidence of dyskinesia was 20% with ropinirole and 45% with L-dopa. "Disabling" dyskinesia was also less frequent in the ropinirole group vs. L-dopa group (hazard ratio for remaining free of dyskinesia, 3.02; 95% CI, 1.52-6.02, p=0.002). At 5 years, before L-dopa supplementation, dyskinesia was extremely uncommon in the ropinirole group (5%) as compared with the L-dopa-treated patients (36%). Wearing-off was less frequent on ropinirole than L-dopa, but the difference was less striking than for dyskinesia and non-significant. No effect was observed on freezing when walking. This study had a quality score of 90%.

Korczyn et al. (1999)[9]: This was a 3-year study conducted in 335 patients with early PD enrolled in a double-blind, bromocriptine-controlled, parallel-group trial. Dyskinesia was assessed using the complications of therapy section (Part IV) of the UPDRS or reported as adverse reactions. Dyskinesia developed only in a minority of patients after 3 years of follow-up, regardless of L-dopa supplementation: 7.7% patients in the ropinirole group and 7.2 % in the bromocriptine-treated patients. There was no significant difference in the occurrence of dyskinesia between the two groups (p=0.84). This study had a quality rating score of 76%.

CONTROL OF MOTOR COMPLICATIONS

Two randomized, double-blind, placebo-controlled (Level-I) studies qualified for this review.

Rascol et al. (1996)[12]: This 3-month, randomized, placebo-controlled, parallel study was conducted in 46 L-dopa-treated patients with PD with motor fluctuations. Ropinirole was used b.i.d. (recommended daily dosing regimen is usually t.i.d.). Drug efficacy was assessed using percentage of awake time spent "off" using patients' diaries, and a clinical global evaluation made by the investigator (CGE). At the dose of 3.3 mg/d, ropinirole decreased time spent "off" by 44% (from 47% at baseline to 27% at endpoint) while placebo had a smaller effect of 24% (from 44% at baseline to 34% at endpoint). This difference did not reach statistical significance in the "intent-to-treat population" (ITT) analysis (p=0.085), but did reach statistical difference in the in the "efficacy-evaluable population" (p=0.039). This was probably related to an insufficient power of the trial due to the small number of patients. CGE analysis was in favor of ropinirole in the ITT analysis (85% improvers vs. 42% on placebo, p=0.012). The main adverse reactions were more frequently reported on ropinirole and included postural hypotension, dizziness, increased dyskinesia, somnolence, headache, and nausea. This study had an overall quality score of 75%.

Lieberman et al. (1998)[13]: This was a randomized, parallel-group, double-blind, placebo-controlled 6-months study conducted in 149 L-dopa-treated patients with PD who had motor fluctuations (mean age not given). The primary endpoint of this trial was defined as the number of patients who achieved a 20% or greater decrease in L-dopa dose and a 20% or greater reduction in the percentage of time spent "off" between baseline and final visit, as monitored using patients diaries. The proportion of patients "improved" on a CGI was also assessed. The mean daily dose of ropinirole used in this trial is unclear (maximum possible titration: 24 mg/d). Overall, 35% of ropinirole-treated patients and 13% of the placebo-treated patients met the primary end-point (p<0.002). Patients randomized to ropinirole achieved a greater reduction in total L-dopa daily dose (242 mg [-31%] vs. 51 mg [-6%] with placebo, p<0.001). Ropinirole-treated patients had a greater reduction from baseline in percent of hours spent "off" (ropinirole 12% vs. placebo5%; p=0.039). A greater proportion of ropinirole-treated patients improved on the CGI (59% vs. 32%, p=0.002). Adverse reactions associated with ropinirole treatment included digestive effects, cardiovascular effects, and worsening of dyskinesia. This study had a quality score of 75%.

REVIEW OF SAFETY

Ropinirole induces the classical dopaminergic peripheral adverse reactions such as nausea, vomiting, hypotension and psychosis. Such adverse reactions appear to have the same incidence and severity in de novo patients with PD treated with ropinirole and bromocriptine.[10] In spite of its greater selectivity for DA receptors and its lack of effects on serotonergic receptors, ropinirole did not induce less psychosis than bromocriptine. In a large, long-term (5 year), L-dopa-controlled trial[8], gastrointestinal, cardiovascular and neuropsychiatric adverse reactions were reported with the same frequency in both treatment-groups. However, when looking at individual psychiatric adverse reactions, hallucinations were more frequent with ropinirole.

In L-dopa-treated dyskinetic patients with PD, ropinirole, like other DA agonists, exacerbated dyskinesia. Conversely, after a 5-year follow-up, when ropinirole was used as a first-line treatment to which L-dopa could be adjuncted as a supplemental treatment, the incidence of dyskinesia was three times lower than when L-dopa was initiated as monotherapy.

Switching overnight from another agonist to ropinirole does not seem to induce special problems or adverse reactions.[14]

Several case-reports have been published in the literature regarding "sleep attacks" while taking ropinirole thereby raising concerns of this adverse reaction for patients that drive.[15,16] Regulatory warnings for patients receiving DA agonists have been established in Europe instructing patients not to drive while taking these medications. The inference that these sleep episodes are a truly new adverse drug reaction related to the non-ergot agonists remains an item of debate.[21] Similar episodes have also been reported with other agonists[17-19] and even with L-dopa monotherapy.[20] Further epidemiological studies are necessary to define if some agonists or some patients are at greater risk for such an adverse reaction.

There are insufficient long-term, post-marketing surveillance studies to assess the risk of pulmonary fibrosis (observed with most ergot derivatives) in patients treated with ropinirole and other non-ergot compounds.

Due to its recent availability for the treatment of PD, there are no studies available that assess the possible impact of ropinirole on mortality.

CONCLUSIONS

About 500 patients with PD treated with ropinirole have been included in several Level-I clinical studies. These are recent studies and their overall quality rating is usually high. These patients have been followed for at least 3 months and up to 5 years.

EFFICACY

PREVENTION OF DISEASE PROGRESSION

Because there are no published reports on ropinirole in the prevention of disease progression, there is INSUFFICIENT EVIDENCE to determine the efficacy of ropinirole as neuroprotection for patients with PD. The results of an ongoing study will report on possible effects of ropinirole in modifying disease progression by using advanced neuroimaging techniques.

SYMPTOMATIC CONTROL OF PARKINSONISM

Monotherapy

Used as monotherapy in de novo patients with PD, there are several Level-I studies demonstrating that ropinirole is EFFICACIOUS as a symptomatic antiparkinsonian medication.[5-10] After 3 and 5 years of follow-up, when ropinirole was used as first-line monotherapy, about one third of the patients who completed the study could be maintained on monotherapy without the need of L-dopa supplementation. However, this population was less than 20% of those included in the ITT population.

Adjunct Therapy in Advanced L-dopa-treated Patients

In the two Level-I studies[12,13], there were no reported UPDRS scores, even as secondary endpoints. Given the paucity of evidence on specific improvements in antiparkinsonian outcomes, there is INSUFFICIENT DATA to assess the role of ropinirole for symptomatic antiparkinsonian efficacy in advanced L-dopa-treated patients with PD.

PREVENTION OF MOTOR COMPLICATIONS

Used early in de novo patients with PD, ropinirole is EFFICACIOUS in reducing the risk of occurrence of dyskinesia, as evidenced after a 5-year of follow-up study.[8] This effect is less striking on motor fluctuations and no data are available on longer follow-up time periods.

CONTROL OF MOTOR COMPLICATIONS

When used as adjunct therapy to L-dopa in patients with PD and L-dopa-induced motor fluctuations, there are two Level-I studies[12,13] that report ropinirole is EFFICACIOUS in reducing time spent "off." However, it is not clear from the available data what is the actual reduction in time spent "off."

SAFETY

The risk of ropinirole is considered ACCEPTABLE, WITHOUT SPECIALIZED MONITORING. However, due to concerns about hypersomnolence and inappropriate episodes of daytime somnolence ("sleep attacks"), clinical monitoring of daytime somnolence is warranted. Ropinirole induces the usual DA adverse reactions that have been reported with other DA agonists (eg. nausea, vomiting, hypotension, dyskinesia, and hallucinations). From the available published clinical trials, there is no evidence that the incidence of adverse reactions is lower or higher than with any other available agonist, but concerns about hypersomnolence require further investigation.

IMPLICATIONS FOR CLINICAL PRACTICE

There is sufficient evidence to conclude that ropinirole is CLINICALLY USEFUL for the management of early PD and in patients with PD and motor fluctuations. In de novo PD patients, the early use of ropinirole (to which L-dopa is supplemented as a second-line treatment in a majority of patients) reduces the risk of occurrence of dyskinesia over 5 years when compared with L-dopa initial therapy. In patients with early PD, the reported superior efficacy (at 6 months of treatment) of L-dopa over ropinirole, or ropinirole over bromocriptine remains marginal, and the clinical relevance of this difference is unclear.[7,9]. No other ropinirole vs. other dopamine agonists comparative trials have been reported. The mean effective daily doses of ropinirole reported in clinical trials usually range form 8 to 18 mg/d with a t.i.d. regimen.

Special concerns about "sleep attacks" have been raised regarding patients taking ropinirole, and this warrants further investigation. Importantly, there are different regulations/recommendations worldwide with each country carrying individual warnings for treatment. There are differences in the policies for driving in different countries, where in some countries patients must simply be informed of the risk of somnolence, and in other countries, patients on ropinirole are advised not to drive.

IMPLICATIONS FOR CLINICAL RESEARCH

A number of important issues remain to be discussed with ropinirole and should be addressed in future studies. Some of these include:

- The antiparkinsonian efficacy of ropinirole in L-dopa-treated PD patients should be better evaluated.
- Comparative trials need to be done with other DA agonists (eg. pergolide, pramipexole) as bromocriptine is not widely used anymore in many countries.
- Ropinirole should be compared to MAO-B inhibitors and COMT inhibitors in patients with advanced PD who have fluctuations.
- The true benefit/risk ratio of ropinirole regarding sleep problems needs to be better investigated, both through large epidemiological studies and specific pharmacodynamic sleep studies. Further studies are required to assess if such cases simply correspond to somnolence, which is frequently observed in clinical trials with ropinirole (and many other dopaminergic agents), if this is a specific problem of some DA agonists like ropinirole, if this is a dose-related effect, and if some patients exhibit a special susceptibility to somnolence.
- Longer follow-up studies (up to and more than 10 years) should be conducted to assess if patients morbidity, mortality and quality of life is improved by ropinirole.
- Pharmacoeconomic trials should be conducted to assess if it is justified to use an expensive DA agonist, like ropinirole, instead of a cheaper one, like bromocriptine.
- The role of ropinirole on non-motor symptoms, depression for example, should be studied.

REFERENCES

1. Matheson AJ, Spencer CM. Ropinirole: a review of its use in the management of Parkinson's disease. Drugs 2000;60:115-137.
2. Tulloch IF. Pharmacologic profile of ropinirole : a nonergoline dopamine agonist. Neurology 1997;49(suppl 1):S58-S62.
3. Pearce RK, Banerji T, Jenner P, Marsden CD. De novo administration of ropinirole and bromocriptine induces less dyskinesia than L-dopa in the MPTP-treated marmoset. Mov Disord 1998;13:234-241.

4, Idia M, Miyazaki I, Tanaka K, Kabuto H, Iwata-Ichikawa E. Ogawa N. Dopamine D2 receptor-mediated antioxidant and neuroprotective effects of ropinirole, a dopamine agonist. Brain Res 1999;838:51-59.
5. Adler CH, Sethi KD, Hauser RA, et al. for the Ropinirole Study Group. Ropinirole for the treatment of early Parkinson's disease. Neurology 1997;49:393-399.
6. Brooks DJ, Abbott RJ, Lees AJ, et al. A placebo-controlled evaluation of ropinirole, a novel D2 agonist, as sole dopaminergic therapy in Parkinson's disease. Clin Neuropharmacol 1998;21:101-107.
7. Rascol O, Brooks DJ, Brunt ER, Korczyn AD, Poewe WH, Stocchi F, on behalf of the 056 Study Group. Ropinirole in the treatment of early Parkinson's disease: a 6-month interim report of a 5-year levodopa-controlled study. Mov Disord 1998;13:39-45.
8. Korczyn AD, Brooks DJ, Brunt ER, Poewe WH, Rascol O, Stocchi F, on behalf of the 053 Study Group. Ropinirole versus bromocriptine in the treatment of early Parkinson's disease: a 6-month interim report of a 3-year study. Mov Disord 1998;13:46-51.
9. Korczyn AD, Brunt ER, Larsen JP, Nagy Z, Poewe WH, Ruggieri S, for the 053 Study Group. A 3-year randomized trial of ropinirole and bromocriptine in early Parkinson's disease. Neurology 1999;53:364-370.
10. Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE, for the 056 Study Group. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. N Engl J Med 2000;342:1484-1491.
11. Sethi KD, O'Brien CF, Hammerstad JP, Adler CH, Davis TL, Taylor RL, Sanchez-Ramos J, Bertoni JM, Hauser RA, et al. for the Ropinirole Study Group. Ropinirole for the treatment of early Parkinson's disease: a 12-month experience. Arch Neurol 1998;55:1211-1216.
12. Rascol O, Lees AJ, Senard JM, Pirtosek Z, Montastruc JL, Fuell D. Ropinirole in the treatment of levodopa-induced motor fluctuations in patients with Parkinson's disease. Clin Neuropharmacol 1996;19:234-245.
13. Lieberman A, Olanow CW, Sethi K, Swanson P, Waters CH, Fahn S, Hurtig H, Yahr M, and the Ropinirole Study Group. A multicenter trial of ropinirole as adjunct treatment for Parkinson's disease. Neurology 1998;51:1057-1062.
14. Caesi M, Antonini A, Mariani CB, Tesei S, Zecchinelli AL, Barichella M, Pezzoli Get al. An overnight switch to ropinirole therapy in patients with Parkinson's disease. J Neural Trans 1999;106:925-929.
15. Frucht S, Rogers JD, Greene PE, Gordon MF, Fahn S. Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. Neurology 1999;52:1908-1910.
16. Ryan M, Slevin JT, Wells A. Non-ergot dopamine agonist-induced sleep attacks. Pharmacotherapy 2000;20:724-726.
17. Ferreira JJ, Desboeuf K, Galitzky M, Thalamas C, Brefel-Courbon C, Fabre N, Senard JM, Montastruc JL, Castro-Caldas A, Rascol O, et al. "Sleep attacks" and Parkinson's disease : results of a questionnaire survey in a movement disorders outpatient clinic. Mov Disord 2000;15(suppl 3):P897.
18. Ferreira JJ, Galitzky M, Montastruc JL, Rascol O. Sleep attacks and Parkinson's disease treatment. Lancet 2000;355:1333-1334.
19. Schapira AH. Sleep attack (sleep episodes) with pergolide. Lancet 2000;355:1332-1333.
20. Ferreira JJ, Galitzky M, Brefel-Courbon C, Senard JM, Montastruc JL, Castro-Caldas A, Rascol O et al. "Sleep attacks" as an adverse drug reaction of levodopa monotherapy. Mov Disord 2000;15(suppl 3):P661
21. Olanow CW, Schapira AH, Roth T. Waking-up to sleep episodes in Parkinson's disease. Mov Disord 2000;15:212-215.

BIBLIOGRAPHY - EXCLUDED FROM ANALYSIS (REASON FOR EXCLUSION)

Boothman BR, Spokes EG. Pharmacokinetic data for ropinirole. Lancet 1990;336:814. (Non-parkinsonian endpoint)

Brefel-Courbon C, Thalamas C, Rayet S, Lopez-Gil A, Fitzpatrick K, Bullman S, Citerone DR, Taylon AC, Montastruc JL, Rascol O. Effect of food on the pharmacokinetics of ropinirole in parkinsonian patients. Br J Clin Pharmacol 1998;45:412-415. (Non-parkinsonian endpoint)

Brunt E, Aitken C. A double-blind comparative study of ropinirole versus bromocriptine in the treatment of parkinsonian patients not optimally controlled on L-dopa. Neurology 1996;243:S38. (Abstract)

Korczyn AD, Brooke D, Murray G, Spokes G, Sagar H, Aharon J. Ropinirole, a placebo controlled study of efficacy as adjunct therapy in parkinsonian patients not optimally controlled on L-dopa. Can J Neurological Sci 1993;20:S211. (Abstract)

Kreider MS, Wilson-Lynch K, Gardiner D, Wheadon DE. A double-blind, placebo-controlled, extension study to evaluate the 12 month efficacy and safety of ropinirole in early Parkinson's disease. Neurology 1997;48:A269. (Abstract)

Rascol O, Lees AG, Senard JM, et al. A placebo-controlled study of ropinirole, a new D2 agonist, in the treatment of motor fluctuations of L-dopa-treated parkinsonian patients. Adv Neurol 1996;69:531-534. (Data reviewed in another paper)

Schrag AE, Brooks DJ, Brunt E, et al. The safety of ropinirole, selective nonergoline dopamine agonist, in patients with Parkinson's disease. Clin Neuropharmacology 1998;21:169-175. (Level-III study)

Stocchi F, Keens J, on behalf of the 056 Study Group. The efficacy at 6 months of ropinirole versus bromocriptine as early therapy in parkinsonian patients. Neurology 1996;243:S38. (Abstract)

Thalamas C, Taylor A, Brefl-Courbone C, Eagle S, Fitzpatrick K, Rascol O. Lack of pharmacokinetic interaction between ropinirole and theophylline in patients with Parkinson's disease. Eur J Clin Pharmacol 1999;55:299-303. (Non-antiparkinsonian endpoint)

Vidailhet MJ, Bonnet AM, Belal S, Dubois B, Marle C, Agid Y. Ropinirole without levodopa in Parkinson's disease. Lancet 1990;336:316-317. (Level III)

Movement Disorders
Vol. 17, Suppl. 4, 2002, p. S103-S111

Published by Wiley-Liss, Inc.
DOI 10.1002/mds.5571

Drugs to Treat Autonomic Dysfunction in Parkinson's Disease

DRUGS TO TREAT ORTHOSTATIC HYPOTENSION

INTRODUCTION

BACKGROUND

Orthostatic hypotension is a common clinical problem in Parkinson's disease (PD) and relates to both the disease and its treatment. Symptomatic orthostatic hypotension is seen in approximately 20% of patients receiving levodopa.[1] The mechanism of orthostatic hypotension in patients receiving levodopa may be a combination of:

(a) Progression of the disease to involve central as well as peripheral autonomic nervous system[2],
(b) Vasodilatation in renal and mesenteric vasculature,
(c) Decrease in total peripheral resistance caused by dopamine[2],
(d) Suppression of renin secretion[3],
(e) Impairment of postganglionic sympathetic nerve function by dopamine as it may act as a false neurotransmitter[4], and
(f) Hypertension caused by central effects of noradrenalin, which is derived from dopamine.[5]

Most of the available information is found in review articles, but few controlled trials have been done.[6-9]

RATIONALE

Symptomatic orthostatic hypotension varies among patients with PD and can significantly impair daily activities and quality of life in those affected. Generally, orthostatic hypotension is treated clinically in patients who have more than a 20 mmHg drop in systolic blood pressure upon standing from the spine position. Identifying the mechanism of orthostatic hypotension (disease versus drug versus environmental) is important and will help in identify treatment strategies to treat this clinical problem in patients with PD. The two primary drug classes used to treat orthostatic hypotension are volume expanders and vasoconstrictors.

METHODS

KEY SEARCH TERMS

Parkinson's disease, orthostatic hypotension, postprandial hypotension, hypotension, midodrine, fludrocortisone, DOPS, dihydroergotamine, and etilefrine.

SPECIAL EXCEPTIONS TO INCLUSION/ EXCLUSION CRITERIA

The published literature of orthostatic hypotension exclusively in patients with PD is limited, and therefore, studies were reviewed if they included subpopulations of patients with PD. Other special exceptions included: no study duration time, and no limit in study duration in sample size; specifically, because no studies on L-DOPS were identified in English literature, one paper was reviewed which was published in Japanese.

The pharmacological therapies used for orthostatic hypotension have not been studied for prevention of disease progression, symptomatic control of PD, prevention of motor complications, and control of motor complications. Overall, there were 26 studies identified in the literature search, of which 8 meet the defined criteria and special exceptions and included in the review.

Treatment	Studies identified	Studies included in review
Midodrine	8	2
Fludrocortisone	4	1
Dihydroergotamine	2	1
Etilefrine hydrochloride	4	1
Indomethacine	1	1
Yohimbine	1	1
L-threo-3.4 -dihydroxyphenylserine	4	1

MIDODRINE

BASIC PHARMACOLOGY

MECHANISM OF ACTION AND PHARMACOKINETICS

Midodrine is a peripherally acting alpha-adrenergic agonist that acts on both the arterial and the venous system but has no direct cardiac effect.[10] After a single oral dose (1 to 4 mg), midodrine is readily absorbed, and the maximum blood level is reached in about 1 hour. Midodrine is a prodrug and is converted (in the liver) to the active form desglymidodrine. The peak plasma level of this active form is reached in 1.5 to 2 hours, and the half life is approximately 3 hours, which is longer than the half life of other sympathomimetic agents. Midodrine does not cross the blood-brain barrier[10], and there is no accumulation by repeated administration. Desglymidodrine and its metabolites are eliminated from the kidney.

REVIEW OF CLINICAL STUDIES

Level-I Studies

No Level-I studies are available that specifically look at the efficacy midodrine for treatment of orthostatic hypotension in PD, however, several studies have included subpopulations of PD patients.[11,12]

Jankovic et al. (1993)[11]: This study was a placebo-controlled trial that tested the efficacy of three different doses of midodrine (7.5 mg/day, 15 mg/day, and 30 mg/day) given for up to 4 weeks.

Ninety-seven patients were included, of which, 22 had PD. (Patients had a decrease in systolic BP greater than or equal to 15 mmHg in response to a change form a supine to a standing position and/or moderate frequency of at least two symptoms of orthostatic hypotension. Clinical diagnosis of enrolled patients (n=97) as follows: idiopathic orthostatic hypotension (IOH) [20], Shy-Drager-Syndrome (SDS) [18], PD [22], diabetes [27], and others [10].) The results showed that all patients treated with 30 mg/day of midodrine showed significant increase in standing systolic blood pressure (midodrine 116.7 mmHg vs. placebo 108.5 mmHg) and diastolic blood pressure (midodrine 76.3 mmHg vs. placebo 72.3 mmHg). Supine systolic hypertension was seen in 8% of patients treated with midodrine. Subgroup analysis revealed that among the 19 PD patients evaluated, 16 received midodrine and three received placebo. Eleven out of 16 who received midodrine responded to the medication; the response rate was 69%, which was better than the response rate of the total subjects (47%); interestingly the three PD patients who received placebo also responded. This study had an overall quality rating score of 71%.

Low et al. (1997)[12]: Low and coworkers treated 162 patients with neurogenic orthostatic hypotension, in which 19 patients had PD. This was a parallel-group, placebo-controlled comparison study of 4 weeks duration. Subjects were treated with either midodrine (30 mg/day, n=70) or with placebo (n=83). (Patients had an orthostatic reduction of at least 15 mmHg and "lightheadedness" with a score of 5 on a scale of 1 to 10 [10=never, 1=always]. Clinical diagnosis of evaluable patients [n=162] as follows: IOH [37], SDS [40], PD [19], diabetes [37], and others [29].) The primary outcome was the increase in blood pressure from baseline to day 15. Patients treated with midodrine showed a mean 22.4 mmHg systolic BP increase and 13.3 mmHg diastolic blood pressure increase from the baseline. Placebo-treated patients showed a mean 6.0 mmHg and 4.3 mmHg increase in systolic and diastolic blood pressure, respectively. The difference was statistically significant. Supine hypertension was observed in 4% of the patients treated with midodrine. Difference in the diagnosis of the patients studied did not affect the results. This study had an overall quality rating score of 75%.

Level-II studies

No qualified studies were identified.

Level-III studies

No qualified studies were identified.

REVIEW OF SAFETY

In two Level-I studies reviewed[11,12] midodrine 30 mg/day was associated with a significantly higher dose-depended incidence in supine systolic hypertension. This is of clinical concern because supine systolic hypertension greater than 180 mmHg should be avoided. Other adverse reactions associated with midodrine included piloerection, pruritus, tingling, paresthesia, urinary retention, urinary urgency, and headache. In some patients, there may be a risk of cardiovascular adverse reactions associated with midodrine.

CONCLUSIONS

EFFICACY

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of midodrine in the treatment of orthostatic hypotension specifically in patients with PD. Studies done to date were in a mixed population of patients of which only a subgroup had PD.

SAFETY

There is INSUFFICIENT EVIDENCE to conclude on the safety of midodrine for the long-term treatment of orthostatic hypotension specifically in patients with PD. Midodrine should be used with caution in patients with coronary insufficiency.

IMPLICATIONS FOR CLINICAL PRACTICE

To date, there is insufficient evidence to establish clinical usefulness of midodrine in the treatment of orthostatic hypotension specifically in PD, and therefore, midodrine is considered INVESTIGATIONAL. However, because two Level-I studies showing efficacy of midodrine in treating neurogenic orthostatic hypotension in study populations that included patients with PD this drug may considered as a practical treatment option in patients with PD. Patients should be monitored for cardiovascular adverse reactions.

IMPLICATIONS FOR CLINICAL RESEARCH

Randomized controlled studies are needed to establish the specific efficacy and safety of midodrine in orthostatic hypotension in PD. Additional studies are needed to differentiate hypotensive mechanisms related to PD as compared to hypotensive adverse reactions from medications used for treatment of the disease itself.

FLUDROCORTISONE (9-ALPHA - FLUOROHYDROCORTISONE)

BASIC PHARMACOLOGY

Fludrocortisone increases sodium reabsorption in the kidney and increases potassium excretion. The rise in blood pressure is specifically thought to be due to hypervolemia and increase in cardiac output secondary to its effects on electrolyte levels (increased sodium and decrease in potassium[13]). Fludrocortisone also has central adrenergic effects. Fludrocortisone is the most potent synthetic mineral corticoid currently available.

After oral administration, fludrocortisone is readily absorbed and the peak blood level is reached in 45 minutes, and the half maximum blood level is reached in about 7 hours. Fludrocortisone and its metabolites are eliminated from the liver and the kidney.

REVIEW OF CLINICAL STUDIES

Level-I Studies

No qualified studies were identified

Level-II Studies

No qualified studies were identified.

Level-III Studies

Hoehn (1975)[13]: This was a small study in only 6 patients with PD who had orthostatic hypotension. Patients were treated with fludrocortisone 0.05 mg to 0.2 mg for 6 to 10 months. The results from this small study report that upright systolic pressure was 70 mmHg to 98 mmHg at baseline and increased to 90 mmHg to 132 mmHg after treatment. Orthostatic symptoms in these patients disappeared completely after the treatment.

REVIEW OF SAFETY

Adverse reactions associated with fludrocortisone include hy-

pokalemia, hypertension, and edema. Fludrocortisone has a potential cardiac steroid-like effect.

CONCLUSIONS

EFFICACY

There is INSUFFICIENT EVIDENCE to conclude on the efficacy regarding the use of fludrocortisone in the treatment of orthostatic hypotension specifically in patients with PD.

SAFETY

There is INSUFFICIENT EVIDENCE to establish the safety of fludrocortisone for treatment of orthostatic hypotension in patients with PD.

IMPLICATIONS FOR CLINICAL PRACTICE

Fludrocortisone is considered INVESTIGATIONAL for the treatment of orthostatic hypotension in patients with PD.

IMPLICATIONS FOR CLINICAL RESEARCH

Randomized, controlled studies are needed to establish the efficacy and safety of fludrocortisone in orthostatic hypotension in patients with PD.

DIHYDROERGOTAMINE

BASIC PHARMACOLOGY

Dihydroergotamine (DHE) binds with high affinity to serotonergic (5-HT1D, 5-HT1A, 5-HT2A, 5-HT2C), noradrenergic (alpha-2A, alpha-2B) and dopaminergic (D2, D3) receptors. Four DHE metabolites have been identified, and the primary excretory route is through the bile in the feces.

REVIEW OF CLINICAL STUDIES

To date, there are no published trials (Level I, Level II or Level III) on the use of dihydroergotamine for the treatment of orthostatic hypotension specifically in patients with PD.

Lubke (1976)[14]: One study by Lubke tested the efficacy of dihydroergotamine in patients (n=36) with a manifest orthostatic syndrome (non-neurogenic orthostatic hypotension). This was a double-blind, placebo-controlled study of 4-weeks duration, and 17 patients were treated with 7.5 mg/day of dihydroergotamine. Treatment with dihydroergotamine was associated with normalization of circulatory regulation and majority of orthostatic symptoms disappeared (as compared to the placebo group (n=19) that showed no change).

CONCLUSIONS

Due the paucity of published clinical studies, there is INSUFFICIENT EVIDENCE to make conclusions regarding efficacy, safety, or implications for clinical use regarding the efficacy of dihydroergotamine for treatment of orthostatic hypotension specifically in patients with PD. Randomized, controlled studies are needed that test the mechanism of action and efficacy of dihydroergotamine in patients with PD.

ETILEFRINE HYDROCHLORIDE

BASIC PHARMACOLOGY

Etilefrine hydrochloride (alpha-[(ethylamino)methyl]-m-hydroxybenzyl alcohol hydrochloride) is a sympathomimetic agent, which stimulates both alpha- and beta-adrenergic receptors[15], and produces a gradual and moderate elevation of blood pressure.[16] Etilefrine hydrochloride increases cardiac contraction, cardiac output, and blood pressure.

After single oral dose (7 mg), etilefrine HCl is readily absorbed, and the maximum blood level is reached in 20 to 30 minutes. The half-maximum blood level is reached in about 2.5 hours. Etilefrine hydrochloride is metabolized in the liver by glucuronization and sulfation.

REVIEW OF CLINICAL STUDIES

Level-I Studies

No qualified studies were identified.

Level -II Studies

Miller et al. (1973)[16]: Miller studied patients who developed postural hypotension during levodopa therapy by treating them with etilefrine hydrochloride in a single-blind study. Fifteen patients were treated with 15 mg of etilefrine daily and 5 with placebo. Blood pressure was evaluated 6 days after the treatment. Etilefrine significantly improved blood pressure values while placebo did not: before treatment, the mean drop in systolic pressure in standing position was 26.3%; after treatment with 15 mg etilefrine chloride daily, the drop was only 4.3%. The mean diastolic pressure drop prior to treatment averaged 9.2% compared to 1.2% after treatment for patients treated with etilefrine. Symptoms related to postural hypotension were improved.

Level-III Studies

No qualified studies were identified.

REVIEW OF SAFETY

As a vasoconstrictor, etilefrine hydrochloride is associated with all sympathomimetic adverse reactions including hypertension, piloerection, pruritus, tingling, paresthesia, urinary retention, and urinary urgency. Theoretically, there can be a potentiation of anticholinergic effects and interaction with MAO inhibitors, and there is a risk of supine hypertension.

CONCLUSIONS

EFFICACY

There is INSUFFICIENT EVIDENCE to conclude on the efficacy regarding the use of etilefrine hydrochloride in the treatment of orthostatic hypotension specifically in patients with PD.

SAFETY

There is INSUFFICIENT EVIDENCE establish the safety of etilefrine hydrochloride for treatment of orthostatic hypotension in patients with PD.

IMPLICATIONS FOR CLINICAL PRACTICE

Etilefrine hydrochloride is considered INVESTIGATIONAL for the treatment of orthostatic hypotension in patients with PD.

IMPLICATIONS FOR CLINICAL RESEARCH

Randomized controlled studies are needed to see the efficacy and safety of etilefrine hydrochloride in orthostatic hypotension in patients with PD.

INDOMETHACINE

BASIC PHARMACOLOGY

Indomethacine is a potent inhibitor of prostaglandin-forming cyclooxygenase and also inhibits motility of polymorphonuclear leukocytes. When given in supratherapeutic doses, it uncouples oxidative phosphorylation and depresses biosynthesis of mucopolysaccarides.[17]

Following oral administration, indomethacine is rapidly absorbed in the gastrointestinal tract with peak fasting plasma concentrations obtained within 2 hours post-treatment. Indomethacin is extensively bound to plasma proteins and tissues (90%), is largely converted to inactive metabolites (e.g., those formed by O-demethylation, conjugation with glucuronic acid, and N-deacylation). Ten to 20% of indomethacine is excreted unchanged in the urine. Because of entoerhepatic cycling, the half life is variable, but averages about 3 hours.[17]

REVIEW OF CLINICAL STUDIES

Level-I Studies

No qualified studies were identified.

Level-II Studies

No qualified studies were identified.

Level-III Studies

Abate et al. (1979)[18]: The use of indomethacine for treatment of orthostatic hypotension was studied in a nonrandomized, noncontrolled trial in 12 patients with PD. Indomethacine was given IV at 50 mg over 30 minutes or orally at 50 kg for 6 days. The results showed that indomethacine significantly reduced the fall of blood pressure on standing and decreased or reversed orthostatic symptoms. The authors suggest that indomethacine offers a positive effect on systemic vascular resistance.

CONCLUSIONS

EFFICACY

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of indomethacine in the treatment of orthostatic hypotension specifically in patients with PD.

SAFETY

There is INSUFFICIENT EVIDENCE to conclude on the safety of indomethacine for the treatment of orthostatic hypotension specifically in patients with PD.

IMPLICATIONS FOR CLINICAL PRACTICE

To date, there is insufficient evidence to establish clinical usefulness of indomethacine in the treatment of orthostatic hypotension specifically in PD, and therefore, indomethacine is considered INVESTIGATIONAL. Based on the report from one clinical trial, indomethacine might be tried when other agents with clinically established efficacy have proven ineffective.

IMPLICATIONS FOR CLINICAL RESEARCH

Randomized controlled studies are needed to verify the specific efficacy and safety of indomethacine in orthostatic hypotension in PD.

YOHIMBINE

BASIC PHARMACOLOCY

Yohimbine is an alpha2 adrenergic antagonist, which increases plasma catecholamine levels by acting on presynaptic alpha2 adrenergic receptors located on sympathetic nerve endings.

Yohimbine has a low and variable bioavailability, its plasma clearance is high and also variable and terminal half-life in healthy subjects is between 1 and 2 hours. Maximum plasma concentrations after oral ingestions are reached between 1 and 2 hours also.[19]

REVIEW OF CLINICAL STUDIES

Senard et al. (1993)[20] in a four-week trial studied the effect of yohimbine 2 mg three times a day on blood pressure and heart rate using ambulatory monitoring of blood pressure in 17 patients with PD. At the end of 4 weeks, no significant changes were observed for blood pressure parameters, and the authors concluded that yohimbine is not effective in correcting orthostatic hypotension in PD. This study had an overall quality score of 90%.

CONCLUSIONS

EFFICACY

Based on one negative Level-I trial, yohimbine is considered NON-EFFICACIOUS in the treatment of orthostatic hypotension in patients with PD.[20] However, this conclusion is based on a single study with less than 20 patients

SAFETY

There is INSUFFICIENT EVIDENCE to conclude on the safety of yohimbine for the treatment of orthostatic hypotension specifically in patients with PD.

IMPLICATIONS FOR CLINICAL PRACTICE

To date, there is insufficient evidence to establish clinical usefulness of yohimbine in the treatment of orthostatic hypotension specifically in PD, and therefore, yohimbine is considered INVESTIGATIONAL.

IMPLICATIONS FOR CLINICAL RESEARCH

Randomized controlled studies are needed to verify the lack of efficacy of yohimbine for treatment of orthostatic hypotension in PD.

L-THREO-3,4-DIHYDROXYPHENYLSERINE (L-DOPS)

BASIC PHARMACOLOGY

L-DOPS is an unnatural precursor of noradrenalin; it is converted to noradrenalin by the action of aromatic l-amino acid decarboxylase.

After single oral dose (100 mg to 300 mg), L-DOPS is readily absorbed and the peak plasma level is reached in 2 hours, and the half-maximum blood level is reached in 3.5 hours. L-DOPS is not detectable after 12 hours in the blood. The peak blood level of norepinephrine is obtained in about 4 hours. Elimination is from the kidney, mainly in the original form.

REVIEW OF CLINICAL STUDIES

Level-I Studies

No qualified studies were identified. However, there is a single

European multicenter placebo controlled study ongoing designed to assess the efficacy of three different doses of L-DOPS in the treatment of orthostatic hypotension and multiple system atrophy (MSA).

Level-II Studies

No qualified studies were identified.

Level-III Studies

No level III study published in English is available on orthostatic hypotension in patients with PD.

Yanagisawa et al. (1998)[21]: Yanagisawa studied 15 patients with PD with orthostatic hypotension, which is published in Japanese with English summary. Patients were treated with 460 mg/day of L-DOPS (average). Upright systolic blood pressure increased by 10.2 to 4.0 mmHg ($P < 0.05$). But when standing for 10 minutes, there was a spontaneous partial recovery of upright systolic as well as diastolic pressure, and the difference before and after the treatment was not significant.

The only other study (Level III) identified was in 6 patients with multiple system atrophy (MSA).[22]

REVIEW OF SAFETY

L-DOPS use may be associated with gastrointestinal adverse reactions such as anorexia and nausea, and central nervous system side effects such as delusion and hallucination.

CONCLUSIONS

EFFICACY

There is INSUFFICIENT EVIDENCE to conclude on the efficacy regarding the use of L-DOPS in the treatment of orthostatic hypotension specifically in patients with PD.

SAFETY

There is INSUFFICIENT EVIDENCE establish the safety of L-DOPS for treatment of orthostatic hypotension in patients with PD.

IMPLICATIONS FOR CLINICAL PRACTICE

L-DOPS is considered INVESTIGATIONAL for the treatment of orthostatic hypotension in patients with PD.

IMPLICATIONS FOR CLINICAL RESEARCH

Randomized controlled studies are needed to see the efficacy and safety of L-DOPS in orthostatic hypotension in patients with PD.

REFERENCES

1. Senard JM, Rai S, Lapeyre Mestre M, Brefel C, Rascol O, Rascol A, Montastruc JL. Prevalence of orthostatic hypotension in Parkinson's disease. J Neurol Neurosurg Psych 1997;63:584-589.
2. Godberg LI, Whitsett TL. Cardiovascular effects of levodopa. Clin Pharmacol Ther 1971;12:376-382.
3. Barbeau A, Gillo-Joffroy L, Boucher R, Nowaczynski W, Genest J. Renin aldosterone system in Parkinson s disease. Science 1969;165:291-292.
4. Whitsett TL, Halushka PV, Goldberg LI. Attenuation of postganglionic sympathetic nerve activity by L-dopa. Circ Res 1970;27:561-570.
5. Kaplan HR, Barker JW, LaSala SA. Direct evidence for a centrally-mediated hypotensive action of L-dopa in anesthetized dogs. Eur J Pharmacol 1972;17:273-278.
6. Mathias CJ, Kimber JR. Postural hypotension: causes, clinical features, investigation, and management. Annu Rev Med 1999;50:317-336.
7. Robertson D, Davis TL. Recent advances in the treatment of orthostatic hypotension. Neurology 1995;45(4 suppl 5):S26-32.
8. Senard JM, Monstastruc JL. Which drug for which orthostatic hypotension? Fund Clin Pharmacol 1996;10(3):225-233.
9. Stumpf JL, Mitrzyk B. Management of orthostatic hypotension. Am J Hosp Pharm 1994;51(5):648-660.
10. McTavish D, Goa KL. Midodrine: a review of its pharmacological properties and therapeutic use in orthostatic hypotension and secondary hypotensive disorders. Drugs 1989;38:757-777.
11. Jankovic J, Gilden JL, Hiner BC, et al. Neurogenic orthostatic hypotension: a double-blind, placebo-controlled study with midodrine. Am J Med 1993;95:38-48.
12. Low PA, Gilden JL, Freeman R, Sheng KN, McElligott MA. Efficacy of midodrine vs. placebo in neurogenic orthostatic hypotension. A randomized, double-blind multicenter study. Midodrine study group. JAMA 1997;277:1046-1051.
13. Hoehn MM. Levodopa-induced postural hypotension. Treatment with fludrocortisone. Arch Neurol 1975;32:50-51.
14. Lubke KO. A controlled study with dihydroergot on patients with orthostatic dysregulation. Cardiology 1976;61(suppl 1):333-341.
15. Danneberg P. Tierexperimentelle Untersuchungen zur Wirkungsdauer von d,l-1-(3-Hydroxy-phenyl)-1-hydroxy-2-acethylaminoaethan-Preparaten. Arzneim Forsch 1965;15:207-213.
16. Miller E, Wiener L, Bloomfield D. Etilefrine in the treatment of levodopa-induced orthostatic hypotension. Arch Neurol 1973;29(2):99-103.
17. Insel PA. Analgesic-antipyretics and anti-inflammatory agents; drugs employed in the treatment of rheumatoid arthritis and gout. In Goodman Gilman A, Tall TW, Nies AS, Taylor P, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics. Eighth Edition. New York, New York: Pergamon Press, 1990.
18. Abate G, Polimeni RM, Cuccurullo F, Puddu P, Lenzi S. Effects of indomethacine on postural hypotension in Parkinsonism. Br Med J 1979;2:1466-1468.
19. Le Corre P, Dollo G, Chevanne F, Le Verge R. Biopharmaceutics and metabolism of yohimbine in humans. Eur J Pharm Sci 1999;9:79-84.
20. Senard JM, Rascol O, Rascol A, Montastruc JL. Lack of yohimbine effect on ambulatory blood pressure recordings: a double-blind cross-over trial in Parkinsonians with orthostatic hypotension. Fundam Clin Pharmacol 1993;7:465-470.
21. Yanagisawa N, Ikeda S, Hashimoto T, et al. Effecta of L-threo-dops on orthostatic hypotension in Parkinson's disease. No To Shinkei (Tokyo) 1998;50:157-163 (Japanese with English summary).
22. Yoshizawa T, Fujita T, Mizusawa H, Shoji S. L-threo-3,4-hydroxyphenylserine enhances the orthostatic responses of plasma renin activity and angiotensin II in multiple system atrophy. Neurology 1999;246:193-197.

BIBLIOGRAPHY - EXCLUDED FROM ANALYSIS (REASON FOR EXCLUSION)

MIDODRINE

Fouad-Tarazi FM, Okabe M, Goren H. Alpha sympathomimetic treatment of autonomic insufficiency with orthostatic hypotension. Am J Med 1995;99:604-610. (Duration of maintenance period less than 5 days, n = 8)

Hoeldtke RD, Horvath GG, Bryner KD, Hobbs GR. Treatment of orthostatic hypotension with midodrine and octereotide. J Clin Endocrinol Metabl 1998;83:339-343. (Acute study, single dose for each dose, non-PD patients)

Kaufmann H, Brannan T, Krakoff L, Yahr MD, Mandeli J. Treatment of orthostatic hypotension due to autonomic failure with a peripheral alpha-adrenergic agonist (midodrine). Neurology 1998;38:951-956. (Insufficient patient numbers; not all patients had PD, some had SMA)

Marini U, Cechi A, Venturini M. Controlled clinical investigation of dimetophrine versus midodrine in the management of moderately decreased arterial blood pressure. Current Med Res Opin 1984;9:265-274. (Clinical subjects had low arterial pressure syndrome not orthostatic hypotension)

Schirger A, Sheps SG, Thomas JE, Fealey RD. Midodrine. A new agent in the mangement of idiopathic orthostatic hypotensiona and Shy-Drager syndrome. Mayo Clin Proc 1981;56:429-433. (Insufficient patient numbers; non-PD patients)

Wright RA, Kaufmann HC, Perera R, et al. A double-blind, dose-response study of midodrine in neurogenic orthostatic hypotension. Neurology 1998;51:120-124. (Acute study, treatment period is less than 6 days, one day for each dose)

FLUDROHYDROCORTISONE

Campbell IW, Ewing DJ, Clarke BF. Therapeutic experience with fludrocortisone in diabetic postural hypotension. Br Med J 1976;1:872-874. (Subjects with diabetic postural hypotension)

Finke J, Sagemuller I. Fludrocortisone in the treatment of orthostatic hypotension: ophthalmodynamography during standing. Dtsch Med Wochenschr 1975;100:1790-1792. (Did not include patients with Parkinson's disease)

Hussain RM, McIntosh SJ, Lawson J, Kenny RA. Fludrocortisone in the treatment of hypotensive disorders in the elderly. Heart 1996;76:507-509. (Study of effects on ECG; no PD patients)

DIHYDROERGOTAMINE

Bobik A, Jennings G, Skews H, Esler M, McLean A. Low oral bioavailability of dihydroergotamine and first-pass extraction in patients with orthostatic hypotension. Clin Pharmacol Ther 1981;30:673-679. (Excluded patients with Parkinson's disease)

Bracharz H, Polzien P. Therapie hypotoner Kreislaufregulationsstoerungen mit einer Kombination aus Dihydroergotamin plus Etilefrin. Münch Med Wochenschr 1981;123:177-180. (non-English language)

Hilke H, Kanto J, Mantyla R, Kleimola T, Syvalahti E. Dihydroergotamine: pharmacokinetics and usefulness in spinal anaesthesia. Acta Anaesth Scand 1978;22:215-220. (Spinal anesthesia, intravenous use)

ETILEFRINE HYDROCHLORIDE

Birke ER. On the action of antihypotensive agents in sympathicotonic orthostatic hypotension in geriatric patients: comparison between placebo and etilefrin. Med Klin 1977;72:1649-1702. (non-English language)

Gemeinhardt S, Schardt F, Polzien P. Abnormalities of hypotonic orthostatic regulation: cardiovascular effects of dihydroergotamine, etilefrine and their combination. Dtsch Med Wochenschr 1981;106:1095-1099. (non-English language)

Jansen W. Comparative studies of the efficacy of amezintum and etilefrin in aged patients with hypotonic blood circulation regulatory disorders. Med Welt 1982;32:1491-1496. (non-English language)

L-THREO-3,4-DIHYDROXYPHENYLSERINE (L-DOPS)

Birkmayer W, Birkmayer G, Lechner H, Riederer P. DL-3,4-threo-DOPS in Parkinson s disease: effects on orthostatic hypotension and dizziness. J Neural Transm 1983;58:305-313. (Acute study, intravenous administration of DL-dops)

Freeman R, Young J, Landsberg L, Lipsitz L. The treatment of postprandial hypotension in autonomic failure with 3,4-DL-threo-dihydroxyphenylserine. Neurology 1996;47:1414-1420. (Excluded patients with Parkinson's disease)

Hoeldtke RD, Climi KM, Mattis-Graves K. DL-Threo-3,4-dihydroxyphenylserine does not exert a pressor effect in orthostatic hypotension. Clin Pharmacol Ther. 1984;36:302-306. (Insufficient patient numbers; non-PD patients)

DRUGS TO TREAT URINARY FREQUENCY, URGENCY, AND/OR URGE INCONTINENCE

INTRODUCTION

BACKGROUND

Urinary frequency, urgency, and urge incontinence are common symptoms in elderly people with Parkinson's disease (PD). One of the difficult issues is that nocturnal urinary frequency disturbs sleep. When elderly peoples complain of urinary frequency, the possibility of prostate hypertrophy and cancer should be considered. When urinary frequency is associated with difficulty in initiating voiding, urologic consultation is warranted. When prostate problems are excluded, urinary frequency, urgency, and/or urge incontinence can be treated symptomatically.

RATIONALE

Urinary frequency and urge incontinence, particularly nocturnal ones, can seriously compromise the quality of life of patients with PD and their caregivers. The three drug classes used to treat these symptoms in the general medical context are (1) anti-cholinergic drugs,(2) anti-spasmodic drugs acting on the detrusor muscles of the urinary bladder, and (3) alpha-1 agonists.

METHODS

KEY SEARCH TERMS

Parkinson's disease, neurogenic bladder, urgency, oxybutynin, flavoxate, propiverine, prazosin, imipramine, and amitriptyline.

REVIEW OF CLINICAL STUDIES

A total of 20 articles were identified by the literature search (11 on oxybutynin; 2 tolteradine, 5 flavoxate, 1 propiverine, 1 prazosin), but none specifically included patients with identified PD. Therefore, no evidence-based analysis of drug treatment for urinary symptoms in PD is possible.

CONCLUSIONS

EFFICACY

There is INSUFFICIENT EVIDENCE to make conclusions on the efficacy of oxybutynin, tolteradine, flavoxate, propiverine, and prazosin in the treatment of urinary symptoms in patients with PD.

SAFETY

There is INSUFFICIENT EVIDENCE to make conclusions on the safety of oxybutynin, tolteradine, flavoxate, propiverine, and prazosin in the treatment of urinary symptoms in patients with PD.

IMPLICATIONS FOR CLINICAL PRACTICE

Based on the absence of clinical study data in patients with PD, oxybutynin, tolteradine, flavoxate, propiverine, and prazosin are considered INVESTIGATIONAL. To the extent that urinary problems in individual PD resemble those in non-PD subjects, drugs whose efficacy has been established in multiple Level-I trials (i.e., oxybutynin and tolteradine) in non-PD patients may be considered as initial treatment options.

IMPLICATIONS FOR CLINICAL RESEARCH

- There is a strong need for clinica trials specifically focusing on the treatment of urinary symptoms in PD.

• Any drugs with established or potential usefulness in neurogenic bladder disturbances in non-PD patients, should be tested in patients with PD.

BIBLIOGRAPHY - EXCLUDED FROM ANALYSIS (REASON FOR EXCLUSION)

OXYBUTYNIN

Adubofour KO, Kajiwara GT, Goldberg CM, King Angell JL. Oxybutynin-induced heatstroke in an elderly patient. Ann Pharmacother 1996;30:144-147. (No PD patients)

Cardozo LD, Cooper D, Versi E. Oxybutynin chloride in the management of idiopathicdetrusor instability. Neurol Urodynam 1987;6:256-257. (No PD patients)

Gajewski JB, Awad SA. Oxybutynin versus propantheline in patients with multiple sclerosis and detrusor hyperreflexia. Urol Neurol Urodynam 1986;135:966-968. (No PD patients)

Hussain RM, Hartigan-Go K, Thomas SH, Ford GA. Effect of oxybutynin on the QTc interval in elderly patients with urinary incontinence. Br J Clin Pharmacol 1996;41:73-75. (Study of effects on ECG; no PD patients)

Kata IR, Sands LP, Bilker W, DiFilippo S, Boyce A, Dangelo K. Identification of medications that cause cognitive impairment in older people: the case of oxybutynin chloride. J Am Geriatr Soc 1998;46:8-13. (No PD patients)

Madersbacher H, Stohrer M, Richter R, Burgdorfer H, Hachen HJ, Murtz G. Trospium chloride versus oxybutynin: a randomized, double-blind multicentre trial in the treatment of detrusor hyper-reflexia. Br J Urol 1995;75:452-456. (No PD patients)

Moisey CU, Stephenson TP, Brendler CB. The urodynamic and subjective results of treatment of detrusor instability with oxybutynin chloride. Br J Urol 1980;52:472-475. (No PD patients)

Moore KH, Hay DM, Imrie AE, Watson A, Goldstein M. Oxybutynin hydrochloride (3 mg) in the treatment of women with idiopathic detrusor instability. Br J Urol 1990;66:479-485. (No PD patients)

Nagy F, Hamvas A, Frang D. Idiopathic bladder hyperactivity treated with Ditropan (Oxybutynin chloride) Internat Urol Nephrol 1990;22:519-524. (No PD patients)

Ouslander JG, Schnelle JF, Uman G, Fingold S, Nigam JG, Tuico E, Jensen BB. Does oxybutynin add to the effectiveness of prompted voiding for urinary incontinence among neusing home residents? A placebo-controlled trial. J Am Geriat Soc 1995;43:610-617. (No PD patients)

Szonyi G, Collas DM, Ding YY, Malone Lee JG. Oxybutynin with bladder retraining for detrusor instability in elderly people: a rondomized controlled trial. Age Ageing 1995;24:287-291. (No PD patients)

Thuroff JW, Bunke B, Ebner A, et al. Randomized, double-blind, multicenter trial on treatment of frequency, urgency and incontinence related to detrusor hyperactivity: oxybutynin versus propantheline versus placebo. J Urol 1991;145:813-816. (No PD patients)

Topp AJ, Cardozo LD, Versi E, Cooper D. The treatment of detrusor instability in post-monopausal women with oxybutynin chloride: a double blind placebo controlled study. Br J Obstet Gynaecol 1990;97:521-526. (No PD patients)

Zorzitto ML, Holliday PJ, Jewett MA, Herscharn S, Fernie GR. Oxybutynin chloridefor geriatric urinary dsyfunction: a double-blind placebo-controlled study. Age Ageing 1989;18:195-200. (No PD patients)

TOLTERODINE

Abrams P, Freeman R, Anderstrom C, Mattiasson A. Tolterodine, a new antimuscarinic agent; as effective but better tolerated than oxybutynin in patients with an overactive bladder. Br J Urol 1998;81:801-810. (No PD patients)

Appell RA. Clinical efficacy and safety of tolterodine in the treatment of overactive bladder: a pooled analysis. Urology 1997;50:90-96. (No PD patients)

Atan A, Konely BR, Erickson JR, Yokoyama T, Kim DY, Chancellor MB. Tolterodine for averactive bladder: time to onset of action, preferred dosage, and 9-month follow-up. Tech Urol 1999;5:67-70. (No PD patients)

Brynne N, Stahl MM, Hall NB, et al. Pharmacokinetics and pharmacodynamics of tolterodine in man: a new drug for the treatment of urinary bladder overactivity. Int J Clin Pharmacol Ther 1997;35:287-295. (No clinical trial)

Hills CJ, Winter SA, Balfour JA. Tolterodine. Drugs 1998;55:813-820. (Review paper; no PD patients)

Jonas U, Hofner K, Madersbacher H, Holmdahl TH, the participants of the international study group. Efficacy and safety to two doses of tolterodine versus placebo in patients with detrusor overactivity and symptoms of frequency, urge incontinence, and urgency: urodynamic evaluation. World J Urol 1997;15:144-151. (No PD patients)

Larsson G, Hallen B, Nilvebrant L. Tolterodine in the treatment of overactive bladder: analysis of the pooled phase II efficacy and safety data. Urology 1999;53:990-998. (Not tested in patients with PD)

Millard R, Tuttle J, Moore K, et al. Clinical efficacy and safety of tolterodine compared to placebo in detrusor overactivity. J Urol 1999;161:1551-1555. (Not tested in patients with PD)

Nilvebrant L, Andersson KE, Gillberg PG, Stahl M, Aparf B. Tolterodine - a new bladder-selective antimuscarinic agent. Eur J Pharmacol 1997;327:195-207. (No PD patients)

Renthog L, Stanton SL, Cardozo L, Nelson E, Fall M, Abrams P. Efficacy and safety of tolterodine in patients with detrusor instability: a dose-ranging study. Br J Urology 1998;81:42-48. (Not studied in patients with PD)

Stahl MM, Ekstrum B, Sparf B, Mattiasson A, Andersson KE. Urodynamic and other effects of tolterodine: a novel antimuscarinic drug for the treatment of detrusor overactivity. Neurourol Urodyn 1995;14:647-655. (Acute study after single dose; no PD patients)

Van Korrebroeck PEVA, Amarenco G, Thuuroff JW, et al. Dose-ranging study of tolterodine in patients with detrusor hyperreflexia. Neurology Urodynam 1998;17:499-512. (Not tested in patients with PD)

FLAVOXATE

Aagaard J, Reuther K, Stimpel H. A comparison between the combination emepronium bromide/flavoxate and emepronium bromide in the treatment of detrusor instability. Urol Int 1983;38:191-192. (No PD patients)

Briggs RS, Castleden CM, Asher MJ. The effect of flavoxate on uninhibited detrusor contractions and urinary incontinence in the elderly. J Urol 1980;123:665-666. (N = 6)

Delaere KPJ, Michiels HE, Debruyne FMJ, Moonen WA. Flavoxate hydrochloride in the treatment od detrusor instability. Urol Int 1977;32:377-381. (Level III, not on PD)

Pederson E. Studies on the effect and mode of action of flavoxate in human urinary bladder and shpincer. Urol Int 1977;32:202-208. (No PD patients)

Heblorn S. Treatment of detrusor hyperreflexia in multiple sclerosis. A double-blind, crossover clinical trial comparing Methantheline bromide (BanthineR), Flavoxate chloride (UrispasR) and Meladrazine tartrate (LisidonilR). Urol Int 1977;32:209-217. (No PD patients)

PROPIVERINE HCL

Mazur D, Wehnert J, Dorschner W, Schubert G, Herfurth G, Alken RG. Clinical and urodynamic effects of propiverine in patients suffering from urgency and urge incontinence. A multicentre dose-optimizing study. Scand J Urol Nephrol 1995;29:289-294. (Not tested in patients with PD)

Okada H, Sengoku J, Gohji K, Arakawa S, Kamidono S, Kobe University Incontinence Study Group. Clinical effect of propiverine in patients with urge or stress incontinence. Acta Urol Jpn 1998;44:65-69. (Not on PD)

PRAZOSIN

Jensen D Jr. Uninhibited neurogenic bladder treated with prazosin. Scand J Urol Nephrol 1981;15:229-233. (Not on PD)

Petersen T, Husted SE, Sidenius P. Prazosin treatment of neurological patients with detrusor hyperreflexia and bladder emptying disability. Scand J Urol Nephrol 1989;23:189-194. (Not tested in patients with PD)

DRUGS TO TREAT GASTROINTESTINAL MOTILITY PROBLEMS

INTRODUCTION

BACKGROUND

Constipation is a very common symptom of PD. Decrease in gastrointestinal motility appears to be the results of reduced cholinergic innervation of the gastrointestinal tract. Degeneration of the dorsal motor nucleus of the vagal nerve and neurons in the myenteric plexus is well known in PD.[1-3]

RATIONALE

Reduced gastric motility may become a cause of "on-off" phenomenon of PD patients with long-term levodopa treatment.[4,5] Improving the gastric motility is important for the better absorption of levodopa. In addition, gastrointestinal side effects such as anorexia, nausea, and vomiting may become limiting factors for dopamine agonist treatment.

METHODS

KEY SEARCH TERMS

The terms used for the search included Parkinson's disease, cisapride, metoclopramide, and domperidone.

SPECIAL EXCEPTIONS TO INCLUSION/ EXCLUSION CRITERIA

Published articles were identified from the Cochrane Library that ranged back as early as 1948. Articles selected for final screening were those where a specific agent was used in order to treat gastrointestinal motility disturbance in a population of PD patients as the prime target of intervention. Level-I and Level-II studies were included if they had a minimum of 10 patients and a 2-week treatment period. Level-III studies were only included if there were no Level-I or Level-II studies available. Studies published in non-English are included only when there was no appropriate English literature identified.

CISAPRIDE

BASIC PHARMACOLOGY

Cisapride, a benzamide derivative, is a prokinetic drug that enhances gastric motility and emptying by increasing release of acetylcholine from postganglionic nerve endings of the myenteric plexus within the stomach wall without blocking the peripheral dopamine receptors.[6] After single oral dose (2.5 mg to 20 mg), cisapride is rapidly absorbed. The peak blood level is reached in 60 minutes, and the half-maximum level in 1.5 and 8 hours. Cisapride has a diphasic plasma level profile, and is metabolized in the liver. N-dealkylated nor-cisapride is the major metabolite, which is excreted into the urine.

REVIEW OF CLINICAL STUDIES

Collectively, five papers were identified that studied the use of cisapride in treating gastric imotility specifically in patients with PD. All these studies were classified as Level-III evidence. Two of these studies by Jost and colleagues reported a reduction in gastrointestinal or colonic transit time.[7,8] One measured clinical improvement on the effects of cisapride on constipation[9], and two measured improved levodopa adsorption with cisapride treatment.[10,11]

REVIEW OF SAFETY

Despite these positive clinical responses associated with cisapride in patients with PD, cisapride was reported to be associated with cardiac arrhythmias and sudden deaths, and its use in several countries is restricted. It also has been suggested that cisapride exerts dopamine antagonist properties that may aggravate parkinsonian symptoms.[12]

CONCLUSIONS

EFFICACY

Given the limited available Level III evidence and the diversity in outcome variables reported, there is INSUFFICIENT EVIDENCE to conclude on the efficacy of cisapride to treat gastrointestinal motility problems patients with PD.

SAFETY

Because of the risk of arrhythmia, sudden death, and aggravation of parkinsonism, cisapride has an UNACCEPTABLE RISK in treating gastrointestinal problems in patients with PD.

IMPLICATIONS FOR CLINICAL PRACTICE

Given a combination of safety concerns and insufficient evidence for efficacy, cisapride is NOT USEFUL as a treatment option for gastrointestinal motility problems in PD. Additional research is needed to identify safe pharmacologic agent to treat gastrointestinal problems specifically in patients with PD.

IMPLICATIONS FOR CLINICAL RESEARCH

Because of severe toxicity concerns no further clinical research is recommended.

DOMPERIDONE

BASIC PHARMACOLOGY

Domperidone, a benzamide derivative, has a dopamine receptor blocking property. Domperidone increases rhythmic contraction of the stomach, improves gastric emptying towards normal, and shows anti-emetic effect. This drug does not cross the blood brain barrier at usual recommended doses.

REVIEW OF CLINICAL STUDIES

There are four studies assessing the efficacy of domperidone in patients with PD on dopaminergic therapy.[13-16] Three assessed the effect of domperidone on DA agonists-associated nausea, two were done in patients receiving bromocriptine[13,15] and one in patients on apomorphine therapy[14]. The results indicated beneficial effects of domperidone in preventing agonist-induced nausea. A further study assessed the effects of domperidone (Level II) on GI emptying and adverse reactions to levodopa. Domperidone (dose range was 60 to 150 mg/day PO in divided doses) was found effective in reducing gastric emptying time and reducing nausea and vomiting associated with levodopa treatment. Only two of these were placebo-controlled[13,15] and had quality scores of 58%[15] and 62%[13].

REVIEW OF SAFETY

From the studies reviewed, domperidone has the potential to exacerbate parkinsonism when given at high doses of up to 150 mg/day. In some instances, acute dystonia has been reported in children, suggesting that domperidone crosses the blood brain barrier.

CONCLUSIONS

EFFICACY

Based on the available evidence, domperidone is LIKELY EF-

FICACIOUS in reducing anorexia, nausea and vomiting associated with levodopa and/or dopamine agonist treatment.

SAFETY

Domperidone can be used with ACCEPTABLE RISK WITHOUT SPECIALIZED monitoring.

IMPLICATIONS FOR CLINICAL PRACTICE

Given positive evidence from two Level-I trials and its wide use in clinical practise in many countries domperidone is considered POSSIBLY USEFUL in the treatment of gastrointestinal side effects such as anorexia, nausea, and vomiting caused by anti-PD drugs such as dopamine agonists and levodopa.

IMPLICATIONS FOR CLINICAL RESEARCH

More randomized controlled studies are needed to see the efficacy and safety of domperidone in nausea and vomiting due to anti-Parkinson medication in patients with PD.

METOCLOPRAMIDE

BASIC PHARMACOLOGY

Metoclopramide, a benzamide derivative, has a dopamine receptor blocking property as domperidone. It acts mainly on peripheral dopamine receptors, but it does cross the blood brain barrier to some extent. Metoclopramide increases gastric motility, gastric emptying, and shows anti-emetic property.

REVIEW OF CLINICAL STUDIES

Only one Level-III study[17] has been identified where the effects of metoclopramide (10 mg IM) in apomorphine-induced nausea and vomiting was assessed in 8 patients. In this acute trial, prior injection of metoclopramide prevented apomorphine-induced vomiting.

REVIEW OF SAFETY

There are a number of case reports that metoclopramide can compromise the antiparkinsonian effects of levodopa and other DA-acting agonists.[18-20]

CONCLUSIONS

EFFICACY

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of metoclopramide in treating nausea and vomiting in patients with PD.

SAFETY

Because of the metoclopramide-induced parkinsonism in non-PD patients and aggravation of symptoms in PD, metoclopramide has an UNACCEPTABLE RISK in patients with PD.

IMPLICATIONS FOR CLINICAL PRACTICE

Due to its potential to aggravate motor symptoms metoclopramide is considered NOT CLINICALLY USEFUL in patients with Parkinson's disease.

REFERENCES

1. Den Hartog Jager WA, Bethlem J. The distribution of Lewy bodies in the central and autonomic nervous system in idiopathic paralysis agitans. J Neurol Neurosurg Psychiatry 1960;23:283-290.
2. Eadie MJ. The pathology of certain medullary nuclei in Parkinsonism. Brain 1963;86:781-792.
3. Ohama E, Ikuta F. Parkinson s disease: distribution of Lewy bodies and monoamine neuron system. Acta Neuropathol (Berl) 1976;34:311-319.
4. Kurlan R., Rothfield KP, Woodward WR, et al. Erratic gastric emptying of levodopa may cause random fluctuations of parkinsonian mobility. Neurology 1988;38:419-421.
5. Deleu D, Ebinger G, Michotte Y. Clinical and pharmacokinetic comparison of oral and duodenal delivery of levodopa/carbidopa in patients with Parkinson's disease with a fluctuating response to levodopa. Eur J Clin Pharmacol 1991;41:453-458.
6. McCullum RW. Cisapride: a new class of prokinetic agent. Am J Gastroenterol 1991;86:135-149.
7. Jost WH, Schimrigk K. The effect of cisapride on delayed colonic transit time in patients with idiopathic Parkinson s disease. Wien Klin Wochenschr 1994;106:673-676.
8. Jost WH, Schimrigk K. Long-term results with cisapride in Parkinson s disease. Mov Disord 1997;12:423-425.
9. Jost WH, Schimrigk K. Cisapride treatment of constipation in Parkinson's disease. Mov Disord 1993;8:339-343.
10. Djaldetti R, Koren M, Ziv I, Achiron A, Melamed E. Effect of cisapride on response fluctuations in Parkinson s disease. Mov Disord 1995;10:81-84.
11. Neira WD, Sanchez V, Mena MA, de Yebenes JG. The effects of cisapride on plasma L-dopa levels and clinical response in Parkinson s disease. Mov Disord 1995;10:66-70.
12. Sempere AP, Duarte J, Cabezas C, Claver LE, Caoria F. Aggravation of parkinsonian tremor by cisapride. Clin Neuropharmacol 1995;18:76-78.
13. Agid Y, Pollak P, Bonnet AM, Signoret JL, Lhermitte F. Bromocriptine associated with a peripheral dopamine blocking agent in treatment of Parkinson's disease. Lancet 1979;1:570-572.
14. Corsini GU, Del-Zompo M, Gessa GL, Mangoni A. Therapeutic efficacy of apomorphine combined with an extracerebral inhibitor of dopamine receptors in Parkinson's disease. Lancet 1979;1:954-956.
15. Quinn N, Illas A, Lhermitte F, Agid Y. Bromocriptine and domperidone in the treatment of Parkinson's disease. Neurology 1981;31:662-667.
16. Soykan I, Sarosiek I, Shifflett J, Wooton GF, McCallum RW. Effect of chronic oral domperidone therapy on gastrointestinal symptoms and gastric emptying in patients with Parkinson's disease. Mov Disord 1997;12:952-957.
17. Corsini GU, Del Zompo D, Cianchetti C, Mangoni A. Therapeutic efficacy of a combination of apomorphine with sulpiride or metoclopramide in parkinsonism. Psychopharmacology 1976;47:169-173.
18. Bateman DN, Rawlins MD, Simpson JM. Extrapyramidal reactions with metoclopramide. Br Med J 1985;291:930-932.
19. Miller LG, Jankovic J. Metoclopramide-induced movement disorders. Clinical findings with a review of the literature. Arch Intern Med 1989;149:2486-2492.
20. Ganzini L, Casey DE, Hoffman WF, McCall AL. The prevalence of metoclopramide-induced tardive dyskinesia and acute extrapyramidal movement disorders. Arch Int Med 1993;153:1469-1475.

BIBLIOGRAPHY - EXCLUDED FROM ANALYSIS (REASON FOR EXCLUSION)

CISAPRIDE

Jost WH. Gastrointestinal motility problems in patients with Parkinson's disease. Effects of antiparkinsonian treatment and guidelines for management. Drugs Aging 1997;10:249-258. (Review article)

DOMPERIDONE

Jost WH. Gastrointestinal motility problems in patients with Parkinson s disease. Effects of antiparkinsonian treatment and guidelines for management. Drugs Aging 1997;10:249-258. (Review article)

Shindler JS, Finnerty GT, Towlson K, Dolan AL, Davies CL, Parkes JD. Domperidone and levodopa in Parkinson s disease. Br J Clin Pharmacol 1984;18:959-962. (Acute study, single dose)

METOCLOPRAMIDE

Bateman DN, Kahn C, Legg NJ, Reid JL. Metoclopramide in Parkinson's disease. Clin Pharmacol Ther 1978;24:459-464. (Safety study, no assessments of gastrointestinal effects)

Mitchelson F. Pharmacological agents affecting emesis. A review (Part I). Drugs 1992;43:295-315. (Review article)

Movement Disorders
Vol. 17, Suppl. 4, 2002, p. S112-S119

Published by Wiley-Liss, Inc.
DOI 10.1002/mds.5572

Treatment of Depression in Idiopathic Parkinson's Disease

INTRODUCTION

BACKGROUND

Although the reported prevalence of depression in patients with Parkinson's disease (PD) varies over a wide range due to factors of selection bias and differences in diagnostic criteria for both depression and PD, there is general consensus that it is a frequent non-motor feature affecting between 40% and 50% of patients.[1-3] Symptoms of depression may antedate overt motor manifestations of PD in up to 30% of patients.[4] Depression is usually of mild-to-moderate intensity and suicide is rare.[2] While some studies estimated that major and minor depression occurred with equal frequency,[1] more recent studies using strict DSM-III-R diagnostic criteria have found lower prevalence rates for major depression. Tandberg et al.[5] reported a prevalence of 3.6% of major depression in nondemented patients as opposed to 26% in cognitively impaired patients.

Clinical features of depression associated with PD include early loss of initiative and self-esteem. Different from major depression found in non-parkinsonian patients, the suicide rate is very low in parkinsonian depression, and the prevalence of panic attacks and other symptoms of anxiety is relatively high. Available validated depression rating scales include a variety of items related to motor behavior, and these measures can confound interpretation of depression ratings in patients with PD.

The inconsistent correlation between mood changes and severity of parkinsonian disability, as well as the occurrence of depression prior to any motor manifestations of Parkinson's disease (PD) all argue against a merely reactive nature of PD-associated depression. Proposed neurobiological substrates include mesocorticolimbic dopaminergic denervation[6], brain serotonin deficiency due to degenerative changes in the brain stem raphe nucleus[2,7,8] as well as noradrenergic deficiency.[7]

RATIONALE

In a recent survey[9], depression was identified as a major factor impacting on the quality of life in PD patients so that antidepressive therapy is an important part of pharmacological treatment of patients with PD. Despite the frequency of depression in PD, there are no uniformly accepted standards for the treatment of PD-associated depressive symptoms. This chapter reviews the available evidence for efficacy and safety of antidepressant pharmacotherapy or electroconvulsive therapy in PD patients with minor or major depression.

METHODS

KEY SEARCH TERMS

Key search terms included Parkinson's disease or parkinson syndrome and depression and antidepressants or antidepressive therapy or one of the following: selective serotonine reuptake inhibitor (SSRI), fluvoxamine, fluoxetine, sertraline, amitriptyline, nortriptyline, imipramine, moclobemide, selegiline or electroconvulsive therapy or ECT or magnetic stimulation or transcranial electromagnetic stimulation.

SPECIAL EXCEPTIONS TO INCLUSION/ EXCLUSION CRITERIA

A total of 265 articles were identified. Articles selected for final screening were those where a specific therapy had used to treat depression in a population of PD patients as a prime target of intervention. Forty articles met this criterion, 19 of which were related to drug-treatment while 21 assessed the effects of ECT. As there were only two randomized controlled trials in this indication a special exception was made for this section to include all randomized controlled trials regardless of patient numbers.

TRICYCLIC ANTIDEPRESSANTS

Of 19 articles selected for final screening, three were about the use of tricyclic antidepressants in PD-associated depression. Only one article met the inclusion criteria of this review and describes the antidepressive effects of nortriptyline in patients with PD.[10]

NORTRIPTYLINE

BASIC PHARMACOLOGY

MECHANISM OF ACTION

The tricyclic antidepressant nortriptyline (a dibenzocycloheptadien) is the secondary-amine congener (or the N-demethylated metabolite) of the tertiary amine compound amitriptyline. As with other antidepressant drugs, knowledge of the pharmacological properties is incomplete. The mechanism of nortriptyline's antidepressant action is thought to be related by its potent and highly selective inhibition of norepinephrine reuptake. In addition, nortriptyline has weak affinity for serotonin neuronal reuptake and it does not inhibit dopamine neuronal reuptake. Like other imipraminic compounds, nortriptyline blocks muscarinic and alpha-adrenergic receptors.

PHARMACOKINETICS

Oral nortriptyline is well absorbed with limited first-pass metabolism. Bioavailability is approximately 61%. As with other tricyclic antidepressants, concentrations in plasma typically peak within 2 to 8 hours. The mean plasma protein binding of nortriptyline is about 89% to 92%. Nortriptyline is oxidized by hepatic microsomal enzymes followed by conjugation with glucuronic acid. Urinary clearance is the major route of excretion for nortriptyline metabolites.[11,12]

The mean half-life of nortriptyline is 28 to 31 hours. Half-life tends to be prolonged in elderly compared to non-elderly subjects.

Serum concentrations of 50 to 150 ng/ml for nortriptyline have been suggested as optimal for patients with major depression.[11,12]

REVIEW OF CLINICAL STUDIES

Level-I Studies

Andersen et al. (1980)[10] was the only study identified in this review, and it included 22 L-dopa-treated patients with PD. Patients were randomized into a double-blind, cross-over study comparing nortriptyline and placebo. All patients presented with moderate degrees of depression scoring at least 13 points on a depression rating scale designed by Andersen himself (maximum score of 93).[10] The two treatment periods lasted 8 weeks each, and 19 patients completed the full trial. Problematic issues related to this study include its crossover design with a short washout period, lack of an analysis of period effect, and the use of an unconventional rating system; nonetheless, this study is the only available randomized study on the efficacy of tricyclic agent.

Nortriptyline was titrated from 25 mg/d to a maximum of 150 mg/d, presumably according to clinical response, but details are not given in the report. Assessments were made before and after the end of each 8-week treatment period and included the Andersen Depression Rating Scale and a 5-point rating scale of posture and gait, a 4-point scale for akinesia, rigidity and tremor as well as a variety of timed tests. There were no statistically significant changes in any of the parkinsonian measures between the post-placebo and post-nortriptyline values, which were all similar to baseline scores. The median depression score was highly significantly reduced in the nortriptyline period compared to baseline or the placebo period. The authors state that the most pronounced effect of nortriptyline was found in those items of their depression scale, which they believed less likely to be affected by parkinsonism itself. The major adverse reaction was orthostatic hypotension, which lead to early dropout of two patients and caused a significant decrease in mean standing blood pressure after active treatment compared to placebo or baseline. This study had an overall quality rating score of 53%.

Level-II Studies

No qualified studies were identified.

Level-III Studies

No qualified studies were identified.

REVIEW OF SAFETY

The main adverse reactions of tricyclic antidepressants are related to their antimuscarinic as well as antiadrenergic, antihistaminergic, and antiserotonergic activities. In addition, they interfere with presynaptic reuptake of catecholamines. Adverse reactions include sedation and memory impairment as well as - particularly in high doses - confusional states, hallucinosis and delirium. Concomitant treatment with tricyclic antidepressants in patients with PD can contribute to drug-induced psychosis, sedation, and daytime sleepiness. The anticholinergic activity of tricyclic antidepressants can potentially slow the gastrointestinal resorption of levodopa, which is of potential importance in motor fluctuations.

There are some concerns regarding interactions between tricyclic antidepressants and Deprenyl causing hyperpyrexia, tremor, agitation, and mental changes similar to the "serotonin syndrome". A recent survey in PD on possible interactions between deprenyl and tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) has identified a very low combined rate of 0.24% of adverse reactions possibly consistent with a serotonin syndrome, which was considered serious in 0.04%[13].

Up to 10% of patients treated with tricyclic antidepressants for major depression have developed signs of orthostatic hypotension. Cardiac arrhythmias are a risk in patients with pre existing cardiac disease in particular with pre existent bundle-blocks.

Abrupt discontinuation of sustained high dose oral treatment with tricyclic antidepressants may induce withdrawal phenomena including dysautonomia, anxiety, and panic.

CONCLUSIONS

EFFICACY

Based on one positive Level-I study of moderate quality nortriptyline is considered LIKELY EFFICACIOUS for the treatment of depression in PD but there is INSUFFICIENT EVIDENCE to conclude on imipraminic antidepressants as a class.

SAFETY

In depressed patients with PD, there is INSUFFICIENT EVIDENCE to conclude on the safety of nortriptyline or other imipraminic antidepressants.

IMPLICATIONS FOR CLINICAL PRACTICE

To the extent that depression in PD parallels that in non-PD patients with major depression, clinical experience suggests that nortriptyline and imipraminic antidepressants are POSSIBLY USEFUL also in the treatment of depression in PD.

IMPLICATIONS FOR CLINICAL RESEARCH

There is a need for well-designed, controlled trials of imipraminic antidepressants in PD patients with depression to better define:

- The short-term and long-term antidepressive efficacy of different imipraminic agents in patients with PD.
- The relative efficacy of imipraminic antidepressants compared to newer antidepressive agents like SSRIs in PD-associated depression.
- Interactions between imipraminic antidepressants and antiparkinsonian drugs in depressed patients with PD.
- The antiparkinsonian effects and their possible relation to the antimuscarinic and monoaminergic properties of imipraminic antidepressants.

MAO-INHIBITORS

Current hypotheses relate depression in PD to neurobiochemical deficits involving dopaminergic, noradrenergic, and serotonergic brain stem ascending systems (see Introduction). Oxidative deamination is a common major pathway of degradation of all free biogenic amine-neurotransmitters believed to be possibly involved in mood changes in PD. Consequently, inhibition of monoamine-oxydase (MAO) seems a plausible approach to the drug treatment of PD-related depression. MAO-A exists in two isoforms: MAO-A primarily deaminates noradrenaline and serotonine, while MAO-B is relatively selective for dopamine metabolism. Most of the brain MAO-activity is related to the B-type enzyme (> 80%), while less than 20% of the total brain MAO activity correspond to the A-type enzyme.[14] Literature data on the use of MAO inhibitors to treat depression in PD are sparse and related to both inhibition of

MAO-A through moclobemide and MAO-B through selegiline.

Of 19 articles screened for final evaluation, 4 assessed the effects of MAO-inhibition on depressive symptoms in PD, of which 2 met inclusion criteria of this review.

MOCLOBEMIDE

In the 1950s, MAO-A-inhibitors were introduced as an antidepressive drug strategy after observations of mood brightening effects of the tuberculostatic drug iproniacide, which is also a non-selective MAO-A.[15]

BASIC PHARMACOLOGY

MECHANISM OF ACTION

Moclobemide is a reversible, competitive inhibitor of the enzyme MAO-A. Selective inhibition of brain MAO-A activity raises noradrenaline and serotonine brain concentrations, and this is generally accepted as the basis of the antidepressant effect of moclobemide. In addition, moclobemide has a negligible effect on monoamine reuptake[16], and there is no relevant interaction with other non-MAO enzyme systems or neurotransmitter receptors.

PHARMACOKINETICS

Moclobemide is rapidly absorbed through the gastrointestinal tract, and maximum plasma concentrations are reached between 0.5 and 2 hours post dosing, corresponding to bioavailability between 50% and 80%. First-pass metabolism is considerable and it is estimated that only about two-thirds of a dose of moclobemide will reach the systemic circulation unmetabolized. Plasma protein binding of moclobemide is around 50%. Terminal half-life of moclobemide is between 1 and 3 hours.[17]

Hepatic metabolism is the major determinant of moclobemide elimination, and the major ways of metabolism include oxidative reactions (hydroxylation, oxidative dealkylation).

SELEGILINE

BASIC PHARMACOLOGY

MECHANISM OF ACTION

Selegiline is a non-competitive, irreversible (suicide) inhibitor of brain MAO-B enzyme. At the usual clinical dose of 10 mg/d, selegiline is selective for MAO-B. At higher doses, the selectivity of selegiline is partially lost. Selegiline was originally developed as an antidepressant; the mechanism involved is believed to be related to increases in brain dopamine concentrations. Selegiline has additional mechanisms beyond MAO-B inhibition including inhibition of catecholamine reuptake and effects at presynaptic catecholamine receptors (see the Chapter on MAO-B inhibitors in this text).

PHARMACOKINETICS

Selegiline is rapidly absorbed from the gastrointestinal tract. Major metabolism occurs in the liver with transformation to desmethyl-selegiline, metamphetamine, and amphetamine. The bioavailability of orally administered selegiline is negligible because of marked first-pass metabolism that yields peak concentrations of the parent drug of 1.1 (±0.4 ng/ml following a 10-mg oral dose. Peak plasma concentrations are reached in 30 minutes to 2 hours, plasma protein binding is 94%, elimination half-life is estimated to be 1.9 (±1.0 hours for the parent compound and the N-desmethyl metabolite). The major plasma component is metamphetamine, which has a half-life of 21 hours, and amphetamine has a half-life of 18 hours.[18,19]

Since Selegiline is an irreversible inhibitor of MAO-B, the half-life of MAO-B inhibition is related to the rate of protein biosynthesis, and persistent, clinically relevant MAO-B inhibition is believed to be present for at least one month after stopping the drug.[20]

REVIEW OF CLINICAL STUDIES

Level-I Studies

No placebo-controlled randomized trials assessing moclobemide or selegiline as antidepressants in PD were identified in this review. The only identified randomized controlled trial was on the use of moclobemide and selegiline.

Steur and Ballering (1997)[21] randomly assigned 10 patients with idiopathic PD and major depression of 3 to 50 months' duration to co-treatment with moclobemide alone (600 mg/d) or moclobemide (600 mg/d) plus selegiline (10 mg/d). Concomitant antiparkinsonian medication had been kept constant in the preceding three months, and study drugs were administered for a period of 6 weeks during which time antiparkinsonian medication was kept unchanged. Depression was rated by the Hamilton Depression Rating Scale (HDRS) one week before and six weeks after treatment

HDRS scores were similar between the two treatment groups, but numerical values are not detailed in the text. However, improvement in the combined moclobemide-selegiline group was significantly more pronounced than in the moclobemide monotherapy group ($p=0.0029$). It is not stated in the paper if improvement in HDRS scores following moclobemide monotherapy was statistically significant compared to baseline.

All patients in the combined moclobemide-selegiline-group experienced improvement in bradykinesia, while this only occurred in one patient in the moclobemide monotherapy group. From the report it appears that at least some patients were fluctuators, but it is stated that daily hours "on" did not change in either of the two treatment arms. Both treatments were well tolerated and there were no increases in blood pressure but the study was performed under tyramine restriction. Interestingly the authors also observed statistically significant increases in MMSE scores in the combined treatment group only. This study had an overall quality score of 74%.

Level-II Studies

Lees et al. (1977)[22] investigated the effects of co-treatment with selegiline in 41 patients with idiopathic PD receiving maximum tolerated doses of levodopa (L-dopa). Depression was present in 15 of these patients and was assessed using the Zung self-rating depression scale. The study was designed as a double-blind, placebo-controlled, cross-over trial where patients were initially treated with selegiline 10 mg/d and reassessed after 1 month of selegiline treatment when they were readmitted to hospital. At varying intervals following post-selegiline assessments patients were switched to placebo in a double-blind fashion, and placebo treatment was maintained for 4 weeks when there was a final assessment. Depression, which was rated as moderate to severe in 15 of 46 patients, did not show any statistically significant improvement during selegiline therapy compared to placebo. However, the main target of this study was the assessment of antiparkinsonian effects of deprenyl in both fluctuating and non-fluctuating PD patients.

Level-III Studies

No qualified studies were identified.

REVIEW OF SAFETY

MOCLOBEMIDE

The most common adverse reactions reported during clinical trials with moclobemide included insomnia, sleep disturbances and restlessness. Furthermore patients treated with moclobemide reported a greater incidence of tremor, nausea and vomiting as compared to placebo-treated patients. The main cardiovascular adverse reactions reported after moclobemide treatment was hypotension.

Concomitant treatment with moclobemide and tricyclic antidepressants can induce severe serotonin-syndrome-like adverse reactions including fatalities so that such combinations are contraindicated. Combined treatment with moclobemide and SSRIs also should be strictly avoided. Moclobemide treatment only has rarely induced hypertensive reactions, and there is no need for dietary tyramine restriction.

SELEGILINE

The safety of selegiline is also summarized elsewhere in this review. The combined use of deprenyl and antidepressants - tricyclic antidepressants and particularly SSRIs - can rarely induce a serotonin syndrome including mental status changes, myoclonus, diaphoresis, agitation, tremor, diarrhoea, and fever.

CONCLUSIONS

EFFICACY

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of MAO-A or MAO-B inhibitors or their combination in the treatment of depression in patients with PD.

SAFETY

There is INSUFFICIENT EVIDENCE to conclude on the safety of MAO-A or MAO-B inhibitors or their combination in depressed patients with PD. However, based on experience in psychiatry, combined treatment with MAO-A inhibitors and either tricyclic antidepressants or SSRIs carries an UNACCEPTABLE RISK.

IMPLICATIONS FOR CLINICAL PRACTICE

Co-treatment of depressed PD patients with the MAO-A inhibitor moclobemide or the MAO-B inhibitor, selegiline, is INVESTIGATIONAL. Combined treatment of depressed parkinsonian patients with moclobemide and tricyclic antidepressants or SSRIs is UNACCEPTABLE, while the risk for a serotonin syndrome during combined treatment with selegiline is very low.

IMPLICATIONS FOR CLINICAL RESEARCH

Because there is a re emergence of interest in the role of MAO inhibitors in the management of depression in the geriatric population, controlled clinical trials assessing these agents in depressed PD patients are warranted. Both placebo-controls and active comparator-controls trials using different antidepressants (imipraminic and SSRIs) are needed to guide clinicians towards "optimal" antidepressive drug regimens for PD patients.

SEROTONIN REUPTAKE INHIBITORS

Six articles included for final screening were about the use of selective serotonine reuptake inhibitors (SSRIs) in PD patients with depression and two qualified (meeting inclusion and exclusion criteria previously described) for final inclusion. Both were open-label uncontrolled studies of the efficacy and safety of paroxetine in depressed PD patients.

PAROXETINE

BASIC PHARMACOLOGY

MECHANISM OF ACTION

Paroxetine hydrochloride is a selective 5-HT reuptake inhibitor (SSRI). The mechanism of action of paroxetine is presumed to be linked to its inhibition of CNS neuronal uptake of 5-HT. Inhibition of presynaptic reaccumulation of neuronally released 5-HT potentiate the action of 5-HT released by neuronal activity. In addition, paroxetine has weak affinity for norepinephrine and dopamine neuronal reuptake.

PHARMACOKINETICS

Paroxetine is efficiently absorbed after oral administration, peak plasma concentrations after oral dosing occur within 2 to 10 hours. Average terminal elimination half-life of plasma paroxetine is about 24 hours. Steady state plasma concentrations are generally achieved within 7-14 days of repeated daily oral dosing of 20 to 30 mg per day. Half-life tends to be prolonged in elderly and patients with renal as well as liver dysfunction. For most patients paroxetine has a linear dose-proportional pharmacokinetics to orally aministered doses. The plasma protein binding of paroxetine is about 95%.

Paroxetine undergoes extensive hepatic first-pass metabolism. The primary metabolic pathway is an oxidation to an intermediate unstable catechol derivate followed a methylisation and subsequent to a glucuronide or sulfat conjugation. These circulating metabolites are substantially less active than the parent compound. Approximately 2% of the administered dose is excreted in urine in 1% in the feces.[23]

REVIEW OF CLINICAL STUDIES

Level-I Studies

No qualified studies were identified.

Level-II Studies

No qualified studies were identified.

Level-III Studies

Ceravolo and co-workers (2000)[24] studied the effects of paroxetine on depressive and motor symptoms in 33 non-demented patients with idiopathic Parkinson's disease and depression. Depression was diagnosed according to DSM-IV criteria and was classified as major depression in fourteen and dysthymia in nineteen patients. All patients were receiving levodopa therapy and eighteen had add-on treatment with dopamine agonists. Antiparkinsonian medication was kept constant during the trial which did not include patients with motor fluctuations. Previous antidepressive treatment (six cases on tricyclic antidepressants) was discontinued at least three months before the study. Paroxetine was given at a starting dose of 5 mg/d and titrated up to 20 mg/d. Depression was rated at baseline and after 1, 3, and 6 months of

treatment using the Beck Depression Inventory (BDI) and the Hamilton Depression Rating Scale 21 (HDRS-21). Parkinsonian motor symptoms were rated at the same time points using UPDRS Part III. Twenty-nine patients completed this 6 months trial, and twenty-five showed clinically evident improvement in mood. BDI and HDRS scores for the whole group improved from baseline to the final visit at month 6 and these score changes were statistically significant. Four patients did not improve.

The UPDRS Motor Score did not change during paroxetine treatment. However, there was a single case of worsened parkinsonian tremor. There were two side-effect related dropouts, both cases developed visual hallucinations after 40 and 55 days of treatment respectively. Other side-effects of this study were considered minor and included dizziness, nausea, anxiety, and palpitation.

Tesei et al.[25] included sixty-five outpatients with idiopathic Parkinson's disease and depression in an open-label prospective tolerability study of paroxetine. Depression was diagnosed according to DSM-IV criteria and HDRS scores were determined at baseline and after three months of treatment with paroxetine. Parkinsonian motor signs were quantified by the UPDRS pre- and post-treatment. Paroxetine was given at a dose of 10 mg/d for the first four weeks and increased to 20 mg/d thereafter. Antiparkinsonian medication (various combinations of levodopa and dopamine agonists in most cases) were kept constant during the course of the trial. The primary outcome parameter for the assessment of paroxetine tolerability was the number of patients withdrawn from the study because of adverse events.

Fifty-two (80%) patients completed the 3-month study period on prescribed dose of paroxetine. These patients had a significant improvement in the HDRS score at month 3 compared to baseline (from a mean of 21.7 to 13.8 points; $p < 0.001$). It is stated that this reduction mainly related to improvements in anxiety and sleep-related symptoms.

Thirteen patients discontinued paroxetine treatment after a mean period of around 12 days because of adverse reactions. These included anxiety, nausea, agitation, confusion, and headache. Two cases (3.1%) were withdrawn because of increases in "off" time and exacerbation of parkinsonian tremor.

SAFETY

SSRIs, when studied in psychiatric populations, have demonstrated an improved safety profile compared to tricyclic antidepressants, particularly related to lower incidences of anticholinergic adverse reactions and cardiac arrhythmias. Common adverse reactions include sleep disorders and gastrointestinal complaints. The use of SSRIs in patients with PD receiving concomitant treatment with deprenyl has been associated with mental status changes, myoclonus, tremor, hyperpyrexia, diarrhoea, hyperreflexia, and diaphoresis ("serotonin syndrome"). A recent survey[13] found a low incidence of 0.24% of reactions possibly consistent with this syndrome and only 0.04% were considered severe.

The two largest prospective Level-III studies on the tolerability of SSRIs in the treatment of parkinsonian depression used paroxetine (see above) and found a low rate of worsening of parkinsonism of about 3% of patients. This worsening included increases in "off" time and exacerbation of tremor[24,25]. There are additional case reports and retrospective observations in the literature describing exacerbation associated both with paroxetine and other SSRIs including fluoxetine and fluvoxamine[26].

In contrast, there are open-label observations reporting beneficial effects of fluoxetine on L-dopa-induced dyskinesias[27].

CONCLUSIONS

EFFICACY

In the absence of data from controlled studies there is INSUFFICIENT EVIDENCE to conclude on the efficacy of paroxetine or SSRIs as a class for treatment of depression specifically in patients with Parkinson's disease.

SAFETY

There is INSUFFICIENT EVIDENCE to conclude on the safety of paroxetine and other SSRIs when used to treat depression in patients with PD. There is sparse and conflicting evidence for a potential of SSRIs to exacerbate parkinsonism, which is based on case reports or small case series that used an open-label study design. Combining SSRIs and selegiline in patients with PD carries a minor risk of inducing a serotonin syndrome.

IMPLICATIONS FOR CLINICAL PRACTICE

To the extent that depression in PD parallels that in non-PD subjects with major depression, clinical experience suggests that administration of paroxetine and other SSRIs is POSSIBLY USEFUL to treat depression in PD. The effects of SSRIs on parkinsonian motor symptoms are presently unclear but probably of little clinical significance.

IMPLICATIONS FOR CLINICAL RESEARCH

There is a strong need to perform well designed, controlled clinical trials of SSRIs in the treatment of depression in patients with PD in order to:

- Compare the efficacy and tolerability of different SSRIs vs. placebo and other antidepressants in PD-associated depression.
- To assess the effects of SSRI co-treatment on parkinsonian symptoms.
- To assess the interaction of various SSRIs with antiparkinsonian drugs, in particular MAO-B inhibitors.

NON-PHARMACOLOGICAL INTERVENTIONS

ELECTROCONVULSIVE THERAPY

Although pharmacotherapy is the mainstay of antidepressive treatment, a number of non-pharmacological interventions are being used by psychiatrists to treat major depression. These include strategies of sleep deprivation and phototherapy in seasonal depression. Electroconvulsive therapy (ECT) has been used for decades as an important therapeutic modality to treat drug-resistant, severe depression, although the frequency of its use has declined considerably following the introduction of effective antidepressive drug treatment.[28,29] More recently, repetitive transcranial magnetic stimulation (TMS) has been introduced as a less invasive replacement for ECT.[30]

Of these various non-pharmacological interventions, only ECT has been used to treat depression in patients with PD, as identified by the results of this literature search for this review.

Electroconvulsive therapy (ECT) was originally introduced as a treatment in psychiatry on the basis of the mistaken belief that schizophrenia and epilepsy were mutually exclusive diseases. With the advent of modern psychopharmacotherapy, the use of ECT

has sharply declined after the 1950's, but problems of drug resistance or intolerance eventually lead to renewed interest in ECT as a treatment modality from the 1980's onward.[29,31]

Recent surveys within the United States indicate that about 80% of patients receive ECT treatment because of major depression.[29,31] Its use is generally restricted to patients with a history of drug resistance and/or those in whom there is a particular need for a rapid clinical response.

Despite the long history of use of ECT in psychiatry its mechanism of action remains largely unknown. Current hypothesis focus on ECT-induced central neurotransmitter changes. Animal studies of electroconvulsive shock have revealed acute increases in brain norepinephrine concentrations together with down regulation of beta-adrenergic and possibly presynaptic alpha-adrenergic receptors. In humans, increases in plasma catecholamine, particularly epinephrine, levels, have been observed following ECT.[28]

Similarly, animal studies using ECS show increases in brain serotonine concentrations, and chronic ECS has been found to enhance behavioral serotonergic responses. Most studies of ECT in humans have failed to detect CSF 5-HIAA changes following ECT, but one study reported ECT-related increases.[32]

Animal studies with ECS also found increases in brain dopamine concentrations[33] and potentiation of dopamine-mediated behavior. In humans, ECT has been reported to enhance the prolactine response to apomorphine.

Not surprisingly, ECS in animals has also been found to induce changes in acetylcholine GABA, endogenous opioids or adenosine receptors. Although it is tempting to speculate that antidepressive effects of human ECT treatment may be related to brain norepinephrine-, serotonine-, or dopamine-changes, the multitude of brain effects resulting from electrically induced seizures - including changes in cerebral blood flow, oxygen and glucose metabolism, protein synthesis, blood brain barrier, disruption and synaptic activity - make it very difficult to define the crucial mechanism of ECT's antidepressive mode of action.[28]

REVIEW OF CLINICAL STUDIES

The search criteria for this review identified 21 articles covering a total of 71 patients with idiopathic PD in whom electroconvulsive therapy was used to treat concomitant depression. All but one study did not qualify for inclusion in this report and were either single-case reports or studies of less than 10 patients and therefore, were excluded.

Level-I Studies

No qualified studies were identified.

Level-II Studies

No qualified studies were identified.

Level-III Studies

Moellentine and co-workers (1998)[34] performed a retrospective chart review from their institution's ECT database. Outcomes of psychiatric symptoms were assessed in 25 patients with parkinsonism vs. 25 age- and gender-matched patients without neurological diseases also receiving ECT for psychiatric indications. Twenty-five patients with parkinsonism were identified, 19 of which received ECT treatment because of major depression according to DSM-III-R diagnostic criteria. Two of the total of 25 may have suffered from drug-induced parkinsonism, while in the others, a diagnosis of idiopathic PD was made by a qualified neurologist. ECT treatment was unilateral or bilateral, patients were given three sessions per week unless postponement or discontinuation was necessary because of ECT-induced delirium. Baseline and post-treatment ratings included the MMSE, global assessment of functioning scale (GAF), brief psychiatric rating scale (BPRS) and the Hamilton Rating Scales for Anxiety and for Depression (HAM-A, HAM-D). Ratings were performed one or two days before the first ECT treatment and one or two days after the last treatment. Patients with PD received a median number of 6 ECT treatments and this number was 7 in the non-neurological control group. The authors noted a significant decrease in both HAM-D and HAM-A scores for both patients with PD and non-neurological controls. Of the 25 patients with PD, 14 reported subjective motor improvement following the course of ECT treatment; however, the article does not give detailed information on concomitant drug treatment. Patients with PD had more ECT-related complications than the non-neurological control group (56% vs. 12%), the most frequent being transient ECT-related delirium. The authors concluded that mood disorders associated with PD are improved by ECT without worsening of the underlying movement disorders, and that depression and anxiety respond in a similar fashion to the same psychiatric symptoms in a non-neurological patient group. The authors, however, also acknowledge that their ratings were performed by an unblinded ECT nurse coordinator introducing a potential of bias.

SAFETY

ECT has been generally well tolerated in patients with PD. In subjects with pre existing L-dopa-induced dyskinesias a transient increase in their severity has been occasionally reported immediately following ECT. The most frequent adverse reactions of ECT in PD has been related to mental status changes including confusional states and transient inter-treatment delirium, affecting up to 50% of patients in some series. This complication may be more frequent in patients with PD compared to non-parkinsonian psychiatric controls.[34,35]

CONCLUSIONS

EFFICACY

There is INSUFFICIENT EVIDENCE available to conclude on the efficacy of ECT in the treatment of depression in patients with PD.

SAFETY

There is INSUFFICIENT EVIDENCE to conclude on the safety of ECT treatment of depression specifically in PD.

IMPLICATIONS FOR CLINICAL PRACTICE

Currently available evidence is insufficient to support the routine use of ECT to treat depression in PD. Its use is considered INVESTIGATIONAL in drug-refractory patients with severe, sustained major depression. There is some indication that the risk of treatment-induced delirium may be greater in patients with PD compared to non-neurological controls. Given the poor quality of efficacy data, the risk-benefit ratio of ECT treatment of depression in PD is presently unclear.

IMPLICATIONS FOR CLINICAL RESEARCH

- Properly designed prospective controlled trials are needed to

establish the efficacy and clinical benefit of ECT treatment in PD patients with major depression. Such studies should be restricted to drug refractory patients and should use sham ECT as a control measure, and blinded evaluators are needed.

- The majority of reports on the use of ECT in depressed patients with PD also find some ECT-related improvement in motor symptoms, including data from one Level-I study.[36] Such effects deserve further study.
- Functional neuroimaging studies before and after ECT may help define mechanisms associated with affective and motoric changes.
- Controlled prospective trials of the possible efficacy of repetitive transcranial magnetic stimulation (rTMS) in patients with PD and depression are warranted.

REFERENCES

1. Cummings JL. Depression and Parkinson's disease: a review. Am J Psychiatry 1992;149:443-454.
2. Mayeux R. The mental status in Parkinson's disease In: Koller WC (ed). Handbook of Parkinson's disease, Second edition. Marcel Dekker Inc. 1992;159-184.
3. Gotham AM, Brown RG, Marsden CD. Depression in Parkinson's disease: a quantitative and qualitative analysis. J Neurol Neurosurg Psychiatry 1986;49:381-389.
4. Santamaria J, Tolosa E, Valles A. Parkinson's disease: a possible subground of idiopathic parkinsonism. Neurology 1986;36:1130-1133.
5. Tandberg E, Larsen JP, Aarsland D, Cumming JL. The occurence of depression in Parkinson's disease. A community-based study. Arch Neurol 1996;53:175-179.
6. Javoy-Agid F, Agid Y. Is the mesocortical dopaminergic system involved in Parkinson's disease. Neurology 1980;30:1326-1330.
7. Hornykiewicz O. Imbalance of brain monoamines and clinical disorders. Prog Brain Res 1982;55:419-429.
8. Mayeux R, Stern Y, Cote L, Williams JBW. Altered serotonin metabolism in depressed patients with Parkinson's disease. Neurology 1984;34:642-646.
9. Findley LJ. Quality of life in Parkinson's disease. Int J Clin Pract 1999;53:404-405.
10. Andersen J, Aabro E, Gulmann N, Hjelmsted A, Pedersen HE. Antidepressive treatment in Parkinson's disease: a controlled trial of the effect of nortriptyline in patients with Parkinson's disease treated with L-Dopa. Acta Neurol Scand 1980;62:210-219.
11. Rollins DE, Alvan G, Bertilsson L, Gillette JR, Mellstrom B, Sjoqvist F, Traskman L. Interindividual differences in amitriptyline demethylation. Clin Pharmacol Ther 1980;28:121-129.
12. Jerling M, Merle Y, Mentre F, Mallet A. Population pharmacokinetics of nortriptyline during monotherapy and during concomitant treatment with drugs that inhibit CYP2D6- an evaluation with the nonparametric maximum likelihood method. Br J Clin Pharmacol 1994;38:453-462.
13. Richard ICH, Kurlan R, Tanner C, Factor S, Hubble J, Suchowe Waters C. Serotonin syndrome and the combined use of deprenyl an antidepressant in Parkinson's disease. Parkinson S Group. Neurology 1997;48:1070-1077.
14. Da Prada M, Kettler R, Keller HH, et al. From Moclobemide to Ro 19-6327 and Ro 41-1049:the development of a new class of reversible, selective MAO-A and MAO-B inhibitors. J Neural Transm 1990;29(suppl):279-292.
15. Crane GE. Iproniazide phosphate: a therapeutic agent for mental disorders and debilitating disease. Psychiatr Res Rep Am Psychiatry Assoc 1957;8:142-152.
16. Da Prada M, Kettler R, Burkard WP, Muggli-Maniglio D, Haefely WE. Neurochemical profile of moclobemide, a short acting and reversible inhibitor of monoamine oxidase type A. J Pharmacol Exp Ther 1989;248:400-414.
17. Mallinger AG, Smith E. Pharmacokinetics of monoamine oxidase inhibitors. Psychopharmacol Bull 1991;27:493-502.
18. Heinonen EH, Anttila MI, Lammintausta RA. Pharmacokinetic aspects of l-deprenyl (selegiline) and its metabolites. Clin Pharmacol Ther 1994;56:742-749.
19. Gerlach M, Youdim MB, Riederer P. Pharmacology of selegiline. Neurology 1996;47:S137-145.
20. The Parkinson Study Group. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. N Engl J Med 1993;328:176-183.
21. Steur EN, Ballering LA. Moclobemide and selegeline in the treatment of depression in Parkinson's disease. J Neurol Neurosurg Psychiatry 1997;63:547.
22. Lees AJ, Shaw KM, Kohout LJ, Stern GM. Deprenyl in parkinson's disease. Lancet 1977;15:791-795.
23. Kaye CM, Haddock RE, Langley PF, Mellows G, et al. A review of the metabolism and pharmacokinetics of paroxetine in man. Acta Psychiatr Scand 1989;350:60-75.
24. Ceravolo R, Nuti A, Piccinni A, Dell'Agnello G, Bellini G, et al. Paroxetine in Parkinson's disease: effects on motor and depressive symptoms. Neurology 2000;55:1216-1218.
25. Tesei S, Antonini A, Canesi M, Zecchinelli A, Mariani CB, Pezzoli G. Tolerability of paroxetine in Parkinson's disease: a prospective study. Mov Disord 2000;15:986-989.
26. Richard IH, Maughn A, Kurlan R. Do Serotonin reuptake inhibitor antidepressants worsen Parkinson's disease? A retrospective case series. Mov Disord 1999;14:155-193.
27. Durif F, Vildailhet M, Bonnet AM, Blin J, Agid Y. Levodopa-induced dyskinesias are improved by fluoxetine. Neurology 1995;45:1855-1858.
28. Sackheim HA, Devanand DP, Nobler MS. Electroconvulsive therapy. In: Bloom FE, Kupfer DJ, eds. Psychopharmacology: The Fourth Generation of Progress. New York: Raven Press, 1995:1123-1141.
29. Thompson JW, Weiner RD, Myers CP. USE of ECT in the United States in 1975, 1980, and -1986. Am J Psychiatry 1994;151:1657-1661.
30. Mally J, Stone TW. Therapeutic and "dose-dependend" effect of repetetive microelectroshock induced by transcranial magnetic stimulation in Parkinson's disease. J Neuroscience Res 1999;57:935-940.
31. National Institute of Health Consensus Conference. Electroconvulsive Therapy. JAMA 1985;254:2103-2108.
32. Rudorfer MV, Manji HK, Potter WZ. Monoaminergic actions of ECT. Clin Neuropharmacol 1992;15:677-678.
33. Nutt DJ, Glue P. The neurobiology of ECT: animal studies. In: Coffey CE, ed. The Clinical Science of Electroconvulsive Therapy. Washington, DC: American Psychiatric Press; 1993: p 213-234.
34. Moellentine C, Rummans T, Ahlskog JE, et al. Effectiveness of ECT in patients with parkinsonism. J Neuropsychiatry 1998;10:187-193.
35. Douyon R, Serby M, Klutchko B, Rotrosen J. ECT and Parkinson's disease revisited: A "naturalistic study. Am J Psychiatry 1989;146:1451-1455.
36. Andersen K, Balldin J, Gottfries CG, Granerus AK, Modigh K, Svennerholm L, Wallin A. A double-blind evaluation of electorconvulsive therapy Parkinson's disease with "On-Off" phenomena. Acta Neurol Scand 1987;76:191-199.

BIBLIOGRAPHY - EXCLUDED FROM ANALYSIS FROM PHARMACOTHERAPY (REASON FOR EXCLUSION)

Cantello R, Aguggia M, Gilli M, et al. Major depression in Parkinson's disease and the mood response to intravenous methylphenidate: possible role of the "hedonic" dopamine synapse. J Neurol Neurosurg Psychiatry 1989;52:724-731. (Single dose study)

Garcia-Monco JC, Padierna A, Beldarrain MG. Selegeline, Fluoxetine, and Depression in Parkinson's disease. Mov Disord 1995;10:352-358. (No valid depression rating)

Goetz CG, Tanner CM, Klawans HL. Bupropion in Parkinson's disease. Neurology 1984;34:1092-1094. (No valid depression rating)

Greenberg R, Barnett S, Meyer S. Treatment of major depression and Parkinson's disease with combined Phenelzine and Amantadine. Am J Psychiatry 1985;142:273-274. (Single case report)

Hargave R, Ashford JW. Phenelzine treatment of depression in Parkinson's disease. Am J Psychiatry 1992;149:1751-1752. (Single case report)

Hauser RA, Zesiewicz TA. Sertraline for the treatment of depression in Parkinson's disease. Mov Disord 1997;12:756-859. (Less than 20 patients)

Jouvent R, Abensour P, Bonnet AM, Widlocher D, Agid Y, Lhermitte F. Antiparkinsonian and antidepressant effects of high doses of Bromocriptine. Journal of Affective Disorders 1983;5:141-145. (Less than 20 patients, duration less than 3 weeks)

Laitinen L. Desipramine in Treatment of Parkinson's disease. Acta Neurol Scand 1969;45:109-113. (No homogenous parkinsonian population)

Mayeux R, Stern Y, Sano M, Williams JBW, Cote LJ. The relationship of serotonin to depression in Parkinson's disease. Mov Disord 1988;3:237-244. (Less than 20 patients)

McCane-Katz EF, Marek KL, Price LH. Serotonergic dysfunktion in depression associated with Parkinson's disease. Neurology 1992;42:1813-1814. (Single case report)

Merea J, Hobson P,. Sertraline for the treatment of depression in Parkinson's disease. Mov Disord 1998;13:622. (No study details reported)

Ritter JL, Alexander B. Retrospective Study of Selegeline-Antidepressant Drug Interactions and a Review of the Literature. Ann Clin Psychiatry 1997;9:7-13. (No valid depression rating)

Strang RR. Imipramine in treatment of Parkinson's disease: a double-blind placebo study. Brit Med J 1965;2:33-34. (No valid depression rating)

Takats A, Tarczy M, Simo M, Szombathelyi E, Bodrogi A, Karpati R. Moclobemide/ aurorix/ treatment in Parkinson's disease with depression. Abstract. 11th International Symposium on Parkinson's disease. Rome, Italy 1994, March 26-30. (Abstract)

BIBLIOGRAPHY - EXCLUDED FROM ANALYSIS FROM ELECTROCONVULSIVE THERAPY (REASON FOR EXCLUSION)

Asnis G. Parkinson's disease, depression, and ECT: a review and case study. Am J Psychiatry 1977;134:191-195. (Single case report)

Atre-Vaidya N, Jampala VC. Electroconvulsive therapy in parkinsonism with affective disorder. Br J Psychiatry 1988;152:55-58. (Single case report)

Barcia D, Martinez PF. Cuadros depresivos en enfermedad de Parkinson tratados con electroshock. Arch Neurobiol 1978;41:393-398. (Single case report)

Baruch P, Jouvent R, Vindreau C, Drouillon C, Widlocher D, Agid Y. Improvement of parkinsonism in ECT-treated depressed patients: Parkinson's disease and depression-related extra-pyramidal disorder. Abstract of the IVth World Congress of Biological Psychology. Philadelphia:PA, 1985. (Abstract)

Brown GC. Parkinsonism, depression and ECT. Am J Psychiatry 1975;132:1084-1085. (No depression rating)

Burke WJ, Peterson J, Rubin EH. Electroconvulsive therapy in the treatment of combined depression and Parkinson's disease. Psychosomatics 1988;29:341-346. (Less than 15 patients)

Dysken M, Evans HM, Chan CH, et al. Improvements of depression and parkinsonism during ECT. Neuropsychobiology 1976;2:81-86. (Single case report)

Figiel GS, Hassen MA, Zorumski C, et al. ECT-induced delirium in depressed patients with Parkinson's disease. J Neuropsychiatry Clin Neurosci 1991;3:405-411. (No depression rating)

Holcomb HH, Sternberg DE, Heninger GR. Effects of electroconvulsive therapy on mood, parkinsonism and tardive dyskinesia in a depressed patients: ECT and dopamine systems. Biol Psychiatry 1983;18:865-873. (Single case report)

Lebensohn ZM, Jenkins RB. Improvement of parkinsonism in depressed patients treated with ECT. Am J Psychiatry 1975;132:283-285. (Less than 15 patients)

Lebensohn ZM. Parkinsonism, depression and ECT. Am J Psychiatry 1975;132:1084. (Less than 15 patients)

Levy LA, Savit JM, Hodes M. Parkinsonism: improvement by electroconvulsive therapy. Arch Phys Med Rehabil 1983;64:432-433. (Single case report)

Lipper S, Bermanzohn PC. Electroconvulsive therapy in patients with parkinsonism. Am J Psychiatry 1975;132:457. (Single case report)

Oh JJ, Rummans TA, O'Connor MK, Ahlskog JE. Cognitive Impairment after ECT in patients with Parkinson's disease and psychiatric illness. Am J Psychiatry 1992;149:271. (No depression rating)

Rainey JM, Faust M. Parkinsonism masked by ECT and psychotropic medication. Am J Psychiatry 1975;132:1084-1085. (Single case report)

Raskin D. Can ECT cure Parkinson's disease. 138th Annual Meeting of the American Psychiatric Association. Abstract of the New Research Program. Dallas: TX, 1985. (Single case report, abstract)

Ward C, Stern GM, Pratt RTC, McKenna P. Electroconvulsive therapy in parkinsonian patients with the „on-off" syndrome. J Neural Transm 1980;49:133-135. (Single case report)

Young RC, Alexopouplos GS, Shamoian CA. Dissociation of motor response from mood and cognition in a parkinsonian patient treated with ECT. Biol Psychiatry 1985;20:566-569. (Single case report)

Yudofsky SC. Parkinson's disease, depression and electroconvulsive therapy: a clinical and neurological synthesis. Compr Psychiatry 1979;20:579-581. (Single case report)

Movement Disorders
Vol. 17, Suppl. 4, 2002, p. S120-S127

Published by Wiley-Liss, Inc.
DOI 10.1002/mds.5573

Drugs to treat Dementia and Psychosis

INTRODUCTION

Contrary to James Parkinson's original belief of lack of impairment of intellectual functions in his disease it is now clear that a majority of patients with idiopathic Parkinson's disease do show signs of distinct and subtle cognitive dysfunction even early in their illness.[1] Many studies have detected deficits in discrete domains of neuropsychological functioning in Parkinson's disease when compared to normal controls including frontal-executive dysfunction[1], as well as impairments of visuo-spatial abilities[2], temporal ordering,[3] memory and attention.[4] Up to 40% of patients with Parkinson's disease[4] eventually fulfill DSM criteria for dementia and these patients are a particular risk for drug-induced psychosis, more rapid progression of disability and reduced survival.[5]

DRUGS FOR TREATING DEMENTIA IN PARKINSON'S DISEASE

Dementia is a late feature of Parkinson's disease where it can affect up to 40% of patients. By contrast, the occurrence of dementia as a presenting feature in a parkinsonian patient suggests an alternative diagnosis such as dementia with Lewy bodies.[6] The prevalence of dementia in idiopathic Parkinson's disease increases with age and it has not been observed in patients with young onset Parkinson's disease.[7] The underlying pathology in dementia of Parkinson's disease is multifactorial and includes concomitant Alzheimer changes, diffuse neocortical Lewy body degeneration as well as vascular co-morbidity.[8]

In contrast to the prevalence and impact of dementia on the progression of disability in Parkinson's disease there is a striking lack of clinical trials assessing interventions aimed at prevention or symptomatic improvement of dementia. To date, no single controlled study is available but this situation is likely to soon change. Given positive evidence for efficacy of cholinesterase inhibitors in the treatment of dementia with Lewy bodies,[9] where a randomized placebo-controlled trial of rivastigmine demonstrated significant improvements on a neuropsychological inventory, there is reason the believe that this class of agents may also show some effect in the dementia of Parkinson's disease. This is supported by anecdotal evidence in a small open-label series with the cholinesterase inhibitor tacrine.[10] Level-I trials of cholinesterase inhibitors in Parkinson's disease are presently being planned.

DRUGS FOR TREATING PSYCHOSIS IN PARKINSON'S DISEASE

BACKGROUND

Drug-induced psychosis is one of the major therapeutic challenges in Parkinson's disease (PD). Drug-induced psychosis can be a dose limiting side-effect even in early monotherapy with levodopa or dopamine agonists in "de-novo" patients and recent double-blind controlled studies have reported incidence figures of up to 6% even in this uncomplicated group of patients.[11-13] The frequency of drug-induced psychosis (DIP) becomes even higher in advanced disease and particularly in patients with dementia[14,15] where up to 22% may be affected. A recent prospective study even found a prevalence rate of 40% when "minor forms" like illusions or transient sensations of presence of a person were included.[16] Psychosis is one of the cardinal risk factors for nursing home placement of patients with PD.[17] The frequency of psychosis is higher with dopamine agonists therapy compared to levodopa monotherapy[12], but anticholinergics, amantadine and deprenyl may all contribute to DIP in patients with PD.[15]

It is frequently impossible to reduce the dose of antiparkinsonian drugs to a level that will lead to resolution of psychosis while maintaining sufficient symptomatic motor control. Such patients need additional antipsychotic therapy to tolerate the required dose levels of L-dopa or dopamine agonists or both.

RATIONALE

In recent years a number of atypical antipsychotic drugs with low potential of causing extrapyramidal adverse reactions have been tested in the setting of DIP in patients with PD in order to control psychiatric symptoms without reducing motor function.

This chapter reviews the available evidence regarding antipsychotic efficacy and effects on PD motor symptoms of various pharmacological approaches used to focal DIP in patients with PD.

METHODS

KEY SEARCH TERMS

Parkinson's disease, parkinsonism and psychosis, hallucinosis, hallucination(s), delusion(s) and antipsychotic(s), antipsychotic therapy, antipsychotic treatment, neuroleptic(s), neuroleptic therapy, and neuroleptic treatment.

SPECIAL EXCEPTIONS TO INCLUSION/ EXCLUSION CRITERIA

Only studies where antipsychotic drugs were specifically tested to control DIP are included in this review. Furthermore, inclusion criteria required that studies used established scales to assess the efficacy of therapies. Reports were excluded if there was a concomitant dose reduction of antiparkinsonian drugs during the trial period, which likely confounded the outcome.

A single randomized double-blind trial[18] comparing olanzapine and clozapine was prematurely stopped and, therefore, less than 20 patients were evaluated. However, since this trial is the only randomized, controlled study providing data on olanzapine in the treatment of DIP, it was included in this review.

CLOZAPINE

BASIC PHARMACOLOGY

MECHANISM OF ACTION

Clozapine is a dibenzodiazepine derivative with potent antipsychotic properties and is classified as an atypical neuroleptic drug because it has been shown to be virtually free of extrapyramidal adverse reactions when used in patients with schizophrenia.[19] The exact pharmacological mechanism of action of clozapine is not fully understood but believed to be mediated by its dopamine receptor binding affinity. Recent evidence supports mesolimbic D1 receptor binding activity with relative sparing of striatal dopamine receptors as well as predominant binding to the D4 receptor subtype.[20,21] Clozapine also acts as an antagonist at adrenergic, cholinergic, histaminergic and serotonergic receptors.

PHARMACOKINETICS

Clozapine is rapidly and almost completely absorbed following oral administration. However, because of extensive hepatic first-pass metabolism, only about 27-50% of an orally administered dose reaches systemic circulation unchanged. Gastrointestinal absorption appears to occur principally in the small intestine and is approximately 90-95% complete within 3.5 hours after an oral dose. Following oral administration of a single 25 mg or 100 mg oral dose of clozapine tablets in healthy adults, it is detectable in plasma within 25 minutes, and peak plasma clozapine concentrations occur at about 1.5 hours.

Clozapine is approximately 95% bound to serum proteins. Clozapine is almost completely metabolized prior to excretion and only trace amounts of unchanged drug are detected in the urine and feces. Approximately 50% of the administered dose is excreted in the urine and 30% in the feces. The desmethylated, hydroxylated, and N-oxide derivatives are the metabolized products found in urine and feces. The desmethyl metabolite has only limited pharmacological activity, while the hydroxylated and N-oxide derivatives are inactive.

Following a single 75 mg or 100 mg oral dose, the elimination half-life of clozapine averages about 8 hours (range: 4-12 hours). Steady-state plasma concentrations of clozapine are achieved after 7-10 days of continuous dosing.

REVIEW OF CLINICAL STUDIES

Twenty-nine reports on clozapine were identified in the literature search. This included only two prospective, randomized, controlled trials, all other reports were uncontrolled trials including the first report by Scholz and Dichgans[22] who described marked antipsychotic efficacy without deterioration of parkinsonism in four patients.

Level-I Studies

Up to now there are only two placebo-controlled, double-blind, randomized, controlled trials[23,24] on the use of clozapine in DIP in PD. A third double-blind, randomized, controlled trial compared the antipsychotic efficacy of olanzapine and clozapine in patients with PD.

The trial conducted by the Parkinson Study Group (1999)[23] included 60 patients with idiopathic PD and DIP. The primary outcome measures were the scores on the 7-point Clinical Global Impression Scale (CGIS; 1 = normal; 7 = among the most severely psychotic patients ever seen) for psychosis and the Unified Parkinson's Disease Rating Scale (UPDRS). Further efficacy parameters included the scores on the Brief Psychiatric Rating Scale (BPRS), on a modified version of the BPRS (four items removed, that were considered unreliable because of confounding with PD, BPRS-M), on the Scale for the Assessment of Positive Symptoms (SAPS), on the Mini-Mental State Examination (MMSE) and the motor as well as tremor score of the UPDRS. The authors report a highly significant improvement in the clozapine group in all psychosis rating scores. The mean (± SE) scores on the CGIS improved by 1.6 ± 0.3 points for the patients receiving clozapine (baseline, mean ± SD, 4.4 ± 0.8), as compared with 0.5 ± 0.2 point for those receiving placebo (baseline 4.4 ± 1.0) ($p<0.001$); the mean scores on the BPRS improved by 9.3 ± 1.5 points for the patients receiving clozapine (baseline 33.1 ± 9.9), as compared with 2.6 ± 1.3 points for those receiving placebo (baseline 35.0 ± 10.7) ($p=0.002$); the mean scores on the BPRS-M improved by 8.6 ± 1.3 points for the patients receiving clozapine (baseline 38.6 ± 12.1), as compared with 2.5 ± 1.2 points for those receiving placebo (baseline 40.6 ± 12.1) ($p=0.003$); the mean scores on the SAPS improved by 11.8 ± 2.0 points for the patients receiving clozapine (baseline 20.9 ± 13.0), as compared with 3.8 ± 1.9 points for those receiving placebo (baseline 22.4 ± 12.3) ($p=0.01$). Seven patients treated with clozapine had an improvement of at least three points on CGIS, as compared with only one patient of the placebo-group. The MMSE score did not change significantly in either group. At the same time there was no evidence of motor decline as assessed by the Unified Parkinson's Disease Rating Scale (total score and motor score). Tremor item 20 of UPDRS Part III showed a significant improvement by clozapine. The clozapine doses necessary to produce the observed effects were less than 25 mg/d with individual cases responding at doses as low as 6.25 mg. Among the 60 patients originally included in the trial, there were 6 dropouts, 3 in each treatment arm. Two of 3 placebo-treated patients discontinued prematurely because of increases in psychosis, another one was hospitalized for pneumonia. One of the dropouts in the clozapine arm was due to reversible leukopenia (white-cell count 2900/m3), one because of myocardial infarction and one because of sedation. No significant difference in the mean neutrophile white-cell blood counts between the placebo and clozapine arm were observed. Similarly there were no significant differences between the groups in changes in orthostatic blood pressure. However, there was a significant but small increase in the mean heart rate of patients on clozapine compared to placebo (on average 3.9 beats per minute), while there was no increase in mean resting heart rate in placebo treated patients. Weight increased by 0.7 kg in the patients receiving clozapine and 0.1 kg in those receiving placebo. Drooling, memory impairment, constipation, confusion, headache, fatigue or day-time sedation occurred with similar frequency and severity in either treatment group without statistically significant differences. This well-designed, four-week, placebo-controlled, prospective trial had a 3- month optional open-label extension in which 53 of 54 patients continued into this phase of the study. There was one further withdrawal from clozapine due to a low white-cell count below 3.000/m3, which returned to normal after discontinuation of therapy. However, there was an unexpectedly high death rate in this open-label extension phase where 6 patients died, 3 of whom had been placed in nursing homes. Their causes of death were: stroke (n=1), bronchitis (n=2) or unknown (n=3). Two further patients died of pneumonia and the 6th case of cardial rest shortly after ending the three months extension treatment. None of the

deaths observed was associated to leukopenia. This study had an overall quality rating score of 93%.

The French Clozapine Parkinson Study Group (1999)[24] also studied 60 patients with PD and DIP; this was a multicenter, four week, double-blind, placebo-controlled trial. Similar to the study conducted by the Parkinson Study Group[23] in the US, the initial clozapine dose was 6.25 mg/day and titrated to a maximum of 50 mg/day. Antiparkinsonian drug doses were kept constant, but it is not stated in the report when attempts to decrease dopaminergic agents had been made. The trial used established scales to rate psychosis (a clinical global impression scale, CGI and the Positive Subscore of the Positive and Negative Syndrome Scale, PANSS) and motor disability (UPDRS) and found significant changes in CGI ($p=0.001$) and PANSS positive subscore ($p<0.001$) items in favor of clozapine at week four (no detailed scores are reported).

Although mean UPDRS motor scores impairment decreased by 3.5 points in the clozapine group versus 3.0 points in the placebo group (no significant difference), 7 patients in the clozapine group reported mild or transient worsening of PD. From the report it appears that such worsening may also have been observed in the placebo group, but it is not clear how many patients reported deterioration of PD. There were no discontinuations due to decreased motor function, and there were no cases of agranulocytosis. Another adverse reaction observed more frequently in the clozapine than in the placebo group was somnolence (no detailed numbers are reported). This study had an overall quality rating score of 58%.

Goetz and colleagues (2000)[18] recently reported a randomized controlled trial comparing clozapine with olanzapine in patients with PD and DIP. Based on statistical power calculations, 28 patients were originally planned for inclusion but the study was prematurely stopped after only 15 patients had completed the study because of unacceptable deterioration of parkinsonism in the olanzapine arm. Primary outcome measure was the scale for Assessment of Positive Symptoms (SAPS) for psychotic symptoms, and secondary outcome measures included the Visual Hallucinations item from the SAPS, the Brief Psychiatric Rating Scale (BPRS) and the ADL and motor subscale of the UPDRS. This was a 9-week trial, and clozapine was initiated at a dose of 6.25 mg/d while the starting dose of olanzapine was 2.5 mg/d. According to clinical need, antipsychotic doses were adjusted to a maximum of 15 mg/d for clozapine or 15 mg/d for olanzapine over 5 weeks; all other medications were kept unchanged for the duration of the trial. At study completion, the mean peak dose for clozapine was 25.8 mg/d and 11.4 mg/d for olanzapine. Patients assigned to clozapine showed statistically significant improvement from baseline in total SAPS (from 13.5 ± 7.7 at baseline to 6.6 ± 6.2 at study end, $p = 0.016$; baseline and study end scores are expressed as mean ± SD) as well as the visual hallucination item on SAPS (from 3.9 ± 1.0 at baseline to 1.9 ± 1.2 at study end, $p = 0.013$) and the BPRS (from 31.4 ± 7.6 at baseline to 23.8 ± 3.9 at study end, $p = 0.031$). UPDRS motor and ADL scores modestly improved in clozapine-treated subjects, but this was not statistically significant over baseline (UPDRS motor score: from 38.9 ± 14.4 at baseline to 32.9 ± 14.4 at study end, $p = 0.125$; UPDRS ADL "on" score: from 13.8 ± 9.4 at baseline to 12.8 ± 10.8 at study end, $p = 0.75$; UPDRS ADL "off" score: from 27.8 ± 7.7 at baseline to 23.3 ± 12.4 at study end, $p = 0.125$). However, change scores (baseline to study end) for the UPDRS assessments of motor examination and ADL between the clozapine and olanzapine groups differed significantly in favor of clozapine (mean change of UPDRS motor score from baseline to study end: clozapine -6.0 ± 8.2, olanzapine $+12.3 \pm 11.5$, $p = 0.004$; mean change of UPDRS ADL "on" score from baseline to study end: clozapine -1.5 ± 4.3, olanzapine $+3.9 \pm 7.2$, $p = 0.017$; mean change of UPDRS ADL "off" score from baseline to study end: clozapine -4.5 ± 10.4, olanzapine $+2.4 \pm 2.1$, $p = 0.005$). Due to a small number of subjects completing the study it was not powered to test significant differences between clozapine and olanzapine regarding antipsychotic efficacy. However, in the olanzapine group, total SAPS and SAPS visual hallucination scores did not change significantly over baseline. The study was terminated (after 15 patients had completed the trial) due to significant deterioration of parkinsonism in the olanzapine group. There were no significant changes in leukocyte counts in either group. This study had an overall quality rating score of 85%.

Level-II Studies

No qualified studies were identified.

Level-III Studies

Three additional Level-III studies[25-27] were included because they met inclusion and exclusion criteria and provided extended follow-up data (12 months or more), which was not reported in the Level-I studies.[18,23,24] A total of 129 patients with idiopathic PD receiving clozapine treatment for DIP is reviewed in these reports. Effective doses reported usually below 50 mg/d and thus similar to effective doses reported in the previous randomized, placebo-controlled, prospective trials. The antipsychotic effects were maintained for up to 37 months in patients remaining in follow-up.

Leukopenia was reported in 5 cases[25,27]. In three of these cases leukopenia was transient, resolving with temporary discontinuation of the drug. Adverse reactions consistently reported in these three studies (even with low doses of clozapine) included sedation, increased drooling and occasionally orthostatic hypotension or "dizziness".

REVIEW OF SAFETY

In all reports identified for this assessment, leukopenia occurred in 12 of a total of 470 parkinsonian patients, with no reported leukopenia-related death. In three of these cases leukopenia was transient, resolving with temporary discontinuation of the drug. Consistently reported side effects, even with the low clozapine doses, included sedation, increased drooling, and occasionally orthostatic hypotension or "dizziness". Clozapine therapy has been associated with potentially fatal myocarditis and cardiomyopathy in physically healthy young adults with schizophrenia[28]. So far no similar cardiac side-effects of clozapine have been reported in patients with PD, and it is presently unclear whether cardiac monitoring should be recommended. In addition, recent reports have associated clozapine treatment with acute interstitial nephritis and venous thromboembolism in psychiatric patients without PD. The addition of low-dose clozapine (less than 50 mg/d) is not usually associated with deterioration of PD-related motor symptoms and may improve parkinsonian rest tremor.[29,30]

CONCLUSIONS

EFFICACY

Based on two Level-I studies, low dose clozapine (less than 50 mg/d) is EFFICACIOUS in short-term (4 weeks) improvement or clearing of drug-induced hallucinosis/psychosis in patients with

PD. Additional Level-III data provides INSUFFICIENT EVIDENCE to conclude on the long-term efficacy of clozapine in patients with PD.

SAFETY

The available evidence suggests that under conditions of weekly blood count monitoring, clozapine treatment of DIP carries an ACCEPTABLE RISK WITH SPECIALIZED MONITORING. The addition of low-dose clozapine (less than 50 mg/d) is not usually associated with worsening of PD-related motor symptoms and may improve parkinsonian rest tremor.

IMPLICATIONS FOR CLINICAL PRACTICE

Clozapine is CLINICALLY USEFUL for the short-term (4 weeks) management of DIP in PD. It is also POSSIBLY USEFUL for the long-term management of some patients. Such treatment does not commonly induce deterioration in parkinsonism. Despite the onerous monitoring, this is the only antipsychotic agent for which there are Level-I studies with positive data specifically in PD.

IMPLICATIONS FOR CLINICAL RESEARCH

- The motor effects of clozapine need further study. This applies to the mechanisms underlying the drugs anti-tremor effect. In addition, properly controlled trials are needed to clarify clozapine's antidyskinetic potentials in levodopa-induced dyskinesias. Further research is needed to develop drugs with similar antipsychotic efficacy but improved safety profile.
- Comparative studies of the efficacy and pharmacoeconomic benefits of clozapine, as compared to other therapies, need to be done.

OLANZAPINE

BASIC PHARMACOLOGY

MECHANISM OF ACTION

Olanzapine is a thienobenzodiazepine of similar chemical structure and antipsychotic properties as clozapine. Four major double-blind, randomized, controlled studies (two vs. placebo, two vs. haloperidol) have established olanzapine's antipsychotic efficacy, which appears to be at least equivalent to that of haloperidol.[31] Also, in schizophrenic patients olanzapine induces less extrapyramidal side-effects than haloperidol. Its mechanism of action is thought to be related to D2-receptor antagonism with predominant effects on the mesolimbic dopaminergic system and comparatively little effect on striatal dopaminergic receptors. In preclinical studies olanzapine exhibited receptor affinities for all subtypes of a D2 and D1 dopamine receptor family. Olanzapine has greater in vitro affinity for serotonin 5HT2 than for dopamine D2 receptors. In addition, binding affinities have been shown for alpha-1 adrenergic, histamine H1, and cholinergic muscarinic receptors.

PHARMACOKINETICS

Olanzapine is well absorbed after oral administration (bioavailability of approximately 80%). Peak plasma concentrations after oral dosing occur within 5 to 8 hours. Olanzapine is metabolized in the liver by conjugative and oxidative pathways. The major circulating metabolite is the 10-N-glucuronide. Oxidative metabolism leads to the formation of N-desmethyl and 2-hydroxymethyl metabolites, both exhibiting minimal in vivo pharmacological activity compared to the parent compound. The plasma protein binding of olanzapine is about 93%, predominantly to albumin and alpha-1-acid-glycoprotein.

The median half-life of olanzapine was 31 hours in both healthy volunteer and patient studies, ranging from 14.5 to 79.5 hours. Half-life tends to be prolonged in elderly compared to non-elderly subjects and in females vs. males. Urinary clearance is the major route of excretion for olanzapine metabolites. Steady-state plasma concentrations of olanzapine are achieved within 7 to 12 days.

REVIEW OF CLINICAL STUDIES

Seven reports were identified, one of which was randomized control trial comparing olanzapine to clozapine (Level-I study). Of the 6 uncontrolled trials, 5 were excluded from final evaluation (see Bibliography), and only one[32] met all inclusion criteria for final evaluation.

Level-I Studies

Goetz et al. (2000)[18]: There is one randomized, controlled trial assessing the efficacy and safety of olanzapine in DIP in PD. In this trial, patients were randomized to clozapine or olanzapine (see section on Clozapine). This trial was originally planned to include 28 patients but was prematurely stopped when safety stopping rules were invoked because of exacerbated parkinsonism in the olanzapine-treated subjects (7 patients treated in this group). Mean peak doses for olanzapine were 11.4 mg/d. Their UPDRS motor scores declined significantly over baseline (from 21.4 ± 12.2 at baseline to 33.7 ± 10.6 at study end, $p = 0.016$), their UPDRS ADL scores showed a statistical trend for deterioration over baseline (UPDRS ADL "on" score: from 11.8 ± 10.4 at baseline to 15.7 ± 8.6 at study end, $p = 0.063$; UPDRS ADL "off" score: from 21.3 ± 10.9 at baseline to 23.9 ± 9.8 at study end, $p = 0.063$); clozapine-treated subjects reported slightly improved UPDRS motor and ADL scores (see section on clozapine). The UPDRS changes were significantly different between the groups (see section on clozapine). Analysis of UPDRS motor subscores showed that the olanzapine-associated decline in motor function was primarily related to deterioration of gait and bradykinesia. At doses used in this trial olanzapine, failed to induce statistically significant improvement in the primary outcome measure (SAPS). Although this trial was not powered to detect statistically significant differences in antipsychotic efficacy between olanzapine and clozapine, clozapine significantly improved psychotic behavior. In combination with the significant negative effect of olanzapine on motor function, the results from this study favor clozapine over olanzapine for treatment of DIP in patients in PD. This study had an overall quality rating score of 85%.

Level-II Studies

No qualified studies were identified.

Level-III Studies

Aarsland and colleagues (1999)[32] performed an open-label, uncontrolled study of olanzapine in 21 patients with PD and psychosis. Antiparkinsonian medication was kept constant for 1 month prior and the first 4 weeks of the 8 week trial. Three subscales of the neuropsychiatric inventory (NPI) for Delusions, Hallucinations, and Agitation were used as primary efficacy parameters together with a clinical global impression rating of psychotic symptoms. Motor symptoms were rated according to the UPDRS Part III. Six

of 21 patients withdrew prematurely (most of them within the first week) due to drowsiness, which led the investigators to decrease the starting dose from initially 5 mg/d to 2.5 mg/d, given as a single evening dose. Maximum doses given were 10 mg/d with a "flexible" non-standardized dose increment schedule. Four weeks into the trial, upward adjustments of dopaminergic treatment were possible and finally performed in 4 of 15 patients remaining in the study. All were on levodopa, and 14 patients received additional antiparkinsonian agents, which were not further detailed in the report. Therefore, it is not clear which drugs were changed in those patients receiving increased dopaminergic therapy after 4 weeks. The sum-score of the NPI items Delusions, Hallucinations, and Agitation decreased by 85% in a statistically significant manner after 8 weeks of olanzapine treatment. By this time, 5 subjects were on 2.5 mg/d, 9 on 5 mg/d, and 1 on 10 mg/d. The mean UPDRS III motor scores were not significantly different between baseline and after 8 weeks of olanzapine treatment. Sedation was the major adverse reaction leading to premature withdrawal from this trial; additional common adverse reactions included concentration and memory impairment, and dry mouth. The results of this study differ from the Level-I study reviewed. The absence of motor deterioration may have been due to increases in antiparkinsonian drugs that were permitted during the trial.

REVIEW OF SAFETY

In addition to the randomized, controlled trial by Goetz and colleagues[18], several of the uncontrolled reports on olanzapine treatment of DIP support olanzapine's possible negative impact on parkinsonian motor symptoms.[33-35] A substantial number of patients mentioned in reports by Graham et al.[33] and Friedman et al.[34,35] seemed to have experienced mild to marked worsening of parkinsonism while receiving olanzapine. Similarly, Molho and Factor[36] recently reported worsened motor function in 9 of 12 patients with PD who received olanzapine for DIP; 6 patients experience marked exacerbations of parkinsonism. Increases in levodopa or dopaminergic dose may have masked motor deterioration in other trials.[37]

Olanzapine has not been associated with hematological adverse reaction in large controlled clinical trials and schizophrenic patients, and there are no reported cases of leukopenia in any of the clinical studies done to date in patients with PD. However, there are two recent case reports where olanzapine exposure in schizophrenic patients was associated with non-fatal agranulocytosis. In one of these cases, olanzapine-induced neutropenia occurred 5 days after resolution of previous clozapine-induced neutropenia.[38,39] Furthermore, Meissner and colleagues[40] recently reported two parkinsonian patients who developed reversible leucopenia while being treated with olanzapine, both had a history of clozapine-induced leucopenia.

CONCLUSIONS

EFFICACY

Reported to date, there is information on 91 patients with PD who have been treated olanzapine, only 28 of which have been treated under clinical study situations meeting study quality criteria for inclusion in this review. The only Level-I study had to be prematurely stopped preventing full evaluation of antipsychotic efficacy. Therefore, there is INSUFFICIENT EVIDENCE to demonstrate efficacy of olanzapine in the treatment of DIP in patients with PD.

SAFETY

Based on Level-I data, olanzapine at low conventional doses carries an UNACCEPTABLE RISK of motor deterioration.

IMPLICATIONS FOR CLINICAL PRACTICE

Given the paucity of efficacy data, established safety concerns, and available alternative treatments, olanzapine is considered NOT USEFUL for the routine management of psychosis in patients with PD.

IMPLICATIONS FOR CLINICAL RESEARCH

- Very low doses of olanzapine have not been tested. Because of the problems with conventional low doses, well-designed, controlled trials in sufficient numbers of patients with predetermined stopping rules would be needed to assess the efficacy, safety and clinical usefulness of olanzapine for the treatment of DIP in PD.

QUETIAPINE

BASIC PHARMACOLOGY

MECHANISM OF ACTION

Quetiapine is an atypical dibenzothiazepine structurally similar to clozapine. It is a potent serotonin 5-HT2 receptor antagonist and moderate dopamine D2 receptor antagonist. The mechanism of Quetiapine's antipsychotic action is thought to be related to its combined serotonin 5-HT2 and dopamine D2 receptor antagonism. In addition, quetiapine is an antagonist of serotonin 5-HT1A, dopamine D1, histamine H1, and alpha1 and alpha2 adrenergic receptors.[41]

From clinical studies, the effect of quetiapine on positive and negative symptoms of schizophrenia appears to be similar to that of haloperidol without causation of significant extrapyramidal symptoms.

PHARMACOKINETICS

Quetiapine is rapidly absorbed after oral administration with peak plasma concentrations occurring in about 1.5 hours. About 83% of the drug is bound to plasma proteins. Quetiapine is extensively metabolized by the liver and major metabolites including an inactive sulfoxide metabolite and an acid metabolite. The mean half-life of quetiapine is about 6 hours in patients with normal hepatic function.[41]

REVIEW OF CLINICAL STUDIES

Level-I Studies

No qualified studies were identified.

Level-II Studies

No such studies were identified.

Level-III Studies

Of eight uncontrolled study reports, only one met the inclusion criteria for this review.[42]

Fernandez et al. (1999)[42]: In this trial, 35 patients with idiopathic PD, 20 of whom were demented, received add-on treatment with quetiapine over 4 weeks. Only 24 had not received neuroleptic pre-treatment, 8 were switched over from previous clozapine treatment, and 3 switched over from previous olanzapine treatment. Only 10 of the previously untreated patients had both baseline assessments and follow-up evaluations of antipsychotic scales

(BPRS; mean BPRS score at baseline 32.6, at follow-up 22.8 at follow-up, p = 0.024) and motor symptoms (UPDRS motor section; UPDRS motor score at baseline 42.2, at follow-up 44.9, p = 0.599). The mean final quetiapine dose was 40.6 mg/day. Twenty of 24 previously untreated patients improved (pre- versus post-treatment BPRS scores were available for 10 patients and showed significant improvement). The mean post-treatment UPDRS motor score was not statistically significant from baseline. Patients pre-treated with the atypical neuroleptics, clozapine and olanzapine, were "successfully switched" to quetiapine in 5 of 11 cases. Six patients were withdrawn from quetiapine because of confusion, erratic behavior, and increased hallucinations (five previously receiving clozapine, one previously on olanzapine). Twenty of 24 previously untreated patients experienced no worsening of motor symptoms while 1 of 11 patients switched from clozapine or olanzapine experienced increased tremor on quetiapine.

REVIEW OF SAFETY

In large controlled clinical trials of schizophrenic patients, associations of quetiapine with hematological side-effects have not been observed and there was no leukopenia in any of the reported clinical studies in PD disease so far.

Information on the motor effects of quetiapine is contradictory but it has been associated with worsening of parkinsonism in a report by Fernandez et al.[43] extending the data on the original 35 patients to a total of 69 patients with Parkinson's disease (44 neuroleptic naive and 25 switch-over patients). Eighteen percent of the patients treated with quetiapine for drug-induced psychosis experienced mild to moderate worsened parkinsonism. By contrast, other reports on quetiapine treatment of drug-induced psychosis in Parkinson's disease that were identified but did not fulfil all inclusion criteria indicate that this drug is effective in controlling drug-induced psychosis in PD without worsening motor symptoms.[44-48]

CONCLUSIONS

EFFICACY

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of quetiapine in treating DIP in patients with PD.

SAFETY

Currently there is INSUFFICIENT EVIDENCE to conclude on short- and long-term safety of quetiapine.

IMPLICATIONS FOR CLINICAL PRACTICE

Based on the available evidence, treatment of DIP in PD with quetiapine is considered INVESTIGATIONAL.

IMPLICATIONS FOR CLINICAL RESEARCH

- Placebo-controlled and clozapine-controlled trials are needed to assess the efficacy, clinical usefulness, and safety of quetiapine treatment of DIP in PD.
- In consideration of the impact of psychoses on nursing home placement, the pharmacoeconomic impact of quetiapine and all antipsychotics should be assessed in appropriate long-term clinical studies.

RISPERIDONE, ZOTEPINE, MIANSERIN AND ONDANSETRON

Several additional drugs have been used to treat DIP in PD, however, none of these reports met inclusion and exclusion criteria for this review. Six reports were identified in the use of risperidone in DIP of PD. All reports were uncontrolled trials, most often in a form of case reports, and the maximum number of patients was 10.[49] The use of zotepine was reported in two letters reviewing results from 4 patients with PD, while a single report assessed the efficacy of the 5-HT2 receptor antagonist mianserin in 12 patients with PD and DIP. Five reports, of whom three were on the same patient group[50-52], were identified in the use of ondansetron for DIP in PD. Only one of these studies[53] included more than 20 patients; however, this was a study, assessing the validity, reliability, and stability of a newly developed Parkinson's Psychosis Rating Scale (PPRS), and did not primarily test efficacy and safety of ondansetron.

CONCLUSIONS

There is INSUFFICIENT DATA for any conclusion about the efficacy/safety for risperidone, zotepine, mianserin and ondansetron in the treatment of drug-induced psychosis in PD.

REFERENCES

1. Lees AJ, Smith E. Cognitive deficits in the early stages of Parkinson's disease. Brain 1983;106:257-270.
2. Ransmayr G, Schmidhuber-Eiler B, Karamat E, et al. Visuoperception and visuospatial and visuorotational perform in Parkinson's disease. J Neurol 1987;235:99-101.
3. Artieda J, Pastor MA, Lacruz F, Obeso JA. Temporal discrimination is abnormal in Parkinson's disease. Brain 1992;115:199-210.
4. Brown RG, Marsden CD. Cognitive function in Parkinson's disease: from description to theory. Trends Neurosci 1990;13:21-29.
5. Poewe WH, Wenning GK. The natural history of Parkinson's disease. Ann Neurol 1998;44:S1-S9.
6. McKeith IG, Galasko D, Kosaka K, Perry EK, et al. Consensus guidelines for the clinical and pathological diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology 1996;47:1113-1124.
7. Schrag A, Ben-Shlomo Y, Brown R, Marsden CD, Quinn N. Young-onset Parkinson's disease revisited - clinical features, nature history, and mortality. Mov Disord 1998;13:885-894.
8. Hughes Aj, Daniel SE, Blankson S, Lees AJ. A clinicopathologic study of 100 cases of Parkinson's disease. Arch Neurol 1993;50:140-148.
9. McKeith I, Del Ser T, Spano P, Emre M, et al. Efficacy of rivastigmine in dementia with Lewy bodies: a randomized, double-blind, placebo-controlled international study. Lancet 2000;356:2031-2036.
10. Hutchinson M, Fazzini E. Cholinesterase inhibition in Parkinson's disease. J Neurol Neurosurg Psychiatry 1996:61:324-325.
11. Parkinson's Disease Research Group in the United Kingdom. Comparisons of therapeutic effects of levodopa, levodopa and selegiline, and bromocriptine in patients with early, mild Parkinson's disease: three year interim report. Parkinson's Disease Research Group in the United Kingdom. BMJ 1993;307:469-472.
12. Rascol O, Brooks DJ, Brunt ER, Korczyn AD, Poewe WH, Stocchi F. Ropinirole in the treatment of early Parkinson's disease: a 6-month interim report of a 5-year levodopa-controlled study. 056 Study Group. Mov Disord 1998;13:39-45.
13. Rinne UK, Bracco F, Chouza C, et al. Cabergoline in the treatment of early Parkinson's disease: results of the first year of treatment in a double-blind comparison of cabergoline and levodopa. The PKDS009 Collaborative Study Group. Neurology 1997;48:363-368.
14. Factor SA, Molho ES, Podskalny GD, Brown D. Parkinson's disease: drug-induced psychiatric states. Adv Neurol 1995;65:115-138.
15. Friedman JH. Management of psychosis in Parkinson's disease. In: Koller WC, Paulson G, eds. Therapy of Parkinson's disease. New York: Marcel Dekker; 1995. p. 521-532.
16. Fénelon G, Mahieux F, Huon R, Ziégler M. Hallucinations in Parkinson's disease. Prevalence, phenomenology and risk factors. Brain 2000;123:733-745.
17. Goetz CG, Stebbins GT. Risk factors for nursing home placement in advanced Parkinson's disease. Neurology 1993;43:2227-2229.
18. Goetz CG, Blasucci LM, Leurgans S, Pappert EJ. Olanzapine and clozapine. Comparative effects on motor function in hallucinating PD patients. Neurology 2000;55:748-749.

19.Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. Arch Gen Psychiatry 1988;45:789-796.
20.Baldessarini RJ, Frankenburg FR. Clozapine. A novel antipsychotic agent. N Engl J Med 1991;324:746-754.
21.Van Tol HH, Bunzow JR, Guan HC, et al. Cloning of the gene for a human dopamine D4 receptor with high affinity for the antipsychotic clozapine. Nature 1991;350:610-614.
22.Scholz E, Dichgans J. Treatment of drug-induced exogenous psychosis in parkinsonism with clozapine and fluperlapine. Eur Arch Psychiatry Neurol Sci 1985;235:60-64.
23.The Parkinson Study Group. Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. The Parkinson Study Group. N Engl J Med 1999;340:757-763.
24.The French Clozapine Parkinson Study Group. Clozapine in drug-induced psychosis in Parkinson's disease. The French Clozapine Parkinson Study Group. Lancet 1999;353:2041-2042.
25.Wagner ML, Defilippi JL, Menza MA, Sage JI. Clozapine for the treatment of psychosis in Parkinson's disease: chart review of 49 patients. J Neuropsychiatry Clin Neurosci 1996;8:276-280.
26.Ruggieri S, De-Pandis MF, Bonamartini A, Vacca L, Stocchi F. Low dose of clozapine in the treatment of dopaminergic psychosis in Parkinson's disease. Clin Neuropharmacol 1997;20:204-209.
27.Widman LP, Burke WJ, Pfeiffer RF, McArthur CD. Use of clozapine to treat levodopa-induced psychosis in Parkinson's disease: retrospective review. J Geriatr Psychiatry Neurol 1997;10:63-66.
28.Killian JG, Kerr K, Lawrence C, Celermajer DS. Myocarditis and cardiomyopathy associated with clozapine. Lancet 1999;354:1841-1845.
29.Hagg S, Spigset O, Soderstrom TG. Association of venous thromboembolism and clozapine [letter]. Lancet 2000;355:1155-1156.
30.Elias TJ, Bannister KM, Clarkson AR, Faull D, Faull RJ. Clozapine-induced acute interstitial nephritis [letter]. Lancet 1999;354:1180-1181.
31.The European Agency for the Evaluation of Medical Products. Zyprexa. International Nonproprietary Name (INN): Olanzapine. Committee for Proprietary Medicinal Products. European Public Assessment Report (EPAR). CPMP/646-96. 1996. (GENERIC) Ref Type: Report
32.Aarsland D, Larsen JP, Lim NG, Tandberg E. Olanzapine for psychosis in patients with Parkinson's disease with and without dementia. J Neuropsychiatry Clin Neurosci 1999;11:392-394.
33.Graham JM, Sussman JD, Ford KS, Sagar HJ. Olanzapine in the treatment of hallucinosis in idiopathic Parkinson's disease: a cautionary note. J Neurol Neurosurg Psychiatry 1998;65:774-777.
34.Friedman J. Olanzapine in the treatment of dopaminomimetic psychosis in patients with Parkinson's disease [letter; comment]. Neurology 1998;50:1195-1196.
35.Friedman JH, Goldstein S, Jacques C. Substituting clozapine for olanzapine in psychiatrically stable Parkinson's disease patients: results of an open label pilot study. Clin Neuropharmacol 1998;21:285-288.
36.Molho ES, Factor SA. Worsening of motor features of parkinsonism with olanzapine [In Process Citation]. Mov Disord 1999;14:1014-1016.
37.Wolters EC, Jansen EN, Tuynman QH, Bergmans PL. Olanzapine in the treatment of dopaminomimetic psychosis in patients with Parkinson's disease. Neurology 1996;47:1085-1087.
38.Benedetti F, Cavallaro R, Smeraldi E. Olanzapine-induced neutropenia after clozapine-induced neutropenia. Lancet 1999;354:567.
39.Naumann R, Felber W, Heilemann H, Reuster T. Olanzapine-induced agranulocytosis. Lancet 1999;354:566-567.
40.Meissner W, Schmidt T, Kupsch A, Trottenberg T, Lempert T. Reversible leucopenia related to olanzapine. Mov Disord 1999;14:872-889.
41.Matheson AJ, Lamb HM. Quetiapine. A review of its clinical potential in the managment of psychotic symptoms in Parkinson's disease. CNS Drugs 2000;14:157-172.
42.Fernandez HH, Friedman JH, Jacques C, Rosenfeld M. Quetiapine for the treatment of drug-induced psychosis in Parkinson's disease. Mov Disord 1999;14:484-487.
43.Fernandez HH. Quetiapine for l-dopa-induced psychosis in PD. Neurology 2000;55:899.
44.Weiner WJ, Minagar A, Shulman LM. Quetiapine for l-dopa-induced psychosis in PD. Neurology 2000;54:1538.
45.Dewey RB, O'Suilleabhain PE. Treatment of drug-induced psychosis with quetiapine and clozapine in Parkinson's disease. Neurology 2000;55:1753-1754.
46.Menza MM, Palermo B, Mark M. Quetiapine as an alternative to clozapine in the treatment of dopamimetic psychosis in patients with Parkinson's disease. Ann Clin Psychiatry 1999;11:141-144.
47.Targum SD, Abbott JL. Efficacy of quetiapine in Parkinson's patients with psychosis. J Clin Psychopharmacol 2000;20:54-60.
48.Parsa MA, Bastani B. Quetiapine (Seroquel) in the treatment of psychosis in patients with Parkinson's disease. J Neuropsychiatry Clin Neurosci 1998;10:216-219.
49.Meco G, Alessandria A, Bonifati V, Giustini P. Risperidone for hallucinations in levodopa-treated Parkinson's disease patients [letter]. Lancet 1994;343:1370-1371.
50.Zoldan J, Friedberg G, Goldberg SH, Melamed E. Ondansetron for hallucinosis in advanced Parkinson's disease [letter]. Lancet 1993;341:562-563.
51.Zoldan J, Friedberg G, Livneh M, Melamed E. Psychosis in advanced Parkinson's disease: treatment with ondansetron, a 5-HT3 receptor antagonist. Neurology 1995;45:1305-1308.
52.Zoldan J, Friedberg G, Weizman A, Melamed E. Ondansetron, a 5-HT3 antagonist for visual hallucinations and paranoid delusional disorder associated with chronic L-DOPA therapy in advanced Parkinson's disease. Adv Neurol 1996;69:541-544.
53.Friedberg G, Zoldan J, Weizman A, Melamed E. Parkinson Psychosis Rating Scale: a practical instrument for grading psychosis in Parkinson's disease. Clin Neuropharmacol 1998;21:280-284.

BIBLIOGRAPHY - EXCLUDED FROM ANALYSIS (REASON FOR EXCLUSION)

CLOZAPINE

Auzou P, Hannequin D, Landrin I, Cochin JP, Moore N. Worsening of psychotic symptoms by clozapine in Parkinson's disease [letter]. Lancet 1994;344:955. (Less than 20 evaluated patients)
Bernardi F, Del-Zompo M. Clozapine in idiopathic Parkinson's disease [letter; comment]. Neurology 1990;40:1151-1152. (No standardized efficacy assessment neither for psychosis nor for parkinsonism; number of evaluated patients not mentioned)
Chacko RC, Hurley RA, Harper RG, Jankovic J, Cardoso F. Clozapine for acute and maintenance treatment of psychosis in Parkinson's disease. J Neuropsychiatry Clin Neurosci 1995;7:471-475. (Less than 20 evaluated patients)
Dewey RB, O'Suilleabhain PE. Treatment of drug-induced psychosis with quetiapine and clozapine in Parkinson's disease. Neurology 2000;55:1753-1754. (No standardized efficacy assessment neither for psychosis nor for parkinsonism; no homogeneous IPD population; not mentioned if antiparkinsonian drugs were reduced)
Fernandez HH. Quetiapine for l-dopa-induced psychosis in PD. Neurology 2000;55:899. (No standardized efficacy assessment neither for psychosis nor for parkinsonism; not mentioned if antiparkinsonian drugs were reduced)
Fernandez HH, Lannon MC, Friedman JH, Abbott BP. Clozapine replacement by quetiapine for the treatment of drug-induced psychosis in Parkinson's disease. Mov Disord 2000;15:579-581. (Less than 20 patients evaluated)
Factor SA, Brown D, Molho ES, Podskalny GD. Clozapine: a 2-year open trial in Parkinson's disease patients with psychosis. Neurology 1994;44:544-546. (Less than 20 evaluated patients)
Factor SA, Brown D. Clozapine prevents recurrence of psychosis in Parkinson's disease. Mov Disord 1992;7:125-131. (Less than 20 evaluated patients)
Friedman JH, Lannon MC. Clozapine in the treatment of psychosis in Parkinson's disease. Neurology 1989;39:1219-1221. (Less than 20 evaluated patients)
Gonski PN. The use of clozapine in Parkinson's disease [letter]. Aust N Z J Med 1994;24:585. (Less than 20 evaluated patients)
Greene P, Cote L, Fahn S. Treatment of drug-induced psychosis in Parkinson's disease with clozapine. Adv Neurol 1993;60:703-706. (Less than 20 evaluated patients)
Greene P. Clozapine therapeutic plunge in patient with Parkinson's disease [letter]. Lancet 1995;345:1172-1173. (Less than 20 evaluated patients)
Kahn N, Freeman A, Juncos JL, Manning D, Watts RL. Clozapine is beneficial for psychosis in Parkinson's disease. Neurology 1991;41:1699-1700. (Less than 20 evaluated patients)
Lew MF, Waters CH. Clozapine treatment of parkinsonism with psychosis. J Am Geriatr Soc 1993;41:669-671. (Less than 20 evaluated patients)
Meltzer HY, Kennedy J, Dai J, Parsa M, Riley D. Plasma clozapine levels and the treatment of L-DOPA-induced psychosis in Parkinson's disease. A high potency effect of clozapine. Neuropsychopharmacology 1995;12:39-45. (Less than 20 evaluated patients)
Ostergaard K, Dupont E. Clozapine treatment of drug-induced psychotic symptoms in late stages of Parkinson's disease [letter]. Acta Neurol Scand 1988;78:349-350. (Less than 20 evaluated patients)
Pfeiffer RF, Kang J, Graber B, Hofman R, Wilson J. Clozapine for psychosis in Parkinson's disease. Mov Disord 1990;5:239-242. (Less than 20 evaluated patients)
Pinter MM, Helscher RJ. Therapeutic effect of clozapine in psychotic decompensation in idiopathic Parkinson's disease. J Neural Transm Park Dis Dement Sect 1993;5:135-146. (Less than 20 evaluated patients)

Rabey JM, Treves TA, Neufeld MY, Orlov E, Korczyn AD. Low-dose clozapine in the treatment of levodopa-induced mental disturbances in Parkinson's disease. Neurology 1995;45:432-434. (Antiparkinsonian dose reduction during clozapine; no standardized efficacy assessment for psychosis)

Roberts HE, Dean RC, Stoudemire A. Clozapine treatment of psychosis in Parkinson's disease. J Neuropsychiatry Clin Neurosci 1989;1:190-192. (Less than 20 evaluated patients)

Rosenthal SH, Fenton ML, Harnett DS. Clozapine for the treatment of levodopa-induced psychosis in Parkinson's disease [letter]. Gen Hosp Psychiatry 1992;14:285-286. (Less than 20 evaluated patients)

Rudolf J, Grond M, Neveling M, Heiss WD. Clozapine-induced agranulocytosis and thrombopenia in a patient with dopaminergic psychosis. J Neural Transm 1997;104:1305-1311. (Less than 20 evaluated patients)

Scholz E, Dichgans J. Treatment of drug-induced exogenous psychosis in parkinsonism with clozapine and fluperlapine. Eur Arch Psychiatry Neurol Sci 1985;235:60-64. (Less than 20 evaluated patients)

Trosch RM, Friedman JH, Lannon MC, et al. Clozapine use in Parkinson's disease: a retrospective analysis of a large multicentered clinical experience. Mov Disord 1998;13:377-382. (Inhomogenous study population (patients with and without DIP); no standardized efficacy assessment neither for psychosis nor for parkinsonism)

Weiner WJ, Minagar A, Shulman LM. Quetiapine for l-dopa-induced psychosis in PD. Neurology 2000;54:1538. (less than 20 evaluated patients)

Wolk SI, Douglas CJ. Clozapine treatment of psychosis in Parkinson's disease: a report of five consecutive cases. J Clin Psychiatry 1992;53:373-376. (Less than 20 evaluated patients)

Wolters EC, Hurwitz TA, Mak E, et al. Clozapine in the treatment of parkinsonian patients with dopaminomimetic psychosis. Neurology 1990;40:832-834. (Less than 20 evaluated patients)

OLANZAPINE

Wolters EC, Jansen EN, Tuynman QH, Bergmans PL. Olanzapine in the treatment of dopaminomimetic psychosis in patients with Parkinson's disease. Neurology 1996;47:1085-1087. (Less than 20 evaluated patients)

Friedman J. Olanzapine in the treatment of dopaminomimetic psychosis in patients with Parkinson's disease [letter; comment]. Neurology 1998;50:1195-1196. (No homogeneous IPD population; antiparkinsonian dose reduction during olanzapine)

Friedman JH, Goldstein S, Jacques C. Substituting clozapine for olanzapine in psychiatrically stable Parkinson's disease patients: results of an open label pilot study. Clin Neuropharmacol 1998;21:285-288. (Less than 20 evaluated patients)

Graham JM, Sussman JD, Ford KS, Sagar HJ. Olanzapine in the treatment of hallucinosis in idiopathic Parkinson's disease: a cautionary note. J Neurol Neurosurg Psychiatry 1998;65:774-777. (Less than 20 evaluated patients)

Menza MM, Palermo B, Mark M. Quetiapine as an alternative to clozapine in the treatment of dopamimetic psychosis in patients with Parkinson's disease. Ann Clin Psychiatry 1999;11:141-144. (Less than 20 evaluated patients)

Molho ES, Factor SA. Worsening of motor features of parkinsonism with olanzapine [In Process Citation]. Mov Disord 1999;14:1014-1016. (Less than 20 evaluated patients)

QUETIAPINE

Fernandez HH. Quetiapine for l-dopa-induced psychosis in PD. Neurology 2000;55:899. (Letter to the Editor)

Matheson AJ, Lamb A. Quetiapine. A review of its clinical potential in the management of psychotic symptoms in Parkinson's disease. CNS Drugs 2000;14:157-172. (Review)

Menza MM, Palermo B, Mark M. Quetiapine as an alternative to clozapine in the treatment of dopamimetic psychosis in patients with Parkinson's disease. Ann Clin Psychiatry 1999;11:141-144. (Less than 20 evaluated patients)

Parsa MA, Bastani B. Quetiapine (Seroquel) in the treatment of psychosis in patients with Parkinson's disease. J Neuropsychiatry Clin Neurosci 1998;10:216-219. (Less than 20 evaluated patients)

Targum SD, Abbott JL. Efficacy of quetiapine in Parkinson's patients with psychosis. J Clin Psychopharmacol 2000;20:54-60. (Less than 20 evaluated patients)

RISPERIDONE

Damecour CL, Turcotte JR. Therapeutic dilemma: psychosis and Parkinson's disease [letter]. Can J Psychiatry 1995;40:640-641. (Less than 20 evaluated patients)

Ford B, Lynch T, Greene P. Risperidone in Parkinson's disease [letter; comment]. Lancet 1994;344:681. (Less than 20 evaluated patients)

Meco G, Alessandri A, Giustini P, Bonifati V. Risperidone in levodopa-induced psychosis in advanced Parkinson's disease: an open-label, long-term study. Mov Disord 1997;12:610-612. (Less than 20 evaluated patients)

Meco G, Alessandria A, Bonifati V, Giustini P. Risperidone for hallucinations in levodopa-treated Parkinson's disease patients [letter]. Lancet 1994;343:1370-1371. (Less than 20 evaluated patients)

Rich SS, Friedman JH, Ott BR. Risperidone versus clozapine in the treatment of psychosis in six patients with Parkinson's disease and other akinetic-rigid syndromes. J Clin Psychiatry 1995;56:556-559. (Less than 20 evaluated patients)

Workman-RH J, Orengo CA, Bakey AA, Molinari VA, Kunik ME. The use of risperidone for psychosis and agitation in demented patients with Parkinson's disease. J Neuropsychiatry Clin Neurosci 1997;9:594-597. (Less than 20 evaluated patients)

ZOTEPINE

Arnold G, Trenkwalder C, Schwarz J, Oertel WH. Zotepine reversibly induces akinesia and rigidity in Parkinson's disease patients with resting tremor or drug-induced psychosis [letter]. Mov Disord 1994;9:238-240. (Less than 20 evaluated patients)

Spieker S, Stetter F, Klockgether T. Zotepine in levodopa-induced Psychosis. Mov Disord 1995;10:795-797. (Less than 20 evaluated patients)

MIANSERIN

Ikeguchi K, Kuroda A. Mianserin treatment of patients with psychosis induced by antiparkinsonian drugs. Eur Arch Psychiatry Clin Neurosci 1995;244:320-324. (Less than 20 evaluated patients)

ONDANSETRON

Eichhorn TE, Brunt E, Oertel WH. Ondansetron treatment of L-dopa-induced psychosis [letter; comment]. Neurology 1996;47:1608-1609. (Less than 20 evaluated patients)

Friedberg G, Zoldan J, Weizman A, Melamed E. Parkinson Psychosis Rating Scale: a practical instrument for grading psychosis in Parkinson's disease. Clin Neuropharmacol 1998;21:280-284. (Study that not primarily test efficacy and safety of ondansetron)

Zoldan J, Friedberg G, Goldberg SH, Melamed E. Ondansetron for hallucinosis in advanced Parkinson's disease [letter]. Lancet 1993;341:562-563. (Less than 20 evaluated patients)

Zoldan J, Friedberg G, Livneh M, Melamed E. Psychosis in advanced Parkinson's disease: treatment with ondansetron, a 5-HT3 receptor antagonist. Neurology 1995;45:1305-1308. (Less than 20 evaluated patients)

Zoldan J, Friedberg G, Weizman A, Melamed E. Ondansetron, a 5-HT3 antagonist for visual hallucinations and paranoid delusional disorder associated with chronic L-DOPA therapy in advanced Parkinson's disease. Adv Neurol 1996;69:541-544. (Less than 20 evaluated patients)

Movement Disorders
Vol. 17, Suppl. 4, 2002, p. S128-S147

Published by Wiley-Liss, Inc.
DOI 10.1002/mds.5574

Surgical Treatment for Parkinson's Disease: Deep Brain Surgery

INTRODUCTION

BACKGROUND

The degeneration of dopaminergic and other transmitter systems in Parkinson's disease (PD) leads to profound disturbances in basal ganglia, thalamic, cortical and brainstem physiology, producing striking abnormalities in motor function. For the first time, the cellular pathophysiology of the motor dysfunction is beginning to be better understood, thereby providing a stronger scientific rationale for surgical interventions. Yet, to date, there are no treatments that prevent, halt, or cure PD. At best these treatments, including surgical strategies, offer only symptomatic relief or control of motor complications associated with drug treatment.

Both pallidotomy and thalamotomy were extensively used in the treatment of PD in the1950's and 1960's. With the introduction of levodopa (L-dopa) in the1960's and the realization of its striking benefits, surgery was almost abandoned and used only for patients with severe tremor. Surgical therapy is now being used earlier and more often due to several factors. First, medications have shortcomings, and a large number of patients continue to be disabled despite the best available drug therapy. Second, technical improvements in brain imaging, in neurosurgical techniques and devices, and in intraoperative electrophysiology have made procedures safer and more accurate. These advances allow for a better understanding of the basis for intervention at specific targets, and initial reports of improvements with surgery have spearheaded a re-evaluation of surgery in patients with PD.

With the rediscovery of functional neurosurgical procedures for the treatment of PD, there have been a large number of reports testing a variety of surgical approaches to treat PD. These surgical procedures are complex, and published reports often are from the early stages in the acquisition of technical skills and experience related to these operations. Due to the novelty of these surgical approaches, there are few studies documenting their efficacy and safety.

RATIONALE

There are currently three brain regions being considered as targets for functional neurosurgery for PD (other than transplantation). They are (1) the ventral intermediate nucleus of the thalamus (Vim), (2) the internal segment of the Globus Pallidus (GPi), and (3) the subthalamic nucleus (STN). Either CNS lesions (thalamotomy, pallidotomy or subthalamic nucleus lesions) or implants of chronic stimulating electrodes at these sites (deep brain stimulation [DBS]) are being used. In general, the Vim target is used to treat tremor, while the pallidal and subthalamic targets are used to treat akinesia, rigidity, gait and postural disturbances, and drug-induced dyskinesias, in addition to tremor. Given the advances in surgical expertise and in understanding the neurodegenerative changes associated with PD, clinical reports are published in the literature reporting on safety and efficacy of these procedures. Consequently, an evidenced-based review of these reports is warranted in order to establish treatment recommendations on the safety and efficacy of surgery for treatment of PD.

METHODS

KEY SEARCH TERMS

Parkinson's disease and surgery with pallidotomy, thalamotomy, subthalamotomy, or pallidal, thalamic or subthalamic stimulation.

MECHANISM OF ACTION

Based on current anatomical and physiological concepts of the basal ganglia, a scheme has been developed to integrate the functional organization of the cortical-basal ganglia-thalamic-cortical circuitry as it relates to motor function. The motor circuit originates in the precentral motor and postcentral somatosensory areas and projects to motor areas of the basal ganglia and thalamus, returning thereafter to the cortex. Cortical inputs to the basal ganglia project through the putamen, and the output travels to the major motor output routes, globus pallidus internus (Gpi) and the pars reticulata of the substantia nigra by two distinct paths, called "direct" and "indirect." With the exception of the subthalamic nucleus, all intrinsic and output projections from the basal ganglia (putamen, globus pallidum interna and externa, and the pars reticulata) are mediated by gamma-aminobutyric acid and are inhibitory systems. Projections from the cortex to the putamen and from the thalamus to the cortex are excitatory.

The known loss of dopaminergic cells in the pars compacta of the substantia nigra that is the hallmark of PD has differential effects on the activities of the striatal cells in the direct and indirect pathways. In the direct pathway, loss of dopamine leads to a decrease in inhibitory activity from the putamen to the globus pallidus internus, whereas in the indirect pathway, loss of putaminal excitation reduces activity in the globus pallidus externus. Excessive excitation from the subthalamic nucleus and internal segment of the globus pallidus results as well in secondary enhanced inhibition of thalamo-cortical pathways leading presumably to the parkinsonian signs of akinesia and rigidity.

Based on this understanding, treatment of PD through lesions or electric stimulation-induced presumed inactivation of nuclei has focused on three primary structures that are functionally overactive as part of the basic pathophysiology of PD: the internal segment of the globus pallidus (pallidotomy and deep brain pallidal stimulation); thalamus (thalamotomy and thalamic stimulation); and subthalamic nucleus (deep brain stimulation). These procedures are critiqued in this review.

SPECIAL EXCEPTIONS TO THE INCLUSION/ EXCLUSION CRITERIA

Due to the paucity of large randomized trials, no sample size restriction was applied for Level-I studies. However, the standard

minimum of 20 patients was required for Level-II and Level-III studies. Additionally, a minimum period of 3 months after surgery was required to allow for postoperative recovery, drug modifications, and stimulation parameter adjustments. Studies were excluded if L-dopa therapy was initiated de novo during the follow-up period.

REVIEW OF CLINICAL STUDIES

The number of studies identified were 533, 231 on pallidotomy and 30 on pallidal stimulation; 218 on thalamotomy and 115 on thalamic stimulation;15 on subthalamotomy and 42 on subthalamic stimulation. Collectively, only 26 efficacy studies were included in this analysis: Level-I (n=3), Level-II (n=2) and Level-III data (n=21). Two studies are listed in the table twice because they compared two surgical interventions, pallidal stimulation vs. subthalamic stimulation[1] and thalamotomy vs. thalamic deep brain stimulation.[2] A few other studies of importance to safety concerns are listed in the table as well, although they did not meet inclusion criteria for efficacy critique.

PALLIDOTOMY

The search identified 231 published efficacy reports on pallidotomy, of which fifteen met inclusion and exclusion criteria: one study was Level-I, two studies were Level-II and the remaining were Level III. A few other studies focusing on safety issues are also critiqued.

PREVENTION OF DISEASE PROGRESSION

No qualified studies were identified.

SYMPTOMATIC CONTROL OF PARKINSONISM

Level-I Studies

De Bie and colleagues (1999)[3] conducted a prospective, single blind, multicenter, study of 37 patients that were randomized to either (1) unilateral pallidotomy, or (2) the best medical treatment. Patients assigned to surgery underwent macroelectrode stimulation guided pallidotomy. Lesion location and size were not verified with microelectrode guidance or postoperative imaging. Patient ages ranged from 44 to 73 years with a mean disease duration of approximately 16 years. Patients were followed for 6 months after surgical treatment. The mean Hoehn and Yahr stages were 4.0 in the "off phase" and 2.5 in the "on phase". The dose of L-dopa ranged between 86 to 925 mg/day "dopa equivalents." The primary outcome measure was improvement in the "off" motor exam of the UPDRS. In the pallidotomy group, the mean UPDRS motor score improved from a mean baseline rating of 47.0 to 32.5, whereas the control subjects had a mean baseline score of 52.5 and deteriorated to 56.6. Other assessments included the UPDRS 2 (activities of daily living ADL section), and Schwab and England scales of daily living all showing a significant positive effect of surgery compared to the controls. Nine of the nineteen patients had adverse reactions, two with events that were considered by the author as major, and seven that were considered as minor. The major events in the perioperative period were dysarthria and depressed level of consciousness in one patient and psychosis in another. Four of the seven patients with mild adverse effects still had them at six-month follow-up, and, of the two with major events, one continued with dysphasia, drooling and postural instability and the second with intermittent hallucinations and psychotic behavior. This study had an overall quality rating score of 72%.

Level-II Studies

Perrine et al. (1998)[4] studied 28 patients over one year who underwent pallidotomy and compared them to 10 control patients, who qualified for surgery but did not desire it immediately. This study assessed neuropsychological morbidity as its primary focus but also collected motor data in the form of the UPDRS motor and ADL data in the two groups. The pallidotomy group showed a change in the mean motor scale from 33.2 at baseline to 10.0 at one year. The control group however deteriorated from a mean score of 27.1 to 31.6. For the ADL scores, the pallidotomy group improved from mean values of 17.4 to 6.6, whereas the control patients deteriorated from a mean score of 17.8 to 20.6. There was no distinction in ON and OFF scores in this report.

Young et al. (1998)[5] studied 51 patients with medically refractory PD underwent stereotactic posteromedial pallidotomy for treatment of bradykinesia, rigidity, and L-DOPA-induced dyskinesias. Two comparison groups were examined: 29 patients whose pallidotomies were performed with the Leksell Gamma Knife; and 22 whose surgery involved the standard radiofrequency (RF) method. Clinical assessment as well as blinded ratings of Unified Parkinson's Disease Rating Scale (UPDRS) scores were carried out pre- and postoperatively. Mean follow-up time was 20.6 months (range 6-48) and all except 4 patients were followed more than one year. Eighty-five percent of patients with dyskinesias were relieved of symptoms, regardless of whether the pallidotomies were performed with the Gamma Knife or radiofrequency methods. About 2/3 of the patients in both Gamma Knife and radiofrequency groups showed improvements in bradykinesia and rigidity, although when considered as a group neither the Gamma Knife nor the radiofrequency group showed statistically significant improvements in UPDRS scores. One patient in the Gamma Knife group (3.4%) developed a homonymous hemianopsia 9 months following treatment and 5 patients (27.7%) in the radiofrequency group became transiently confused postoperatively. This study is limited because raw data were not reported, but only percent changes and p values. Because of the similarity of outcomes with the two procedures, the authors suggested however that Gamma Knife pallidotomy may be as effective as radiofrequency pallidotomy in controlling certain symptoms of PD.

Level-III Studies

Kondziolka et al. (1999)[6] conducted an open label prospective analysis of a consecutive series of 58 patients who underwent pallidotomy and were followed for up to 1 year. The mean age was 67 years with a disease duration of 13.3 years. The UPDRS in "on" and "off" periods was evaluated, and this study showed a significant improvement in the total OFF UPDRS score (mean 95.8 to 77.6). The predominant component responsible for the improvement was the motor section of the UPDRS, showing a mean change from 58.3 at baseline to 44.7 after surgery. Significant improvements were also noted for tremor, rigidity, bradykinesia, and contralateral dyskinesia. In the 21 patients who were evaluated after 1 year, improvements in dyskinesia and tremor were maintained. Adverse events were mild and occurred in 9% of the patients including dysarthria (4) and transient confusion (1).

Giller and colleagues (1998)[7] reported experience with pallidotomy and in a combined article on thalamotomies and

pallidotomies. The only pallidotomy procedure with at least 20 subjects was unilateral and in this group there were 49 subjects, of which 47 received extensive testing. Mean off UPDRS motor scores improved from 42.0 preoperatively to 29.4 at six months (N=27) and to 24.9 at 12 months (N=12). Three patients suffered hemiparesis and one patient had cognitive deficits, infection or confusion. The authors reported that the speech complications were higher in patients undergoing bilateral procedures. Eight patients out of the original 55 patients developed speech problems postoperatively. All but one had had bilateral surgery and in these seven, four had serious speech problems. In the one unilateral pallidotomy subject with speech problems, the severity of deficit was mild.

Shannon et al. (1998)[8] studied 26 patients undergoing pallidotomy, of which 22 patients had outcome measures reported 6 months post-treatment. The primary outcome measure was UPDRS "off phase" scores which improved at 6 months from mean 49.0 at baseline to 41.7. Contralateral parkinsonian signs improved when the investigators analyzed the collapsed components that referred to that side (mean 16.3 at baseline vs. 12.1 at six months). "On" ratings did not change. Significant complications included one death, three superficial frontal lobe hemorrhages, two significant cognitive and personality changes, one with subfluent aphasia, three with signs of frontal lobe dysfunction, and one report of hemiparesis.

Samuel et al. (1998)[9] reported the results from 26 patients who underwent unilateral pallidotomy. Twenty-two subjects were assessed for UPDRS motor score improvement (two patients died and two patients were unable to carry out the UPDRS assessment).

Following the CAPIT-recommended protocol for examining patients "on/off" over 3 months after sugery, the investigators found that the UPDRS total Off motor score improved from a baseline median score of 53.5 to 42.5. Most effects concerned the contralateral side with improvements in rigidity, tremor and bradykinesia. Contralateral dyskinesia also improved. Two patients had fatal complications, one cerebral hemorrhage and one hemorrhagic infarction. Of the remaining subjects, 15% experienced major complications including contralateral facial weakness, contralateral motor hemineglect, severe dysarthria and dysphagia and minor complications including visual field defect in 8%, dysarthria in 27%, dysphagia in 19%, and hypophonia in 15%.

Kishore et al. (1997)[10] reported on 23 patients who underwent unilateral pallidotomy; twenty had six-month follow-up and 11 were evaluated after 1 year. Using the CAPIT protocol recommendations for patient evaluation, they studied patients in ON and OFF states, and found that OFF UPDRS total score significantly improved from a mean score of 47.3 at baseline to 30.0 (N=20) and 25.5 (N=11). The OFF ADL scores likewise showed progressive improvement from mean baseline function of 23.6 to 17.7 at six months and 17.2 at one year. The results were most prominent for the contralateral side. Adverse effects included a delayed intracerebral hemorrhage and death 4%, transient hemiparesis and visual field deficit 12.5% and facial paresis in 1 patient.

Krauss et al. (1997)[11] reported six-month data on 36 patients with advanced PD undergoing unilateral pallidotomy and focused on correlations between lesion size and clinical outcome. They documented significant improvements in motor UPDRS OFF scores (mean 58.1 vs. 33.0), and OFF ADL scores (mean 31.4 vs. 18.2). There was no clear association with lesion size and clinical outcome. Six patients had transient adverse effects from the surgery and two infarctions were documented on MR.

Lang et al. (1997)[12] described unilateral pallidotomy in 40 patients followed for 1 to 2 years. Thirty-nine were examined at six months, 27 at one year and 11 at two years. The primary outcome measure was UPDRS total score with secondary outcome measures, Schwab & England, ADL and UPDRS subscores for tremor, rigidity, bradykinesia, postural instability, gait disorders, and dyskinesias. There was a significant improvement in "off" period UPDRS from mean 68.8 to 47.9 at six months and "on" UPDRS from mean 27.6 to 23.6. The Schwab and England scores improved from a mean OFF rating of 39% to 65% and a mean ON rating from 78.2 to 85.2 at six months. All "off" features of parkinsonism improved significantly on the side contralateral to surgery. Ipsilateral tremor and rigidity were not changed, but ipsilateral bradykinesia improved. Twenty-five patients had adverse effects; most of these were mild, but many of them persisted. These included weakness in two subjects, dysarthria in three, dysphagia in two and impaired memory or concentration faculties in three. There was one intracerebral hemorrhage.

Kazumata et al. (1997)[13] correlated clinical motor outcome measures with functional brain imaging using 18F-fluorodeoxyglucose (FDG) and positron emission tomography (PET) in 22 patients with advanced PD receiving stereotaxic unilateral pallidotomy. The clinical outcome following pallidotomy was assessed at three months after surgery and also correlated with intraoperative measures of spontaneous pallidal single-unit activity as well as postoperative MRI measurements of lesion volume and location. They found that unilateral pallidotomy produced clinical improvement in off-state CAPIT scores for the contralateral limbs (mean preoperative OFF UPDRS 75.3 vs. mean 52.8 after surgery). On the ipsilateral side to surgery, scores also improved from mean OFF UPDRS preoperatively of 59.8 to mean 49.9 after surgery. Clinical outcome following surgery correlated significantly with preoperative measures of CAPIT score, change with L-dopa administration and with preoperative FDG/PET measurements of lentiform glucose metabolism. Operative outcome did not correlate with intraoperative measures of spontaneous pallidal neuronal firing rate. The authors concluded that preoperative measurements of lentiform glucose metabolism and L-dopa responsiveness may be useful indicators of motor improvement following pallidotomy.

Melnick et al. (1996)[14] investigated the effects of pallidotomy on postural reactions and other motor parkinsonian deficits. They compared performance by 29 PD patients before and after pallidotomy on tests of balance and function. They assessed the UPDRS, activities of daily living and motor subscales (parts II and III) and posturography before and 3 to 6 months after surgery with patients in the practically defined off state (medication withheld for at least 12 hours). They found a significant improvement in UPDRS motor subscale score after pallidotomy (before surgery, mean 52.4 vs. mean 43.9 after surgery). There were no significant changes in the UPDRS activities of daily living subscale or average stability scores when the group was examined as a whole. Examination of individual data revealed that 9 (56%) of 16 patients who could stand independently before surgery showed improvement in either the number of falls or the average stability score. No patient who was unable to stand independently before surgery was able to stand independently after it. They concluded that pallidotomy helped improve overall motor function in patients with parkinsonism and, for some patients, also improved postural stability.

Uitti et al. (1997)[15] studied 20 consecutive patients with PD un-

dergoing MRI/electrophysiologically-guided medial pallidotomy. The mean age of patients was 65.5 years (median 66.5). Pallidotomy significantly improved motor function in both "on" and "off" states as measured by Unified Parkinson's Disease Rating Scale (UPDRS) motor scores and timed tests (Purdue pegboard and counter tapping) in the arm contralateral to surgery 3 months postoperatively. The total UPDRS score improved from mean 82.6 to 63.8. Patients also improved in the UPDRS activity of daily living and complications of therapy scoring. There was also a reduction in L-dopa-induced dyskinesias. Six of 11 patients who could not walk in an "off" state prior to surgery could do so postoperatively. The improvements occurred similarly in patients greater than (n = 11) or less than 65 years (n = 9) at surgery. Neuropsychological measures indicated that although the majority of cognitive function remained unchanged in right-handed PD patients following dominant (left) hemisphere pallidotomy, mild specific declines in word generation occurred in some patients. No significant operative complications developed. The findings of this study suggest that unilateral pallidotomy is safe and associated with improved motor functioning in elderly as well as younger PD patients experiencing significant disability despite optimal medical therapy.

PREVENTION OF MOTOR COMPLICATIONS

No qualified studies were identified.

CONTROL OF MOTOR COMPLICATIONS

Of all results related to pallidotomy, the most consistent and clinically significant contribution has been the control of dyskinesias, especially contralateral to the side of the lesion. Kondziolka[6] found contralateral dyskinesia dropped from mean scores of 1.5 to 0.9 by nine months with persistence of effects at 18 months in the 21 patients followed for that duration. In Giller's[7] report using a 0-3 severity rating system, they found dyskinesia dropped from a mean 5.5 preoperatively to 2.1 at two weeks and remained improved. The scores were even more dramatic when only the contralateral dyskinesia ratings were considered (2.5 to 0.2). Shannon found similar improvements using the UPDRS-based dyskinesia ratings, finding significant improvements in both duration score (mean baseline 2.2 vs. 1.0 at six months) and severity score (mean 1.5 vs. 0.5). Kishore[10] found contralateral dyskinesia significantly improved (mean score 7.5 before surgery vs. 3.8 at six months and 4.3 at one year). Krauss[11] assessed percent of the waking day with dyskinesia and documented six-month improvement with a change score from baseline man 37.5 to 18.1. Uitti and colleagues[15] found the mean Goetz Dyskinesia score improved from mean 1.4 to mean 1.2 and the Mayo Dyskinesia score from mean 11.6 to mean 7.6 after surgery. "On" time, obtained in nine patients only, improved from a mean 4.1 hours before surgery to mean 8.8 hours after surgery.

CONTROL OF NON-MOTOR COMPLICATIONS

Level-II Studies

Perrine et al. (1998)[4] studied 28 patients who underwent pallidotomy and compared them to 10 control patients, who qualified for surgery but did not desire it immediately. This study assessed neuropsychological morbidity and tests that included the minimental test, Beck Depression Inventory, Stroop tests, and Wisconsin Card Sorting Test were performed at baseline and between 3 and 12 months later. There were no significant changes in neuropsychological outcome between these two groups. The mean minimental state examination scores were 28.3 at baseline in the pallidotomy group and 27.5 at retesting; the two scores for the control group were 26.7 at baseline and 28.4 at retesting. Across all tests administered, only five of the surgery patients showed significant decline, and of these, non-decline on more than one test. The pallidotomy group showed a significant improvement in motor function, although the actual numeric changes in the UPDRS were not given.

Level-III Studies

Trépanier et al.(1998)[16] studied changes in neuropsychological function in patients with idiopathic PD after unilateral posteroventral pallidotomy. The study included 42 PD patients (24 right and 18 left hemisphere). All patients were evaluated in the "on state" before the procedure (n = 42) and at intervals of 3 (n = 26), 6 (n = 27), and 12 or more (n = 24) months after surgery. At baseline, patients had mild to moderate executive dysfunction. Modest improvement in sustained attention occurred as measured by the Paced Auditory Serial Addition Task, mean preoperative score 53.9 vs. 61.0 after surgery. In contrast, there was a decline in working memory by 6 months after surgery as measured by the Digit Span-Backwards Test, mean 6.7 preoperatively vs. 6.1 after surgery. Left hemisphere lesions led to a loss of verbal learning and verbal fluency in 60% of patients at their first evaluation at 3 or 6 months. No patients returned to baseline on the verbal fluency task and most (71%) did not recover verbal-learning ability by 12 months after surgery. Right hemisphere lesions led to a loss of visuospatial constructional abilities, which fully resolved by 12 months for all but one patient. Evidence of further decline of frontal-executive functioning was noted within other tasks but not on a "direct" test (i.e., Conditional Associative Learning). Behavioral changes of a "frontal nature" were reported in 25% to 30% of patients. These cognitive and emotional costs increased dependence and in some cases restricted their ability to function properly at work or in social settings. Although patients and caregivers were generally pleased with the clinical neurological outcome of the procedure, the authors concluded that neurological benefits of unilateral pallidotomy must be weighed against modest cognitive and behavioral risks.

Honey and colleagues (1997)[17] studied 50 patients undergoing pallidotomy for the presence of pre-operative pain related to PD. Of these, 21 qualified with PD-related pain syndromes. These patients (age, disease severity and demographics not specified) were interviewed with an ordinal 0-10 pain scale and their pain type was categorized based on a modification of the Goetz classification scheme. After pallidotomy, the pain score improved significantly from a mean of 6 to 2 (data taken from table, no numbers given in text) at six weeks and mean 3 at one year. Most patients had musculoskeletal pain at baseline, but the most marked improvements occurred in dystonic pain (four patients at baseline, 100% improved at 6 weeks and 50% improved at one year).

REVIEW OF SAFETY

Adverse reactions are common with pallidotomy. The majority is minor and well tolerated, but there is a risk of serious adverse reactions including of intracerebral hemorrhage (common to all stereotactic operations), speech impairment, especially with bilateral surgery, and visual adverse reactions.

Biousse et al. (1998)[18] described the incidence and types of vi-

sual field defects after microelectrode-guided posterior GPi pallidotomy in 40 patients with PD. Sixteen of these patients formed the basis of a report on motor efficacy, but these data did not meet the entry criteria of at least 20 patients, so they are not critiqued in this report (see Baron et al. bibliography of excluded references). In the visual field study, Goldmann visual field testing was performed in all patients post-operatively after two different surgical techniques: the first 18 subjects had a lesion threshold of 5 mA and the remaining had an increased threshold of 1.0 mA with the lesion placed more distant from the optic tract. Three patients (7.5%) had visual field defects likely related to the pallidotomy. These were contralateral homonymous superior quadrantanopsia, associated in two patients with small paracentral scotomas. The incidence of visual field defects with the early technique was 11% (2/18) and decreased to 4.5% (1/22) with modification of their surgical technique.

Hariz and De Salles (1997)[19] studied complications of posteroventral pallidotomy in 138 consecutive patients who underwent 152 pallidotomies. Transient adverse reactions, lasting less than three months, appeared in 18% of the patients (16.5% of the surgical procedures). Long-term complications, lasting more than 6 months, were noted in 10% of the patients (9.2% of the surgical procedures). Sixteen complications occurred alone or in various combinations in 14 patients and included fatigue and sleepiness (2), worsening of memory (4), depression (1), aphonia (1), dysarthria (3), scotoma (1), slight facial and leg paresis (2) and delayed stroke (2). Complications such as dysarthria and paresis were attributed to MR- or CT-verified pallidal lesions encroaching on the internal capsule. Two of the patients with post-operative deterioration in memory had some memory impairment before surgery, and the aphonic patient had dysphonia preoperatively. The authors suggested that stereotactic MRI and careful impedance monitoring and macro-stimulation of the posteroventral pallidum area should be sufficient for minimizing the risk of complications, concluding that pallidotomy is a safe procedure if performed on cognitively alert patients.

Post-operative cognitive deficits have been documented in the non-motor outcomes section above, although the study by Perrine did not document a systematic pattern of decline from pallidotomy. The Trépanier[16] study focused on verbal language deficits and "frontal lobe" behaviors, the latter occurring post-operatively in approximately 25% of subjects. The study by Krauss and colleagues focused primarily on MR data and they found evidence of three infarctions, two ischemic and one venous. One ischemic infarction was associated with subfluent aphasia, and the others were asymptomatic.

CONCLUSIONS

EFFICACY

Pallidotomy has only been studied in patients with advanced disease and motor complications with inadequate response to medical management.

PREVENTION OF DISEASE PROGRESSION

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of pallidotomy in the prevention of disease progression in patients with PD.

SYMPTOMATIC CONTROL OF PARKINSON'S DISEASE

Monotherapy

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of pallidotomy in the symptomatic control of Parkinson's disease as a sole therapy.

Adjunct therapy

Based on one Level-I study, two Level-II studies, and several Level-III studies, unilateral Pallidotomy improves contralateral rigidity, tremor and akinesia. Although gait disturbances of PD also improve, the magnitude and duration of the response is limited. Therefore, unilateral pallidotomy is considered LIKELY EFFICACIOUS for symptomatic control of PD.

PREVENTION OF MOTOR COMPLICATIONS

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of pallidotomy regarding prevention of motor complications in patients with PD.

CONTROL OF MOTOR COMPLICATIONS OR OTHER COMPLICATIONS

There are no controlled studies on the effects of pallidotomy on motor complications. There is a consistent body of Level-III data suggesting efficacy specifically on contralateral drug-induced dyskinesias. There is INSUFFICIENT EVIDENCE to conclude on the efficacy of pallidotomy in this indication.

There is INSUFFICIENT EVIDENCE to judge efficacy of bilateral pallidotomy in all indications.

SAFETY

Unilateral pallidotomy carries an ACCEPTABLE RISK, WITH SPECIALIZED MONITORING that includes choosing appropriate patients and adequate surgical expertise. Studies reveal that serious adverse events occur infrequently but that minor adverse events are common. There is INSUFFICIENT EVIDENCE to assess the safety of bilateral pallidotomy, but serious concerns have been voiced on the risk of speech, balance, gait, and cognitive problems consequent to bilateral surgery.

IMPLICATIONS FOR CLINICAL PRACTICE

Unilateral pallidotomy is POSSIBLY USEFUL in patients who, despite best available medical treatment, suffer with "on" period dyskinesias and "off" period parkinsonian motor disability. Because the positive effects in Level III Studies are consistently seen for dyskinesia, patients without dyskinesia are generally considered less suitable candidates for surgery of this type. Although the procedure has been performed at many medical centers, even those without movement disorder neurological expertise, the number of cerebrovascular accidents consequent to this surgery still should make this procedure a serious consideration only after medication trials to control motor fluctuations and dyskinesia have failed. Bilateral pallidotomy remains INVESTIGATIONAL because it has not been extensively studied.

IMPLICATIONS FOR CLINICAL RESEARCH

There are very limited data on the duration of benefit after unilateral pallidotomy and longitudinal follow-up studies are required. The definition of the optimal patient, the size and location of the pallidotomy lesion, and an explanation of the mechanism through which pallidotomy improves motor function are all areas open to research. The safety and efficacy of bilateral procedures is unknown, and modifications that are not associated with risk of speech deficits would be important surgical advances.

PALLIDAL STIMULATION

Whereas most studies related to pallidal surgery have involved destructive lesions, the advent of deep brain stimulation techniques has provided the option to induce physiological "lesions" through selective electrical stimulation of the internal segment of the globus pallidus. Although stimulation procedures involve special surgical techniques, leave a foreign body (wire and electrodes) within the central nervous system, and require costly equipment, the lesions are theoretically reversible, because the stimulator can be turned on and off as well as re-programmed.

REVIEW OF CLINICAL STUDIES

Of the articles reviewed, two Level-I studies were identified. Neither had a non-surgical control arm, but rather compared outcome from stimulator on vs. off or compared two deep brain stimulation procedures, bilateral pallidal stimulation and bilateral subthalamic nucleus stimulation. One of these studies also included open-label follow-up information and therefore is discussed under Level III data along with one additional open observation trial.

PREVENTION OF DISEASE PROGRESSION

No qualified studies were identified.

SYMPTOMATIC CONTROL OF PARKINSONISM

Level-I Studies

Burchiel and colleagues (1999)[1] conducted a small, randomized study of ten patients who were assigned to either bilateral pallidal stimulation or bilateral subthalamic stimulation. All patients had severe Parkinson's disease-related motor impairment with motor fluctuations and peak-dose dyskinesias. The data presentation is not always clear in this manuscript because one patient randomized to subthalamic stimulation was not included in the 12-month analysis, so that baseline values for several important measures are not given for the analyzed group. Mean baseline UPDRS motor scores off L-dopa were 67 in the pallidal stimulation group and 49 in the subthalamic nucleus group. Assessments were made by an investigator blinded to the patient assignment, and baseline function was compared with scores obtained after surgery (10 days, 3, 6, and 12 months). Complete follow-up data were available for four patients with pallidal stimulation and five patients with subthalamic nucleus stimulation and comparisons were made on these patients. Almost all data analysis concerns comparison between the outcomes in the two groups, rather than comparisons with baseline. The UPDRS motor score without L-dopa at 12 months improved in both groups compared to baseline (39% improvement with pallidal stimulation vs. 44% with subthalamic stimulation, specific numbers not given). No statistically significant differences between the two surgeries were identified for measures obtained off L-dopa. At peak L-dopa effect ("on") with the stimulator turned on, patients showed improvement over baseline function, but for almost all measures, the two surgeries improved patients similarly. Only bradykinesia changes were significantly more improved with pallidal stimulation. Daily medication dosage of L-dopa was significantly decreased in the subthalamic nucleus stimulation group (mean change from mean 735 to 360 mg/d) whereas it remained unchanged (doses not given) in the pallidal stimulation patients. When clinical function at peak dose effect of medication ("on") with the stimulator turned on was assessed at 12 months, patients with pallidal stimulation showed significant improvement in bradykinesia compared to baseline (mean 17.5 vs. 11.0 at 12 months) whereas no statistically significant objective motor changes occurred in the subthalamic stimulation group. This study had an overall quality rating score of 64%.

The Deep Brain Stimulation for Parkinson's Disease Study Group[20] conducted a ten-center, 41 patient study with Level I data on randomized double-blind crossover assessments of the acute effects of pars interna pallidal stimulation three months after bilateral electrode placement. Open-label Level III data on long-term effects were included in the report as well (see Level III). The pulse generators were programmed individually for maximal patient benefit in the first three months after surgery with four electrode contacts, monopolar or bipolar activation, frequencies up to 185 Hz, voltage up to 10.5 V, and pulse widths up to 450 microseconds. Six enrolled patients were not assessed: three did not receive bilateral surgery because of operative complications during the first surgery, one died before the three-month assessment, and the others withdrew participation for this acute trial.

The study design tested acute changes in early morning function without medication when the stimulator was turned on for two hours compared to when the stimulator was turned off for two hours. Subjects and investigators were blind to the stimulator setting and in all patients, both conditions were tested in random order (first, stimulator on; then, stimulator off or first, stimulator off; then, stimulator on). The primary outcome measure was the UPDRS motor score.

When the stimulator was turned on for two hours, UPDRS motor scores were significantly better than when the stimulator was off (mean score off 44 ± 16 changing to 28 ±13 with the stimulator on, $p<0.001$, and, when the reverse order was used, mean scores changed from 34 ±16 with the stimulator turned on, changing to 48 ±17 with the stimulator off, $p>0.001$). There was no carryover effect or period effect. Median improvement greater than 25% was observed in nine of the ten centers participating in the study. This study had an overall quality rating score of 84%.

Level- III Studies

The Deep Brain Stimulation for Parkinson's Disease Study Group[20] extended the Level I acute study to include open-label longitudinal assessments of motor function and dyskinesias. In this portion of their study, they used the UPDRS motor, UPDRS activities of daily living, and a dyskinesia rating scale. They monitored patients at baseline, one month, three months, and six months after electrode placement. At the evaluations, four conditions were assessed: off medication and off stimulation; off medication and with the stimulator turned on, usually for thirty minutes; on medication and with the stimulator turned off; on medication and on stimulation. Of the 38 subjects with presurgical scores, 36 completed the four evaluations in the four conditions. Comparing the baseline to six month scores, without medication and with the stimulator turned off, scores did not change (mean baseline UPDRS motor score 50.8 ± 11.6 vs. 49.7 ± 14.0 at six months). In the off medication/stimulator on condition, significant improvement occurred compared to baseline (33.9 ± 12.3 at six months vs. 50.8 ± 11.6 at baseline, 33% change, $p<0.001$). On medication scores without the stimulator remained stable over the trial (24.1 ± 14.6 at baseline vs. 19.4 ± 10.0 at six months). When the stimulator was turned on and patients had taken their mediciations, patients improved significantly (mean 16.5 ± 9.5 at six months compared to the on medication baseline score of 24.1 ± 14.6, 27% improve-

ment, p=0.003. The Activities of Daily Living UPDRS scores significantly improved, as well as scores for tremor and postural stability (all p<0.001).

PREVENTION OF MOTOR COMPLICATIONS

No qualified studies were identified.

CONTROL OF MOTOR COMPLICATIONS

Level-I Studies

The Burchiel[1] study examined effects of pallidal stimulation and subthalamic nucleus stimulation on dyskinesias. The analysis was confounded by significant reduction in daily L-dopa doses in the subthalamic surgery group. At 12 months, the two groups were not different from one another, although both had improved in comparison to their baseline. In the pallidal stimulation group, the mean baseline dyskinesia score was 9.5 and at 12 months was 5.0 (not statistically significant) whereas the group receiving subthalamic stimulation changed significantly from a mean baseline score of 11.6 to 3.8 at 12 months.

Level-III Studies

The Deep Brain Stimulation for Parkinson's disease Study Group[20] trial assessed motor complications using diaries to capture "on without dyskinesia" and "off" function during the waking hours. These were completed two days prior to the office visits. They also used a dyskinesia rating scale at the time of the office assessments. Between baseline and six months, the percentage of time with good mobility and without dyskinesias during the waking day increased from 28% to 64% (p<0.001). The dyskinesia rating score improved from mean 2.1 ± 1.5 at baseline to 0.7 ± 0.8 at six months (p<0.01). The mean daily dose of levodopa equivalents (100 mg levodopa=10 mg bromocriptine=1 mg pergolide) did not change.

CONTROL OF NON-MOTOR COMPLICATIONS LEVEL-I STUDIES

The Burchiel[1] study also examined cognitive and affective changes consequent to bilateral pallidal stimulation and compared results with those obtained with bilateral subthalamic stimulation. Memory, attention, and visuomotor processing were unchanged from baseline 12 months after either surgery. Depression improved from baseline when the entire study group was considered (mean Beck Depression Inventory score 14.3 at baseline compared to mean 7.3 at 12 months), but no breakdown by pallidal and subthalamic surgery was provided.

REVIEW OF SAFETY

In the Burchiel[1] report, there were no serious intraoperative complications, but misplaced electrodes occurred. Post-operative complications include paresthesias, balance impairment and speech deficits when the stimulator is turned on. Inadvertent switching off of the stimulators by external electromagnetic fields and interference with pulse generator output by theft detectors, high-power transmitters and other appliances has occurred with these devices (Ghika, 1999).[21] Among the group in the Deep Brain Stimulation Study Group,[20] intracranial hemorrhages occurred in 4 of 41 subjects, three experiencing hemiparesis and one developing seizures. Migration of the electrode occurred in two subjects, infection in one, and lead break in one. Enhanced dyskinesias occurred in three and dystonia in two.

CONCLUSIONS

EFFICACY

In spite of wide clinical perceptions of efficacy for treating parkinsonism and motor complications, the evidence supporting this remains limited. Similar to pallidotomy pallidal deep brain stimulation has only been studied in patients with advanced disease and motor complications with inadequate response to medical management.

PREVENTION OF DISEASE PROGRESSION

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of pallidal stimulation in the prevention of disease progression in patients with PD.

SYMPTOMATIC CONTROL OF PARKINSON'S DISEASE

Monotherapy

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of pallidal stimulation in the symptomatic control of Parkinson's disease as a sole therapy.

Adjunct therapy

Neither of the Level-I studies had a medical control group though randomization and blinding of evaluations was performed, in the first, the pre- vs. post-surgery assessments were clearly known by the raters, and in the second, the assessments evaluated acute effects of two hours of pallidal stimulation only. The long-term evidence of improvement is based on Level-III data. Because these results are consistent and positive, the evidence is sufficient to conclude that pallidal stimulation is LIKELY EFFICACIOUS for the treatment of parkinsonism.

PREVENTION OF MOTOR COMPLICATIONS

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of pallidal stimulation regarding prevention of motor complications in patients with PD.

CONTROL OF MOTOR COMPLICATIONS OR OTHER COMPLICATIONS

There are no controlled studies on the effects of pallidal stimulation on motor complications. There is INSUFFICIENT EVIDENCE to conclude on the efficacy of pallidal stimulation in this indication.

SAFETY

From the evidence cited, numerous adverse effects can occur but are limited to relatively small numbers of patients. However, because the study follow-up periods are short, the likelihood that technical problems like further migration of electrodes or lead breaks will become more frequently reported. These risks are no different than those for any other deep brain stimulation procedure. For these reasons, pallidal stimulation carries an ACCEPTIBLE RISK WITH SPECIALIZED MONITORING that includes the choice of appropriate patients, adequate surgical expertise, and careful medical and neurological follow-up.

IMPLICATIONS FOR CLINICAL PRACTICE

Based on the consistent, but limited, data on improved function after pallidal stimulation, pallidal stimulation is POSSIBLY USEFUL. The potential advantages of this procedure over pallidotomy

are several and include reversibility (the stimulation can be turned off) and the surgery can be performed bilaterally. The Burchiel study did not show any pattern of improvement that favored pallidal stimulation over subthalamic nucleus stimulation, other than L-dopa reduction in the subthalamic surgery group. So, until a larger body of data is collected on pallidal stimulation, the practicing clinician will more likely turn to centers offering subthalamic stimulation as an option for treating advanced PD and its complications.

IMPLICATIONS FOR CLINICAL RESEARCH

The very small body of clinical research published on pallidal stimulation underscores the need for larger studies. No randomized blinded study with a medical (no surgical intervention) arm as comparison has been conducted and this program would define what features of PD respond better to pallidal surgery than best medical management. Long-term follow-up of the patients receiving this surgery is essential to defining the chronic sequelae of stimulation. Basic science and animal work must be performed to understand if there are positive or negative long-term results on neuronal membrane structure and function in fields of high frequency electrical exposure.

THALAMOTOMY

The thalamic nuclei have been the target of studies related to stereotaxic surgery for several decades. Whereas the nucleus ventralis intermedius (Vim) is the primary target, the nucleus ventralis lateralis, including ventro-oral-thalamic (Voa and Vop) as well as the reticular thalamic nucleus have also been studied.

REVIEW OF CLINICAL STUDIES

Of the 218 references to thalamotomy, five studies met the review criteria, one Level I and the remaining Level III, all focusing on the treatment of motor signs of parkinsonism.

PREVENTION OF DISEASE PROGRESSION

No qualified studies were identified.

SYMPTOMATIC CONTROL OF PARKINSONISM

Level-I Studies

Schuurman and colleagues (2000)[2] compared the efficacy of thalamotomy and thalamic DBS for treatment of drug-resistant tremor in 45 patients with PD. Patients were randomized to treatment, and the primary outcome measure was the change in functional abilities measured by Frenchay Activities Index scores 6 months after surgery. As a secondary outcome, they measured the tremor score from the UPDRS motor section. In both groups, the target nucleus was the nucleus ventralis intermedius (Vim). Functional status improved in both groups, and were significantly greater in stimulation group. On the Frenchay scale, the mean score changed from 32.0 to 32.5 in the thalamotomy group and from 31.4 to 36.3 in the stimulator group. The difference between groups for change scores was 4.7 (95% CI 1.2, 8.0) in favor of DBS. Tremor was more improved with stimulation as well, but the differences between this treatment and thalamotomy was not not statistically significant. Electrical stimulation was favored additionally because of safety issues with 11 patients having persistent adverse effects at six months after surgery in the thalamotomy group compared to only 2 in the stimulation group. Among the persisting effects in the thalamotomy subjects, cognitive deterioration, dysarthria, hyperasthesia, gait and balance disturbance and arm ataxia occurred. In the stimulator group, dysarthria was the only persisting effect and in both cases was considered mild. One patient in the stimulation group, however, died perioperatively after a cerebral hemorrhage. This study had a quality score of 70%.

Level-III Studies

Duma et al. (1998)[22] reported on the efficacy of gamma-knife thalamotomy delivered to 34 elderly PD patients (mean age 73 years). In 30 subjects, the lesions were unilateral and in 4 they were bilateral. The target was the nucleus ventralis intermedius and the median radiation dose was 130 Gy. They assessed subjective patient reports and UPDRS tremor scores, but did not specifically analyze the unilateral surgery in contrast to the bilateral procedures. The intervention produced no change in tremor in 10.5% of patients, mild improvement in 10.5%, good results in 29% and excellent results in 26%. Tremor was eliminated completely in 24%. The follow-up period was a median of 28 months, and medication usage before or after surgery was not stated. No specific tremor scores were given, but there was a high correlation between patient reports and tremor change scores (Pearson correlation coefficient 0.89) There were no reported neurological complications.

Jankovic et al. (1995)[23] evaluated 43 PD patients undergoing stereotaxic thalamotomy of the ventralis intermedius nucleus using a global tremor rating and the tremor score from the UPDRS. L-dopa doses were also monitored. Thirty-nine patients had one lesion and three had repeated operations on the same side. Two had bilateral surgery. All these operations were considered together for the analysis of patient outcome. In 72%, abolition of tremor occurred and 14% showed significant improvement. One patient died in the first week after surgery, so the data were based on 42 subjects. In addition, several permanent and transient adverse effects were reported, but their frequency in PD cannot be determined because the report included other diagnoses like essential tremor, post-traumatic tremor, and cerebellar tremor. In the entire series of 61 subjects, 23% had permanent and 58% had transient complications. The permanent adverse effects included contralateral weakness in nine subjects, dysarthria in 6, increased ipsilateral tremor in one, blepharospasm in one.

Wester and Hauglie-Hanssen (1990)[24] reported the results of thalamotomy aimed at the ventro-oral thalamic nucleus and the reticular thalamic nucleus in 33 patients with PD. Their outcome measure was a 5 point scale based on a questionnaire completed by the referring physician (good, moderate, small, no improvement, worse function). At follow-up, (median time 24 months), they reported good benefit to contralateral tremor in 64% of cases and moderate benefit in 15%. Nine percent each showed small or no improvement. No patient showed worse tremor than baseline. Three patients (10%), however, had permanent serious complications including mental changes in three, dysphasia in one and dysarthria in two. There was a 36% occurrence of mild adverse effects not associated with serious disability including mental changes in four subjects, hemiparesis in three, dysphasia in 4 and dysarthria in one. The report included the results of patients with other diagnoses than PD and in one patient with multiple sclerosis, a subdural hematoma occurred.

Giller et al.(1998)[7] reported experience with thalamotomies aimed at the ventral intermedius nucleus on 31 patients using a scoring method that included four options, complete resolution, near-com-

plete resolution, partial resolution or failure. Thirty-five thalamotomies were performed on 31 subjects resulting in 27 unilateral procedures and 4 bilateral operations. Results were reported together. At follow-up (mean 21 weeks), 65% experienced complete or near complete resolution, 23% had partial resolution, and 13% were considered treatment failures. Six patients experienced temporary neurological deficits such as hemiparesis and dysarthria (numbers not given), balance instability in one and superficial infection in one. No deaths occurred and no permanent residua.

PREVENTION OF MOTOR COMPLICATIONS

No qualified studies were identified.

CONTROL OF MOTOR COMPLICATIONS

No qualified studies were identified.

REVIEW OF SAFETY

Transient adverse reactions are common and some patients experience permanent complications most commonly pertaining to speech (e.g., low volume, dysarthria, dysphasia) and cognition (e.g., confusion, mental status changes). Hemiparesis also has been reported, but usually is transient. Rare deaths have also occurred in PD patients during the perioperative period. Post-operative sympathetic nervous system defects have been reported in patients after thalamotomy, but the series of patients reported was not reviewed because it did not specifically focus on PD subjects and included numerous other disorders with dyskinesias (see bibliography of excluded references, Carmel 1968).

CONCLUSIONS

EFFICACY

All studies of thalamotomy have been performed in patients with tremor insufficiently controlled by oral medications.

PREVENTION OF DISEASE PROGRESSION:

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of thalamotomy in the prevention of disease progression in patients with PD.

SYMPTOMATIC CONTROL OF PARKINSON'S DISEASE

Monotherapy

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of thalamotomy in the symptomatic control of Parkinson's disease as a sole therapy.

Adjunct therapy

Data available comes only from Level-III studies that despite being consistent are INSUFFICIENT EVIDENCE to conclude on the efficacy of unilateral ventral intermediate nucleus thalamotomy.

PREVENTION OF MOTOR COMPLICATIONS

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of thalamotomy regarding prevention of motor complications in patients with PD.

CONTROL OF MOTOR COMPLICATIONS OR OTHER COMPLICATIONS

There is INSUFFICIENCENT EVIDENCE to conclude on the efficacy of bilateral thalamotomy or on the effect of thalamotomy on motor complications.

SAFETY

Unilateral thalamotomy has an ACCEPTABLE RISK, WITH SPECIALIZED MONITORING. It is important to select appropriate patients, and surgical expertise is required. There is INSUFFICIENT EVIDENCE to make safety conclusion related to bilateral thalamotomy, but serious concern about high rates of speech and cognitive complications have been voiced in selected series.

IMPLICATIONS FOR CLINICAL PRACTICE

Unilateral thalamotomy is POSSIBLY USEFUL for the control of motor elements of PD impairment, most specifically contralateral control of upper extremity tremor. Because the procedure has been available for many years, surgeons outside of a specialized movement disorder center may have experience with this operation. Physicians with patients who have severe and unremitting tremor that is unresponsive to available antiparkinsonian medications, may consider referral to a neurosurgeon for evaluation of unilateral thalamotomy. Because there is insufficient data on the safety and efficacy of destructive lesions placed into both thalami, bilateral thalamotomy is considered INVESTIGATIONAL.

IMPLICATIONS FOR CLINICAL RESEARCH

More Level-I studies on the efficacy and safety of thalamotomy are needed in order to place its role in the management of parkinsonism along side the other available surgical interventions. The use of non-physiological guided gamma-knife thalamotomy is new and there is insufficient data to judge its safety or efficacy. There are small series of patients with L-dopa-induced dyskinesia who experience reported improvement of dyskinesia after thalamotomy, but this antidyskinetic effect has not been studied in well-controlled trials. The cellular substrate of changes induced by thalamotomy has not yet been delineated, and the best nucleus to lesion has not yet been defined.

THALAMIC DEEP BRAIN STIMULATION (DBS)

Of the 115 articles identified by the search methodology on thalamic stimulation, four met inclusion criteria. One (Schuurman[2]) was discussed under thalamotomy, so this critique includes three additional studies.

REVIEW OF CLINICAL STUDIES

PREVENTION OF DISEASE PROGRESSION

No qualified studies were identified.

SYMPTOMATIC CONTROL OF PARKINSONISM

Level-I Studies

As reviewed above, (see full discussion in thalamotomy section) Schuurman and colleagues (2000)[2] compared the efficacy of thalamic DBS to thalamotomy for treatment of drug-resistant tremor (45 patients had PD). The authors concluded that thalamic DBS and thalamotomy are equally effective in suppressing drug-resistant tremor in patients with PD, but thalamic DBS is more effective than thalamotomy in restoring function. This study had a quality score of 70%.

In a study with mixed Level I and Level III results, Koller et al. (1996)[26] reported three month and one year results of unilateral thalamic DBS of the ventral intermedius nucleus in 24 patients with PD. Efficacy of the thalamic DBS was evaluated using UPDRS tremor score as the primary outcome measure and functional ratings as secondary outcomes. Follow-up with a blinded assessment of the effects of stimulation on tremor was done at 3 months (Level I), and an open label assessment (Level III) at 12 months. At 3 months, the patient's stimulator was left off overnight before a blinded evaluation was conducted. Patients first were evaluated with the stimulator in the "off" state and then randomly assigned to stimulators "on or off." Lastly, they also were assessed when stimulators were appropriately set. Because certain patients felt transient paresthesias associated with turning on the stimulators, the effectiveness of patient blinding was uncertain. At three months, mean tremor score for the contralateral body changed from 3.0 with the stimulator off to 0.5 with the stimulator on (numbers taken from the figure and not specifically provided in text). This same pattern was maintained at 12 months. One patient did not improve. There was no effect on tremor on the side ipsilateral to the stimulator placement. There was no functional improvement in the PD patients despite the improvements in tremor. Adverse effects could not be determined precisely because of the mixing of ET and PD patients, however, 6 patients or 10% did not go on to implantation due to intraoperative events including failure to suppress tremor, hemorrhage in two subjects, microthalamotomy effects in two, and intraoperative consent withdrawal in one.

Level-III Studies

Limousin et al. (1999)[25] reported 73 PD patients undergoing thalamic DBS in the ventral intermedius nucleus for treatment of drug-resistant tremor. The OFF UPDRS tremor score taken 12 hours after the last dose of parkinsonian medication was used as the primary outcome measure and other measures of the motor and ADL sections of the UPDRS were secondary outcomes. Implantation of the electrodes without turning the stimulator on had no effect on tremor. With the stimulator turned on, the total tremor item score (items 20 and 21) for the side contralateral to the stimulation changed from mean 7.46 to 1.73 at three months and at 12 months from 8.12 to 2.04. The side that was not stimulated also improved at 3 months. Rigidity and akinesia on the side opposite the stimulation significantly improved. Adverse effects were tabulated for the larger series in the report that included PD patients and other tremorous subjects (total 111 evaluated patients). One patient had breathing difficulties during surgery and was not implanted. Four patients had major adverse effects considered unrelated to surgery, three dying from other causes and one with a stroke on the unoperated hemisphere three months after surgery. Two patients had subdural hematomas that resolved without intervention and two developed subcutaneous hematomas. The electrode needed to be replaced in five patients because of unsatisfactory results. Dysarthria (seven), disequilibrium (three patients, all bilateral), dystonia (one patient) developed only while the stimulator was on).

Benabid et al. (1996)[27] reported the results of thalamic stimulation in 80 patients with PD: 38 had bilateral implantation, and eight additional patients had had previous thalamotomy on the side that did not receive stimulation. They used a qualitative tremor score as well as UPDRS scores. Fifty patients were evaluated at 12 months. Of all parkinsonian signs, only tremor was helped. At three months, with the stimulator on, 92% of patients showed complete or near complete tremor resolution. At 12 months, 89% had these major improvements in tremor with thalamic DBS. L-dopa doses decreased by more than 30%. There was a higher incidence of complications with bilateral procedures including dysarthria, disequilibrium, dystonia, dysesthesias and perceptions of weakness. These stimulation-induced complications were reversible when the stimulator was turned off, but could recur, often immediately, when the stimulator was switched on. Dysarthria was particularly frequent (40%) in the group of patients receiving stimulation on one side after having received a prior thalamotomy on the contralateral side.

PREVENTION OF MOTOR COMPLICATIONS

No qualified studies were identified.

CONTROL OF MOTOR COMPLICATIONS

No qualified studies were identified.

REVIEW OF SAFETY

Three types of adverse reactions are observed with thalamic DBS:

- Events directly related to the surgical procedure (e.g., intraoperative confusion, intracerebral hematoma),
- Effects from stimulation (e.g., dysarthria, paresthesia, ataxia, motor contraction), or
- Events related to the actual device (e.g., hardware erosion through the skin, infection, breakage, battery failure, lead migration). The stimulation-induced adverse events are reversible but may limit the therapeutic efficacy.

Based on the comparison of findings from the Level-I study of thalamic stimulation and thalamotomy by Shuurman and colleagues, DBS is considered safer than lesioning of the thalamus.

CONCLUSIONS

EFFICACY

All studies of thalamic deep brain stimulation have been performed in patients with tremor insufficiently controlled by medications.

PREVENTION OF DISEASE PROGRESSION

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of thalamic deep brain stimulation in the prevention of disease progression in patients with PD.

SYMPTOMATIC CONTROL OF PARKINSON'S DISEASE

Monotherapy

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of thalamic deep brain stimulation in the symptomatic control of Parkinson's disease as a sole therapy.

Adjunct therapy

Although there are consistent reports of efficacy specifically improving contralateral arm tremor, in the absence of a Level-I study that has a non-intervention control arm, and with only a small number of level-III studies, there is INSUFFICIENT EVIDENCE to conclude about the efficacy of thalamic deep brain stimulation in the signs of PD.

PREVENTION OF MOTOR COMPLICATIONS

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of thalamic deep brain stimulation regarding prevention of motor complications in patients with PD.

CONTROL OF MOTOR COMPLICATIONS OR OTHER COMPLICATIONS

There is INSUFFICIENCENT EVIDENCE to conclude on the efficacy of thalamic deep brain stimulation on motor complications.

Furthermore there is INSUFFICIENT EVIDENCE to judge the efficacy of bilateral thalamic stimulation surgery in all indications.

SAFETY

Unilateral thalamic stimulation has an ACCEPTABLE RISK WITH SPECIALIZED MONITORING. It is important to chose appropriate patients, and surgical expertise is required.

IMPLICATIONS FOR CLINICAL PRACTICE

Although there is a paucity of Level-I data, the consistent reports of marked improvement in contralateral tremor make unilateral thalamic stimulation a POSSIBLY USEFUL option for clinicians faced with a tremor-predominant PD patient whose tremor is medically refractory and predominantly on one side of the body. The surgery requires special equipment and availability of staff to adjust and monitor the electrode placement and clinical response, so referral to specialized centers is essential. Community neurologists can refer their patients to such centers for special protocols as well as clinical service. Insurance reimbursement practices vary for this procedure. Because dysarthria and other side effects are more prevalent in subjects receiving bilateral thalamic stimulation, this procedure is no longer regularly utilized for patients with prominent tremor on both sides of the body, and other deep brain stimulation procedures like subthalamic stimulation are usually used.

IMPLICATIONS FOR CLINICAL RESEARCH

Unilateral thalamic stimulation requires additional studies on the safety and efficacy in order to provide adequate Level-I and II evidence on its precise role in PD therapeutics. Bilateral thalamic stimulation is of unknown safety or usefulness. Studies that investigate the mechanism by which DBS improves tremor also are needed to delineate the cellular basis of stimulation-associated clinical changes. The long-term duration of effects and the plasticity response of the nervous system to chronic DBS has not been studied in depth and has direct implications to PD therapeutics.

SUBTHALAMIC NUCLEUS LESIONS

Although 16 articles were identified, none met inclusion criteria, and, hence this topic is not critiqued.

SUBTHALAMIC NUCLEUS STIMULATION (STN DBS)

REVIEW OF CLINICAL STUDIES

There were 43 articles identified in the search; for efficacy assessments, two Level I, already cited under Pallidal Stimulation, and two Level-III studies qualified for review. A few others are discussed in relation to safety issues.

PREVENTION OF DISEASE PROGRESSION

No qualified studies were identified.

SYMPTOMATIC CONTROL OF PARKINSONISM

Level-I Studies

A blinded, randomized comparison of pallidal stimulation and STN DBS by Burchiel and colleagues (1999)[1] involved five patients who received stimulation to the subthalamic nucleus. Whereas the emphasis of the trial was a comparison between two different surgical procedures, the UPDRS motor scores improved by 44% one year after surgery in the STN DBS group. This level of improvement was statistically equivalent to the improvement seen with stimulation of the globus pallidus. Most of the improvement seen was due to decreased rigidity (mean baseline score on item 22 of the UPDRS motor scale 9.4 vs. 5.0 at 12 months). Medication was significantly reduced in the post-operative time and two patients stopped L-dopa altogether. In contrast, the patients who had received pallidal stimulation maintained their preoperative doses of L-dopa.

The Deep Brain Stimulation for Parkinson's Disease Study Group[20] conducted a 16-center (there were 18 centers overall but 2 did not perform STN DBS), 96 patient study with Level I data on randomized double-blind crossover assessments of the acute effects of subthalamic nucleus stimulation three months after bilateral electrode placement. Open-label Level III data on long-term effects were included in the report as well (see Level III). The pulse generators were programmed individually for maximal patient benefit in the first three months after surgery with four electrode contacts, monopolar or bipolar activation, frequencies up to 185 Hz, voltage up to 10.5 V, and pulse widths up to 450 microseconds.

The study design tested acute changes in early morning function without medication when the stimulator was turned on for two hours compared to when the stimulator was turned off for two hours. Subjects and investigators were blind to the stimulator setting and in all patients, both conditions were tested in random order (first, stimulator on; then, stimulator off or first, stimulator off; then, stimulator on). The primary outcome measure was the UPDRS motor score.

When the stimulator was turned on for two hours, UPDRS motor scores were significantly better than when the stimulator was off (mean score off 50 ± 17 changing to 27 ± 14 with the stimulator on, $p<0.001$. Likewise, when the first score was taken with the stimulator on, the mean score was 31 ± 17, changing to 52 ± 17 with the stimulator was turned off, $p>0.001$). There was no carryover effect or period effect. Median improvement greater than 25% was observed in 15 of the 16 centers participating in the study.

Level-III Studies

The Deep Brain Stimulation for Parkinson's Disease Study Group[20] extended the Level I acute study to include open-label longitudinal assessments of motor function and dyskinesias. In this portion of their study, they used the UPDRS motor, UPDRS activities of daily living, and a dyskinesia rating scale. They monitored patients at baseline, one month, three months, and six months after electrode placement. At the evaluations, four conditions were assessed: off medication and off stimulation; off medication and with the stimulator turned on, usually for thirty minutes; on medication and with the stimulator turned off; on medication and on

stimulation. Of the 96 subjects who received bilateral subthalamic nucleus stimulation, 91 were available for the six month evaluation and completed the UPDRS motor evaluation in the four conditions. Comparing the baseline to six month scores, without medication and with the stimulator turned off, scores did not change (mean baseline UPDRS motor score 54.0 ± 15.0 vs. 53.1 ± 17.1 at six months). In the off medication/stimulator on condition, significant improvement occurred compared to baseline (25.7 ± 14.1 at six months vs. 54.0 ± 15.1 at baseline, p<0.001). On medication scores without the stimulator remained stable over the trial (23.6 ± 10.2 at baseline vs. 31.2 ± 18.8 at six months). When the stimulator was turned on, patients improved significantly (mean 17.8 ± 12.2 at six months compared to the on medication baseline score of 23.6 ± 10.2, improvement, p<0.001). Off medications but with the stimulator turned on, the Activities of Daily Living UPDRS scores significantly improved, as well as scores for tremor and postural stability (all p<0.001).

Limousin et al. (1998)[28] reported on 24 patients undergoing bilateral STN DBS for the treatment of advanced PD. Twenty patients completed the assessment at 12 months and were the basis of the analysis of efficacy. Patients were assessed on medication and off medication before surgery and after surgery, evaluations were repeated with the stimulator off in both conditions and then on in both conditions. STN DBS significantly improved UPDRS scores in both the on-medication and off-medication conditions. The mean off-medication UPDRS motor score before surgery was 55 and, at one year, with the stimulator turned on without medication, the mean score was 25 (numbers derived from figure and not given in text). The mean UPDRS on-medication before surgery was 18 vs. 14 on-medication and stimulator-on at one year. When the stimulator was turned off, UPDRS scores were better at one year than before surgery in both the off-medication and on-medication conditions as well. Ten patients were followed for 24 months and their UPDRS scores both on medication and off medication with the stimulator turned on remained improved. L-dopa was reduced from a mean dose of 1224 mg/day to 615 mg/day with one patient stopping the drug.

Four of the 24 subjects who received surgery were not included in the efficacy analysis. Two of these had serious adverse effects related to surgery, one with an intracerebral hematoma with persistent paralysis and aphasia and one developed an infection at the implantation site that required removal of the implant. One died of unrelated causes at 11 months after surgery and one could not travel for the evaluations. In eight of the 20 studied subjects, transient mental confusion, hallucinations or abulia occurred. In 18, dyskinesia could be induced by increasing the stimulation voltage. Five patients developed eyelid dyspraxia.

PREVENTION OF MOTOR COMPLICATIONS

No qualified studies were identified.

CONTROL OF MOTOR COMPLICATIONS

In the Burchiel[1] study, dyskinesias significantly improved from a baseline mean score of 11.6 to a mean 12 month score of 3.8. This observation occurred in the context of significantly lower doses of L-dopa after surgery.

In the Deep Brain Stimulation Study Group report[20], based on patient diaries covering the two days before the office evaluations, "on" time without dyskinesias increased from 27% at baseline to 74% at six months (p<.001). The mean dyskinesia scores improved from 1.9 ± 1.1 at baseline to 0.8 ± 0.8 at six months (p<0.001). Daily medication doses also significantly declined after surgery from a baseline mean of 1218.8 ± 575 mg/day to 764.0 ± 507 (p<0.001) [levodopa equivalents: 100 mg levodopa=10 mg bromocriptine=1 mg pergolide]

The Limousin[30] study monitored three motor complications of PD, painful dystonia, dyskinesias, and motor fluctuations. Among the 16 patients with painful off-dystonia before surgery, all improved and 12 experienced full resolution. L-dopa-induced dyskinesias decreased, but the improvements did not reach statistical significance. The motor fluctuation assessment (item 39 from Part IV of the UPDRS) improved, changing from a mean score before surgery of 2.2 to 0.6 at one year.

CONTROL OF NON-MOTOR COMPLICATIONS

Level-I Studies

The Burchiel[1] study also examined cognitive and affective changes consequent to bilateral pallidal stimulation and compared results with those obtained with bilateral subthalamic stimulation. Memory, attention, and visuomotor processing were unchanged from baseline 12 months after either surgery. Depression improved from baseline when the entire study group was considered (mean Beck Depression Inventory score 14.3 at baseline compared to mean 7.3 at 12 months), but no breakdown by pallidal and subthalamic surgery was provided.

Level-II Studies

Ardouin et al. (1999)[29] conducted a study assessing the neuropsychological effects of bilateral GPi DBS or STN DBS. Overall, 49 patients received STN DBS and 13 in GPi DBS. Some of the data reported combine the groups and therefore are difficult to interpret for STN alone. The mean age of participants in the STN group was 54.7 yrs with a disease duration of 15 years of PD. The neuropsychological measures included the Mattis Dementia rating, Wisconsin Card Sorting, lexical fluency, graphic, and Beck Depression Inventory, evaluated before surgery, and 3 to 6 months after surgery with the stimulator turned on. Most measures did not change. Stimulation improved the Trail-Making Test. Trail A scores improved from mean 56.8 before surgery to mean 49.6 and Trail B improved from mean 14.2 to 10.1. Depression scores improved, but literal and total lexical fluency declined. No additional safety data were documented specifically for the STN group, but of the entire 62, including the GPI stimulation group, had ten patients with intracerebral hemorrhages that resolved without long-term deficits. The authors concluded that overall cognitive performance was not greatly affected by STN stimulation surgery. In no instance did patients, family or staff perceive any change in language, memory, or cognition after surgery.

REVIEW OF SAFETY

Three types of adverse reactions are described with deep brain stimulation of the subthalamic nucleus including those relating to:

- The surgical procedure (e.g. intraoperative confusion, intracerebral hematoma, hemorrhage), with possible long-term residua like hemiparesis or seizures.
- The effects of stimulation (e.g. increased or new dyskinesias, dysarthria, paresthesias) which are generally considered reversible but may limit therapeutic efficacy. These effects can be reduced by lowering the stimulation and in the case of dyskinesias,

by reducing the levodopa daily dose.[28]

• The device (e.g. hardware erosion through the skin, infection, breakage, battery failure, lead migration).

The frequencies of these problems are usually less than 5% each, although with long-term follow-up, more technical problems may well arise with lead migration or breaks.

CONCLUSIONS

EFFICACY

All studies of STN DBS have been performed in patients with advanced disease and motor complications with inadequate response to medical management.

PREVENTION OF DISEASE PROGRESSION

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of STN DBS in the prevention of disease progression in patients with PD.

SYMPTOMATIC CONTROL OF PARKINSON'S DISEASE

Monotherapy

There is INSUFFICIENT EVIDENCE to conclude on the efficacy STN DBS in the symptomatic control of Parkinson's disease as a sole therapy.

Adjunct therapy

In spite of wide clinical perceptions of efficacy for treating parkinsonism and motor complications the evidence supporting this remains limited. The Level-I studies are without a non-intervention arm as a control group. Based on the one Level-I comparison between pallidal stimulation and STN DBS, the acute changes documented with Level I methods and Level-III studies with one of them showing a large effect for to one year, STN DBS is LIKELY EFFICACIOUS for treatment of motor symptoms of PD.

PREVENTION OF MOTOR COMPLICATIONS

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of STN deep brain stimulation regarding prevention of motor complications in patients with PD.

CONTROL OF MOTOR COMPLICATIONS OR OTHER COMPLICATIONS

The Level I and III data are consistent in showing that dyskinesias and motor fluctuations improve with subthalamic nucleus stimulation, but the observations on dyskinesias are confounded by reductions in medication. Only 3 studies of STN stimulation met inclusion criteria for this review and only two of these examined both dyskinesias and motor fluctuations. Therefore, in specific regards to the effects of the surgery, there is INSUFFICIENT EVIDENCE to conclude on the efficacy of STN DBS on motor and non-motor complications of PD.

SAFETY

The reports suggest that bilateral STN DBS presents ACCEPTABLE RISKS WITH SPECIALIZED MONITORING. Because the procedure is bilateral and the subthalamic nuclei are located near to vital neuroanatomic structures, surgical expertise is required.

IMPLICATIONS FOR CLINICAL PRACTICE

Based on the limited evidence published to date, the bilateral STN DBS is POSSIBLY USEFUL for the symptomatic control of PD. Clinicians considering this procedure can view its major advantages to include the reversible nature of stimulation surgery and the fact that bilateral surgery is possible. Whereas tremor has been helped, the most substantial change in the Burchiel study was on rigidity. The use of STN stimulation to control motor complications remains INVESTIGATIONAL, but it may allow levodopa doses to be lowered and consequently drug-induced dyskinesias to diminish. As such, the clinician facing a patient who is progressively disabled on both sides of the body by PD with or without tremor predominance and whose medications cannot be increased because of dyskinesias should consider referring this patient to a specialty center performing this procedure. Because extensive expertise, special physiological testing machines and careful follow-up to adjust the two separate stimulators (left and right), the number of centers where this surgery is currently performed worldwide is small.

IMPLICATIONS FOR CLINICAL RESEARCH

Level-I and Level-II studies are needed on the efficacy and safety of STN DBS. The mechanism of action of bilateral STN DBS also needs to be better understood. Patient selection, target selection within the STN region, and optimization of stimulation parameters require further study. An assessment of which parkinsonian features respond or are resistant to STN DBS also needs to be further investigated clinically.

REFERENCES

1. Burchiel KJ, Anderson VC, Favre J, Hammerstad JP. Comparison of pallidal and subthalamic nucleus deep brain stimulation for advanced Parkinson's disease: results of a randomized, blinded pilot study. Neurosurgery 1999;45(6):1375-1382.
2. Schuurman PR, Bosch DA, Bossuyt PM, et al. A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. N Engl J Med 2000;17(7):461-468.
3. de Bie RM, de Haan RJ, Nijssen PC, et al. Unilateral pallidotomy in Parkinson's disease: a randomized, single-blind, multicentre trial. Lancet 1999;354(9191):1665-1669.
4. Perrine K, Dogali M, Fazzini E, et al. Cognitive functioning after pallidotomy for refractory Parkinson's disease [see comments]. J Neurol Neurosurg Psychiatry 1998;65:150-154.
5. Young RF, Vermeulen S. Posewitz A, Shumway-Cook. Pallidotomy with the gamma knife: A positive experience. Stereotact Funct Neurosurg 1998;70(Suppl 1):218-2286.
6. Kondziolka D, Bonaroti E, Baser S, Brandt F, Kim YS, Lunsford LD. Outcomes after stereotactically guided pallidotomy for advanced Parkinson's disease. J Neurosurg 1999;90:197-202.
7. Giller CA, Dewey RB, Ginsburg MI, Mendelsohn DB, Berk AM. Stereotactic pallidotomy and thalamotomy using individual variations of anatomic landmarks for localization. Neurosurgery 1998;42:56-65.
8. Shannon KM, Penn RD, Kroin JS, et al. Stereotactic pallidotomy for the treatment of Parkinson's disease. Efficacy and adverse effects at 6 months in 26 patients. Neurology 1998;50:434-438.
9. Samuel M, Caputo E, Brooks DJ. A study of medial pallidotomy for Parkinson's disease: clinical outcome, MRI location and complications. Brain 1998;121:59-75.
10. Kishore A, Turnbull IM, Snow BJ, et al.Efficacy, stability and predictors of outcome of pallidotomy for Parkinson's disease. Six-month follow-up with additional 1-year observations. Brain 1997;120:729-737.
11. Krauss JK, Desaloms JM, Lai EC, King DE, Jankovic J, Grossman RG. Microelectrode-guided posteroventral pallidotomy for treatment of Parkinson's disease: postoperative magnetic resonance imaging analysis [see comments]. J Neurosurg 1997;87:358-367.
12. Lang AE, Lozano AM, Montgomery E, Duff J, Tasker R, Hutchinson W. Posteroventral medial pallidotomy in advanced Parkinson's disease. N Engl J Med 1997;337:1036-1042.
13. Kazumata K, Antonini A, Dhawan V, et al. Preoperative indicators of clinical outcome following stereotaxic pallidotomy. Neurology 1997;49:1083-1090.
14. Melnick ME, Dowling GA, Aminoff MJ, Barbaro NM. Effect of pallidotomy on postural control and motor function in Parkinson disease. Arch Neurol 1999;56:1361-1365.

15.Uitti RJ, Wharen RE Jr, Turk MF, et al. Unilateral pallidotomy for Parkinson's disease: Comparison of outcome in younger versus elderly patients. Neurology 1997;49:1072-1077.
16.Trépanier LL, Saint-Cyr JA, Lozano AM, Lang AE. Neuropsychological consequences of posteroventral pallidotomy for the treatment of Parkinson's disease. Neurology 1998;51:207-215.
17.Honey CR, Stoessl AJ, Tsui JK, Schulzer M, Calne DB. Unilateral pallidotomy for reduction of parkinsonian pain. J Neurosurg 1999;91:198-201.
18.Biousse V, Newman NJ, Carroll C, Mewes K, Vitek JL, Bakay RAE, Baron MS, DeLong MR. Visual fields in patients with posterior GPi pallidotomy. Neurology 1998;50:258-265.
19. Hariz MI, DeSalles AAF. The side-effects and complications of posteroventral pallidotomy. Acta Neurochir 1997;(Suppl)68:42-48.
20.Deep Brain Stimulation for Parkinson's Disease Study Group. Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. New Engl J Med 2001;345:956-963.
21.Ghika J, Ghika-Schmid F, Fankhauser H, et al. Bilateral contemporaneous posteroventral pallidotomy for the treatment of Parkinson's disease: neuropsychological and neurological side effects. Report of four cases and review of the literature. J Neurosurg 1999;91:313-21.
22.Duma CM, Jacques DB, Kopyov OV, Mark RJ, Copcutt B, Farokhi HK. Gamma knife radiosurgery for thalamotomy in parkinsonian tremor: a five- year experience [see comments]. J Neurosurg 1998;88:1044-1049.
23.Jankovic J, Cardoso F, Grossman RG, Hamilton WJ. Outcome after stereotactic thalamotomy for Parkinsonian, essential, and other types of tremor. Neurosurgery 1995;37:680-686.
24.Wester K, Hauglie-Hanssen E. Stereotaxic thalamotomy—experiences from the levodopa era. J Neurol Neurosurg Psychiatry 1990;53:427-430.
25.Limousin P, Speelman JD, Gielen F, Janssens M. Multicentre European study of thalamic stimulation in parkinsonian and essential tremor. J Neurol Neurosurg Psychiatry 1999;66: 289-296.
26.Koller W, Pahwa R, Busenbark K, et al. High-frequency unilateral thalamic stimulation in the treatment of essential and parkinsonian tremor. Ann Neurol 1997;42:292-299.
27.Benabid AL, Pollak P, Gao DM, et al. Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. J Neurosurg 1996;84:203-214.
28.Limousin P, Krack P, Pollak P, et al. Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 1998;339:1105-1111.
29.Ardouin C, Pillon B, Peiffer E, et al. Bilateral subthalamic or pallidal stimulation for Parkinson's disease affects neither memory nor executive functions: a consecutive series of 62 patients. Ann Neurol 1999;46(2):217-223.
30.Limousin P, Pollak, Hoffmann D, et al. Abnormal involuntary movements induced by subthalamic nuclear stimulation in parkinsonian patients. Mov Disord 1996;11:231-235.

BIBLIOGRAPHY - EXCLUDED FROM ANALYSIS (REASON FOR EXCLUSION)

Key for Reasons for exclusion

- Diagnosis unclear: Study did not specifically identify results on PD patients (Diagnosis unclear)
- Minimum of 20 patients (unless Level 1) (N<20)
- Minimal follow-up must be 4 weeks or 3 months for surgery (insufficient follow-up)
- Ambiguity of presentation (unclear outcome definition, incomplete reporting) (Ambiguity of presentation)
- Study not reported in English (Not English)
- Abstracts, letters, and reviews
- Not a clinical trial (Not a clinical trial)

Alesch F, Pinter MM, Helscher RJ, Fertl L, Benabid AL, Koos WT. Stimulation of the ventral intermediate thalamic nucleus in tremor dominated Parkinson's disease and essential tremor. Acta Neurochir 1995;136:75-81. (Diagnosis unclear)
Alesch F. [Neurosurgical methods in Parkinson disease]. Wien Med Wochenschr 1995;145:305-9. (Review article)
Almgren PE, Andersson AL, Kullberg G. Long-term effects on verbally expressed cognition following left and right ventrolateral thalamotomy. Confin Neurol 1972;34:162-8. (Diagnosis unclear-series includes several conditions other than PD)
Alterman RL, Kelly PJ. Pallidotomy technique and results: the New York University experience. Neurosurg Clin N Am 1998;9:337-43. (Review article)
Alvarez L, Macias R, Guridi J, et al. Dorsal subthalamotomy for Parkinson's disease. Mov Disord 2001;16:72-78. [Level-III with less than 20 subjects]
Aminoff MJ. Treatment of Parkinson's disease. West J Med 1994;161:303-8. (Review article)
Andrew J, Edwards JM, Rudolf NdM. The placement of stereotaxic lesions for involuntary movements other than in Parkinson's disease. Acta Neurochir (Wien) 1974;Suppl:39-47. (Diagnosis unclear)
Anno Y, Hirao J, Okamoto H, et al. Juvenile parkinsonism treated with bilateral pallidotomies-case report. Neurol Med Chir (Tokyo) 1995;35:680-2. (N<20)
Anonymous. Stereotactic radiofrequency pallidotomy without microelectrode mapping for the treatment of Parkinson's disease. Tecnologica 1995:8-9. (Letter/Editorial)
Anonymous. Pallidotomy for Parkinson's disease. Med Lett Drugs Ther 1996;38:107. (Letter/Editorial)
Anonymous. Stereotactic radiofrequency pallidotomy with microelectrode mapping for treatment of Parkinson's disease. Tecnologica 1996:8-10. (Letter/Editorial)
Asser TK, Kaasik AE. [Late results of ventrolateral thalamotomy in parkinsonism and their mathematical prognosis]. Zh Vopr Neirokhir Im N N Burdenko 1988:37-9 (Ambiguity of presentation)
Averbuch-Heller L, Stahl JS, Hlavin ML, Leigh RJ. Square-wave jerks induced by pallidotomy in parkinsonian patients. Neurology 1999;52:185-8. (N<20)
Bakay RA, DeLong MR, Vitek JL. Posteroventral pallidotomy for Parkinson's disease [letter; comment]. J Neurosurg 1992;77:487-8. (Letter/Editorial)
Baron JC, Levasseur M, Mazoyer B, et al. Thalamocortical diaschisis: positron emission tomography in humans. J Neurol Neurosurg Psychiatry 1992;55:935-42. (N<20)
Baron MS, Vitek JL, Bakay RA. Treatment of advanced Parkinson's disease by posterior GPi pallidotomy: 1-year results of a pilot study [see comments]. Ann Neurol 1996;40:355-66. (N<20)
Bejjani B, Damier P, Arnulf I, et al. Pallidal stimulation for Parkinson's disease. Two targets? [see comments]. Neurology 1997;49:1564-9. (N<20)
Bell S, Bleazel K. Cryogenic thalamotomy in Parkinson's disease. Med J Aust 1967;2:500-5. (Ambiguity of presentation-no specific measures used)
Bell DS. Speech functions of the thalamus inferred from the effects of thalamotomy. Brain 968;91:619-38. (Ambiguity of presentation-no specific speech methods or standarized assessments used).
Benabid AL, Pollak P, Louveau A, Henry S, de Rougemont J. Combined (thalamotomy and stimulation) stereotactic surgery of the Vim thalamic nucleus for bilateral Parkinson disease. Appl Neurophysiol 1987;50:344-6. (N<20)
Benabid AL, Pollak P, Hommel M, Gaio JM, de Rougemont J, Perret J. [Treatment of Parkinson tremor by chronic stimulation of the ventral intermediate nucleus of the thalamus]. Rev Neurol 1989;145:320-3. (N<20; not published in English)
Benabid AL, Pollak P, Seigneuret E, Hoffmann D, Gay E, Perret J. Chronic Vim thalamic stimulation in Parkinson's disease, essential tremor and extra-pyramidal dyskinesias. Acta Neurochir Suppl 1993;58:39-44. (Duplicate study report)
Benabid AL, Pollak P, Gross C, et al. Acute and long-term effects of subthalamic nucleus stimulation in Parkinson's disease. Stereotact Funct Neurosurg 1994;62:76-84. (N<20)
Benabid AL, Benazzouz A, Hoffmann D, Limousin P, Krack P, Pollak P. Long-term electrical inhibition of deep brain targets in movement disorders. Mov Disord 1998;13:119-25. (Review article)
Bennett KM, O'Sullivan JD, Peppard RF, McNeill PM, Castiello U. The effect of unilateral posteroventral pallidotomy on the kinematics of the reach to grasp movement. J Neurol Neurosurg Psychiatry 1998;65:479-87. (N<20)
Boecker H, Wills AJ, Ceballos-Baumann A, et al. Stereotactic thalamotomy in tremor-dominant Parkinson's disease: an H2(15)O PET motor activation study. Ann Neurol 1997;41:108-11. (N<20)
Bonnema R. Steriotactic posteroventral pallidotomy. Semin Perioper Nurs 1997;6:49-58. (Review article)
Bonnen JG, Iacono RP, Lulu B, Mohamed AS, Gonzalez A, Schoonenberg T. Gamma knife pallidotomy: case report. Acta Neurochir 1997;139:442-5. (N<20)
Bricolo A, Da Pian R, Perbellini D, Dalle Ore G. [Electroclinical manifestations of generalized epilepsy after unilateral thalamotomy for extrapyramidal syndromes]. Minerva Neurochir 1966;10:369-74. (N<20; not published in English)
Bricolo A. [Clinical and electroencephalographic considerations on a case of insomnia appearing after bilateral stereotaxic thalamotomy]. Riv Neurobiol 1966;12:622-38. (N<20)
Bricolo A. Insomnia after bilateral stereotactic thalamotomy in man. J Neurol Neurosurg Psychiatry 1967;30:154-8. (N<20)
Brock M, Kern BC, Funk T, Afshar HF. Pallidal or subthalamic stimulation [letter; comment]. J Neurosurg 1998;89:345-6. (Letter/Editorial)
Broggi G, Giorgi C, Servello D. Stereotactic neurosurgery in the treatment of tremor. Acta Neurochir Suppl 1987;39:73-6. (Ambiguity of presentation)
Bronstein JM, DeSalles A, DeLong MR. Stereotactic pallidotomy in the treatment of Parkinson disease: an expert opinion. Arch Neurol 1999;56:1064-9. (Review article)

Brophy BP, Kimber TJ, Thompson PD. Thalamotomy for parkinsonian tremor. Stereotact Funct Neurosurg 1997;69:1-4. (Ambiguity of presentation).
Brophy BP. Surgical palliation of dyskinesiae in Parkinson's disease. Stereotact Funct Neurosurg 1998;70:107-13. (Review article)
Burchiel KJ. Thalamotomy for movement disorders. Neurosurg Clin N Am 1995;6:55-71. (Review article)
Cahn DA, Sullivan EV, Shear PK, et al. Neuropsychological and motor functioning after unilateral anatomically guided posterior ventral pallidotomy. Preoperative performance and three-month follow-up. Neuropsychiatry Neuropsychol Behav Neurol 1998;11:136-45. (insufficient follow-up)
Caparros-Lefebvre D, Blond S, Pecheux N, Pasquier F, Petit H. [Neuropsychological evaluation before and after thalamic stimulation in 9 patients with Parkinson disease]. Rev Neurol 1992;148:117-22. (N<20)
Caparros-Lefebvre D, Blond S, Vermersch P, Pecheux N, Guieu JD, Petit H. Chronic thalamic stimulation improves tremor and levodopa induced dyskinesias in Parkinson's disease. J Neurol Neurosurg Psychiatry 1993;56:268-73. (N<20)
Carmel PW. Sympathetic deficits following thalamotomy. Arch Neurol 1968;18:378-87. (Unclear diagnosis-sample mixes PD with other conditions)
Ceballos-Baumann AO, Obeso JA, Vitek JL, et al. Restoration of thalamocortical activity after posteroventral pallidotomy in Parkinson's disease [letter]. Lancet 1994;344:814. (N<20)
Ceballos-Baumann AO, Boecker H, Bartenstein P, et al. A positron emission tomographic study of subthalamic nucleus stimulation in Parkinson disease: enhanced movement-related activity of motor-association cortex and decreased motor cortex resting activity. Arch Neurol 1999;56:997-1003. (N<20)
Chapman AH, Vieira e Silva D, Santana MC. [Stereotaxic thalamotomy and pallidotomy in the treatment of Parkinson disease (letter; comment)]. Arq Neuropsiquiatr 1999;57:151-2. (Letter/Editorial)
Charles PD, Esper GJ, Davis TL, Maciunas RJ, Robertson D. Classification of tremor and update on treatment. Am Fam Physician 1999;59:1565-72. (Review article)
Chen HR, Heimburger RF, Lu CS, Cheng CS. [The stereotactic thalamotomy in parkinsonism]. Taiwan I Hsueh Hui Tsa Chih 1985;84:423-8. (Letter; not published in English)
Chodakiewitz JW. Ventroposterior medial pallidotomy in patients with advanced Parkinson's disease [letter; comment]. Neurosurgery 1996;38:1261. (Letter/Editorial)
Chodakiewitz JW. Localizing pallidotomy lesions [letter; comment]. J Neurosurg 1998;88:1125; discussion 1126. (Letter/Editorial)
Conley SC, Kirchner JT. Medical and surgical treatment of Parkinson's disease. Strategies to slow symptom progression and improve quality of life. Postgrad Med 1999;106:41-4, 49, 52. (Review article)
Cooper IS. Neurosurgical treatment of the dyskinesias. Clin Neurosurg 1977;24:367-90. (Review)
Cooper IS. Clinical, physiological and philosophical implications of innovative brain surgery in humans. Ciba Found Symp 1979;69:255-65. (Review)
Cosgrove GR, Penney J, Shinobu L. Outcomes assessment for pallidotomy. Clin Neurosurg 1997;44:385-99. (Review)
Couldwell WT, Grafton ST. Pallidotomy in advanced Parkinson's disease [letter; comment]. Neurosurgery 1995;37:1234. (Letter/Editorial)
Dalvi A, Winfield L, Yu Q, Cote L, Goodman RR, Pullman SL. Stereotactic posteroventral pallidotomy: clinical methods and results at 1-year follow up. Mov Disord 1999;14:256-61. (Insufficient follow-up)
Date I, Ohmoto T. Neural transplantation and trophic factors in Parkinson's disease: special reference to chromaffin cell grafting, NGF support from pretransected peripheral nerve, and encapsulated dopamine-secreting cell grafting. Exp Neurol 1996;137:333-44. (Review)
Davie JC. Cryogenic sterotactic thalamotomy for Parkinson's disease. J Med Assoc State Ala 1967;37:405-10. (Ambiguous presentation)
Davis KD, Taub E, Houle S, Lang AE, Dostrovsky JO, Tasker RR, Lozano AM. Globus pallidus stimulation activates the cortical motor system during alleviation of parkinsonian symptoms [see comments]. Nat Med 1997;3:671-4. (N<20)
de Bie RM, Speelman JD, Schuurman PR, Bosch DA. Transient hiccups after posteroventral pallidotomy for Parkinson's disease [letter]. J Neurol Neurosurg Psychiatry 1999;67:124-5. (Letter/Editorial)
De Divitiis E, Giaquinto S, Signorelli CD. Peripheral influences on VPM-VPL thalamic nuclei in the human. A study on evoked potentials. Confin Neurol 1971;33:174-85. (N<20)
Defebvre L, Blatt JL, Blond S, Bourriez JL, Gieu JD, Destee A. Effect of thalamic stimulation on gait in Parkinson disease. Arch Neurol 1996;53:898-903. (N<20)
Dengler R, Kossev A, Struppler A. Unilateral reduction of the early and late blink reflex component in hemiparkinson syndrome. Electroencephalogr Clin Neurophysiol 1982;54:689-98. (N<20)
Desaloms JM, Krauss JK, Lai EC, Jankovic J, Grossman RG. Posteroventral medial pallidotomy for treatment of Parkinson's disease: preoperative magnetic resonance imaging features and clinical outcome. J Neurosurg 1998;89:194-9. (duplicate study report)
Diederich N, Goetz CG, Stebbins GT, et al. Blinded evaluation confirms long-term asymmetric effect of unilateral thalamotomy or subthalamotomy on tremor in Parkinson's disease. Neurology 1992;42:1311-4. (N<20)
Diederich NJ, Alesch F. [Neurosurgical methods in treatment of Parkinson disease. Current status]. Nervenarzt 1997;68:466-76. (Review; not published in English)
Diemath HE, Hibler N. Vestibular function before and after thalamotomy. Acta Neurochir (Wien) 1974;Suppl:65-70. (NCT)
Dogali M, Sterio D, Fazzini E, Kolodny E, Eidelberg D, Beric A. Effects of posteroventral pallidotomy on Parkinson's disease. Adv Neurol 1996;69:585-90. (Review)
Dong YR, Lin YJ, Li YH. [Stereotactic thalamotomy in the treatment of Parkinson's disease]. Chung Hua Wai Ko Tsa Chih 1987;25:428-9, 446-7. (Letter; not published in English)
Duff J, Sime E. Surgical interventions in the treatment of Parkinson's disease (PD) and essential tremor (ET): medial pallidotomy in PD and chronic deep brain stimulation (DBS) in PD and ET. Axone 1997;18:85-9. (Review)
Duma CM, Jacques D, Kopyov OV. The treatment of movement disorders using Gamma Knife stereotactic radiosurgery. Neurosurg Clin N Am 1999;10:379-89. (Review)
Dzugaeva SB, Irger IM, Popova LT, Rivina E, Beritashvili SI. [Clinical and morphologic findings in akinetic speech conditions]. Zh Nevropatol Psikhiatr Im S S Korsakova 1980;80:1028-32. (NCT)
Eidelberg D, Moeller JR, Ishikawa T, et al. A. Regional metabolic correlates of surgical outcome following unilateral pallidotomy for Parkinson's disease. Ann Neurol 1996;39:450-9. (N<20)
Eller TW, Dan DA. Stereotactic pallidotomy for treatment of Parkinson's disease [published erratum appears in AORN J 1997 Aug;66(2):224]. Aorn J 1997;65:903-4, 907-16; quiz 917-20. (Review)
England C. Stereotactic thalamotomy. Nurs Mirror Midwives J 1970;130:36-40. (Review)
Eskandar EN, Cosgrove GR, Shinobu LA, Penney JB, Jr. The importance of accurate lesion placement in posteroventral pallidotomy. Report of two cases. J Neurosurg 1998;89:630-4. (N<20)
Fasano VA, Hahn R, Demichelis G. [Changes of auditory function after cryo-thalamotomy]. Minerva Otorinolaringol 1967;17:19-21. (NCT)
Favre J, Taha JM, Nguyen TT, Gildenberg PL, Burchiel KJ. Pallidotomy: a survey of current practice in North America. Neurosurgery 1996;39:883-90; discussion 890-2. (Review)
Fazzini E, Dogali M, Sterio D, Eidelberg D, Beric A. Stereotactic pallidotomy for Parkinson's disease: a long-term follow-up of unilateral pallidotomy. Neurology 1997;48:1273-7. (N<20)
Fernandez PM, Dujovny M. Pallidotomy, editorial review [editorial]. Neurol Res 1997;19:25-34. (Review)
Fernando Pitty L. [Stereotaxic surgery in Parkinson's disease. A preliminary report of 2 cases]. Rev Med Panama 1992;17:101-8. (N<20; not published in English)
Ferraz FP, Aguiar PM, Ferraz HB, Bido JO, Bouza AA, De Andrade LA. [Stereotaxic thalamotomy and pallidotomy with computerized planning in Parkinson's disease: short-term evaluation of motor function in 50 patients (see comments)]. Arq Neuropsiquiatr 1998;56:789-97. (Insufficient follow-up; not published in English)
Figueiras-Mendez R, Marin-Zarza F, Antonio Molina J, et al.Subthalamic nucleus stimulation improves directly levodopa induced dyskinesias in Parkinson's disease [letter]. J Neurol Neurosurg Psychiatry 1999;66:549-50. (Letter/Editorial)
Fox MW, Ahlskog JE, Kelly PJ. Stereotactic ventrolateralis thalamotomy for medically refractory tremor in post-levodopa era Parkinson's disease patients. J Neurosurg. 1991;75:723-730. (Unable to interpret, because some patients started levodopa after surgery).
Friedman JH, Epstein M, Sanes JN, et al. Gamma knife pallidotomy in advanced Parkinson's disease. Ann Neurol 1996;39:535-8. (N<20)
Friedman DP, Goldman HW, Flanders AE. MR imaging of stereotaxic pallidotomy and thalamotomy. AJR Am J Roentgenol 1997;169:894-6. (NCT)
Friedman DP, Goldman HW, Flanders AE, Gollomp SM, Curran WJ, Jr. Stereotactic radiosurgical pallidotomy and thalamotomy with the gamma knife: MR imaging findings with clinical correlation-preliminary experience. Radiology 1999;212:143-50. (N<20)
Friehs GM, Ojakangas CL, Pachatz P, Schrottner O, Ott E, Pendl G. Thalamotomy and caudatotomy with the Gamma Knife as a treatment for parkinsonism with a comment on lesion sizes. Stereotact Funct Neurosurg 1995;64:209-21. (N<20)
Fujimoto Y, Isozaki E, Yokochi F, Yamakawa K, Takahashi H, Hirai S. [A case of chorea-acanthocytosis successfully treated with posteroventral pallidotomy]. Rinsho Shinkeigaku 1997;37:891-4. (Diagnosis unclear)
Fujiwara R. [Servo-analysis study on the manual control system of Parkinson patients, with special reference to changes in dynamic characteristics before and after stereotaxic VL-thalamotomy]. No To Shinkei 1968;20:675-85. (Letter)
Galler RM, Hallas BH, Fazzini E. Current trends in the pharmacologic and surgical treatment of Parkinson's disease. J Am Osteopath Assoc 1996;96:228-32. (Review)

Galvez-Jimenez N, Lozano A, Tasker R, Duff J, Hutchison W, Lang AE. Pallidal stimulation in Parkinson's disease patients with a prior unilateral pallidotomy. Can J Neurol Sci 1998;25:300-5. (N<20)

Galvez-Jimenez N. [Advances in the surgical treatment of Parkinson disease and other movement disorders]. Rev Neurol 1999;29:146-52. (Review; not published in English)

Gentil M, Tournier CL, Pollak P, Benabid AL. Effect of bilateral subthalamic nucleus stimulation and dopatherapy on oral control in Parkinson's disease. Eur Neurol 1999;42:136-40. N<20)

Ghika J, Ghika-Schmid F, Fankhauser H, et al. Bilateral contemporaneous posteroventral pallidotomy for the treatment of Parkinson's disease: neuropsychological and neurological side effects. Report of four cases and review of the literature. J Neurosurg 1999;91:313-21. (N<20)

Gilbert M, Counsell CM, Snively C. Pallidotomy: a surgical intervention for control of Parkinson's disease. J Neurosci Nurs 1996;28:215-6, 221. (Review)

Gill SS, Heywood P. Bilateral dorsolateral subthalamotomy for advanced Parkinson's disease [letter]. Lancet 1997;350:1224. N<20)

Gimenez Roldan S. [Posteroventral pallidotomy in Parkinson's disease (editorial)]. Neurologia 1999;14:49-52. (Letter/Editorial)

Goetz CG, De Long MR, Penn RD, Bakay RA. Neurosurgical horizons in Parkinson's disease [see comments]. Neurology 1993;43:1-7. (Review)

Goetz CG, Diederich NJ. There is a renaissance of interest in pallidotomy for Parkinson's disease. Nat Med 1996;2:510-4. (Review)

Golbe LI. Pallidotomy for Parkinson's disease: hitting the target? Lancet 1998;351:998-9. (Review)

Goto S, Kunitoku N, Soyama N, et al. Posteroventral pallidotomy in a patient with parkinsonism caused by hypoxic encephalopathy. Neurology 1997;49:707-10. (Diagnosis unclear or includes non PD patients)

Grafton ST, Waters C, Sutton J, Lew MF, Couldwell W. Pallidotomy increases activity of motor association cortex in Parkinson's disease: a positron emission tomographic study. Ann Neurol 1995;37:776-83. (N<20)

Greene KA, Wallace RC, Fram EK, Shetter AG, Lieberman AN. Transient resolution of bilateral tremor after unilateral thalamotomy, associated with focal injury of the corpus callosum: case report. J Neurol Sci 1995;129:25-8. (N<20)

Gregory R. Unilateral pallidotomy for advanced Parkinson's disease [editorial; comment]. Brain 1999;122:381-2. (Letter/Editorial)

Gross C, Rougier A, Guehl D, Boraud T, Julien J, Bioulac B. High-frequency stimulation of the globus pallidus internalis in Parkinson's disease: a study of seven cases. J Neurosurg 1997;87:491-8. (N<20)

Gross RE, Lozano AM, Lang AE, Tasker RR, Hutchison WD, Dostrovsky JO. The effects of pallidotomy on Parkinson's disease: study design and assessment techniques. Acta Neurochir Suppl 1997;68:24-8. (Review)

Gross CE, Boraud T, Guehl D, Bioulac B, Bezard E. From experimentation to the surgical treatment of Parkinson's disease: prelude or suite in basal ganglia research? Prog Neurobiol 1999;59:509-32. (Review)

Guridi J, Luquin MR, Herrero MT, Obeso JA. The subthalamic nucleus: a possible target for stereotaxic surgery in Parkinson's disease [see comments]. Mov Disord 1993;8:421-9. (Review)

Guridi J, Lozano AM. A brief history of pallidotomy. Neurosurgery 1997;41:1169-80; discussion 1180-3. (Review)

Hailey D, Harstall C. Posteroventral pallidotomy for Parkinson's disease: assessment and policy on a technology in transition. Health Policy 1998;43:55-64. (Review)

Hariz MI. Correlation between clinical outcome and size and site of the lesion in computed tomography guided thalamotomy and pallidotomy. Stereotact Funct Neurosurg 1990;55:172-85. (N<20)

Hariz MI, Hirabayashi H. Is there a relationship between size and site of the stereotactic lesion and symptomatic results of pallidotomy and thalamotomy? Stereotact Funct Neurosurg 1997;69:28-45. (Outcomes measured unconventional or uncertain)

Hariz MI. Controversies in pallidal surgery. Acta Neurochir Suppl 1997;68:1-10. (N<20)

Hariz GM, Bergenheim AT, Hariz MI, Lindberg M. Assessment of ability/disability in patients treated with chronic thalamic stimulation for tremor. Mov Disord 1998;13:78-83. (NCT)

Hariz MI. Microelectrode recording during posteroventral pallidotomy: impact on target selection and complications [letter]. Neurosurgery 1999;45:675-6. (Letter/Editorial)

Hariz MI, Bergenheim AT, Fodstad H. Crusade for microelectrode guidance in pallidotomy [letter; comment]. J Neurosurg 1999;90:175-9. (Letter/Editorial)

Hariz MI. Current controversies in pallidal surgery. Adv Neurol 1999;80:593-602. (Review)

Hariz MI, Johansson F, Shamsgovara P, Johansson E, Hariz GM, Fagerlund M. Bilateral subthalamic nucleus stimulation in a parkinsonian patient with preoperative deficits in speech and cognition: persistent improvement in mobility but increased dependency: a case study [In Process Citation]. Mov Disord 2000;15:136-9. (N<20)

Heikkinen ER. Stereotactic neurosurgery: new aspects of an old method. Ann Clin Res 1986;18:73-83. (Review)

Henderson JM, Dunnett SB. Targeting the subthalamic nucleus in the treatment of Parkinson's disease [published erratum appears in Brain Res Bull 1998 Sep 15;47(2):193]. Brain Res Bull 1998;46:467-74. (Review)

Hirai T, Ryu H, Nagaseki Y, Gaur MS, Fujii M, Takizawa T. Image-guided electrophysiologically controlled posteroventral pallidotomy for the treatment of Parkinson's disease: a 28-case analysis. Adv Neurol 1999;80:585-91. (Review)

Hirato M, Ohye C, Shibazaki T, Nakamura M, Inoue HK, Andou Y. Gamma Knife thalamotomy for the treatment of functional disorders. Stereotact Funct Neurosurg 1995;64:164-71. (N<20)

Hirato M, Ohye C, Takahashi A, Negishi M, Shibasaki T. Study on the function of the basal ganglia and frontal cortex using depth microrecording and PET scan in relation to the outcome of pallidotomy for the treatment of rigid-akinesia-type Parkinson's disease. Stereotact Funct Neurosurg 1997;69:86-92. (N<20)

Hitchcock E, Flint GA, Gutowski NJ. Thalamotomy for movement disorders: a critical appraisal. Acta Neurochir Suppl 1987;39:61-5. (Review)

Hugdahl K, Wester K, Asbjornsen A. The role of the left and right thalamus in language asymmetry: dichotic listening in Parkinson patients undergoing stereotactic thalamotomy. Brain Lang 1990;39:1-13. (NCT)

Hugdahl K, Wester K. Lateralized thalamic stimulation: effects on verbal memory. Neuropsychiatry Neuropsychol Behav Neurol 1997;10:155-61. (Not a clinical trial, concerns intraoperative stimulation and immediate memory effects)

Hullay J, Velok J, Gombi R, Boczan G. Subthalamotomy in Parkinson's disease. Confin Neurol 1970;32:345-8. (NCT)

Hullay J. Subthalamotomy in Parkinson's disease. Analysis of responses to electrostimulation. Acta Med Acad Sci Hung 1971;28:57-68. (Not a clinical trial)

Hurtado JM, Gray CM, Tamas LB, Sigvardt KA. Dynamics of tremor-related oscillations in the human globus pallidus: a single case study. Proc Natl Acad Sci U S A 1999;96:1674-9. (N<20)

Hurtig HI, Stern MB. Thalamotomy for Parkinson's disease [letter]. J Neurosurg 1985;62:163-5. (Letter/Editorial)

Husby J, Korsgaard AG. Proceedings: Late results of thalamotomy in Parkinsonism with and without the influence of levodopa. Acta Neurochir 1975;31:260. (Review)

Iacano RP, Mohamed AS, Schoonenberg T. Parkinson's disease: consider pallidotomy as a therapeutic option[letter]. Geriatrics 1996;51:26. (Letter/Editorial)

Iacono RP, Lonser RR, Mandybur G, Morenski JD, Yamada S, Shima F. Stereotactic pallidotomy results for Parkinson's exceed those of fetal graft. Am Surg 1994;60:777-82. (Ambiguous presentation)

Iacono RP, Lonser RR. Reversal of Parkinson's akinesia by pallidotomy [letter] [see comments]. Lancet 1994;343:418-9. (Letter/Editorial)

Iacono RP, Lonser RR, Yamada S. Contemporaneous bilateral postero-ventral pallidotomy for early onset "juvenile type" Parkinson's disease. Case report. Acta Neurochir 1994;131:247-52. (N<20)

Iacono RP, Shima F, Lonser RR, Kuniyoshi S, Maeda G, Yamada S. The results, indications, and physiology of posteroventral pallidotomy for patients with Parkinson's disease [see comments]. Neurosurgery 1995;36:1118-25; discussion 1125-7. (Ambiguous presentation)

Iacono RP, Lonser RR, Oh A, Yamada S. New pathophysiology of Parkinson's disease revealed by posteroventral pallidotomy. Neurol Res 1995;17:178-80. (Review)

Iacono RP, Henderson JM, Lonser RR. Combined stereotactic thalamotomy and posteroventral pallidotomy for Parkinson's disease. J Image Guid Surg 1995;1:133-40. (Ambiguous presentation)

Iacono RP, Lonser RR, Kuniyoshi S. Unilateral versus bilateral simultaneous posteroventral pallidotomy in subgroups of patients with Parkinson's disease. Stereotact Funct Neurosurg 1995;65:6-9. (Ambiguous presentation)

Iacopino DG, Lucerna S, Giller CA, et al. Pallidotomy improves quality of life in selected parkinsonian patients: an Italian report. Funct Neurol 1998;13:105-15. (N<20)

Jacques DS, Eagle KS, Kopyov OV. Use of posteroventral pallidotomy for treatment of Parkinson's disease: is pallidotomy still an experimental procedure? A review and commentary. Stereotact Funct Neurosurg 1998;70:19-31. (Review)

Jankovic J, Lai E, Ben-Arie L, Krauss JK, Grossman R. Levodopa-induced dyskinesias treated by pallidotomy. J Neurol Sci 1999;167:62-7. (Duplicate study report)

Jankovic J, Ben-Arie L, Schwartz K, Chen K, Khan M, Lai EC, Krauss JK, Grossman R. Movement and reaction times and fine coordination tasks following pallidotomy. Mov Disord 1999;14:57-62. (N<20)

Johansson F, Malm J, Nordh E, Hariz M. Usefulness of pallidotomy in advanced Parkinson's disease. J Neurol Neurosurg Psychiatry 1997;62:125-32. (Ambiguous presentation)

Joint C. A multi-disciplinary approach to pallidotomy and thalamotomy in the management of Parkinson's disease [published erratum appears in Br J Theatre Nurs 1998 Apr;8(1):48]. Br J Theatre Nurs 1997;7:5-8. (Review)

Junque C, Alegret M, Nobbe FA, et al. Cognitive and behavioral changes after unilateral posteroventral pallidotomy: relationship with lesional data from MRI. Mov Disord 1999;14:780-9. (N<20)
Jurko MF, Andy OJ. Psychological changes correlated with thalamotomy site. J Neurol Neurosurg Psychiatry 1973;36:846-52. (NCT)
Kawashima Y, Takahashi A, Hirato M, Ohye C. Stereotactic Vim-Vo-thalamotomy for choreatic movement disorder. Acta Neurochir Suppl 1991;52:103-6. (Diagnosis unclear)
Keller TM, Tcheng TK, Burkhard PR, Richard H, Tamas LB. Stereotactically guided thalamotomy for treatment of parkinsonian tremor isolated to the lower extremity. Case report. J Neurosurg 1998;89:314-6. (N<20)
Kelly PJ, Ahlskog JE, Goerss SJ, Daube JR, Duffy JR, Kall BA. Computer-assisted stereotactic ventralis lateralis thalamotomy with microelectrode recording control in patients with Parkinson's disease. Mayo Clin Proc 1987;62:655-64. (Duplicate study report)
Kelly PJ. Pallidotomy in Parkinson's disease [editorial; comment] [see comments]. Neurosurgery 1995;36:1154-7. (Review)
Kim YK, Buscher HP. [Control of autonomic tonus in stereotaxic subthalamotomy]. Neurochirurgia (Stuttg) 1970;13:151-64. (NCT)
Kim YK, Umbach W. The effects of stereotaxic subthalamotomy on sympathetic tonus. Confin Neurol 1972;34:156-61. (NCT)
Kimber TE, Tsai CS, Semmler J, Brophy BP, Thompson PD. Voluntary movement after pallidotomy in severe Parkinson's disease. Brain 1999;122:895-906. (N<20)
Klockgether T, Loschmann PA, Wullner U. New medical and surgical treatments for Parkinson's disease. Curr Opin Neurol 1994;7:346-52. (Review)
Klumbis LA, Shidishkis Iu K. [Thalamotomy in older parkinsonism patients]. Zh Vopr Neirokhir Im N N Burdenko 1991:7-8. (Not published in English)
Kocher U, Siegfried J, Perret E. Verbal and nonverbal learning ability of Parkinson patients before and after unilateral ventrolateral thalamotomy. Appl Neurophysiol 1982;45:311-6. (Insufficient follow-up)
Koller WC, Wilkinson S, Pahwa R, Miyawaki EK. Surgical treatment options in Parkinson's disease. Neurosurg Clin N Am 1998;9:295-306. (Review)
Koller WC, Pahwa R, Lyons KE, Albanese A. Surgical treatment of Parkinson's disease. J Neurol Sci 1999;167:1-10. (Review)
Komai N. [Surgical treatment of Parkinson's disease]. Nippon Rinsho 1993;51:2940-6. (Review)
Kopyov O, Jacques D, Duma C, et al. Microelectrode-guided posteroventral medial radiofrequency pallidotomy for Parkinson's disease. J Neurosurg 1997;87:52-9. (Outcome measures unconventional or uncertain)
Krack P, Limousin P, Benabid AL, Pollak P. Chronic stimulation of subthalamic nucleus improves levodopa-induced dyskinesias in Parkinson's disease [letter]. Lancet 1997;350:1676. (N<20)
Krack P, Pollak P, Limousin P, Benazzouz A, Benabid AL. Stimulation of subthalamic nucleus alleviates tremor in Parkinson's disease [letter]. Lancet 1997;350:1675. (N<20)
Krack P, Pollak P, Limousin P, Hoffmann D, Benazzouz A, Le Bas JF, Koudsie A, Benabid AL. Opposite motor effects of pallidal stimulation in Parkinson's disease. Ann Neurol 1998;43:180-92. (N<20)
Krack P, Benazzouz A, Pollak P, Limousin P, Piallat B, Hoffmann D, Xie J, Benabid AL. Treatment of tremor in Parkinson's disease by subthalamic nucleus stimulation. Mov Disord 1998;13:907-14. (Duplicate study reported)
Krack P, Pollak P, Limousin P, et al. Subthalamic nucleus or internal pallidal stimulation in young onset Parkinson's disease. Brain 1998;121:451-7. (N<20)
Krack P, Hamel W, Mehdorn HM, Deuschl G. Surgical treatment of Parkinson's disease. Curr Opin Neurol 1999;12:417-25. (Review)
Krack P, Pollak P, Limousin P, Benazzouz A, Deuschl G, Benabid AL. From off-period dystonia to peak-dose chorea. The clinical spectrum of varying subthalamic nucleus activity. Brain 1999;122:1133-46. (N<20)
Krauss JK, Jankovic J. Surgical treatment of Parkinson's disease. Am Fam Physician 1996;54:1621-9. (Review)
Krauss JK, Grossman RG, Lai EC, Schwartz K, Jankovic J. [Medial posteroventral pallidotomy for the treatment of Parkinson's disease]. Zentralbl Neurochir 1997;58:153-62. (Duplicate study report)
Krauss JK, Jankovic J, Lai EC, Rettig GM, Grossman RG. Posteroventral medial pallidotomy in levodopa-unresponsive parkinsonism. Arch Neurol 1997;54:1026-9. (N<20)
Kruszewski P, Antonaci F, Bordini C, Wester K, Sjaastad O. Sympathetic functions in parkinsonism treated with stereotactic surgery: observations in ten patients. Funct Neurol 1991;6:263-8. (N<20)
Kullberg G. A clinical study on acute confusion occurring in connection with ventrolateral thalamotomy. Confin Neurol 1975;37:167-71. (NCT)
Kullberg G, Risberg J. Changes in cerebral blood flow after stereotactic thalamotomy. Appl Neurophysiol 1985;48:362-6. (NCT)
Kumar R, Lozano AM, Montgomery E, Lang AE. Pallidotomy and deep brain stimulation of the pallidum and subthalamic nucleus in advanced Parkinson's disease. Mov Disord 1998;13:73-82. (N<20)
Kumar R, Lozano AM, Kim YJ, Hutchison WD, Sime E, Halket E, Lang AE. Double-blind evaluation of subthalamic nucleus deep brain stimulation in advanced Parkinson's disease. Neurology 1998;51:850-5. (N<20)
Kumar R, Lozano AM, Sime E, Halket E, Lang AE. Comparative effects of unilateral and bilateral subthalamic nucleus deep brain stimulation. Neurology 1999;53:561-6. (Review)
Kupsch A, Earl C. Neurosurgical interventions in the treatment of idiopathic Parkinson disease: neurostimulation and neural implantation. J Mol Med 1999;77:178-84. (Review)
LaFia DJ. Acute subdural hematoma as a complication of stereotaxic thalamotomy. Confin Neurol 1965;26:441-4. (NCT)
LaFia DJ. Hemiballismus as a complication of thalamotomy: report of two cases. Confin Neurol 1969;31:42-7. (N<20)
Laitinen LV, Ohno Y. Effects of thalamic stimulation and thalamotomy on the H reflex. Electroencephalogr Clin Neurophysiol 1970;28:586-91. (NCT)
Laitinen LV, Bergenheim AT, Hariz MI. Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease [see comments]. J Neurosurg 1992;76:53-61. (Ambiguous presentation)
Laitinen LV, Bergenheim AT, Hariz MI. Ventroposterolateral pallidotomy can abolish all parkinsonian symptoms. Stereotact Funct Neurosurg 1992;58:14-21. (Duplicate study report)
Laitinen LV. Ventroposterolateral pallidotomy. Stereotact Funct Neurosurg 1994;62:41-52. (Duplicate study report)
Laitinen LV. Pallidotomy for Parkinson's disease. Neurosurg Clin N Am 1995;6:105-12. (Review)
Lang AE, Lozano A, Duff J, Tasker R, Miyasaki J, Galvez-Jimenez N, Hutchison W, Dostrovsky J. Medial pallidotomy in late-stage Parkinson's disease and striatonigral degeneration. Adv Neurol 1997;74:199-211. (Duplicate study report)
Lang AE, Lozano A, Tasker R, Duff J, Saint-Cyr J, Trepanier L. Neuropsychological and behavioral changes and weight gain after medial pallidotomy [letter; comment]. Ann Neurol 1997;41:834-6. (Duplicate study report)
Lang AE, Duff J, Saint-Cyr JA, Trepanier L, Gross RE, Lombardi W, Montgomery E, Hutchinson W, Lozano AM. Posteroventral medial pallidotomy in Parkinson's disease. J Neurol 1999;246 Suppl 2:II28-41. (Duplicate study report)
Lang AE, Lozano A, Montgomery EB, Tasker RR, Hutchison WD. Posteroventral medial pallidotomy in advanced Parkinson's disease. Adv Neurol 1999;80:575-83. (Duplicate study report)
Lee ST, Lu CS. Ventrolateral thalamotomy for dyskinesia following levodopa therapy of Parkinson's disease. J Formos Med Assoc 1996;95:943-5. (N<20)
Lenz FA, Suarez JI, Metman LV, et al. Pallidal activity during dystonia: somatosensory reorganisation and changes with severity. J Neurol Neurosurg Psychiatry 1998;65:767-70. (Diagnosis unclear).
Lilker ES, Woolf CR. Pulmonary function in Parkinson's syndrome: the effect of thalamotomy. Can Med Assoc J 1968;99:752-7. (NCT)
Lim JK, Tasker RR, Scott JW. Quantitative assessment of thalamotomy for Parkinsonism. Confin Neurol 1969;31:11-21. (NCT)
Limousin P, Pollak P, Benazzouz A, et al. Bilateral subthalamic nucleus stimulation for severe Parkinson's disease. Mov Disord 1995;10:672-4. (Duplicate study report)
Limousin P, Pollak P, Benazzouz A, Hoffmann D, Le Bas JF, Broussolle E, Perret JE, Benabid AL. Effect of parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. Lancet 1995;345:91-5. (Duplicate study report)
Limousin P, Pollak P, Hoffmann D, Benazzouz A, Perret JE, Benabid AL. Abnormal involuntary movements induced by subthalamic nucleus stimulation in parkinsonian patients. Mov Disord 1996;11:231-5. (Duplicate study report)
Limousin-Dowsey P, Pollak P, Van Blercom N, Krack P, Benazzouz A, Benabid A. Thalamic, subthalamic nucleus and internal pallidum stimulation in Parkinson's disease. J Neurol 1999;246 Suppl 2:II42-5. (Review)
Linazasoro G, Guridi J, Vela L, et al. [Stereotactic surgery in Parkinson's disease]. Neurologia 1997;12:343-53. (Review)
Linazasoro G, Gorospe A, Rodriguez MC, et al. [Pallidotomy in the treatment of complicated Parkinson's disease: clinical results at two years and analysis of prognostic factors]. Neurologia 1999;14:53-61. (Language other than English)
Loyo-Varela M. Pallidotomy in Parkinson's disease [letter; comment]. Neurosurgery 1996;38:230; discussion 231. (Language other than English)
Lozano AM, Lang AE, Galvez-Jimenez N, et al. Effect of GPi pallidotomy on motor function in Parkinson's disease [see comments] [published erratum appears in Lancet 1996 Oct 19;348(9034):1108]. Lancet 1995;346:1383-7. (Duplicate study report)
Lozano AM, Hutchison WD, Dostrovsky JO. Microelectrode monitoring of cortical and subcortical structures during stereotactic surgery. Acta Neurochir Suppl 1995;64:30-4. (Review)
Lozano AM, Lang AE, Hutchison WD, Dostrovsky JO. Microelectrode recording-guided posteroventral pallidotomy in patients with Parkinson's disease. Adv Neurol 1997;74:167-74. (Diagnosis unclear)

Lozano AM, Kumar R, Gross RE, et al. Globus pallidus internus pallidotomy for generalized dystonia [see comments]. Mov Disord 1997;12:865-70. (Diagnosis unclear or contains patients with diagnosis other than PD)

Lozano AM, Lang AE, Hutchison WD. Pallidotomy for tremor. Mov Disord 1998;13:107-10. (Duplicate study report)

Lozano AM, Lang AE. Pallidotomy for Parkinson's disease. Neurosurg Clin N Am 1998;9:325-36. (Review)

Luczywek E, Mempel E, Sobotka S, Witkiewicz B. [Processes of verbal memory in patients with involuntary movements treated by thalamotomy]. Neurol Neurochir Pol 1985;19:247-52. (Language not English)

Luczywek E, Mempel E. [Verbal, visual and aural memory in the early postoperative period in patients treated by thalamotomy]. Neurol Neurochir Pol 1987;21:528-33. (Language not English)

Lund-Johansen M, Hugdahl K, Wester K. Cognitive function in patients with Parkinson's disease undergoing stereotaxic thalamotomy. J Neurol Neurosurg Psychiatry 1996;60:564-71. (Language not English)

Luquin MR. [Surgical therapy of Parkinson's disease]. Rev Neurol 1997;25 Suppl 2:S180-4. (Review)

Madrazo I. Pallidotomy in Parkinson's disease [letter; comment]. Neurosurgery 1996;38:230-1. (Letter/Editoiral)

Maeshima S, Nakai K, Nakai E, Uematsu Y, Ozaki F, Terada T, Nakakita K, Itakura T, Komai N. [Effects on cognitive function and activities of daily living after stereotactic thalamotomy for Parkinson's disease]. No Shinkei Geka 1995;23:417-21. (Language not English)

Marks PV, Wild AM, Gleave JR. Long-term abolition of parkinsonian tremor following attempted ventriculography. Br J Neurosurg 1991;5:505-8. (N<20)

Martinez-Martin P, Valldeoriola F, Molinuevo JL, Nobbe FA, Rumia J, Tolosa E. Pallidotomy and quality of life in patients with Parkinson's disease: an early study [In Process Citation]. Mov Disord 2000;15:65-70. (N<20)

Mason LJ, Cojocaru TT, Cole DJ. Surgical intervention and anesthetic management of the patient with Parkinson's disease. Int Anesthesiol Clin 1996;34:133-50. (NCT)

Masterman D, DeSalles A, Baloh RW, et al. Motor, cognitive, and behavioral performance following unilateral ventroposterior pallidotomy for Parkinson disease. Arch Neurol 1998;55:1201-8. (Insufficient follow-up)

Matsumoto K, Asano T, Baba T, Miyamoto T, Ohmoto T. Long-term follow-up results of bilateral thalamotomy for parkinsonism. Appl Neurophysiol 1976;39:257-60. (Ambituity of presentation).

Matsumoto K, Shichijo F, Fukami T. Long-term follow-up review of cases of Parkinson's disease after unilateral or bilateral thalamotomy. J Neurosurg 1984;60:1033-44. (Ambiguity of presentation)

Meier MJ, Story J, French LA, Chou SN. Quantitative assessment of behavioral changes following subthalamotomy in the treatment of Parkinson's disease. Confin Neurol 1966;27:154-61. (NCT).

Meier-Ewert K, Reischle W, Glotzner F. [Subthalamotomy inhibiting the appearance of uremic "flapping tremor"]. Nervenarzt 1970;41:148-50. (Language not English)

Melendez-Manzano JA, Gonzalez-Ortiz J, Melendez-Manzano E, Lavalle-Martinez J, Schiaffini-Ruiz MC, Velez-Quintana Roo JO. [Stereotaxic surgery in 4 cases of Parkinson's disease]. Rev Invest Clin 1996;48:449-52. (N<20)

Mempel E, Tarnecki R, Kucinski L, Ligezinska B, Pawlowski G. [Effect of cryosurgery of the thalamic nuclei on somatosensory evoked potentials]. Neurol Neurochir Pol 1984;18:453-8. (Language not English)

Merello M. Subthalamic stimulation contralateral to a previous pallidotomy: an erroneous indication? [letter]. Mov Disord 1999;14:890. (Letter)

Merello M, Lees AJ, Balej J, Cammarota A, Leiguarda R. GPi firing rate modification during beginning-of-dose motor deterioration following acute administration of apomorphine. Mov Disord 1999;14:481-3. (N<20)

Merello M, Nouzeilles MI, Cammarota A, Betti O, Leiguarda R. Comparison of 1-year follow-up evaluations of patients with indication for pallidotomy who did not undergo surgery versus patients with Parkinson's disease who did undergo pallidotomy: a case control study. Neurosurgery 1999;44:461-7; discussion 467-8. (N<20)

Merello M, Nouzeilles MI, Kuzis G, et al. Unilateral radiofrequency lesion versus electrostimulation of posteroventral pallidum: a prospective randomized comparison. Mov Disord 1999;14:50-6. (N<20)

Meyer CH. Unilateral pallidotomy for Parkinson's disease promptly improves a wide range of voluntary activities-especially gait and trunk movements. Acta Neurochir Suppl 1997;68:37-41. (Ambiguity of presentation)

Miles J, Redfern RM. The place of thalamotomy in the treatment of parkinsonism. Br J Neurosurg 1987;1:311-5. (Review)

Miyamoto T, Bekku H, Moriyama E, Tsuchida S. Present role of stereotactic thalamotomy for parkinsonism. Retrospective analysis of operative results and thalamic lesions in computed tomograms. Appl Neurophysiol 1985;48:294-304. (Review)

Modesti LM, Van Buren JM. Hemiballismus complicating stereotactic thalamotomy. Appl Neurophysiol 1979;42:267-83. (N<20)

Modesti LM, Blumetti AE. Long term effects of stereotaxic thalamotomy on parameters of cognitive functioning. Acta Neurochir Suppl 1980;30:401-3. (Non-motor symptoms reported)

Mohamed AS, Iacono RP, Yamada S. Normalization of middle latency auditory P1 potential following posterior ansa-pallidotomy in idiopathic Parkinson's disease. Neurol Res 1996;18:516-20. (NCT)

Molina H, Quinones-Molina R, Munoz J, et al. Neurotransplantation in Parkinson's disease: from open microsurgery to bilateral stereotactic approach: first clinical trial using microelectrode recording technique. Stereotact Funct Neurosurg 1994;62:204-8. (Review)

Montgomery EB, Jr. Deep brain stimulation reduces symptoms of Parkinson disease. Cleve Clin J Med 1999;66:9-11. (Review)

Moriyama E, Beck H, Miyamoto T. Long-term results of ventrolateral thalamotomy for patients with Parkinson's disease. Neurol Med Chir (Tokyo) 1999;39:350-6; discussion 356-7. (Ambiguity of presentation)

Moro E, Scerrati M, Romito LM, Roselli R, Tonali P, Albanese A. Chronic subthalamic nucleus stimulation reduces medication requirements in Parkinson's disease. Neurology 1999;53:85-90. (N<20)

Mosso JA, Rand RW. Management of parkinson's disease—combined therapy with levodopa and thalamotomy. West J Med 1975;122:1-6. (Review)

Mundinger F. [Subthalamotomy for the treatment of extrapyramidal movement disorders]. Dtsch Med Wochenschr 1965;90:2002-7. (Language not English).

Mundinger F, Zinsser O. [Clinico-experimental studies of stereotaxic thalamotomy of the oral ventral nuclei in extrapyramidal motor system disorders. (Somatotopics, optimal lesion sites and angle position of the electrode)]. Neurochirurgia (Stuttg) 1966;9:41-61. (Language not English)

Nagaseki Y, Shibazaki T, Hirai T, et al. [Long-term follow-up study of selective Vim-thalamotomy]. No To Shinkei 1985;37:545-54. (Ambiguity of presentation)

Nagaseki Y, Shibazaki T, Hirai T, et al. Long-term follow-up results of selective Vim-thalamotomy. J Neurosurg 1986;65:296-302. (Ambiguity of presentation)

Nakamura R, Taniguchi R, Narabayashi H, Yokochi F. Postural dependence of reaction time after a VL thalamotomy. Appl Neurophysiol 1980;42:325-34. (Not a clinical trial)

Narabayashi H. Physiological analysis of ventrolateral thalamotomy for rigidity and tremor. Confin Neurol 1965;26:264-8. (Non-English)

Narabayashi H. [Indications for stereotaxic thalamotomy. Part 1: Extrapyramidal symptoms (author's transl)]. No Shinkei Geka 1976;4:329-35. (Non-English)

Narabayashi H, Yokochi F, Nakajima Y. Levodopa-induced dyskinesia and thalamotomy. J Neurol Neurosurg Psychiatry 1984;47:831-9. (N<20)

Narabayashi H, Maeda T, Yokochi F. Long-term follow-up study of nucleus ventralis intermedius and ventrolateralis thalamotomy using a microelectrode technique in parkinsonism. Appl Neurophysiol 1987;50:330-7. (Ambiguity of presentation)

Narabayashi H. Pallidotomy revisited. Analysis of posteroventral pallidotomy. Stereotact Funct Neurosurg 1997;69:54-61. (Review)

Narabayashi H. Stereotactic surgery and Parkinson's disease. Stereotact Funct Neurosurg 1998;70:114-21. (Review)

Nasser JA, Confort CI, Ferraz A, Bouza AA. Preliminary results in surgery of Parkinson's disease. Arq Neuropsiquiatr 1998;56:533-9. (Insufficient follow-up)

Niclot P, Pollin B, N'Guyen J, Cesaro P, Degos JD. [Treatment of tremor by stereotactic surgery]. Rev Neurol 1993;149:755-63. (Review)

Nittner K. [Observations and considerations in stereotaxic brain operations]. Zentralbl Neurochir 1970;31:213-30. (Review)

Obeso JA, Linazasoro G, Rothwell JC, Jahanshahi M, Brown R. Assessing the effects of pallidotomy in Parkinson's disease [letter; comment]. Lancet 1996;347:1490. (Letter/Editorial)

Obeso JA, Rodriguez MC, Gorospe A, Guridi J, Alvarez L, Macias R. Surgical treatment of Parkinson's disease. Baillieres Clin Neurol 1997;6:125-45. (Review)

Obeso JA, Linazasoro G, Gorospe A, Rodriguez MC, Guridi J, Ramos E. [Pathophysiological bases, clinical results and indications for surgical treatment in Parkinson disease]. Neurologia 1999;14 Suppl 1:54-71. (Review)

Ohye C, Shibazaki T, Hirato M, Inoue H, Andou Y. Gamma thalamotomy for parkinsonian and other kinds of tremor. Stereotact Funct Neurosurg 1996;66:333-42. (N<20)

Ojemann GA, Hoyenga KB, Ward AA, Jr. Prediction of short-term verbal memory disturbance after ventrolateral thalamotomy. J Neurosurg 1971;35:203-10. (Not a clinical trial)

Ojemann GA, Ward AA, Jr. Speech representation in ventrolateral thalamus. Brain 1971;94:669-80. (Not a clinical trial)

Olanow CW. GPi pallidotomy—have we made a dent in Parkinson's disease? [editorial; comment]. Ann Neurol 1996;40:341-3. (Letter/Editorial)

Ondo WG, Jankovic J, Lai EC, et al. Assessment of motor function after stereotactic pallidotomy. Neurology 1998;50:266-70. (Duplicate study report)

Ondo W, Jankovic J, Schwartz K, Almaguer M, Simpson RK. Unilateral thalamic deep brain stimulation for refractory essential tremor and Parkinson's disease tremor. Neurology 1998;51:1063-9. (N<20)

Orthner H. [Influences exerted by pallidotomy on postencephalitic oculogyric crises]. Nervenarzt 1966;37:317-9. (Diagnosis unclear or contains patients with diagnosis other than PD)
Ostertag CB, Lucking CH, Mehdorn HM, Deuschl G. [Stereotactic treatment of movement disorders]. Nervenarzt 1997;68:477-84. (Review)
Otsuki T, Jokura H, Takahashi K, et al. Stereotactic gamma-thalamotomy with a computerized brain atlas: technical case report. Neurosurgery 1994;35:764-7; discussion 767-8. (N<20)
Pahwa R, Wilkinson S, Smith D, Lyons K, Miyawaki E, Koller WC. High-frequency stimulation of the globus pallidus for the treatment of Parkinson's disease. Neurology 1997;49:249-53. (N<20)
Pan L, Dai JZ, Wang BJ, Xu WM, Zhou LF, Chen XR. Stereotactic Gamma thalamotomy for the treatment of parkinsonism. Stereotact Funct Neurosurg 1996;66:329-32. (N<20)
Perani D, Nardocci N, Broggi G. Neglect after right unilateral thalamotomy. A case report. Ital J Neurol Sci 1982;3:61-4. (N<20)
Perlmutter I, Fairman D. Stereotactic thalamotomy in the treatment of extrapyramidal disorders: criteria for selection of parkinsonian patients. J Am Geriatr Soc 1968;16:468-71. (Review)
Perret E, Eggenberger E, Siegfried J. Simple and complex finger movement performance of patients with Parkinsonism before and after a unilateral stereotaxic thalamotomy. J Neurol Neurosurg Psychiatry 1970;33:16-21. (Unconventional outcome measure)
Perry VL, Lenz FA. Ablative therapy for movement disorders. Thalamotomy for Parkinson's disease. Neurosurg Clin N Am 1998;9:317-24. (Review)
Petrovici JN. Speech disturbances following stereotaxic surgery in ventrolateral thalamus. Neurosurg Rev 1980;3:189-95. (N<20)
Pfann KD, Penn RD, Shannon KM, Corcos DM. Pallidotomy and bradykinesia: implications for basal ganglia function. Neurology 1998;51:796-803. (N<20)
Pikielny RT. [Parkinson's disease: from pallidotomy to L-dopa and back to pallidotomy]. Medicina 1997;57:104-10. (Review)
Pinter MM, Alesch F, Murg M, Helscher RJ, Binder H. Apomorphine test: a predictor for motor responsiveness to deep brain stimulation of the subthalamic nucleus. J Neurol 1999;246:907-13. (N<20)
Poewe W. What is new in movement disorders? Wien Klin Wochenschr 1999;111:664-71. (Review)
Pollak P, Benabid AL, Gross C, Gao DM, Laurent A, Benazzouz A, Hoffmann D, Gentil M, Perret J. [Effects of the stimulation of the subthalamic nucleus in Parkinson disease]. Rev Neurol 1993;149:175-6. (Diagnosis unclear or contains patients with diagnosis other than PD)
Pollak P, Benabid AL, Limousin P, Krack P. Treatment of Parkinson's disease. New surgical treatment strategies. Eur Neurol 1996;36:400-4. (Review)
Porter RW, Bors E. Neurogenic bladder in parkinsonism: effect of thalamotomy. J Neurosurg 1971;34:27-32. (Not a clinical trial)
Quaglieri CE, Celesia GG. Effect of thalamotomy and levodopa therapy on the speech of Parkinson patients. Eur Neurol 1977;15:34-9. (Ambiguity of presentation-some patients also treated with levodopa during the follow-up).
Quinn N. Reversal of Parkinson's akinesia by pallidotomy [letter; comment]. Lancet 1994;343:1095-6. (Letter/Editorial)
Quinn NP. Stereotaxic posteroventral pallidotomy in idiopathic Parkinson's disease [letter]. Ann Neurol 1996;39:826. (Letter/Editorial)
Rafael H, Mego R. Ablative surgery and deep brain stimulation for Parkinson's disease [letter]. Neurosurgery 1999;45:199-200. (Letter/Editorial)
Ramamurthi B. Selective ventralis intermedius-thalamotomy [letter]. J Neurosurg 1987;67:787. (Letter/Editorial)
Rand RW, Jacques DB, Melbye RW, Copcutt BG, Fisher MR, Levenick MN. Gamma Knife thalamotomy and pallidotomy in patients with movement disorders: preliminary results. Stereotact Funct Neurosurg 1993;61:65-92. (N<20)
Robinson RG. Cryosurgical thalamotomy. Proc Aust Assoc Neurol 1968;5:305-7. (Not a clinical trial).
Rocamora R, Aranda L, Asenjo A, Chiorino R, Donoso P. Electrophysiological studies of the thalamic nuclei. Confin Neurol 1966;27:253-7. (Not a clinical trial)
Rodriguez MC, Guridi OJ, Alvarez L, Mewes K, Macias R, Vitek J, DeLong MR, Obeso JA. The subthalamic nucleus and tremor in Parkinson's disease. Mov Disord 1998;13:111-8. (Review)
Ross DA. Thalamotomy for parkinsonian tremor [letter; comment]. J Neurosurg 1998;88:1121-2. (Letter/Editorial)
Ryan L. Pallidotomy in advanced Parkinson's disease [letter; comment]. N Engl J Med 1998;338:262-3; discusssion 263. (Letter/Editorial)
Samii A, Turnbull IM, Kishore A, Schulzer M, Mak E, Yardley S, Calne DB. Reassessment of unilateral pallidotomy in Parkinson's disease. A 2-year follow-up study [see comments]. Brain 1999;122:417-25. (Duplicate study report)
Schafer JH. [On the changes in vestibular function in stereotaxic thalamic surgery in man]. Confin Neurol 1966;28:117-56. (Not a clinical trial)
Schnieden H, Williams T. Effect of thalamotomy on urinary dopamine levels in patients with Parkinsonism. Eur Neurol 1970;3:290-2. (Not a clinical trial).
Schrag A, Samuel M, Caputo E, et al. Unilateral pallidotomy for Parkinson's disease: results after more than 1 year. J Neurol Neurosurg Psychiatry 1999;67:511-7. (Duplicate study report)
Schulz GM, Peterson T, Sapienza CM, Greer M, Friedman W. Voice and speech characteristics of persons with Parkinson's disease pre- and post-pallidotomy surgery: preliminary findings. J Speech Lang Hear Res 1999;42:1176-94. (N<20)
Schuurman PR, de Bie RM, Speelman JD, Bosch DA. Bilateral posteroventral pallidotomy in advanced Parkinson's disease in three patients. Mov Disord 1997;12:752-5. (N<20)
Schuurman PR, de Bie RM, Speelman JD, Bosch DA. Posteroventral pallidotomy in movement disorders. Acta Neurochir Suppl 1997;68:14-7. (N<20)
Schuurman PR, Speelman JD, de Bie RM, Bosch DA. [Neurosurgical stereotactic treatment in Parkinson's disease]. Ned Tijdschr Geneeskd 1998;142:10-4. (Review)
Scott RM, Brody JA, Cooper IS. The effect of thalamotomy on the progress of unilateral Parkinson's disease. J Neurosurg 1970;32:286-8. (Ambiguity of presentation)
Scott RB. Cognitive function and pallidotomy [editorial; comment]. J Neurol Neurosurg Psychiatry 1998;65:148. (Letter/Editorial)
Scott R, Gregory R, Hines N, et al. Neuropsychological, neurological and functional outcome following pallidotomy for Parkinson's disease. A consecutive series of eight simultaneous bilateral and twelve unilateral procedures. Brain 1998;121:659-75. (N<20)
Seino O. [Resting tremor in parkinsonism and ventrolateral thalamotomy]. No To Shinkei 1970;22:1281-91. (Non-English).
Selby G. The influence of previous stereotactic thalamotomy on l-dopa therapy in Parkinson's disease. Proc Aust Assoc Neurol 1976;13:55-60. (Not a clinical trial)
Selby G. Treatment of parkinsonism. Drugs 1976;11:61-70. (Review)
Shibasaki H, Shima F, Kuroiwa Y. Clinical studies of the movement-related cortical potential (MP) and the relationship between the dentatorubrothalamic pathway and readiness potential (RP). J Neurol 1978;219:15-25. (Not a clinical trial).
Shibasaki T. [Glucose metabolism and blood flow studies in 2 cases with juvenile Parkinson's disease]. Nippon Rinsho 1997;55:95-100. (N<20)
Shima F. [Posteroventral pallidotomy for Parkinson's disease: renewal of pallidotomy]. No Shinkei Geka 1994;22:103-10. (Review)
Shima F. [Pallidotomy in patients with Parkinson disease]. Fukuoka Igaku Zasshi 1995;86:355-61. (Review)
Shima F, Ishido K, Sun SJ, et al. Surgical control of akinesia in Parkinson's disease. Eur Neurol 1996;36:55-61. (Ambiguity of presentation).
Siegfried J, Wiesendanger M. Respiratory alterations produced by thalamic stimulation during stereotaxic operations. Confin Neurol 1967;29:220-3. (Not a clinical trial)
Siegfried J, Zumstein H. [Stereotaxic thalamotomy for functional disorders in the aged]. Neurochirurgie 1976;22:536-9. (Review)
Siegfried J. Therapeutic stereotactic procedures on the thalamus for motor movement disorders. Acta Neurochir 1993;124:14-8. (Review)
Skalabrin EJ, Laws ER, Jr., Bennett JP, Jr. Pallidotomy improves motor responses and widens the levodopa therapeutic window in Parkinson's disease. Mov Disord 1998;13:775-81. (N<20)
Smirnov VM, Shandurina AN. [The stereotaxic semiology of speech]. Vopr Neirokhir 1973;37:37-43. (Non-English)
Soukup VM, Ingram F, Schiess MC, Bonnen JG, Nauta HJ, Calverley JR. Cognitive sequelae of unilateral posteroventral pallidotomy [see comments]. Arch Neurol 1997;54:947-50. (N<20)
Speelman JD, Bosch DA. [Continuous electric thalamus stimulation for the treatment of tremor resistant to pharmacotherapy]. Ned Tijdschr Geneeskd 1995;139:926-30. (N<20)
Speelman JD, Bosch DA. Resurgence of functional neurosurgery for Parkinson's disease: a historical perspective. Mov Disord 1998;13:582-8. (Review)
Speelman JD, Schuurman PR, de Bie RM, Bosch DA. Thalamic surgery and tremor. Mov Disord 1998;13:103-6. (Review)
Spiegelman R. [Stereotactic pallidotomy—effective surgery for Parkinson's disease]. Harefuah 1996;131:324-6. (Non-English)
Starikov AS. [Effect of destruction of the ventrolateral nucleus of the thalamus on the motor analyzer]. Zh Vopr Neirokhir Im N N Burdenko 1981:45-51. (Ambiguity of presentation)
Starr PA, Vitek JL, Bakay RA. Ablative surgery and deep brain stimulation for Parkinson's disease. Neurosurgery 1998;43:989-1013; discussion 1013-5. (Review)
Stefani A, Mazzone P, Bassi A, et al. Electrophysiological and clinical desensitization to apomorphine administration in parkinsonian patients undergoing stereotaxic neurosurgery. Exp Neurol 1999;156:209-13. (N<20)
Stellar S. Outcome after stereotactic thalamotomy for parkinsonian, essential, and other types of tremor [letter; comment]. Neurosurgery 1996;39:421. (Letter/Editorial)

Stracciari A, Guarino M, Cirignotta F, Pazzaglia P. Development of palilalia after stereotaxic thalamotomy in Parkinson's disease. Eur Neurol 1993;33:275-6. (N<20)
Struppler A, Gurfinkel V, Mathis J, Max T. Motor performance in parkinsonism following stereotactic thalamotomy. Adv Neurol 1993;60:403-7. (Review)
Suarez JI, Metman LV, Reich SG, Dougherty PM, Hallett M, Lenz FA. Pallidotomy for hemiballismus: efficacy and characteristics of neuronal activity. Ann Neurol 1997;42:807-11. (Ambiguity of presentation)
Sutton JP, Couldwell W, Lew MF, et al. Ventroposterior medial pallidotomy in patients with advanced Parkinson's disease [see comments]. Neurosurgery 1995;36:1112-6; discussion 1116-7. (N<20)
Taha JM, Janszen MA, Favre J. Thalamic deep brain stimulation for the treatment of head, voice, and bilateral limb tremor. J Neurosurg 1999;91:68-72. (N<20)
Tan AK, Yeo TT, Tjia HT, Khanna S, Nowinski WL. Stereotactic microelectrode-guided posteroventral pallidotomy and pallidal deep brain stimulation for Parkinson's disease. Ann Acad Med Singapore 1998;27:767-71. (N<20)
Tarnecki R, Mempel E, Kolodziejak A, Witkiewicz B. [Somatosensory evoked potentials in a patient with Parkinson's disease before and after cryothalamotomy]. Neurol Neurochir Pol 1997;31:357-66. (N<20)
Tasker RR, Siqueira J, Hawrylyshyn P, Organ LW. What happened to Vim thalamotomy for Parkinson's disease? Appl Neurophysiol 1983;46:68-83. (Review)
Tasker RR. Tremor of parkinsonism and stereotactic thalamotomy. Mayo Clin Proc 1987;62:736-9. (Review)
Tasker RR. Thalamotomy. Neurosurg Clin N Am 1990;1:841-64. (Review)
Tasker RR, DeCarvalho GC, Li CS, Kestle JR. Does thalamotomy alter the course of Parkinson's disease? Adv Neurol 1996;69:563-83. (Outcome measures unconventional or uncertain)
Tasker RR, Munz M, Junn FS, Kiss ZH, Davis K, Dostrovsky JO, Lozano AM. Deep brain stimulation and thalamotomy for tremor compared. Acta Neurochir Suppl 1997;68:49-53. (Ambiguity of presentation)
Tasker RR, Lang AE, Lozano AM. Pallidal and thalamic surgery for Parkinson's disease. Exp Neurol 1997;144:35-40. (Review)
Tasker RR. Ablative therapy for movement disorders. Does thalamotomy alter the course of Parkinson's disease? Neurosurg Clin N Am 1998;9:375-80. (Review)
Tasker RR. Deep brain stimulation is preferable to thalamotomy for tremor suppression. Surg Neurol 1998;49:145-53; discussion 153-4. (Ambiguity of presentation)
Temlett JA. Pallidotomy in Parkinson's disease [editorial]. S Afr Med J 1996;86:1248-9. (Letter/Editorial)
Trépanier L, Saint-Cyr J, Lang A, Lozano A. Hemisphere-specific cognitive and motor changes after unilateral posteroventral pallidotomy [letter; comment]. Arch Neurol 1998;55:881-3. (Letter/Editorial)
Tronnier VM, Fogel W, Kronenbuerger M, Krause M, Steinvorth S. Is the medial globus pallidus a site for stimulation or lesioning in the treatment of Parkinson's disease? Stereotact Funct Neurosurg 1997;69:62-8. (N<20)
Tronnier VM, Fogel W, Kronenbuerger M, Steinvorth S. Pallidal stimulation: an alternative to pallidotomy? [see comments]. J Neurosurg 1997;87:700-5. (Review)
Troster AI, Fields JA, Wilkinson SB, et al. Unilateral pallidal stimulation for Parkinson's disease: neurobehavioral functioning before and 3 months after electrode implantation. Neurology 1997;49:1078-83. (Insufficient follow-up)
Troster AI, Wilkinson SB, Fields JA, Miyawaki K, Koller WC. Chronic electrical stimulation of the left ventrointermediate (Vim) thalamic nucleus for the treatment of pharmacotherapy-resistant Parkinson's disease: a differential impact on access to semantic and episodic memory? Brain Cogn 1998;38:125-49. (N<20)
Tsukamoto Y, Gillingham FG. Stereotactic thalamotomy and L-dopa induced involuntary movement in Parkinsonism. Neurol Med Chir 1973;13:38-45. (Not a clinical trial)
Uitti RJ, Wharen RE, Jr., Turk MF. Efficacy of levodopa therapy on motor function after posteroventral pallidotomy for Parkinson's disease. Neurology 1998;51:1755-7. (Duplicate study report)
Van Buren JM, Li CL, Shapiro DY, Henderson WG, Sadowsky DA. A qualitative and quantitative evaluation of parkinsonians three to six years following thalamotomy. Confin Neurol 1973;35:202-35. (Ambiguity of presentation)
van Manen J, Speelman JD, Tans RJ. Indications for surgical treatment of Parkinson's disease after levodopa therapy. Clin Neurol Neurosurg 1984;86:207-18. (Ambiguity of presentation)
Velasco-Suarez MM, Escobedo Rios E. Vegatative symptoms in Parkinsonism and their modifications after thalamotomy. Confin Neurol 1967;29:123-6. (Not a clinical trial)
Vilkki J, Laitinen LV. Differential effects of left and right ventrolateral thalamotomy on receptive and expressive verbal performances and face-matching. Neuropsychologia 1974;12:11-9. (Not a clinical trial)
Vilkki J. Visual hemi-inattention after ventrolateral thalamotomy. Neuropsychologia 1984;22:399-408. (Not a clinical trial)
Vingerhoets G, van der Linden C, Lannoo E, et al. D. Cognitive outcome after unilateral pallidal stimulation in Parkinson's disease. J Neurol Neurosurg Psychiatry 1999;66:297-304. (Insufficient follow-up)
Vitek JL, Bakay RA, DeLong MR. Microelectrode-guided pallidotomy for medically intractable Parkinson's disease. Adv Neurol 1997;74:183-98. (Review)
Vitek JL, Bakay RA. The role of pallidotomy in Parkinson's disease and dystonia. Curr Opin Neurol 1997;10:332-9. (Review)
Vittadini M. [The effect of unilateral pallidotomy and thalamotomy on the performance of Parkinson patients in psychometric tests]. Sist Nerv 1966;18:397-405. (Non-English)
Vlahovitch B, Gros C, Frerebeau P. [Anatomo-clinical study of 2 cases of Parkinson's disease treated successfully by thalamotomy (survival of 5 and 14 months)]. Neurochirurgie 1967;13:357-74. (N<20)
Volkmann J, Sturm V, Weiss P, et al. Bilateral high-frequency stimulation of the internal globus pallidus in advanced Parkinson's disease. Ann Neurol 1998;44:953-61. (N<20)
Watanabe M, Kuramoto S, Aiba H. L-dopa therapy and stereotaxic thalamotomy for parkinsonism. Confin Neurol 1975;37:259-64 (Not a clinical trial).
Weiner WJ. Pallidotomy in advanced Parkinson's disease [letter; comment]. N Engl J Med 1998;338:263. (Letter/Editorial)
Wester K, Hugdahl K. Thalamotomy and thalamic stimulation: effects on cognition. Stereotact Funct Neurosurg 1997;69:80-5. (Ambiguity of presentation)
Widner H, Rehncrona S. Transplantation and surgical treatment of parkinsonian syndromes. Curr Opin Neurol Neurosurg 1993;6:344-9. (Review)
Yasui N, Kondo T, Ohye C, Narabayashi H. [Minimum cerebellar symptoms in thalamotomy—its neurological and neurophysiological analysis (author's transl)]. No To Shinkei 1977;29:1199-206. (Non-English)
Yokoyama T, Sugiyama K, Nishizawa S, Uemura K, Ito T. Localizing pallidotomy lesions [letter; comment]. J Neurosurg 1998;88:1125-6. (Letter/Editorial)
Yokoyama T, Imamura Y, Sugiyama K, et al. Prefrontal dysfunction following unilateral posteroventral pallidotomy in Parkinson's disease. J Neurosurg 1999;90:1005-10. (Insufficient follow-up)
Yokoyama T, Sugiyama K, Nishizawa S, Yokota N, Ohta S, Uemura K. Subthalamic nucleus stimulation for gait disturbance in Parkinson's disease. Neurosurgery 1999;45:41-7; discussion 47-9. (N<20)
York MK, Levin HS, Grossman RG, Hamilton WJ. Neuropsychological outcome following unilateral pallidotomy [In Process Citation]. Brain 1999;122:2209-20. (Review)
Young RF. Functional neurosurgery with the Leksell Gamma knife. Stereotact Funct Neurosurg 1996;66:19-23. (Duplicate study report)
Young MS, Triggs WJ, Bowers D, Greer M, Friedman WA. Stereotactic pallidotomy lengthens the transcranial magnetic cortical stimulation silent period in Parkinson's disease. Neurology 1997;49:1278-83. (Duplicate study report)
Young RF, Shumway-Cook A, Vermeulen SS, Grimm P, Blasko J, Posewitz A, Burkhart WA, Goiney RC. Gamma knife radiosurgery as a lesioning technique in movement disorder surgery. J Neurosurg 1998;89:183-93. (Duplicate study report)
Zager EL. Neurosurgical management of spasticity, rigidity, and tremor. Neurol Clin 1987;5:631-47. (Review)
Zegers de Beyl D. [Surgical treatment of Parkinson disease: indications and limitations]. Rev Med Brux 1999;20:A261-3. (Review)
Zoll JG. Transient anosognosia associated with thalamotomy: is it caused by proprioceptive loss? Confin Neurol 1969;31:48-55. (N<20)
Zoll JG. Inversion or pronation of the foot following thalamotomy for Parkinson's disease. Appl Neurophysiol 1978;41:232-6. (N<20)

Movement Disorders
Vol. 17, Suppl. 4, 2002, p. S148-S155

Published by Wiley-Liss, Inc.
DOI 10.1002/mds.5575

Surgical Treatment for Parkinson's Disease: Neural Transplantation

INTRODUCTION

BACKGROUND

Current treatment for Parkinson's disease (PD) is primarily based on a dopamine replacement strategy using levodopa with a peripheral decarboxylase inhibitor and dopaminergic agents.[1] These therapies provide clinical benefit to virtually all PD patients, but long-term treatment is complicated by motor fluctuations and dyskinesia in the majority of patients.[2] Further, disease progression is associated with the development of clinical features that do not respond to levodopa such as freezing, postural instability, autonomic dysfunction, and dementia. Thus, many PD patients eventually experience disability that cannot be satisfactorily controlled with medical therapy. This dilemma has led to a search for new therapies to complement traditional pharmacological treatment. In the surgical arena, there are two strategies: (1) lesional or inhibitory, and (2) constructive or restorative in the form of neurotransplantation.

RATIONALE

Neural and other cellular transplantation therapies are based on several considerations. First, PD is associated with a relatively specific degeneration of dopamine neurons in the select brain region of the substantia nigra pars compacta. Second, dopaminergic replacement therapy provides dramatic clinical benefit in PD. Third, under physiological conditions, dopamine neurons provide tonic stimulation of target receptors. Fourth, there is a well-defined and relatively large target area for implantation. Finally, grafts of dopaminergic neurons have been shown to be capable of ameliorating the features of experimental parkinsonism in animal models.[3]

Given the dopaminergic cell depletion in PD, cells that have been used in transplantation studies are known to synthesize dopamine, either as their primary metabolic product or as an intermediary. To date, clinical interventions in PD have involved two primary cell types, human adult cells (either adrenal medullary or cervical sympathetic ganglion cells) from the patient, with and without additional peripheral nerve fragments, and fetal mesencephalic cells, derived from human or animal (porcine) tissue. As indicated below (see Special Exceptions to Inclusion/Exclusion Criteria below), only human and porcine fetal mesencephalic transplants are critiqued herein.

METHODS

KEY SEARCH TERMS

Parkinson's disease, neurotransplantation, fetal surgery, adrenal medulla, dopamine cells, neurosurgery, clinical trials.

SPECIAL EXCEPTIONS TO THE INCLUSION/EXCLUSION CRITERIA

The studies critiqued in this report are restricted to those that concern surgical procedures that are being studied in 1999-2000, document the specific transplant variables used, and describe clinical outcome using statistical methods. Whereas, most studies reviewed in this *Movement* Disorder Society effort require 20 subjects for inclusion, this limitation would exclude nearly all currently published studies, and therefore this criterion has been waived. As a result of these Inclusion/Exclusion criteria, some procedures are not critiqued for the following reasons: adrenal medullary transplants with or without addition of peripheral nerve fragments (no longer being performed) [4,5], autotransplants of cervical sympathetic ganglion cells (very limited data and no statistical analysis).[6,7]

HUMAN FETAL MESENCEPHALIC CELL TRANSPLANTS

MECHANISM OF ACTION

Behavioral improvement following transplantation of human fetal nigral cells is thought to relate primarily to survival of grafted nigral neurons, neuritic outgrowth with synaptic connection to host neurons, and graft-derived dopamine production.[3] Clinical benefits in open-label studies have been associated with a progressive increase in striatal [18F]fluorodopa uptake[8-11] and postmortem studies have demonstrated robust survival of implanted cells with organotypic innervation of the striatum.[12,13] It is possible that benefit following a transplantation procedure relates to host-derived sprouting, although host-derived sprouting has not been seen with fetal nigral transplant even in cases with clinical benefits.[12,13] Because of the extensive surgery and emotional involvement in this area of research by patients, investigators, and families, researchers have been concerned that placebo effects can play a role in post operative benefits observed with this surgery.[14]

REVIEW OF CLINICAL STUDIES

Several hundred transplant procedures have now been performed across the world, demonstrating the feasibility of performing fetal nigral transplantation in PD patients. However, many reports are descriptively imprecise and very difficult to compare among one another because of the absence of statistical analysis and variations in patient selection, transplant variables, rating systems employed, and clinical expertise.[3]

One hundred and twenty-one studies were identified through the search process, but only 23 met the review criteria as clinical trials for inclusion in this review. Because of the scientific interest in this area of treatment, often several publications concern the same patients reported on multiple occasions. For this review, reports from such cohorts are collapsed, summarized and critiqued as a single series. All included studies treated patients with advanced PD in need of enhanced symptomatic control of parkinsonism and improved treatment of motor complications. None has

focused on prevention of disease progression. In all cases, fetal transplant surgery was performed on patients already on levodopa, sometimes with other dopaminergic agents.

PREVENTION OF DISEASE PROGRESSION

No qualified studies were identified.

SYMPTOMATIC CONTROL OF PARKINSONISM

Level-I Studies

Spencer et al. (1992)[15] conducted a randomized, open-label comparison trial of fetal transplant in four patients with clinically diagnosed PD. They compared treatment outcome at one year to three patients who were treated medically over the same period and then offered surgery. Patients received stereotactically implanted cryopreserved fragments of mesencephalic tissue into the right caudate nucleus. Clinical evaluations including UPDRS "on and off" medication, Hoehn and Yahr (HY) stage, and Schwab and England evaluations. After transplantation, no improvement in transplanted patients occurred in comparison to medical controls. There were isolated statistically significant improvements in some motor function measures compared to baseline in the implanted patients. Mean UPDRS ADL score before surgery 29.0 vs. 12.67 (18 months after surgery). One patient died and at autopsy did not have PD. There was evidence of extremely limited survival of implanted tissue.[16] This study had an overall quality rating score of 58%.

Kopyov et al. (1997)[17] conducted a randomized controlled and blinded trial comparing low dose implantation (one to two fetal donors) vs. high dose implantation (three or more donors). Human fetal tissues was placed bilaterally into both putamens in 13 patients. Preoperatively, these patients were staged using the HY scale and stages were 1 to 3 "on" and 3 to 5 "off". They received solid grafts of 6 to 9 week gestational material by stereotaxic implantation. The randomization was determined by the availability of tissue on the day of surgery, and the patient and evaluating team were unaware of the dosage assignment. Post-operatively, patients were evaluated at three-month intervals for 6 months. At 6 months, there were significantly improved effects on UPDRS ("on" and "off"), levodopa reduction, dyskinesias, hours "off", and some timed motor tasks. High dose was significantly better than low dose for: (a) reducing hours "off" (mean 3.0 vs. 8.7), (b) dyskinesia intensity (mean 1.5 vs. 2.6) , and (c) dyskinesia duration (mean 1.0 vs. 2.9). The NIH is currently funding two prospective, double-blind, randomized studies. This study had an overall quality rating score of 68%.

Freed et al.[18] performed a randomized double-blind sham-surgery controlled study of fetal transplantation. They chose 40 subjects, aged 34-75, with advanced Parkinson's disease and motor fluctuations. Half received cultured mesencephalic tissue from four human embryos, seven to eight weeks post conception, transplanted into the putamen bilaterally. The placebo group received a sham-surgery that involved the placement of burr holes in the skull without penetration of the dura. No patient received immunosuppressive therapy. Subjects were followed for one year, and the primary outcome was a subjective clinical global assessment by the patient assessing change from baseline. One year after surgery, patients compared their current state in comparison to pre-operative function and chose phrases with corresponding anchor numbers ranging from "parkinsonism markedly worse" (-3) through "no change" (0), to "parkinsonism markedly improved" (+3). Secondary clinical outcomes included the Schwab and England scale and the total and motor UPDRS scores taken in the early morning off medication ("off scores").

There was no difference in the global change score between the transplantation group and the subjects who received sham-surgery (0.0 ± 2.1 vs. -0.4 ± 1.7). The Schwab and England scale of independent living was however significantly better after transplant surgery (specific numbers not given in text, but, based on Figure 1, approximately 60 vs. 48 in the controls, $p=0.008$). Likewise, The UPDRS motor score off medication significantly improved in the transplantation group (pre- vs. post-surgery improvement of 18%, $p=0.04$). The total UPDRS score off medication improved as well with transplant surgery, but the difference between transplantation and control groups did not reach statistical significance.

When the group was divided by age at the time of surgery, the young patients (= 60 years) showed significant improvement in both Schwab and England ($p=0.006$), off-medication total UPDRS ($p=0.01$) and UPDRS motor ratings ($p=0.005$). The older patients showed the same pattern of improvement, but the changes did not reach statistical significance.

Fluorodopa PET scans one year after surgery showed a significant increase in uptake in the putamen in the group receiving implants compared to the placebo surgery patients.[19] Increases in uptake were similar in both the younger and older transplant recipients. Correlations between PET changes and clinical outcome were significant for the younger patients. Significant declines in putamen uptake occurred in the younger placebo-operated subjects over one year. These findings suggest that transplantation induces enhanced and viable dopaminergic cell function in the first year after surgery that is not influenced by recipient age. The behavioral outcome of this viable change, however, appears to differ according to patient age with only the younger patients showing significant clinical improvement in this time frame.

Two subjects died, one during the study from a motor vehicle accident, and the other three years after surgery from a myocardial infarction. At autopsy, both showed the histological findings of Parkinson's disease. Additionally, there were abundant dopaminergic neurons in the transplant sites with extensive outgrowth into the host tissue.

In the open-label follow-up period covering up to three years after surgery, 15% of the transplanted patients (three from the original transplant group and two original sham-surgery patients who subsequently received transplants after the study completed) developed dystonia and dyskinesia that persisted after a substantial reduction or elimination of dopaminergic therapy (see paragraph on "motor complications").

Level-II Studies

No qualified studies were identified.

Level-III Studies

Swedish investigators have examined fetal implantation in a number of reports that cover ten patients, some of them examined and reported in multiple studies.

Lindvall et al. (1989)[20] were the first to report on the results of fetal nigral grafting in PD patients. They performed a unilateral transplantation procedure into the caudate nucleus and anterior putamen in two PD patients using donors aged 7 to 9 weeks post-conception. Patients exhibited a small but clinically significant

improvement in motor performance during "off" periods (mean time to perform 20 pronation/supination movements was approximately 29 seconds before surgery vs. 18 after surgery). There was no change in striatal of [18F]fluorodopa uptake on PET. Follow-up studies did not substantiate significant clinical improvement. At 18 months follow-up, one patient continued to show statistically significant improvement in timed motor tasks (mean time to perform 20 pronation/supination movements was approximately 29 seconds before surgery vs. 17 seconds after surgery.[21] Subsequently, the same investigators treated two PD patients with fetal tissue derived from donor aged 6 to 7 weeks post-conception implanted exclusively into the putamen using a smaller gauge needle.[9,22-24] These patients were followed for 3 years. They experienced significant clinical improvement in motor performance during "off" episodes and a reduction in percent "off" time and in the number of daily "off" periods. One patient changed from 40% "off" time preoperatively to 20% after 3 years and the other changed from 60% "off" time before surgery to 0% by the third year. Striatal FD uptake on PET demonstrated a progressive increase in tracer uptake within the grafted putamen consistent with survival of grafted neurons coupled with a decline in tracer uptake on the non-operated side consistent with disease progression.[24] In a later summary report that included a total of six patients including three of those reported above, benefits persisted for as long as 6 years and levodopa had been discontinued in two patients.[8] Enhanced benefits were attributed to implanting larger amounts of donor tissue in the correct donor age window and reduced tissue trauma due to the use of a smaller transplant needle.

Remy et al. (1995)[10]; Defer et al. (1996)[25]: This pattern of improvement in clinical function and in striatal [18F]fluorodopa uptake was also observed by French researchers using a similar protocol of implanting fetal mesencephalic cells into the putamen or caudate and putamen.[10,25] In five patients studied clinically and with PET at 12 and 24 months, they found significant improvement in timed motor tasks. For a standardized pronation/supination task during "off" time changed from mean 30.5 seconds to mean 22.7 seconds, and during "on" time, the change mean was 13.7 seconds to 12.1 seconds. These clinical benefits correlated closely with striatal [18F]fluorodopa uptake on PET. Medical and post-surgical complications were not discussed. Peschanski (1994)[26] examined two patients and both showed statistically significant bilateral improvement in timed motor tasks in "on" and "off" state after long-term follow up at 10 and 17 months. On a timed finger dexterity task, the preoperative scores during "off" were 19 seconds (patient 1) and 36 seconds (patient 2) and at follow-up were 12 seconds (seventeen months) and 21 seconds (10 months; approximate numbers from numerical data taken from figures]).

Freeman et al. (1995)[11] and Hauser et al. (1998)[27] conducted a prospective, open-label study in 6 patients who were followed for a mean duration of 20.5 months after fetal cell implantation. All patients received bilateral transplants into the post-commissural putamen using fetal cells (aged 6.5 to 9 weeks post conception). Four donors were implanted per side. Six to 8 needle tracts per side were employed to ensure that graft deposits were separated by no more than 5 mm throughout the three dimensional configuration of the target. Benefits were seen in each patient. Total UPDRS score in the "off" state (mean 80.3 vs. 58.0), Schwab-England disability "off" score (mean 51.3 vs. 72.5) , percent "on" time (66% vs. 88%) and percent "on" time without dyskinesia (mean 56% vs. 96%) were all significantly improved 6 months after surgery.[11] Several variables remained improved through 2 years of follow-up including mean total UPDRS score in "off" state (mean 56.4), and percent "on" time without dyskinesia.[27] Clinical changes were associated with a progressive and significant increase in striatal [18F]fluorodopa uptake on PET. Changes in striatal [18F]fluorodopa uptake were strongly correlated with clinical improvement on UPDRS scale and with the number of surviving fetal nigral neurons at subsequent post-mortem studies in two individuals. These subjects died 18 months after surgery from unrelated causes, and autopsy studies demonstrated healthy appearing grafts with survival of approximately 82,000 to 138,000 dopaminergic neurons per side.[12,13] Extensive striatal innervation with patch-matrix distribution occurred along with normal staining for markers of dopamine terminals and metabolic activity.[26] In situ hybridization studies demonstrated extensive TH mRNA formation in the striatum suggesting that implanted neurons were functional. Ultrastructure studies demonstrated normal appearing graft-host and host-graft synaptic connections. No evidence of host-derived sprouting was detected.[28] In addition, within this series of patient there was one asymptomatic cortical hemorrhage and one patient with an elevated creatinine on cyclosporin treatment, leading to cessation of cyclosporin.

Freed et al. (1990, 1992, 1992)[29-31]: Seven patients from the University of Colorado received nigral grafts from a single fetus (gestational age 7-8 weeks) and were followed for up to 46 months.[29-31] Embryonic tissue was implanted unilaterally into the caudate and putamen on the side opposite the maximal deficit in two patients and bilaterally into the putamen in the remainder. At 12 months, there was a modest but statistically significant improvement in activities of daily living in both "on" and "off" states. Improvement was noted in postural control, gait, and bradykinesia, but the UPDRS motor "on" scores did not change significantly. Levodopa dose was reduced by an average of 39%. The mean HY stage changed from mean 3.7 to 2.5. Four of seven subjects had immunosuppression and both groups improved. Safety was not extensively discussed.

Lopez-Lozano et al. (1995, 1997)[32,33] provided the longest published follow-up (5 years) on a relatively large sample of ten subjects with advanced PD who received fetal implantation.[32,33] At study entry, all had advanced disease (HY stages 4 and 5) and efficacy was monitored with the UPDRS, "on-off" assessments, and the Northwestern University Disability Scale. Significant improvements occurred in the UPDRS scores "on" (mean baseline 56 vs. 30 at 5 years), UPDRS "off" (mean 90 vs. 66), amount of time "on" (mean baseline 40% vs. 70% post-operatively) and amount of time "on" without dyskinesias (32% vs. 66%). The improvements occurred between 5 and 7 months after surgery with a second phase of improvement at approximately 15 months. At 5 years, seven of ten patients remained better than baseline. Levodopa was reduced, and in some instances, stopped.

Kopyov et al. (1996)[34] studied patients who received unilateral or bilateral fetal transplants to putamen or putamen and caudate. Follow-up ranged from 6 to 24 months (mean 13.1 months). Although the report did not give numerical scores, the authors reported statistically significant improvements in UPDRS and HY scores in both the "on" and "off" states, as well as dyskinesia intensity and duration measures. Hours spent "on" also significantly improved as well as some timed motor tasks. Surgical morbidity was not discussed.

Molina et al. (1993)[35] performed fetal transplants in five patients with advanced PD and documented significant improvements in "on" UPDRS (baseline mean "on" 50 vs. 40 [numbers derived from figure] and "off" (mean 110 vs. 60) and magnitude of response to a standard dose of levodopa. The daily requirement of levodopa was significantly reduced 3 months after surgery and the mean number of "off" periods decreased from 4.4 to 1.5.

CONTROL OF MOTOR COMPLICATIONS

Level-I Studies

Spencer et al. (1992)[15] and Freed (2000)[18] did not assess "on-off" times and therefore are not reviewed.

Kopyov et al. (1997)[17] The high dose vs. low-dose comparison conducted by Kopyov[17] monitored intensity and duration of dyskinesia (using their own scale) and noted that the high-dose implantation group had significantly less severe (mean high-dose score 1.5 vs. 2.6 for low-dose transplant) and shorter duration dyskinesia (mean high-dose score 1.0 vs. 2.0 for the low-dose transplant). Likewise, the number of hours spent "off" was significantly less in the high-dose group compared to the low-dose group (mean 3.0 vs. 8.7). Because all patients received some form of surgical implant, the 6 months vs. baseline results are Level-III results, and they likewise demonstrated significant improvement, although the numerical data were not published.

Level-II Studies

No qualified studies were identified.

Level-III Studies

Wenning et al. (1997)[8]; Lindvall et al. (1994)[9]; Hoffer et al. (1992)[21]; Lindvall et al. (1990)[23]: In the Swedish studies[8,9,21,23], significant improvement occurred in reduced "off" time and enhanced "on" time over the time periods studied. The analyses varied among the reports, sometimes expressed as 95% confidence intervals. In the French study, percent "on" time correlated with enhanced [18F]fluorodopa uptake.[10] In the Freeman et al. (1995)[11] and Hauser et al. (1999)[27] studies, significant improvement occurred in percent "off" time and percent "on" time without dyskinesia. The percent "on" time improved from baseline 66% to 88% by 6 months and still persisted to be significantly higher (80%) after one year. Using an all-day computer assessment of "on-off" fluctuations, Freed[27] showed significantly improved "on" time at one year after surgery (86% of the waking day vs. 69% before surgery). Kopyov found significantly reduced "off" time at 6, 12, 18 and 24 months, although no numerical data were given in his report.[34] Likewise Lopez-Lozano showed that even at 5 years after fetal implants, the amount of time "on" and amount of time "on" without dyskinesias remained significantly better than baseline: mean "on" time at 5 years 70% vs. 40% at baseline; mean "on" time without dyskinsia 66% vs. 32%.[32,33]

CONTROL OF NON-MOTOR COMPLICATIONS

Level-III Studies

Yale study population (1992)[15], and Sass (1995)[36] examined the surgically treated patients for cognitive changes over 36 months. After surgery, verbal memory significantly improved compared to baseline, but declined again by 26 months. At baseline, mean immediate verbal memory scores were 12.7, improved to 17.1 at one years but declined to 9.1 at 3 years; in parallel, delayed verbal memory scores showed a mean of 9.8 at baseline, with improvement to 13.3 at one and 2 years, but a decline to a mean 4.1 by 36 months. Other measures of verbal and non-verbal cognitive abilities did not change. Price[37] studied these same patients, along with the original control group and two other patients who eventually received surgery (nine patients total, no control group), for psychiatric changes. There was a mild increase in depression and non-specific emotional problems, but no significant changes. Specifically, there was no increase in hallucinations or psychotic behavior.

REVIEW OF SAFETY

Fetal nigral transplantation has been well tolerated in most studies. There have been hemorrhages that are usually asymptomatic[11,17,27,33], subdural hematoma[18], transient confusion[11,17,27] and enhanced psychiatric problems.[18,32,33] Cyclosporin can be associated with renal impairment[11,27] or infection from immunosuppression.[32,33] Fractures, motor vehicle accidents, myocardial infarctions and a late-occurring stroke occurred in one series, but these events were not considered likely to have been related to surgery.[18] There have been a total of 14 deaths in fetal graft recipients of which two are thought to have been related to the transplant procedure: one from a perioperative complication[30] and one from obstructive hydrocephalus due to migration of the graft into the fourth ventricle with brain stem compression.[38,39] Postmortem study in the latter case revealed that the tissue was derived from multiple germ layers and contained bone, cartilage, hair, and squamous epithelium.[38] This case illustrates the dangers of inexperienced investigators employing improper dissection and transplant techniques, and underscores the importance of adequate training prior to performing a transplant procedure.[39] On the other hand, other series have documented abundant dopaminergic neurons in the transplant sites with extensive outgrowth into the host tissue.[18]

In the Freed study, increased dyskinesia occurred more frequently in the sham-operated patients than in the transplanted subjects.[18] In the open-label follow-up period covering up to three years after surgery, 15% of the transplanted patients (three from the original transplant group and two original sham-surgery patients who subsequently received transplants after the study completed) developed dystonia and dyskinesia that persisted after a substantial reduction or elimination of dopaminergic therapy. All were in the younger patient group, transplanted at age 60 or less. This type of "off medicine" dyskinesia is unusual in advanced Parkinson's disease, but does occur without transplantation.[40] Concerns that this form of dyskinesia may relate to aberrant reinnervation in the striatum remains to be studied in more detail.

TRANSPLANTATION WITH ALTERNATE SOURCES OF DOPAMINERGIC CELLS

In an effort to avoid the use of human fetal nigral cells, a limited number of trials of transplantation with other sources of dopaminergic cells have been performed. Adrenal medullary transplant trials with or without additional peripheral nerve fragments aimed to deliver nerve growth factors, have been largely abandoned and are not reviewed here.[4,5] Autologous sympathetic ganglion cells have been performed but data have not been analyzed statistically.[6,7] Other cells sources remain restricted to laboratory settings and have not been tested in humans. Among these alternate, non-human sources, porcine fetal mesencephalon transplants have been a focus of scientific study. One clinical trial has been reported.

PORCINE FETAL MESENCEPHALON SYMPTOMATIC TREATMENT OF PARKINSONISM

Schumacher et al. (2000)[41]: Twelve patients with PD received unilateral implants of embryonic porcine mesencephalic tissue into the caudate and putamen. Six received cyclosporin treatment for immunosuppression and six received fetal tissue treated with a monoclonal antibody directed against major histocompatibility Class I.[41] The groups were considered together. At one year, there was significant improvement in "off" total UPDRS scores with a mean improvement of 19% over baseline (mean 66.8 vs. 83.7). Off UPDRS ADL score was also improved from mean 27.1 before surgery to mean 20.4 one year after surgery. Only two patients, both in the cyclosporin group, individually showed significant improvements. [18F]fluorodopa PET scans failed to show changes on the implanted side. In two patients who died, small numbers of implanted cells that included dopaminergic neurons and other porcine neural and glial cells were detected.[42] A multicenter, prospective, randomized, double-blind, placebo-controlled study, is presently underway to evaluate this therapy further.

CONTROL OF MOTOR COMPLICATIONS

No qualified studies were identified.

CONTROL OF NON-MOTOR COMPLICATIONS

No qualified studies were identified.

REVIEW OF SAFETY

Only one study has been reported using porcine fetal material.[41] One patient had a small subdural hematoma, one patient fell and fractured a leg 12 months after surgery, one patient had confusion that required adjustment of medications, one patient had body shaking contralateral to the surgery, and one patient died of pulmonary emboli. There was no evidence of endogenous retrovirus DNA.[42]

CONCLUSIONS

The scientific rationale for undertaking fetal nigral transplantation studies in PD patients is compelling and is founded on a strong base of laboratory information. Indeed, the prospect of restoring physiologic dopaminergic innervation to the striatum by non-ablative procedures is particularly appealing. However, clinical information to establish the value of the procedure in PD patients is lacking.

EFFICACY

PREVENTION OF DISEASE PROGRESSION

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of fetal transplantation in the prevention of disease progression in patients with PD.

SYMPTOMATIC CONTROL OF PARKINSON'S DISEASE

Monotherapy

There is INSUFFICIENT EVIDENCE to conclude on the efficacy fetal transplantation in the symptomatic control of Parkinson's disease as a sole therapy.

Adjunct therapy

In view of inconsistent results in three Level-I trials there is INSUFFICIENT EVIDENCE to conclude on the efficacy of fetal transplantation to improve symptomatic control (or motor complications).

Another study with a sham operation control group is ongoing (CW Olanow, principle investigator). The techniques and outcomes are suitably different to prevent solid conclusions on efficacy. In open-label Level-III studies, results are encouraging, but inconclusive in regards to clinical-derived and PET-derived outcomes. Postmortem studies suggest, however, that following some protocols, fetal transplant tissue can survive in the brain

PREVENTION OF MOTOR COMPLICATIONS

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of fetal transplantation regarding prevention of motor complications in patients with PD.

CONTROL OF MOTOR COMPLICATIONS OR OTHER COMPLICATIONS

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of fetal transplantation on motor and non-motor complications of PD.

SAFETY

Based on the multiple studies reported with monitoring safety, fetal transplantation is considered to have ACCEPTABLE RISK WITH SPECIALIZED MONITORING. This monitoring involves the restriction of this work to specialized teams of experts involved in the acquisition, dissection, and implanting of tissue and use of cyclosporine. Specialized tests are required for screening the tissue to assure that it is maximally free of contaminants and infectious potential. Specialized teams that can monitor clinical efficacy in the form of standardized rating scales and PET technology are also essential to the evaluation of this experimental area of research. Particular attention to dyskinesias before surgery and after surgery are essential to define whether dyskinesia occurs, especially in the "off-medication" state.

IMPLICATIONS FOR CLINICAL PRACTICE

Current studies are not sufficient to permit a clear determination of the magnitude or duration of benefit or the long-term side effects associated with fetal nigral transplantation. From a practical point of view, fetal transplantation is not recommended within the context of routine clinical practice. Tissue transplantation is considered INVESTIGATIONAL and should be restricted to research centers performing studies under high-quality surveillance.

IMPLICATIONS FOR CLINICAL RESEARCH

Further studies are warranted in the area of transplantation for treatment of PD because:

- Open-label trials have shown substantial benefits with minimal adversity following fetal nigral transplantation in patients with advanced PD who could not otherwise be improved with available medical therapies, and
- Clinical benefits have been confirmed by more objective measures such as an increase in striatal [18F]fluorodopa uptake on PET and robust survival of implanted nigral neurons at postmortem.

This arena of neuroscience opens several horizons for research including:

- An evaluation of the benefits of transplantation with larger number of donor cells,

- Delineation of the benefits of concomitant use of antioxidant and/or antiapoptotic drugs,
- The role of immunosuppression, and
- Determination of clinical benefits or risks associated with transplantation into alternate targets such as the substantia nigra pars compacta.

Proof of concept studies demonstrating meaningful clinical benefit with fetal nigral transplantation will undoubtedly catalyze research efforts aimed at developing alternate sources of dopaminergic cells that do not necessitate using human embryonic cells for transplantation. Finally, there is considerable research interest in the potential of extending transplant effects with stem cells and gene therapies that over-express or upregulate dopamine, dopamine decarboxylase, trophic factors, and other molecules that enhance survival of dopaminergic nerve cells.

REFERENCES

1. Olanow CW, Koller WC. An algorithm (decision tree) for the management of Parkinson's disease. Neurology 1998;50(3 Suppl 3):S1-57.
2. Fahn S. Adverse effects of levodopa. In: Olanow CW, Lieberman AN, eds. The Scientific Basis for the Treatment of Parkinson's Disease. UK, Lancs: Arthenon Publishing Group, 1992: p. 89-112.
3. Olanow CW, Kordower JH, Freeman TB. Fetal nigral transplantation as a therapy for Parkinson's disease. Trends Neurosci 1996;19:102-109.
4. Goetz CG, Olanow CW, Koller WC, et al. Multicenter study of autologous adrenal medullary transplantation to the corpus striatum in patients with advanced Parkinson's disease. N Engl J Med 1989;320:337-341.
5. Olanow CW, Koller W, Goetz, et al. Autologous transplantation of adrenal medulla in Parkinson's disease: 18-month results. Arch Neurol 1990;47:1286-1289.
6. Itakura T, Kamei I, Nakai K, et al. Autotransplantation of the superior cervical ganglion into the brain. A possible therapy for Parkinson's disease. J Neurosurg 1988;68:955-959.
7. Itakura T, Uematsu Y, Nakao N, et al. Transplantation of autologous sympathetic ganglion into the brain with Parkinson's disease. Long-term follow-up of 35 cases. Sterotactic Funct Neurosurg 1997;69:112-115.
8. Wenning GK, Odin P, Morrish P, et al. Short- and long-term survival and function of unilateral intrastriatal dopaminergic grafts in Parkinson's disease. Ann Neurol 1997;42:95-107.
9. Lindvall O, Sawle G, Widner H, et al. Evidence for long-term survival and function of dopaminergic grafts in progressive Parkinson's disease. Ann Neurol 1994;35:172-180.
10. Remy P, Samson Y, Hantrave P, et al. Clinical correlates of [18F]fluorodopa uptake in five grafted parkinonian patients. Ann Neurol 1995;38:580-588.
11. Freeman TB, Olanow CW, Hauser RA, et al. Bilateral fetal nigral transplantation into the postcommissural putamen in Parkinson's disease. Ann Neurol 1995;38(3):379-88.
12. Kordower JH, Freeman TB, Snow BJ, et al. Neuropathological evidence of graft survival and striatal reinnervation after the transplantation of fetal mesencephalic tissue in a patient with Parkinson's disease. N Engl J Med 1995;332:1118-1124.
13. Kordower JH, Rosenstein JM, Collier TJ, et al. Functional fetal nigral grafts in a patient with Parkinson's disease; chemoanatomic, quantitative, ultrastructural, and metabolic studies. J Comp Neurol 1996;370:203-230.
14. Freeman TB, Vawter DE, Leaverton PE, et al. Use of placebo surgery in controlled trials of a cellular-based therapy for Parkinson's disease. N Engl J Med 1999;341:988-992.
15. Spencer DD, Robbins RJ, Naftolin F, et al. Unilateral transplantation of human fetal mesencephalic tissue into the caudate nucleus of patients with Parkinson's disease. N Engl J Med 1992;327(22):1541-1548.
16. Redmond DE Jr., Leranth C, Spencer DD, et al. Fetal neural graft survival. Lancet 1990;336:820-822.
17. Kopyov OV, Jacques DS, Lieberman A, Duma CM, Rogers RL. Outcome following intrastriatal fetal mesencephalic grafts for Parkinson's patients is directly related to the volume of grafted tissue. Exp Neurol 1997;146:536-545.
18. Freed CR, Greene PE, Breeze RE, Tsai WY, et al. Transplantation of embryonic dopamine neurons are severe Parkinson's disease. N Engl J Med 2001;344:710-719.
19. Nakamura T, Dhawan V, Chaly T, Kukuda M, et al. Blinded positron emission tomography study of dopamine cell implantation for Parkinson's disease. Ann Neurol 2001;50:181-187.
20. Lindvall O, Rechnerona S, Brundin P, et al. Human fetal dopamine neurons grafted into the striatum in two patients with severe Parkinson's disease. A detailed account of methodology and a 6-month follow-up. Arch Neurol 1989;46:615-631.
21. Hoffer BJ, Leenders KL, Young D et al. Eighteen month course of two patients with grafts of fetal dopamine neurons for Parkinson's disease. Exp Neurol 1992;118:243-252.
22. Lindvall O, Widner H, Rehncrona S, et al. Transplantation of fetal dopamine neurons in Parkinson's disease: one-year clinical and neurophysiological observations in two patients with putaminal implants. Ann Neurol 1992;31:155-165.
23. Lindvall O, Widner H, Rehncrona S, et al. Grafts of fetal dopamine neurons survive and improve motor function in Parkinson's disease. Science1990;247:574-577.
24. Sawle GV, Bloom field PM, Bjorklund A, et al. Transplantation of fetal dopamine neurons in Parkinson's disease: PET [18F]6-L-fluorodopa studies in tow patients with putaminal implants. Ann Neurol 1992;31:166-173.
25. Defer GL, Geny C, Ricolfi F, et al. Long-term outcome of unilaterally transplanted parkinsonian patients. I. Clinical approach. Brain 1996;119:41-50.
26. Peschanski M, Defer G, N'Guven JP, et al. Bilateral motor improvement and alternation of L-dopa effect in two patients with Parkinson's disease following intrastriatal transplantation of foetal ventral mesencephalon. Brain 1994;117:487-499.
27. Hauser RA, Freeman TB, Snow BJ, et al. Long-term evaluation of bilateral fetal nigral transplantation in Parkinson's disease. Arch Neurol 1999;56:179-187.
28. Kordower JH, Freeman TB, Chen EY, et al. Fetal nigral grafts survival and mediate clinical benefit in a patient with Parkinson's disease. Mov Disord 1998;13:383-393.
29. Freed CR, Breeze RE, Rosenberg NL, et al. Tranplantation of human fetal dopamine cells for Parkinson's disease. Results at 1 year. Arch Neurol 1990;47:505-512.
30. Freed CR, Breeze RE, Rosenberg NL, et al. Survival of implanted fetal dopamine cells and neurologic improvement 12 to 46 months after transplantation for Parkinson's disease. N Engl J Med 1992;327(22):1549-1555.
31. Freed CR, Rosenberg NL, Schneck SA, Breeze RE. Improved drug responsiveness following fetal tissue implant for Parkinson's disease. Neurochem Int 1992;20(suppl):321S-327S.
32. Lopez-Lozano JJ, Bravo G, Brera B, et al. Long-term follow-up in 10 Parkinson's disease patients subjected to fetal brain grafting into a cavity in the caudate nucleus: the Clinica Puerta de Hierro experience. CPH Neural Transplantation Group. Transplant Proc 1995;27:1395-1400.
33. Lopez-Lozano JJ, Bravo G, Brera B, et al. Long-term improvement in patients with severe Parkinson's disease after implantation of fetal ventral mesencephalic tissue in a cavity of the caudate nucleus: 5-year follow-up in 10 patients. Clinica Puerta de Hierro Neural transplantation Group. J Neurosurg 1997;86:931-942.
34. Kopyov OV, Jacques D, Lieberman A, Duma CM, Rogers RL. Clinical study of fetal mesencephalic intracerebral transplants for the treatment of Parkinson's disease. Cell Transplant 1996;5:327-337.
35. Molina H, Quinones R, Ortega I, et al. Computer assisted CT-guided stereotactic transplantation of foetal ventral mesencephalon to the caudate nucleus and putamen in Parkinson's disease. Acta Neurochir Suppl (Wien) 1993:58;17-19.
36. Sass KJ, Buchanan CP, Westerveld M, et al. General cognitive ability following unilateral and bilateral fetal ventral mesencephalic tissue transplantation for treatment of Parkinson's disease. Arch Neurol 1995;52:680-686.
37. Price LH, Spencer DD, Marek KL et al. Psychiatric status after human fetal mesencephalic tissue transplantation in Parkinson's disease. Biol Psychiatry 1995;38:498-505.
38. Cubo E, Gracies JM, Benabou R, Olanow CW, et al. Early morning off-medication dyskinesias, dystonia and choreic subtypes. Arch Neurol 2001;58:1379-1382.
39. Folkerth RD, Durso R. Survival and proliferation of nonneural tissues, with obstruction of cerebral ventricles, in a parkinsonian patient treated with fetal allogafts. Neurology 1996;46:1219-1225.
40. Kordower JH, Freeman TB, Bakay RA, Goetz CG, Olanow CW. Treatment with fetal allografts. Neurology 1997;48:1737-1738.
41. Schumacher JM, Ellias SA, Palmer EP, et al. Transplantation of embryonic porcine mesencephalic tissue in patients with PD. Neurology 2000;54:1042-1050.
42. Deacon T, Schumacher J, Dinsmore J, et al. Histological evidence of fetal pig neural cell survival after transplantation into a patient with Parkinson's disease. Nat Med 1997;3:350-353.

BIBLIOGRAPHY - EXCLUDED FROM ANALYSIS (REASON FOR EXCLUSION)

Alexander GE, Crutcher MD, DeLong MR. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, 'prefrontal and limbic functions. Prog Brain Res 1990;85:119-146. (Not a clinical trial)

Ansari AA, Mayne A, Freed CR, et al. Lack of detectable systemic humeral/cellular allogeneic response in human and non-human primate recipients of embryonic mesencephalic allografts for the therapy of Parkinson's disease. Transplant Proc 1995;27:1401-1405. (Not a clinical trial)

Backlund EO, Granberg PO, Hamberger B, et al. Transplantation of adrenal medullary tissue to striatum in parkinsonism. First clinical trials. J Neurosurg. 1985;62:169-173. (Adrenal cells)

Bakay RA, Barrow DL, Fiandaca MS, Iuvone PM, Schiff A, Collins DC. Biochemical and behavioral correction of MPTP like-syndrome by fetal cell transplantation. Ann NY Acad Sci 1987;495:623-640. (Not a clinical trial)

Bankiewicz KS, Plunkett RJ, Jacobowitz DM, Kopin IJ, Oldfield EH. Fetal nondopaminergic neural implants in parkinsonian primates. Histochemical and behavioral studies. J Neurosurg 1991;74:97-104. (Not a clinical trial)

Bankiewicz KS, Plunkett RJ, Jacobawitz DM, et al. The effect of fetal mesencephalon implants on primate MPTP-induced parkinsonism. Histochemical and behavioral studies. J Neurosurg 1990;72:231-244. (Not a clinical trial)

Bankiewicz KS, Plunkett RJ, Kopin IJ, et al. Transient behavioral recovery in heiparkinsonisan primates after adrenal medullary autografts. In: Gash DM, Sladek, RJ Jr. eds. Transplantation into the mammalian CNS. Progress in Brain Res 1988;78:543-550. (Not a clinical trial)

Bankiewicz KS, Whitwell HL, Sofroniew MV, et al. Survival of TH-positive cells and graft-induced host dopaminergic sprouting in patients with Parkinson's disease after intrastriatal grafting of fetal ventral mesencephalus. Soc Neurosci Abst 1993;19:864. (Not a clinical trial, abstract).

Björklund A, Stenevi U, Dunnett SB, Iversen SD. Functional reactivation of the deafferented neostriatum by nigral transplants. Nature 1981;289:497-499. (Not a clinical trial)

Björklund A, Stenevi U, Schmidt RH, Dunnett SB, Gage FH.. Intracerebral grafting of neuronal cell suspensions. II Survival and growth of nigral cell suspensions implanted in different brain sites. Acta Physiol Scan Suppl 1983;522:9-18. (Not a clinical trial).

Björklund A, Stenevi U. Reconstruction of the nigrostriatal dopamine pathway by intracerebral nigral transplants. Brain Res 1979;177:555-560. (Not a clinical trial)

Bohn MC, Cupit L, Marciano F, Gash DM. Adrenal medulla grafts enhance recover of striatal dopamine fibers. Science 1987;237:913-916. (Non-human study)

Breeze RE, Wells TH Jr., Freed CR. Implantation of fetal tissue for the management of Parkinson's disease: a technical note. Neurosurgery 1995;36:1044-1048. (Not a clinical study).

Brundin P, Isacson O, Bjorklund A. Monitoring of cell viability in suspensions of embryonic CNS tissue and its use as a criterion for intracerebral graft survival. Brain Res 1985;331:251-259. (Not a clinical trial)

Brundin P, Strecker RE, Widner H, et al. Human fetal dopamine neurons grafted in a rat model of Parkinson's disease: immmunological aspects, spontaneous and drug-induced behavior, and dopamine release. Ex Brain Res 1988;70:192-208. (Not a clinical trial)

Brundin P, Widner H, Nilsson OG, Strecker RE, Bjorklund A. Intracerebral xenografts of dopamine neurons: the role of immunosuppression and the blood-brain-barrier. Exp Brain Res 1989;75:195-207. (Not a clinical trial)

Clarke DJ, Brundin P, Strecker RE, Nilsson OG, Bjorklund A, Lindvall O. Human fetal dopamine neurons grafted in a rat model of Parkinson's disease: ultrastructure evidence for synaptic formation using tyrosine hydroxylase immunocytochemistry. Exp Brain Res 1988;73:115-126. (Not a clinical trial)

Cohen J. New Fight Over Fetal Tissue Grafts. Science 1994;263:600-601. (Not a clinical trial)

Collier TJ, Gallagher MJ, Sladek CD. Cryopreservation and storage of embryonic rat mesencephalic dompaine neurons for one year: comparison to fresh tissue in culture and neural grafts. Brain Res 1993;623:249-256. (Not a clinical trial)

Dunnett SB, Bjorklund A, Stenevi U, Iversen SD. Behavioral recovery following transplantation of substantia nigra in rats subject to 6-OHDA lesions of the nigrostriatal pathway. I. Unilateral lesions. Brain Res 1981;215:147-161. (Not a clinical trial)

Dunnett SB, Hernandez TD, Summerfield A, Jones GH, Arbuthnott G. Graft-derived recovery from 6-OHDA lesions: specificity of ventral mesencephalic graft tissues. Exp Brain Res 1988;71:411-424. (Not a clinical trial).

Dymecki J, Zabek M, Mazurowski, et al. 30-month results of foetal dopamine cell transplantation into the brains of parkinsonian patients. J Neural Trans & Plasticity 1992;3:325-326. (No statistical analysis)

Fahn S. Fetal tissue transplants in Parkinson's disease. N Engl J Med 1992;327:1589-1590. (Editorial).

Fiandaca MS, Kordower JH, Hansen JT, Jiao SS, Gash DM. Adrenal medullary autografts into the basal ganglia of Cebus Monkeys; injury-induced regeneration. Exp Neurol 1988;102:76-91. (Adrenal cells).

Freed CR, Breeze RE Greene PE, et al. Double blind, placebo-controlled human fetal dopamine cell transplants in advanced Parkinson's disease. Soc Neurosci Abst 1999;25:212. (Abstract)

Freed CR, Breeze RE, Rosenberg NL, Schneck SA. Embryonic dopamine cell implants as a treatment for the second phase of Parkinson's disease. In: Narabayashi H, Nagatsu T, Yanagisawa N, Mizuno Y, eds. Advances in Neurology Vol 60. New York, NY: Raven Press 1993:721-728. (Not a clinical study)

Freed CR, Breeze RE, Schnock SA, et al. Human fetal dopamine cells survive and develop processes after implantation into humans with Parkinson's disease. Soc Neurosci Abs 1994;20:9. (Abstract).

Freed WJ, Morihisa JM, Spoor E, et al. Transplanted adrenal chromaffin cells in rat brain reduce lesion-induced rotational behavior. Nature 1981;292:351-352. (Not a clinical trial, adrenal cells)

Freed WJ, Patel-Vaidya U, Geller HM. Properties of PC12 pheochromocytomja cells transplanted to the adult rat brain. Exp Brain Res 1986;63:557-566. (Not a clinical trial)

Freed WJ, Perlow MJ, Karoum F, et al. Restoration of dopaminergic function by grafting of fetal rat substantia nigra to the caudate nucleus: long term behavioral, biochemical, and histological studies. Ann Neurol 1980;8:510-519. (Not a clinical trial)

Freeman TB, Sanberg PR, Nauert GM, et al. The influence of donor age on the survival of solid and suspension intraparenchymal human embryonic nigral grafts. Cell Transplant 1995;4:141-154. (Not a clinical trial)

Freeman TB, Spence MS, Boss BD, et al. Development of dopaminergic neurons in the human substantia nigra. Exp Neurol 1991;113:344-353. (Not a clinical trial)

Freeman TB. From transplants to gene therapy for Parkinson's disease. Exp Neurol 1997;144:47-50. (Review, no original data).

Goetz CG, Stebbins GT, Klawans HL, et al. United Parkinson Foundation Neurotransplantation Registry on adrenal medullary transplants: presurgical, and 1- and 2-year follow-up. Neurology 1991;41(11):1719-1722. (Adrenal cells)

Greene PE, Fahn S, Tsai WY, et al. Severe spontaneous dyskinesias: a disabling complication of embryonic dopaminergic tissue implants in a subset of transplanted patients with advanced Parkinson's disease. Mov Disord 1999;14:904. (Abstract)

Hallett M, Litvan I. Evaluation of surgery for Parkinson's disease: a report of the Therapeutic and Technology Assessment Subcommittee of the American Academy of Neurology. The Task Force on Surgery for Parkinson's Disease. Neurology 1999;53:1910-1921. (Review and critique, no original data).

Hefti F, Hartikka J, Schlumpf M. Implantation of PC12 cells into the corpus striatum of rats with lesions of the dopaminergic nigrostriatal neurons. Brain Res 1985;348:283-288. (Not a clinical trial).

Henderson BT, Clough CG, Hughs RC, Hitchcock ER, Kenny BG. Implantation of human ventral mesencephalon to the right caudate nucleus in advanced Parkinson's disease. Arch Neurol 1991;48:822-827. (No statistical analysis).

Henderson BT, Kenny BG, Hitchcock ER, Hughes RC, Clough CG. A comparative evaluation of clinical rating scales and quantitative measurements in assessment pre and post striatal implantation of human foetal mesencephalon in Parkinson's disease. Acta Neurochir Suppl (Wien) 1991;52:48-50. (No statistical analysis).

Hitchcock E. Current trends in neural transplantation. Neurol Res 1995;17:33-37. (Review, no original data).

Hitchcock ER, Clough CG, Hughes RC, Kenny B. Embryos and Parkinson's disease. Lancet 1988;1(8597):1274. (No statistical analysis).

Hitchcock ER, Kenny BG. Henderson BT, Cough CG, Hughes RC, Detta A. A series of experimental surgery for advanced Parkinson's disease by foetal mesencephalic transplantation. Acta Neurochir Suppl (Wien) 1991;52:54-57. (No statistical analysis).

Iacono RP, Tang ZS, Mazziotta JC, Grafton S, Hoehn M. Bilateral fetal grafts for Parkinson's disease: 22 months' results. Stereotact Funct Neurosurg 1992;58:84-87. (No statistical analysis).

Isaacson O, Pakzaban P, Galpern WR. Transplanting fetal neural xenogeneic cells in Parkinson's and Huntington disease models. In: Freedman TB, Widner H, eds. Cell Tranplantation for Neurological Disorders. New Jersey, Totowa:Humana Press, 1998:189-210. (Not a peer review journal; not a clinical trial)

Kish SJ, Shannak K, Hornykiewicz O. Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. Pathophysiologic and clinical implications. N Engl J Med 1988;318:876-880. (Not a clinical trial)

Kordower JH, Cochran E, Penn RD, Goetz CG. Putative chromaffin cell survival and enhanced host derived TH-fiber innervation following a functional adrenal medulla autograft for Parkinson's disease. Ann Neurol 1991;29:405-412. (Adrenal cells)

Kordower JH, Goetz CG, Freeman TB, Olanow CW. Dopaminergic transplants in patients with Parkinson's disease: neuroanotomical correlates of clinical recovery. Exp Neurol 1997;144:41-46. (Review article)

Kordower JH, Styren S, Clarke M, DeKosky ST, Olanow CW, Freeman TB. Fetal grafting for Parkinson's disease: expression of immune markers in two patients with functional fetal nigral implants. Cell Transplant 1997;6:213-219. (Not a clinical trial)

Kunzle H. Bilateral projections from precentral motor cortex to the putamen and other parts of the basal ganglia. An autoradiographic study in Macaca fascicularis. Brain Res 1975;88:195-209. (Not a clinical trial)

Kunzle H. An autoradiographic analysis of the efferent connections from premotor and adjacent prefrontal regions (areas 6 and 9) in Macac fascicularis. Brain Behav Evol 1978;15:185-234. (Not a clinical trial)

Lang AE, Benabid AL, Koller WC, et al. The core assessment program for intracerebral transplantation. Mov Disord 1995;10:527-528. (Not a clinical trial)

Langston JW, Widner H, Goetz CG, et al. Core assessment program for intracerebral transplantations (CAPIT). Mov Disord 1992;7:2-13. (Not a clinical trial)

Leenders KL, Salmon EP, Tyrrell P, et al. The nigrostriatal dopaminergic system assessed in vivo by positron emission tomography in health volunteers subjects and patients with Parkinson's disease. Arch Neurol 1990;47:1290-1298. (Not a clinical trial)

Levivier M, Dethy S, Rodesch F, et al. Intracerebral transplantation of fetal ventral mesencephalon for patients with advanced Parkinson's disease. Methodology and 6-month to 1-year follow-up in 3 patients. Stereotact Funct Neurosurg 1997;69:99-111. (No statistical analysis)

Lopez-Lozano JJ, Bravo G, Brera B, et al. Can an analogy be drawn between the clinical evolution of Parkinson's disease patient who undergo autoimplantation of adrenal medulla and those of fetal ventral mesencephalon transplant recipients? In: Bjorklund A, Widner H, eds. Transplantation in Movement Disorders. Elsevier Science Publisher, 1993:87-98. (Not a peer review journal).

Madrazo I, Drucker-Colin R, Diaz V, et al. Open microsurgical autograft of adrenal medulla to right caudate nucleus in two patients with intractable Parkinson's disease. N Engl J Med 1987;316:831-834. (Adrenal cells)

Madrazo I, Franco-Bourland R, Ostrosky-Solis F, et al. Fetal homotransplants (ventral mesencephalon and adrenal tissue) to the striatum of parkinsonian subjects. Arch Neurol 1990;47:1281-1285. (No statistics)

Mahalik TJ, Finger TE, Stromberg I, Olson L. Substantia nigra tranplants into denervated striatum of the rat: ultrastructure of graft-host interconnections. J Comp Neurol 1985;240:60-70. (Not a clinical trial)

Markham CM, Rand RW, Jacques DB, Diamond SG, Kopyov OV, Snow B. Transplantation of fetal mesencephalic tissue in Parkinson's disease. Stereotact Funct Neurosurg 1994;62:134-140. (No statistical analysis).

Molina H, Quinones R, Alvarez L, et al. Transplantation of human fetal mesencephalic tissue in caudate nucleus as treatment for Parkinson's disease: the Cuban experience. In: Lindvall O, Bjorklund A, Widner IL, eds. Intracerebral Transplantation in Movement Disorders: Experimental Basis and Clinical Experience. Amsterdam: Elsevier, 1991:99-110. (Not a peer review journal).

Molina H, Quinones-Molina R, Munoz J, et al. Neurotransplantation in Parkinson's disease: from open microsurgery to bilateral stereotactic approach: first clinical trial using microelectrode recording technique. Stereotact Funct Neurosurg 1994;62:204-208. (No statistical analysis).

Nicholas MK, Antel JP, Stefansson K, Amason BGW. Rejection of fetal neocortical neural transplants by H-2 incompatible mice. J Immunol 1987;139:2275-2283. (Not a clinical trial)

Olanow CW, Kordower JH, Freeman TB. Fetal nigral transplanatation as a therapy for Parkinson's disease. Trends Neurosci 1996;19:102-109. (Review article with no new data)

Perlow MJ, Freed WJ, Hoffer BJ, Seiger A, Olson L, Wyatt RJ. Brain grafts reduced motor abnormalities produced by destruction of nigrostriatal dopamine system. Science 1979;204:643-647. (Not a clinical trial)

Redmond DE, Sladek JR Jr., Roth RH, et al. Fetal neuronal grafts in monkeys given methylphenyltetrahydropyridine. Lancet 1986;1(8490):1125-1127. (Not a clinical trial)

Redmond DE, Robbins RJ, Naftolin F, Marek KL. Cellular replacement of dopamine deficit in Parkinson's disease using human fetal mesencephalic tissue. In: Waxman SG, ed. Molecular and Cellular Approaches to the Treatment of Neurological Disease. New York: Raven Press, 1993:325-359. (Not a peer-review journal).

Schmidt RH, Ingvar M, Lindvall O, Stenevi U, Bjorklund A. Functional activity of substantia nigra grafts reinnervating the striatum: neurotransmitter metabolism and [14C]2-deoxy-D-glucos autoradiography. J Neurochem 1982;38:737-748. (Not a clinical trial)

Sladek Jr JR, Collier TC, Haber SN, et al. Survival and growth of fetal catecholamine neurons transplanted into the primate brain. Brain Res Bull 1986;17:809-818. (Not a clinical trial)

Sladek JR Jr, Redmond DE Jr, Collier TJ, et al. Fetal dopamine neural grafts: extended reversal of methylphenyltetrahydropyridine-induced parkinsonism in monkeys. In: Gash DM, Sladek JR Jr, eds. Transplantation into the Mammalian CNS. Prog Brain Res 1988;78:497-506. (Not a clinical trial)

Stromberg I, Almqvist P, Bygdeman M, et al. Human fetal mesencephalic tissue grafted to dopamine-denervated striatum of athymic rats: light- and electron-microscopical histochemistry and in vivo chronoamperometric studies. J Neurosci 1989;9:614-624. (Not a clinical trial)

Stromberg I, Herrera-Marschitz M, Ungerstedt U, Ebendal T, Olson L. Chronic implants of chromaffin tissue into the dopamine-denervated striatum. Effects of NGF on graft survival, fiber growth and rotational behavior. Exp Brain Res 1985;60:335-349. (Not a clinical trial)

Subrt O, Tichy M, Vladyka V, Hurt K. Grafting of fetal dopamine neurons in Parkinson's disease. The Czech experience with severe akinetic patients. Acta Neurochir Suppl (Wien) 1991;52:51-53. (No statistical analysis)

Szabo J. Organization of the ascending striatal afferents in monkeys. J Comp Neurol 1980;189:307-321. (Not a clinical trial)

van Horne CG, Mahalik T, Hoffer B, et al. Behavioral and electrophysiological correlates of human mesencephalic dopamine xenograft function in the rat striatum. Brain Res Bull 1990;25:325-334. (Not a clinical trial)

Watts RL, Subramanian T, Freeman A, et al. Effect of sterotaxic intrastriatal cografts of autologous adrenal medulla and peripheral nerve in Parkinson's disease, two year follow-up study. Exp Neurol 1997;147:510-517. (Adrenal cells)

Widner H, Tetrud JW, Rehncrona S, et al. Bilateral fetal mesencephalic grafting in two patients with MPTP-induced parkinsonism. N Engl J Med 1992;327:1556-1563. (Not Parkinson's disease).

Wu CY, Zhou MD, Bao XF, et al. The combined method of transplantation of foetal substantia nigra and stereotactic thalamotomy for Parkinson's disease. Br J Neurosurg 1994;8:709-716. (No statistical analysis).

Wuerthele SM, Freed WJ, Olson L, et al. Effect of dopamine agonists and antagonists on the electrical activity of substantia nigra neurons transplanted into the lateral ventricle of the rat. Exp Brain Res 1981;44:1-10. (Not a clinical trial)

Movement Disorders
Vol. 17, Suppl. 4, 2002, p. S156-S159

Published by Wiley-Liss, Inc.
DOI 10.1002/mds.5576

Physical and Occupational Therapy in Parkinson's Disease

INTRODUCTION

BACKGROUND

The pronounced motor deficits associated with Parkinson's disease has led to the long-standing empiric emphasis dating from the nineteenth century, which includes gait and fine motor therapy in various forms.[1] The early appreciation of weakness from disuse of muscles and arthropathies associated with Parkinson's disease led physicians to advocate rehabilitation efforts focused on large and small muscle groups.[2]

RATIONALE

Interventions that emphasize enhanced muscle strength and coordination may seem rational, emotionally positive, and proactive, but few controlled clinical trials studies have actually tested the impact of physical or occupational therapies for treatment in Parkinson's disease. The cost of such therapy is substantial, and medical insurance does not necessarily cover all expenses, especially if the therapy is frequent (more than once weekly) and prolonged (more than six weeks).[3] For these reasons, solid information on the short-term and long-term benefits of physical rehabilitation are necessary. In this report, physical therapy (which concentrates primarily on large muscle groups and gait training) and occupational therapy (which focuses on fine motor skills) are considered together.

A critique of these therapies is limited by the multiplicity of different exercise programs all considered under the rubric "physical or occupational therapy". Exercise programs may emphasize spinal flexibility, enhanced strength, motor coordination and timing, or balance. No two studies cited have tested the exact same therapy program. The factor that links them, however, is a programmatic effort to involve Parkinson's disease subjects in some form of regular exercise, for a prescribed period of time. Consequently, motor function should be tested immediately and, in some cases, several weeks or months thereafter.

METHODS

KEY SEARCH TERM

Parkinson's disease, physical therapy, and occupational therapy.

SPECIAL EXCEPTION TO INCLUSIONS AND EXCLUSION CRITERIA

Most studies reviewed in this *Movement* Disorder Society effort require 20 subjects for inclusion, but there are very few studies of this size in the physical/occupational therapy arena. Because the methodology of smaller studies includes both randomization and control groups, these studies provide a basis for review in Parkinson's disease therapy, and therefore, this critique includes studies with a minimum of ten enrolled subjects.

MECHANISM OF ACTION

Physical and occupational therapies aim to strengthen muscles involved with axial and appendicular motor function in both volitional activities as well as more automatic movements like walking. Conscious retraining for techniques of standing, sitting, and turning are included, as well as the proper usage of apparatus-like canes, walkers, and specialized utensils such as writing and eating implements. There are no large studies that examine issues of central neurotransmitter changes or anatomical-functional correlates of improved motor function after these interventions in Parkinson's disease.

REVIEW OF CLINICAL STUDIES

The design of physical and occupational therapies is on empiric observations of the motoric deficits of Parkinson's disease subjects rather than on specific physiological hypotheses. No studies have examined the anatomical or central physiological changes that may occur after such rehabilitation interventions. Allied to physical therapy protocols, but not reviewed in this report, are several studies documenting the utility of various cuing devices, such as walking canes, metronomes or other auditory stimuli, and visual lines to enhance stride length and pace walking rhythm. These fall outside physical or occupational therapies and are often considered as behavior modification therapies. Furthermore, none of these modalities has been tested in large, randomized (and blinded), controlled clinical trials.

Eight studies are included in this critique, dating from 1981 to 1998, five were considered as Level-I evidence and three were Level-II evidence. All were designed as interventions to treat symptomatic control of parkinsonism.

PREVENTION OF DISEASE PROGRESSION

No qualified studies were identified.

SYMPTOMATIC CONTROL OF PARKINSONISM

Level-I Studies

Palmer et al. (1986)[4]: Palmer and colleagues compared two types of physical therapy, either stretching exercises as described in the published United Parkinson Foundation exercise brochure or active upper body karate training; each type of therapy was given for 12 weeks. The two groups, composed of patients being treated with antiparkinsonian medications, were matched for age, Hoehn and Yahr (HY) stage, and gender. There was significant improvement in tremor, pronator/supinator speed, and grip strength with both forms of therapy. Timed walking speed also improved in both groups, although the improvement was statistically significant only with karate therapy. Rigidity did not change with either form of therapy. Assessments ended at the completion of therapy and no

long-term follow-up evaluations occurred. The comparable findings in both therapies suggest that activity per se may be more important to clinical improvement than any one set of muscle toning or muscle development exercises. This study had an overall quality rating score of 40%.

Gauthier et al. (1987)[5]: These authors designed a study to examine patients during a five-week session of occupational therapy given twice weekly with follow-up assessment at six months and one year thereafter. The study enrolled 59 subjects: 30 received therapy and 29 received no physical therapy. The outcome measures were the Barthel Index of Activities of Daily Living, the Purdue pegboard test for dexterity, and items from the Extrapyramidal Symptom Rating Scale for the evaluation of motor signs. Evaluators were blinded to treatment group. At the end of the therapy period, the active therapy group showed significant improvement in bradykinesia, tremor, gait and posture ratings. Over the subsequent six months after therapy ended, the control group deteriorated, but the therapy group maintained the improved function over baseline. By the one-year follow-up period, the only significant item that remained improved over baseline function was bradykinesia. This unique study with long-term follow-up showed that objective motor gains from therapy could be maintained for six months as compared to the level of deterioration seen in the control group that received no therapy. It was not specifically stated in the report whether the patients continued to follow the exercises during the one year after the formal therapy course. This study had an overall quality rating score of 46%.

Comella et al. (1994)[6]: Comella and coworkers conducted a randomized, single-blind, crossover study of four weeks of outpatient physical therapy aimed at enhancing balance and flexibility in large muscle groups compared to no specific therapy. The physical therapy program was designed to be comparable to regularly prescribed treatment programs in the community and involved one-hour sessions given three times weekly. Sixteen patients received both phases in randomized order, and then were all re-evaluated six months later. The primary outcome measure was the total Unified Parkinson Disease Rating Scale (UPDRS). At the end of four weeks, the therapy group showed significant improvement in the UPDRS, with improvement occurring in both the Motor section and the Activities of Daily Living section. Within the motor scale, bradykinesia and rigidity specifically improved. There were no improvements during the control phase. Like the Gautier study, improvements were demonstrated after the active therapy, but unlike the first study, Comella found that improvements did not persist. Six months after the study program finished, during which time no specific therapy had been continued, all gains were lost. In combination, the data from these two studies argue strongly for short-term gains from physical therapy. They do not precisely clarify the expected duration of benefit of these types of physical therapy. This study had an overall quality rating score of 57%.

Katsikitis and Pilowsky (1996)[7]: An unusual form of therapy involved a study that focused on exercises of facial muscles. In this randomized evaluation of 16 patients, one half received four weeks of one-hour sessions of orofacial physiotherapy given twice weekly, and one half received no treatment. Isolated indices of increased facial mobility improved in the treatment group, but there were many measures and the investigators did not statistically correct for multiple comparisons. Nonetheless, the improvements persisted four weeks after the therapy stopped. This study had an overall quality rating score of 43%.

Schenkman et al. (1998)[8]: Schenkman performed a randomized, controlled evaluation of physical therapy with attempted blinded evaluations, although some patients revealed their therapies accidentally. Forty-six patients with Parkinson's disease were randomly assigned to active physical therapy or no therapy for 10 weeks. The exercises specifically focused on spinal flexibility and improved physical performance as measured by a functional reaching task and a timed supine-to-standing test. The group was mixed in terms of their medication requirements (14 on no medications, 32 on levodopa), and ranged from HY stage 2 to 3. Significant improvement occurred in functional axial rotation and function reaching. Because no long-term follow-up evaluations were performed, the duration of these benefits was not determined. This study had an overall quality rating score of 45%.

Level-II Studies

Gibberd et al. (1981)[9]: Gibberd and colleagues performed a crossover study to compare four weeks of active physical therapy with the same period of normal activity without therapy. Although no single primary outcome measure was described, they rated speech, gait, balance, tremor, rigidity and timed motor tasks and found no improvement with physical therapy. The report was sketchy in terms of descriptions of the therapy sessions and the statistical methods used for analysis. Evaluations were made immediately after therapy was completed, and there were no follow-up evaluations. Medications were not specified in this study, but the authors indicated that the medications were not changed during the trial.

Formisano et al. (1992)[10]: A second Level-II study[10] examined physical therapy compared to no therapy and focused primarily on subjective assessments using components of the Northwestern University Disability Scale for primary outcomes. Formisano and colleagues (1992)[10] studied two groups of Parkinson's disease patients, balanced for age, disease duration, and disease severity. They compared active/passive physical therapy given as an outpatient program over four months versus no specific therapy but equal staff attention time and encouragement. Whereas most measures did not improve, walking speed was significantly better in the therapy group. Because most therapy programs in the community do not last for four months, the data from this study are not easily extrapolated to usual medical practice in Parkinson's disease management.

Dam et al. (1996)[11]: This study gathered two groups of Parkinson's disease subjects balanced for HY stage, gender, disease duration, and current age, and compared two types of physical therapy interventions: conventional exercises versus the same exercises with additional sensory enhancement. This enhancement included performing physical therapy in front of a mirror, using special colored blocks and other visual cues during the exercises and listening to audio-cued tapes. The advantage of this study is that it was long-term and involved patients receiving therapy for one month, then a rest period for 3 months, then a repeat of the therapy with rest, and a third one-month treatment followed by rest for three months. This design closely mimics outpatient treatment available for many patients with Parkinson's disease, whose insurance does not permit continual therapy, but does permit treatment for short periods after a hiatus of interruption. Raters, blinded to treatment assignment, evaluated subjects. After one month of therapy, both groups improved, and there was no significant benefit of the specially cued therapy program. One month after the

second and third therapy sessions, the conventional therapy groups were no better than baseline. The sensory-enhanced group continued to function with subjectively derived gait and motor scores from the Northwestern University Disability Scale at a higher level than baseline. Because this form of physical therapy is unusual and not readily available, it is difficult to extrapolate these findings to an average clinical setting.

PREVENTION OF MOTOR COMPLICATIONS

No qualified studies were identified.

CONTROL OF MOTOR COMPLICATIONS AND NON-MOTOR COMPLICATIONS

No qualified studies were identified.

REVIEW OF SAFETY

The interventions discussed are exercises that were conducted under supervision. Conceivably, during the therapy, patients could have fallen and injured themselves or sprained muscles that were not actively used prior to the intervention. In all the studies cited, no morbidity was reported, but the absence of morbidity was not specifically documented.

CONCLUSIONS

EFFICACY

PREVENTION OF DISEASE PROGRESSION

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of physical or occupational therapy in the prevention of disease progression in patients with PD.

SYMPTOMATIC CONTROL OF PARKINSON'S DISEASE

Monotherapy

There is no single study assessing physiotherapy as monotherapy - thus there is INSUFFICIENT EVIDENCE to conclude on its potential efficacy as sole treatment in any indication in Parkinson's disease.

Adjunct therapy

Low quality Level-I and Level-II data suggest a positive effect of physical/occupational therapy, as a class of treatment for improving motor impairments in Parkinson's disease when administered as adjunct to pharmacotherapy. It is not established if there is any long-term benefit after physical/occupational therapy concludes.

The number of studies on any single intervention is limited, and the studies do not include all groups of Parkinson's disease patients examined (e.g., medication-free versus on medication, young versus elderly, severely affected versus mildly affected), and only one study used the "gold standard" of the UPDRS. Furthermore, the interventions are varied as to specific exercises and muscle therapies. Therefore, conclusions regarding any single intervention therapy are not possible at this time. There is INSUFFICIENT EVIDENCE to conclude on the efficacy of physical/occupation therapy as adjunct treatment.

PREVENTION OF MOTOR COMPLICATIONS

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of physical/occupation therapy regarding prevention of motor complications in patients with PD.

CONTROL OF MOTOR COMPLICATIONS OR OTHER COMPLICATIONS

There is INSUFFICIENT EVIDENCE to conclude on the efficacy physical/occupation therapy on motor and non-motor complications of PD.

SAFETY

Although none of the reports focused on safety, the consistent absence of any mention of problems related to the interventions suggests that physical and occupational therapy has an ACCEPTABLE RISK, WITHOUT SPECIALIZED MONITORING.

IMPLICATIONS FOR CLINICAL PRACTICE

In the practical therapeutic setting, physical/occupational therapy is POSSIBLY USEFUL. To date, it has been primarily studied in patients with mild-to-moderate severity of disability (HY stages 2 and 3) that are already on antiparkinsonian medications. Most treatments are approximately one to three months and involve combined active and passive exercises. No single type of physical/occupational therapy program has been shown to be superior to another. Motor gains can be expected in patients at the end of the therapy session, but patients and physicians should not assume that gains will be maintained after the therapy sessions end.

IMPLICATIONS FOR CLINICAL RESEARCH

Because physical/occupational therapy studies have been positive but have been relatively few and without large numbers of patients, larger, randomized, prospective controlled trials with longer follow-up are needed. Further, because the reports published to date sometimes involved therapy that extends beyond the typical treatments that patients receive in the community, trials of physical/occupational therapy protocols that are closer to typically available therapy would define the overall clinical usefulness of physical therapy to patients with Parkinson's disease.

There are different forms of occupational/physical therapy and several have been reported to be beneficial to Parkinson's disease patients, therefore, comparative trials must be conducted to establish if one can be recommended over another. Additional areas of research include development of validated research tools, and overcoming the difficulties of adequate blinding, and placebo effects. Neuroimaging studies examining patients before and after physical/occupational therapy will help define the anatomical basis of physical impairments in Parkinson's disease that respond to physical/occupational therapy.

REFERENCES

1. Weiner WJ, Singer C. Parkinson's disease and non-pharmacologic treatment programs J Am Geriatr Soc 1989;37:359-363.
2. Charcot JM. De la paralysie agitante. Oeuvres complètes, Vol. 1 (Leçon 5). Paris: Bureaux du Progrès Mèdical, 1892. In English: Charcot JM. On Parkinson's disease. The diseases of the nervous system delivered at the Salpêtrière. (Translator, G. Sigerson.) London: New Sydenham Society, 1877.
3. Dodel RC Eggert KM, Singer MS, Eichhorn TE, Pogarell O, Oertel WH. Cost of drug treatment in Parkinson's disease. Mov Disord 1998;13:249-254.
4. Palmer SS, Mortimer JA, Webster DD, Bistevins R, Dickinson GL. Exercise therapy for Parkinson's disease. Arch Phys Med Rehabil 1986;67:741-745.
5. Gautier L, Dalziel S, Gautier S. The benefits of group occupational therapy for patients with Parkinson's disease. Am J Occup Ther 1987;41:360-365.
6. Comella CL, Stebbins GT, Brown-Toms N, Goetz CG. Physical therapy and Parkinson's disease: a controlled clinical trial. Neurology 1994;44:376-378.
7. Katsikitis M, Pilowsky I. A controlled study of facial mobility treatment in Parkinson's disease. J Psychosom Res 1996;40:387-396.

8. Schenkman M, Cutson TM, Kuchibhatla M, et al. Exercise to improve spinal flexibility and function for people with Parkinson's disease: a randomized, controlled study. J Am Geriatr Soc 1998;46:1207-1216.
9. Gibberd FB, Page NG, Spencer KM, Kinnear E, Hawksworth JB. Controlled trial of physiotherapy and occupational therapy for Parkinson's disease. Br Med J 1981;282:1196.
10. Formisano R, Pratesi L, Modarelli FT, Bonifati V, Meco G. Rehabilitation and Parkinson's disease. Scand J Rehabil Med 1992;24:157-160.
11. Dam M, Tonin P, Casson S, et al. Effects of conventional and sensory-enhanced physiotherapy on disability of Parkinson's disease patients. Adv Neurol 1996;69:551-555.

BIBLIOGRAPHY - EXCLUDED FROM ANALYSIS (REASON FOR EXCLUSION)

Andrews K. Rehabilitation of conditions associated with old age. Int Rehabil Med 1985;7:125-129. (No specific data given)

Blonsky ER, Minnigh EC. The modifying influence of L-dopa on the physical therapy program in Parkinson's disease. Prog Phys Ther 1970;1:55-74. (Examines the effect of levodopa on physical therapy in general)

Bohannon RW. Physical rehabilitation in neurologic diseases. Curr Opin Neurol 1993;6:765-772. (General review, but no new data given in this report)

Burford K. The physiotherapists role in Parkinson's disease. Geriatr Nurs and Home Care 1988;8:14-16. (Commentary without data)

Davis JC. Team management of Parkinson's disease. Am J Occup Therapy 1997;31(5):300-308. (Several recommendations given, but no data on physical therapy)

Dietz MA, Goetz CG, Stebbins GT. Evaluation of a modified inverted walking stick as a treatment for parkinsonian freezing episodes. Mov Disord 1990;5(3):243-247. (No physical/occupational therapy. Examines effect of a walking stick, used as a visual cue on freezing)

Ebeling P. The medical management of Parkinson's disease before the introduction of L-dopa. Aust N Z J Med 1971 1(1):35-38. (Refers to physical therapy, but no data given)

Feldman MC, DiScipio WJ. Integrating physical therapy with behavior therapy. A case study. Phys Ther 1972; 52(12):1283-1285. (Case report)

Franklyn S, Stern GM. Controlled trial of physiotherapy and occupational therapy for Parkinson's disease [Letter]. Br Med J 1981;282:1969-1970. (Letter, anectodal reporting)

Gibberd FB. The management of Parkinson's disease. Practitioner 1986;230:139-146. (General discussion, but no specific data on physical therapy)

Hammond JL, Henriksen JD. Use of track table for upper extremity exercises. Arch Phys Med Rehabil 1970;51:242-244. (No specific data-suggestion for a new apparatus)

Handford F. Towards a rational basis for physiotherapy in Parkinson's disease. Baillière's Clin Neurol 1993;2(1):141-158. (Justifies use of physical therapy, no data given on intervention results)

Henneberg A. Additional therapies in Parkinson's disease patients: useful tools for the improvement of the quality of life or senseless loss of resources? J Neurol 1998;245(suppl 1):S23-S27. (Discussion of scales used to assess motor disability-no interventions)

Hömberg V. Motor training in the therapy of Parkinson's disease. Neurology 1993;43(suppl 6):S45-S46. (General discussion, but no data given)

Jones DL, Phillips JG, Bradshaw JL, Iansek R, Bradshaw JA. Impairment in bilateral alternating movements in Parkinson's disease. J Neurol Neurosurg Psychiatry 1992;55:503-506. (Motor control study, but no physical therapy intervention)
Kokko S-M, Paltamaa J, Ahola E, Mälkiä E. The assessment of functional ability in patients with Parkinson's disease: the PLM-test and three clinical tests. Physiother Res Int 1997;2(2):29-45. (Discussion of new tests for motor function, but no physical therapy intervention)

Koller WC, Glatt S, Vetere-Overfield B, Hassanein R. Falls and Parkinson's disease. Clin Neuropharmacol 1989;12(2):98-105. (Overview of falls and Parkinson disease, but not specifically about physical therapy)

MacKay-Lyons M, Turnbull G. Physical therapy in Parkinson's disease [Letter]. Neurology 1995;45:205. (Letter with commentary, but no data)

Minnigh EC. The changing picture of parkinsonism. II. The Northwestern University concept of rehabilitation through group physical therapy. Rehabil Lit 1971;32(2):38-39. (Recommendations but not study)

Mohr B, Pulvermuller F, Mittelstadt K, Rayman J. Multiple simultaneous stimulus presentation facilitates lexical processing. Neuropsychologia 1996;34(10):1003-1013. (No physical/occupational therapy. Behavioral modification)

Montgomery EB, Lieberman A, Singh G, Fries JF.Patient education and health promotion can be effective in Parkinson's disease: a randomized controlled trial. PROPATH Advisory Board. Am J Med 1994;97(5):429-435. (Patient education is tested, not specific physical/occupational therapy)

Morris ME, Matyas TA, Iansek R, Summers JJ. Temporal stability of gait in Parkinson's disease. Phys Ther 1996;76(7):763-780. (Study of gait function, no therapy interventions)

Muller V, Mohr B, Rosin R, Pulvermuller F, Muller F, Birbaumer N. Short-term effects of behavioral treatment on movement initiation and postural control in Parkinson'' disease: a controlled clinical study. Mov Disord 1997;12(3):306-314. (Behavioral modification: structured learning, relaxation, social skill training)

Mutch QJ, Strudwick A, Roy SK, Downie AW. Parkinson's disease: Disability, review, and management. Br Med J 1986; 293:675-677. (Review of motoric disability in Parkinson's disease, but no physical therapy intervention)

Pascual-Leone A, Valls-Solé J, Brasil-Neto JP, Cohen LG, Hallett M. Akinesia in Parkinson's disease. I. Shortening of simple reaction time with focal, single-pulse transcranial magnetic stimulation. Neurology 1994; 44:884-891. (Transcranial magnetic stimulation - not physical/occupational therapy)

Pearce V, Jones R. Total care in Parkinson's disease. The Practitioner 1994; 238:142-145. (General review of therapies, no specific data)

Pedersen SW, Oberg B, Insulander A. Group training in parkinsonism: quantitative measurements of treatment. Scand J Rehab Med 1990;22:207-211. (Level III study)

Platz T, Brown RG, Marsden CD. Training improves the speed of aimed movements in Parkinson's disease. Brain 1998;121:505-514. (One-hour training of motor tasks to test effect of learning. This one-hour testing is not specifically physical/occupational therapy)

Schenkman M, Laub KC, Kuchibhatla M, Ray L, Shinberg M. Measures of shoulder protraction and thoracolumbar rotation. J Orthop Sports Phys Ther 1997;25(5):329-335. (No specific study, case histories and empiric recommendations)

Schenkman M, Donovan J, Tsubota J, Kluss M, Stebbins P, Butler RB. Management of individuals with Parkinson's disease: rationale and case studies. Phys Ther 1989;69(11):944-955. (Not a therapy intervention study. Description of new methods of measurement)

Smithson F, Morris ME, Iansek R. Performance on clinical tests of balance in Parkinson's Disease. Phys Ther 1998;78(6):577-592. (Study focused on best tests to assess balance, no therapy intervention)

Soliveri P, Brown RG, Jahanshahi M, Marsden CD. Effect of practice on performance of a skilled motor task in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 1992;55:454-460. (Effects on repetitive practice of a motor task tested immediately thereafter; not specifically physical/occupational therapy.)

Steiner T, Flewitt B. Controlled trial of physiotherapy and occupational therapy for Parkinson's disease [Letter]. Br Med J 1981;282:1969-1970. (Letter, anectodal reporting)

Stern PH, McDowell F, Miller JM, Robinson M. Levodopa and physical therapy in treatment of patients with Parkinson's disease. Arch Phys Med Rehabil 1970;51:273-277. (No specific data)

Szekely BC, Kosanovich NN, Sheppard W. Adjunctive treatment in Parkinson's disease: physical therapy and comprehensive group therapy. Rehabil Lit 1982;43(3-4):72-76. (Clinical observations on 7 Parkinson's disease patients undergoing physical therapy - no controls)

Thaut MH, McIntosh GC, Rice RR, Miller RA, Rathbun J, Brault JM. Rhythmic auditory stimulation in gait training for Parkinson's disease patients. Mov Disord 1996;11(2):193-200. Testing external auditory cues, not physical/occupational therapy)

Ulm G. The current significance of physiotherapeutic measures in the treatment of Parkinson's disease. J Neural Transm Suppl 1995;46:455-460. (No new data in this report)

Weiner WJ, Singer C. Parkinson's disease and nonpharmacologic treatment programs. J Am Geriatr Soc 1989;37:359-363. (No specific data)

Wroe M, Greer M. Parkinson's disease and physical therapy management. Phys Ther 1973;53(8):849-855. (General recommendations without specific data)

Movement Disorders
Vol. 17, Suppl. 4, 2002, p. S160-S162

Published by Wiley-Liss, Inc.
DOI 10.1002/mds.5577

Psychosocial Counseling in Parkinson's Disease

INTRODUCTION

BACKGROUND

Parkinson's disease (PD) is a neurodegenerative disorder that poses a burden to the patient, family, and society.[1,2] James Parkinson described patients as "unhappy", "dejected", and "melancholic".[3]

Once diagnosed with PD, the affected individuals and family are confronted with numerous psychosocial issues that may benefit from intervention. PD is an evolving disease, and the relevant psychosocial issues change in content and often intensity over time, requiring numerous readjustments in coping skills for patient, spouse, family and caregivers.

RATIONALE

Medical and surgical therapies have a clear and visible effect on the motor signs of disease. However, psychosocial functioning also may have an impact on the physical functioning of patients with neurodegenerative disorders. This critique will review the reports in which psychosocial intervention is used as a therapeutic treatment in the management of the PD patient.

METHODS

KEY SEARCH TERMS

Parkinson or Parkinson's disease and: coping or psychosocial or psychosocial support or behavior therapy or support group. All citations with a title suggesting information on the psychosocial status of PD patients, either with or without an abstract, were reviewed. Studies of depression in PD were specifically excluded from this review and are detailed in the chapter on Depression.

REVIEW OF CLINICAL STUDIES

The results from the literature search identified 279 reports; of these, 44 were related to the psychosocial aspects of PD. Forty-two involved description of psychosocial problems, the development of rating scales to measure such problems, or empiric suggestions on coping strategies. Only two reports specifically addressed psychosocial techniques as a therapeutic intervention in PD, and these two studies are the focus of this critique.

PREVENTION OF DISEASE PROGRESSION

No qualified studies were identified.

SYMPTOMATIC CONTROL OF PARKINSONISM

MONOTHERAPY AND ADJUNCT THERAPY (COMBINED)

Level-I Studies

Montgomery et al. (1994)[4]: This study reported the results from a randomized, controlled trial that evaluated the effectiveness of patient education as a part of the PROPATH health promotion program (N=298). This educational program, which was targeted to patients taking bromocriptine, was delivered by mail and focused on disease-specific questions completed by the patient or caregiver at 0, 2, 4, and 6 months. The questions gathered information derived primarily from the ADL section (Part II) of the UPDRS as well as patient estimates of amount of time off and medication doses. One group of patients received the questionnaires followed by computer-generated reports and personalized letters sent to the patients and their physicians after each assessment (intervention group), and the control group received only the questionnaires. At 6 months, both groups received the original questionnaire. The intervention group remained stable in ADL function whereas the control group had progression of impairment. The mean "on" ADL score in the intervention group changed from 21.7 to 22.1 whereas the control group significantly declined from a mean score of 21.6 to 24.6. Likewise, the mean "off" ADL score in the intervention group changed from 31.1 to 30.6, whereas the control group significantly declined from a mean score of 32.0 to 35.2 (misprinted as 64.0 in Table 2) Additionally, the mean required levodopa significantly increased by 66.1 mg/day in the control group over the six-month study whereas the interventional group mean dose decreased by a mean 1 mg/day. A total "Self Efficacy" assessment that combined impressions of symptoms, motor fluctuations and management at the six-month evaluation favored the intervention group with statistically significant differences in the scores (mean 904 vs 795). These data suggest that an intervention program, administered by mail to patients and their physicians may be an effective stabilizing intervention in PD. Although it is included here as a psychosocial study, in fact, the program provided general medical information on disease management to patients and physicians, and therefore, the observed changes cannot be solely ascribed to the psychosocial benefits of interactive communication. This study had an overall quality rating score of 38%.

Muller et al. (1997)[5]: This study examined the impact of specific behavioral therapy on movement initiation and postural control in PD subjects. Their randomized controlled-study examined 29 PD subjects, 15 patients assigned to behavioral interventions posited to improve gait and 14 subjects receiving non-specific psychological and physical treatment as a control group. Neither patient nor evaluating raters were aware of the group assignment. Treatments lasted ten weeks with two 90-minute sessions each week. Subjects were tested with clinical rating scales and an electronic movement analysis system before and after the treatments. The specific psychosocial behavioral intervention tested was a behavioral modification technique with muscle relaxation exercises, "chaining" or sequential breakdown of complex movements into simple movements with positive reinforcement, and encouragement to use such skills in social situations outside the specific training sessions. After treatment, the group with behavioral intervention significantly improved in Hoehn and Yahr stage, improv-

ing from mean 2.13 at baseline to 1.93 at follow-up. The UPDRS motor and ADL scores improved significantly as well, although the numbers printed in the text may not be correct (mean UPDRS motor 1.37 at baseline vs 1.18, and mean UPDRS ADL 1.06 at baseline vs 0.89). No motor elements of the UPDRS changed in the control group. For the movement analysis data, no significant improvements occurred with the behavioral intervention, although there were trends towards improved gait initiation and movement coordination. This study had an overall quality rating score of 54%.

Level-III Studies

Ellgring (1993)[6]: Ellgring conducted a non-randomized cohort study of the impact on overall patient and caregiver function of a series of five two-hour group seminars over a 2 to 3 month interval. There was no control group. These seminars addressed the development of skills for coping in difficult social situations, education about stress and disease, methods for increasing activity, initiative and independence, and ways to change attitudes about the disease. This study included stress management, cognitive restructuring, social skills training, modeling and role-playing, relaxation training, and transfer of contents into daily activity. An independent assessor evaluated the transfer of techniques to everyday life as an index of outcome of therapy one month after the last session. The results from 34 patients who completed five seminars assessment demonstrated effective use of newly learned skills in 74% of patients. The actual measurement scales were not given. The authors also reported on the impact of three sessions of individual psychological counseling on 12 PD patients. Of the specific problems addressed during therapy, 64% improved with therapy, and, even among the problems not specifically addressed during therapy 50% improved. In terms of safety, 23% of the problems being actively addressed during therapy actually worsened with therapy and 23% of problems not being addressed during therapy likewise worsened. This report favors psychological interventions for dealing with numerous issues of stress and social dysfunction in PD, but the paucity of numbers, absence of a control group, and lack of statistical analysis precludes solid conclusions.

PREVENTION OF MOTOR COMPLICATIONS

No qualified studies were identified.

CONTROL OF MOTOR COMPLICATIONS

No qualified studies were identified.

REVIEW OF SAFETY

The studies reviewed did not specifically address safety issues that might be associated with psychosocial intervention.

CONCLUSIONS

EFFICACY

PREVENTION OF DISEASE PROGRESSION

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of psychosocial intervention in the prevention of disease progression in patients with PD.

SYMPTOMATIC CONTROL OF PARKINSON'S DISEASE

Monotherapy

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of psychosocial intervention as sole treatment in any indication in Parkinson's disease.

Adjunct therapy

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of psychosocial intervention as adjunct treatment to medications in the symptomatic control of Parkinson's disease.

PREVENTION OF MOTOR COMPLICATIONS

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of psychosocial intervention regarding prevention of motor complications in patients with PD.

CONTROL OF MOTOR COMPLICATIONS OR OTHER COMPLICATIONS

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of psychosocial intervention on motor and non-motor complications of PD.

SAFETY

Similarly, there is INSUFFICIENT EVIDENCE to conclude on the safety of psychosocial counseling in the treatment of PD.

IMPLICATIONS FOR CLINICAL PRACTICE

In the practical therapeutic setting, psychosocial therapy is INVESTIGATIONAL. A wide variety of patient support groups and special-interest gatherings currently exists locally throughout the world and are especially frequent in the United States. On the one hand, such gatherings may provide patients and families with a ready outlet for the expression of their psychosocial stresses and concerns. On the other hand, such gatherings frequently cluster subjects with very advanced disease and desperate social situations that may frighten or exasperate patients with less disability or shorter disease duration. The clinician is therefore called to understand the psychosocial needs of individual patients and to know the available psychosocial therapeutic options available in the community and medical system before recommending such an intervention. Because psychosocial treatments can be short or long term, a clear definition of the goals of recommended interventions is particularly important to the evaluation of efficacy and safety in a clinical practice setting.

IMPLICATIONS FOR CLINICAL RESEARCH

The impact of psychosocial intervention in either individual or group counseling has not been adequately studied. In particular, there is a lack of clinical trials, and basic methodological aspects have not been defined. Although there are reports of patient perspectives of beneficial effects[7] and recommendations, resources, and guidelines have been empirically provided[3,8-11], new studies are needed that will include the impact of psychosocial intervention on the (a) patient, (b) caregiver, (c) utilization of health care services, and (d) the economic impact on the patient and family. Studies identifying which individuals are most likely to benefit from psychosocial intervention also are needed. It is also important to define which psychosocial interventions will provide the most benefit for patients with PD. These clinical trials will be difficult to conduct because standardized tools to assess outcomes in this area are lacking.

REFERENCES

1. Bunting LK, Fitzsimmons B. Depression in Parkinson's disease. J Neurosci Nurs 1991;23(3):158-164.
2. Fitzsimmons B, Bunting LK. Parkinson's disease. Quality of life issues. Nurs Clin North Am 1993;28(4):807-818.
3. Parkinson J. Essay on the Shaking Palsy. London, Whittingham and Rowland for Sherwood, Neely and Jones, 1817.
4. Montgomery EB Jr, Lieberman A, Sigh G, Fries JF on behalf of the PROPATH Advisory Board. Patient education and health promotion can be effective in Parkinson's disease: a randomized controlled trial. Am J Med 1994;97:429-435.
5. Muller V, Mohr B, Rosin R, Pulvermuller F, Muller F, Birbaumer N. Short-term effects of behavioral treatment on movement initiation and postural control in Parkinson's disease: a controlled clinical study. Mov Disord 1997;12:306-314.
6. Ellgring H. Seiler S, Perleth B, Frings W, Gasser T, Oertel W. Psychosocial aspects of Parkinson's disease. Neurology 1993;43(12 suppl 6):S41-S44.
7. Andersen S. Patient perspective and self-help. Neurology 1999;52(7 suppl 3):S26-S28.
8. Wright JC. Nonpharmacologic management strategies. Med Clin North Am 1999;83(2):499-508.
9. Langan RJ. Parkinson's disease: assessment procedures and guidelines for counseling. Nurse Pract 1976:2(2):13-16.
10. Oertel WH, Ellgring H. Parkinson's disease—medical education and psychosocial aspects. Patient Educ Couns 1995;26(1-3):71-79.
11. Heijman A. The role of lay associations: difficulties encountered. Patient Educ Couns 1995;26(1-3):277-280.

BIBLIOGRAPHY - EXCLUDED FROM ANALYSIS (REASON FOR EXCLUSION)

Brown R, Jahanshahi, M. Depression in Parkinson's disease: a psychosocial viewpoint. Adv Neurol 1995;65:61-84. (Subject is Depression - see chapter on Depression)

Carter JH, Stewart BJ, Archbold PG, et al. and the Parkinson's Study Group. Living with a person who has Parkinson's disease: the spouse's perspective by stage of disease. Mov Disord 1998;13(1):20-28. (Descriptive, non-interventional report)

Dakof GA, Mendelsohn GA. Patterns of adaptation to Parkinson's disease. Health Psychol 1989;8:355-372. (Descriptive, non-interventional report)

Dakof GA, Mendelsohn GA. Parkinson's disease: the psychological aspects of a chronic illness. Psychol Bull 1086;99(3):375-387. (Descriptive, non-interventional report)

de Boer AG, Wijker W, Speelman JD, de Haes JC. Quality of life in patients with Parkinson's disease: development of a questionnaire [see comments]. J Neurol Neurosurg Psychiatry 1996;61(1):70-74. (Descriptive, non-interventional report)

Ehmann TS, Beninger RJ, Gawel MJ, Riopelle RJ. Coping, social support, and depressive symptoms in Parkinson's disease. J Geriatr Psychiatry Neurol 1990;3(2):85-90. (Descriptive, non-interventional report)

Felton BJ, Revenson TA. Coping with chronic illness: a study of illness controllability and the influence of coping strategies on psychological adjustment. J Consult Clin Psychol 1984;52:343-353. (Descriptive, non-interventional report)

Fowler SB. Hope and a health-promoting lifestyle in persons with Parkinson's disease. J Neurosci Nurs 1997;29(2):111-116. (Descriptive, non-interventional report)

Frazier LD. Coping with disease-related stressors in Parkinson's disease. Gerontologist 2000;40(1):53-63. (Descriptive, non-interventional report)

Greene SM, Griffin WA. Symptom study in context: effects of marital quality on signs of Parkinson's disease during patient-spouse interaction. Psychiatry 1998;61:35-45. (Descriptive, non-interventional report)

Griffin WA, Greene SM. Social interaction and symptom sequences: a case study of orofacial bradykinesia exacerbation in Parkinson's disease during negative marital interaction [see comments]. Psychiatry 1994;57:269-274. (Descriptive, non-interventional report)

Hainsworth MA, Eakes GG, Burke ML. Coping with chronic sorrow. Issues Ment Health Nurs 1994;15(1):59-66. (Descriptive, non-interventional report)

Herth K. Abbreviated instrument to measure hope: development and psychometric evaluation. J Adv Nurs 1992;17:1251-1259. (Description of a scale, not an interventional report)

Herth K. Hope in older adults in community and institutional settings. Issues Ment Health Nurs 1993;14:139-156. (Descriptive, non-interventional report)

Jenkinson C, Peto V, Fitpatrick R, Greenhall R, Hyman N. Self-reported functioning and well-being in patients with Parkinson's disease: comparison of the short-form health survey (SF-36) and the Parkinson's Disease Questionnaire (PDQ-39) [see comments]. Age Ageing 1995;24(6):505-509. (Descriptive, non-interventional report)

Koplas PA, Gans HB, Wisely MP, et al. Quality of life and Parkinson's disease. J Gerontol A Biol Sci Med Sci. 1999;54(4):M197-M202. (Descriptive, non-interventional report)

Krakow K, Haltenhof H, Buhler KE. Coping with Parkinson's disease and refractory epilepsy. A comparative study. J Nerv Ment Dis 1999;187:503-508. (Descriptive, non-interventional report)

Langan RJ, Cotzias GC. Do's and don'ts for the patient on levodopa therapy. Am J Nurs 1976;76:917-918. (Descriptive, non-interventional report)

Lindgren CL. Chronic sorrow in persons with Parkinson's and their spouses. Sch Inq Nurs Pract 1996;10(4):351-366. (Descriptive, non-interventional report)

Longstreth WT Jr., Nelson L, Linde M, Munoz D. Utility of the sickness impact profile in Parkinson's disease. J Geriatr Psychiatry Neurol 1992;5:142-148. (Concerns scale development and implementation)

MacCarthy B, Brown R. Psychosocial factors in Parkinson's disease. Br J Clin Psychol 1989;28:41-52. (Descriptive, non-interventional report)

Manyam BV, Sanchez-Ramos JR. Traditional and complementary therapies in Parkinson's disease. Adv Neurol 1999;80:565-574. (Descriptive, non-interventional report)

Martinez-Martin P, Frades PB. Quality of life in Parkinson's disease: validation study of the PDQ-39 Spanish version. The Grupo Centro for Study of Movement Disorders. Neurology 1998;245(suppl 1):S34-S38. (Concerns scale development and testing)

Metzer WS. Severe essential tremor compared with Parkinson's disease in male veterans: diagnostic characteristics, treatment, and psychosocial complications. South Med J 1992;85:825-828. (Descriptive, non-interventional report)

Payne JA. Group learning for adults with disabilities or chronic disease. Rehabil Nurs 1995;20(5):268-272. (Descriptive, non-interventional report)

Peace G. Living with Parkinson's disease. Nurs Times 1995;91(32):40-41. (Descriptive, non-interventional report)

Pentland B, Barnes MP, Findley LJ, et al. Parkinson's disease: the spectrum of disabilities. J Neurol Neurosurg Psychiatry 1992;55(Suppl):32-35. (Descriptive, non-interventional report)

Peto V, Jenkinson C, Fitzpatrick R, Greenhall R. The development and validation of a short measure of functioning and well being for individuals with Parkinson's disease. Qual Life Res 1995:4(3):241-248. (Concerns scale development and testing)

Straits-Troster, Fields JA, Wilinson SB, Bahwa R. Health-related quality of life in Parkinson's disease after pallidotomy and deep brain stimulation [In Process Citation]. Brain Cogn 2000;42(3):399-416. (Descriptive, non-interventional report)

Trimmer E. When your patients ask: coping with Parkinsonism. Midwife Health Visit Community Nurse 1985;21(8):288. (Descriptive, non-interventional report)

Walker SN, Volkan K, Sechrist KR, Pender NJ. Health-promoting life styles of older adults: comparisons with young and middle-aged adults, correlates and patterns. ANS Adv Nurs Sci 1988;11:76-90. (Descriptive, non-interventional report)

Whetten-Goldstein K, Sloan F, Kulas E, Cutson T, Schenkman M. The burden of Parkinson's disease on society, family, and the individual. J Am Geriatr Soc 1997;45:844-849 (Descriptive, non-interventional report)

Whitehouse C. A new source of support. The nurse practitioner role in Parkinson's disease and dystonia. Prof Nurse 1994;9(7):448:450-451. (Descriptive, non-interventional report)

Movement Disorders
Vol. 17, Suppl. 4, 2002, p. S163-S166

Published by Wiley-Liss, Inc.
DOI 10.1002/mds.5578

Speech Therapy in Parkinson's Disease

INTRODUCTION

BACKGROUND

Seventy-five percent of patients with Parkinson's disease (PD) have speech impairment during some part of their disease and for many, this deficit limits their effective integration into society.[1-3] The characteristics of speech impairment include reduced volume, monotonous pitch and loudness, imprecise articulation, and disordered speech rate.[4,5] Impaired speech has been variably reported to improve with levodopa therapy, and in such cases, especially in subjects with motor fluctuations, speech improves during? "ON" medication effects and deficits reappear during "OFF" episodes.[4,6,7] Speech can also be adversely affected by medication therapies due to lingual facial buccal choreic movements or tongue or jaw dystonia.

RATIONALE

Speech therapies are highly variable in technique, and exercises specializing in addressing the various enumerated features of speech impairment in PD have been developed.[8] Many reports exist that laud the benefits of speech therapy. But, because they have included only very small numbers of patients and contain serious study design problems, these articles must be considered as observational reports rather than clinical trials. Over the last decade, agreed-upon outcome measures have been developed in the speech pathology literature, so that testing the efficacy of specified speech programs can now be performed with accepted primary outcome variables. Using such methods, a few relatively rigorous studies have recently been reported.

A critique of these therapies is limited by the multiplicity of different therapy programs all considered under the rubric "speech therapy". Programs may emphasize prosody, intelligibility, volume, or timing rates. No two studies cited have tested the exact same therapy program. The factor that links them, however, is a programmatic effort to involve PD subjects in some form of regular speech rehabilitation for a prescribed period of time and then test their speaking function immediately and in some cases several weeks or months thereafter.

METHODS

KEY SEARCH TERMS

Parkinson's disease, speech, speech therapy, and dysphasia.

SPECIAL EXCEPTIONS TO INCLUSION/ EXCLUSION CRITERIA

Whereas most studies reviewed in this *Movement* Disorder Society effort require 20 subjects for inclusion, the overall number of speech therapy studies that fit the above criteria are so few and generally very short-term that the minimal criteria for numbers of patients and study duration were waived.

MECHANISM OF ACTION

Speech therapy aims to strengthen muscles involved with volume production and articulation. Conscious retraining of timing for speech production and attention to clarity are also included in some therapies. There are no large studies that examine issues of central neurotransmitter changes or anatomical-functional correlates of improved speech in PD

REVIEW OF CLINICAL STUDIES

All English language articles were examined along with their bibliographies. The referenced studies that are critiqued in this report are restricted to randomized controlled studies with a duration of at least two weeks of therapy, a study population of idiopathic PD patients, and at least 10 enrolled subjects. All cited studies report objective assessments of speech with comparisons before and after speech therapy intervention. Book chapters and abstracts have not been included.

The selected studies for discussion are organized as four reports, although one combines multiple reports that used the same or overlapping groups of patients.[9-11] All reports focused on the utility of speech therapies for symptomatic control of parkinsonism, and none studied the use of this intervention for prevention of disease progression, prevention of motor complications, or control of motor or other treatment complications of PD. The design of speech therapies has been based on empiric observations of clinical deficits of PD subjects rather than on specific physiological hypotheses. No studies have examined the central anatomical or physiological changes that are associated with speech aberrations or changes that may occur after such rehabilitation interventions. Preference has been given to those with randomization and a control PD group not receiving any speech therapy, but followed for the same period. Likewise, more emphasis has been placed on a study if the evaluations were performed by blinded observers and if there was a long follow-up period to assess the duration of benefit.

SYMPTOMATIC CONTROL OF PARKINSONISM

There are four Level-I studies that will be critiqued, two comparing speech therapy to no specific intervention and two comparing two different types of therapies.

Robertson and Thomson (1984)[12]: These authors studied 18 PD subjects, 12 assigned to speech therapy and six randomized to no treatment. The speech therapy involved two weeks of daily exercises focusing on respiratory, coordination and voice control training that emphasized prosody, each lasting 3.5 to 4.0 hours daily. The disability level of the patients was not specified although all subjects were on antiparkinsonian medications. The control group was originally larger (ten subjects) but four dropped out and were not available for follow-up comparison studies. The primary out-

come measure was the Dysarthria Profile that showed a significant improvement in the subjects after speech therapy, an improvement that was still demonstrable three months after the speech program. The control subjects showed no change from baseline. In spite of the positive and long-lasting benefit, the study was weakened by a serious methodological flaw in that different evaluators studied the two groups of patients. Whereas the study group receiving speech therapy was evaluated by raters unfamiliar with the hypothesis, the control subjects were scored by the investigators themselves, introducing a serious concern of bias. This study had an overall quality rating score of 24%.

Johnson and Prang (1990)[13]: A similar set of exercises was studied in a four-week speech program.[13] Twelve PD patients, six receiving prosody-focused therapy for four weeks, and six receiving no therapy, were evaluated at baseline and at five weeks, one week after the speech therapy group finished their program. The group assignments were randomized to create two similar patient groups in terms of age and gender. To correct the prior concerns of bias, this study was completely blinded and raters evaluated tapes of speech. The primary outcome variable in this study was the Frenchay Dysarthria Scale, and other variables included Loudest Volume, Fundamental Frequency, and Pitch Range. After four weeks of therapy, the speech therapy group showed significant improvement in the primary and several other secondary speech measures. The control group showed decline. There was no long-term follow-up in either group. Together these studies demonstrate that exercises focusing on prosody benefit patients immediately after the therapy and for at least one week. They are intensive therapies in terms of time commitment (more than twice weekly in both instances). This study had an overall quality rating score of 43%.

Scott and Cairn (1983)[5]: The two other studies did not use a control group receiving no therapy, but rather compared two different types of treatments. Scott and Cairn[5] randomized patients to either regular speech therapy or to the same therapy with the addition of a Vocalite apparatus that was used as a vocal reinforcement tool. Prior to either intervention, they followed the patients for two weeks without any intervention and speech scores were stable. The evaluation tools were the Prosodic Abnormality Score and the Intelligibility Score, two measures regularly used in the speech literature. Ratings were performed by two specialists, one blinded to treatment assignment and the other aware of treatment group with the final data being the mean of these two raters. Treatment sessions were identical in timing, occurring 2-3 times weekly for approximately three weeks. Patients were assigned in random order with 13 subjects in each group. With both therapies, there was significant improvement in both outcome measures; no additional benefit occurred with the vocal reinforcement. This study also included a second post-treatment evaluation three months after completion of therapy. At this follow-up visit, the primary outcome measures were still significantly better over baseline in the sensory-enhanced treatment group, but the improvement had not been maintained in the regular speech therapy group. This study had an overall quality rating score of 28%.

Ramig et al. (1996)[10]: Ramig also did not use a control group, but tested two therapies, respiratory exercises and respiratory training along with voice therapy. The former was termed placebo in this report, but another report by this author considered both to be active interventions.[9] The combined respiratory and speech therapy was termed the Lee Silverman Voice Therapy program (LSVT). Thirty-five PD subjects were randomly assigned to the two therapies and treatment of each lasted one month and involved 16 sessions.[10] LSVT was aimed to increase vocal cord adduction and loudness. The total study lasted 13 months, because follow-up evaluations occurred at 6 and 12 months after completion of the two comparative therapy arms. The groups were matched for PD duration, age and HY disability, and no medication changes occurred during the one-month speech therapies. Vocal intensity significantly improved with the combined vocal/respiratory therapy after one month of treatment and this improvement over baseline persisted at 6 and 12 months. The most significant changes occurred in sustained phonation with less substantial improvements in speech volume. The group that received respiratory therapy alone showed no improvement at one month and actual speech deterioration at 12 months. Whereas these data are published in the neurological literature, a study by the same authors (possibly with significant subject overlap) from the speech pathology literature and with larger patient numbers used somewhat different analytic techniques and concluded that both forms of therapy induced significant short-term improvement.[9] Both of these studies had an overall quality rating score of 48%.

Smith et al. (1995)[11]: Another publication reported on laryngostroboscopic findings in PD patients receiving these therapies, and after four weeks of combined vocal/respiratory treatment, patients showed improved glottal competence. Although there were gains in other areas, no change in voice intensity occurred in the group receiving respiratory therapy alone. The mean vocal intensity increase with vocal/respiratory treatment was 12.5 dB compared to only 1.9 dB in the respiratory therapy group. In all reports by this group, the combined vocal/respiratory therapy group benefited more than the group receiving respiratory training alone. A NIH-funded multicenter clinical trial of the Ramig method of voice therapy is currently organized by the American Speech-Language-Hearing Association.

REVIEW OF SAFETY

The interventions discussed are exercises that have no implicit risk. No specific data on morbidity of speech therapy were provided in these studies.

CONCLUSIONS

EFFICACY

PREVENTION OF DISEASE PROGRESSION

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of speech therapy in the prevention of disease progression in patients with PD.

SYMPTOMATIC CONTROL OF PARKINSON'S DISEASE

Monotherapy

Very few well-controlled studies of speech therapy have been performed. None of them assessed speech therapy administered as monotherapy. There is INSUFFICIENT EVIDENCE to conclude on the efficacy of speech therapy as sole treatment in any indication in Parkinson's disease.

Adjunct therapy

Randomized, controlled (Level I) clinical evidence of low quality suggests that speech therapy emphasizes prosody and perhaps speech loudness given as adjunct to antiparkinsonian drug treatment. There are not enough data at the present time to comment

on the duration of benefit nor on the type of patient (stable vs. fluctuating disease) most amenable to this type of intervention. In all studies cited, the speech therapy involved frequent therapy sessions (at least three times weekly) during the treatment phase. There is INSUFFICIENT EVIDENCE for speech improvement.

PREVENTION OF MOTOR COMPLICATIONS

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of speech therapy regarding prevention of motor complications in patients with PD.

CONTROL OF MOTOR COMPLICATIONS AND NON-MOTOR COMPLICATIONS

There is INSUFFICIENT EVIDENCE to conclude on the efficacy of speech therapy on motor and non-motor complications of PD.

SAFETY

Based on the Level-I evidence and the absence of morbidity associated with the reports of speech therapy in PD, speech therapy is SAFE and has an ACCEPTABLE RISK, WITHOUT SPECIALIZED MONITORING.

IMPLICATIONS FOR CLINICAL PRACTICE

In the practical therapeutic setting, because most reported speech therapy has been very intensive and outside the range of sessions usually prescribed in the community, speech therapy is considered INVESTIGATIONAL. For patients seeking improved short-term speech function, speech therapy should therefore be intensive and emphasize prosody and speech loudness. After 2 to 4 weeks, testing should be repeated to document objective changes. There are insufficient data to recommend continuation of therapy after four weeks.

IMPLICATIONS FOR CLINICAL RESEARCH

Although speech therapy reports have been positive, there have been so few studies done. Studies that are larger (more patient numbers), expanded, randomized, prospective and controlled with longer follow-up periods are essential. Further, because the reports published to date involved intensive speech therapy that extends beyond the treatments that patients often receive in the community, trials of speech therapy protocols that more closely mimic typically available therapy would define the overall clinical usefulness of speech therapy to patients with PD. Functional neuroimaging studies examining patients before and after speech therapy may help define the anatomical basis of speech impairment in PD and changes related to speech therapy.

REFERENCES

1. Darley FL, Aronson AE, Brown JR. Differential diagnostic patterns of dysarthria. J Speech Hear Res 1969a;12:246-269.
2. Darley FL, Aronson AE, Brown JR. Clusters of deviant speech dimensions in the dysarthrias. J Speech Hear Res 1969b;12:462-496.
3. Logemann JA, Fisher HB, Boshes B, Blonsky ER. Frequency and cooccurrence of vocal tract dysfunctions in the speech of a large sample of Parkinson's disease patients. J Speech Hear Disord 1978;43:47-57.
4. Ramig LO, Dromey C. Aerodynamic mechanisms underlying treatment-related changes in vocal intensity in patients with Parkinson's disease. J Speech Hear Res 1996;39:798-807.
5. Scott S, Caird FI. Speech therapy for Parkinson's disease. J Neurol Neurosurg Psychiatry 1983;46:140-144.
6. Leanderson R, Meyerson BA, Persson A. Effect of L-dopa on speech in Parkinsonism. An EMG study of labial articulatory function. J Neurol Neurosurg Psychiatry 1971;34:679-681.
7. Nakano KK, Zubrick H, Tyler HR. Speech defects of parkinsonian patients. Effects of levodopa therapy on speech intelligibility. Neurology 1973;23:865-870.
8. de Angelis EC, Mourao LF, Ferraz HB, Behlau MS, Pontes PA, Andrade LA. Effect of voice rehabilitation on oral communication of Parkinson's disease patients. Acta Neurol Scand 1997;96:199-205.
9. Ramig LO, Countryman S, Thompson LL, Horii Y. Comparison of two forms of intensive speech treatment for Parkinson's disease. J Speech Hear Res 1995;38:1232-1251.
10. Ramig LO, Countryman S, O'Brien. Intensive speech treatment for patients with Parkinson's disease. Neurology 1996;47:1496-1504.
11. Smith ME, Ramig LO, Dromey C. Perez KS, Samandari R. Intensive voice treatment in Parkinson's disease: laryngostroboscopic findings. J Voice 1995;9:453-459.
12. Robertson SJ, Thomson F. Speech therapy in Parkinson's disease: a study of the efficacy and long term effects of intensive treatment. Br J Disord Commun 1984;19:213-224.
13. Johnson JA, Pring TR. Speech therapy and Parkinson's disease: a review and further data. Br J Disord Commun 1990;25:183-184.

BIBLIOGRAPHY - EXCLUDED FROM ANALYSIS (REASON FOR EXCLUSION)

Allan CM. Treatment of non fluent speech resulting from neurological disease-treatment of dysarthria. Br J Disord Commun 1970;5(1):3-5. (Not specifically about Parkinson's disease)

Buckman GF Jr. Speech rehabilitation for the geriatric patient. J Am Geriatr Soc 1971;19(12):996-999. (General discussion of speech in the elderly, not specifically Parkinson's disease)

Caird FI. Non-drug therapy of Parkinson's disease. Scott Med J 1986;31(2):129-132. (General discussion, no specific data on speech clinical trials)

Clarke CE, Gullaksen E, Macdonald S, Lowe F. Referral criteria for speech and language therapy assessment of dysphagia caused by idiopathic Parkinson's disease. Acta Neurol Scand 1998;97:27-35. (Not a clinical trial)

Coppen A, Metcalfe M, Carroll JD, Morris JG. Levodopa and L-tryptophan therapy in parkinsonism. Lancet 1972;1(7752):654-658. (Not a clinical trial)

Cooper IS, Riklan M, Stellar S, et al. A multidisciplinary investigation of neurosurgical rehabilitation in bilateral parkinsonism. J Am Geriatr Soc 1968;16(11):1177-1306. (General discussion of rehabilitation efforts in association with neurosurgery for Parkinson's disease)

de Angelis EC, Mourao LF, Ferraz HB, Behlau MS, Pontes PA, Andrade LA. Effect of voice rehabilitation on oral communication of Parkinson's disease patients. Acta Neurol Scand 1997;96:199-205. (Open label, no control group, no blinding)

Downie AW, Low JM, Lindsay DD. Speech disorder in parkinsonism; of delayed auditory feedback in selected cases [Letter]. J Neurol Neurosurg Psychiatry 1981;44:852. (Case histories only)

Dupuis M. [Functional rehabilitation in Parkinson's Disease] [French]. Union Med Can 1970;99(9):1642-1649. (Not a clinical trial)

Erb E. Improving speech in Parkinson's disease. Am J Nurs 1973;73(11):1910-1911. (General discussion, but no specific data)

Greene MC, Watson BW, Gay P, Townsend DB. A therapeutic speech amplifier and its use in speech therapy. J Laryngol Otol 1972;86(6):595-605. (Description of voice amplification, but not a clinical trial)

Hammen VL, Yorkston KM, Minifie FD. Effects of temporal alterations on speech intelligibility in parkinsonian dysarthria. J Speech Hear Res 1994;37:244-253. (Only 6 patients)

Hartelius L, Svensson P. Speech and swallowing symptoms associated with Parkinson's disease and multiple sclerosis: a survey. Folia Phoniatr Logop 1994;46(1):9-17. (General discussion, but not focused on therapeutic trials)

Hartman DE, Abbs JH. The response of the apparent receptive speech disorder of Parkinsonism to speech therapy. J Neurol Neurosurg Psychiatry 1985;48:606. (Letter, not a clinical trial)

Henneberg A. Additional therapies in Parkinson's disease patients: useful tools for the improvement of the quality of life or senseless loss of resources. J Neurol 1998;245(suppl1):S23-S27. (Work in progress, not a full report)

Lang AE. Fishbein V. The "pacing board" in selected speech disorders of Parkinson's disease [Letter]. J Neurol Neurosurg Psychiatry 1983;46(8):789. (Letter, not a clinical trial)

Leder SB. Adult onset of stuttering as a presenting sign in a parkinsonian-like syndrome: a case report. J Commun Disord 1996;29(6):471-478. (Concerns stuttering and not therapy)

Le Dorze G, Dionne L, Ryalls J, Julien M, Ouellet L. The effects of speech and language therapy for a case of dysarthria associated with Parkinson's disease. Eur J Disord Commun 1992;27(4):313-324. (Single subject case report)

Rubow R. Swift E. A microcomputer-based wearable biofeedback device to improve transfer of treatment in Parkinsonian dysarthria. J Speech Hear Disord 1985;50(2):178-185. (Open label observations without a control group)
Sarno MT. Speech impairment in Parkinson's disease. Arch Phys Med Rehabil 1968;49(5):269-275. (General discussion, but no specific data on treatment outcomes)
Scott S, Caird FI. Speech therapy for patients with Parkinson's disease. Br Med J 1981;283:1088. (Only 9 subjects)
Scott S, Caird FI. The Response of the apparent receptive speech disorder of Parkinson's disease to speech therapy. J Neurol Neurosurg Psychiatry 1984;47:302-304. (Open label observations with no control group)
Weiner WJ, Singer C. Parkinson's disease and nonpharmacologic treatment programs. J Am Geriatr Soc 1989;37(4):359-363. (General discussion of non-pharmacological therapies)