Update on Treatments for the Non-Motor Symptoms of Parkinson's Disease – an Evidence-Based Medicine Review

Tables

Table 1: Indications of non-motor symptoms covered by this review

- Neuropsychiatric symptoms:
  - Depression and depressive symptoms
  - Anxiety and anxiety symptoms
  - Apathy
  - Psychosis
  - Impulse control and related disorders
  - Dementia
  - Cognitive impairment (other than dementia; mainly mild cognitive impairment [MCI])
- Autonomic dysfunction
  - Drooling
  - Orthostatic hypotension
  - Urinary dysfunction
  - Erectile dysfunction
  - Gastrointestinal dysfunction
  - Excessive sweating
- Disorders of sleep and wakefulness
  - Sleep fragmentation and insomnia
  - Rapid eye movement sleep behavior disorder (RBD)
  - Excessive daytime sleepiness (EDS)
- Others
  - Pain
  - Fatigue
  - Olfactory dysfunction
  - Ophthalmologic dysfunction

Table 2: Interventions to treat depression including depressive symptoms in PD

INTERVENTION		EFFICACY	SAFETY	PRACTICE IMPLICATIONS
DRUG CLASS/ INTERVENTION STRATEGY	**DRUG/ INTERVENTION**			
DOPAMINE AGONISTS	Pramipexole	Efficacious	Acceptable risk without specialized monitoring	Clinically useful
	Pergolide	Insufficient evidence	Acceptable risk with specialized monitoring	Not useful
	Rotigotine	*Unlikely efficacious*	*Acceptable risk without specialized monitoring*	*Investigational*
MAO-B inhibitors	**Rasagiline**	*Insufficient evidence*	*Acceptable risk without specialized monitoring*	*Investigational*
	Selegeline	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
	Moclobemide	Insufficient evidence	Acceptable risk with specialized monitoring [1]	Investigational

TRICYCLIC ANTIDEPRESSANTS (TCA)	Nortriptyline	Likely efficacious	Acceptable risk without specialized monitoring [3]	Possibly useful
	Desipramine	Likely efficacious	Acceptable risk without specialized monitoring [3]	Possibly useful
	Amitriptyline	Insufficient evidence	Acceptable risk without specialized monitoring [3]	*Possibly useful* [2]
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)/ SELECTIVE SEROTONIN NOREPINEPHRINE REUPTAKE INHIBITORS	Citalopram	Insufficient evidence	Acceptable risk without specialized monitoring [5]	*Possibly useful* [4]
	Sertraline	Insufficient evidence	Acceptable risk without specialized monitoring [5]	*Possibly useful* [4]
	Paroxetine	insufficient evidence	Acceptable risk without specialized monitoring [5]	*Possibly useful* [4]
	Fluoxetine	Insufficient evidence	Acceptable risk without specialized monitoring [5]	*Possibly useful* [2]
	Venlafaxine	*Efficacious*	*Acceptable risk without specialized monitoring* [5]	*Clinically useful*

OTHER ANTIDEPRESSANTS	Atomoxetine	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
	Nefazodone	Insufficient evidence	Unacceptable risk	Not useful
ALTERNATIVE THERAPIES	Ω-3 fatty acids	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
NON-PHARMACOLOGICAL INTERVENTIONS	**rTMS**	*Insufficient evidence*	*Acceptable risk without specialized monitoring*[6]	*Possibly useful (short-term)*
	CBT	*Likely efficacious*	*Insufficient evidence* [7]	*Possibly useful*

[1] Combined treatment with either TCAs or SSRIs carries an unacceptable risk.

[2] Although RCTs did not contain a placebo arm, the practice implication is ""possibly useful" due to proven antidepressant efficacy and license outside of PD.

[3] Typical antimuscarinic adverse events (AEs) have to be considered, such as dry mouth, constipation, urinary retention, and hyperhidrosis. Moreover, concomitant treatment of PD patients with TCAs can contribute to psychosis, sedation, and daytime sleepiness, as well as to cognitive dysfunction or delirium when used in patients with PD dementia.[2] The risk of mortality has to be considered if overdosing occurs. TCAs should be used with caution in patients with a history of urinary retention, angle-closure glaucoma, increased intraocular pressure, cardiovascular disorders and cognitive dysfunction. Available data indicate that TCAs pose a risk for QT prolongation in older adults.[176]

[4] Although RCTs for PD depression report conflicting data for efficacy, the practice implication is "possibly useful" due to proven antidepressant efficacy and license outside of PD.

[5] There are concerns about the induction of the serotonin syndrome when used in conjunction with the MAO-B inhibitors selegiline and rasagiline.[2] Hyponatremia may be associated with SSRI use, especially in elderly people with low body weight and concomitant use of diuretics, thought to be secondary to the development of the syndrome of inappropriate antidiuretic hormone (SIADH).[2] Of all SSRIs available data indicate that citalopram at higher dosages poses the greatest risk for QT prolongation in older adults (aged 60 years and anove),[176] such as , regular electrocardiograph (ECG) monitoring should be performed with citalopram when prescribed at a dose >20 mg/day in elderly patients.

[6] The FDA notes that labeling should include precautions for the use of rTMS devices in the treatment of patients with depressive or related conditions where safety and efficacy have not been established such as in movement disorders.[177]

[7] In general, reporting of AEs in CBT trials is limited;[85,86] in most behavioral health clinical trials there is a lack of monitoring of AEs, including serious AEs such as suicide attempts, completed suicides, and psychiatric hospitalizations.[86] Temporary increases in anxiety during behavioral health clinical trials are often considered a normal part of therapy and are therefore not documented as possible AEs.[86]

Table 3: Interventions to treat apathy in PD

INTERVENTION		EFFICACY	SAFETY	PRACTICE IMPLICATION
DRUG CLASS/ INTERVENTION STRATEGY	**DRUG/ INTERVENTION**			
DOPAMINE AGONISTS	**Piribedil** [1]	*Likely efficacious*	*Acceptable risk without specialized monitoring*	*Possibly useful*
	Rotigotine	*Unlikely efficacious*	*Acceptable risk without specialized monitoring*	*Investigational*
ACETYLCHOLINESTERASE INHIBITORS	**Rivastigmine**	*Efficacious*	*Acceptable risk without specialized monitoring* [2]	*Possibly useful*

[1] Recommendations apply only for PD patients following STN stimulation

[2] Worsening of tremor may occur in some patients treated with cholinesterase inhibitors. Medical monitoring for cholinergic effects could include blood pressure or ECG monitoring but acetylcholinesterase inhibitors are considered to pose an acceptable risk even without specialized monitoring.[2]

Table 4: Interventions to treat impulse control and related disorders in PD

INTERVENTION		EFFICACY	SAFETY	PRACTICE IMPLICATIONS
DRUG CLASS/ INTERVENTION STRATEGY	**DRUG/ INTERVENTION**			
NMDA ANTAGONISTS	Amantadine [1]	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
ANTI-OPIOIDS	**Naltrexone [2]**	*Insufficient evidence*	*Insufficient evidence*	*Investigational*
NON-PHARMACOLOGICAL INTERVENTIONS	**CBT [2]**	*Likely efficacious*	*Insufficient evidence* [3]	*Possibly useful*

[1] Recommendations apply for PD patients with pathological gambling
[2] Recommendations apply for PD patients with ICDs
[3] See table 2

Table 5: Interventions to treat dementia and non-dementia cognitive impairment in PD

DRUG CLASS	DRUG	EFFICACY	SAFETY	PRACTICE IMPLICATIONS
DRUG CLASS/ INTERVENTION STRATEGY	**DRUG/ INTERVENTION**			
DEMENTIA				
ACETYLCHOLINESTERASE INHIBITORS	**Donepezil**	Insufficient evidence	Acceptable risk without specialized monitoring [3]	*Possibly useful*[1]
	Rivastigmine	Efficacious	Acceptable risk without specialized monitoring [3]	Clinically useful
	Galantamine	Insufficient evidence	Acceptable risk without specialized monitoring [3]	*Possibly useful*[2]
NMDA ANTAGONISTS	MEMANTINE	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
NON-DEMENTIA COGNITIVE IMPAIRMENT				
ACETYLCHOLINESTERASE INHIBITORS	**RIVASTIGMINE**	*Insufficient evidence*	*Acceptable risk without specialized monitoring* [4]	*Investigational*

MAO-B INHIBITORS	**RASAGILINE**	*Insufficient evidence*	*Acceptable risk without specialized monitoring*	*Investigational*
NON-PHARMACOLOGICAL INTERVENTIONS	**T-DCS**	*Insufficient evidence*	*Insufficient evidence*	*Investigational*
	COGNITIVE REHABILITATION	*Insufficient evidence*	*Insufficient evidence*	*Investigational*

[1] Refers to donepezil 10mg; although RCTs to treat dementia in PD with donepezil report conflicting data for efficacy, the practice implication for donepezil is “possibly useful” due to the proven antidementive efficacy and license outside of PD.

[2] Although there is “insufficient evidence” for galantamine to be rated for the treatment of dementia in PD, the practice implication is “possibly useful” due to the proven antidementive efficacy and license outside of PD. Moreover, there were positive signals in favor for galantamine in the trial performed for PD dementia.

[3] See table 1

[4] See table 3

Table 6: Interventions to treat psychosis in PD

DRUG	EFFICACY	SAFETY*	PRACTICE IMPLICATIONS
CLOZAPINE	Efficacious	Acceptable risk with specialized monitoring	Clinically useful
OLANZAPINE	*Not efficacious*	Unacceptable risk	*Not useful*
QUETIAPINE	Insufficient evidence	Acceptable risk without specialized monitoring	*Possibly useful* [1]
PIMAVANSERIN	*Efficacious*	*Acceptable risk without specialized monitoring* [2]	*Clinically useful*

* The FDA mandates that antipsychotic drug manufacturers add black box warnings to labels and prescribing information because of the link found between antipsychotics and an increased mortality risk in elderly dementia patients. Moreover, antipsychotic medication may be associated with QT prolongation.[178]

[1] Although there is insufficient evidence for quetiapine to be rated for the treatment of psychosis in PD, the practice implication is "possibly useful". There are no high-quality RCTs available for the treatment of quetiapine for psychosis in PD and quetiapine was similarly efficacious to clozapine in the clozapine-controlled trials.

[2] There is a lack of safety data regarding durability beyond 6 weeks. There were more serious AEs in the pimavanserin arm (7.9%) compared to the placebo arm (3.5%), but without a unifying pattern and as such it is difficult to interpret these as drug-related.[29] Nevertheless, the FDA has very recently conducted an evaluation of available information about pimavanserin after the publication of reports of post-marketing adverse events.[90] Based on the analysis of all available data, the FDA did not identify any new or unexpected safety findings with pimavanserin. After a thorough review, the FDA's conclusion remains unchanged that the drug's benefits outweigh its risks for patients with hallucinations and delusions of Parkinson's disease psychosis.[91] Although the FDA did not identify any new or unexpected safety risks, there should be awareness of the possible adverse effects of pimavanserin including QT prolongation (especially with the concomitant use of other antipsychotic drugs or drugs that can cause QT prolongation) and a potential to cause a paradoxical worsening of symptoms.[142]

Table 7: Drugs to treat disorders of sleep and wakefulness in PD

DISORDERS OF SLEEP AND WAKEFULNESS	DRUG	EFFICACY	SAFETY	PRACTICE IMPLICATIONS
DRUG CLASS/ INTERVENTION STRATEGY	**DRUG/ INTERVENTION**			
INSOMNIA				
LEVODOPA	Controlled-release formulation of levodopa/carbidopa	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
DOPAMINE AGONISTS	Pergolide	Insufficient evidence	Acceptable risk with specialized monitoring	Not useful
	Piribedil	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational
	Rotigotine	Likely efficacious	Acceptable risk without specialized monitoring	Possibly useful
HYPNOTICS	Eszopiclone	Insufficient evidence	Acceptable risk without specialized monitoring[1]	*Possibly useful*[1]
MELATONIN	3-5mg	Insufficient evidence	Acceptable risk without	*Possibly useful* [2]

			specialized monitoring	
	50mg	Insufficient evidence	Insufficient evidence	Investigational
NON-PHARMACOLOGICAL INTERVENTIONS	**Continuous positive airway pressure (CPAP)** [3]	*Likely efficacious*	*Acceptable risk without specialized monitoring*	*Possibly useful*
EXCESSIVE DAYTIME SOMNOLENCE AND SUDDEN ONSET OF SLEEP				
DRUG CLASS	**DRUG**			
PSYCHOACTIVE DRUGS	Modafinil	Insufficient evidence	Insufficient evidence[5]	*Possibly useful* [4]
	Caffeine	*Insufficient evidence*	*Acceptable risk without specialized monitoring*	*Investigational*
NON-PHARMACOLOGICAL INTERVENTIONS	**Continuous positive airway pressure (CPAP)** [3]	*Likely efficacious*	*Acceptable risk without specialized monitoring*	*Possibly useful*

[1] Although there is insufficient evidence for eszopiclone to be rated for the treatment of insomnia in PD, it can improve global and sleep outcomes for insomnia disorder, and it can be associated with associated with infrequent but serious harms such as fractures, and major injury.[179] Therefore, the practice implication is suggested to be possibly useful.

[2] Although there is insufficient evidence for melatonin to be rated for the treatment of insomnia in PD, it provided significant benefits on measures of insomnia compared to placebo in patients with PD and insomnia. Moreover, melatonin has not only been approved in the EU for patients aged 55 or over suffering from primary insomnia, but is available over-the-counter in the United States since the mid-1990s. Therefore, the practice implication is "possibly useful".

[3] Recommendations apply for PD patients with obstructive sleep apnea

[4] Modafinil provided significant benefits on measures of excessive daytime somnolence compared to placebo in patients with PD and excessive daytime somnolence[2] and a recent meta-analysis of three trials evaluating modafinil, which were also included in the previous

review,[2] showed a significant reduction in sleepiness, as assessed by the Epworth Sleepiness Scale.[94]

[5] Rare cases of serious or life-threatening rash, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) have been reported in adults and children in worldwide post-marketing experience. Estimates of the incidence rate for these serious skin reactions in the general population range between 1 to 2 cases per million-person years. Psychiatric AEs have been reported in patients treated with modafinil with many, but not all, patients having had a prior psychiatric history; postmarketing AEs associated with the use of modafinil have included mania, delusions, hallucinations, suicidal ideation, and aggression, some resulting in hospitalization.[2]

Table 8: Interventions to treat autonomic dysfunction in PD

	DRUG/ INTERVENTION	EFFICACY	SAFETY	PRACTICE IMPLICATIONS
ORTHOSTATIC HYPOTENSION	Fludrocortisone	Insufficient evidence	Insufficient evidence	*Possibly useful* [1]
	Midodrine	Insufficient evidence	Insufficient evidence	*Possibly useful* [2]
	Domperidone	Insufficient evidence	*Acceptable risk with specialized monitoring* [3]	Investigational
	Yohimbine	Non efficacious	Insufficient evidence	Investigational
	Droxidopa [4]	*Efficacious (short-term)*	Acceptable risk without specialized monitoring (short-term) [5]	*Possibly useful*
SEXUAL DYSFUNCTION	**Sildenafil**	*Efficacious*	Acceptable risk without specialized monitoring	*Clinically useful*
CONSTIPATION	Macrogol	Likely efficacious	Acceptable risk without specialized monitoring	Possibly useful
	Lubiprostone	*Likely efficacious*	*Acceptable risk without specialized monitoring*	*Possibly useful*

	Probiotics and prebiotic fiber	*Efficacious*	*Acceptable risk without specialized monitoring*	*Clinically useful*
	Abdominal massages	*Insufficient evidence*	*Insufficient evidence*	*Investigational*
ANOREXIA, NAUSEA AND VOMITING ASSOCIATED WITH LEVODOPA AND/OR DOPAMINE AGONIST TREATMENT	Domperiodone	Likely efficacious	*Acceptable risk with specialized monitoring*[3]	Possibly useful
DROOLING	Ipratropium Bromide Spray	Insufficient evidence	Insufficient evidence	Investigational
	Glycopyrrolate	Efficacious	Insufficient evidence	Possibly useful
	Botulinum Toxin B	Efficacious	Acceptable risk with specialized monitoring	Clinically useful
	Botulinum Toxin A	Efficacious	Acceptable risk with specialized monitoring	Clinically useful
URINARY FREQUENCY, URGENCY, AND/OR URGE INCONTINENCE	**Solifenacin**[6]	*Insufficient evidence*	*Acceptable risk without specialized monitoring* [7]	*Possibly useful* [8]

[1] Although there is insufficient evidence for fludrocortisone to be rated for the treatment of OH in PD, it provided some significant benefits in one RCT.[2] Therefore, the practice implication is “possibly useful”.

[2] Although there is insufficient evidence for midodrine to be rated for the treatment of OH in PD, it provided some significant benefits on measures of OH in RCTs in mixed population of patients of which only a subgroup had PD.[1] Therefore, the practice implication is “possibly useful”.

[3] Due to the risk of QT prolongation and the association with ventricular tachyarrhythmia /sudden cardiac death in PD patients with preexisting cardiac disease.[96]

[4] Recommendations are for the very short-term treatment of OH in PD, while there is insufficient evidence to conclude on the efficacy and safety of droxidopa for the treatment of OH in PD for the long-term.

[5] A recent systematic review evaluated the cardiovascular safety of droxidopa in patients with symptomatic neurogenic OH who participated in RCTs (short-term RCTs: 1 to 2 weeks, n=444; intermediate RCTs: 8 to 10-weeks, n=222) and long-term open-label studies (n=422).[97] Adjusting for exposure time, cardiovascular AEs rates were 0.30 events/patient-year in the short- and intermediate-term studies, and 0.15 events/patient-year in the long-term open-label studies, and most evident in patients with preexisting cardiac disorders. Moreover, the risk for supine hypertension has to be considered. Indeed, in the post-marketing surveillance, one case with intracranial hemorrhages has been reported.[98]

[6] for the treatment of overactive bladder

[7] A systematic review including 4,188 subjects (3 952 subjects in placebo-controlled trials; 650 of them randomized to solifenacin) aged 65 or older randomized to antimuscarinic medications for 4 to 12 weeks and 3 026 randomized to placebo, revealed that treatment for overactive bladder using antimuscarinics in adults aged 65 or older resulted in significant increased risk of several AEs compared to placebo including both anticholinergic (e.g., dry mouth, constipation) and non-anticholinergic (e.g., dyspepsia, dizziness, headaches) AEs.[101] Moreover, incidence of urinary tract infections with solifenacin was significantly higher compared to placebo.

[8] There were some significant benefits in the active arm and as such the practice implications for solifenacin for the treatment of overactive bladder is “possibly useful” due to the established efficacy and license of solifenacin in this indication outside PD.

Table 9: Interventions to treat fatigue in PD

INTERVENTION		EFFICACY	SAFETY	PRACTICE IMPLICATIONS
DRUG CLASS	**DRUG**			
MAO-B INHIBITORS	**Rasagiline**	*Efficacious*	*Acceptable risk without specialized monitoring*	*Possibly useful*
PSYCHOACTIVE DRUGS	**Methylphenidate**	Insufficient evidence	Insufficient evidence	Investigational
	Modafinil	Insufficient evidence	Insufficient evidence [1]	Investigational
NON-PHARMACOLOGICAL INTERVENTIONS	**Acupuncture**	*Insufficient evidence*	*Acceptable risk without specialized monitoring*	*Investigational*

[1] See table 7

Table 10: Interventions to treat pain in PD

DRUG	EFFICACY	SAFETY	PRACTICE IMPLICATIONS
ROTIGOTINE	*Insufficient evidence*	*Acceptable risk without specialized monitoring*	*Investigational*
OXYCODONE-NALOXONE PROLONGED RELEASE	*Insufficient evidence*	*Acceptable risk without specialized monitoring*	*Possibly useful* [1]

[1] There were some significant benefits in the active arm such as the practice implications for oxycodone/naloxone prolonged release for the treatment of pain is “possibly useful” due to the established efficacy and license of oxycodone/naloxone prolonged release in adults with severe chronic pain outside PD. [112,113]