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Reviews

Serotonin and Parkinson's Disease: On Movement, Mood, and Madness

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Abstract: An appreciation of the multiple roles that serotonin (5-HT) may play in Parkinson's disease (PD) has increased in recent years. Early pathological studies in PD demonstrated nonselective reductions of 5-HT in brain tissue but little correlation to comorbidities such as dyskinesia and mood disturbance. This, combined with treatment failures using serotonergic drugs in comparison to levodopa, meant the field was largely neglected until recently. The multitude of subtypes of 5-HT receptors in the brain and an increased understanding of the potential function 5-HT may play in modulating other neurotransmitter systems, including dopamine, GABA, and glutamate, have meant an expansion in efforts to develop potential serotonergic drugs for both motor and nonmotor symptoms in PD. However, several unanswered questions remain, and future studies need to focus on correlating changes in 5-HT neurotransmission in both pathological and *in vivo* imaging studies with a full clinical phenotype. © 2009 Movement Disorder Society

Key words: Parkinson's disease; serotonin; 5-HT; dyskinesia; depression; anxiety; psychosis; constipation

INTRODUCTION

Serotonin, initially identified in 1948 as a chemical within the blood stream (serum) that was able to cause vasoconstriction (tonus), was subsequently determined to be 5-hydroxytryptamine (5-HT).[1] Over the past 60 years, increased understanding of the role of serotonin as a neurotransmitter within the CNS has expanded knowledge of many brain functions. Thus, the serotonergic system is one of the most widely distributed, highly conserved neurotransmitters, innervating virtually all regions of the CNS and allowing it to participate in basic physiological functions such as sleep, arousal, feeding, and satiety, as well as more complex activities such as mood and emotion. This diversity of function is manifested by the large number and wide distribution of 5-HT receptors. To date, there are 14 distinct subtypes of the 5-HT receptor, with many more isoforms; this large number has been suggested to reflect the fact that the 5-HT system is one of the oldest neurotransmitter systems in evolutionary terms and has thus had the longest to diversify.[2] The advantage in terms of therapeutics is that selective regional localization of 5-HT subtypes theoretically allows for relatively selective targeting of drugs in disease states without inducing off target side-effects.

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EVIDENCE FOR ALTERED SEROTONERGIC NEUROTRANSMISSION IN PARKINSON'S DISEASE

In the normal brain, there is a dense serotonergic innervation of the basal ganglia from the raphe nuclei, particularly the dorsal raphe nuclei (DRN) that also send projections to the frontal cortex, limbic system,

and diencephalon.[3] In particular, the striatum and the output regions of the basal ganglia, the substantia nigra pars reticulata (SNr), and medial globus pallidus (GPm) receive a dense serotonergic input,[4] thus suggesting a potential role for serotonin in Parkinson's disease (PD). In early postmortem studies of patients with PD, depletion of serotonin in the caudate as well as hypothalamus and frontal cortex was reported, although not to the same degree as dopamine loss.[5–7,8] A recent pathological study has confirmed some of these findings, showing preferential loss of 5-HT in the caudate compared with the putamen, but with relatively less loss of 5-HT (66%) than dopamine (98%).[9] Imaging studies in vivo have also suggested depletion of 5-HT innervation to the striatum as measured via decreased serotonin transporter binding.[10–12] The loss of striatal 5-HT in PD may be secondary to neurodegeneration within the raphe nuclei as Lewy bodies are seen in the raphe nuclei[13,14] and there is associated cell loss.[15,16] However, none of these studies reported a correlation with motor disability, dyskinesia, mood, or psychiatric comorbidities.

SEROTONERGIC INVOLVEMENT IN MOTOR SYMPTOMS AND LEVODOPA-INDUCED DYSKINESIA IN PD

While pathological and imaging studies have suggested a depletion of 5-HT in PD, early attempts to administer serotonergic agents to treat motor symptoms of PD were generally unsuccessful.[17,18] This lack of effect may relate to multiple subtypes of 5-HT receptor mediating opposing actions. For instance, in the normal, non-parkinsonian brain, 5-HT generally facilitates dopaminergic release via a variety of 5-HT receptors, for example 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_3, and 5-HT_4, whereas 5-HT_{2C} receptors tend to inhibit dopamine release.[19] In the dopamine-depleted parkinsonian brain, as well as in the brain following long-term L-dopa use and the development of dyskinesia (LID), the effects of 5-HT on remaining dopamine release are unclear and may depend on the subtype of 5-HT receptor targeted and the animal model of PD used (see later).

In addition to dopamine, 5-HT also modulates the actions of other neurotransmitters, including GABA and glutamate, as well as providing feedback mechanisms on 5-HT neurotransmission itself via an action in the DRN.[20] Given the extensive loss of dopamine in PD, it is likely that the effects of 5-HT are to modulate non-dopaminergic neurotransmission. Both GABA and glutamate are involved in the basal ganglia circuitry in PD and following the development of LID.[21–23] The subtypes of 5-HT receptor that may mediate such actions are unclear as, to date, there are limited studies investigating changes in specific 5-HT subtypes in PD and LID. Many of the studies performed used older, nonselective 5-HT agents with limited clinical data on concomitant medication use, presence of LID, or comorbidities such as depression or anxiety. As such, interpretation is limited. In addition, animal models of PD, although providing some information regarding possible changes in 5-HT receptors following parkinsonism and long-term L-dopa use, need to be interpreted with caution. Thus, the unilateral 6-OHDA-lesioned rat exhibits compensatory serotonergic hyperinnervation of the striatum,[24] an effect not reported in human PD to date. The 6-OHDA-lesioned model may therefore not be predictive of 5-HT receptor changes in PD. The 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned primate may provide a more valuable model as MPTP can deplete 5-HT in the striatum as well as in the cingulate and frontal cortex,[25,26] though this is not consistent across all groups or implementaions.[27]

Drugs Targeting 5-HT Receptors in the Treatment of Motor Symptoms in PD

Selective serotonergic drugs that target specific receptors have not been studied in the treatment of the motor symptoms of PD, probably because of earlier failures. In addition, case studies have suggested that enhancing 5-HT levels with selective serotonin reuptake inhibitors (SSRIs) can potentially worsen PD,[28,29] although epidemiological studies have not suggested any increased risk of worsening PD when SSRIs have been prescribed for depression.[30] Thus, current means of influencing 5-HT mediated neurotransmission in the treatment of motor symptoms in PD comes from use of dopamine agonists, many of which also have 5-HT binding properties, or with nonselective 5-HT agents used specifically for treatment of PD tremor.

5-HT Binding Properties of Dopamine Receptor Agonists: A Possible Factor in Variable Efficacy and Side-Effect Profile?

The different pharmacological profiles, in terms of 5-HT receptor affinity, of dopamine agonists (DAs) may account for potential side-effects and/or variable efficacy. Thus, the ergoline DAs apomorphine, pergolide, bromocriptine, cabergoline, and lisuride bind to several 5-HT receptors, including 5HT_{1A}, 5-HT_{1D}, 5-HT_{2A}, and 5-HT_{2B} receptors, while the nonergoline agonists ropinirole and pramipexole have a more selec-

TABLE 1. *Relative affinity of clinically available dopamine receptor agonists for 5-HT receptors*

Dopamine agonist		5-HT_{1A}	5-HT_{1B}	5-HT_{1D}	5-HT_{2A}	5-HT_{2B}	5-HT_{2C}
Non ergoline	Ropinirole	+	0/+	+	0/+	0/+	0/+
	Pramipexole	+	0/+	+	0/+	0/+	0/+
Ergoline	Apomorphine	+	+	+	+	+	+
	Cabergoline	+	+	++	++	++	+
	Pergolide	++	+	+	+	++	+
	Bromocriptine	++	+	++	+	+	+
	Lisuride	+++	+	+++	++	−−	++

+ = agonist; − = antagonist; 0 = no activity; 0/+ = low activity; + to ++++ = increased potency (adapted from ref. 31).

tive affinity for 5-HT_{1A} receptors[31] (Table 1). To date, the most well-defined clinical effect related to this 5-HT binding property is the 5-HT_{2B}-agonist action of some ergoline DAs that has been linked to the potentially serious but rare problem of restrictive cardiac valulopathy.[32,33] Lisuride is a 5-HT_{2B} antagonist and, as such, has not been reported to cause this problem.[34] 5-HT_{2B} receptors are located on cardiac valves, and their stimulation results in fibroblast mitogenesis.[35] Pleuropulmonary and retroperitoneal fibrosis have also been reported to be caused by 5-HT_{2B}, and possibly 5-HT_{2A}, receptor binding activity.[36,37]

Clinical experience would suggest that ergoline DAs, particularly lisuride, induce more psychiatric side-effects than nonergoline DAs, although this has not been shown in randomized clinical trials (RCTs). Such findings may be related to greater 5-HT binding of ergoline versus nonergoline DAs (Table 1). However, some studies have reported impulse control disorders, in particular pathological gambling, in patients with PD associated with nonergoline DAs such as pramipexole.[38,39] In contrast, other studies have not shown any specific association with a particular DA or dose of DA.[40–42] These findings may reflect prescribing habits rather than true effects of receptor binding selectivity.[43]

Several systematic reviews have been published and report similar clinical benefits, or risk of inducing dyskinesia, with all DAs,[44–46] although few head-to-head studies have been performed. Studies comparing bromocriptine with ropinirole or pramipexole have shown no significant differences in efficacy.[47] Thus, despite the potential difference in binding at 5-HT receptors implicated in motor function and LID, no clinically relevant differences have so far emerged between the DAs. However, future development of new DAs may need to take into account 5-HT binding potential as it becomes clearer that these receptors may have a role in LID and psychiatric disorders in PD (see later).

5-HT Drugs in the Treatment of Parkinsonian Tremor

One motor feature of PD that may be mediated in part by 5-HT is tremor. Clinical observations suggest tremor in PD is less responsive to dopaminergic drugs than rigidity and bradykinesia. A PET study in advanced patients with PD showed a 27% reduction in midbrain raphe 5-HT_{1A} binding potential compared with healthy controls, a change that correlated with tremor but not with bradykinesia or rigidity.[48] Early loss of 5-HT transporter binding was also noted in the thalamus in drug naïve patients with PD with tremor compared with those without; however, after 17 months follow-up, this difference was not significant.[49] Mirtazapine, an antidepressant with multiple mechanisms of actions, including 5-HT_{1A} agonist and 5-HT_2 and 5-HT_3 antagonist actions, can reduce parkinsonian tremors[50] (Table 2). In addition, the atypical antipsychotic clozapine, which binds to 5-$HT_{2A/2C}$ receptors, also suppresses tremor.[51] The mechanism of action or subtype of 5-HT receptor mediating an anti-tremor effect is unknown. However, in a proposed model of PD tremor, tacrine-induced tremulous jaw movements in rodents, 5-HT_{2A} antagonists reduce tremor via a selective action in the SNr.[52]

Drugs Targeting 5-HT Receptors in the Treatment of L-dopa -Induced Dyskinesia

While 5-HT drugs have generally not shown promise as treatment for the motor symptoms of PD, several 5-HT receptors have been implicated in LID (Table 2).

5-HT_{1A} Receptor Agonists Reduce Dyskinesia but may Worsen PD Motor Symptoms

5-HT_{1A} receptors are principally located as autoreceptors on the cell bodies of the DRN, where they inhibit cell firing. Lower levels are located postsynaptically within the striatum and subthalamic nucleus.[53] In

TABLE 2. *Serotonergic drugs evaluated for motor symptoms and levodopa-induced dyskinesia in PD*

Drug	5-HT subtype	Effective on PD motor symptoms	Effective on levodopa-induced dyskinesia	Comments
Mirtazapine	5-HT_{1A} agonist; 5-HT_2, 5-HT_3 antagonist	Reduces PD tremor	Yes	Mirtazapine also binds to non 5-HT receptors including acetylcholine and noradrenaline
Clozapine	5-$HT_{2A/2C}$ receptor antagonist	Reduces tremor; no worsening of PD	Yes	Practical issues with regulatory monitoring
Quetiapine	5-$HT_{2A/2C}$ receptor antagonist	At low doses (25–50 mg) no adverse effects seen	No	No studies have been preformed using higher doses of quetiapine (>50mg/d)
Buspirone	5-HT_{1A} agonist	No worsening	Possible	Single trial in 10 patients with PD
Sarizotan	5-HT_{1A} agonist	Potential to worsen parkinsonism	Non significant compared to placebo	Sarizotan also has dopamine D2 antagonist binding. Large placebo effect (development has now stopped)
Pimavanserin	5-HT_{2A} inverse agonist	Unknown	Possible	Preliminary reports to date; on going study

the untreated MPTP-lesioned primate model of PD, 5-HT_{1A} receptors are upregulated in the putamen.[54] Postmortem studies in patients with PD have shown either no change[55] or increased 5-HT_{1A} receptors in the neocortex compared with age-matched controls.[56] Thus, these studies suggest a possible compensatory increase in 5-HT_{1A} receptors in PD; however, the changes that may occur with development of LID are unclear.

Some studies suggest that the relatively intact serotonergic input to the basal ganglia in PD is the site of conversion of L-dopa to dopamine; dopamine is then released from 5-HT neurons as a false neurotransmitter.[57–59] However, because this is a non-physiological mechanism of dopamine release, the resulting abnormal activation of striatal dopamine receptors may be partly responsible for LID.[60] Indeed, reducing serotonergic activation can reduce dopamine release in the striatum.[61] In the 6-OHDA-lesioned rat, the 5-HT_{1A} agonist R-(+)-8-OH-DPAT when administered with L-dopa reduces extracellular dopamine levels.[62] Thus, activation of presynaptic 5-HT_{1A} receptors in the DRN with 5-HT_{1A} agonists may reduce firing of this raphe-striatal input, thereby reducing LID. This action, however, may also result in worsening of parkinsonism—an effect seen when some 5-HT_{1A} agonists are administered with L-dopa (see below). Nevertheless, this cannot provide a complete explanation as identical effects on LID and worsening parkinsonism can occur when R-(+)-8-OH-DPAT is administered with the direct postsynaptic dopamine $D_{2/3}$ agonist pramipexole.[63] Recent evidence has also implicated 5-HT in the development of "runaway dyskinesias," which may occur in patients with PD following transplanted fetal ventral mesencephalic (FVM) tissue because of the presence of serotonergic neurons in grafted tissue. Thus, using FVM in 6-OHDA-lesioned rats, worse LID developed in serotonin-rich grafts than in dopamine-rich grafts—an effect that correlated with the degree of dopaminergic degeneration.[64]

Other potential areas where 5-HT_{1A} agonists may reduce LID include postsynaptic 5-HT_{1A} receptor stimulation and reduced glutamate activity. Thus, intracortical injection of the presumptive 5-HT_{1A} agonist sarizotan reduces cortical and striatal glutamate levels in rodents, an effect blocked by selective 5-HT_{1A} antagonists.[65] In normal, awake monkeys, 5-HT, acting via 5-HT_{1A} receptors, suppresses pallidal bursting activity via glutamatergic mechanisms.[66] The effects, however, occur within both medial and lateral pallidal segments, and thus, depending on site of action, could potentially both reduce LID and worsen PD motor function.

Preclinical studies using 5-HT_{1A} agonists have shown potential promise as antidyskinetic drugs but also have the potential to worsen parkinsonism. Thus, the selective 5-HT_{1A} agonist R-(+)-8-OH-DPAT or the partial 5-HT_{1A} agonist buspirone reduces LID in the 6-OHDA-lesioned rat.[60,67–69] R-(+)-8-OH-DPAT also reduced LID by 50% in MPTP-lesioned primates; however, this was accompanied by a worsening of parkinsonian motor scores.[63] The serotonergic drug "ecstasy" (3,4-methylenedioxymethamphetamine, MDMA) reduced LID in the 6-OHDA-lesioned rat—an effect blocked by pretreatment with a 5-HT_{1A} antagonist.[70] MDMA also reduced LID in the MPTP-lesioned primate, with no detrimental effect on parkinsonism.[71] Sarizotan reduced LID by >90% in the MPTP-primate; an effect blocked by the selective 5-HT_{1A} antagonist WAY100635, also suggesting the responses were mediated via the 5-HT_{1A} receptor.[72]

In clinical studies, the nonselective 5-HT_{1A} agonist buspirone (20 mg/d) reduced LID without worsening

parkinsonian disability in 10 patients with PD,[73] while the antidepressant mirtazapine also reduced LID without worsening parkinsonism.[74,75] Sarizotan has been assessed as a potential treatment for LID, and in an initial Phase IIa study, sarizotan (10 mg) reduced LID by 40% without affecting antiparkinsonian action.[76] In an open label study in 64 patients with PD, sarizotan (20 mg) also reduced LID, measured using diaries as percentage on time with dyskinesia, but worsened parkinsonism requiring dose reduction in more than half of study patients.[77] Three larger RCT trials of sarizotan have been conducted. One study, using 2, 4, and 10 mg/d (n = 398), failed to demonstrate any significant change in dyskinesia scores compared with placebo, and higher doses were associated with increased off time.[78] Two studies using sarizotan 2 mg (PADDY-1, n = 504 and PADDY-2, n = 403), demonstrated no significant improvement in LID compared with placebo.[79] These studies suggest that either 5-HT_{1A} agonists have to be used at a critical dose because of the potential to reduce dopamine release (as discussed above), or in the case of sarizotan, the worsening of PD may relate to actions at non-5-HT receptors as sarizotan is also a dopamine D_2/D_3 receptor antagonist.[80]

5-HT_{1B} Receptor Agonists have Potential to Reduce Dyskinesia, but No Clinical Studies have been Performed

5-HT_{1B} receptors are selectively located on the terminals of 5-HT neurons in the striatum and on GABAergic striatopallidal output neurons in the SNr and globus pallidus, suggesting a potential role in modulating the activity of these pathways and in motor function in PD.[81,82] 5-HT_{1B} knockout mice exhibit hyperactivity, suggesting a role in movement.[83] A single postmortem study demonstrated no change in 5-HT_{1B} receptor levels within the stratum and substantia nigra in six patients with PD compared with age-matched controls.[84] In the 6-OHDA-lesioned rat, repeated L-dopa treatment results in an increase in 5-HT_{1B} receptors and an associated adaptor protein p11 on the direct D1-mediated direct striatonigral pathway, suggesting a role of 5-HT_{1B} receptors in LID.[85]

5-HT_{1B} agonists have potential to reduce LID via several mechanisms. Thus, stimulation of 5-HT_{1B} receptors within the striatum can reduce 5-HT release,[86] which may reduce L-dopa metabolism to dopamine, and hence reduce dopamine release in a way similar to 5-HT_{1A} agonist actions.[60] In addition, stimulation of 5-HT_{1B} receptors in the SNr[87] and globus pallidus suppresses GABA release,[66,88] effects that may reduce inhibition of the basal ganglia output regions (SNr and GPm) and improve LID. Preclinical studies using the 6-OHDA-lesioned rat have shown a reduction in LID with a selective 5-HT_{1B} agonist, CP-94253.[60,85] In the MPTP-primate, the nonselective 5-$HT_{1B/1D}$ agonist SKF-99101 reduced LID but with a worsening of parkinsonian disability.[89] The antidyskinetic action of MDMA can also be blocked by 5-HT_{1B} antagonists.[63] Thus, 5-HT_{1B} agonists have potential as antidyskinetic agents, but no clinical trials have yet evaluated selective 5-HT_{1B} agonists in PD. A recent study has also demonstrated the potential synergistic effect of subthreshold doses of combined 5-HT_{1A} agonist and 5-HT_{1B} agonist to reduce LID in the MPTP-primate without affecting the antiparkinsonian action.[90]

Mixed 5-$HT_{2A/2C}$ Receptor Antagonists may Reduce Dyskinesia Without Worsening PD Motor Symptoms

5-HT_{2A} receptors are the most widely distributed subtype in the brain, found in the cortex, basal ganglia, and claustrum. In PD, a single study showed an increase in 5-HT_{2A} receptors in the neocortex but no clinical correlation to presence of LID.[56] In the 6-OHDA-lesioned rat, 5-HT_{2A} mRNA is increased in the striatum but not in the cortex or the subthalamic nucleus,[24,91] an effect reversed by L-dopa.[92] This suggests 5-HT_{2A} receptors are modulated by nigrostriatal dopamine, but the exact mechanism in LID remains unclear. In preclinical studies, a selective 5-HT_{2A} receptor antagonist, M100907, failed to reduce LID but reduced dyskinesia induced by a dopamine D_1 agonist.[93] In the MPTP-lesioned primate, methysergide, a nonselective 5-HT_2 antagonist, reduced LID but with adverse effects on parkinsonism.[94] ACP-103 (pimavanserin), a selective 5-HT_{2A} inverse agonist, was recently demonstrated to reduce LID by 36% in the MPTP-primate without worsening motor scores.[95]

The atypical antipsychotic drugs clozapine and quetiapine have mixed 5-$HT_{2A/2C}$ antagonist properties, as well as dopamine D_2 antagonist properties.[96] Both drugs reduce LID in the MPTP-primate.[97–99] One potential mechanism whereby clozapine and quetiapine can reduce LID without worsening parkinsonism may relate to 5-HT_{2C} receptor antagonism. Thus, 5-HT_{2C} receptors are selectively located within the SNr and GPm.[100] 5-HT via 5-HT_{2C} receptors is excitatory in the SNr,[92,101,102] which may contribute to the increased activity of these regions in PD. Systemic administration of selective 5-HT_{2C} antagonists to 6-OHDA-lesioned rodents potentiates the antiparkinsonian action

of dopamine D_1 and D_2 agonists,[103,104] which is an action mediated via 5-HT_{2C} receptors in the SNr.[103] Thus, 5-HT_{2C} receptor antagonists may improve parkinsonism, and drugs with HT_{2C} receptor antagonist action are unlikely to worsen PD.

Clinical studies with clozapine and quetiapine have shown mixed benefit in reducing LID in PD. Thus, low dose clozapine (mean dose 39 mg/d) reduced on-time with LID in a RCT in PD.[105] However, practical use of clozapine is difficult because of mandatory blood monitoring for the potential risk of agranulocytosis. A RCT of low dose quetiapine (mean dose 25 mg) had no effect on LID.[106] Pimavanserin, an inverse 5-HT_{2A} agonist, was reported as reducing in LID without worsening of parkinsonian symptoms in 12 patients with PD.[107]

SEROTONERGIC INVOLVEMENT IN DEPRESSION AND ANXIETY IN PD

There is inconsistent evidence for 5-HT involvement in PD depression and anxiety.

In PD, mood disturbances such as depression and anxiety are extremely common. Anxiety and depression have also been associated with an increased risk of later development of PD.[108,109] The pathophysiological mechanisms involved in mood disturbances in PD remain unclear, but serotonergic dysfunction has been postulated as such systems are involved in mood disorders in non-PD and the raphe nuclei, as well as hippocampus and prefrontal cortex, appear to be the primary sites affected.[110,111] Transcranial ultrasound studies have suggested an association with reduced brainstem raphe echogenicity and nigral hyperechogenicity in patients with depression preceding PD onset compared with nondepressed patients with PD.[112] Thus, depression prior to the onset of motor symptoms in PD may relate to early involvement of serotonin in the raphe nuclei. However, the parts of the raphe initially affected (Braak stage 2) are the lower raphe nuclei,[14] which project predominantly to the somatic nuclei of the brainstem and spinal cord, rather than the rostral group, which ascends to the forebrain and is more likely implicated in mood. The rostral group, including the DRN, only becomes affected in Braak stage 3, when Lewy body pathology appears in the substantia nigra pars compacta and motor symptoms occur.[14] Moreover, a PET study in five early patients with PD showed no change in serotonin transporter binding in the medulla compared with 8 age-matched controls.[12] Thus, the cause of early depression and anxiety in presymptomatic PD is unclear.

As the disease progresses, Lewy bodies occur within the rostral raphe, thalamus, and limbic and cortical regions,[113] which may result in the mediating of mood disturbance in advanced PD. However, direct evidence of a selective disturbance of serotonergic neurotransmission linked to depression or anxiety in advanced PD is lacking because of limited clinicopathological studies.[16,114] Postmortem evidence has shown a lower density of neurons in the DRN in depressed versus nondepressed patients with PD,[16] and CSF measurements in vivo have shown reduced serotonin metabolite (5-HIAA) levels in depressed patients with PD.[115] In contrast, imaging studies have found no evidence for disruption of the brainstem raphe serotonin system (reduced [^{123}I]β-CIT SPECT uptake in the dorsal midbrain) in patients with PD with and without depression.[116] A [^{11}C]-DASB PET study in seven patients with PD with untreated depression showed elevated serotonin transporter binding in the prefrontal cortex compared with non-PD age-matched controls.[117] In an acute tryptophan depletion study performed in patients with PD with depression, no effect on mood was found, which contrasts with the classical mood lowering effects of acute tryptophan depletion seen in patients with non-PD at risk of depression and suggests that serotonin might contribute less to PD depression.[118] The phenomenology of depression in PD is also different from that in patients with non-PD with less anhedonia and feelings of guilt.[119] Many patients with PD may also experience depression, even on adequate doses of antidepressant therapy,[120] again suggesting the pathophysiology of depression in PD may be different from that in patients with non-PD and questioning the role of 5-HT.

Treatment of Depression and Anxiety in PD Involves SSRIs and TCAs

Despite the lack of direct evidence of 5-HT involvement, the current management of depression and anxiety in PD involves use of SSRIs, mixed serotonin and noradrenergic re-uptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs). The subtypes of 5-HT receptor implicated in mood in non-PD include 5-HT_{1A} receptors in the raphe nuclei[121] and postsynaptic 5-HT_{1A} and 5-HT_{2A} receptors in limbic and cortical regions.[122] Other subtypes, such as 5-HT_3, 5-ht_6, and 5-HT_7, may be involved, although the evidence is less clear.[123] Most antidepressants in current use enhance serotonergic neurotransmission by inhibiting 5-HT reuptake and by indirectly affecting these postsynaptic 5-HT receptors. Indeed, the ability to affect multiple

5-HT receptors appears to be an important factor in the efficacy of antidepressants as, to date, agents that target a single receptor, for example selective 5-HT_{1A} agonists, appear less effective than SSRIs or TCAs that indirectly target multiple 5-HT receptors.[124]

The true efficacy of these antidepressants in PD, however, is unclear as there have been limited RCTs and many have used low, possibly subtherapeutic doses of antidepressants with short-term follow-up.[120,125] The latter may be due to the perceived risk of worsening parkinsonism with SSRIs that has been reported (see earlier), although in practice the risk is very small. In addition, the potential side-effects of TCAs, such as postural hypotension and sedation, may also limit adequate dosing, so the potential to improve depression in patients with PD may not be fully evaluated. Serotonin syndrome, consisting of confusion, agitation, or hypomania with fever, myoclonus, tremor, and diaphoresis and which occurs due to increased 5-HT_{1A} stimulation,[126] is also a perceived risk of cotreatment of patients with PD with antidepressants and monoamine oxidase B (MAO-B) inhibitors. The manufacturers of available MAO-B inhibitors advise against concomitant use because of the potential risk of the serotonin syndrome. While the syndrome has been described when serotonergic drugs such as SSRIs, TCAs, and tryptophan are combined with nonspecific MAO inhibitors,[127] in patients with PD, serotonin syndrome is extremely rare because of the selective MAO B-inhibition properties of selegiline and rasagiline. In one retrospective series of 4,568 patients with PD on both selegiline and an antidepressant, only 11 patients (0.24%) experienced symptoms suggestive of the serotonin syndrome, and in nine, these were mild.[128] In the recent RCT of early versus delayed use of rasagiline in 1,176 early patients with PD, 17% were on antidepressants, and there were no reports of serotonin syndrome.[129]

SEROTONERGIC INVOLVEMENT IN PSYCHOSIS IN PD

Psychotic symptoms in PD can be a major cause of morbidity. Patients with PD frequently describe well-formed, complex visual hallucinations (VH), that may be chronic and nonbothersome but can often become frightening; some may develop paranoid delusions and frank psychosis.[130] The cause of these symptoms is probably the interplay between pathological processes and an effect of PD medications, as VH are most often associated with cognitive decline and more advanced disease. The effects of serotonergic drugs such as LSD have led to suggestions that 5-HT may be involved in psychotic symptoms in other disorders such as schizophrenia.[131–134] In PD, postmortem studies have suggested a relative preservation of $5HT_2$ receptors in the temporal cortex in patients with PD with VH compared with patients without.[135] Thus, abnormalities in $5HT_2$ receptor neurotransmission may be involved in the neural mechanisms underlying VH and psychosis associated with PD.

Treatment of Psychosis in PD with 5-$HT_{2A/2C}$ Antagonists

The atypical antipsychotic clozapine is currently the most effective treatment for psychotic symptoms in PD because of both a benefit in reducing symptoms as well as lack of worsening parkinsonism.[136,137] This benefit occurs at much lower doses than are used to treat schizophrenia, typically 50 mg. At low doses, clozapine has a higher affinity for 5-HT_{2A} than for dopamine D_2 receptors, suggesting the effect on psychosis in PD is mediated via 5-HT_{2A} receptors.[96] Low doses of quetiapine (40 mg/d[138] and 62.5 mg),[139] when assessed in open label studies, also improved psychosis without worsening motor symptoms, although some patients with PD with dementia experienced worsening motor scores.[140,141] However, RCTs failed to demonstrate a significant effect of quetiapine compared with placebo, even up to doses of 200 mg/day.[142–144] This apparent lack of benefit in RCTs compared with open label studies may be due to small numbers of patients, larger than expected improvement in the placebo groups, and the fluctuating nature of VH and psychosis in PD. To date, there are no purely selective 5-HT_{2A} antagonists in clinical use. An open label study with the nonselective 5-HT_2 antagonist mianserin suggested an improvement in VH in 10 patients with PD, with no effect on PD. A RCT study using the inverse 5-HT_{2A} agonist pimavanserin in psychosis in PD is ongoing, and preliminary reports from a Phase II study in 60 patients with PD reported a trend towards improvement in psychosis without affecting PD motor scores.[145]

SEROTONINERGIC INVOLVEMENT IN GASTROINTESTINAL FUNCTION IN PARKINSON'S DISEASE

5-HT receptors located in the peripheral nervous system may also play a role in PD. Constipation is a frequent complication of PD that is principally due to reduced gastrointestinal (GI) motility. The cause is thought to be loss of parasympathetic innervation of

the GI tract from the dorsal motor nucleus of the vagus.[146–148] Treatment is usually directed at nonspecific stool softeners which generally have variable efficacy. 5-HT_4 receptors are located in the GI tract and can trigger acetycholine release, an action that enhances gastric and colonic motility.[149] Thus, 5-HT_4 agonists may be a potential treatment for constipation in PD. Mosapride, a 5-HT_4 agonist, demonstrated increased colonic motility and improved constipation in an open label study in seven patients with PD.[150] Tegaserod, another 5-HT_4 agonist, had a mild benefit in a small RCT in 15 patients with PD.[151] (However, tegaserod has now been withdrawn because of safety issues related to ischemic colitis and cardiovascular disease). Both agents can cross the blood brain barrier, but neither study reported any adverse effects on PD motor symptoms.

CONCLUSIONS

Serotonergic dysfunction appears to play a role in a number of parkinsonian symptoms, including motor function, L-dopa -induced dyskinesia, mood, psychosis, and constipation. To date, the exact mechanisms remain unclear because of a lack of clinicopathological and in vivo studies. However, future studies are promising given the emerging availability of selective 5-HT receptor ligands.

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