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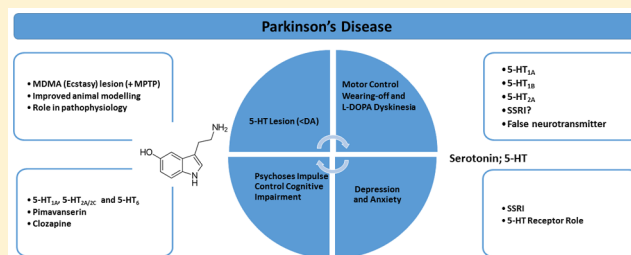
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## Serotonergic Approaches in Parkinson's Disease: Translational Perspectives, an Update

Philippe Huot,<sup>†,‡,§,||</sup> Véronique Sgambato-Faure,<sup>⊥,#</sup> Susan H. Fox,<sup>∇</sup> and Andrew C. McCreary<sup>\*,○,□</sup><sup>†</sup>Centre de Recherche du Centre Hospitalier de l'Université de Montréal, Montreal, QC H2X 0A9, Canada<sup>‡</sup>Department of Pharmacology, Université de Montréal, Montreal, QC H3T 1J4, Canada<sup>§</sup>Unité des Troubles du Mouvement André Barbeau, Centre Hospitalier de l'Université de Montréal, Montreal, QC H2L 4M1, Canada<sup>||</sup>Division of Neurology, Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada<sup>⊥</sup>Institute of Cognitive Neuroscience Marc Jeannerod, UMR 5229 CNRS, 69 675 Cedex Bron, France<sup>#</sup>University Lyon 1, 69100 Villeurbanne, France<sup>∇</sup>Movement Disorder Clinic, Toronto Western Hospital, University of Toronto, Toronto, ON M5T2S8, Canada<sup>○</sup>Janssen Vaccines & Prevention B.V., Archimedesweg 4, 2333 CN Leiden, The Netherlands

**ABSTRACT:** Parkinson's disease (PD) has long been seen as a disorder caused by degeneration of the dopaminergic system, leading to the classic motor manifestations of the disease. However, there is now overwhelming evidence that PD is more than a disease merely caused by dopamine depletion. It is well-known that a myriad of other neurotransmitters are affected by the disease process. One such neurotransmitter is serotonin (5-HT). 5-HT has been shown to play a role in several motor and nonmotor manifestations of PD, including tremor, cognition, depression and psychosis. 5-HT also seems to play a critical role in L-3,4-dihydroxyphenylalanine (L-DOPA)-induced dyskinesia. A breadth of preclinical studies and clinical trials have been conducted that aimed at modulating the 5-HT system in order to alleviate depression, cognitive deficits, psychosis, and dyskinesia. In this Review, we summarize recent advances in the 5-HT field in PD, but with a translational emphasis. We start by presenting a novel nonhuman primate model of PD that presents with dual dopamine and 5-HT lesions. We then present preclinical and clinical data that introduce new concepts, such as the use of biased and partial agonists, as well as molecules recently introduced to the field of PD, such as eltoprazine, pimavanserin, nelotanserin, and SYN-120, to enhance therapeutic benefit while minimizing adverse events, notably on parkinsonian disability.

**KEYWORDS:** 5-HT, Parkinson's disease, clinical, animal models, dyskinesia



## INTRODUCTION

Parkinson's disease (PD) has long been regarded as a disease where dopamine-producing neurons originating in the substantia nigra pars compacta (SNc) degenerate. This leads to reduced dopamine (DA) levels within the striatum, which translates to the clinical presentation of the classic, or cardinal, features of bradykinesia, rigidity, and resting tremor.<sup>1</sup> However, degeneration of other brain areas appears key to the expression and modulation of different symptoms and treatment-related side-effects.<sup>2</sup> Therefore, there are key circuitry and neurochemical changes beyond nigrostriatal dopaminergic deficits, including the cholinergic, cannabinoid, opioid, and glutamatergic systems,<sup>3–6</sup> as well as the serotonin (5-hydroxytryptamine, 5-HT) system.<sup>7,8</sup> This altered neurochemical profile is critical to the pathophysiology of the disease and may be involved not only in motor effects, but also in treatment-related side effects, as well as neuropsychiatric and cognitive complications.

Although the 5-HT system consists of at least 14 receptors and a 5-HT-specific transporter (SERT),<sup>9</sup> most of the studies conducted in PD patients and animal models have focused on 5-HT 1A (5-HT<sub>1A</sub>) and 2A (5-HT<sub>2A</sub>) receptors, as well as on SERT. Thus, in vivo imaging and postmortem studies demonstrated involvement of 5-HT<sub>2A</sub> receptors from the infero-lateral temporal cortex in visual hallucinations (VHs),<sup>10,11</sup> while a postmortem study found a possible permissive role of 5-HT<sub>1A</sub> receptors in VHs.<sup>12</sup> Positron emission tomography (PET) studies suggested that the SERT is upregulated in the frontal cortex of depressed PD patients,<sup>13</sup> while 5-HT<sub>1A</sub> receptors are downregulated in the hippocampus and the temporal, cingulate, and orbito-frontal cortices.<sup>14</sup> More

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recently, altered SERT levels were documented in the cingulate cortex of apathetic PD patients.<sup>15</sup> In addition to this involvement in nonmotor manifestations of PD, studies conducted in animal models and patients have provided evidence of a role of the 5-HT system in motor complications, notably L-3,4-dihydroxyphenylalanine (L-DOPA)-induced dyskinesia (LID). Thus, studies conducted in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned nonhuman primate (NHP) have demonstrated increased 5-HT<sub>2A</sub><sup>16,17</sup> and 5-HT<sub>1A</sub><sup>18</sup> receptors within the striatum and the motor cortex. Moreover, changes in serotonergic fibers have been suggested to be involved in LID and the neuropsychiatric symptoms of PD, along with neuritic morphological changes in the striatum and globus pallidus.<sup>19,20</sup>

There is therefore a wealth of data, both preclinical and clinical, that indicates an involvement of the 5-HT system, particularly 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors, in nonmotor manifestations of PD and treatment-related motor complications. As such, several preclinical and clinical studies have assessed the therapeutic potential of drugs acting on 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors.

Here, we review recent literature on 5-HT and more particularly the role that certain 5-HT receptors might play in the pathogenesis and treatment options for PD. We start by presenting ways in which one might improve NHP modeling of PD by inducing lesions of both the dopamine and 5-HT systems, as seen in the disease, and discuss how this new model could be used to study nonmotor manifestations of the disease. We then present data from preclinical studies and clinical trials where the 5-HT system was modulated, mostly through stimulation of 5-HT<sub>1A</sub> receptors and blockade of 5-HT<sub>2A</sub> receptors, to alleviate psychosis, anxiety and LID. We also discuss hurdles that have impaired the clinical development of serotonergic drugs, as well as ways to circumvent these potential obstacles by the use of novel highly selective drugs.

## ■ A NOVEL NONHUMAN PRIMATE MODEL OF PARKINSON'S DISEASE

NHP models of PD have, until recently, been based on the destruction of nigrostriatal dopaminergic neurons using the neurotoxin MPTP.<sup>21</sup> This toxin can be administered via a variety of systemic routes (intramuscularly, intravenously, intraperitoneally or, more rarely, intracarotid, to induce a hemi-Parkinsonian phenotype). MPTP readily crosses the blood-brain barrier and is transformed to MPDP<sup>+</sup> (1-methyl-4-phenyl-2,3-dihydropyridinium), via monoamine oxidase B (MAO-B), which gives rise to MPP<sup>+</sup> (1-methyl-4-phenylpyridinium) in 5-HT neurons and glial cells.<sup>22–25</sup> MPP<sup>+</sup> is released into the synaptic space before being taken up into dopaminergic neurons following binding to neuromelanin<sup>26</sup> or dopamine transporter and subsequent internalization.<sup>27</sup> Once within dopaminergic neurons, a chain of neurotoxic events leads to either cell death or quiescence, by a variety of mechanisms such as mitochondrial complex-1 inhibition with failure to produce ATP, oxidative stress, lipid and protein peroxidation, ultimately causing DNA damage. Dopaminergic neurons are thought to die via both apoptotic and necrotic mechanisms.<sup>28</sup>

A variety of different MPTP administration protocols have been described and are used routinely (i.e., the so-called acute, chronic, and subchronic models), and vary considerably between different primate species.<sup>29–32</sup> The acute treatment model consists of high dose of MPTP administration over a few

days, which leads to a rapid and severe dopaminergic loss.<sup>33–35</sup> Chronic administration protocols with lower MPTP doses are used to obtain a more progressive degeneration of dopaminergic neurons over time, perhaps better recapitulating the human disease.<sup>32,36–43</sup> Finally, subchronic protocols are often used to overcome time constraints.<sup>44,45</sup> Generally, the symptoms, or phenotypes, can vary depending on the species (e.g., marmosets, squirrel monkeys, baboons, macaques, or vervet monkeys) and treatment regime used. Notwithstanding the species, MPTP-induced parkinsonism in the NHP is characterized by bradykinesia, rigidity and a slumped body posture with episodic freezing, with occasional resting tremor.<sup>36–38</sup> In order to evaluate the severity of motor symptoms, different scales have been developed, e.g., eight scales in the macaque.<sup>46–53</sup> These scales gather different behavioral components, encompassing bradykinesia, posture, and tremor. Interestingly, as seen in idiopathic PD, MPTP-lesioned NHPs may also have cognitive impairment, e.g., visuospatial and planning or strategy deficits.<sup>39,41,54,55</sup>

There are many differences between the MPTP-lesioned NHP models and idiopathic PD. For instance, unlike the disease, some recovery from the motor symptoms after MPTP injections can be seen following the cessation of MPTP-treatment.<sup>56,57</sup> However, this may depend on lesion severity<sup>19,58</sup> and the NHP species (e.g., marmosets and squirrel monkeys may recover).<sup>35,59,60</sup> In the macaque, using progressive or acute MPTP administration paradigms, animals may present with transient or persistent motor symptoms, and may therefore be divided into recovered (MPTP-recovered) and symptomatic (MPTP-symptomatic) monkeys.<sup>19,42</sup> There is a clear link between symptomatology severity and dopaminergic loss.<sup>19,45,58</sup> This can be detected using a variety of techniques, such as, but not limited to, PET imaging using [<sup>18</sup>F]-DOPA or [<sup>11</sup>C]-PE2I as dopaminergic radioligands or by using postmortem immunohistochemistry staining for tyrosine hydroxylase-like immunoreactivity. While there are clear advantages of using MPTP-lesioned NHPs, e.g., reproducing the motor symptoms of dopamine depletion, they are also particularly appropriate to study the role of other neurotransmitters in the development of motor symptoms. Furthermore, MPTP-lesioned NHPs represent excellent models for studying the therapeutic effects of various drug classes, notably dopaminomimetic strategies. However, as stated earlier, MPTP-lesioned NHP models also have some significant limitations insofar as they do not recapitulate the complete pathology encountered in the disease. Thus, no Lewy body pathology or  $\alpha$ -synuclein increases are seen, and the early involvement of brainstem nuclei or the (late) cortical involvement is absent. Extranigral pathologies have not received as much attention as nigrostriatal degeneration.<sup>61</sup> To improve the current models and more closely recapitulate the neuropharmacological profile of the human condition, a novel NHP model of PD was recently generated, that exhibits dual dopaminergic and serotonergic lesions, achieved by sequential administration of MPTP and 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy).<sup>19,62</sup> MDMA is an amphetamine derivative with high SERT affinity.<sup>63</sup> Acutely, it induces massive release of 5-HT by reversing the SERT gradient and depleting intracellular vesicular pools of 5-HT.<sup>64,65</sup> Upon chronic administration, MDMA triggers the decrease of serotonergic markers and lesions serotonergic terminals by formation of free radicals and resulting oxidative stress.<sup>66</sup> PET imaging using a SERT ligand, 4-[<sup>18</sup>F]-ADAM, demonstrated that MDMA

specifically binds to SERT in macaques.<sup>67</sup> The neurotoxic effects of MDMA on 5-HT have been described in the normal primate in several species, including the macaque,<sup>68–71</sup> using different approaches, such as immunohistochemistry<sup>69,72</sup> and autoradiographic binding.<sup>73</sup> MDMA, administered at a low dose (5 mg/kg) twice daily for four consecutive days, induced massive and stable (7 years) destruction of serotonergic terminals (while soma was spared) in the NHP.<sup>72</sup> In humans, diffusion-tensor imaging studies have shown that MDMA impacts axonal integrity, notably in the thalamus.<sup>74</sup> A recent PET study demonstrated that MDMA users have a strong decrease of [<sup>11</sup>]-DASB binding in cortical regions, rather than in basal ganglia and midbrain,<sup>75</sup> evidencing the specific susceptibility of certain (cortical) brain regions vs subcortical regions to MDMA, independently of their density of serotonergic or dopaminergic innervation. There is therefore compelling evidence suggesting that the administration of MDMA to primates can cause serotonergic pathology similar to that seen in PD.

Based on prior work, MDMA was administered to macaques previously lesioned with MPTP, using a protocol described by Ricaurte's group, i.e., 5 mg/kg twice daily for 4 days, and the effects of MDMA administration to MPTP-lesioned NHPs was then investigated, with behavioral and in vivo imaging approaches.<sup>19,62</sup> At the behavioral level, acute injections of MDMA induced pupillary dilation and hypoactivity associated with a slumped body posture and somnolence. Macaques also exhibited myoclonic jerks in the tail and feet. These behavioral manifestations stopped after cessation of MDMA injections. The neurotoxic effect of MDMA in MPTP-lesioned NHPs was assessed using PET 2–3 weeks after MDMA was discontinued. MDMA administration resulted in lower [<sup>11</sup>C]-DASB binding in all regions of interest, in both MPTP-symptomatic and MPTP-recovered monkeys. The neurotoxic effects of MDMA on 5-HT fibers were further assessed by examining postmortem tissues, which demonstrated strong decreases of staining of all serotonergic markers at both cortical and subcortical levels in double-lesioned macaques. MDMA had no impact on the 5-HT soma in the raphe nuclei or on the remaining dopaminergic neurons in the SNc. From a translational perspective, it is highly relevant and interesting to compare this dual dopamine-5-HT-lesioned NHP with the clinical situation. PD patients exhibit around 80% of dopamine cell loss in the SNc,<sup>76</sup> while severely lesioned NHPs present with a nigral loss of 80–90%. For the 5-HT somas, PD patients present a loss of 37% in the dorsal raphe,<sup>8</sup> while the loss in the MPTP-severely lesioned macaque could reach 25–30%.<sup>19,77</sup> PD patients have a decrease of 31% of the [<sup>11</sup>]-DASB in the whole brain,<sup>78</sup> suggesting a reduction of serotonergic inputs to the regions of interest, coupled with a specific decrease of 5-HT markers in the striatum of 50–60%.<sup>79</sup> In severely MPTP-lesioned NHPs, there appears to be a loss of 60% of the serotonergic fibers in the striatum.<sup>19</sup> This loss of 5-HT fibers was extended to other regions in both moderately- and severely lesioned MPTP NHPs following MDMA administration. In conclusion, MPTP is not totally selective for dopaminergic neurons, and a limitation of MDMA is the lack of 5-HT soma loss. However, there are several key advantages of combining the two agents, which allows the better modeling of the disease, with stronger and more homogeneous 5-HT lesion, but with the relative preservation of serotonergic vs dopaminergic terminals, allowing the role of the dopamine and/or 5-HT systems to be assessed in a systematic manner.

This MPTP-MDMA-lesioned NHP model has therefore been interrogated to provide key answers pertaining to outstanding questions relative to the dopaminergic and serotonergic systems in PD. With regards to the cardinal manifestations of PD, it appears that only rigidity was impacted, as MDMA administration did not exacerbate bradykinesia or tremor. In MPTP-lesioned NHPs, bradykinesia and rigidity predominate<sup>42,47,80</sup> and are underpinned by the key dopaminergic lesion. Importantly and interestingly, MDMA administration and subsequent 5-HT lesion abolished L-DOPA-induced dyskinesia,<sup>81</sup> which is consistent with data obtained in rodents and in humans regarding the deleterious role of 5-HT fibers to capture and transform L-DOPA to dopamine.<sup>82</sup> Last, but not least, in MPTP-recovered NHPs, the administration of L-DOPA triggered a behavioral hyperactivity resembling neuropsychiatric-like symptoms but these symptoms were reduced in animals that had received an MDMA lesion. The severity of these behavioral symptoms correlated with reduced [<sup>11</sup>]-DASB binding in the posterior ventral putamen and the external globus pallidus. Of note, the external globus pallidus is a brain area involved in compulsive grooming in both normal<sup>83,84</sup> and parkinsonian<sup>85,86</sup> NHPs. These findings reinforce the possibility that serotonergic fibers may play a deleterious role, not only in movement disorders, but also in neuropsychiatric complications often seen in PD. By using this novel dual MPTP-MDMA lesion model, it will be possible to investigate the contribution of the serotonergic system in the expression of nonmotor symptoms associated with the disease itself rather than to dopamine replacement therapy.<sup>19</sup> One important question that remains to be investigated is whether MPTP-recovered-MDMA double-lesioned macaques develop an apathetic-like or anxious-like state. Indeed, a prominent role of serotonergic degeneration has been shown recently in apathy, anxiety, and depression in de novo PD patients.<sup>15</sup> Another important possibility offered by this model is to reverse the order in which toxins are used (e.g., administering MDMA before MPTP), allowing the impact of an early and selective 5-HT lesion on the appearance and severity of the parkinsonian motor and nonmotor symptoms to be assessed. Therefore, this double-lesioned model opens important new preclinical research possibilities that will lead to novel therapeutic avenues.

## ■ THE 5-HT SYSTEM AS A THERAPEUTIC TARGET IN PD: PRECLINICAL STUDIES

**5-HT<sub>1A</sub> Receptor Modulation.** Serotonin, 5-HT<sub>1A</sub> receptors are located both somato-dendritically in the raphe nuclei and postsynaptically in terminal fields, such as the striatum and cortices (for detailed review, see ref 87). Generally, as nigrostriatal dopamine neurons are lost and the cardinal motor symptoms become unresponsive to dopamine agonists such as ropinirole and pramipexole, patients will need to be managed with the gold-standard therapy, L-DOPA. However, eventually there will be a loss of therapeutic window, coupled with an increase in LID. It seems that this latter phenomenon might be driven by the uptake of L-DOPA and subsequent release of synaptic dopamine from serotonergic neurons, which might cause a reduction in serotonergic neurotransmission via actions of DA at SERT.<sup>88</sup> This occurs in a highly uncontrolled manner due to the absence of negative feedback machinery for dopamine in this cell type. Therefore, the dopamine transporter and inhibitory dopamine D<sub>2</sub> and D<sub>3</sub> autoreceptors are absent, leading to continual and prolonged



dopamine release, which dramatically increases synaptic dopamine levels and drives LID. While L-DOPA sparing methods can be successful in reducing the latency to onset of LID, there are a lack of approved treatment strategies, with the exception of strategies linked to expensive deep-brain stimulation or nonpulsatile L-DOPA.<sup>89</sup> Arguably, however, some success has been seen using amantadine, although long-term efficacy and tolerability remain of concern.<sup>90</sup> Therefore, based on the serotonergic theory of LID, strategies that might serve to reduce serotonergic neurotransmission, and thereby indirectly dopaminergic neurotransmission by so-called “false neurotransmitter” release, could help reduce LID. In this respect, it is well-known that administration of 5-HT<sub>1A</sub> and 5-HT<sub>1B</sub> (5-HT<sub>1B</sub>) receptor agonists and SERT blockade can reduce serotonergic neurotransmission by either direct or indirect actions at somatodendritic, 5-HT<sub>1A</sub> autoreceptors and terminal 5-HT<sub>1B</sub> receptors, respectively. Therefore, compounds which possess such activity might be considered as potentially interesting candidates for treating these devastating side effects.<sup>87,91</sup> However, postsynaptic 5-HT<sub>1A</sub> receptors are more than probably involved (see further on).

In MPTP-lesioned marmosets primed with L-DOPA to elicit stable dyskinesia, there are profound changes in serotonergic neurites in the striatum and globus pallidus.<sup>20</sup> In the rat, stereotaxic application of a serotonergic neurotoxin, 5,7-dihydroxytryptamine, reduced the rodent analogue of dyskinesia, so-called Abnormal Involuntary Movements (or AIMs).<sup>91</sup> Therefore, strategies that reduce serotonergic neurotransmission should be capable of reducing LID; accordingly, 5-HT<sub>1A</sub> receptor agonists, such as buspirone, tandospirone, sarizotan and eltoprazine, have shown various degrees of clinical efficacy (see below; Table 1) to treat LID<sup>92–95</sup> and preclinical studies support this notion.

**Table 1. Key 5-HT<sub>1A</sub> Receptor Partial, Full, and Biased Agonists Which Have Demonstrated a Reduction of LID in Preclinical and Clinical Studies**

compd	type agonist	clinical evidence	ref, examples
buspirone	partial	yes	165, and others
eltoprazine	partial	yes	95, 98, 99, 101
sarizotan	full	yes	95, 112
tandospirone	full	yes	166
8-OHDPAT	full	no	107, 108, and others
F15,599	biased	no	116, 117
NLX112 (F13,640, befiradol)	full	no	122, 123
F13,714	biased	no	119

Sarizotan is a nonselective 5-HT<sub>1A</sub> receptor full agonist and dopamine D<sub>2</sub>, D<sub>3</sub>, and D<sub>4</sub> receptor antagonist.<sup>96,97</sup> Low dose sarizotan effectively alleviated L-DOPA-induced chorea in the MPTP-lesioned macaque without reducing the anti-parkinsonian benefit conferred by L-DOPA.<sup>98</sup> However, high dose sarizotan impaired L-DOPA anti-parkinsonian action.<sup>99</sup> Presently, however, it remains unclear whether the exacerbation of parkinsonism after administration of sarizotan was mediated through activation of 5-HT<sub>1A</sub> receptors, antagonism of dopamine receptors, or both. Rodent studies have also demonstrated that sarizotan reduces dyskinesia-like behavior. Therefore, repetitive jaw movements induced by the partial D<sub>1</sub> receptor (partial) agonist SKF-38,393, similar to dyskinesia,

were reduced by pretreatment with sarizotan.<sup>100</sup> Sarizotan was directly injected into the subthalamic nucleus of dyskinetic rats and alleviated L-DOPA-induced AIMs.<sup>101</sup> However, while 5-HT<sub>1A</sub> receptors may be critically involved in the effects of sarizotan, there is also a prominent role for of dopamine D<sub>3</sub> receptors in alleviating at least part of the dyskinesia-like paradigm in rats<sup>102</sup> in addition to a potential role played by dopamine D<sub>4</sub> receptor blockade.<sup>103,104</sup>

8-Hydroxy-2-(di-*n*-propylamino)tetralin (8-OHDPAT) and particularly its enantiomer, *R*-(+)-OHDPAT, is a full 5-HT<sub>1A</sub> receptor agonist that, unlike sarizotan, is highly selective, exhibiting nearly 400-fold selectivity.<sup>105,106</sup> There are ample rodent data demonstrating that 8-OHDPAT reduces AIMs behavior, but data from Bishop's lab demonstrates that these effects can be attributed to actions at the level of the dorsal raphe nucleus (DRN).<sup>107</sup> Interestingly, however, other work from Bishop's lab suggests that striatal postsynaptic heteroreceptors may additionally be involved.<sup>108</sup> In the MPTP-lesioned marmoset, *R*-(+)-OHDPAT significantly reduced the severity of L-DOPA-induced chorea, but it was not possible to obtain an antidyskinetic benefit without hindering L-DOPA anti-parkinsonian action.<sup>109</sup> Because of the high selectivity of *R*-(+)-OHDPAT, an off-target interaction with other receptors appears not to explain the reduction of antiparkinsonian benefit observed in this study.

Unlike sarizotan and *R*-(+)-OHDPAT, which are both full agonists, eltoprazine is a 5-HT<sub>1A</sub> receptor partial agonist, with a maximal efficacy ( $E_{max}$ ) ~ 50%. However, eltoprazine exhibits relatively high affinity for other serotonergic targets including 5-HT<sub>1B</sub>, 5-HT<sub>2A</sub>, and 5-HT<sub>2C</sub> receptors.<sup>110,111</sup> Like other 5-HT<sub>1A</sub> receptor agonists, eltoprazine reduces AIMs in the rat, possibly through actions at both 5-HT<sub>1A</sub> and 5-HT<sub>1B</sub> receptors.<sup>112,113</sup> In a study conducted in the MPTP-lesioned macaque, eltoprazine significantly diminished LID severity, but it was impossible to dissociate the antidyskinetic effect from the reduction of L-DOPA antiparkinsonian action.<sup>112</sup> These results suggest that activation of 5-HT<sub>1A</sub> receptors with partial agonists may alleviate LID, but may hinder L-DOPA antiparkinsonian action. However, data interpretation is complex here, as eltoprazine is not 5-HT<sub>1A</sub>-selective; as such any therapeutic effect achieved or adverse event(s) triggered may not be mediated by interaction with 5-HT<sub>1A</sub> receptors solely.

F-15,599 is a highly potent and highly selective 5-HT<sub>1A</sub> receptor full agonist with over 1000-fold selectivity over its next target.<sup>114,115</sup> Moreover, unlike all of the 5-HT<sub>1A</sub> receptor agonists discussed in this section, F-15,599 is a biased agonist that preferentially binds to postsynaptic 5-HT<sub>1A</sub> receptors.<sup>116</sup> In a study conducted in the MPTP-lesioned macaque, F-15,599 reduced LID without interfering with L-DOPA antiparkinsonian action.<sup>117</sup> Although brain receptor occupancy was not measured in this study, it nevertheless suggests that preferential activation of postsynaptic 5-HT<sub>1A</sub> receptors may reduce LID without impairing L-DOPA antiparkinsonian action.

Rodent studies have also suggested that F-15,599 and its congener F-13,714, which are full agonists with preferential affinity for postsynaptic and presynaptic 5-HT<sub>1A</sub> receptors,<sup>115,118</sup> respectively, potently inhibited AIMs behavior at low doses<sup>119</sup> after acute administration and induced 5-HT<sub>1A</sub> receptor dependent ipsilateral rotation. However, some reduction in rotarod performance was seen for both compounds, but this was only observed at the highest doses tested. Further investigations into the actions of these molecules suggested that they both profoundly reduced

synaptic 5-HT in the 6-OHDA-lesioned and normal striata of nondyskinetic rats, but the key locus of effects is not totally clear and additional studies are warranted. However, no effects were observed on dopamine, glutamate, or  $\gamma$ -aminobutyric acid.

NLX-112 (F-13,640 or befiradol) is a congener of F-15,599 and F-13,714. NLX-112 has nanomolar affinity and high selectivity for 5-HT<sub>1A</sub> receptors. NLX-112 has undergone extensive clinical development for the treatment of neuropathic pain<sup>120,121</sup> and is presently being considered for the treatment of LID. Therefore, the compound effectively alleviated AIMs behavior, while reducing 5-HT overflow, in both lesioned and nonlesioned striata.<sup>122</sup> As 5-HT<sub>1A</sub> agonists may have utility for the treatment of mood disorders.<sup>87</sup> Therefore, it would make sense to consider this highly selective compound, at least, in putative models of mood disorders, since these symptoms are commonly observed in PD patients. Accordingly, NLX-112 was tested in the forced swim test of depression and demonstrated potent and complete reduction of immobility, in 6-OHDA-lesioned rats, suggesting antidepressant-like actions.<sup>122</sup> Based on data following acute administration of NLX-112, further studies were designed to test whether the effects of NLX-112 were robust following chronic administration,<sup>123</sup> whether NLX-112 prevents the developments of AIMs when given in the priming phase; whether it consistently reduces AIMs in animals with established dyskinesia; and finally what the effects of NLX-112 are on synaptic overflow of 5-HT, dopamine and other neurotransmitters in the priming and the established AIMs phases. These experiments showed that NLX-112 reduced AIMs both in the priming and the established AIMs phases, and that the blunting of AIMs in the priming phase did not equate to a reduction of AIMs development. Microdialysis measurements suggested that 5-HT levels were reduced, as might be expected. Moreover, in the presence of L-DOPA, NLX-112 effectively reduced dopamine overflow in the lesioned striatum, suggesting that 5-HT<sub>1A</sub> receptor activation reduces dopamine release, leading to a reduction in dyskinesia.

Collectively, these studies conducted in the parkinsonian rodent and NHP demonstrate that 5-HT<sub>1A</sub> activation is an effective approach to alleviate dyskinesia. The limiting factor with this approach is that under some circumstances there may be an exacerbation of parkinsonian disability, whether the drug used is a full agonist (e.g., *R*-(+)-OHDPAT) or a partial agonist (e.g., eltoprazine). However, it is noteworthy that none of sarizotan, *R*-(+)-OHDPAT, and eltoprazine are biased agonists and do not discriminate between pre- and postsynaptic 5-HT<sub>1A</sub> receptors. In contrast, more recently described compounds such as F-15,599, F-13,714, and NLX-112, alleviated dyskinesia without impacting on parkinsonism, suggesting that targeting postsynaptic or somatodendritic autoreceptors by highly selective and highly efficacious 5-HT<sub>1A</sub> agonists, might be an effective and well-tolerated way to reduce dyskinesia. Whether preferential activation of presynaptic and/or postsynaptic 5-HT<sub>1A</sub> (and/or 5-HT<sub>1B/1D</sub>) receptors would be equally effective and well tolerated remains to be demonstrated.

Indeed, stimulation of 5-HT<sub>1B/1D</sub> receptors in parkinsonism is less well studied than studies assessing 5-HT<sub>1A</sub> receptor activation. Thus, in the MPTP-lesioned marmoset, the 5-HT<sub>1B/1D</sub> agonist SKF-99-101-H significantly reduced dyskinesia but also hindered L-DOPA antiparkinsonian benefit.<sup>124</sup> In contrast, in the MPTP-lesioned macaque, the 5-HT<sub>1B</sub> receptor agonist CP-94,253 did not reduce dyskinesia and had no effect on parkinsonism.<sup>125</sup> With so few studies conducted in the NHP, it is difficult to make strong conclusions about the

efficacy and tolerability of 5-HT<sub>1B/1D</sub> agonists in PD and additional studies are needed to further characterize the therapeutic potential of this category of drugs. In the rat, the 5-HT<sub>1B</sub> agonist CP-94,253 reduced AIMs behavior following treatment with either L-DOPA, apomorphine or the dopamine D<sub>1</sub> agonist SKF-81,297.<sup>126,127</sup> Generally, however, many studies focused on the combination of 5-HT<sub>1A</sub> and 5-HT<sub>1B</sub> receptor agonists, and as such it is not always possible to directly discern the role of the latter subtype.<sup>126,128</sup>

**5-HT<sub>2A</sub> Receptor Modulation: A Role in LID and Psychosis.** Clozapine is an atypical antipsychotic that interacts with several receptors, including 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub>, alpha-adrenergic, muscarinic and dopamine D<sub>2</sub> and D<sub>4</sub> receptors.<sup>129-131</sup> In the MPTP-lesioned marmoset, clozapine effectively reduced both LID and psychosis-like behaviors, without affecting parkinsonism.<sup>132,133</sup> These results suggest that 5-HT<sub>2A</sub> antagonism is effective at reducing both PD psychosis and dyskinesia, without diminishing the action of L-DOPA; however, because of the lack of selectivity of clozapine, it is unclear whether this effect is exclusively mediated via 5-HT<sub>2A</sub> receptor blockade, or whether other receptors are involved.

JL-18 is a clozapine analogue that harbors high affinity at 5-HT<sub>2A</sub> and dopamine D<sub>2</sub>, D<sub>3</sub> and D<sub>4</sub> receptors.<sup>134</sup> In the MPTP-lesioned macaque, JL-18 reduced LID, but considerably hindered L-DOPA therapeutic effect.<sup>135</sup> Due to the fact that JL-18 is not 5-HT<sub>2A</sub>-selective, no claim can be made as to whether a 5-HT<sub>2A</sub>-mediated effect underlies the reduction of L-DOPA action following its administration, especially since it antagonizes dopamine D<sub>1</sub> and D<sub>2</sub> receptors at higher doses.<sup>134</sup> Rodent data suggest that 5-HT<sub>2A</sub> receptor blockade does not convey anti-LID effects per se, while treatment with 5-HT<sub>2A</sub> receptor antagonists may modify D<sub>1</sub> receptor responses.<sup>136-138</sup>

Methysergide is a nonselective 5-HT<sub>2A</sub> receptor antagonist that significantly reduced dyskinesia in the MPTP-lesioned macaque, but by interfering with the antiparkinsonian effect of L-DOPA.<sup>52</sup> However, caution should be taken in concluding that 5-HT<sub>2A</sub> receptors have an exclusive role as methysergide lacks selectivity,<sup>139</sup> therefore it is not possible to pinpoint a single mechanism of action underlying both the therapeutic and detrimental effects in the MPTP-lesioned primate.

The case of MDMA is very interesting (see previous and next sections for additional discussions about MDMA). The racemate MDMA alleviated L-DOPA- and pramipexole-induced dyskinesia without interfering with their antiparkinsonian effect in the MPTP-lesioned marmoset.<sup>140</sup> In a further study conducted on the MPTP-lesioned marmoset,<sup>141</sup> the *R*-enantiomer of MDMA, which acts as a 5-HT<sub>2A</sub> partial agonist,<sup>142</sup> alleviated both dyskinesia and psychosis, without affecting the benefit of L-DOPA on parkinsonism. These studies suggest that selective 5-HT<sub>2A</sub> receptor partial activation may be effective for both PD psychosis and dyskinesia. Again, caution is warranted based on the psychotomimetic actions of racemic MDMA via dopamine release and the ability of 5-HT<sub>2A</sub> receptor agonists to drive hallucinations.

Pimavanserin is a selective 5-HT<sub>2A/2C</sub> inverse agonist without significant affinity for any other target.<sup>143</sup> In the MPTP-lesioned macaque, pimavanserin reduced LID, without interfering with its antiparkinsonian action.<sup>144</sup> Clinically it is now used to treat psychosis in PD patients (see next section) and rodent data have suggested its actions in a variety of animal models of psychosis.<sup>145-147</sup> It is possible that the doses used clinically cause antagonist/inverse agonist actions at both 5-

HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors may have impact on the antipsychotic efficacy.<sup>148</sup>

Quetiapine is a nonselective 5-HT<sub>2A</sub> antagonist and atypical antipsychotic agent that exhibits moderate affinity at dopamine D<sub>2</sub>, muscarinic and alpha-adrenoceptors.<sup>149</sup> In the MPTP-lesioned macaque<sup>150</sup> and the MPTP-lesioned marmoset,<sup>133</sup> quetiapine alleviated dyskinesia without affecting L-DOPA-induced reversal of parkinsonism. Moreover, quetiapine also reduced dopaminergic psychosis-like behaviors in the MPTP-lesioned marmoset.<sup>133</sup>

Collectively, these studies suggest that antagonising 5-HT<sub>2A</sub> receptors is an effective strategy to alleviate both dyskinesia and psychosis, without interfering with the antiparkinsonian effect of L-DOPA. Because of their lack of selectivity, we postulate that the detrimental effect of JL-18 and methysergide on L-DOPA antiparkinsonian action may be due to interaction with other targets. The lack of selectivity of some compounds described, e.g., clozapine and quetiapine, prevents attributing their beneficial action to a 5-HT<sub>2A</sub>-selective mechanism exclusively. However, data with pimavanserin and the therapeutic benefits it confers appear mediated via actions at 5-HT<sub>2A</sub> sites.

## ■ CLINICAL STUDIES USING SEROTONERGIC AGENTS IN PD

**Motor Symptoms of PD.** Reducing involuntary movements secondary to LID in the clinic has been a key therapeutic strategy for which a variety of serotonergic agents have been assessed. In addition, as discussed earlier, the serotonergic system may be involved in the expression of motor symptoms, particularly resting tremor.

**5-HT May Contribute to LID.** As discussed above, preclinical studies suggest that targeting presynaptic 5-HT<sub>1A</sub> receptors on serotonergic fibers to reduce aberrant dopamine release, as well as postsynaptic 5-HT<sub>1A</sub> receptors to reduce overactive cortico-striatal glutamate neurotransmission,<sup>151,152</sup> may reduce LID. Clinical investigations to verify these findings have used PET in PD patients with LID, compared to age-matched PD subjects without LID. Higher striatal SERT:dopamine transporter ratios were seen, suggesting relative preservation of serotonergic terminal.<sup>94,153</sup> Additional clinical evidence implicates 5-HT in the development of so-called “runaway dyskinesia” that may occur in PD patients following transplanted fetal ventral mesencephalic tissue, possibly due to the presence of serotonergic neurons in grafted tissue.<sup>154</sup>

An early, indirect, suggestion that 5-HT agents may reduce LID came from the anecdotal evidence of a young-onset PD patient who reported that his LID (and PD) improved after taking MDMA, and this was the subject of a BBC documentary and an “*n-of-1*” double-blind acute challenge study suggesting that MDMA could reduce LID and extend the action of L-DOPA. The effect of MDMA on LID was thought to involve 5-HT, as there was no effect on dopaminergic transmission as demonstrated by a raclopride PET study.<sup>81</sup> Clearly the psychotropic actions of MDMA cannot be discounted, but the possible principle of 5-HT modulators was subsequently evaluated in many preclinical studies.<sup>87,123,140,141,155,156</sup>

Clinical trials in PD subjects with LID, have evaluated novel 5-HT<sub>1A</sub> agonists and 5-HT<sub>2A</sub> antagonists, as well as clinically available mixed 5-HT<sub>1A</sub> agonists that are already approved for other indications, such as anxiety and depression, e.g., buspirone and tandospirone (see later).

**Novel 5-HT<sub>1A</sub> Receptor Agonists.** The first novel 5-HT<sub>1A</sub> receptor agonist to be clinically evaluated for LID was sarizotan. Sarizotan is both a 5-HT<sub>1A</sub> receptor agonist, as well as a dopamine D<sub>2</sub>, D<sub>3</sub>, and D<sub>4</sub> receptor antagonist.<sup>96</sup> Early studies were promising, with a phase IIa study reporting a reduction in LID of 40%, without worsening motor PD symptoms.<sup>157</sup> However, in an open-label trial sarizotan reduced LID, but also worsened motor symptoms (reduced on-time) in half of study participants.<sup>158</sup> Three large randomized controlled trials of sarizotan have been conducted. One study, using 2, 4, and 10 mg/day ( $n = 398$ ) failed to demonstrate any significant change in dyskinesia scores compared to placebo. In addition, higher doses were also associated with an increased duration of off-time. Two studies using sarizotan 2 mg daily (the PADDY-1 study,  $n = 504$  and the PADDY-2 study,  $n = 403$ ) demonstrated no significant improvement in LID compared to placebo.<sup>159,160</sup> The conclusion was that either 5-HT<sub>1A</sub> receptor agonists have to be used at a critical dose with a potentially narrow therapeutic window, due to the potential to reduce dopamine release (as discussed above), or, in the particular case of sarizotan, the worsening of PD may well be related to actions at non-5-HT receptors, since sarizotan is also a dopamine receptor antagonist.<sup>96</sup> There has been no further clinical development of sarizotan for the treatment of LID.

**Clinically Available Serotonergic Drugs.** A number of clinically available anxiolytics have been evaluated in small studies. These include the mixed 5-HT<sub>1A</sub> (partial) receptor agonists buspirone (which lacks appreciable selectivity and is also a dopamine D<sub>2</sub>-like receptor partial agonist),<sup>161,162</sup> tandospirone and eltoprazine, as well as the selective 5-HT reuptake inhibitor (SSRI) fluoxetine. The antipsychotics clozapine and quetiapine, and the antidepressant mirtazapine, have “rich”, or aselective actions. Each of the compounds have a myriad of actions including 5-HT<sub>2A</sub> antagonistic properties, along with activity at other targets. In general the studies have been positive but of low quality (e.g., open-label, short duration and small numbers). Therefore, true efficacy is unknown as of yet, as is the precise pharmacological target. Further studies using some clinically available agents are ongoing.

A small open-label study in seven PD subjects with LID reported a 47% reduction with the SSRI fluoxetine (40 mg/day for 11 days).<sup>163</sup> The mechanism of action of SSRIs may involve 5-HT<sub>1A</sub> and/or 5-HT<sub>1B/1D</sub> receptor indirect agonist effects, in part.<sup>164</sup> However, no further double-blind randomized controlled trials have been performed to evaluate this role, and anecdotal studies using SSRIs in depression for PD have not reported any observations that coexistent LID is also reduced.

A double-blind randomized controlled crossover study for 3 weeks reported that buspirone (20 mg/day) reduced LID without worsening parkinsonian disability in 7 out of 10 PD patients.<sup>165</sup> As part of the PET imaging study described above to evaluate the role of 5-HT<sub>1A</sub> receptors in PD,<sup>94</sup> acute pretreatment with buspirone (0.35 mg/kg), prior to L-DOPA, reduced LID by approximately one-third, with no effect on motor symptoms ( $n = 24$ ). The dose selected was thought to preferentially bind to 5-HT<sub>1A</sub> rather than dopamine D<sub>2</sub> receptors. Thus, buspirone appears to have some benefit, but longer term evaluation needs to be performed. A 12-week double-blind randomized controlled trial is ongoing evaluating buspirone (20 mg/day) for bothersome LID in PD (NCT02617017).



Eltoprazine is a 5-HT<sub>1A</sub> receptor partial agonist that also exhibits affinity for 5-HT<sub>1B</sub> and 5-HT<sub>2C</sub> receptors.<sup>110</sup> A phase IIa crossover randomized controlled trial in 18 PD patients, using single acute dosing (5–7.5 mg), reduced peak-dose and total LID (~10–15%) without worsening PD motor scores. Side-effects were nausea and dizziness.<sup>95</sup> There is also an ongoing double-blind, placebo-controlled, crossover, dose-range finding study over 3 weeks evaluating eltoprazine 2.5–7.25 mg/day for LID (NCT02439125). Other similar 5-HT<sub>1A</sub> receptor partial agonists include tandospirone, which is clinically available in Japan. An open-label study reported that tandospirone (15–60 mg/day) reduced LID in 5 out of 10 subjects, but with worsening of PD motor symptoms in 3 after 12 weeks.<sup>166</sup>

Postsynaptic 5-HT<sub>2A</sub> receptors have also been implicated in LID. Thus, the atypical antipsychotic and preferential 5-HT<sub>2A</sub> receptor antagonist clozapine (low dose, <50 mg/day) was shown to significantly reduce the duration of daily LID by about 1 h, without worsening motor function, in a single double-blind randomized controlled trial in 50 subjects.<sup>167</sup> The other atypical antipsychotic, quetiapine (25 mg/day), failed however to show a significant reduction in LID in a double-blind randomized controlled trial in 9 PD patients; open-label trials with 50 mg/day reported some antidyskinetic benefit and no worsening of PD motor scores.<sup>168</sup> The antidepressant, mirtazapine (which has a mixed pharmacological profile including anticholinergic as well as 5-HT<sub>2A</sub> receptor antagonist actions),<sup>169</sup> also reduced LID without worsening parkinsonism.<sup>170,171</sup> However, these trials were also small open-label studies, so true efficacy remains unclear. The use of SSRI in the treatment of LID has been suggested in the animal literature (e.g., refs 172, 173). Clinically, anecdotal reports also suggest that SSRIs reduce LID.<sup>174</sup> However, more extensive double-blind placebo controlled studies are warranted.

**5-HT Antagonism in PD Resting Tremor.** Resting tremor is another motor symptom that can sometimes be challenging to treat. Many patients do not have a good reduction with L-DOPA, suggesting the pathophysiology may be mediated by nondopaminergic systems, including 5-HT.<sup>175</sup> Clozapine at low dose can also reduce PD tremor, which may reflect 5-HT<sub>2A</sub> receptor antagonist properties.<sup>176</sup>

## ■ NONMOTOR SYMPTOMS

**Depression and Anxiety.** There are several nonmotor issues experienced by PD subjects which may respond to serotonergic compounds. For example, mood disorders are very common in PD and are seen in around 50% of patients (although large ranges are reported).<sup>177</sup> Classical antidepressants have been evaluated for use in PD with generally positive, although variable, effects.<sup>178</sup> A recent meta-analysis of trials for PD depression (which included 13 pharmacological studies) reported the overall standard mean difference for all pharmacologic interventions was 0.30 (95% CI 0.00, 0.61,  $p = 0.054$ ) and suggested that SSRIs may have better outcomes than other interventions,<sup>179</sup> but other authors have suggested that SSRIs might represent the last treatment choice.<sup>180,181</sup> Prevailing clinical experience and practice suggest that SSRIs are the first choice for the management of depressive symptoms in PD, but no head to head randomized control trials supporting the better efficacy or tolerability of specific SSRIs have been reported. Interestingly, the relative preservation of serotonergic vs dopaminergic terminals in PD appeared unrelated to depressive symptoms per se, but the reduction

in serotonin could be a potential limitation to antidepressant activity associated with SSRIs treatment in PD patients.<sup>182,183</sup> However, overall, side-effects and safety appear similar to other antidepressant treatments and there appears to be no clinically relevant worsening of PD motor symptoms.

**Psychosis.** Dopamine drugs may clearly be a trigger for onset or exacerbation of PD psychosis. In the case of L-DOPA this may be due to extrastriatal dopamine increase.<sup>88</sup> PD psychosis has also been suggested to involve 5-HT, and there is preclinical and clinical evidence for a role for 5-HT<sub>2A</sub> receptors in PD psychosis.<sup>184,185</sup> Drugs that target 5-HT<sub>2A</sub> receptors may be effective and include low doses of the atypical antipsychotics quetiapine, clozapine, and the new 5-HT<sub>2A/2C</sub> inverse agonist pimavanserin. Quetiapine (25–150 mg/day) has been evaluated in a number of studies but did not show significant benefit compared to placebo.<sup>186–188</sup> At higher doses, subjects with PD dementia may experience worsening of motor symptoms which may reflect a loss of 5-HT<sub>2A</sub>-selective binding and dopamine D<sub>2</sub> receptor antagonism instead. The most efficacious agent for PD psychosis is clozapine and low doses (12.5–75 mg/day) are very effective<sup>189,190</sup> without worsening of PD motor symptoms. The main issues relate to the mandatory blood counts for agranulocytosis.<sup>191</sup> Other side-effects include postural hypotension and sedation. There is a black box warning on use of antipsychotics in general in the elderly due to higher overall cardiac risks, and a higher hazard ratio of death of 2.16 with quetiapine use.<sup>192</sup> The 5-HT<sub>2A/2C</sub> inverse agonist pimavanserin, which has been described more recently in the literature (see above for references), has lately been licensed in the United States on the basis of positive data showing reduced PD psychosis compared to placebo, without worsening PD motor scores, and with added benefit on sleep and caregiver burden.<sup>193,194</sup> Another 5-HT<sub>2A</sub> inverse agonist, nelotanserin, is currently being evaluated in a phase II double-blind placebo controlled trial in patients with Lewy body disease experiencing visual hallucinations (NCT02640729).

**Cognitive Impairment.** Dementia is a major issue in PD and has been extensively reviewed by a number of authors.<sup>195</sup> 5-HT<sub>6</sub> receptors are located in frontal and entorhinal cortices, dorsal hippocampus, nucleus accumbens, and striatum, and have been implicated in learning and memory via the modulation of cholinergic, monoaminergic, and glutamatergic functions.<sup>196</sup> 5-HT<sub>6</sub> receptor antagonists improve cognitive function in Alzheimer's disease.<sup>197</sup> There is an ongoing study evaluating the 5-HT<sub>6</sub>/5-HT<sub>2A</sub> dual antagonist SYN120 in a safety and tolerability double blind randomized controlled studies in 80 subjects with PD dementia over 16 weeks (NCT02258152).

## ■ DISCUSSION

The 5-HT system is involved in a breadth of manifestations and treatment-related complications of PD. A better understanding of the role played by 5-HT in PD has led to several trials, at both preclinical and clinical levels. Most of these have focused on 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors, as well as SERT modulation, as discussed above. Although the potential of 5-HT modulation to alleviate PD manifestations and treatment-related complications appears immense, several hurdles have been encountered.

In summary:

(i) The development of a new NHP model that mimics more closely the disease, with dual dopamine/5-HT lesion, might provide ways to better model the human condition and advance drugs to the market for nonmotor symptoms.



(ii) With 5-HT<sub>1A</sub> stimulation, it seems difficult to separate any benefit from an interaction with L-DOPA antiparkinsonian action, at least in the case of the 5-HT<sub>1A</sub> full agonists R-(+)-OH-DPAT and sarizotan. In the case of the latter, however, because the drug interacts with several receptors besides 5-HT<sub>1A</sub> receptors, caution is warranted when discussing its deleterious effect on L-DOPA action. Moreover, sarizotan had to put up with an unexpectedly strong placebo performance,<sup>160</sup> which has also been the case with the 5-HT<sub>2A/2C</sub> inverse agonist pimavanserin,<sup>198</sup> ultimately leading to a phase III trial with a run-in phase where effectiveness vs placebo was achieved.<sup>193</sup> Therefore, optimal design of clinical trials may be critical to bring 5-HT modulators to the clinic.

(iii) The use of 5-HT<sub>1A</sub> receptor partial agonists also seems marred by a potential detrimental effect on L-DOPA antiparkinsonian action, suggesting that such drugs may have a narrow therapeutic window. Thus, whereas the partial agonist eltopazine alleviated LID in the MPTP-lesioned NHP, it worsened parkinsonian disability.<sup>112</sup> Tansospirone had similar effects, in a small open-label clinical trial.<sup>166</sup>

(iv) Perhaps compounds with biased agonistic properties represent a new way to alleviate LID that will be devoid of effects on parkinsonism, but too few studies and no clinical trials have been conducted with these compounds, and their safety (in the patient population) and efficacy need to be further demonstrated.

In conclusion, modulation of the 5-HT system is a promising way to address several manifestations and complications of PD. Studies are ongoing that aim at developing drugs that will provide the maximal benefit with minimal adverse events, to improve patients and care givers quality of life.

## AUTHOR INFORMATION

### Corresponding Author

\*E-mail: [amccrear@its.njn.com](mailto:amccrear@its.njn.com); [andy MCCREARY@yahoo.co.uk](mailto:andy MCCREARY@yahoo.co.uk).

### ORCID

Andrew C. McCreary: [0000-0003-3614-9117](https://orcid.org/0000-0003-3614-9117)

### Author Contributions

P.H.: conceived, organized, and executed the research project, wrote the first draft of the manuscript, and contributed review and critique of the manuscript. V.S.-F.: conceived and executed the research project, wrote the first draft of the manuscript, and contributed review and critique of the manuscript. S.H.F.: conceived and executed the research project, wrote the first draft of the manuscript, and contributed review and critique of the manuscript. A.C.M.: conceived, organized, and executed the research project, wrote the first draft of the manuscript, and contributed review and critique of the manuscript.

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