

# Chapter 11

## The Serotonergic System in Levodopa-Induced Dyskinesia

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**Abstract** An increasing body of experimental evidence suggests that serotonergic neurons play a major role in the production of levodopa-derived dopamine when dopaminergic neurons have degenerated, and that unregulated release of dopamine from serotonergic neurons is responsible for the appearance of levodopa-induced dyskinesia (LID) in animal models of Parkinson's disease (PD).

Promising preclinical findings show that the activation of 5-HT<sub>1</sub> receptors, induced by the administration of 5-HT<sub>1A</sub> and/or 5-HT<sub>1B</sub> receptor agonists, suppressed LID in 6-OHDA-lesioned rat, as well as in MPTP-treated nonhuman primate models of PD, suggesting a possible clinical application. This chapter will provide an overview of these preclinical findings concerning the role of serotonergic neurons and serotonergic receptors in the appearance of LID, with a brief review of relevant clinical studies.

**Keywords** Levodopa • LID • Dopamine • Serotonin • 5-HT receptors

### The Serotonergic System in Parkinson's Disease

Serotonin (5-hydroxytryptamine, 5-HT) is an important modulator of the central nervous system (CNS), and its action is mediated by a large variety of receptor subtypes. Serotonin is synthesized from L-tryptophan by a two-step reaction: the tryptophan hydroxylase enzyme generates 5-hydroxytryptophan (5-HTP), which is then converted to serotonin by the L-amino acid decarboxylase enzyme (AADC). The serotonergic system originates from the raphe nuclei and is one of the most widely distributed, innervating virtually all regions of the CNS and

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199

participating in mechanisms of cognition, feeding and satiety, mood and emotion, circadian and sleep-wake cycle regulation, pain, and motor functions [1, 2]. An increasing body of experimental evidence demonstrates the involvement of the serotonergic system in modulating the function of basal ganglia circuits and its interaction with the dopaminergic system. Both serotonergic and dopaminergic systems are affected in neurodegenerative disorders such as Parkinson's disease (PD) and have been implicated in the pathophysiology of depression and schizophrenia [3]. A role of the serotonergic system in the regulation of motor function is suggested by the dense serotonergic input received by areas such as the striatum, substantia nigra pars reticulata, and globus pallidus [4, 5]. Interestingly, postmortem studies of patients with PD have shown loss of serotonergic markers in the caudate, as well as hypothalamus and frontal cortex [6, 7]. However, as also seen in PET imaging studies, the degree of serotonergic terminal loss appears to be less severe than that affecting the dopaminergic system, and there is no correlation with motor disability, or dyskinesia [8]. On the other hand, it has been suggested that the partial loss of serotonergic innervation may contribute to the development of depression in PD patients [9], although consistent evidence is lacking [5].

Serotonin exerts its actions via specific receptors, which are located in most of the brain, especially in the hippocampus, basal ganglia, and striatum. To date, 14 distinct subtypes of the serotonergic receptors have been identified [10, 11]; among all serotonergic receptors, some have been shown to participate in the regulation of motor function and/or induction of dyskinesia in PD, such as the 5-HT1A, 5-HT1B, 5-HT2A, 5-HT2C, and the 5-HT3 receptors.

5-HT1A receptors are located somato-dendritically in the dorsal raphe nuclei, where they regulate cell firing [12]. 5-HT1A receptors have been also identified postsynaptically in other brain regions, such as the cerebral cortex, striatum, and subthalamic nucleus [13], where they serve to control release of other neurotransmitters, such as glutamate [14]. Interestingly, the activation of postsynaptic 5-HT1A receptors located at prefrontal cortex has also been shown to affect serotonin neuron activity through an indirect loop to the raphe nuclei [15–17]. 5-HT1B receptors are also expressed as autoreceptors at serotonergic terminals in target areas, where they contribute to control serotonin release. Moreover, these receptors are also localized in non-serotonergic neurons, such as the striatal medium spiny neurons, and regulate GABA release [18–20].

Among the other 5-HT receptors, the 5-HT2A receptors are involved in a variety of behaviors and diseases including anxiety, hyperactivity disorders, aggression, and social interaction. Moreover, they play a role in drug addiction and in the mechanism of action of anti-psychotic drugs. It has been shown that 5-HT2A receptors are abundant in the neocortex, striatum, and nucleus accumbens, where they appear to have a role in the emergence of motor complications [21, 22].

Another interesting serotonergic receptor that has been shown to play a role in the regulation of motor functions is the 5-HT2C receptor. This receptor subtype shows high and moderate expression in limbic areas and basal ganglia, respectively. The activation or blockade of 5-HT2C receptors results in an opposite effect on

dopamine release; indeed, their activation induces a reduction of dopamine release along the dopaminergic pathway, while their blockade increases dopamine release along the meso-cortico-limbic as well as nigrostriatal pathways [23, 24]. Despite the influence of 5-HT<sub>2C</sub> receptors in modulating dopaminergic system, very little is known on their role in PD and dyskinesia.

5-HT<sub>3</sub> receptors are mostly localized in limbic areas and brainstem nuclei, while they show low expression in the basal ganglia areas. Unlike other serotonergic receptors, 5-HT<sub>3</sub> receptors are ion channels. They have been found to be involved in anxiety, schizophrenia, learning, and attention, as well as in craving and pain. Although 5-HT<sub>3</sub> receptors have been reported to play a role in controlling striatal dopamine release [25], their involvement in PD and dyskinesia is poorly studied.

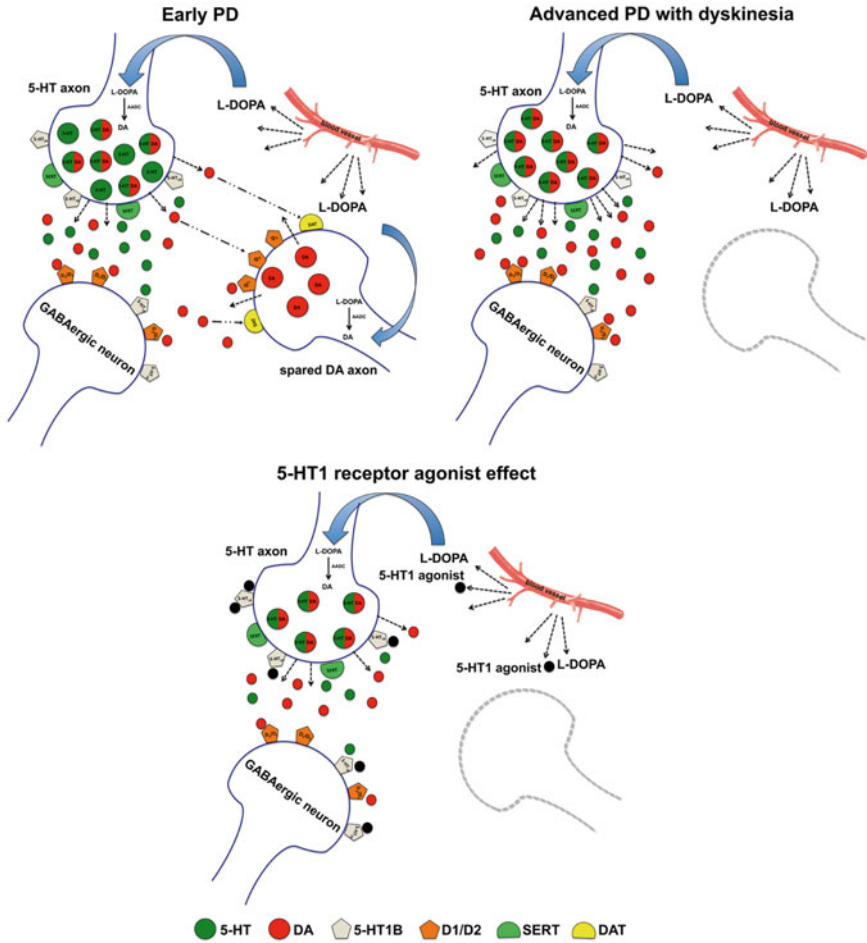
Despite the important role of serotonergic receptors in regulating motor functions, selective agonists for these receptors were generally unsuccessful for the treatment of parkinsonian motor symptoms [26]; on the other hand, the serotonergic receptors have been implicated in the development of motor complications induced by drug treatment in parkinsonian patients, such as levodopa-induced dyskinesia (LID).

## **Involvement of the Serotonergic System in Levodopa-Induced Dyskinesia**

The therapeutic efficacy of levodopa during the first few years of treatment is conceivably due to the presence of a sufficient number of spared dopamine neurons that can provide conversion of levodopa and mediate physiological release of dopamine; however, with the progression of the disease, most of dopaminergic neurons are lost, and levodopa-derived dopamine is produced in non-dopaminergic elements, including the serotonergic terminals. In fact, serotonergic neurons are able to convert exogenous levodopa to dopamine and store and release dopamine in an activity-dependent manner in a number of experimental conditions, both *in vitro* and *in vivo* [27–29]. Indeed, serotonergic neurons share the same enzymatic machinery as dopaminergic terminals (aromatic amino acid decarboxylase and vesicular monoamine transporter 2 enzymes) and are able to convert levodopa to dopamine and to mediate storage of dopamine into synaptic vesicles.

It is conceivable to think that conversion of levodopa takes place into serotonergic neurons also in earlier stages of disease; however, as long as there are sufficient spared dopaminergic terminals, the contribution of serotonergic neurons may be beneficial, as dopaminergic terminals provide a buffering system for the levodopa-derived dopamine (through the dopamine transporter). By contrast, as the disease progresses and spared dopaminergic terminals are lost, the contribution of serotonergic neurons becomes detrimental (see Fig. 11.1).

In fact, unlike dopaminergic neurons, serotonergic neurons cannot regulate the extracellular levels of dopamine due to the lack of an autoregulatory feedback mechanism for dopamine release. As a consequence, levodopa-derived dopamine is released in uncontrolled way following levodopa administration. This will act in



**Fig. 11.1** In the early stage of PD, the ability to release dopamine is partially preserved due to the presence of a sufficient number of spared dopaminergic neurons that have not yet degenerated. At this stage, serotonergic terminals may contribute to levodopa-derived dopamine release, due to an ability to convert exogenous levodopa to dopamine and store and release dopamine in an activity-dependent manner. However, their contribution may be beneficial as synaptic dopamine levels are kept within a physiological range due to the presence of an efficient buffering system provided by the spared dopamine terminals (through the dopamine transporter). With the progression of the disease, when most of dopaminergic terminals are lost, the contribution of serotonergic neurons becomes detrimental due to the lack of autoregulatory feedback mechanisms able to regulate synaptic dopamine levels. The uncontrolled release of dopamine from serotonergic neurons will act in concert with the intermittent nature of the orally administered levodopa to produce swings in synaptic dopamine levels and pulsatile stimulation of striatal dopaminergic receptors, which is responsible for the onset of dyskinesia. 5-HT1 receptor agonists will act to reduce levodopa-derived dopamine release from serotonin neurons, which will dampen swings in synaptic dopamine levels

concert with the intermittent nature of the orally administered levodopa, to cause swing in synaptic dopamine levels, which is responsible for pulsatile stimulation of striatal dopaminergic receptors and aberrant downstream signaling cascade (see Fig. 11.1). In line with this view, it has been shown that removal of the forebrain serotonergic innervation by the selective toxin 5,7-dihydroxy-tryptamine (5,7-DHT) produces an almost complete suppression of LID [30, 31]. Dramatic reduction of levodopa-derived striatal dopamine levels appears to account for the anti-dyskinetic effect of 5,7-DHT lesions [29].

Support for the important role of serotonergic neurons in dyskinesia also came from a rat PET imaging study, where the administration of the 5-HT<sub>1A</sub> receptor agonist 8-OH-DPAT (which reduced LID) reversed levodopa-induced decrease of [(11)C]raclopride binding and increase of extracellular dopamine [32].

Interestingly, Rylander and colleagues have demonstrated a correlation between the density of serotonergic terminals in the striatum and the severity of LID across different species. In fact, dyskinetic rats and primates, as well as postmortem tissue of PD patients, have shown a growth-promoting effect on the striatal serotonergic fibers, accompanied by an increase of serotonin transporter (SERT) expression, induced by levodopa treatment. Regenerative sprouting of the serotonergic neurons was also accompanied by increased BDNF (Brain Derived Neurotrophic Factor) levels and increased BDNF-induced levodopa-derived dopamine release in rat striatal slices [33]. This is interesting as intracerebral delivery of BDNF has previously been shown to promote serotonergic terminal sprouting [34].

Further evidence for the involvement of serotonergic neurons in the appearance of LID came from recent experimental studies, where increased serotonergic tone by administration of either selective serotonin reuptake blockers (SSRIs) or the serotonergic precursor 5-hydroxytryptophan significantly reduced LID expression in hemiparkinsonian rats, without compromising the levodopa therapeutic efficacy [35–37].

Swings in synaptic dopamine levels, rather than high dopamine levels, are suggested to be a key factor for the development of LID. Indeed, postsynaptic dopaminergic receptors are highly plastic and can adapt to either low or high synaptic dopamine levels by altering the efficiency of intracellular signal transduction; by contrast, rapid changes in synaptic neurotransmitter levels, with high dopaminergic receptor occupancy (following each levodopa dose), followed by dramatic reduction (few hours after each levodopa dose), would impair this ability. In agreement with this view, it has been shown that dyskinetic patients present higher synaptic dopamine levels 1 h after levodopa administration compared to stable responders, while this difference disappeared few hours later [38]. Furthermore, dyskinesia is significantly dampened in advanced dyskinetic patients receiving continuous intraduodenal infusion of levodopa, which is effective in reducing swing in synaptic dopamine levels [39].

All together, these experimental findings provide strong evidences supporting the important role of serotonergic neurons in the induction and expression of LID, at least in animal models of PD.

## 5-HT1A and 5-HT1B Receptor Agonists in the Treatment of Dyskinesia

The activation of serotonergic autoreceptors is a physiological mechanism meant to avoid excessive synaptic neurotransmitter release. Thus, while in normal conditions this mechanism is able to keep synaptic serotonin levels within a physiological range, under levodopa treatment in parkinsonian states, the activation of serotonergic autoreceptors is also able to inhibit serotonergic neuron-derived dopamine release. In fact, accumulating evidence support the efficacy of 5-HT1 receptor agonists for the treatment of LID, with the 5-HT1A receptors having received most of the attention, as they are able to control serotonin neuron firing and release (See Fig. 11.1).

Several 5-HT1A receptor agonists have displayed acute and chronic anti-dyskinetic effects in both animal models and in clinical studies [30, 31, 40–44]. Unfortunately, some of these studies have also shown that the administration of 5-HT1 agonists is associated with the induction of side effects, including worsening of the anti-parkinsonian efficacy of levodopa (See Table 11.1). For instance, the partial 5-HT1A receptor agonist sarizotan demonstrated potent efficacy in reducing dyskinesias in primate and rodent models of PD and in idiopathic PD patients in early open-label studies [41]; however, the anti-dyskinetic efficacy of sarizotan could not be shown to be significant compared to placebo in a following study, where the drug increased also off-time duration [45]. Moreover, in rats, high doses of sarizotan resulted in the induction of “serotonin syndrome” components, i.e., body posture associated with motor depression. Furthermore, the selective 5-HT1A receptor agonist 8-OH-DPAT inhibited LID in dyskinetic MPTP primates but only with increased motor disability [46, 47]. The partial, non-selective 5-HT1A receptor agonist buspirone was found to reduce LID in patients [48], but two other studies have found that this effect was again associated with a reduction of the anti-parkinsonian efficacy of levodopa [49, 50].

It has recently been demonstrated that 5-HT1B receptor agonists can also elicit anti-dyskinetic effects in animal models of PD [30, 51, 52]. However, to date, no clinical trials have been performed with these agonists.

It should be stressed that the anti-dyskinetic effect of 5-HT1 receptor agonists, as seen in the studies reported above, is likely not exclusively due to the activation of 5-HT1 autoreceptors. In fact, the activation of postsynaptic 5-HT1A and 5-HT1B receptors has also been shown to produce anti-dyskinetic effect by reducing striatal release of glutamate and GABA, respectively [30, 53–55]. Accordingly, relatively high doses of 5-HT1 receptor agonists have been shown to reduce dyskinesia induced by direct dopamine receptor agonists, such as apomorphine, which is not dependent on serotonergic neuron release [30, 52, 56].

Recent results have also shown that simultaneous activation of 5-HT1A and 5-HT1B receptors, using low doses of 8-OH-DPAT and CP-94253, respectively, produced a synergistic effect on suppression of LID in 6-OHDA-lesioned rats and in MPTP-treated macaques, with near to full inhibition at doses of the two drugs

**Table 11.1** 5-HT1 receptor agonists for the treatment of LID

Reference	Drug name	Acute/chronic treatment	Animal model/ patients	Efficacy against LID	Effect on therapeutic action of levodopa
[40]	Sarizotan	Acute	6-OHDA-lesioned rats	no	
		Acute	<i>Macaca fascicularis</i>	yes	
[41]	Sarizotan	Acute	Patients in moderate-advance state of PD	yes	
[30]	8-OH-DPAT + CP-94253	Acute	6-OHDA-lesioned rats	yes	Not affected
[31]	8-OH-DPAT	Acute	6-OHDA-lesioned rats	yes	Increased
[42]	Buspirone	Acute	6-OHDA-lesioned rats	yes	
		Chronic	6-OHDA-lesioned rats	yes	
[44]	Eltoprazine	Chronic	6-OHDA-lesioned rats	yes	Partial reduction
		Acute	<i>Macaca fascicularis</i>	yes	Partial reduction
[43]	Anpirtoline	Acute	6-OHDA-lesioned rats	yes	Not affected
		Acute	<i>Macaca fascicularis</i>	yes	Partial reduction

The effects of 5-HT1 receptor agonists on LID and levodopa-induced therapeutic effects are summarized in this table

that were ineffective when given individually [30, 56]. In contrast, the same combined doses did not affect dyskinesia induced by apomorphine, suggesting that the observed effect is mainly due to the activation of presynaptic receptors [30]. Accordingly, combination of 8-OH-DPAT and CP-94253 was found to reduce extracellular dopamine levels following levodopa administration [57].

Recently, the mixed 5-HT1A/5-HT1B receptor agonist eltoprazine has been characterized for its anti-dyskinetic properties, both in rat and monkey models of PD. Eltoprazine, developed for the treatment of aggression, exhibited a safe toxicological profile and lack of serious side effects [58, 59], and is currently investigated in a clinical trial for the treatment of attention-deficit hyperactivity disorder (ADHD) (ClinicalTrials.gov Identifier: NCT01266174). In the rat 6-OHDA as well as macaque MPTP lesion models of PD, eltoprazine displayed high effectiveness in blocking LID at doses that were ineffective to reduce dyskinesia induced by apomorphine, supporting a presynaptic effect of this drug; however, the anti-dyskinetic effect of eltoprazine was accompanied by a partial reduction of the levodopa therapeutic efficacy [44, 60]. Similarly, anpirtoline, a mixed 5-HT1A/5-HT1B receptor agonist, with higher affinity for the 5-HT1B receptor, was very effective in reducing dyskinesia in rats and monkeys but at the expense of PD score at significantly effective doses [43].

Thus, as seen with other selective 5-HT<sub>1</sub> receptor agonists, the maintenance of the levodopa therapeutic effect may represent a concern in this approach, not only for eltoprazine but, possibly, for any drug with similar profile. In spite of this, eltoprazine is under investigation in a phase 2 double-blind clinical trial employing a limited number of patients, with encouraging preliminary results (see <http://www.psychogenics.com/press2012.html>).

Based on the preclinical observation that combination of 5-HT<sub>1A</sub> and 5-HT<sub>1B</sub> receptor agonists showed anti-dyskinetic effects, without worsening levodopa therapeutic properties [56], it is also possible that the ideal compound has to possess the right affinity for the two serotonergic autoreceptors to be clinically useful. Nevertheless, the narrow therapeutic window is a concern and may require a careful titration of the selected compound in each patient.

A plausible explanation for the worsening of the levodopa therapeutic effect observed after the administration of 5-HT<sub>1</sub> receptor agonists is the advanced stage of dopaminergic neuron degeneration characterizing the animal models employed in these investigations, as well as the patients recruited in the sarizotan trial. In fact, under this condition, the serotonergic neurons may mediate not only the prodyskinetic effect of levodopa but also its residual therapeutic efficacy. If so, the anti-dyskinetic effect of 5-HT<sub>1</sub> receptor agonists should unavoidably lead to parallel reduction of the therapeutic effect of levodopa. Therefore, 5-HT<sub>1</sub> receptor agonists may find better clinical efficacy in a situation of less severe dopaminergic neuron degeneration, where spared dopamine neurons can mediate the effect of levodopa, and silencing of serotonergic neurons should be less detrimental. PET imaging studies could be useful to identify patients retaining some residual dopaminergic innervation that may be more likely to benefit from 5-HT<sub>1</sub> receptor agonists. On the other hand, for the same reason, these patients are also less likely to suffer from severe dyskinesia.

It should also be mentioned that sarizotan, like other 5-HT<sub>1</sub> receptor agonists, such as buspirone, has antagonistic activity for the dopaminergic D<sub>2</sub> receptors that may have contributed to the negative outcome of the clinical trial [61, 62]. Moreover, these compounds are able to target only one autoreceptor subtype, and sufficient anti-dyskinetic efficacy may be obtained at relatively high doses of the drugs, which are likely to also affect postsynaptic 5-HT<sub>1</sub> receptors.

Therefore, new large clinical investigations employing more selective 5-HT<sub>1A</sub>/5-HT<sub>1B</sub> receptor agonists are warranted to clarify the role of serotonin neurons in the appearance of LID in PD patients and to verify whether pharmacological silencing of serotonin neurons is a feasible therapeutic approach for the treatment of LID.

## **5-HT<sub>2A</sub> Receptors Antagonists in the Treatment of Dyskinesia**

Serotonergic 5-HT<sub>2A</sub> receptors are localized at postsynaptic level, and in general they exert an excitatory effect. The role of 5-HT<sub>2A</sub> receptors in the expression of dyskinesia has been recently confirmed in a study by Riahi et al. [63] where they



showed an increase at striatal level of these receptors in levodopa dyskinetic compared to non-dyskinetic monkeys, suggesting a possible use of drugs targeting these receptors for the treatment of dyskinesia. Preclinical and clinical studies have demonstrated the effect of drugs acting on 5-HT<sub>2A</sub> receptors in controlling levodopa-induced motor complications [64, 65]; interestingly, one clinical study reported the ability of aripiprazole, a 5-HT<sub>2A</sub> receptor antagonist and partial 5-HT<sub>1A</sub> and dopamine D<sub>2</sub> receptor agonist, to reduce LID without worsening motor performance in PD patients [66]; however, it is difficult to establish the contribution of each receptor subtype, given that the effect may also be due to the activation of 5-HT<sub>1A</sub> receptors. In MPTP-treated primates, the selective 5-HT<sub>2A</sub> inverse agonist pimavanserin was recently demonstrated to reduce LID by 36 % without worsening motor scores [67]. However, it has also been reported that the selective 5-HT<sub>2A</sub> antagonist ritanserin alleviated LID but at the expense of levodopa-induced therapeutic action [68, 69]. By contrast, the selective 5-HT<sub>2A</sub> antagonist volinanserin was not effective in reducing LID in 6-OHDA-lesioned rats [70].

Further work is required to establish whether 5-HT<sub>2A</sub> antagonists could be useful in dyskinetic patients.

## **SERT as a Possible Target for Dyskinesia**

Recent evidence has demonstrated the implication of the SERT in the pathophysiology of LID; Rylander et al. [33] observed a significant upregulation of SERT expression in the striatum of dyskinetic animals, both in rats and nonhuman primates, as well as in dyskinetic patients, which provided support to the idea that the serotonergic system is involved in the appearance of LID also in PD patients. Accordingly, few preclinical studies have shown a significant reduction of dyskinesia after blockade of the serotonin transporter by SSRIs. Thus, acute [35] and chronic [37, 71] administration of the serotonin reuptake inhibitors citalopram and paroxetine in levodopa-dyskinetic rats resulted in a significant reduction in AIMS severity, without affecting the anti-parkinsonian action of levodopa [35]. The anti-dyskinetic effect of SSRIs is likely to be due to a combination of different mechanisms: (i) activation of presynaptic 5-HT<sub>1</sub> receptors by serotonin, which may reduce dopamine release, as seen for selective 5-HT<sub>1</sub> agonists; (ii) blockade of dopamine reuptake by serotonergic neurons, which may reduce swings in synaptic dopamine levels; and (iii) activation of postsynaptic serotonin receptors. In fact, the activation of postsynaptic 5-HT<sub>1</sub> receptors by selective agonists has been shown to provide anti-dyskinetic effect in parkinsonian rats. In support of a possible postsynaptic effect of SSRIs, a significant 47 % reduction of apomorphine-induced dyskinesias was observed in patients treated with fluoxetine, without modification of parkinsonian motor disability [72]. In contrast, short-term paroxetine treatment did not affect dyskinesia induced by intravenous levodopa [73]. Clinical investigations are needed to further explore the use of SSRIs as anti-dyskinetic agents.

## Conclusions

An overwhelming body of experimental evidence suggests that the serotonin system is implicated in the appearance of LID in animal models of PD. Moreover, accumulating clinical results appear to support a key role of this system also in PD patients. Dampening the release from the serotonin neurons has been shown to be a promising approach in preclinical models. Concerns have been raised about the clinical feasibility of this approach, as not only dyskinesia but also the therapeutic effect of levodopa may depend on dopamine release from the serotonin neurons in advanced stages of disease. However, few compounds have been tested in patients so far, and most of them also presented antagonist activity for the dopamine receptors, which may have played a role in the observed worsening of the levodopa therapeutic efficacy. Thus, new clinical trials employing more selective serotonin 5-HT<sub>1</sub> receptor agonists are warranted. The effect of SSRIs should also be further investigated.

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