5-HT_{1A} agonists and dyskinesia in Parkinson's disease: a pharmacological perspective

Philippe Huot*,^{1,2,3}

¹Neurodegenerative Disease Group, Montreal Neurological Institute, Montreal, QC, H3A 2B4, Canada

²Department of Neurology & Neurosurgery, McGill University, Montreal, QC, H3A 2B4, Canada

³Division of Neurology, McGill University Health Centre, Montreal, QC, H3A 2B4, Canada

*Author for correspondence: Tel.: + 1 514 398 5957; Fax: + 1 514 398 2304; philippe.huot@mcgill.ca

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Activation of 5-HT_{1A} receptors is a potential approach to reduce L-3,4-dihydroxyphenylalanine (L-DOPA)-induced dyskinesia in Parkinson's disease (PD). However, in clinical trials, 5-HT_{1A} agonists have either failed to be superior to placebo or have worsened motor function. Here, we briefly discuss these trials and reflect on possible causes for these so far disappointing results with these promising drugs.

L-DOPA-induced dyskinesia eventually affects as many as 94% of patients with PD [1]. Because the dopaminergic system undergoes degeneration in PD, taking advantage of nondopaminergic neurotransmitters, such as the serotonin (5-HT) system, has been the focus of pharmacological research to alleviate dyskinesia over the past decades. The 5-HT system is complex, with 14 subtypes of receptors and 1 transporter [2]. Despite the complexity of the 5-HT system, only three 5-HT-related targets have been consistently studied to alleviate dyskinesia, 5-HT_{1A} and 5-HT_{2A} receptors as well as the 5-HT transporter. More recently, drugs targeting the 5-HT_{1A} receptor have reached clinical trials for dyskinesia-related end points and these will be the focus of this editorial.

In the dyskinetic state, the 5-HT system plays a significant role in the conversion of L-DOPA into dopamine and an ensuing erratic, nonphysiological, dopamine release into the striatum [3]. An important subset of 5-HT_{1A} receptors are autoreceptors and upon activation in the dyskinetic state, these 5-HT_{1A} autoreceptors regulate dopamine release [4]. If striatal dopamine release is reduced beyond a certain level, yet maintained above a certain threshold, it might theoretically be possible to reduce dyskinesia while relieving parkinsonian symptoms [5]. However, it has so far proven difficult to remain within this therapeutic window in clinical trials. Thus, despite promising results in experimental models of PD [6], the nonselective 5-HT_{1A} full agonist sarizotan did not alleviate dyskinesia compared with placebo in two Phase III studies [7] and in a Phase II study, high dose of sarizotan worsened motor function [8]. Similarly, tandospirone, a 5-HT_{1A} partial agonist, reduced dyskinesia, but also negatively impacted on parkinsonian symptoms, in a Phase II trial [9]. Comparable results were obtained at the Phase II level with the 5-HT_{1A} partial agonist buspirone, with which it was difficult to separate antidyskinetic benefit from deleterious effect on motor function [10]. Two clinical trials are currently ongoing that explore the antidyskinetic potential of buspirone on L-DOPA-induced dyskinesia as well as its effect on motor function (<https://clinicaltrials.gov>: NCT02589340, NCT02617017). More recently, the 5-HT_{1A} partial agonist eltoprazine effectively alleviated dyskinesia in a dose-finding Phase I/IIa trial, without adversely affecting the antiparkinsonian action of L-DOPA [11]. Despite these encouraging findings, eltoprazine did have deleterious effects on L-DOPA antiparkinsonian benefit in experimental PD [12], suggesting that it may have a narrow therapeutic window. Another Phase II trial that assesses the antidyskinetic potential of eltoprazine as well as its effects on motor function is currently ongoing and will provide important details regarding the tolerability of eltoprazine by PD patients (NCT02439125).

The studies cited above indicate that 5-HT_{1A} agonists may alleviate dyskinesia in PD, but concerns remain. Indeed, all of the positive results cited above were achieved at the Phase II level, with sarizotan failing in Phase III trials; whether other 5-HT_{1A} agonists would do better than the placebo in Phase III studies remains to be demonstrated. Second, this class of drugs may have a narrow therapeutic window, as highlighted by their propensity to adversely affect motor function.

With respect to the latter, an argument that can be raised against this possibly narrow therapeutic window is that the drugs discussed above, despite being labelled as 5-HT_{1A} agonists, interact with other receptors, which may possibly be incriminated in their adverse effects on motor function. Thus, sarizotan [13] and bupirone [14] both antagonize dopamine D₂ receptors, the former more than the latter. Unlike sarizotan and bupirone, eltoprazine does not appear to interact with dopamine receptors, but harbors significant affinity for 5-HT_{1B} and 5-HT_{2C} receptors, at which it acts as an agonist and an antagonist, respectively [15]. Although it has not been established that antagonizing 5-HT_{2C} receptors hinders motor function, stimulation of 5-HT_{1B} receptors interfered with the antiparkinsonian action of L-DOPA, in a preclinical study [16] and perhaps the interaction of eltoprazine with 5-HT_{1B} receptors underlies its possibly narrow therapeutic window. However, clinical trials on dyskinesia with selective 5-HT_{1B} agonists are lacking and would provide important information pertaining to the tolerability of this class of drugs in the PD population.

However, this selectivity-based argument cannot be convincingly raised in the case of tandospirone, which is more selective than each of sarizotan, bupirone and eltoprazine for its primary target [17]. Then, does the fact that tandospirone is a partial 5-HT_{1A} agonist underlie its negative effect on motor function? Could a partial agonist effect also underlie the possible worsening of motor function with eltoprazine and bupirone or is the propensity of eltoprazine and bupirone to interfere with motor function related to their affinity for 5-HT_{1B} and dopamine D₂ receptors? These questions remain unanswered.

Emanating from the discussion above, another equally unanswered question is: will it be possible to alleviate dyskinesia through stimulation of 5-HT_{1A} receptors, in a way that will be safe and well tolerated by PD patients? Although there have been few studies with a limited number of molecules, the studies cited above suggest that 5-HT_{1A} agonists that also antagonize dopaminergic and/or activate 5-HT_{1B} receptors might adversely affect motor function. Then, perhaps agonists with high selectivity for 5-HT_{1A} receptors are the way forward, but the tandospirone trial cited above suggests that these highly-selective 5-HT_{1A} agonists should not be partial agonists.

Highly-selective full agonists at 5-HT_{1A} receptors have not entered dyskinesia-related clinical trials yet, but evidence from preclinical studies somewhat casts doubt on the potential tolerability of these drugs by PD patients. Thus, in a study conducted in the parkinsonian nonhuman primate, the highly-selective 5-HT_{1A} full agonist F-15599 alleviated dyskinesia and had no impact on parkinsonism [18]. In contrast, in another study performed in the parkinsonian primate, another highly-selective 5-HT_{1A} full agonist, *R*-(+)-OH-DPAT reduced dyskinesia, but at the expense of worsening motor function [19]. Based on these two studies, whether PD patients would be able to tolerate 5-HT_{1A} full agonists is uncertain, but promising candidates such as befiradol (www.parkinsons.org.uk/news/investing-new-treatment-dyskinesia) could soon be advanced to clinical testing and were it to happen, would provide important information as to the efficacy and tolerability of highly-selective 5-HT_{1A} full agonists, which will be informative as to the potential to further develop this class of agents.

The evidence discussed above suggests that separating antidyskinetic effect from adverse effect on motor function through 5-HT_{1A} receptor stimulation might prove to be an arduous task. This might be linked to what is regarded as the key mechanism of action of 5-HT_{1A} agonists in dyskinesia, regulation of dopamine release, as seen above. However, 5-HT_{1A} agonists may not act solely through reduction of dopamine release, but may also dampen glutamatergic transmission [20]. It has previously been suggested that the development of 5-HT_{1A} agonists that would be able to act selectively to modulate glutamatergic transmission, while interfering with dopaminergic transmission to a minimum or not at all, might be an effective way to alleviate dyskinesia without adversely affecting motor function [21]. However, such compounds have not been tested in clinical settings for dyskinesia yet and much remains to be learnt about their efficacy and tolerability in the clinic.

In conclusion, despite their attractive mechanism of action, 5-HT_{1A} agonists have yet to reach their full potential as effective and well-tolerated antidyskinetic agents. Clinical trials are ongoing and drugs are in preclinical development which will, hopefully, enable us to improve the quality of life of PD patients with dyskinesia with this promising, yet complex pharmacological target.

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