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Viewpoint

Adjuncts to Dopamine Replacement: A Pragmatic Approach to Reducing the Problem of Dyskinesia in Parkinson's Disease

Jonathan M. Brotchie, BSc(Hons), PhD

Manchester Movement Disorder Laboratory, Division of Neuroscience, School of Biological Sciences, University of Manchester, U.K.

Summary: Dyskinesias following long-term dopamine replacement therapy are a major limitation of current treatments for Parkinson's disease. Recently, attention has been focused on the concept of using non-dopaminergic adjuncts to currently available therapies in an attempt to reduce the problem of dyskinesia. Thus, an enhanced understanding of the neural mechanisms underlying dyskinetic symptoms has led to the realization that it might be possible to manipulate non-dopaminergic systems and reduce dyskinesia without compromising the anti-parkinsonian efficacy of drugs such as L-dopa. This article discusses how non-dopaminergic manipulations could reverse the abnormalities in basal ganglia circuitry responsible for generating dyskinesia. It is proposed that potential anti-dyskinetic drugs might include glutamate (NMDA) receptor antagonists, opioid receptor antagonists, cannabinoid receptor agonists or antagonists, α_2 adrenergic receptor antagonists, and 5-HT-enhancing agents. **Key Words:** Parkinson's disease—Dyskinesia—MPTP

Should patients with Parkinson's disease be treated with antihypertensive drugs even if they do not have problems with their blood pressure? Should these patients receive antidepressant therapy even if they are not depressed? This article discusses the possibility of targeting non-dopaminergic transmitter systems to reduce the side effects of dopamine replacement in Parkinson's disease.

Dyskinesias following long-term dopamine replacement therapy are arguably the major limitation of current treatments for Parkinson's disease. This dyskinesia, characterized by idiosyncratic mixtures of chorea and dystonia, can become so debilitating as to essentially remove the clinical benefit of dopamine replacement therapy. Although it appears possible to avoid the appearance of dyskinesias if certain subtype-selective dopamine receptor agonists such as bromocriptine, rather than L-dopa, are administered de novo, L-dopa-based therapy remains a major weapon in our anti-parkinsonian armory. The reasons behind the continued reliance on L-dopa probably involve combinations of the poor anti-parkinsonian efficacy, side effects, limited availability, and limited experience of directly acting dopamine receptor agonists. Indeed, although studies in MPTP-lesioned primates show promise (no dyskinesia is observed after several weeks of treatment with the dopamine D2 receptor agonist ropinirole de novo), to date we still await convincing evidence from the clinic that the newer dopamine receptor agonists such as ropinirole, pramipexole, and ABT-431 will not elicit dyskinesia following long-term treatment. Furthermore, it is not clear that the anti-parkinsonian efficacy of these agents is as great as L-dopa, or the mixed agonist apomorphine, in more severely affected patients.

Once the basal ganglia have been primed to elicit dyskinesia in response to L-dopa, primate and clinical studies suggest that it is extremely difficult, if not impossible, to alleviate parkinsonian symptoms with these direct dopamine receptor agonists without eliciting dyskinesia. Single doses of L-dopa may be sufficient to prime for

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Address correspondence and reprint requests to Dr. Jonathan M. Brotchie, Manchester Movement Disorder Laboratory, Division of Neuroscience, 1.124 Stopford Building, School of Biological Sciences, University of Manchester, M13 9PT, U.K.

dyskinesia not only in response to L-dopa, but also for subsequent treatment with direct dopamine receptor agonists. Thus, for the vast majority of patients with Parkinson's disease who have been treated at some time or another with L-dopa, the appearance of dyskinesias is all but inevitable. The treatment of these patients will remain a challenge well into the next century. At the present time, the treatment options for patients with dyskinesia are limited and largely experimental. For instance, pallidotomy can directly reduce dyskinesia whereas subthalamic nucleus stimulation can, by lowering the dose of L-dopa required to alleviate parkinsonian symptoms, indirectly reduce the problem of dyskinesia. However, functional neurosurgery requires a combination of neurologic and neurosurgical expertise that makes it difficult to apply widely. A pharmacologic therapy for Parkinson's disease that was not compromised by dyskinesia would represent a major advance in anti-parkinsonian therapeutics.

Despite nearly 40 years of research, no drug has emerged that is better than dopamine replacement at reversing parkinsonian symptoms and so L-dopa remains the gold standard to which all new therapies must be compared. One might therefore take the pragmatic view that we must develop pharmacologic strategies that will allow us to continue to take advantage of the anti-parkinsonian actions of dopamine replacement in a manner that is not compromised by dyskinesia. Thus, attention, both in animal studies and increasingly in the clinic, has been focused on the concept of using non-dopaminergic adjuncts to dopamine replacement therapy that reduce dyskinesia.

Theoretically one can imagine that adjuncts to dopamine replacement might provide a solution to the problem of dyskinesia by:

1. Preventing the priming of dyskinesia. Thus, one might inhibit the neural mechanisms responsible for the conversion of the brain from a state in which dopamine receptor stimulation has anti-parkinsonian effects to one in which dopamine receptor stimulation generates dyskinesia. However, while it is clear that fluctuating stimulation of dopamine receptors is the driving force behind priming for subsequent generation of dyskinesia, the cellular changes underlying these effects and the role of non-dopaminergic systems remain to be fully elucidated. It therefore appears unlikely that, in the short-term, clinically applicable strategies can be developed. Furthermore, for this approach to be effective, it would obviously have to be initiated before dyskinesia became established and so would not be applicable to the vast numbers of patients with dyskinesia.
2. Preventing the generation of dyskinetic symptoms in the patient who has been primed. Recent advances in our understanding of the neural mechanisms underlying the generation of dyskinetic symptoms have made this approach a realistic possibility and are considered in some detail below.
3. Reversing the changes in neural function responsible for priming, that is, "depriming," the dyskinetic patient such that, in essence, the pharmacologic clock may be turned back and one might treat successfully once more with dopamine replacement. As with the priming process, at present, the molecular and cellular mechanisms underlying the maintenance of the brain in the dyskinetic state are poorly understood. However, great advantages would emerge if one were able to flip the appropriate molecular switches and reset the basal ganglia to respond to dopamine replacement therapy in a manner similar to that expected in a previously untreated patient. Such a treatment might allow a dramatic extension in the time for which L-dopa could be beneficially used or might even allow the introduction of the new generation dopamine receptor agonists if ongoing trials demonstrate that their long-term administration truly does not lead to the generation of dyskinesia.

The remainder of this article focuses on how our increased understanding of the neural mechanisms responsible for the generation of dyskinetic symptoms in the primed brain might allow the development of novel adjunctive approaches to dopamine replacement in Parkinson's disease. It now appears possible to manipulate non-dopaminergic systems to reduce L-dopa-induced dyskinesia. In all cases, the development of potential therapies based on adjuncts to dopamine replacement is either at the stage of animal experiments (predominantly in the MPTP-treated primate model of Parkinson's disease) or in the early stages of clinical study.

THE NEURAL MECHANISMS UNDERLYING THE GENERATION OF L-DOPA-INDUCED DYSKINESIA IN PARKINSON'S DISEASE

Studies from several laboratories across the world, using a wide range of techniques, have suggested that the firing rate of neurons in the output regions of the basal ganglia (the medial pallidal segment, GPm, and substantia nigra pars reticulata, SNr) is dramatically lower in situations where dopamine replacement therapy elicits

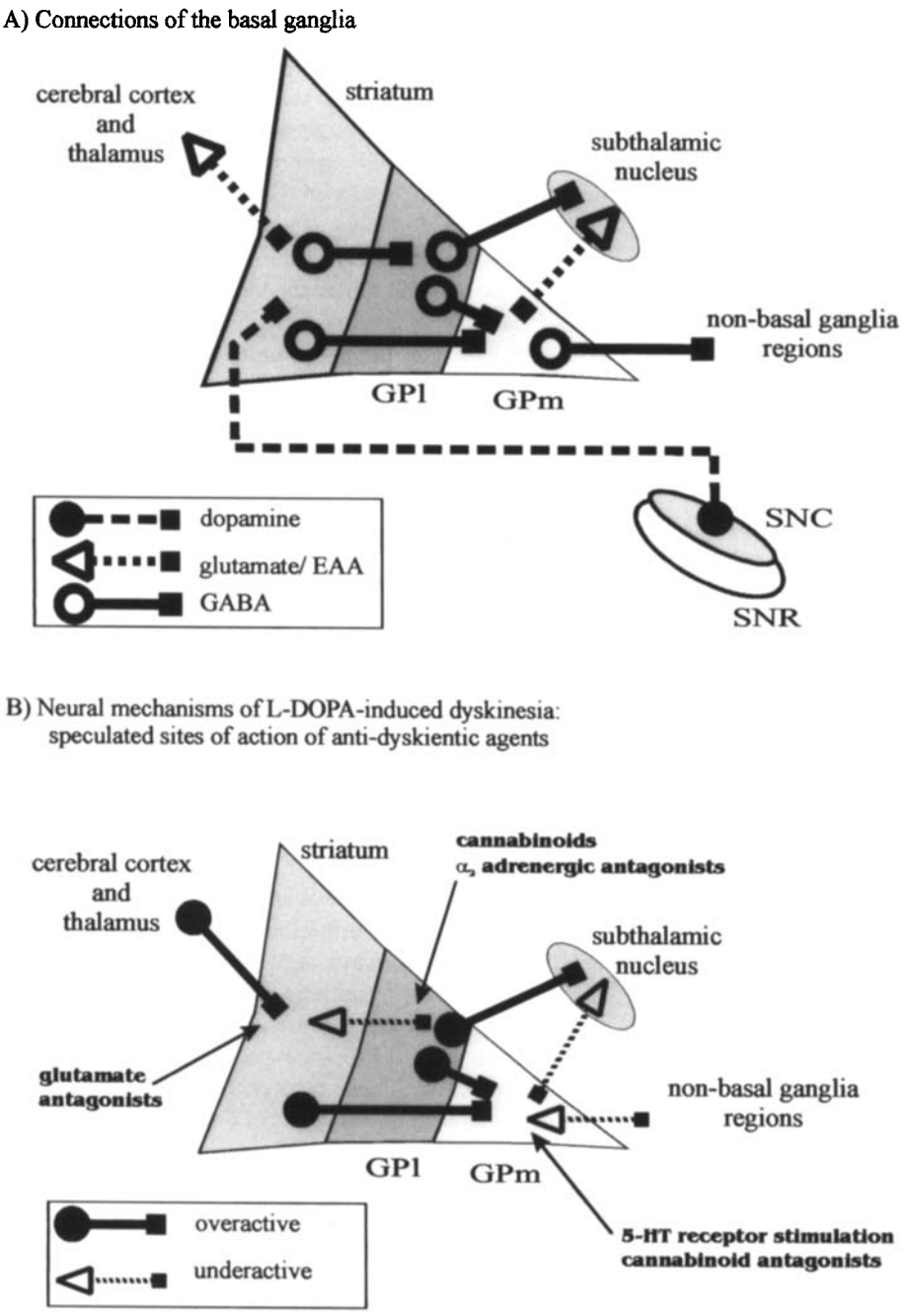

FIG. 1. Neural mechanisms underlying L-dopa-induced dyskinesia in Parkinson's disease: potential sites of pharmacologic manipulation. This figure illustrates the major connections between the components of the basal ganglia (**A**) and the changes in the firing rates these pathways thought to occur in L-dopa-induced dyskinesia (**B**). The proposed sites of action of drugs shown to reduce L-dopa-induced dyskinesia are also highlighted (**B**). Abbreviations: GPl, lateral segment of the globus pallidus; GPm, medial segment of the globus pallidus; SNC, substantia nigra pars compacts; SNR, substantia nigra pars reticulata; EAA, excitatory amino acid.

dyskinesia rather than simply alleviating parkinsonian symptoms.[1,2] Several abnormalities in the functioning of the circuitry of the basal ganglia may underlie this. For instance, it is thought that the lateral pallidal segment (GPl) becomes overactive in L-dopa-induced dyskinesia. It has thus been suggested that such changes lead to underactivity of the subthalamic nucleus and reduced excitation of the output regions of the basal ganglia. This situation is reminiscent of underlying the generation of symptoms in other forms of dyskinesia, for example, hemiballism and choreiform movements in Huntington's disease. Furthermore, overactivity of the GPl would lead to increased inhibition of the output regions by virtue of a connection between GPl and GPm/SNr. Additionally, it has been suggested that, in L-dopa-induced dyskinesia, the "direct" connection between the striatum and GPm/SNr may become overactive leading directly to increased inhibition of the output regions of the basal ganglia.

NON-DOPAMINERGIC ADJUNCTS TO DOPAMINE REPLACEMENT: THEORY AND APPLICATION

This enhanced understanding of the neural mechanisms underlying dyskinetic symptoms has led to the realization that it might be possible to manipulate non-dopaminergic systems and reduce the side effects of dopamine replacement therapy without compromising the anti-parkinsonian efficacy of such treatments. However, in the cases described below, one can offer speculations as to how non-dopaminergic manipulations could reverse the abnormalities in basal ganglia circuitry responsible for generating dyskinesia (Fig. 1).

Thus, it is proposed that non-dopaminergic drugs could attenuate dyskinesia by:

- Reducing the activity of the direct striatal output pathway—glutamate receptor antagonists
- Increasing GABAergic inhibition of the GPl—opioid receptor antagonists, cannabinoid receptor agonists, α_2 adrenergic receptor antagonists
- Increasing the activity of the output regions of the basal ganglia—opioid receptor antagonists, cannabinoid receptor antagonists, 5-HT-enhancing agents

Glutamate Receptor Antagonists

If L-dopa-induced dyskinesia is generated, in part at least, by overactivity of the direct pathway, then it might be hypothesized that reducing the excitatory drive to striatal neurons would reduce dyskinetic symptoms. Such a hypothesis is consistent with several reports, both in the MPTP-treated primate model of Parkinson's disease and in the clinic, that agents acting to antagonize the NMDA subtype of glutamate transmission can reduce L-dopa-induced chorea.[3] However, it is apparent that glutamate antagonists exacerbate L-dopa-induced dystonia. This suggests different, although potentially overlapping, neural mechanisms for these two major forms of L-dopa-induced dyskinesia. For instance, overactivity of the direct striatal output pathway may play a greater role in generating chorea than dystonia whereas the neural mechanisms underlying dystonia may rely more on underactivity of striatal outputs to GPl. Alternatively, the glutamate receptors driving striatal output neurons may have different pharmacologic characteristics in chorea as opposed to dystonia. As our understanding of the effects of potential antidyskinetic drugs emerges, it is likely that different adjuncts to L-dopa may prove to be more appropriate for certain patients with specific patterns of dyskinesia.

Opioid Receptor Antagonists

The force-driving overactivity of the GPl in L-dopa-induced dyskinesia was unclear until recently. 2-deoxyglucose metabolic tracing studies found that nerve terminal activity in GPl was unchanged suggesting no major changes in action in firing rate in the indirect striatal output cells. Thus, attention focused on identifying abnormalities in the mechanisms that might modulate GABAergic transmission in the indirect pathway. Striatal output neurons projecting to GPl use enkephalin as a co-transmitter with GABA. One of the roles of this enkephalin is to modulate the actions of the GABA with which it is released. Enkephalin, acting at δ opioid receptors, reduces the release of GABA from the terminal. It is thus apparent that the GABAergic actions induced by a given number of action potentials can be carefully modulated such that the higher the enkephalinergic tone, the less the GABAergic influence. Indeed, enhanced enkephalinergic transmission appears to accompany the generation of L-dopa-induced dyskinesia. Our group has found that, in MPTP-treated primates, the levels of mRNA encoding the enkephalin precursor preproenkephalin-A (PPE-A) are elevated after the induction of dyskinesia subsequent to repeated dopamine replacement therapy. Similar changes are also seen in the dopamine-depleted striatum of the 6-OHDA-lesioned rat model of Parkinson's disease following repeated dopamine replacement therapies that would be expected to elicit dyskinesia in the clinic. Furthermore, repeated treatment of MPTP-lesioned monkeys with ropinirole in a manner that does not elicit dyskinesia reduces the expression of PPE-A. It should be noted, however, that two other groups have studied PPE-A expression in primate models of dyskinesia. These reports did not demonstrate a treatment-induced elevation in PPE-A expression above that seen in the untreated parkinsonian state. (The reason behind this discrepancy may reflect the fact that these studies did not account for the topographic organization of basal ganglia circuitry in their analyses.)

We have thus suggested that enhanced enkephalinergic transmission in GPl would lead to dyskinesia by reducing GABA release.[5] If the balance of transmitter release is altered such that enkephalin predominates over GABA, less GABA will be released from the terminals of the striatal projection to GPl. Reduced GABAergic inhibition would lead to overactivity of the GPl projections to STN, GPm, and SNr and subsequent generation of dyskinesia as described above.

It has also been suggested that repeated dopamine receptor stimulation may lead to enhanced dynorphinergic transmission in the striatal output pathway projecting di-

rectly to the output regions of the basal ganglia. Within the output regions of the basal ganglia, dynorphin acting at κ opioid receptors reduces glutamate release from subthalamic nucleus efferents. Such a reduction in the excitatory drive to basal ganglia output neurons would, as outlined above, also be expected to generate dyskinesia.

Data are now beginning to emerge suggesting that enhanced opioidergic transmission may be a cause, rather than an effect, of the generation of L-dopa-induced dyskinesia. Thus, we have been able to demonstrate that in MPTP-treated marmosets that normally show florid dyskinesia when treated with dopamine-replacing agents, co-administration of L-dopa with the opioid receptor antagonists naltrexone and naloxone significantly reduces the severity of dyskinesia without affecting the anti-parkinsonian efficacy of L-dopa. Similar results have been observed in small-scale trials in patients with Parkinson's disease.[6,7] However, the development of opioid antagonist adjunctive therapy to dopamine replacement requires further refinement because previous studies in both MPTP-treated macaques and Parkinson's disease patients have reported that naltrexone and low doses of naloxone do not have antidyskinetic effects.[8,9]

α_2 Adrenergic Receptor Antagonists and Cannabinoid Receptor Agonists

Whereas the favored candidate for the cause of decreased GABAergic inhibition of the GPl may now be regarded as elevated enkephalinergic inhibition of release, several studies in both people and monkeys suggest that it might be possible to reduce dyskinesia by increasing pallidal GABA transmission by targeting other modulatory receptors. Both cannabinoid and α_2 adrenergic receptors are synthesized by striatal output neurons and are expressed on the terminals of the striatal outputs to GPl. Activation of cannabinoid receptors can decrease GABA uptake, whereas activation of α_2 adrenergic receptors reduces GABA release. Thus, either cannabinoid receptor agonists or α_2 adrenergic receptor antagonists might be capable of enhancing GABA levels in GPl and so reduce the changes in neural activity responsible for generating dyskinesia. In both monkeys and people, α_2 adrenergic receptor antagonists (such as yohimbine, idazoxan, and rauwolscine) appear to be capable of providing potentially clinically useful relief of dyskinesia with little or no reduction in anti-parkinsonian efficacy of L-dopa.[8,10,11] Both choreic and dystonic dyskinesia appear to respond equally. In the MPTP-treated primate, the cannabinoid receptor agonist nabilone can provide significant, but not total, alleviation of dyskinesia. In the clinic, preliminary studies suggest that cannabinoids might be most effective in reducing dystonia.

5-HT Enhancement

In recent years it has become apparent that, in addition to glutamate and GABA, one of the most important influences on the activity of basal ganglia outputs is 5-HT-driven excitation of GPm and SNr neurons. These excitatory effects are mediated by 5-HT_{2c} receptors that are elevated specifically in these regions in patients with L-dopa-induced dyskinesia. Stimulation of 5-HT_{2C} receptors may therefore be a means to increase the activity of GPm/SNr and alleviate dyskinesia. To date, no selective 5-HT_{2C} agonists have been tested for antidyskinetic efficacy either in animal models or in the clinic. However, in both MPTP-treated monkeys and people, it appears that enhancing 5-HT transmission with 5-HT reuptake inhibitors (SSRIs) such as fluoxetine can attenuate dyskinesia observed subsequent to dopamine replacement therapy.[8,12]

Cannabinoid Receptor Antagonists

Most recently, it has been reported, in MPTP-treated monkeys, that the cannabinoid receptor antagonist SR141716A can abolish L-dopa-induced dyskinesia without diminishing the anti-parkinsonian action of L-dopa.[13] These data are particularly exciting because they suggest for the first time that endogenous cannabinoids have a role to play in the control of voluntary movement. It is proposed that, after dopaminergic stimulation of the direct pathway, dyskinesia is generated because endogenous cannabinoids are released as co-transmitters with GABA and dynorphin. These cannabinoids then activate cannabinoid receptors on the terminals of the direct pathway and act to reduce GABA re-uptake from the synapse. In this way, cannabinoids would act to enhance inhibition of GPm and SNr. Blockade of this mechanism would reduce dyskinesia. The fact that cannabinoid receptor stimulation can enhance GABA transmission in GPl and GPm/SNr probably underlies the inability of exogenous cannabinoids to completely alleviate akinesia (see above). Targeting of the GPl must be achieved if cannabinoid receptor-stimulating drugs would have maximal effect. However, by blocking the actions of endogenous cannabinoids released selectively from the direct pathway in the dyskinetic state, cannabinoid receptor antagonists will selectively target one of the key mechanisms responsible for generating dyskinesia. The development of clinically available cannabinoid receptor antagonists is awaited with great anticipation.

CONCLUSION

The last 5 years have witnessed the emergence of an initial understanding of symptom generation in L-dopa-induced dyskinesia. Many non-dopaminergic manipula-

tions have been clearly shown to be capable of reducing L-dopa- and dopamine receptor agonist-induced dyskinesia. The mechanism of actions for many of these can be speculated on. Much work needs to be done; the proposed mechanisms of action of the anti-dyskinetic therapies described above remain to be confirmed. Furthermore, as our understanding progresses, we will undoubtedly identify additional approaches to reducing dyskinesias, for instance the β adrenergic receptor antagonist propranolol can reduce L-dopa-induced dyskinesia,[14] although whether these actions result from actions within the basal ganglia is at present unclear. However, it is now realistic to expect that it will prove possible to maintain our reliance on the powerful anti-parkinsonian effects of dopamine replacement and, by using adjuncts that modulate non-dopaminergic systems, reduce the complication of dyskinesia in Parkinson's disease.

REFERENCES

1. Crossman AR. A hypothesis on the pathophysiological mechanisms that underlie levodopa or dopamine agonist-induced dyskinesia in Parkinson's disease: implications for future strategies in treatment. *Mov Disord* 1990;5:100–108.
2. Blanchet PJ, Gomez-Mancilla B, Bedard PJ. Dopa-induced 'peak-dose' dyskinesia: clues implicating D2 receptor-mediated mechanisms using dopaminergic agonists in MPTP monkeys. *J Neural Transm Suppl* 1995;45:103–112.
3. Papa SM, Chase TN. Levodopa-induced dyskinesias improved by a glutamate antagonist in parkinsonian monkeys. *Ann Neurol* 1996; 39:574–578.
4. Maneuf YP, Mitchell IJ, Crossman AR, Brotchie JM. On the role of enkephalin co-transmission in the GABAergic striatal efferents to the globus pallidus. *Exp Neurol* 1994;125:65–71.
5. Henry B, Brotchie JM. Potential of opioid antagonists in the treatment of levodopa-induced dyskinesias in Parkinson's disease. *Drugs Aging* 1996;9:149–158.
6. Trabucchi M, Bassi S, Frattola L. Effect of naloxone on the 'on–off' syndrome in patients receiving long-term levodopa therapy. *Arch Neurol* 1982;39:120–121.
7. Sandyk R, Snider SN. Naloxone treatment of L-dopa-induced dyskinesias in Parkinson's disease. *Am J Psychiatry* 1986;143:118.
8. Gomez-Mancilla B, Bedard PJ. Effect of non-dopaminergic drugs on L-dopa-induced dyskinesias in MPTP-treated monkeys. *Clin Neuropharmacol* 1993;16:418–427.
9. Rascol O, Fabre N, Blin O, et al. Naltrexone, an opiate antagonist, fails to modify motor symptoms in patients with Parkinson's disease. *Mov Disord* 1994;9:437–440.
10. Rascol O, Arnulf I, Brefel C, et al. L-dopa-induced dyskinesias improvement by an α_2 antagonist, idazoxan, in patients with Parkinson's disease. *Mov Disord* 1997;12:111.
11. Henry B, Plowright A, Fox SH, et al. *Alpha$_2$-adrenergic receptor antagonists reduce symptoms in animal models of L-dopa-induced dyskinesia.* Proceedings of the Society for Neuroscience (USA) 1997;23:291.4.
12. Durif F, Vidailhet M, Bonnet AM, Blin J, Agid Y. Levodopa-induced dyskinesias are improved by fluoxetine. *Neurology* 1995; 45:1855–1858.
13. Brotchie JM, Fox S, Henry B, et al. The cannabinoid receptor antagonist SR141716A reduces L-dopa-induced dyskinesia in the MPTP-treated primate model of Parkinson's disease. *Br J Pharmacol* 1997;123:67P.
14. Carpentier AF, Bonnet AM, Vidailhet M, Agid Y. Improvement of levodopa-induced dyskinesia by propranolol in Parkinson's disease. *Neurology* 1996;46:1548–1551.