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Continuous dopaminergic stimulation and novel formulations of dopamine agonists

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Abstract There is now accumulating evidence that the combination of progressive pathology of Parkinson's disease, the change in drug pharmacodynamics, and the pulsatile manner in which short-acting dopaminergic agents stimulate striatal dopamine receptors are the key contributing factors to the priming of the basal ganglia for induction of motor complications. Long-acting drugs provide a more physiological dopaminergic stimulation. Dopamine agonists have been extensively used as monotherapy and add-on therapy to levodopa to treat Parkinson's disease in the early stage and with motor complications. Today, the new long-acting formulation offers the advantages of an easy use and a more continuous delivery of drug. In this paper the role of new formulations of dopamine agonists in the treatment of parkinsonian patients at different stages of the disease is reviewed.

Keywords Parkinson's disease · Motor complications · Dyskinesia · Dopamine agonist · Continuous dopaminergic stimulation

Introduction

After 40 years of clinical use, levodopa therapy still offers the best symptomatic control of Parkinson's disease (PD), and all patients will require it during the course of their disease [1–5]. However, with each year of levodopa treatment, about 10% of patients will develop levodopa-associated motor complications [6, 7]. These include motor fluctuations and different types of dyskinesias [8, 9]. In many patients, 'off' periods (motor difficulty) are associated with pain, panic attacks, severe depression, confusion, and a sense of death, which makes this clinical status even more distressing for patients and their caregivers. Sometimes these non-motor symptoms can appear without a clear worsening of the motor performances (non-motor off) [10, 11].

Different drugs and therapeutic strategies have been tested in the course of the last 30 years to delay and improve motor complications. Dopamine agonists (DA) played a prominent role in this scenario and remain the a very effective treatment alone or in combination with levodopa to improve motor and non-motor fluctuations. Moreover, because of their pharmacokinetic characteristics, DA can provide a more continuous dopaminergic stimulation [12].

The concept of continuous dopaminergic stimulation

Substantia nigra pars compacta (SNc) dopaminergic neurons normally fire tonically at a rate of 3–6 Hz independent of movement, although phasic firing activity or bursting can be seen in association with reward or novel stimuli [13, 14]. This in turn is associated with relatively constant striatal dopamine levels as demonstrated by both microdialysis and amperometry [15, 16].

The situation changes in the dopamine denervated state. Here, the loss of nigral neurons impairs dopaminergic modulation of corticostriatal activity [17], resulting in plastic changes, an impaired capacity to form long-term potentiation, and long-term depression [17–19]. While

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surviving dopaminergic cells show little change in firing rate, autoregulatory mechanisms are impaired and there is a loss of stability associated with non-renewal. This implies that small fluctuations in firing rate are not compensated for, leading to less stable dopaminergic nigrostriatal activity [20]. Further, dendritic spines on striatal neurons, which are the sites of glutamate–dopamine interactions, are reduced in density and size in the denervated striatum [21, 22]. As a consequence of these changes, there is a loss of the somatotopic selectivity of neuronal firing and reduced inhibitory center surround in response to peripheral stimuli in both the striatum and GPi [23, 24]. These changes fundamentally impair basal ganglia function and its capacity to appropriately select and facilitate normal movement.

Standard replacement of levodopa does not restore basal ganglia physiology to normal. The exogenous administration of repeated doses of a short-acting formulation of levodopa (half-life of about 60–90 min) results in large and uncontrolled oscillations in striatal dopamine levels [15]. These oscillations increase with disease progression [25] due to the progressive loss of striatal dopamine terminals and their capacity to buffer fluctuations in plasma levodopa levels. This leads to a change from the normal situation in which dopamine receptors are continuously exposed to dopamine, to one in which they are exposed to alternating high and low concentrations of dopamine. This discontinuous activation of dopamine receptors is referred to as pulsatile stimulation, and further destabilizes a denervated, and already unstable basal ganglia network.

Evidence that pulsatile stimulation contributes to the development of motor complications

Both the degree of dopamine denervation and the half-life of the dopaminergic agent employed contribute to the likelihood that pulsatile stimulation of dopamine receptors will occur. In early PD patients who have an estimated 40–60% loss of SNc dopamine neurons, dyskinesias typically develop after months or years of levodopa treatment, while patients initiated on treatment with more severe dopaminergic lesions develop dyskinesias within weeks of starting levodopa [26].

The half-life of the dopaminergic agent employed is also a critical factor in the development of dyskinesia. In MPTP-lesioned monkeys, short-acting dopaminergic agents such as levodopa and some dopamine agonists (e.g. PHNO, apomorphine), rapidly induce severe dyskinesias. In contrast, long-acting dopaminergic agents (e.g. ropinirole, bromocriptine), matched to provide comparable motor benefit to levodopa-treated animals, experience a markedly reduced frequency and severity of dyskinesias [27–29]. Indeed, treatment with intermittent injections of a short-acting dopamine agonist, such as U-91356A or apomorphine, induce dyskinesia, while continuous infusion of the same agent does not [30, 31]. Dyskinesia induced by pulsatile stimulation is also associated with a series of gene and protein changes in striatal neurons [32–36]. Interestingly, these gene changes do not occur with long-acting or continuous administration of dopaminergic agents where animals do not develop dyskinesia. The pattern of neuronal firing in basal ganglia output neurons is also influenced by pulsatile administration of a dopaminergic agent. Changes in the number and duration of pauses as well as in firing frequency have been observed with pulsatile dopaminergic stimulation in STN and GPi neurons of MPTP monkeys as well as PD patients [37, 38]. Similar evidence supports the concept that motor fluctuations and wearing off are related to pulsatile stimulation [39–41]. These examples illustrate that non-physiological, pulsatile or discontinuous replacement of dopamine to the denervated striatum induces further disruptions of basal ganglia activity leading to the development of motor complications [12].

These experimental observations have been extended to the clinic. Several prospective, double-blind controlled trials support continuos dopaminergic stimulation (CDS)-based treatment approaches in early untreated PD patients. Each has demonstrated that patients randomized to initiate therapy with a long-acting dopamine agonist have a reduced risk of developing motor complications in comparison to patients randomized to initiate therapy with a short-acting formulation of levodopa [42–45]. Indeed, very few, if any, patients treated exclusively with a dopamine agonist experience dyskinesia.

Long-lasting and dramatic reductions in motor complications have also been observed in advanced PD patients, where treatment with continuous infusion of levodopa or a dopamine agonist (apomorphine, lisuride) is associated with reduced ‘off’ periods and dyskinesias [46]. For example, patients randomized to receive a continuous subcutaneous infusion of lisuride have marked reductions in both ‘off’ periods and dyskinesias in comparison to those randomized to treatment with standard oral formulations of levodopa [47].

Dopamine agonists

Since the introduction of bromocriptine in the early 1980s, several dopamine agonists have become available for the treatment of PD. Dopamine agonists are frequently employed in the management of early PD based on their having a relatively low potential to induce dyskinesia [42–45], but were initially developed as an adjunct to levodopa for more advanced patients. The addition of a dopamine agonist such as pergolide, ropinirole, pramipexole or cabergoline to levodopa in patients with motor complications

can reduce 'off' time by about 1.1–1.5 h per day [48–51]. These benefits can be obtained in conjunction with a reduction in dyskinesia, probably by permitting a reduction about a 30% reduction in the levodopa dose.

Talati et al. [52]. performed a meta-analysis of randomized placebo-controlled trials evaluating the use of dopamine agonist (DA) or placebo to pre-existing levodopa therapy for the treatment of advanced Parkinson's disease (PD). They included in the meta-analysis a total of 15 trials ($n = 4{,}380$ subjects). Adjunctive DA use resulted in greater improvement as measured by the UPDRS ADL (weighted mean difference [WMD] −2.20, 95% CI −2.64 to −1.76; $P < 0.0001$) and motor score reduction (WMD −5.56, 95% CI −6.82 to −4.31; $P < 0.0001$) as well as reduction in 'off' time measured in hours/day (WMD −1.20, 95% CI −1.78 to −0.62; $P < 0.0001$) and reduction in levodopa dose (WMD −128.5 mg, 95% CI −175.0 to −82.1; $P < 0.0001$) versus placebo. Incidence of dyskinesia and hallucinations were higher with DAs (odds ratio [OR] 3.27, 95% CI 2.65–4.03; $P < 0.0001$) and (OR 3.34, 95% CI 2.44–4.58; $P < 0.0001$). Non-ergot DAs were qualitatively better, although both ergot and non-ergot DAs showed statistically significant improvements in all UPDRS scores. The authors concluded that adjunctive DA use to levodopa is superior to levodopa alone at reducing PD symptoms in patients not controlled with monotherapy.

Novel formulations of DA-agonists

Prolonged release formulations are now available for ropinirole and pramipexole and a patch formulation for rotigotine. All of these new formulations were tested in parkinsonian patients at different stages of their disease.

Clinical studies in early Parkinson's disease

Ropinirole

Efficay and safety evaluation in Parkinson's disease (EASY PD) [53] was a multicentre, double-blind, non-inferiority crossover study involving 161 patients randomized to one of four formulation sequences: (1) immediate release-immediate release-prolonged release; (2) immediate release-prolonged release-prolonged release; (3) prolonged release-prolonged release-immediate release; (4) prolonged release-immediate release-immediate release. After a run-in period of 7 days, patients entered a 12-week dose-titration period followed by three consecutive, flexible-dose, 8-week phases of maintenance. Ropinirole immediate release (IR) was titrated according to the approved schedule; titration of ropinirole 24-h prolonged release (PR) started at a higher dose and was more rapid. At the end of the first maintenance period, half of the patients in each formulation group switched to the same or closest dose of the alternative formulation; remaining patients switched at the end of the second maintenance period.

At the end of titration, before the first dose switch, there were substantial reductions in the UPDRS motor scores: 10.4 (SD 6.06) points for PR and 8.9 (SD 5.90) for IR. During maintenance periods, both groups showed similar efficacy on the UPDRS motor score. Overall mean (standard error) change from period baseline was −0.1 (0.28) for PR, and 0.6 (0.30) IR (adjusted mean treatment difference −0.7). The study demonstrated non-inferiority of PR versus IR. In all sequences of treatment, the UPDRS motor score remained unchanged after overnight switch, indicating that similar doses of the two formulations had the same efficacy. Ropinirole 24-h prolonged release was well-tolerated when titrated more rapidly than ropinirole immediate release; overnight switching between formulations was also well-tolerated. In both groups of treatment the most common side effects were nausea and somnolence of mild to moderate severity, more frequent during titration phase and independent from ropinirole formulation.

Pramipexole

In one study the feasibility, in early Parkinson's disease (PD), of an overnight switch from immediate release (IR) pramipexole to the once-daily extended release (ER) formulation was studied [54]. Non-fluctuating patients on pramipexole IR three-times daily, alone or with levodopa, for early PD were randomly switched overnight to double-blind IR three-times daily ($n = 52$) or ER once-daily ($n = 104$) at initially unchanged daily dosage. Successful switching (defined as no worsening >15% of baseline UPDRS II + III score and no drug-related adverse event withdrawal) was assessed at 9 weeks, after optional dosage adjustments (primary endpoint), and at 4 weeks, before adjustment. Absolute difference between percentage of successful switch to ER versus IR was tested for ER non-inferiority, defined as a 95% confidence-interval lower bound not exceeding −15%. At 9 weeks, 84.5% of the ER group had been successfully switched, versus 94.2% for IR. Non-inferiority was not demonstrated, with a difference of −9.76% (95% CI: [−18.81%, +1.66%]). Both formulations were safe and well tolerated. In this study pramipexole ER was not equivalent to IR; however, the overnight switch at unchanged dosage for IR to ER was feasible in most patients.

In a second study [55] the efficacy and safety of pramipexole ER was tested in a randomized, double-blind, placebo and active comparator-controlled trial in subjects with early PD. Two hundred fifty-nine subjects were randomized 2:2:1 to treatment with ER, IR, or placebo.

Levodopa rescue was required by seven subjects in the placebo group (14%), three subjects in the pramipexole ER group (2.9%, $P = 0.0160$), and one subject in the pramipexole IR group (1.0%, $P = 0.0017$). Adjusted mean [standard error (SE)] change in Unified Parkinson Disease Rating Scale (UPDRS) II [activities of daily living (ADL)] + III (motor) scores from baseline to week 18, including post-levodopa rescue evaluations, was −5.1 (1.3) in the placebo group, −8.1 (1.1) in the pramipexole ER group ($P = 0.0282$), and −8.4 (1.1) in the pramipexole IR group ($P = 0.0153$). Adjusted mean (SE) change in UPDRS ADL + motor scores, censoring post-levodopa rescue data, was −2.7 (1.3) in the placebo group, −7.4 (1.1) in the pramipexole ER group ($P = 0.0010$), and −7.5 (1.1) in the pramipexole IR group ($P = 0.0006$). Adverse events more common with pramipexole ER than placebo included somnolence, nausea, constipation, and fatigue.

Rotigotine

The efficacy and tolerability of rotigotine transdermal system was assessed in a randomized, double-blind, multicentre, placebo-controlled study in 277 patients with early Parkinson's disease [56]. Rotigotine was administered at 2, 4, or 6 mg during 24 h, for 24 weeks. Significant differences were observed between the rotigotine-treated and placebo groups for the 20% responder rate (48% for the rotigotine group and 19% for the placebo group; $P < 0.001$). In the rotigotine group there was an improvement of 3.5 points and a worsening of 1.3 points in the placebo group in the Unified Parkinson Disease Rating Scale subtotal (parts II and III) (−15.1% for rotigotine vs. 7.3% for placebo; $P < 0.001$). Rotigotine treatment significantly increased the patients' Clinical Global Impression Scale scores (57% for rotigotine vs. 30% for placebo; $P < 0.001$) and had a positive effect on their quality of life. The most common adverse events were application site reactions, nausea, and somnolence. Rotigotine patch proved to be efficacious in the treatment of early PD.

In a head to head trial with ropinirole IR [57], where the primary endpoint was the proportion of patients with a minimum of 20% decrease in the combined Unified Parkinson's Disease Rating Scale Part II and Part III scores, rotigotine at doses < or = 8 mg/24 h did not show non-inferiority to ropinirole at doses < or = 24 mg/day. In a post-hoc subgroup analysis, rotigotine < or = 8 mg/24 h had a similar efficacy to ropinirole at doses < or = 12 mg/day.

Patients non optimally controlled with levodopa

After a few years of levodopa therapy, the majority of patients start to notice a non-optimal control of parkinsonian symptoms and a reduction of the duration of benefit following each administration. At this point the therapeutic options include the increase of levodopa or the addition of a dopamine agonist. These two options were evaluated in a study [58] where the addition of once-daily ropinirole 24-h prolonged release in PD patients not optimally controlled with levodopa at the dosage of ≤ 600 mg/day after up to 3 years of therapy was compared to increasing doses of levodopa ($n = 104$). Ropinirole prolonged release was found to significantly delay the onset of dyskinesia. During the study, the incidence of dyskinesia was inferior in the ropinirole prolonged-release group (at mean dose 10 mg/die) compared to the levodopa group (mean additional dose 284 mg/day) developed dyskinesia (3 vs. 17%, $P < 0.001$). There were no significant differences in change in Unified Parkinson's Disease Rating Scale, motor scores and activities of daily living, suggesting comparable efficacy between the two treatments. Adverse events were comparable in the two groups with nausea, dizziness, insomnia, back pain, arthralgia, somnolence, fatigue, and pain most commonly reported.

Patients with motor fluctuations

In a double-blind, placebo-controlled trial (EASE-PD) 393 subjects with PD were randomized to ropinirole 24-h or placebo [59]. At the end of the study (24 weeks) the mean dose of ropinirole was 18.8 mg/day with a mean reduction in daily levodopa of 278 mg. There was a mean reduction in daily 'off' time of 2.1 h in the ropinirole 24-h group and 0.3 h with placebo. In this trial, an interesting secondary outcome exploring non-motor symptoms were measured including depression (Beck Depression Inventory-II), quality of life (PDQ-39) and sleep (PD Sleep Scale). All these measurements were significantly improved at week 24 with ropinirole 24-h. The most common adverse events (AE) with ropinirole 24-h were dyskinesia, nausea, dizziness, somnolence, hallucinations, and orthostatic hypotension.

In a unique randomized, parallel-group, double-blind, multicentre study (PREPARED study) ropinirole PR showed to be more efficacious than ropinirole IR. In fact at week 24, ropinirole PR significantly increased the proportion of patients maintaining ≥ 20% reduction in 'off' time versus ropinirole IR (adjusted odds ratio: 1.82; 95% CI: 1.26, 2.86; $P = 0.009$. Mean (SD) doses at week 24 LOCF were: ropinirole PR, 18.6 (6.5) mg/day; ropinirole IR, 10.4 (6.4) mg/day; mean (SD) reductions from baseline in levodopa dose were −162 (226) mg and −113 (138) mg, respectively [60].

Rotigotine transdermal delivery was tested in a randomized, double-blind, placebo-controlled trial (PREFER Study) in patients with advanced Parkinson's disease [61].

Rotigotine was use at 8 or 12 mg/24 h. Compared to placebo, there were significant decreases in mean 'off' time of 1.8 h/day for the rotigotine 8 mg/24 h group and 1.2 h/day for the 12 mg/24 h group. 'On' time without dyskinesia after awakening was more than doubled in both rotigotine treatment groups versus placebo. Drug-related adverse effects included typical dopaminergic side effects, which were generally mild/moderate in intensity. Patch application site reactions including erythema and pruritus were mild to moderate and transient in the majority of instances.

Rotigotine was also compared to pramipexole in a controlled trial in patients with fluctuating Parkinson's disease. The two dopamine agonists showed the same efficacy versus placebo in reducing 'off' time and increasing 'on' time [62].

Long-acting agents do have the potential of improving nocturnal symptoms and early morning 'off' episodes as demonstrated in a recent study with rotigotine [63].

Safety

Dopamine agonists may be associated with orthostatic hypotension, cognitive impairment, psychosis, and leg swelling. Recent reports have also linked dopamine agonists with sleep disturbances and impulsive behaviors, such as pathologic gambling, compulsive eating, and hypersexuality [64–67]. A more serious concern is the risk of cardiac valvulopathy that has been observed with ergot dopamine agonists. This has been reported with pergolide and cabergoline, and is thought to relate to their 5HT-2B agonist activities [68]. Many physicians no longer prescribe this class of drug because of this problem; patients receiving them should have periodic cardiac ECHO studies.

Conclusion

There is compelling evidence that motor complications are associated with short-acting dopaminergic agents that induce pulsatile stimulation of receptors. In experimental animals CDS provided by long-acting dopamine agonists avoid dyskinesia. Further, treatment strategies employing more continuous dopaminergic stimulation from the outset of therapy delay the onset and reduce the frequency of motor complications in PD patients. The novel formulations of dopamine agonists proved to be efficacious in the treatment of Parkinson's disease. They are easier to use and provide a more continuous deliver of drug. Ropinirole PR proved to be more efficacious than the IR formulation in improving 'off' time in fluctuating parkinsonian patients. The smoother plasma profile may result also in a better tolerability and less incidence of side effects.

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References

1. Olanow CW, Watts RL, Koller WC (2001) An algorithm (decision tree) for the management of Parkinson's disease: treatment guidelines. Neurology 56(Suppl 5):S1–S86
2. Agid Y, Olanow C, Mizuno Y (2002) Levodopa: why the controversy? Lancet 360:575
3. Miyasaki JM, Martin W, Suchowersky O, Weiner WJ, Lang AE (2002) Practice parameter: initiation of treatment for Parkinson's disease: an evidence-based review. Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 58:11–17
4. Rascol O, Goetz C, Koller W, Poewe W, Sampaio C (2002) Treatment interventions for Parkinson's disease: an evidence-based assessment. Lancet 359:1589–1598
5. Korczyn AD, Nussbaum M (2002) Emerging therapies in the pharmacological treatment of Parkinson's disease. Drugs 62: 775–786
6. Marsden CD, Parkes JD (1977) Success and problems of long-term levodopa therapy in Parkinson's disease. Lancet 1:345–349
7. Marsden CD (1994) Parkinson's disease. J Neurol Neurosurg Psychiatry 57:672–681
8. Luquin MR, Scipioni O, Vaamonde J, Gershanik O, Obeso JA (1992) Levodopa-induced dyskinesias in Parkinson's disease: clinical and pharmacological classification. Mov Disord 7:117–124
9. Marconi R, Lefebvre-Caparros D, Bonnet AM, Vidailhet M, Dubois B, Agid Y (1994) Levodopa-induced dyskinesias in Parkinson's disease: phenomenology and pathophysiology. Mov Disord 9:2–12
10. Stocchi F (2009) The hypothesis of the genesis of motor complications and continuous dopaminergic stimulation in the treatment of Parkinson's disease. Parkinsonism Relat Disord 15(Suppl 1):S9–S15 (Review)
11. Stacy M, Bowron A, Guttman M, Hauser R, Hughes K, Larsen JP et al (2005) Identification of motor and non motor wearing-off in Parkinson's disease: Comparison of a patient questionnaire versus a clinician assessment. Mov Disord 20:726–733
12. Olanow CW, Obeso JA, Stocchi F (2006) Continuous dopamine-receptor treatment of Parkinson's disease: scientific rationale and clinical implications. Lancet Neurol 5:677–687
13. Grace AA (1991) Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. Neuroscience 41:1–24
14. Schultz W (1998) Predictive reward signal of dopamine neurons. J Neurophysiol 80:1–27
15. Abercrombie ED, Bonatz AE, Zigmond MJ (1990) Effects of L-DOPA on extracellular dopamine in striatum of normal and 6-hydroxydopamine-treated rats. Brain Res 525:36–44
16. Venton BJ, Zhang H, Garris PA, Phillips PE, Sulzer D, Wightman RM (2004) Real-time decoding of dopamine concentrating changes in the caudate-putamen during tonic and phasic firing. J Neurochem 89:1284–1295
17. Calabresi P (1993) Electrophysiology of dopamine–denervated striatal neurons; implications for Parkinson's disease. Brain 116:433–452

18. Centonze D, Gubellini P, Picconi B, Calabresi P, Giacomini P, Bernardi G (1999) Unilateral dopamine denervation blocks corticostriatal LTP. J Neurophysiol 82:3575–3579
19. Picconi B, Centonze D, Hakansson K, Bernardi G, Greengard P, Fisone G et al (2003) Loss of bidirectional striatal synaptic plasticity in L-DOPA-induced dyskinesia. Nat Neurosci 6:501–506
20. Rodriguez M, Gonzalez J, Sabate M, Obeso J, Pereda E (2003) Firing regulation in dopaminergic cells: effect of the partial degeneration of nigrostriatal system in surviving neurons. Eur J Neurosci 18:53–60
21. Stephens B, Mueller AJ, Shering AF, Hood SH, Taggart P, Arbuthnott GW et al (2005) Evidence of a breakdown of corticostriatal connections in Parkinson's disease. Neuroscience 132:741–754
22. Zaja-Milatovic S, Milatovic D, Schantz AM, Zhang J, Montine KS, Samii A et al (2005) Dendritic degeneration in neostriatal medium spiny neurons in Parkinson disease. Neurology 64: 545–547
23. Tremblay L, Filion M, Bedard PJ (1989) Responses of pallidal neurons to striatal stimulation in monkeys with MPTP-induced Parkinsonism. Brain Res 498:17–33
24. Filion M, Tremblay L, Bedard PJ (1988) Abnormal influences of passive limb movement on the activity of globus pallidus neurons in parkinsonian monkeys. Brain Res 444:165–176
25. De la Fuente-Fernandez R, Sossi V, Huang Z, Furtado S, Lu JQ, Calne DB et al (2004) Levodopa-induced changes in synaptic dopamine levels increase with progression of Parkinson's disease: implications for dyskinesias. Brain 127:2747–2754
26. Ballard PA, Tetrud JW, Langston JW (1985) Permanent human Parkinsonism due to 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP): seven cases. Neurology 35:949–956
27. Bédard PJ, Di Paolo T, Falardeau P, Boucher R (1986) Chronic treatment with L-dopa, but not bromocriptine induces dyskinesia in MPTP-parkinsonian monkeys. Correlation with [^{3}H]spiperone binding. Brain Res 379:294–299
28. Pearce RK, Banerji T, Jenner P, Marsden CD (1998) De novo administration of ropinirole and bromocriptine induces less dyskinesia than L-dopa in the MPTP-treated marmoset. Mov Disord 13:234–241
29. Jenner P (2000) Factors influencing the onset and persistence of dyskinesia in MPTP-treated primates. Ann Neurol 47:S90–S99
30. Blanchet PJ, Calon F, Martel JC, Bédard PJ, Di Paolo T, Walters RR et al (1995) Continuous administration decreases and pulsatile administration increases behavioral sensitivity to a novel dopamine D2 agonist (U-91356A) in MPTP-exposed monkeys. J Pharmacol Exp Ther 272:854–859
31. Bibbiani F, Costantini LC, Patel R, Chase TN (2005) Continuous dopaminergic stimulation reduces risk of motor complications in parkinsonian primates. Exp Neurol 192:73–78
32. Morissette M, Goulet M, Soghomonian JJ, Blanchet PJ, Calon F, Bédard PJ et al (1997) Preproenkephalin mRNA expression in the caudate-putamen of MPTP monkeys after chronic treatment with the D2 agonist U91356A in continuous or intermittent mode of administration: comparison with L-DOPA therapy. Brain Res Mol Brain Res 49:55–62
33. Aubert I, Guigoni C, Hakansson K, Li Q, Dovero S, Barthe N et al (2005) Increased D1 dopamine receptor signaling in levodopa-induced dyskinesia. Ann Neurol 57:17–26
34. Calon F, Grondin R, Morissette M, Goulet M, Blanchet PJ, Di Paolo T et al (2000) Molecular basis of levodopa-induced dyskinesias. Ann Neurol 47:70–78
35. Cenci MA, Tranberg A, Andersson M, Hilbertson A (1999) Changes in the regional and compartmental distribution of FosB- and JunB-like immunoreactivity induced in the dopamine-denervated rat striatum by acute or chronic L-dopa treatment. Neuroscience 94:515–527
36. Calon F, Birdi S, Rajput AH, Hornykiewicz O, Bedard PJ, Di Paolo T (2002) Increase of preproenkephalin mRNA levels in the putamen of Parkinson disease patients with levodopa-induced dyskinesias. J Neuropathol Exp Neurol 61:186–196
37. Boraud T, Bezard E, Bioulac B, Gross CE (2001) Dopamine agonist-induced dyskinesias are correlated to both firing pattern and frequency alterations of pallidal neurones in the MPTP-treated monkey. Brain 124:546–557
38. Brown P, Oliviero A, Mazzone P, Insola A, Tonali P, Di Lazzaro V (2001) Dopamine dependency of oscillations between subthalamic nucleus and pallidum in Parkinson's disease. J Neurosci 21:1033–1038
39. Juncos JL, Engber TM, Raisman R, Susel Z, Thibaut F, Ploska A et al (1989) Continuous and intermittent levodopa differentially affect basal ganglia function. Ann Neurol 25:473–478
40. Engber TM, Susel Z, Juncos JL, Chase TN (1989) Continuous and intermittent levodopa differentially affect rotation induced by D-1 and D-2 dopamine agonists. Eur J Pharmacol 168:291–298
41. Engber TM, Susel Z, Kuo S, Gerfen CR, Chase TN (1991) Levodopa replacement therapy alters enzyme activities in striatum and neuropeptide content in striatal output regions of 6-hydroxydopamine lesioned rats. Brain Res 552:113–118
42. Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE (2000) A 5 year study of the incidence of dyskinesia in patients with early parkinson's disease who were treated with ropinirole or levodopa. N Engl J Med 342:1484–1491
43. Parkinson Study Group (2000) Pramipexole versus levodopa as initial treatment for Parkinson disease. JAMA 284:231–238
44. Whone AL, Watts RL, Stoessl AJ, Davis M, Reske S, Nahmias C et al (2003) Slower progression of Parkinson's disease with ropinirole versus levodopa: The REAL-PET study. Ann Neurol 54:93–101
45. Parkinson Study Group (2002) Dopamine transporter brain imaging to assess the effects of pramipexole versus levodopa on Parkinson disease progression. JAMA 287:1653–1661
46. Nutt JG, Obeso JA, Stocchi F (2000) Continuous dopamine receptor stimulation in advanced Parkinson's disease. Trends Neurosci 23:109–115
47. Stocchi F, Ruggieri S, Vacca L, Olanow CW (2002) Prospective randomized trial of lisuride infusion versus oral levodopa in PD patients. Brain 125:2058–2066
48. Olanow CW, Fahn S, Muenter M et al (1994) A multi-center, double-blind, placebo-controlled trial of pergolide as an adjunct to Sinemet in Parkinson's disease. Mov Disord 9:40–47
49. Lieberman A, Olanow CW, Sethi K et al (1998) A multi-center double blind placebo-controlled trial of ropinirole as an adjunct to L-dopa in the treatment of Parkinson's disease patients with motor fluctuations. Neurology 51:1057–1062
50. Pinter MM, Pogarell O, Oertel WH (1999) Efficacy, safety, and tolerance of the non-ergoline dopamine agonist pramipexole in the treatment of advanced Parkinson's disease: a double blind, placebo controlled, randomised, multicentre study. J Neurol Neurosurg Psychiatry 66:436–441
51. Clarke CE, Deane KH (2001) Cabergoline for levodopa-induced complications in Parkinson's disease. Cochrane Database Syst Rev 1:CD001518
52. Talati R, Baker WL, Patel AA, Reinhart K, Coleman CI (2009) Adding a dopamine agonist to preexisting levodopa therapy versus levodopa therapy alone in advanced Parkinson's disease: a meta analysis. Int J Clin Pract 63:613–623
53. Stocchi F, Hersh BP, Scott BL, Nausieda PA, Giorgi L (2008) Ease-PD Monotherapy Study Investigators. Ropinirole 24-h prolonged release and ropinirole immediate release in early

Parkinson's disease: a randomized, double-blind, non-inferiority crossover study. Curr Med Res Opin 24:2883–2895
54. Rascol O, Barone P, Hauser RA et al (2010) Pramipexole Switch Study Group Efficacy, safety, and tolerability of overnight switching from immediate- to once daily extended-release pramipexole in early Parkinson's disease. Mov Disord 25:2326–2332
55. Hauser RA, Schapira AH, Rascol O et al (2010) Randomized, double-blind, multicenter evaluation of pramipexole extended release once daily in early Parkinson's disease. Mov Disord 25:2542–2549
56. Jankovic J, Watts RL, Martin W, Boroojerdi B (2007) Transdermal rotigotine: double-blind, placebo-controlled trial in Parkinson disease. Arch Neurol 64:676–682
57. Giladi N, Boroojerdi B, Korczyn AD, Burn DJ, Clarke CE, Schapira AH, SP513 investigators (2007) Rotigotine transdermal patch in early Parkinson's disease: a randomized, double-blind, controlled study versus placebo and ropinirole. Mov Disord 22:2398–2404
58. Watts RL, Lyons KE, Pahwa R et al (2010) Onset of dyskinesia with adjunct ropinirole prolonged-release or additional levodopa in early Parkinson's disease. Mov Disord 25:858–866
59. Pahwa R, Stacy MA, Factor SA et al (2007) EASE-PD. Ropinirole 24-h prolonged release: randomized, controlled study in advanced Parkinson disease. Neurology 68:1108–1115
60. Stocchi F, Giorgi L, Hunter B, Schapira AH. PREPARED: comparison of prolonged and immediate release ropinirole in advanced Parkinson's disease. Mov Disord (in press)
61. LeWitt PA, Lyons KE, Pahwa R, SP 650 Study Group (2007) Advanced Parkinson disease treated with rotigotine transdermal system: PREFER Study. Neurology 68:1262–1267
62. Poewe WH, Rascol O, Quinn N et al (2007) Efficacy of pramipexole and transdermal rotigotine in advanced Parkinson's disease: a double-blind, double-dummy, randomised controlled trial. Lancet Neurol 6:513–520
63. Trenkwalder C, Kies B, Rudzinska M et al (2011) Rotigotine effects on early morning motor function and sleep in Parkinson's disease: A double-blind, randomized, placebo-controlled study (RECOVER). Mov Disord 1:90–99
64. Stocchi F (2005) Pathological gambling in Parkinson's disease. Lancet Neurol 4:590–592
65. Driver-Dunckley E, Samanta J, Stacy M (2003) Pathological gambling associated with dopamine agonist therapy in Parkinson's disease. Neurology 61:422–423
66. Nirenberg MJ, Waters C (2006) Compulsive eating and weight gain related to dopamine agonist use. Mov Disord 21:524–529
67. Brodsky MA, Godbold J, Roth T, Olanow CW (2003) Sleepiness in Parkinson's disease: a controlled study. Mov Disord 18:668–672
68. Zanettini R, Antonini A, Gatto G et al (2007) Valvular heart disease and the use of dopamine agonists for Parkinson's disease. N Engl J Med 35:639–646