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·Review·

Application of the concept of continuous dopaminergic stimulation for the management of Parkinson's disease

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Continuous dopaminergic stimulation (CDS) is a prominent therapeutic concept for the treatment of Parkinson's disease (PD), which proposes that continuous brain dopamine-receptor stimulation, rather than intermittent doses of oral *L*-dopa, prevents or manages *L*-dopa-induced dyskinesias (LIDs). In the normal situation, dopaminergic neurons in the substantia nigra pars compacta fire tonically to keep the dopamine receptor stimulation at a steady-state level. But when the dopaminergic pathway is impaired, the dopamine receptor stimulation becomes intermittent or pulsatile. This pulsatile stimulation causes a series of gene and protein changes in striatal neurons, leading to alterations in the firing patterns of basal ganglia neurons that result in LIDs. Studies in animal models and clinical trials of PD have shown that approaches providing CDS, currently including patches, extended-release formulations of *L*-dopa or dopamine agonists, continuous delivery of apomorphine and duodenal *L*-dopa infusion, are associated with a decreased risk of LIDs. In this review, we summarize both preclinical and clinical evidence for the five methods that may provide CDS in theory and compare the advantages and disadvantages of these methods.

Keywords: continuous dopaminergic stimulation; application; Parkinson's disease; *L*-dopa-induced dyskinesias

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder worldwide. In 2005, there were almost 4 million PD patients over age 50 and the number is predicted to double by 2030[1]. *L*-dopa has been the most effective drug in the treatment of PD since its introduction in the late 1960s and benefits almost all PD patients[2]. However, the long-term use of *L*-dopa is often accompanied by various motor complications, such as *L*-dopa-induced dyskinesias (LIDs). After 4–6 years of *L*-dopa therapy, LIDs occur in slightly less than 40% of PD patients, but with continuous treatment this eventually increases to ~90%[3]. The most significant risk factors associated with the development of LIDs are age of onset, severity of denervation, and duration and dose of *L*-dopa treatment[4]. LIDs may decrease the quality of life, and even causes severe disability. Meanwhile, LIDs substantially raise the cost of health care[5], and their treatment is still a major challenge for physicians.

The exact mechanisms underlying LIDs remain to be fully elucidated, but evidence shows that pulsatile stimulation of striatal postsynaptic receptors related to the short plasma half-life of the drug is a key point[6]. Based on this hypothesis, the concept of continuous dopaminergic stimulation (CDS) has become central in the treatment of LIDs. CDS refers to the notion that continuous brain dopamine receptor stimulation rather than intermittent doses of oral *L*-dopa prevents pulsatile stimulation and reduces the risk of LIDs[7]. To understand the basis of using CDS in PD therapies to avoid LIDs, it is necessary to have a thorough overview of the changes that occur in LIDs[6]. In healthy individuals, dopaminergic neurons in the substantia nigra pars compacta (SNc) fire tonically at 3–6 Hz, independent of movement. In this manner, the reuptake systems maintain the synaptic dopamine at a stable level[8]. However, in

PD patients the situation is different. In advanced PD, there is severe degeneration of dopaminergic SNc neurons. Decarboxylation of *L*-dopa to dopamine then occurs in non-dopaminergic neurons, such as serotoninergic neurons, which cannot store and release dopamine in a controlled fashion. Thus the striatal dopamine levels no longer remain constant but mirror the fluctuations in plasma *L*-dopa concentration[9]. Consequently, pulsatile stimulation of dopamine receptors causes a series of gene and protein changes in striatal neurons, leading to the alterations in the firing patterns of basal ganglia neurons that result in LIDs. However, many studies have shown that therapies providing more CDS reduce or eliminate these changes[10]. For instance, in dopamine-denervated animal models, the regulation of preproenkephalin, cFos, delta FosB, JunB, [^{35}S] GTPγS, cyclin-dependent protein kinase 5, preprodynorphin, ERK1/2 DARPP-32 and D1-signalling proteins is altered when LIDs finally occur[11-15]. Similar changes have also be found in post-mortem brains from PD patients; preproenkephalin mRNA levels are significantly increased in the putamen of dyskinetic patients compared to controls and non-dyskinetic patients. Interestingly, neither gene changes nor LIDs develop in animals when the brain dopamine receptors are stimulated in a more continuous way[12]. A large body of evidence suggests that treatments offering CDS decrease LIDs. The concept of CDS has served as a rational basis for many new therapeutic methods and interventions in PD to avoid LIDs.

Currently, there are various approaches to offering CDS, such as transdermal rotigotine patches, extended-release formulations of *L*-dopa or dopamine agonists (pramipexole, for example), continuous delivery of apomorphine and duodenal *L*-dopa infusion[16] (Table 1). In this review, we summarize the current preclinical and clinical evidence concerning these methods and compare their benefits and drawbacks.

Transdermal Rotigotine Patches

Preclinical Evidence

Rotigotine is a non-ergot, enantio-selective, D3/D2/D1 dopamine agonist drug that is effective in treating PD. It was initially used orally, but the effect was limited due to its relative short half-life. Fortunately, transdermal rotigotine patches provide a relative CDS and reduce the risk of LIDs[22]. This has been reported in many classic PD animal models. In the 6-hydroxydopamine (6-OHDA)-lesioned rat, pulsatile dopaminergic treatment makes it more sensitive to locomotor activity and might induce abnormal involuntary movements. But when rotigotine is delivered in a more continuous way, no such movements occur, suggesting that continuous delivery of rotigotine has no tendency to induce LIDs in this experimental model[23]. More recently, using the MPTP-treated common marmoset as a model to mimic the behavioral characteristics of PD, Stockwell *et al.*[24] found that (1) LIDs are reduced by both pulsatile and continuous rotigotine administration compared to *L*-dopa alone, (2) continuous rotigotine delivery by the transdermal route reduces LIDs compared with pulsatile treatment, and (3) continuous rotigotine administration does not prevent *L*-dopa from inducing LIDs[24]. These observations indicate that continuous rotigotine delivery can prevent LIDs in the common marmoset, but not reverse the neuroplastic

Table 1. Potential approaches for continuous dopaminergic stimulation

Drugs	Application methods	Maximum doses
Rotigotine	Continuous transdermal patches	8 mg/24 h for early PD 16 mg/24 h for advanced PD[17]
Pramipexole	Oral administration once daily	4.5 mg/24 h[18]
Apomorphine	Continuous subcutaneous	160 mg/24 h[19]
L-dopa/carbidopa	Continuous duodenal	96 mg/24 h[20]
L-dopa/carbidopa/entacapone	Oral administration four times daily	*L*-dopa/carbidopa/entacapone 200/50/200 mg 5*/24 h[21]

PD, Parkinson's disease.

changes underlying LIDs.

Clinical Evidence

In 2009, a double-blind, open-label extension study involving 216 patients (79 placebo, 137 rotigotine) was carried out to assess the long-term safety of transdermal rotigotine patches in PD. The results from 4 years of observation indicate that long-term treatment with rotigotine is safe, efficient, and accompanied by a lower incidence of LIDs. Particularly, the rate of LIDs following the initiation of *L*-dopa is 82% in most cases, but after 4-year continuous delivery of rotigotine it decreases to 16%[25]. In another up to 6-year double-blind, randomized study involving 217 patients, daily transdermal rotigotine in patients with early-stage idiopathic PD was accompanied by only 25% LIDs, while the majority (83%) developed LIDs after initiating *L*-dopa[26]. This study is the longest interventional study of rotigotine to date and also shows that transdermal rotigotine is well tolerated for up to 6 years[26]. In general, long-term use of transdermal rotigotine provides more CDS and largely reduces LIDs in PD patients.

Extended-Release Formulations of Pramipexole

Preclinical Evidence

Pramipexole (brand name Sifrol) is a selective, non-ergoline dopamine D2 receptor agonist. Animal studies of pramipexole showed that its early use, alone or in combination with levodopa, has symptomatic benefits and reduces LIDs[18]. In MPTP-induced hemiparkinsonian monkeys, pramipexole alleviates the parkinsonian motor signs with no more drug-induced dyskinesias[27]. Conventionally, the standard pramipexole formulation is taken three times daily. However, based on the concept of CDS, an extended-release (ER) formulation to be administered once daily is a novel option. Preclinical data confirm that pramipexole ER and pramipexole immediate-release (IR) have much in common, like the receptor profile, receptor binding, half-life and efficacy. The only difference is the release of the active agent from the tablet[18]. Continuous release of pramipexole ER leads to a prolonged plasma level to achieve CDS and is believed to reduce the risk of LIDs in PD.

Clinical Evidence

Pramipexole ER has been approved for PD treatment in many European countries and in the United States since October 2009. Several clinical trials have been conducted to compare it with the traditional pramipexole IR. In both early and late PD, pramipexole ER is as safe, tolerable and efficacious as pramipexole IR[28,29]. Besides, an overnight switch from pramipexole IR to the new once-daily pramipexole ER is practicable in most PD patients, for >80% of patients successfully switched overnight at the same dosage. Also, patients with early or advanced PD prefer the ER over the IR form[30]. Overall, pramipexole ER administered once daily is becoming a promising way to attain CDS. It is well-tolerated and convenient for PD patients.

Continuous Delivery of Apomorphine

Preclinical Evidence

Apomorphine is one of the most potent short-acting D1 and D2 receptor dopamine agonists, and plays a vital role in antiparkinsonian therapy through binding to the postsynaptic D2 receptors in the caudate-putamen. In 2002, Battaglia *et al.*[31] demonstrated that continuous subcutaneous infusion of apomorphine (CSAI) relieves the motor symptoms and suppresses the ongoing degeneration of nigrostriatal dopaminergic neurons in MPTP-treated mice. Nevertheless, this protection diminishes when apomorphine is administered once daily. Thus, CSAI could improve the “long-term *L*-dopa syndrome” caused by the degeneration of substantia nigra neurons[31].

Clinical Evidence

In a 6-month prospective study involving 12 PD patients with disabling dyskinesias, single-dose *L*-dopa and apomorphine challenges were given before the use of an apomorphine pump and 6 months of pump therapy later. After 6 months, compared with baseline, both *L*-dopa challenges and apomorphine challenges experienced induced a moderate reduction of LIDs. In addition, after 6 months, four PD patients who remained on apomorphine monotherapy without oral *L*-dopa adjuvant therapy had a reduction in LID duration and severity. This indicated that CSAI therapy rather than oral antiparkinson drugs can prevent the development of LIDs[32]. Another multicenter study assessed the efficacy of long-term CSAI in advanced PD with motor fluctuations. One hundred sixty-six PD patients participated in this study for 5 years and the clinical data of 82 were analyzed. The results showed a significant reduction in the total motor Unified Parkinson’s Disease Rating Scale score and of LID

severity in these patients[19]. All the clinical observations certify that CSAI is an effective treatment for patients with PD or with severe LIDs.

Duodenal *L*-dopa Infusion

Preclinical Evidence

In 1975, *L*-dopa was first delivered by intravenous injection[33], and then reported to improve motor fluctuations in PD[34]. In the 6-OHDA-lesioned rat, *L*-dopa/carbidopa was delivered intermittently or continuously for 14 days[25] and the results showed that intermittent and continuous intraduodenal infusions both induced moderate-to-severe LIDs. But after 14 days, continued intermittent administration of *L*-dopa/carbidopa was accompanied by severe LIDs, while switching to continuous administration was associated with shorter durations of LIDs. This demonstrated that continuous intraduodenal *L*-dopa/carbidopa reduces the duration of LIDs, but may not reduce the risk of LIDs in early PD[25].

Clinical Evidence

A randomized crossover study comparing duodenal *L*-dopa infusion with oral polypharmacy in advanced PD indicated that continuous intraduodenal *L*-dopa/carbidopa is superior in clinical effects with no more increase in LIDs[35]. Another survey revealed that in most French patients, if an apomorphine pump and neurosurgical treatment fail or are contraindicated, duodenal *L*-dopa infusion is the last option for motor complications. This survey also revealed that after long-term treatment by duodenal *L*-dopa infusion, >90% of patients show improvement in motor fluctuations and quality of life[36]. Another 2-year follow-up study involving 22 PD patients confirmed the above results, which show that "off" period duration as well as LID severity is considerably reduced in these patients[20]. In conclusion, preclinical and clinical evidence confirm the benefits of intestinal *L*-dopa infusion in the treatment of advanced PD. These results demonstrate that intestinal *L*-dopa infusion is a pragmatic approach to achieving a satisfactory clinical outcome and reducing LID severity.

Extended-Release Formulations of *L*-dopa

Preclinical Evidence

Peripheral *L*-dopa is catabolized to 3-O-methyldopa (3-OMD) by catechol-O-methyltransferase (COMT). The combination of *L*-dopa/carbidopa and the COMT inhibitor entacapone increases the bioavailability of *L*-dopa in plasma and extends its half-life to 2.5 h[37], which helps to provide more CDS. This has been demonstrated in many classical animal models. In hemiparkinsonian rats, early administration of entacapone in association with *L*-dopa lowers the incidence of LIDs and delays their onset[38]. In the MPTP-treated common marmoset, co-administration of *L*-dopa/carbidopa with entacapone four times daily at 3.5-h intervals provides more continuous motor benefits with less LIDs, while this combination twice daily at 7-h intervals has no major effect on the motor response[39]. This indicates that small divided doses of *L*-dopa plus a COMT inhibitor allow oral treatment to provide continuous dopaminergic therapy in PD patients.

Clinical Evidence

L-dopa/carbidopa/entacapone (LCE, Stalevo) has been approved for the treatment of PD, but the results of clinical trials are controversial. For example, a 39-week randomized, double-blind study suggested that LCE improves the clinical symptoms more than *L*-dopa/carbidopa (LC, Sinemet IR) and does not induce motor complications[40]. In contrast, the recent Stalevo Reduction in Dyskinesia Evaluation in Parkinson's Disease (STRIDE-PD) reported the unexpected results that LCE not only fails to reduce the risk of LIDs when administered four times daily at 3.5-h intervals, but increases the risk of LIDs compared to standard LC[41]. Clinical trials of Stalevo raises the importance of optimizing the *L*-dopa therapy to prevent LIDs. Further studies are ongoing to evaluate whether Stalevo at shorter time-intervals can match a state of CDS and provide more benefits.

Benefits and Risks of Each Approach

Rotigotine was the first dopamine agonist to be successfully delivered by transdermal patches, and has been used in clinical therapy for PD patients. This special method has numerous advantages. For instance, because it can release continuous and consistent rotigotine, the plasma levels over 24 h are constant[42]. Preclinical experiments have demonstrated that constant plasma levels of rotigotine can provide CDS[43]. Thus, the continuous delivery of rotigotine is a potential means of reducing LIDs in the treatment of PD. For PD patients, transdermal rotigotine is also convenient as a once-daily formulation. Moreover, transdermal infusion avoids gastrointestinal dysfunction, which

may contribute to the motor complications[44]. But it also has limitations. Long-term use of transdermal rotigotine is accompanied by known adverse dopaminergic effects such as nausea, fatigue and dizziness in some patients[45]. In addition, a local skin reaction may occur after long-term use. Whether this affects the long term compliance of PD patients is not known[44].

Pramipexole ER has recently been approved. There are several potential advantages of this formulation. First of all, once-daily drugs are more convenient and improve compliance[28]. Moreover, it is well known that the action of medication on peripheral dopamine receptors causes some adverse dopamine events, such as nausea and orthostatic hypertension[46]. So more constant stimulation of peripheral receptors would be associated with less nausea and orthostatic hypertension in theory, but the clinical evidence is still lacking. With a once-daily formulation, the possibility of taking medicine before bedtime may avoid the excessive daytime somnolence caused by traditional dopamine agonists. Last, the once-daily formulation would prevent or reverse motor complications much better than traditional formulations for it can provide more CDS[7]. The defect is that they cannot provide as strong CDS as *L*-dopa and apomorphine. Clinical trials are still needed to assess the incidence of adverse effects, such as somnolence, nausea and orthostatic hypertension, in the pramipexole ER formulation [29].

CSAI is based on a mini-pump, and this therapy is only available in Europe. In the United States, apomorphine is used for the acute treatment of hypomobility, “off” times in advanced PD[47]. CSAI is efficient in reducing LIDs and it is usually applied in PD patients with severe fluctuations. However, after long-term use there are always several side effects, most often the skin nodules, skin inflammation and neuropsychiatric reactions. Adverse events at the injection site usually limit the continued usage of the apomorphine pump[19].

Duodopa is a carboxymethylcellulose, gel formulation of *L*-dopa. It is delivered through an intrajejunal pump system at 20 mg/mL and has already been approved in most European countries. In the United States, commercialization of Duodopa has already been approved in 2012[47]. Duodenal *L*-dopa infusion is believed to be valid for the treatment of severe motor fluctuations, including troublesome dyskinesias, and also provides benefits on health-related quality of life[36]. The most common drawbacks are the heavier pump, technical problems (e.g., potential percutaneous gastrostomy infections, tubes pulled out or dislocated), and the high cost of its use and nursing care[48].

Theoretically, LCE is able to deliver CDS. Nevertheless, the STRIDE-PD study showed an unexpected outcome in patients with early PD. In contrast with LC, LCE not only fails to reduce LIDs but is associated with an earlier onset and higher frequency of LIDs[41]. This result has triggered an intense discussion on LCE, and even the concept of CDS. But some questions may need to be answered. First of all, does LCE administered 4 times daily at intervals of 3.5 h provide true CDS? Second, PD patients receiving LCE had a shorter time to onset of and increased frequency of dyskinesia compared to those receiving LC[41]. Whether the increased risk of LIDs in LCE group is just limited to patients who possibly have more severe disease (on account of receiving dopamine agonists)? Third, rodent studies suggest that lower peak drug levels occur with continuous *L*-dopa administration[49], while LCE patients always receive higher doses of *L*-dopa. Do higher doses of *L*-dopa, even administered in a continuous way, increase the frequency of LIDs[50]? More research is needed to answer these questions and to evaluate the practical applicability of LCE in PD.

These approaches all have their unique risks and benefits (Table 2). Compared to pramipexole, transdermal rotigotine patches have not shown superiority in terms of changes in the “off” time, and their clinical efficacy is similar to that of oral pramipexole in PD patients with motor fluctuations[51]. Besides, transdermal rotigotine and pramipexole ER cannot provide as strong CDS as CSAI and duodenal *L*-dopa infusion[47]. Apomorphine and Duodopa are usually used in advanced PD patients. Compared with apomorphine, Duodopa shows a slightly stronger effect in reducing the “off” time and is a more potent anti-dyskinetic[52,53]. Moreover, many patients tolerate Duodopa better than apomorphine when infused continuously[54]. In general, to choose the proper therapeutic schedules for PD patients, physicians should weigh the benefits and risks of these approaches.

Conclusion

This review aimed to elucidate the methods of providing CDS in relation to the occurrence of LIDs in preclinical and

Table 2. Benefits and risks of each approach

Approaches	Benefits	Risks
Transdermal rotigotine patches	Improved control of LIDs[42]	Dopaminergic adverse effects such as nausea, fatigue and dizziness[45]
	Once-daily formulation is convenient[44]	Skin reaction[44]
	Avoids gastrointestinal dysfunction[44]	
Extended-release formulations of pramipexole	Improved control of LIDs[7]	Clinical efficacy is not so strong as *L*-dopa and apomorphine[47]
	Once-daily formulation is convenient[28]	Adverse effects, such as somnolence, nausea and orthostatic hypertension[55]
	High compliance[30]	
	Avoids excessive daytime somnolence[7]	
Continuous delivery of apomorphine	Improved control of LIDs[19]	Skin nodes, skin inflammation[19]
	Portable mini-pump[56]	Neuropsychiatric reactions[19]
Duodenal *L*-dopa infusion	Improved control of LIDs[53]	Pump may be cumbersome for PD patients[48]
	Provides health-related benefits on quality of life[36]	Tube may pull out[48]
		Percutaneous gastrostomy infections[48]
	Valid for the treatment of troublesome dyskinesias[53]	High cost for its use and nurse care[48]
Extended-release formulations of *L*-dopa	Oral administration is convenient[40]	Clinical outcomes are conflicting[40, 41]
	High compliance[40]	Adverse effects, such as nausea, diarrhea and dizziness[41]

LIDs, *L*-dopa-induced dyskinesias; PD, Parkinson's disease.

clinical experiments. The extent of the nigrostriatal pathway lesion clearly affects the phasic and tonic DA release from the striatum. LID induction and expression in PD patients are strongly associated with the fluctuations of administered *L*-dopa. The pulsatile stimulation of postsynaptic receptors may cause gene and protein changes that underlie LIDs. Hence it is necessary to explore ways of producing stable dopaminergic stimulation to avoid the remarkable drug fluctuations, and finally, to avoid drug-induced dyskinesias. We discussed the five approaches providing CDS in theory, and summarized the extensive evidence that supports their use in PD patients.

In sum, the approaches providing CDS should be carefully selected according to the patient's condition. In the early, middle and late stages of PD, transdermal rotigotine patches and pramipexole ER are good choices to delay the onset and reduce the risk of LIDs. Although the effects of dopamine agonists such as rotigotine and pramipexole are not as strong as apomorphine and *L*-dopa, transdermal rotigotine patches and the once-daily formulation of pramipexole are convenient for patients. Moreover, both formulations are well tolerated for long-term treatment. In advanced PD patients, even with severe LIDs, CSAI and duodenal *L*-dopa infusion are able to reduce LIDs. However, these approaches still have limitations, such as adverse effects and technical problems, which discourage their usage. Moreover, patients receiving long-term apomorphine therapy show relatively worse tolerance than with Duodopa. Finally, current studies cannot fully support the clinical application of Stalevo because the clinical outcomes are conflicting. Investigations of Stalevo's curative effect are still under way. Anyway, the application of CDS-based therapies for the management of PD is promising for obtaining symptomatic improvement without LIDs.

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REFERENCES

[1] Dorsey ER, Constantinescu R, Thompson JP, Biglan BM, Holloway RG, Kieburtz K, *et al.* Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. Neurology 2007, 68(5): 384–386.

[2] Olanow CW. The scientific basis for the current treatment of Parkinson's disease. Annu Rev Med 2004, 55: 41–60.

[3] Ahlskog JE, Muenter MD. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. Mov Disord 2001, 16(3): 448–458.

[4] Linazasoro G. New ideas on the origin of *L*-dopa-induced dyskinesias: age, genes and neural plasticity. Trends Pharmacol Sci 2005, 26(8): 391–397.

[5] Dodel RC, Berger K, Oertel WH. Health-related quality of life and healthcare utilisation in patients with Parkinsons disease: impact of motor fluctuations and dyskinesias. Pharmacoeconomics 2001, 19(10): 1013–1038.

[6] Olanow CW, Obeso JA, Stocchi F. Continuous dopamine-receptor treatment of Parkinson's disease: scientific rationale and clinical implications. Lancet Neurol 2006, 5(8): 677–687.

[7] Rascol O. Drugs and drug delivery in PD: optimizing control of symptoms with pramipexole prolonged-release. Eur J Neurol 2011, 18(Suppl 1): 3–10.

[8] Grace A. Phasic *versus* tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. Neuroscience 1991, 41(1): 1–24.

[9] Metman LV, Konitsiotis S, Chase TN. Pathophysiology of motor response complications in Parkinson's disease: hypotheses on the why, where and what. Mov Disord 2000, 15(1): 3–8.

[10] Stocchi F. The therapeutic concept of continuous dopaminergic stimulation (CDS) in the treatment of Parkinson's disease. Parkinsonism Relat Disord 2009, 15(3): 68–71.

[11] Aubert I, Guigoni C, Hakansson K, Li Q, Dovero S, Barthe N. Increased D1 dopamine receptor signaling in levodopa-induced dyskinesia. Ann Neurol 2005, 57(1): 17–26.

[12] Calon F, Birdi S, Rajput AH, Hornykiewicz O, Bédard PJ, Di Paolo T. Increase of preproenkephalin mRNA levels in the putamen of Parkinson disease patients with levodopa-induced dyskinesias. J Neuropathol Exp Neurol 2002, 61(2): 186–196.

[13] Morissette M, Goulet M, Soghomonian JJ, Blanchet PJ, Calon F, Bédard PJ, *et al.* 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 1997, 49(1–2): 55–62.

[14] Pavón N, Martín AB, Mendialdua A, Moratalla R. ERK phosphorylation and FosB expression are associated with *L*-DOPA-induced dyskinesia in hemiparkinsonian mice. Biol Psychiatry 2006, 59(1): 64–74.

[15] Henry B, Duty S, Fox SH, Crossman AR, Brotchie JM. Increased striatal pre-proenkephalin B expression is associated with dyskinesia in Parkinson's disease. Exp Neurol 2003, 183(2): 458–468.

[16] Wolters EC. Deep brain stimulation and continuous dopaminergic stimulation in advanced Parkinson's disease. Parkinsonism Relat Disord 2007, 13(Suppl): 18–23.

[17] Elshoff JP, Braun M, Andreas JO, Middle M, Cawello W. Steady-state plasma concentration profile of transdermal rotigotine: an integrated analysis of three, open-Label, randomized, phase I multiple dose studies. Clin Ther 2012, 34(4): 966–978.

[18] Eisenreich W, Sommer B, Hartter S, Jost WH. Pramipexole extended release: a novel treatment option in Parkinson's disease. Parkinsons Dis 2010, 2010: 1–7.

[19] García Ruiz PJ, Sesar Ignacio Á, Ares Pensado B, Castro García A, Alonso Frech F, Álvarez López M*, et al.* Efficacy of long-term continuous subcutaneous apomorphine infusion in advanced Parkinson's disease with motor fluctuations: A multicenter study. Mov Disord 2008, 23(8): 1130–1136.

[20] Honig H, Antonini A, Martinez-Martin P, Forgacs I, Faye GC, Fox T*, et al*. Intrajejunal levodopa infusion in Parkinson's disease: A pilot multicenter study of effects on nonmotor symptoms and quality of life. Mov Disord 2009, 24(10): 1468–1474.

[21] Sethi KD, Hauser RA, Isaacson SH, McClain T. Levodopa/carbidopa/entacapone 200/50/200 mg (Stalevo® 200) in the treatment of Parkinson's disease: a case series. Cases J 2009, 2(1): 7134.

[22] Jenner P. A novel dopamine agonist for the transdermal treatment of Parkinson's disease. Neurology 2005, 65(2 Suppl 1): 3–5.

[23] Schmidt WJ, Lebsanft H, Heindl M, Gerlach M, Gruenblatt E, Riederer P, *et al*. Continuous versus pulsatile administration of rotigotine in 6-OHDA-lesioned rats contralateral rotations and abnormal involuntary movements. Neural Transm 2008, 115(10): 1385–1392.

[24] Stockwell KA, Scheller D, Rose S, Jackson MJ, Tayarani-Binazir K, Iravani MM*, et al.* Continuous administration of rotigotine to MPTP-treated common marmosets enhances anti-parkinsonian activity and reduces dyskinesia induction. Exp Neurol 2009, 219(2): 533–542.

[25] Jenner P, McCreary AC, Scheller DK. Continuous drug delivery in early- and late-stage Parkinson's disease as a strategy for avoiding dyskinesia induction and expression. J Neural

Transm 2011, 118(12): 1691–1702.

[26] Elmer LW, Surmann E, Boroojerdi B, Jankovic J. Long-term safety and tolerability of rotigotine transdermal system in patients with early-stage idiopathic Parkinson's disease: A prospective, open-label extension study. Parkinsonism Relat Disord 2012, 18(5): 488–493.

[27] Domino EF, Ni L, Zhang H, Kohno Y, Sasa M. Talipexole or pramipexole combinations with chloro-APB (SKF 82958) in MPTP-induced hemiparkinsonian monkeys. Eur J Pharmacol 1997, 325(2–3): 137–144.

[28] Schapira AH, Barone P, Hauser RA, Mizuno Y, Rascol O, Busse M, *et al*. Extended-release pramipexole in advanced Parkinson disease: a randomized controlled trial. Neurology 2011, 77(8): 767–774.

[29] Hauser RA, Schapira AH, Rascol O, Barone P, Mizuno Y, Salin L*, et al.* Randomized, double-blind, multicenter evaluation of pramipexole extended release once daily in early Parkinson's disease. Mov Disord 2010, 25(15): 2542–2549.

[30] Rascol O, Barone P, Hauser RA, Mizuno Y, Poewe W, Schapira AH*, et al.* Efficacy, safety, and tolerability of overnight switching from immediate- to once daily extended-release pramipexole in early Parkinson's disease. Mov Disord 2010, 25(14): 2326–2332.

[31] Battaglia G, Busceti CL, Cuomo L, Giorgi FS, Orzi F, De Blasi A, *et al.* Continuous subcutaneous infusion of apomorphine rescues nigro-striatal dopaminergic terminals following MPTP injection in mice. Neuropharmacology 2002, 42(3): 367–373.

[32] Katzenschlager R, Hughes A, Evans A, Manson AJ, Hoffman M, Swinn L*, et al.* Continuous subcutaneous apomorphine therapy improves dyskinesias in Parkinson's disease: A prospective study using single-dose challenges. Mov Disord 2005, 20(2): 151–157.

[33] Shoulson I, Glaubiger GA, Chase TN. On-off response. Clinical and biochemical correlations during oral and intravenous levodopa administration in parkinsonian patients. Neurology 1975, 25(12): 1144–1148.

[34] Quinn N, Marsden CD, Parkes JD. Complicated response fluctuations in Parkinson's disease: response to intravenous infusion of levodopa. Lancet 1982, 2(8295): 412–415.

[35] Nyholm D, Nilsson Remahl AI, Dizdar N, Constantinescu R, Holmberg B, Jansson R, *et al.* Duodenal levodopa infusion monotherapy *vs* oral polypharmacy in advanced Parkinson disease. Neurology 2005, 64(2): 216–223.

[36] Devos D. Patient profile, indications, efficacy and safety of duodenal levodopa infusion in advanced Parkinson's disease. Mov Disord 2009, 24(7): 993–1000.

[37] Nutt JG, Woodward WR, Beckner RM, Stone CK, Berggren K, Carter JH, *et al*. Effect of peripheral catechol-O-methyltransferase inhibition on the pharmacokinetics and pharmacodynamics of levodopa in parkinsonian patients. Neurology 1994, 44(5): 913–919.

[38] Marin C, Aguilar E, Obeso JA. Coadministration of entacapone with levodopa attenuates the severity of dyskinesias in hemiparkinsonian rats. Mov Disord 2006, 21(5): 646–653.

[39] Smith LA, Jackson MJ, Al-Barghouthy G, Rose S, Kuoppamaki M, Olanow W*, et al.* Multiple small doses of levodopa plus entacapone produce continuous dopaminergic stimulation and reduce dyskinesia induction in MPTP-treated drug-naive primates. Mov Disord 2005, 20(3): 306–314.

[40] Hauser RA, Panisset M, Abbruzzese G, Mancione L, Dronamraju N, Kakarieka A. Double-blind trial of levodopa/carbidopa/entacapone versus levodopa/carbidopa in early Parkinson's disease. Mov Disord 2009, 24(4): 541–550.

[41] Stocchi F, Rascol O, Kieburtz K, Poewe W, Jankovic J, Tolosa E*, et al.* Initiating levodopa/carbidopa therapy with and without entacapone in early Parkinson disease: The STRIDE-PD study. Ann Neurol 2010, 68(1): 18–27.

[42] Braun M, Cawello W, Poole K. Steady-state pharmacokinetics of rotigotine in patients with early-stage Parkinson's disease. Eur J Neurol 2005, 12(Suppl 2): 37.

[43] Kehr J, Scheller DKA. Continuous delivery of rotigotine leads to continuous dopamine receptor stimulation in a rat model. Eur J Neurol 2005, 12: 37.

[44] Giladi N, Boroojerdi B, Korczyn AD, Burn DJ, Clarke CE, Schapira AH. Rotigotine transdermal patch in early Parkinson's disease: A randomized, double-blind, controlled study versus placebo and ropinirole. Mov Disord 2007, 22(16): 2398–2404.

[45] Schnitzler A, Leffers KW, Häck HJ. High compliance with rotigotine transdermal patch in the treatment of idiopathic Parkinson's disease. Parkinsonism Relat Disord 2010, 16(8): 513–516.

[46] Antonini A TE, Mizuno Y, Yamamoto M, Poewe WH. A reassessment of risks and benefits of dopamine agonists in Parkinson's disease. Lancet Neurol 2009, 8(10): 929–937.

[47] Espay AJ. Management of motor complications in Parkinson disease: current and emerging therapies. Neurol Clin 2010, 28(4): 913–925.

[48] Hilker R, Antonini A, Odin P. What is the best treatment for fluctuating Parkinson's disease: continuous drug delivery or deep brain stimulation of the subthalamic nucleus? J Neural Transm 2010, 118(6): 907–914.

[49] Trugman JM, Hubbard CA, Bennett JP Jr. Dose-related effects of continuous levodopa infusion in rats with unilateral lesions of the substantia nigra. Brain Res 1996, 725(2): 177–183.

[50] Stoessl AJ. Continuous Dopaminergic Therapy in Parkinson disease time to stride back. Ann Neurol 2010, 68(1): 3–5.

[51] Poewe WH, Rascol O, Quinn N, Tolosa E, Oertel WH, Martignoni E, *et al*. Efficacy of pramipexole and transder-

mal rotigotine in advanced Parkinson's disease a double-blind,double-dummy,randomised controlled trial. Lancet Neurol 2007, 6(6): 513–520.

[52] Antonini A. Continuous dopaminergic stimulation-from theory to clinical practice. Parkinsonism Relat Disord 2007, 13: S24–28.

[53] Eggert K, Schrader C, Hahn M, Stamelou M, Rüssmann A, Dengler R, *et al.* Continuous jejunal levodopa infusion in patients with advanced Parkinson disease: practical aspects and outcome of motor and non-motor complications. Clin Neuropharmacol 2008, 31(3): 151–166.

[54] Gancher ST, Woodward WR, Nutt JG. Apomorphine tolerance in Parkinson's disease: lack of a dose effect. Clin Neuropharmacol 1996, 19(1): 59–64.

[55] Hauser RA, Schapira AH, Rascol O, Barone P, Mizuno Y, Salin L. Randomized, double-blind, multicenter evaluation of pramipexole extended release once daily in early Parkinson's disease. Mov Disord 2010, 25(15): 2542–2549.

[56] Stocchi F, Vacca L, De Pandis MF, Barbato L, Valente M, Ruggieri S. Subcutaneous continuous apomorphine infusion in fluctuating patients with parkinson disease: long-term results. Neurol Sci 2001, 22(1): 93–94.