

Continuous dopamine-receptor treatment of Parkinson's disease: scientific rationale and clinical implications

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Levodopa-induced motor complications are a common source of disability for patients with Parkinson's disease. Evidence suggests that motor complications are associated with non-physiological, pulsatile stimulation of dopamine receptors. In healthy brains, dopamine neurons fire continuously, striatal dopamine concentrations are relatively constant, and there is continuous activation of dopamine receptors. In the dopamine-depleted state, standard levodopa therapy does not normalise the basal ganglia. Rather, levodopa or other short-acting dopaminergic drugs induce molecular changes and altered neuronal firing patterns in basal ganglia neurons leading to motor complications. The concept of continuous dopaminergic stimulation proposes that continuous delivery of a dopaminergic drug will prevent pulsatile stimulation and avoid motor complications. In monkeys treated with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) and patients with Parkinson's disease, long-acting or continuous infusion of a dopaminergic drug reduces the risk of motor complications. The current challenge is to develop a long-acting oral formulation of levodopa that provides clinical benefits but avoids motor complications.

Introduction

Since its introduction in the late 1960s, levodopa has been the most widely used and most effective drug for the symptomatic therapy of Parkinson's disease. However, chronic levodopa therapy is complicated by the development of motor complications, which can be disabling, difficult to treat, and limit the usefulness of the drug.^{1,2} The development of surgical therapies, such as pallidotomy and deep brain stimulation of the subthalamic nucleus and the internal segment of the globus pallidus (GPi), can provide effective treatment for levodopa-induced motor complications, but surgery has risks, is expensive, and does not provide antiparkinsonian benefits beyond what can be attained with levodopa. Medical therapy that provides the benefits of levodopa without motor complications would be a major advance in the treatment of Parkinson's disease.

During the past two decades, substantial evidence has accumulated indicating that levodopa-related motor complications in Parkinson's disease are associated with non-physiological, discontinuous, or pulsatile stimulation of striatal dopamine receptors, and can be prevented or reversed by long-acting dopaminergic drugs that theoretically provide more continuous stimulation of striatal dopamine receptors.² Central to this concept are observations indicating that dopamine neurons in the substantia nigra pars compacta (SNc) fire tonically at a nearly constant rate,^{3,4} that striatal dopamine is maintained at a fairly constant concentration,^{5,6} and that there is continuous activation of striatal dopamine receptors. Experience with continuous infusions of levodopa and dopamine agonists has shown the potential advantages of continuous delivery of dopaminergic drugs and inspired the therapeutic concept of continuous dopaminergic stimulation.^{7,8} In this review, we describe the advances in our understanding of the organisation of the basal ganglia, the molecular and physiological changes that underlie motor complications, and the experimental and clinical data supporting treatment

strategies based on continuous dopaminergic stimulation in Parkinson's disease.

Motor complications of dopaminergic therapy

In the early stages of levodopa treatment, patients with Parkinson's disease typically experience excellent benefits that are sustained even if an individual dose is missed. However, with chronic treatment, the duration of benefit after a given dose of levodopa becomes progressively shorter and begins to mirror the plasma half-life of levodopa.⁹ Patients begin to experience fluctuations in motor function alternating between on responses with a good antiparkinsonian effect and off responses when levodopa does not adequately treat parkinsonian features. Fluctuations can also occur in non-motor features of the disease (eg, pain, anxiety, depression). In the most severe cases, patients can experience rapid oscillations between on and off states without an apparent association with the levodopa dose.¹⁰

Levodopa-treated patients can also experience involuntary movements or dyskinesias.¹¹ Dyskinesias typically occur in association with high concentrations of levodopa in the plasma and maximum improvement in the motor response (peak-dose dyskinesia). These dyskinesias are usually choreiform in nature, although they can also manifest as dystonia and other movement disorders. Less commonly, dyskinesias can appear at or just before the onset of the on response, disappear during the on period, and re-emerge as the off period begins (diphasic dyskinesias). Diphasic dyskinesias are typically comprised of large amplitude stereotypic, rhythmic, and repetitive movements of the legs that can be associated with parkinsonian features in other body regions. Patients with Parkinson's disease can also have off-period dystonia mostly localised to their legs and commonly accompanied by pain and a sustained abnormal posture.

In extreme cases, patients treated with levodopa can cycle between on periods, which are complicated by disabling dyskinesias, and off periods in which

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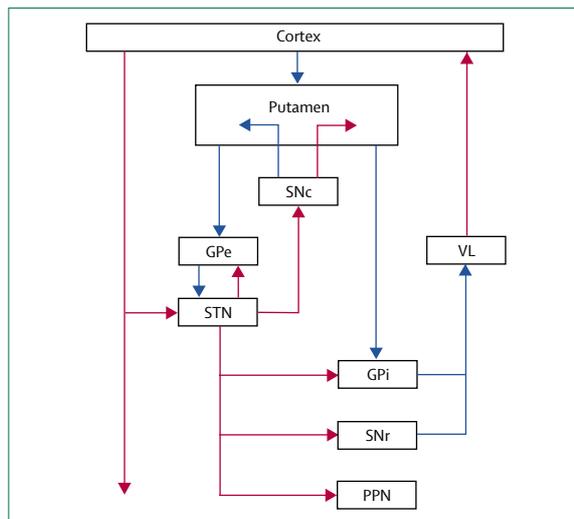


Figure 1: Classic pathways of the basal ganglia

GPe=globus pallidus; STN=subthalamic nucleus; SNr=substantia nigra pars reticulata; PPN=pedunculopontine nucleus; VL=ventrolateral nucleus of the thalamus. This classic model of the basal ganglia shows the direct and indirect striatopallidal pathways and that SNc neurons provide dopaminergic input to the striatum. The red arrows represent the excitatory pathways and the blue arrows the inhibitory pathways.

parkinsonism is uncontrolled and the patient is akinetic and frozen. With disease progression, delivery of a dose of levodopa that provides both a satisfactory antiparkinsonian effect and avoids dyskinesia becomes increasingly difficult.

Motor complications occur in about 50% of patients with Parkinson's disease who have received levodopa for more than 5 years, and in as many as 100% of patients with young-onset disease.^{11,12} High doses of standard levodopa formulations are associated with an increased risk of motor complications in both animal models with MPTP lesions and patients with Parkinson's disease.^{13,14} The recent ELLDOPA study showed that motor complications in levodopa-treated patients are dose-related and begin earlier than was previously appreciated.¹⁵ After just 9 months of levodopa treatment (200 mg three times daily), 20% of patients experienced wearing off and 16% had dyskinesias.

Dopaminergic organisation of the basal ganglia

The classic model of the basal ganglia emphasises the direct and indirect striatopallidal pathways and the selective innervation of the striatum by dopaminergic neurons originating in the SNc (figure 1).^{16,17} However, it is now appreciated that the basal ganglia function as a complex, integrated network with multiple feedback and feedforward loops rather than as the linear firing-rate-dependent system depicted in the classic model (figure 2).¹⁸ Furthermore, dopaminergic innervation from the SNc is not restricted to the striatum but extends to include the subthalamic nucleus, internal and external segments of the globus pallidus, thalamus, and cerebral cortex.¹⁹

In healthy brain

Dopamine neurons fire tonically at a rate of 3–6 Hz independent of movement,^{3,4} and striatal dopamine is maintained at a nearly constant concentration, as shown by both microdialysis and amperometry.^{5,6} Phasic or burst firing of SNc neurons with release of larger amounts of dopamine can occur in association with reward or exposure to new stimuli.^{20,21} However, the robust reuptake capacity of the dopamine transporter maintains constant striatal dopamine concentrations independent of the SNc neuronal firing rate.^{3,6,22} Furthermore, axons of dopamine neurons that are activated by rapid firing branch profusely within the striatum²³ and interact primarily with dopamine receptors located within or next to the synapse where dopamine-transporter density is maximum.²⁴ These factors combine to maintain constant synaptic and extrasynaptic dopamine concentrations, thus permitting striatal dopamine receptors to be continuously exposed to dopamine. The constant firing rate of SNc dopamine neurons, stable striatal dopamine concentration, and the continuous activation of striatal dopamine receptors are essential for normal basal-ganglia function.²⁵

SNc neurons also possess autoregulatory mechanisms, such as non-renewal, that help maintain stable neuronal firing rates.²⁶ Non-renewal firing implies that neuronal excitability is influenced by previous firing activity (for up to a few seconds), so that abrupt changes in discharge rates are modulated and overall firing activity remains fairly constant. Non-renewal in SNc neurons is probably mediated by intracellular mechanisms, such as after hyperpolarisation (calcium-dependent potassium current), local inhibitory effects of dopamine release, and feedback circuits such as striatonigral inhibitory projections.²⁷ These factors influence the probability of spike generation and regulate interspike variability.

A primary role of dopamine is to exert presynaptic modulation (in both up and down directions) on the glutamate-mediated excitation of striatal medium spiny neurons.^{28–35} Most striatal neurons are medium spiny GABAergic neurons that receive massive glutamatergic inputs (ie, substantially more than 1000 per neuron) from terminals that originate in the cortex and thalamus and form asymmetric contacts with the heads of dendritic spines.^{36,37} A smaller proportion of striatal inputs come from dopaminergic, cholinergic, and GABAergic neurons and form symmetric synaptic contacts. Striatal neurons primarily project to the globus pallidus (both external and internal portions) and make between 10 000 and 30 000 synaptic contacts per neuron.³⁷ Such an arrangement requires a precise selection mechanism to filter incoming and outgoing signals associated with movement, a function mediated in part by the effects of dopamine on both presynaptic and postsynaptic mechanisms. A study in mouse brain slices showed that dopamine can both enhance or suppress specific subsets of corticostriatal afferents by

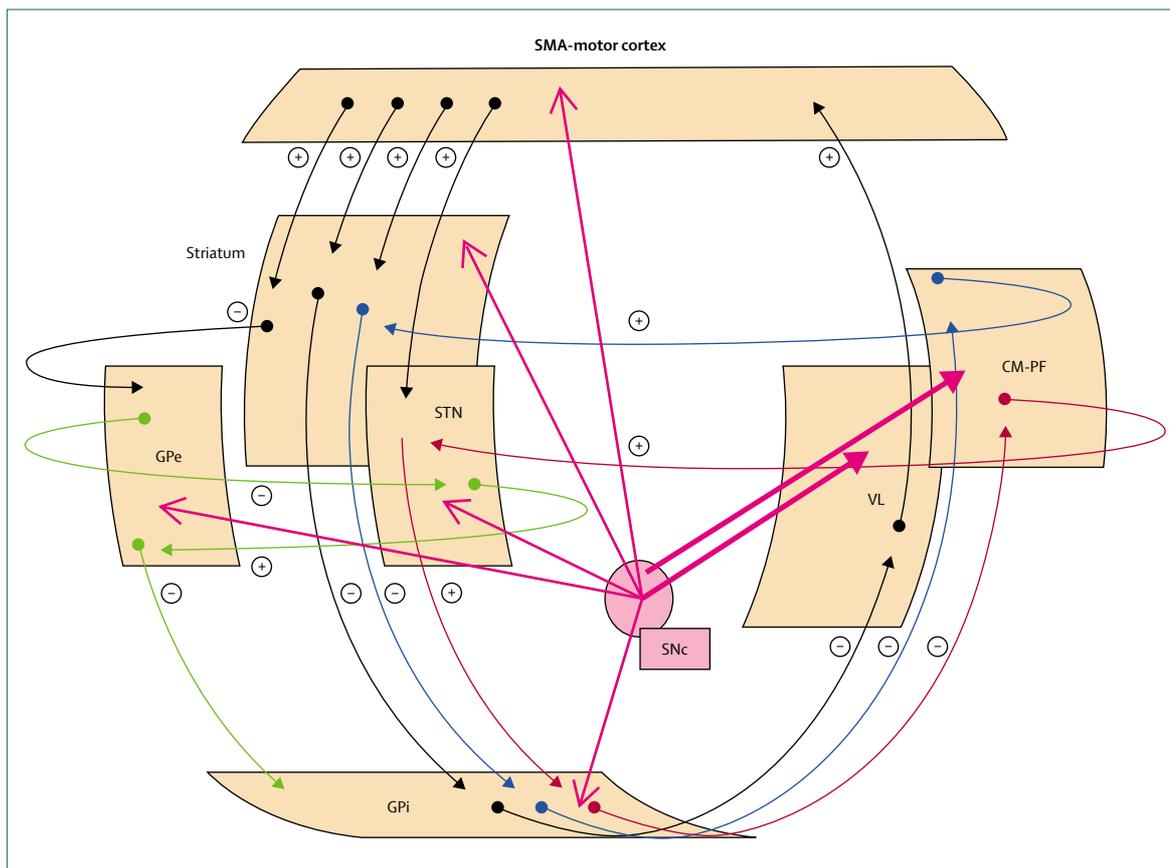


Figure 2: Modern paradigm of the basal ganglia pathways

SMA=supplementary motor area; GPe=globus pallidus; CM-PF=centromedian parafascicular nucleus; STN=subthalamic nucleus. This paradigm emphasises that the basal ganglia is a complex network manner with multiple feedback and feedforward loops. Note that SNc dopamine neurons provide dopaminergic innervation to multiple components of the basal ganglia in addition to the striatum. Reproduced with permission from Elsevier.²⁵

activation of D2 receptors located presynaptically in glutamatergic terminals.³⁰ In this study, dopamine was shown to inhibit glutamate release from less actively firing corticostriatal afferents and to potentiate release from more active neurons. In functional terms, when a series of different cortical afferent signals converge on to a striatal medium spiny neuron, dopamine selectively enhances activity in the most powerful volley and inhibits others. We envision this mechanism allows a desired movement or action to be facilitated, while minimising the possibility of interference from conflicting neuronal activity.

Dopamine also acts postsynaptically to stabilise the firing rate and excitability of striatal neurons. Dopamine inhibits (via D2 receptors) or facilitates (via D1 receptors) striatopallidal neuronal activity.³⁸ Medium spiny striatal neurons usually express either D1 or D2 receptors, which give rise to projections forming the direct and indirect striatopallidal pathways, respectively (figures 1 and 2), although there is considerable crosstalk between these systems and they are probably not totally discrete.^{39,40} Movement facilitation is associated with

increased activity in the direct pathway and reduced activity in the indirect pathway.^{16–18} Dopamine facilitates activity in D1-bearing neurons, which have an inhibitory effect on the pallidum, and inhibits activity in D2-bearing neurons, which lead to excitation of the pallidum.³³ Phasic firing induces the release of dopamine, which primarily activates D1 and D2 receptors within the synapse, whereas dopamine release associated with tonic firing primarily excites extrasynaptically located D1 receptors by volume transmission.⁴¹ Under physiological conditions, tonic SNc firing predominates so that dopamine primarily activates extrasynaptic D1 receptors on neurons in the direct pathway that facilitate movement. Dopamine also modulates glutamate-mediated long-term potentiation and long-term depression and thereby regulates plasticity in striatal neurons.⁴² Furthermore, dopamine exerts tonic inhibitory effects on cholinergic interneurons, which otherwise tend to increase the excitability of medium spiny striatal neurons by raising the amplitude of postsynaptic excitatory potentials evoked by cortical stimulation.^{43,44}

Parkinsonian state

The studies described above illustrate that dopamine plays a major part in maintaining the stability of the basal ganglia network and is essential for the selection and processing of neuronal activity associated with normal movement. The situation changes in the dopamine-denervated state. The loss of dopamine nigral neurons impairs dopaminergic modulation of corticostriatal activity⁴⁵ and the capacity to develop long-term potentiation and long-term depression.^{45–47} Although surviving dopamine cells in the SNc show little change in firing rate, autoregulatory mechanisms are impaired and there is a loss of the firing rate stability provided by non-renewal mechanisms.⁴⁸ As a result, there is a reduced capacity to compensate for small fluctuations in firing rate that promote instability of the basal-ganglia network. Dendritic spines on striatal medium spiny neurons, which are the sites of glutamate–dopamine interactions, are profoundly reduced in size and density.^{49,50} Dual photon imaging shows that these changes are triggered by dysregulation of L-type calcium channels and selectively affect striatopallidal but not striatonigral neurons.⁵¹

The striatal dopamine deficit may initially be compensated for by downregulation of the dopamine transporter, heightened postsynaptic receptor sensitivity, and changes in subthalamic nucleus and GPi firing. These compensations might explain the interval between disease and symptom onset.^{52,53} However, compensatory mechanisms eventually fail: D2-bearing medium spiny neurons (which coexpress enkephalin) become overactive whereas D1-bearing medium spiny neurons (which coexpress substance P and dynorphin) become hypoactive. This failure results in hyperactivity of neuronal activity in subthalamic nucleus and GPi neurons, excessive inhibition of thalamocortical and brainstem motor neurons, and the development of parkinsonian features.^{16,17} In association with these changes, there is a reduction in the inhibitory centre surround—inhibition of neuronal firing in an area surrounding a firing neuron—that occurs in response to peripheral stimuli and abnormal synchronisation of neuronal firing in the striatum, subthalamic nucleus, and GPi of MPTP-lesioned monkeys and patients with Parkinson's disease.^{54–60} The discharge rate of individual neurons in the globus pallidus is irregular and independent of firing in other nerve cells in normal monkeys, whereas in parkinsonian monkeys the discharge is oscillatory in individual neurons and synchronised between pairs of neurons.⁶¹ These changes result in a loss of somatotopic selectivity and fundamentally impair the capacity of the basal ganglia to appropriately select and facilitate normal motor movement.

Levodopa-treated state

Dopamine replacement with standard doses of regular levodopa does not make the basal ganglia physiologically

normal. Exogenous administration of repeated doses of short-acting levodopa (half-life of about 60–90 min) leads to large and uncontrolled oscillations in striatal and synaptic dopamine concentrations,^{5,62,63} probably due to the loss of dopamine terminals and their capacity to buffer fluctuations in striatal dopamine concentrations. 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 abnormally high or abnormally low concentrations of the neurotransmitter. This pulsatile stimulation destabilises an already unstable basal ganglia.

Acute administration of dopaminergic drugs like apomorphine or levodopa can reverse the firing-rate changes that accompany dopamine denervation in patients with Parkinson's disease and MPTP monkeys.^{64–67} However, dopaminergic replacement with short-acting drugs does not restore basal ganglia neuronal firing patterns to normal. Heimer and colleagues⁶⁸ showed that although levodopa therapy influences GPi and GPe firing rates in MPTP-lesioned monkeys, they move in opposite directions such that the GPe to GPi firing-rate ratio is substantially increased in comparison to normal.⁶⁸ Furthermore, although levodopa reduces the percentage of correlated pairs of neurons with synchronous firing in the GPi and GPe of MPTP monkeys, they are not reduced to normal concentrations in the on state, and remain grossly abnormal during the off state. Levodopa use is also associated with specific changes in the expression and distribution of NMDA-receptor subunits. Gardoni and colleagues⁶⁹ showed that levodopa-induced dyskinesia is associated with profound changes in the distribution of NR2B subunits (from a synaptic to an extrasynaptic location) and in their association with members of the membrane-associated guanylate kinase (MAGUK) family of proteins. These and many other studies showed that standard levodopa therapy does not normalise the parkinsonian basal ganglia but shifts it to a different state of abnormality.

Discontinuous or pulsatile stimulation of striatal dopamine receptors

In Parkinson's disease, the progressive loss of SNc dopaminergic neurons causes striatal dopamine concentrations to be increasingly dependent on the peripheral availability of levodopa and impairs the capacity of dopamine terminals to buffer fluctuations in plasma levodopa concentrations. Thus variability in plasma levodopa concentrations associated with drugs having a short half-life results in variability in striatal dopamine concentrations and pulsatile stimulation of striatal dopamine receptors.

The effect of half-life in the production of dyskinesia can be readily observed in MPTP-lesioned monkeys. Short-acting dopaminergic drugs such as levodopa rapidly induce severe dyskinesias, whereas longer-acting dopaminergic drugs (eg, ropinorole, bromocriptine,

cabergoline) matched to provide comparable motor benefit are associated with little or no dyskinesias.⁷⁰⁻⁷³ Indeed, intermittent injections of a short-acting dopamine agonist such as U-91356A or apomorphine rapidly induce dyskinesia, whereas continuous infusion of the same drug does not.^{74,75} These experiments show that the same dopaminergic drug may or may not induce dyskinesia depending on whether it is given in a pulsatile or continuous manner.

Disease severity can also influence the risk that a drug will induce pulsatile stimulation and motor complications. MPTP-lesioned monkeys—with about a 95% loss of dopamine neurons—develop dyskinesias within days of starting levodopa treatment,^{70,71} whereas partially lesioned or normal animals are much more resistant to the development of levodopa-induced dyskinesias.^{73,76} Similarly, patients with Parkinson's disease are estimated to have a 40–60% loss of SNc dopamine neurons at the time of diagnosis and typically do not develop severe dyskinesias for years after starting levodopa. By contrast, patients with MPTP toxicity or parkin mutations who have severe dopaminergic lesions can develop severe dyskinesias within weeks of starting levodopa.^{77,78}

Pulsatile stimulation of striatal dopamine receptors can induce molecular and neurophysiological changes in striatal neurons that are associated with dyskinesias. Studies in dopamine-denervated mice, rats, and monkeys showed that dyskinesia induced by short-acting dopaminergic drugs is associated with altered expression of various genes or proteins including preproenkephalin, preprodynorphin, cFos, delta FosB, JunB, Cdk5 (cyclin-dependent protein kinase 5), ERK1/2, DARP32, and D1-signalling proteins.⁷⁹⁻⁸⁴ Similar findings have been reported in post-mortem brains of patients with Parkinson's disease; preproenkephalin expression was substantially higher in patients who had levodopa-induced dyskinesia than in patients treated with levodopa who did not have dyskinesia or normal controls.⁸⁵ Neither the gene changes nor the dyskinesia associated with a short-acting dopaminergic drug are reported when the same drug is given by continuous infusion.⁷⁹ The neurophysiological firing pattern of basal-ganglia neurons is also influenced by pulsatile dosing with a dopaminergic drug. Changes in the number and duration of pauses and bursts as well as in firing frequency have been reported in both MPTP-lesioned monkeys and patients with Parkinson's disease.^{86,87} Furthermore, pulsatile administration of levodopa substantially changes GPe to GPi firing-rate ratios,⁶⁸ does not fully eliminate synchronous firing,⁶⁸ and impairs mechanisms involved in long-term depression and striatal plasticity.⁴⁷ How precisely these molecular and physiological changes lead to dyskinesia is not clearly understood.

Similar evidence supports the idea that motor fluctuations (ie, wearing off) are associated with pulsatile stimulation. In 6-hydroxydopamine-lesioned rats, chronic

treatment with intermittent doses of levodopa is associated with a progressive reduction in the duration of the motor response following a single levodopa dose, but there is no shortening in the duration of the motor response after a dose of levodopa in animals that had previously been treated with continuous levodopa infusion.^{88,89} As with dyskinesia, levodopa treatment regimens that induced shortening of the duration of the motor response were associated with altered expression of striatal preprodynorphin and prometkephalin, whereas these gene changes did not occur with continuous levodopa administration.⁹⁰

These findings show the inability of standard doses of oral levodopa therapy to restore basal-ganglia physiological activity to normal. They further demonstrate that non-physiological discontinuous or pulsatile dopamine replacement induces further disruptions in the dopamine-denervated basal ganglia leading to the development of motor fluctuations and dyskinesia.

Continuous-dopaminergic-stimulation-based therapy for Parkinson's disease

These laboratory observations have been extended to the clinic. In patients with early Parkinson's disease, several prospective double-blind, controlled trials have shown that patients randomised to initiate therapy with a long-acting dopamine agonist have a low risk of motor complications in comparison with patients treated with standard, short-acting levodopa—even though patients in both groups could receive supplementation with open-label levodopa if deemed necessary.⁹¹⁻⁹⁴ Indeed, very few, if any, patients treated exclusively with a long-acting dopamine agonist experience any dyskinesia at all. In each of these studies, patients initially randomised to receive levodopa had improved motor responses at all time points compared with patients initially assigned to receive a dopamine agonist. This finding prompted some to question if the reduced dyskinesia in the agonist group is associated with a less effective dopaminergic regimen.⁹⁵ However, agonist-treated patients could receive levodopa supplementation, and the very low frequency of dyskinesia seen with long-term dopamine-agonist monotherapy and the low rate of motor complications when the same drug is delivered by infusion make this explanation unlikely.

In patients with advanced Parkinson's disease, continuous infusion of levodopa or a dopamine agonist (apomorphine, lisuride) has been shown to provide long-lasting and dramatic improvement in established motor complications.⁹⁶ A prospective, controlled study with 40 patients with advanced Parkinson's disease with severe levodopa-related motor complications showed the benefit of continuous infusion. Patients randomly assigned to switch to a continuous subcutaneous infusion of lisuride had significantly less off time and dyskinesias than those remaining on standard oral formulations of levodopa.⁹⁷ These benefits lasted throughout the 4 year duration of

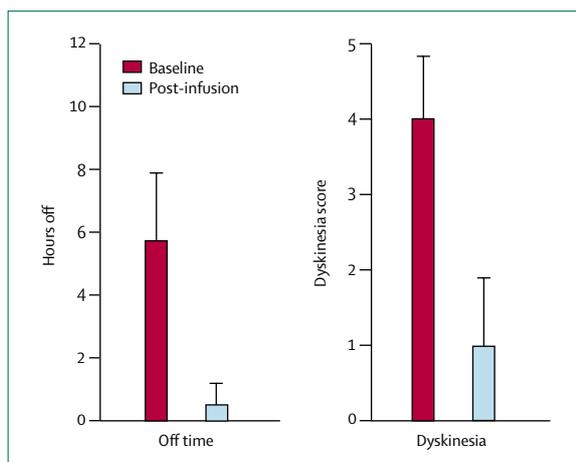


Figure 3: Effect of continuous intrainestinal levodopa infusion on motor complications in Parkinson's disease

Comparison of off time and dyskinesia scores at baseline when patients were on intermittent doses of standard levodopa, and at 6 months when patients were receiving levodopa by continuous intrainestinal infusion. Note that levodopa infusion was associated with a significant reduction in both off time and dyskinesia. Reproduced with permission from the American Medical Association.¹⁰⁹

the study. Infusion was only given during the waking day to avoid tolerance. As a consequence, patients experienced some wearing off and dystonia when the infusion was discontinued at night, but both patient and physician global-rating scales indicated that infusion was associated with substantial and significant overall increases in quality of life. It should be noted that this was an open-label study, and double-blind trials of infusion therapies have not yet been done.

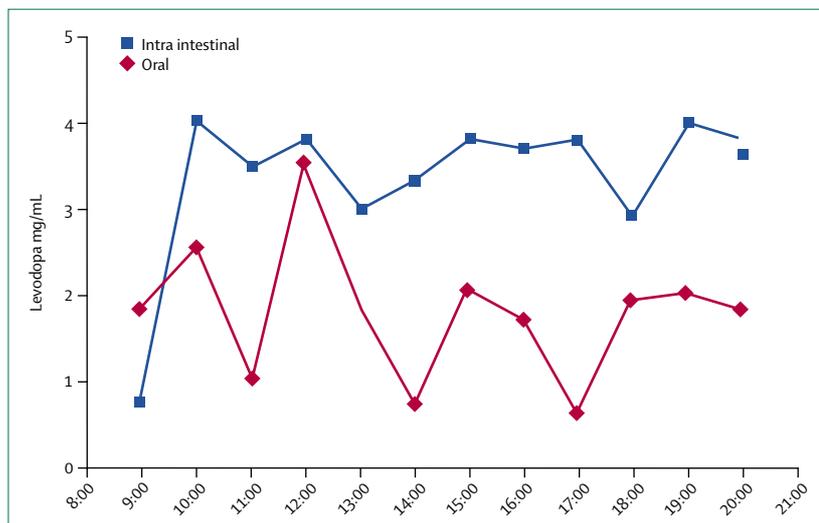


Figure 4: Plasma levodopa concentrations after oral and continuous intrainestinal levodopa administration When levodopa was given orally patients experienced substantial motor complications but at 6 months, when levodopa was given by infusion, motor complications were much reduced. Note that infusion avoids the low trough concentrations seen with repeated oral doses of a standard levodopa formulation. Reproduced with permission from the American Medical Association.¹⁰⁹

Implications for current treatment

On the basis of laboratory and clinical findings, many physicians now start treatment in appropriate patients with Parkinson's disease with a long-acting dopamine agonist and use levodopa when patients can no longer be satisfactorily controlled with dopamine agonist monotherapy.⁹⁸ This decision is partly based on the potential for short-term exposure to levodopa to prime for the development of dyskinesia. The concept of priming or sensitisation implies that patients exposed to levodopa for even a short time are more prone to develop dyskinesia when the drug is reintroduced than are patients who have never been exposed to levodopa.⁸³ This finding is thought to be associated with the capacity of levodopa to induce long-term plastic changes in striatal medium spiny neurons. Priming has been reported in MPTP-lesioned monkeys,⁸¹ but remains a theoretical concept in patients with Parkinson's disease; this concept nonetheless represents another argument for beginning therapy with a dopamine agonist. Dopamine agonists are not without complications (gastrointestinal problems, sleep disturbances with excess daytime sleepiness, peripheral oedema, psychosis, and possibly the induction of impulse disorders such as gambling) and are not typically used in elderly patients or in those with cognitive impairment. Although dopamine agonist monotherapy can be effective in early disease, patients eventually require supplementation with levodopa,^{91,92} and levodopa can induce motor complications even if given in conjunction with a dopamine agonist.^{73,91,92} Indeed, the time until the development of motor complications after the initiation of levodopa is about the same when levodopa is used as initial therapy as it is when levodopa is added to a dopamine agonist.⁹¹ Thus dopamine agonists delay the introduction of levodopa but do not prevent or delay the development of motor complications once levodopa is initiated.

Current understanding of basal-ganglia physiology suggests that longer-acting or more continuous delivery of levodopa might avoid these motor complications. Controlled release formulations of levodopa did not reduce the risk of motor complications compared with standard levodopa in double-blind controlled trials,⁹⁹ but the controlled-release drug has variable absorption and was only given twice daily, so it is unlikely that continuous dopaminergic stimulation was achieved in this trial. Patch delivery provides a means of attaining stable plasma concentrations; however, this has proven difficult to achieve with levodopa because the drug is acidic and needs to be given with large volumes of fluid.¹⁰⁰ The only antiparkinsonian drugs currently being tested in a patch formulation are the monoamine oxidase-B inhibitor selegiline (primarily studied in depression) and the dopamine agonist rotigotine.¹⁰¹ Neither of these drugs are effective enough to avoid the need for levodopa. Continuous infusion of a dopamine agonist has been shown to reduce motor complications in patients with

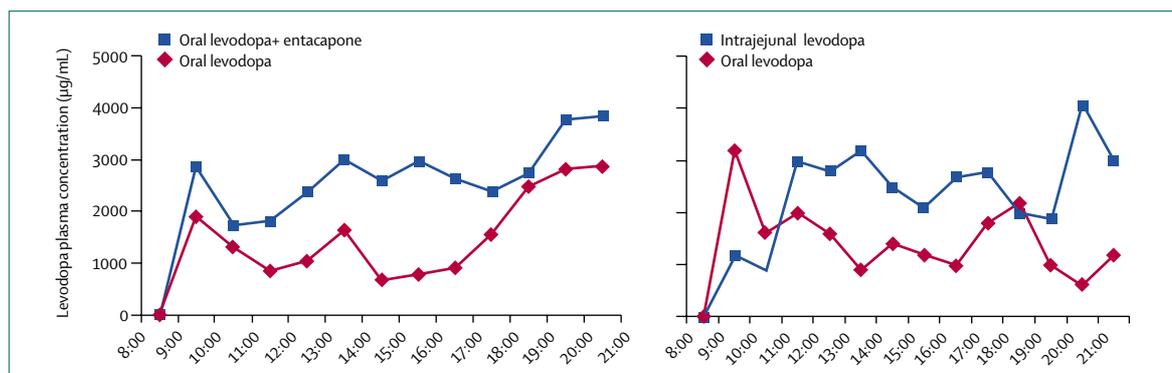


Figure 5: Effect of intrainestinal infusion and addition of entacapone on levodopa pharmacokinetics

Left: comparison of levodopa plasma pharmacokinetic profiles when levodopa and carbidopa were given at 3 h intervals with intermittent oral doses of a standard formulation and then 1 day later to the same patient at the same frequency, but in combination with the catechol-o-methyltransferase inhibitor entacapone. Note that oral levodopa is associated with low trough concentrations that are avoided when levodopa is combined with entacapone, thereby providing a pattern strikingly similar to that delivered continuously by infusion. Right: comparison of plasma pharmacokinetic profiles when levodopa is delivered orally with intermittent doses of a standard levodopa formulation and then again in the same patient when levodopa is given by continuous intrainestinal infusion. Note that oral levodopa in standard formulations is associated with low trough concentrations that are avoided when levodopa is delivered continuously by infusion or when it is combined with entacapone and given at 3 h intervals.¹¹¹ Reproduced with permission from Lippincott, Williams, and Wilkins.

advanced disease.⁹⁶ However, infusions are cumbersome and are associated with side-effects at the site of administration, and patients with early disease will probably resist this treatment approach. Continuous levodopa delivery by intrainestinal infusion has been shown to reduce established dyskinesia in patients with advanced disease,^{102–108} showing the value of continuous delivery of the drug. However, in addition to the problems associated with agonist infusions, continuous intrainestinal levodopa delivery requires a surgical procedure and frequent repositioning or replacement of the catheter.

An oral levodopa therapy that reflects the pharmacokinetics of a levodopa infusion would be a better alternative. To better understand the pharmacokinetic basis of motor complications, we compared the plasma levodopa pharmacokinetic profile in patients receiving oral doses of standard levodopa complicated by motor complications with that obtained in the same patients treated with a continuous levodopa infusion and who had experienced substantial improvement in off time and dyskinesias (figure 3).¹⁰⁹ These studies showed that levodopa infusion avoided the very low trough concentrations reported with intermittent doses of standard oral levodopa formulations (figure 4).¹⁰⁹ We speculated that in dopamine-lesioned patients with Parkinson's disease who cannot buffer fluctuations in plasma concentrations, low trough concentrations lead to low striatal dopamine concentrations and discontinuous or pulsatile stimulation of striatal dopamine receptors leading to the development of motor complications. We further speculated that the development of an oral levodopa treatment strategy, which mirrors the pharmacokinetic profile obtained with a levodopa infusion, might similarly avoid motor complications. To try and accomplish this goal, we

combined standard oral levodopa with a catechol-O-methyltransferase inhibitor, which blocks the peripheral metabolism of levodopa and extends its elimination half-life from about 90 min to about 3 h.¹¹⁰ We found by giving levodopa and carbidopa in conjunction with entacapone at 3 h intervals we could avoid the low plasma levodopa trough concentrations observed with standard formulations of levodopa and carbidopa, and provide a plasma pharmacokinetic profile similar to that obtained from a continuous infusion (figure 5).¹¹¹ These findings suggest that levodopa, carbidopa, and entacapone given orally at 3 h intervals might provide more continuous dopamine stimulation than standard levodopa and reduce the risk of motor complications. Indeed, studies in MPTP-lesioned monkeys showed that levodopa-induced dyskinesias were significantly reduced when levodopa was given at approximate 3 h intervals in combination with entacapone.¹¹² The importance of avoiding pulsatile stimulation is shown by the fact that the addition of entacapone increases dyskinesia when levodopa is given at 6 h intervals and continuous dopaminergic stimulation is not achieved.¹¹³ A prospective multicentre, double-blind study comparing the risk of motor complications in patients with Parkinson's disease randomly assigned to receive levodopa plus entacapone versus levodopa alone is currently underway (the STRIDE-PD study). Monoamine oxidase-B inhibitors, which block the central metabolism of dopamine, provide another theoretical opportunity to stabilise dopamine concentrations in the brain, although there is no experimental data for this approach.

Prospects for the future

The development of therapies based on continuous dopaminergic stimulation as a treatment for Parkinson's disease raises certain practical questions. Foremost,

will these therapies induce tolerance (or desensitisation) with degradation of the motor response? Studies in animals show that continuous 24 h administration of a dopaminergic drug can be associated with tolerance.¹¹⁴ Similar results have been reported with 24 h infusions in patients.¹¹⁵ Patients receiving round-the-clock 24 h infusions can also experience psychiatric problems with severe hallucinations.⁹⁶ These problems can generally be avoided with infusions that are given only during waking hours and we have not encountered tolerance or serious psychiatric problems with such infusion protocols.^{97,109}

Finally, this review has focused on the scientific rationale and clinical results obtained with continuous dopaminergic stimulation as a treatment approach to Parkinson's disease. Other factors, such as the topography of the striatum, pattern of receptor denervation and activation, postsynaptic transcriptional alterations in medium spiny neurons, and abnormalities in glutamate and other neurotransmission systems may also play a part in the pathogenesis of motor complications. Indeed, other antidyskinesia treatment strategies may ultimately prove to be as or more effective than continuous-dopaminergic-stimulation-based strategies. Research has focused on the possibility that dyskinesia is associated with activation of specific dopamine receptor subtypes and dyskinesia has at times been linked to selective activation of either D1 or D2 receptors. However, dyskinesias can be induced with selective short-acting D1^{116–118} or D2^{119,120} agonists in MPTP-lesioned monkeys and patients. D3 receptors have also been implicated in the pathophysiology of dyskinesia in studies showing that a selective partial D3 agonist reduces dyskinesia and improves motor function in MPTP monkeys.¹²¹ The levodopa molecule might also be particularly prone to induce dyskinesia. Indeed, Maratos and colleagues¹²² reported less dyskinesia with short acting D1 and D2 agonists than with levodopa in MPTP-lesioned marmosets.¹²² These findings do not, however, detract from the concept of continuous dopaminergic stimulation in the treatment of Parkinson's disease, because there are many studies in both animal models and patients in which dyskinesias associated with intermittent delivery of either levodopa or an agonist can be avoided with continuous delivery of the same drug.^{74,75,109,119} Interestingly, parallel effects have been reported with respect to the ventral tegmental area and accumbens dopamine system and addiction where it has been found that intermittent discrete doses of psychostimulants result in rapid sensitisation, whereas continuous infusion of the same drug causes desensitisation.¹²³ We have also not considered the potential role of non-dopaminergic systems in the development of dyskinesia, and the possibility that other targets for antidyskinesia therapies might include glutamate, cholinergic, adenosine2A and opioid receptors.¹²⁴ We have also not addressed diphasic dyskinesia, which may result from a different mechanism

Search strategy and selection criteria

References for this review were identified by searches of PubMed between 1980 and March 2006 using the search term "continuous dopaminergic stimulation".

than peak-dose dyskinesia and may not be improved, or may even be worsened, by continuous delivery of suboptimal dopamine concentrations as we speculated have occurred in patients who underwent fetal nigral transplantation.¹²⁵ Nonetheless, a large body of scientific and clinical information supports the idea that discontinuous or pulsatile stimulation of striatal dopamine receptors contributes to the development of levodopa-induced motor complications and favours the use of continuous dopaminergic stimulation-based therapies in an attempt to obtain the symptomatic benefits of levodopa without motor complications. It is fascinating that 40 years after the introduction of levodopa, there is still a fundamental lack of knowledge on how to optimally give the drug.

Contributors

All authors contributed equally to the design, organisation, and writing of this review.

Conflicts of interest

CWO has consulted with Boehringer Ingelheim, Teva Neuroscience, Novartis/Orion Pharma, Schwarz, GSK, and Valeant. JAO has consulted with GSK, Boehringer Ingelheim, Teva/Lundbeck, and Novartis/Orion. FS has consulted with GSK, Boehringer Ingelheim, Teva Neuroscience, and Novartis/Orion.

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