

## Novel Treatment Options for Advanced Parkinson's Disease

a report by

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It is thought that motor fluctuations in Parkinson's disease (PD) to a large extent result from pulsatile dopaminergic stimulation due to the short half-life and erratic absorption of oral levodopa therapy. Providing more continuous dopaminergic stimulation (CDS) has therefore become a central dogma in the prevention or treatment of hypo- and hyperkinetic fluctuations in PD. Several novel treatment options that improve CDS in PD have recently become available, including transdermal patch and oral controlled-release formulations of dopamine agonists and the continuous enteral delivery of levodopa/carbidopa via a pump system. Deep brain stimulation of the subthalamic nucleus (DBS-STN), which targets the abnormal neuronal activity downstream of the striatal dopamine deficiency, is increasingly being accepted as a surgical treatment alternative for patients with severe tremor or motor complications of levodopa therapy. This article will introduce the treatment options for patients with advanced PD and discuss their differential indications.

### The Concept of 'Continuous Dopaminergic Stimulation'

PD is a progressive neurodegenerative disorder with prominent motor features. The cardinal motor signs – bradykinesia, rigidity and tremor – are treated effectively by dopaminergic therapies. Levodopa is the most potent dopaminergic drug for PD and all patients suffering from PD will eventually require levodopa therapy. However, with continued treatment and as the disease progresses the response to oral levodopa becomes unstable and motor fluctuations emerge, including off-periods (when medication effects wear off) and dyskinesia (dystonic or choreatic movements). In this stage the pharmacokinetic properties of levodopa, with its short half-life of 90–120 minutes, gain increasing importance for the duration of the motor response. Many peripheral factors have an additional impact on plasma levels of levodopa: abnormal gastric acidity, reduced gut motility and dietary amino acids competing with levodopa uptake via the duodenal amino acid transporter may lead to irregular fluctuations of plasma levels despite regular oral intake of the drug. As the number of striatal dopaminergic terminals decreases to <20% with disease progression, their buffering and transforming capacity is lost. Levodopa is increasingly metabolised by non-

dopaminergic cells (e.g. serotonergic neurons), which do not provide a regulated release and do not possess the re-uptake facilities of dopaminergic cells. As a consequence, large fluctuations in the extracellular striatal concentration of dopamine parallel the fluctuations in levodopa plasma levels. The striatal medium spiny neurons, which are normally exposed to a relatively stable synaptic release of dopamine, become 'sensitised' by these erratic inputs and alter their firing pattern, which causes downstream abnormalities in the neuronal activity of the basal ganglia. Motor off-states are characterised by abnormal increases in the neuronal firing of the STN, which drives the inhibitory output nuclei of the basal ganglia, internal globus pallidus and substantia nigra pars reticulata. The increased gamma-aminobutyric acid (GABA)-ergic output of these nuclei inhibits thalamocortical and brainstem motor pathways and causes akinesia. Opposite changes in firing rate and additional abnormalities in the patterning of neuronal activity are observed during dyskinetic on-states.

CDS by means of subcutaneous or intravenous infusion of lisuride, apomorphine or levodopa has been shown to dramatically improve motor fluctuations, even in severely affected patients. Moreover, experimental studies in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)–primate model of parkinsonism and clinical trials have demonstrated that the early use of dopamine agonists with a medium to long half-life can delay the onset of dyskinesia or hypokinetic fluctuations compared with levodopa monotherapy. The downside may be a less pronounced improvement of motor symptoms, which becomes increasingly apparent when the disease progresses beyond Hoehn and Yahr stage II. Nevertheless, providing a more continuous central dopaminergic stimulation either by using dopamine agonists or by stabilising peripheral levodopa plasma levels through the addition of catecholamine-O-methyl (COMT) or monoamine oxidase (MAO) inhibitors is now a central issue in the early and late treatment of PD, and governs evidence-based treatment guidelines. Recently, new dopamine agonist formulations have become available for clinical practice, such as the transdermal patch application of rotigotine<sup>1</sup> or the controlled-release version of ropinirole,<sup>2</sup> with pharmacokinetic properties that are close to ideal in providing constant drug levels. However, despite the theoretical framework of CDS, no clinical trial has so far proved the superiority of these new dopamine agonist formulations over older formulations in terms of reducing or delaying fluctuating treatment responses.

DBS-STN is another way of providing continuous stimulation within the basal ganglia. It targets the abnormal neuronal activity of the basal ganglia resulting from the striatal dopaminergic deficiency downstream of the lesion in PD. High-frequency electrical stimulation via implanted electrodes is thought to overwrite the pathological basal ganglia input to cortical and brainstem regions, which mediate the motor symptoms of parkinsonism. Although the exact mechanisms of DBS are still poorly understood, it is well established that its benefit is closely linked to the responsiveness of motor



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symptoms to levodopa. After surgery, on average 60% of the dopaminergic drug dosage can be replaced by stimulation and approximately 10% of patients no longer require any levodopa therapy.<sup>3</sup> Interestingly, the sensitisation phenomenon leading to dyskinesia is reversible by DBS, as was demonstrated in patients who no longer exhibited the same amount of dyskinesia in response to a levodopa challenge after one year of treatment.<sup>4</sup> Whether this is a consequence of the secondary changes in medical therapy or of continuous electrical stimulation itself remains undetermined.

Recently, continuous delivery of a gel formulation of levodopa/carbidopa into the duodenum via a percutaneous tube and a portable pump has become commercially available in several European countries. The continuous duodenal infusion provides more constant levodopa plasma levels than oral therapy because it circumvents the problems of gastric emptying and unpredictable absorption in the small bowel. It is an alternative to intravenous administration of levodopa, which is impractical because the drug is hydrophobic and requires very large liquid volumes to dissolve. Duodenal levodopa infusion is an advanced treatment for patients with severe motor fluctuations or dyskinesia. Levodopa responsiveness is the most important prerequisite for a benefit from this infusion therapy. The same principal selection criteria apply to DBS-STN.

There are still no comparative trials of these two invasive treatment options. However, some published data and clinical experience suggest that there may be subgroups of PD patients who might be more suitable for either duodenal levodopa infusion or DBS. The following sections will summarise the evidence for both therapies and provide practical advice on how to individualise treatment decisions in patients with advanced PD and motor complications.

### Deep Brain Stimulation

Over the last two decades a firm place has been established for surgical therapies in the treatment of PD. DBS is accomplished by implanting an electrode with four contacts into the target area within the brain and connecting it to an internal pulse generator, usually located in the chest region. The stimulator settings can be adjusted telemetrically with respect to electrode configuration, current amplitude, pulse width and pulse frequency. By passing high-frequency electrical current (>100Hz) into the target area, DBS reversibly mimics the effect of lesioning the stimulated brain area. Stimulation at lower frequencies has no beneficial effects, and may even aggravate symptoms.<sup>5</sup> The exact cellular mechanisms of DBS are still unknown, although several hypotheses have been postulated.<sup>6</sup> In animal models of PD, neuronal activity is abnormally increased in the STN and internal pallidum (GPI) as a consequence of striatal dopaminergic depletion, and lesioning or high-frequency stimulation of these structures reverses symptoms of MPTP-induced parkinsonism, probably by releasing cortical and brainstem projection areas from abnormal neuronal inputs that interfere with normal motor control. DBS has rapidly replaced ablative stereotactic surgery in movement disorders for several reasons: DBS does not require a destructive lesion to be made in the brain; DBS can be performed bilaterally with relative safety compared with most lesioning procedures; stimulation parameters can be adjusted post-operatively to improve efficacy, reduce adverse effects and adapt DBS to the course of disease; and DBS is in principle reversible and does not preclude the use of possible future therapies in PD that require integrity of the basal ganglia circuitry.

The symptomatic benefit of STN-DBS has been established in a large number of clinical studies. A recent systematic review identified a total of 34 articles

from 1993 until 2004 that reported on the outcome from 37 cohorts comprising 921 patients.<sup>7</sup> STN-DBS significantly improved off-period motor symptoms and activities of daily living, as indicated by an average reduction of the Unified Parkinson Disease Rating Scale (UPDRS) II (activities of daily living) and III (motor) scores by 50 and 52%, respectively. The levodopa equivalent daily dosage of dopaminergic drugs could be reduced by 55.9% following surgery. Dyskinesia scores decreased after surgery by an average of 69.1%, and the duration of daily off-periods as assessed by diaries by 68.2%. More severe off-period motor symptoms at baseline and a better responsiveness to levodopa predicted a better outcome of STN-DBS, according to this review. The most common serious adverse event related to surgery was intracranial haemorrhage, which occurred in 3.9% of patients included in this meta-analysis. The true surgical risk, however, may be difficult to estimate from these collated data because the individual studies often reported on the initial patients in a larger series and surgical complication rate may underlie a learning curve. A recent survey on the 30-day complication rate after DBS that included 1,183 consecutively operated patients from five German centres reported a mortality of 0.4% and a permanent morbidity of 1%.<sup>8</sup> Intracranial bleedings amounted to 2.9%, but were often asymptomatic. Treatment-related adverse effects of STN-DBS are probably more important than the surgical risk; these may result from stimulation itself, the necessary drug withdrawal or disease-related factors. Psychiatric sequelae are not uncommon and include transient confusion, apathy, depression, suicidal ideation or (hypo)mania. These adverse events are most frequent during the first weeks after surgery and are often related to the complex interaction between drug withdrawal and stimulation adjustment during this initial stabilisation period.<sup>9</sup>

Because STN-DBS aims at improving a patient's functional capacity and reducing disability by alleviating motor fluctuations and dyskinesia, it was important to prove that quality of life is indeed improved despite the potential adverse effects of the therapy on motor or non-motor domains. This fundamental question was addressed by a recent randomised, controlled, multicentre study comparing neurostimulation with best medical management over a six-month period.<sup>10</sup> The study included 156 patients with severe motor symptoms of PD who were randomly assigned in pairs to receive either bilateral DBS-STN in combination with medical treatment or best medical therapy alone. The primary outcome of the trial was the change in health-related quality of life on the Parkinson's Disease Questionnaire-39 (PDQ-39) after six months. The PDQ-39 summary improved in the surgically treated group by about 25%, but remained virtually unchanged in the medically treated patients. While serious adverse events were more common with neurostimulation than with medication alone and included a fatal intracerebral haematoma and a suicide, the total number of adverse events was higher among medication-only patients. They included typical treatment-related complications in advanced PD such as increased motor fluctuations, dyskinesia, falls or delusions. One patient in the medication-only group died from a car accident during a psychotic episode. By including a control group, this study could demonstrate for the first time that advanced PD is associated with major risks of disease or treatment-related complications that need to be carefully balanced against the risks of an invasive therapy. In the patients selected for this study, the benefits of STN-DBS clearly outweighed the risks in that an improvement in quality of life was indeed achieved. The durability of improved health-related quality of life has not been assessed. The open-label follow-up of several cohorts suggests that symptomatic benefits are sustained for up to five years after STN-DBS.<sup>11-13</sup>

However, disease progression is not halted, as is reflected by a worsening of the on-period motor scores, in particular axial symptoms such as dysarthria, gait freezing or postural imbalance. Cognitive decline, apathy and frontal dysexecutive symptoms pose additional problems in the long-term management of DBS-treated patients; this is particularly true in older patients undergoing STN-DBS. A study retrospectively stratifying the treatment response by age at surgery found that patients over 70 years of age had a worsening of their axial symptom scores after surgery that did not recover even with additional levodopa treatment.<sup>14</sup> In addition, older patients have significantly less improvement in quality of life despite experiencing symptomatic benefit from DBS as assessed by the UPDRS score.<sup>15,16</sup> This has raised the question as to whether the inclusion criteria for DBS should include an age cut-off.

Ideal candidates for STN-DBS have idiopathic PD with a preserved excellent levodopa response but either severe tremor that is not adequately managed by dopaminergic therapy or motor fluctuations as a side effect of long-term medical treatment. Dementia, acute psychosis and major depression are usually exclusion criteria. Most centres have primarily operated on patients suffering from young-onset PD, because they best fulfil these criteria. Older age, however, was not regarded as an exclusion criterion *per se*, as long as patients did not suffer from cognitive decline or too severe levodopa-resistant symptoms.

## Duodenal Levodopa/Carbidopa Infusion

Continuous levodopa delivery through enteral infusion smoothes out the large-scale fluctuations in levodopa plasma levels with oral levodopa therapy and thereby controls motor fluctuations and dyskinesia. The therapy has been approved in several European countries under an orphan drug exemption and is currently being used in approximately 1,000 patients. The evidence base for this therapy is still evolving. Nyholm and colleagues conducted the first randomised, cross-over study and proved the superiority of duodenal levodopa infusion over oral polypharmacy in reducing off-periods and on-time with severe dyskinesia.<sup>17</sup> This symptomatic benefit has been confirmed in open-label studies. Most recently, Antonini prospectively evaluated the longer-term impact of the therapy on health-related quality of life in nine patients with advanced PD. Seven patients completed the follow-up of at least 12 months.<sup>18</sup> The therapy significantly shortened the daily duration of off-periods and dyskinesia and led to significant improvements in four domains (mobility, activities of daily living, stigma and bodily discomfort) of a disease-specific quality-of-life scale (PDQ-39). The average age (66–68 years) in the studies of Antonini and Nyholm was higher than in most DBS trials and suggests that duodenal infusion therapy has been offered to an older patient group that was less likely to benefit from DBS as an alternative treatment. While the principal efficacy of duodenal levodopa infusions has been established, there are fewer data on the long-term tolerance of this technically complex treatment. In our own clinical experience, application problems – such as tube dislocations, leakage or tube obstruction –

are more likely to cause termination of the treatment than the re-emergence of dyskinesia or motor fluctuations.

## Choosing Deep Brain Stimulation or Duodenal Levodopa Infusion for Individual Patients

In a recent survey using strict inclusion and exclusion criteria only 1.6–4.5% of an unselected sample of PD patients attending the outpatient service of a movement disorder centre were found to be eligible for STN-DBS,<sup>19</sup> although 30.9% suffered from uncontrolled motor complications. An age cut-off of 70 years excluded more than half of the patients. This underlines a need for treatment alternatives in a relatively large group of patients with motor complications that are not adequately controlled by oral medication. Duodenal levodopa infusion could target this group because it is less restrictive in terms of age, cognitive status or general health status despite sharing the prerequisite of levodopa responsiveness with DBS. Personal preference is the decisive factor when a patient meets the inclusion criteria for both DBS and infusion therapy. The decision for either treatment may be influenced by a number of subjective factors, including the willingness to accept the risks of brain surgery for the benefit of a fully implantable device or the stigma of a visible infusion system that requires daily care.

## Future Perspectives of Continuous Dopaminergic Stimulation

Several invasive approaches are currently being explored to provide more continuous local dopaminergic stimulation within the striate. Cell replacement therapy is in principle one option, but clinical transplantation research has come to a halt after two independent sham-controlled trials failed to prove the efficacy of foetal mesencephalic transplantations in PD.<sup>20,21</sup> Another way of providing continuous striatal dopaminergic stimulation is currently being explored in a phase II study using the intraputaminar implantation of human retinal pigment epithelial (RPE) cells. RPE cells produce levodopa and can be isolated from *post mortem* human eye tissue, grown in culture and implanted into the brain attached to microcarriers. They do not make any synaptic contact with the surrounding tissue, but act as local levodopa 'bioreactors'. In an open-label pilot study, six patients with advanced PD were followed after unilateral implantation and had an average improvement of 48% in the off-period motor score after one year<sup>22</sup> without any increase in the severity or duration of dyskinesia. Intra-striatal infusion of an adeno-associated viral vector containing the gene for the human aromatic L-amino acid decarboxylase has recently been reported in a phase I safety trial.<sup>23</sup> Transduced striatal neurons are able to convert levodopa to dopamine, which could potentially lead to a more stable intra-striatal dopamine release.

While all of these therapies are still in an experimental stage and far from entering clinical practice, they still emphasise the fact that the concept of continuous dopaminergic stimulation will remain a central topic of therapeutic research in PD in the near future. ■

1. Poewe WH, et al., *Lancet Neurol*, 2007;6(6):513–20.

2. Pahwa R, et al., *Neurology*, 2007;68(14):1108–15.

3. Deuschl G, et al., *J Neurol*, 2003;250(Suppl. 1):143–146.

4. Bejjani BP, et al., *Ann Neurol*, 2000;47(5):655–8.

5. Moro E, et al., *Neurology*, 2002;59(5):706–13.

6. McIntyre CC, et al., *J Clin Neurophysiol*, 2004;21(1):40–50.

7. Kleiner-Fisman G, et al., *Mov Disord*, 2006;21(Suppl. 14):S290–304.

8. Voges J, et al., *Mov Disord*, 2007;22(10):1486–9.

9. Deuschl G, et al., *Mov Disord*, 2006;21(Suppl. 14):S219–37.

10. Deuschl G, et al., *N Engl J Med*, 2006;355(9):896–908.

11. Krack P, et al., *N Engl J Med*, 2003;349(20):1925–34.

12. Schupbach WM, et al., *J Neurol Neurosurg Psychiatry*, 2005;76(12):1640–44.

13. Rodriguez-Oroz MC, et al., *Brain*, 2005;128(Pt 10):2240–49.

14. Russmann H, et al., *Neurology*, 2004;63(10):1952–4.

15. Derost PP, et al., *Neurology*, 2007;68(17):1345–55.

16. Ory-Magne F, et al., *Mov Disord*, 2007;22(10):1457–63.

17. Nyholm D, et al., *Neurology*, 2005;64(2):216–23.

18. Antonini A, et al., *Mov Disord*, 2007;22(8):1145–9.

19. Morgante L, et al., *Parkinsonism Relat Disord*, 2008;14(3):264–5.

20. Freed CR, et al., *N Engl J Med*, 2001;344(10):710–19.

21. Olanow CW, et al., *Ann Neurol*, 2003;54(3):403–14.

22. Stover NP, et al., *Arch Neurol*, 2005;62(12):1833–7.

23. Eberling JL, et al., *Neurology*, 2008;70(21):1980–83.





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A temporary nasoduodenal tube is recommended to find out if the patient responds favourably to this method of treatment. **Dosage:** the total dose/day of Duodopa is composed of three individually adjusted doses: the morning bolus dose, the continuous maintenance dose and extra bolus doses. **Morning dose:** The morning bolus dose is administered by the pump to rapidly achieve the therapeutic dose level (within 10-30 minutes). The total morning dose should not exceed 15 ml (300 mg levodopa). **Continuous maintenance dose:** The maintenance dose is adjustable in steps of 2 mg/hour (0.1 ml/hour). The continuous maintenance dose is adjusted individually. It should be kept within a range of 1-10 ml/hour (20-200 mg levodopa/hour). **Extra bolus doses:** To be given as required if the patient becomes hypokinetic during the day. The extra dose should be adjusted individually. Treatment must be monitored. **Contraindications:** hypersensitivity to levodopa, carbidopa or any of the excipients; severe liver and renal insufficiency; severe heart failure; severe cardiac arrhythmia; acute stroke. **Special warnings and precautions for use:** Duodopa should be administered with caution to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease, or history of peptic ulcer disease or of convulsions. In patients with a history of myocardial infarction who have residual atrial nodal or ventricular arrhythmias, cardiac function should be monitored with particular care during the period of initial dosage adjustments. All patients treated with Duodopa should be monitored carefully. Patients with past or current psychosis and chronic wide-angle glaucoma can be treated with caution. Levodopa has been associated with somnolence and episodes of sudden sleep onset in patients with Parkinson's disease and caution should therefore be exercised when driving and operating machines. Previous surgery in the upper part of the abdomen may lead to difficulty in performing gastrostomy or jejunostomy. **Interaction with other medicinal products and other forms of interaction:** Caution is needed in concomitant administration of Duodopa with the following medicinal products: antihypertensives, antidepressants, anticholinergics, COMT inhibitors, some antipsychotics and benzodiazepines. Duodopa can be taken concomitantly with the recommended dose of an MAO inhibitor, which is selective for MAO type B (for instance selegiline-HCl). Concomitant use of selegiline and levodopa-carbidopa has been associated with serious orthostatic hypotension. Amantadine has a synergic effect with levodopa and may increase levodopa related adverse events. Sympathomimetics may increase cardiovascular adverse events related to levodopa. Levodopa forms a chelate with iron in the gastrointestinal tract leading to reduced absorption of levodopa. As levodopa is competitive with certain amino acids, the absorption of levodopa can be disturbed in patients who are on a protein rich diet. The effect of administration of antacids and Duodopa on the bioavailability of levodopa has not been studied. **Pregnancy:** Duodopa should not be used during pregnancy unless the benefits for the mother outweigh the possible risks to the foetus. **Lactation:** Levodopa is excreted in the breast milk. It is unknown whether carbidopa is excreted in human breast milk. Duodopa should not be used during breast-feeding. **Effects on ability to drive and use machines:** Caution should be exercised when driving or using machines. **Undesirable effects:** Undesirable effects that occur frequently with levodopa/carbidopa are those due to the central neuropharmacological activity of dopamine. These reactions can usually be diminished by levodopa dosage reduction. **The device:** Complications with the devices may occur, e.g. connector leakage and dislocation of the intestinal tube. Dislocation of the intestinal tube backwards into the stomach leads to reappearance of motor fluctuations. In general, relocation of the tube can be done using a guide-wire to steer the tube into the duodenum under fluoroscopy. Occlusion, kinks, or knots of the intestinal tube lead to high pressure signals from the pump. Occlusions are usually remedied by flushing the tube with tap water; kinking, knotting, or a tube displacement may need readjustment of the tubing. The stoma usually heals without complications. However, abdominal pain, infection and leakage of gastric fluid may occur shortly after surgery; it is rarely a problem long-term. Reported complications include wound infection (the most common complication) and peritonitis. Local infections around the stoma are usually treated conservatively with a disinfectant. **Overdose:** Most prominent clinical symptoms of an overdose with levodopa/carbidopa are dystonia and dyskinesia. Blepharospasm can be an early sign of overdose. The treatment of an acute overdose of Duodopa is in general the same as that of an acute overdose of levodopa. Electrocardiographic monitoring should be used and the patient observed carefully for the development of cardiac arrhythmias; if necessary an appropriate antiarrhythmic therapy should be given. The possibility that the patient took other medicinal products together with Duodopa should be taken into consideration. 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<sup>1</sup> Nyholm D. et al. Duodenal levodopa infusion monotherapy versus oral polypharmacy in advanced Parkinson's disease. *Neurology* 2005; 64: 216-223.