Selecting Patients for Continuous Dopaminergic Stimulation Therapy

Per Odin,[1] Angelo Antonini,[2] Erik Wolters[3] and K Ray Chaudhuri[4]

1. Professor, Department of Neurology, Lund University and Chairman, Department of Neurology, Central Hospital, Bremerhaven; 2. Professor, Institute of Neurology, Istituto Di Ricovero e Cura a Carattere Scientifico, San Camillo, Venice and University of Padua; 3. Professor, Department of Neurology, Vrije Universiteit Medical Centre, Amsterdam; 4. Consultant Neurologist and Professor, King's College/University Hospital Lewisham, King's College London and Institute of Psychiatry

Abstract

In patients with advanced Parkinson's disease (PD), worsening motor symptoms, mainly owing to motor response complications and dyskinesia, may be treated optimally by switching to a continuous dopaminergic stimulation (CDS) treatment approach. There are three CDS options widely available for the treatment of PD: levodopa/carbidopa intraduodenal gel infusion (Duodopa®), subcutaneous apomorphine infusion (APO) and deep brain stimulation (DBS), which is not strictly a CDS treatment but has similar effects. Although large-scale direct comparisons of the CDS treatment options do not exist, there is a growing body of evidence that helps direct the choice of CDS therapy for individual patients. APO is the 'simplest' treatment, in terms of administration, but may be slightly less effective in treating motor complications than DBS or Duodopa. Furthermore, different CDS treatments appear to improve different non-motor symptoms. Several cases are presented in this article to illustrate some of the issues that lead to initiation of CDS therapy and that determine the choice between Duodopa, APO and DBS. In the absence of comparative trials, sharing clinical experience will help inform others of the best method of selecting patients for CDS therapy. Some simple algorithms have also been developed to direct this selection, but many unanswered questions remain, such as how early CDS therapies should be initiated. Future clinical studies and shared clinical experience should provide more definitive guidelines on the use of CDS therapy in the near future.

Keywords

Parkinson's disease, continuous dopaminergic stimulation, deep brain stimulation, subcutaneous apomorphine infusion, levodopa/carbidopa intraduodenal gel infusion, patient selection

Disclosure: Per Odin has received honoraria for lectures and participation in advisory boards from Boehringer Ingelheim, Abbott, Cephalon and GlaxoSmithKline (GSK). Angelo Antonini has received honoraria for consulting services and symposia from Abbott, Boehringer Ingelheim, GSK, Lundbeck, Union Chimique Belge (UCB), Novartis and Merck-Serono. Erik Wolters has no conflicts of interest to declare. K Ray Chaudhuri has received honoraria for symposium lectures and advisory boards from UCB, Abbott, Boehringer-Ingelheim, Britannia, Cephalon and GSK, and academic grants from UCB, Britannia and Abbott.

Acknowledgements: This work was supported by an unrestricted grant from Abbott. Editorial support was provided by Martin Gilmour, ESP Bioscience (Sandhurst, UK) funded by Abbott.

Received: 21 February 2011 **Accepted:** 15 March 2011 **Citation:** *European Neurological Review*, 2011;6(Suppl. 1):21–6

Correspondence: Per Odin, Department of Neurology, Skane University Hospital, SE-221 85 Lund, Sweden. E: per.odin@t-online.de

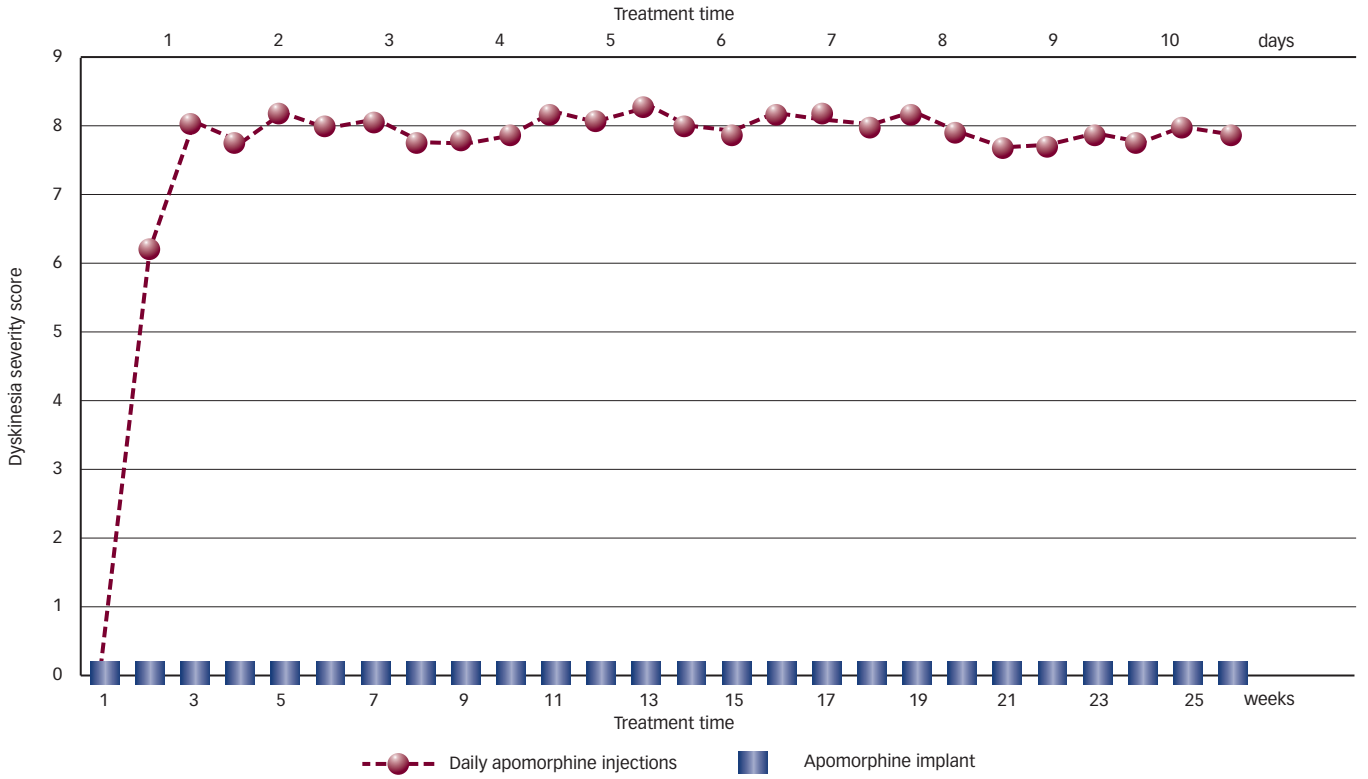
Rationale for Continuous Dopaminergic Stimulation Treatment

The link between long-term levodopa treatment for Parkinson's disease (PD) and the development of motor fluctuations and dyskinesia is well established.[1] As the therapeutic window narrows in advanced disease, the patient has more 'off' time and more dyskinesia with levodopa treatment. This relationship between motor complications and levodopa is dose-dependent – studies have demonstrated a clear increase in dyskinesia at higher levodopa doses.[2,3] However, a prerequisite for the development of motor complications and dyskinesias in PD is pulsatile dopaminergic stimulation. It is suggested that pulsatile stimulation of the PD-related dopamine-denervated striatum enhances the likelihood of a cascade of events, downstream to dopamine receptors, including D1 receptor-dependent induction of immediate early genes, increased DNA binding, phosphorylation of dopamine- and cyclic adenosine monophosphate (cAMP)-regulated neuronal phosphoprotein (DARPP-32) and loss of depotentiation of long-term induction. These events result in an irreversible enhanced sensitivity to dopamine D1 receptor stimulation with induction of extracellular signal-regulated kinases in the direct striato-nigral pathway.[4] This is not unique to oral levodopa treatment but has been demonstrated also with other dopaminergic drugs, as shown in a study of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned monkeys that received daily apomorphine injections or an apomorphine implant. All animals receiving injections developed dyskinesia by a mean of 8.3 days, no animals with continuous delivery of apomorphine developed dyskinesia (see *Figure 1*).[5] Providing more continuous dopaminergic stimulation (CDS) with treatment is, therefore, an important goal to prevent and reduce motor complications.

Options for Continuous Dopaminergic Stimulation

Dopamine agonists are longer-acting than levodopa and are therefore often used as initial treatment for PD to reduce the risk of developing dyskinesia, dystonia and motor fluctuations.[6] However, the clinical effects are inferior to those with levodopa and most

Figure 1: Effect of Continuous versus Intermittent Dopaminergic Stimulation in a Primate Model of Motor Complications[5]



Red = all animals developed dyskinesia by a mean of 8.3 days; blue = no animals developed dyskinesia after six months.
Source: Reprinted with permission from Elsevier.[5]

patients subsequently require levodopa or other treatments to achieve optimum control of their disease. Adding catechol-*O*-methyl transferase (COMT) inhibitors to levodopa treatment in early-PD patients, in order to provide more continuous delivery of levodopa to the brain, also appears to be of limited efficacy in preventing and/or reducing motor fluctuations and dyskinesia;[7] as does the addition of monoamine oxidase (MAO)-B inhibitors. To achieve more powerful CDS, there are three options widely available for the treatment of PD: levodopa/carbidopa intraduodenal gel infusion (Duodopa®), subcutaneous apomorphine infusion (APO) and deep brain stimulation (DBS), which is not strictly CDS treatment but has similar effects. These therapies are well established and there is a growing number of studies that provide high-quality evidence (i.e. from open-label, non-randomised studies through to randomised controlled trials),[8] but there have been no direct comparisons of the three CDS options. We must therefore rely on indirect comparisons and clinical experience to judge the appropriateness of each CDS therapy for individual patients.

Method of Administration

APO is the least invasive procedure and DBS is the most invasive. This could affect patient perceptions and preferences and for elderly patients (>65 years), DBS is not recommended. APO and Duodopa are both infusion therapies provided by pumps, but the subcutaneous infusion of APO is less invasive than the intraduodenal infusion of Duodopa (which requires surgical implantation). However, Duodopa use is more likely to be provided as monotherapy, which again may influence patient preference for simpler drug regimens.

Motor Fluctuations

When assessing publications investigating the efficacy of APO, a mean reduction in 'off' time of approximately 60 % (range 40–85 %) has been observed after 3–44 months of treatment.[9–17] However, additional levodopa administration is often required to achieve these response rates. Furthermore, patients sustain APO treatment for a limited period of time.[18] Greater reductions in 'off' time of 70–90 % have been observed with Duodopa treatment, but this is based on fewer patients and fewer studies.[19–22] These reductions with Duodopa appear to be similar to effects on motor status achieved after DBS.[23]

Dyskinesia

The tendency to react with dyskinesias is reduced by approximately 40 % after six months of APO treatment.[24] DBS produces around 80 % reduction of dyskinesias.[23] Small-scale studies with Duodopa suggest that dyskinesia intensity may be reduced by 75–90 %[19] (includes unpublished data from the Bremerhaven clinic) – larger-scale studies would be useful to better assess these effects.

Non-motor Symptoms

It is increasingly obvious that in addition to motor symptoms in PD, non-motor symptoms have a detrimental effect on patient quality of life (QoL). As of yet, the effects of the three CDS treatments on non-motor symptoms cannot be fully understood. From the data that are available, Duodopa has a statistically significant benefit in six of the nine domains of the non-motor symptoms scale (NMSS) including gastrointestinal, urinary, cardiovascular, sleep/fatigue, memory/attention and other miscellaneous non-motor symptoms (see *Figure 2*).[25] The other three domains also showed a trend towards improvement. In preliminary reports, DBS reduced sleep, urinary and miscellaneous symptoms[26] and APO improved depression (in the 'off' phase), anhedonia, nocturia and pain after one month (see *Figure 2*).[27] Because there is a wide range of non-motor symptoms that affect a large proportion of patients with PD, and because different CDS

treatments may improve different non-motor symptoms, the effects of CDS treatments on these symptoms may, in future, be a crucial factor in the choice of treatment.

Health-related Quality of Life

Because non-motor symptoms may have such an important impact upon QoL, the benefits of CDS treatments described above may have a positive effect on QoL. Using the Parkinson's disease questionnaire (PDQ)-8 as a measure, there was a significant improvement in health-related quality of life (HRQoL) with Duodopa among 22 patients with PD and 77 % of patients had improved HRQoL.[25] In a second report, nearly 90 % of patients receiving Duodopa had a great or moderate improvement in QoL as measured on a five-point rating scale from 'great improvement' to 'worsening'.[28] Similarly using PDQ-8, APO resulted in a significant improvement in HRQoL,[27] and there is good evidence that DBS also significantly improved HRQoL.[29]

Side Effects and Complications

The most frequently observed complications with Duodopa are technical issues with the percutaneous endoscopic gastrostomy (PEG) tubing such as leaking, occlusion and dislocation.[30] The pharmacological adverse events are the same as those expected with oral levodopa and include, among others, cobalamine-deficiency-induced polyneuropathy.[31] New types of tubing are being developed by the manufacturer, with promising results and these technical problems are usually reduced with increasing experience. The most common adverse events with APO are skin reactions – noduli at the point of infusion is a very common side effect – but complications such as hypotension, eosinophilia and nausea are also relatively common (>5 % in one patient series).[32] Among the most common complications of DBS are behavioural and cognitive changes, with more than 40 % of patients experiencing cognitive problems in one study – depression and mania also occur relatively frequently with DBS.[33,34]

Patient Selection

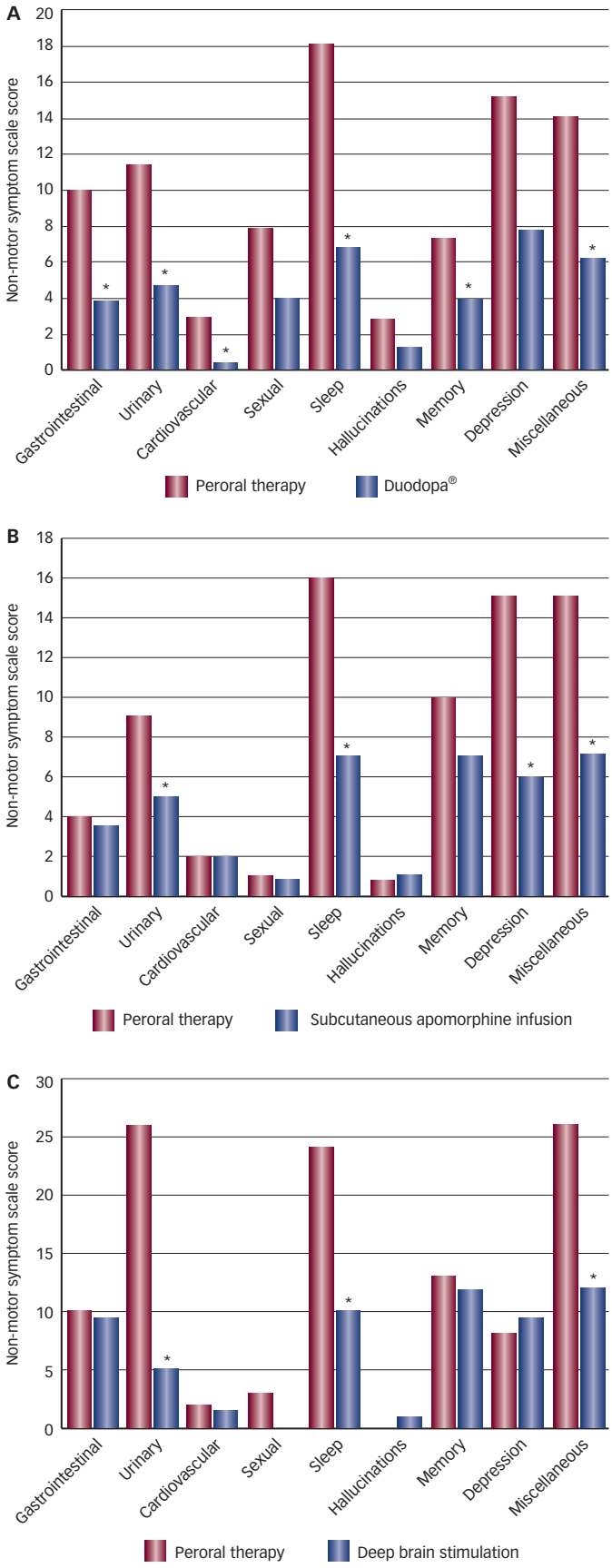
The indications for using any CDS treatment are similar and include: severe disease, pronounced motor fluctuations, dyskinesias, nocturnal akinesia and severe tremor that does not respond to medication. A simple algorithm has been proposed (see *Figure 3*)[35] and factors that play an important part in the decision-making process are age of patient and severity of dyskinesia. Such an algorithm may be useful for choosing the most appropriate CDS therapy for an individual patient and in the following case studies, we present some examples of the issues that can contribute to clinical decisions and discuss alternative scenarios for each case. At the fourth International Forum on Advanced Parkinson's Disease, interactive electronic voting was used to gauge the opinions of the whole audience. Where interesting issues were raised through this voting, these are included in the report of the case studies below.

Case 1 – A Patient with Early Onset Disease

Patient History

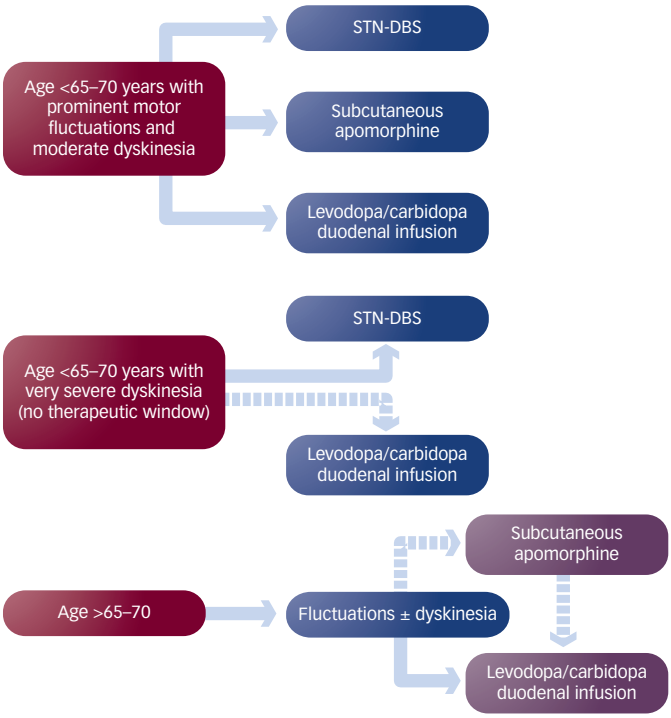
A 27-year-old man was diagnosed with PD in 1998 – three years after the onset of slowly progressive tremor and slowness of the right hand and leg. Therapy was initiated with a dopamine agonist, but none of the dopamine agonists that were available in 1998 (pergolide, ropinirole and pramipexole) were well tolerated. Owing to persistent dopamine agonist-induced nausea and vomiting (domperidone was not effective at reducing this), this treatment was withdrawn and levodopa/carbidopa 100 mg three times daily (tid) was given. Initial symptomatic improvement was observed.

Figure 2: The Effect of Continuous Dopaminergic Stimulation on Non-motor Symptoms of Parkinson's Disease – Duodopa® (A), Subcutaneous Apomorphine Infusion (B) and Deep Brain Stimulation (C)[25–27]



** = Statistical difference between Duodopa®/apomorphine/deep brain stimulation and peroral therapy.*

Figure 3: Patient Selection Algorithm For Choosing Continuous Dopaminergic Stimulation Treatment[35]



STN-DBS = subthalamic nucleus deep brain stimulation.
Source: Reproduced with permission from Expert Reviews Ltd.[35]

Subsequent Treatment

Approximately four years after starting levodopa therapy, motor fluctuations and mild dyskinesia developed (in 2002). This was managed initially by adding low-dose dopamine agonist (cabergoline, which at that point in time was tolerated), amantadine and a COMT inhibitor.

In 2006 (approximately three to four years later), the patient was receiving levodopa/carbidopa 100 mg six times daily (every three hours), the COMT inhibitor tolcapone tid and the dopamine agonist cabergoline 4 mg daily.

The patient had three hours of 'off' time per day, with some peak-dose dyskinesia and non-motor symptoms that included sleep fragmentation, 'off-time' anxiety and bladder urgency. It was decided at this time that a change in therapy was needed to improve symptoms.

Five possible options were considered at the meeting:

- CDS with either APO or Duodopa;
- DBS;
- an increased dose of dopamine agonists;
- a levodopa controlled-release formulation; or
- doing nothing.

The group opinion was split between the three CDS options (approximately 64 % voted for the first two options), with others suggesting that dopamine agonists or levodopa controlled-release could be tried before 'progressing' to these more invasive and expensive treatments. In the real-life case, the patient was switched to APO initially at 1 mg/h and titrated to 1.5 mg/h, because the managing team did not want to increase the medications being administered or increase the frequency of oral levodopa doses.

Outcomes on Continuous Dopaminergic Stimulation Therapy

While receiving APO, the patient had some reductions in 'off' time but developed nausea and compliance was poor. APO was therefore withdrawn and the patient was administered the following treatment regimen:

- levodopa/carbidopa 600 mg/day in eight administrations;
- tolcapone tid (300 mg/day);
- cabergoline 2 mg in the evening; and
- pramipexole 0.7 mg/day.

However, the patient still had severe dyskinesia for three hours/day, frequent 'off' periods totalling 5.5 hours in the daytime and a unified Parkinson's disease rating scale (UPDRS) III ('off') score of 40 and UPDRS III ('on') score of 15. The audience was polled again at this point and group opinion was split (approximately 1:1) between DBS and Duodopa as the next best option for treatment.

DBS would be an excellent option for this patient, but he was reluctant to receive this (as he felt he was still young and would leave this as a 'last resort' as he had had a previous bad experience with surgery) and he was administered Duodopa. The patient was started on an infusion rate of 2.1 ml/h for 15–16 hours with a morning bolus of 3 ml and up to three extra bolus doses of 2.2 ml (total levodopa dose of 700 mg/day). The outcome was UPDRS III ('off') score of 27 and UPDRS III ('on') score of 15; 'off' time was 45 minutes/day and 'on' time with dyskinesia was 60 minutes/day. More than two years after starting Duodopa therapy, the patient continues on a stable dose (infusion rate of 2.1 ml/h for 12–16 hours with a morning bolus of 2.7 ml, and one extra bolus dose of 2.2 ml [total levodopa dose of 500–700 mg/day]) and has a UPDRS III ('off') score of 37 and a UPDRS III ('on') score of 22; 'off' time was 60 minutes/day and 'on' time with dyskinesia was unchanged at 60 minutes/day.

Case 2 – A Patient with Motor Complications and 'Off' Time Depression

Patient History

A 58-year-old man who had PD from the age of 44 years, developed motor fluctuations and dyskinesia at the age of 54 years. Non-motor symptoms included depressive thoughts and sleep fragmentation. His treatment regimen consisted of:

- levodopa/carbidopa 150 mg every three hours (seven doses/day);
- entacapone 200 mg seven times/day;
- pramipexole 0.7 mg tid;
- selegiline 5 mg once daily; and
- amantadine 100 mg tid.

Despite this polypharmacy, the patient had two hours 'on' time with dyskinesia and four hours 'off' time/day.

Continuous Dopaminergic Stimulation Treatment and Outcome

Increasing the dose of levodopa or dopamine agonists would have added to the high level of oral medication that this patient was already receiving, so consensus was reached to treat this patient with CDS treatments. In this patient, APO 6 mg/h for 16 hours was initiated and supplemented with levodopa 100 mg six times/day and amantadine 100 mg tid. After six months, 'off' time was decreased to

1.5 h/day and 'on' time with dyskinesia was decreased to 1.5 h/day. After two years (and an increased infusion rate of 7 mg/h), 'off'-time was 2 h/day and 'on' time with dyskinesia was decreased to 2.5 h/day. Because at that time motor complications were worsening, the other options considered were:

- switching to oral dopamine agonists;
- increasing levodopa dose;
- Duodopa;
- DBS; or
- increasing the APO infusion rate.

In this patient, DBS of the subthalamic nucleus (STN-DBS) was chosen because the patient had already been treated with APO and did not want another infusional therapy. The resulting outcome was very positive; 'off' time was approximately 90 minutes/day and the patient had no more dyskinesia.

Case 3 – A Patient with Impulse Control Disorder

Patient History

A 58-year-old man had PD since the age of 45 years (otherwise healthy). He had motor fluctuations and dyskinesia since the age of 52 years, which included 'on/off' fluctuations, severe 'off' phases with freezing and 'on' phases with pronounced dyskinesias. He had depressive symptoms, but no dementia. His treatment consisted of:

- pramipexole 1.4 mg/day;
- levodopa 525 mg/day;
- entacapone 1,400 mg/day;
- amantadine 200 mg/day; and
- quetiapine 50 mg/day.

Unfortunately, the patient developed dopamine dysregulation syndrome (DDS), consuming up to 3 g levodopa daily and neglecting the advice to restrict medication. He not only gradually suffered more and more from punding, but also from impulse control disorder (ICD), including hypersexuality and gambling. On top of this, he developed psychotic symptoms, which included hallucinations and confusion. Eventually he lost his family and home, went into a nursing home and needed a legal guardian to control his finances.

Continuous Dopaminergic Stimulation Treatment and Outcome

The patient was initially switched to a supervised regimen of levodopa 800 mg/day monotherapy. Psychotic symptoms improved, but did not disappear. DDS and ICD did not change, however, and motor fluctuations and dyskinesia worsened. The next step was to add quetiapine 200 mg/day, but again DDS and ICD did not change. Similarly, clozapine 50 mg/day did not improve DDS and ICD. At this stage, CDS treatment was considered. The group consensus (70 %) was that Duodopa was the best treatment option for this patient, which confirmed the actual strategy as the patient was treated with Duodopa 5.2 ml/h daytime and 3.6 ml/h night-time, with a maximum of five boluses of 2 ml and the quetiapine dose was reduced to 75 mg/day. The outcome was:

- DDS resolved almost completely;
- ICD resolved completely;
- psychotic symptoms and confusion decreased further;
- cognitive function returned to normal;
- motor fluctuations improved; but
- there were problems with the PEG/J tube on two occasions.

The positive outcome was encouraging, as there is a potential risk that patients with DDS may intentionally stop Duodopa therapy in order to enjoy the oral levodopa-related 'kick' again.

Case 4 – A Patient Seeking to Maintain an Active Lifestyle

Patient History

A male farmer who enjoyed many sports including windsurfing was diagnosed with PD at the age of 38 years in 1998. He was initiated on 'levodopa-free' therapy that consisted of cabergoline (titrated up to 12 mg/day), amantadine (up to 400 mg/day) and selegiline (10 mg/day). The patient responded well to this treatment and continued with his active life for approximately five years.

Treatment Intensification

In 2003, levodopa therapy was deemed necessary and small doses were added to the patient's existing treatment regimen. After one year, levodopa was being administered at doses of 500 mg/day and by 2005, the patient had 'on-off' fluctuations with moderate dyskinesia and severe 'off' periods. Following a freezing episode while windsurfing, which resulted in the patient being stranded at sea and requiring air-rescue, further therapy was discussed.

Continuous Dopaminergic Stimulation Treatment and Outcome

APO, Duodopa and DBS were all considered for this patient. APO treatment was chosen as it was reversible (unlike DBS) and was less invasive and the patient felt there was, therefore, less stigma than Duodopa treatment. After three months of APO treatment, 'off' time was dramatically reduced to less than 30 minutes/day and this could be managed with bolus doses. The patient was now on a monotherapy with APO at a dose of 5.5 mg/h for 16 h/day. He was taking a long-acting levodopa preparation in the evening to cover the night. The patient had no skin reactions or other adverse events resulting from APO treatment and although he has stopped windsurfing, he continues an active lifestyle that includes sailing.

Conclusions

The case studies presented here illustrate some examples of the issues that can influence CDS treatment choice. Decision trees have been developed and some general contraindications can be identified from the literature (see *Figure 3*). Pronounced dementia and a lack of support/compliance are contraindications for APO and Duodopa. Additionally, a tendency to have hallucinations restricts the use of APO and contraindications for abdominal surgery rule out Duodopa use. DBS is contraindicated when the patient is unsuitable for brain surgery, when dementia, depression or anxiety are present and, most importantly, in patients aged >70 years – this last contraindication rules out a large number of patients for DBS.

More good-quality evidence of the main CDS therapies is needed, before consensus on more detailed treatment algorithms can be achieved. In particular, trials directly comparing CDS treatments would be most worthwhile. However, using the general principles outlined above and using clinical experience such as that presented in the cases here, will help with selection of the most appropriate CDS therapy for individuals with advanced PD. ■

1. Obeso JA, Rodriguez-Oroz MC, Chana P, et al., The evolution and origin of motor complications in Parkinson's disease, *Neurology*, 2000;55:S13–20; discussion S21–13.
2. Fahn S, Oakes D, Shoulson I, et al., Levodopa and the progression of Parkinson's disease, *N Engl J Med*, 2004;351:2498–508.
3. Fahn S, Parkinson disease, the effect of levodopa, and the ELLDOPA trial. Earlier vs Later L-DOPA, *Arch Neurol*, 1999;56:529–35.
4. Stoessl AJ, Continuous dopaminergic therapy in Parkinson disease: time to stride back?, *Ann Neurol*, 2010;68:3–5.
5. Bibbiani F, Costantini LC, Patel R, Chase TN, Continuous dopaminergic stimulation reduces risk of motor complications in parkinsonian primates, *Exp Neurol*, 2005;192:73–8.
6. Stowe RL, Ives NJ, Clarke C, et al., Dopamine agonist therapy in early Parkinson's disease, *Cochrane Database Syst Rev*, 2008:CD006564.
7. Stocchi F, Rascol O, Kieburtz K, et al., Initiating levodopa/carbidopa therapy with and without entacapone in early Parkinson disease: the STRIDE-PD study, *Ann Neurol*, 2010;68:18–27.
8. Clarke CE, Worth P, Grosset D, Stewart D, Systematic review of apomorphine infusion, levodopa infusion and deep brain stimulation in advanced Parkinson's disease, *Parkinsonism Relat Disord*, 2009;15:728–41.
9. Chaudhuri KR, Critchley P, Abbott RJ, et al., Subcutaneous apomorphine for on-off oscillations in Parkinson's disease, *Lancet*, 1988;2:1260.
10. Antonini A, Odin P, Pros and cons of apomorphine and L-dopa continuous infusion in advanced Parkinson's disease, *Parkinsonism Relat Disord*, 2009;15(Suppl. 4):S97–100.
11. Kreczy-Kleedorfer B, Wagner M, Bosch S, Poewe W, [Long-term results of continuous subcutaneous apomorphine pump therapy in patients with advanced Parkinson disease], *Nervenarzt*, 1993;64:221–5.
12. De Gaspari D, Siri C, Landi A, et al., Clinical and neuropsychological follow up at 12 months in patients with complicated Parkinson's disease treated with subcutaneous apomorphine infusion or deep brain stimulation of the subthalamic nucleus, *J Neurol Neurosurg Psychiatry*, 2006;77:450–3.
13. Hughes AJ, Bishop S, Kleedorfer B, et al., Subcutaneous apomorphine in Parkinson's disease: response to chronic administration for up to five years, *Mov Disord*, 1993;8:165–70.
14. Gancher ST, Nutt JG, Woodward WR, Apomorphine infusional therapy in Parkinson's disease: clinical utility and lack of tolerance, *Mov Disord*, 1995;10:37–43.
15. Pietz K, Hagell P, Odin P, Subcutaneous apomorphine in late stage Parkinson's disease: a long term follow up, *J Neurol Neurosurg Psychiatry*, 1998;65:709–16.
16. Kanovsky P, Kubova D, Bares M, et al., Levodopa-induced dyskinesias and continuous subcutaneous infusions of apomorphine: results of a two-year, prospective follow-up, *Mov Disord*, 2002;17:188–91.
17. Morgante L, Basile G, Epifanio A, et al., Continuous apomorphine infusion (CAI) and neuropsychiatric disorders in patients with advanced Parkinson's disease: a follow-up of two years, *Arch Gerontol Geriatr Suppl*, 2004:291–6.
18. Antonini A, Isaias IU, Rodolfi G, et al., A 5-year prospective assessment of advanced Parkinson disease patients treated with subcutaneous apomorphine infusion or deep brain stimulation, *J Neurol*, 2011;258:579–85.
19. Antonini A, Isaias IU, Canesi M, et al., Duodenal levodopa infusion for advanced Parkinson's disease: 12-month treatment outcome, *Mov Disord*, 2007;22:1145–9.
20. Eggert K, Schrader C, Hahn M, 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;31:151–66.
21. Puente V, De Fabregues O, Oliveras C, et al., Eighteen month study of continuous intraduodenal levodopa infusion in patients with advanced Parkinson's disease: Impact on control of fluctuations and quality of life, *Parkinsonism Relat Disord*, 2010;16:218–21.
22. Nyholm D, Constantinescu R, Holmberg B, et al., Comparison of apomorphine and levodopa infusions in four patients with Parkinson's disease with symptom fluctuations, *Acta Neurol Scand*, 2009;119:345–8.
23. Volkmann J, Deuschl G, Deep brain stimulation, *Handb Clin Neurol*, 2007;84:261–77.
24. Katzenschlager R, Hughes A, Evans A, et al., Continuous subcutaneous apomorphine therapy improves dyskinesias in Parkinson's disease: a prospective study using single-dose challenges, *Mov Disord*, 2005;20:151–7.
25. Honig H, Antonini A, Martinez-Martin P, 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;24:1468–74.
26. Simkin S, Chaudhuri KR, Selway R, et al., Subthalamic nucleus (STN) deep brain stimulation (DBS) and the non-motor symptom scale (NMSS) in Parkinson's disease (PD), Presented at: 10th International Congress of Parkinson's Disease and Movement Disorders; October 28–November 2, 2006; Kyoto, Japan.
27. Naidu Y, Tluk S, Martin A, et al., Initiation of apomorphine infusion in advanced Parkinson's disease and effect on non motor symptoms compared to non-invasive strategies, *Mov Disord*, 2009;24(Suppl. 1):S360.
28. Devos D, Patient profile, indications, efficacy and safety of duodenal levodopa infusion in advanced Parkinson's disease, *Mov Disord*, 2009;24:993–1000.
29. Deuschl G, Schade-Brittinger C, Krack P, et al., A randomized trial of deep-brain stimulation for Parkinson's disease, *N Engl J Med*, 2006;355:896–908.
30. Nyholm D, Lewander T, Johansson A, et al., Enteral levodopa/carbidopa infusion in advanced Parkinson disease: long-term exposure, *Clin Neuropharmacol*, 2008;31:63–73.
31. Toth C, Breithaupt K, Ge S, et al., Levodopa, methylmalonic acid, and neuropathy in idiopathic Parkinson disease, *Ann Neurol*, 2010;68:28–36.
32. Odin P, Hagell P, Shing M, (Eds), *Apomorphine in Parkinson's disease*, Bremen: Uni-Med Verlag AG; 2008.
33. Temel Y, Kessels A, Tan S, et al., Behavioural changes after bilateral subthalamic stimulation in advanced Parkinson disease: a systematic review, *Parkinsonism Relat Disord*, 2006;12:265–272.
34. Kleiner-Fisman G, Herzog J, Fisman DN, et al., Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes, *Mov Disord*, 2006;21(Suppl. 14):S290–304.
35. Antonini A, Tolosa E, Apomorphine and levodopa infusion therapies for advanced Parkinson's disease: selection criteria and patient management, *Expert Rev Neurother*, 2009;9:859–67.