Deep Brain Stimulation and Duodopa

Treating Patients with Deep Brain Stimulation or Duodopa – Pros and Cons

Alexander Storch

Abstract
There is a growing body of evidence from pre-clinical and clinical investigations that pulsatile stimulation of striatal dopamine receptors is a major factor in the development of levodopa-induced motor complications in Parkinson’s disease (PD). Levodopa remains the most efficacious drug for the treatment of PD, but motor fluctuations and dyskinesias are long-term complications that limit its utility. These adverse effects are a significant clinical problem. Current thinking attributes the development of dyskinesias to two major factors: the loss of nigro–striatal dopamine neurones leading to a reduced capability of the system to store dopamine, and the maladaptive changes produced by pulsatile stimulation of the post-synaptic dopamine receptors. These changes include alterations in gene expression of various neuropeptides, immediate early genes and transcription factors, as well as synaptic and molecular rearrangements in striatal synapses with functional changes of dopamine-receptor-dependent signalling affecting mainly glutamatergic cortico-striatal synapses. In addition to these post-synaptic mechanisms, recent pre-clinical work indicates that some pre-synaptic factors, mainly involving dopamine release and metabolism, may also show plasticity during levodopa treatment. From a clinical point of view, the risk of developing motor fluctuation and dyskinesias has been linked to disease severity, dosage of levodopa and patient age. This paper will discuss the pros and cons of continuous dopaminergic stimulation (CDS) with intra-duodenal levodopa versus deep brain stimulation of the subthalamic nucleus (DBS-STN) in patients with advanced PD.

There are no controlled trials providing comparative data for high-frequency deep brain stimulation of the subthalamic nucleus (DBS-STN) and intra-duodenal levodopa (Duodopa®) in Parkinson’s disease (PD). Furthermore, as Duodopa is an orphan medication, there are only limited data available for this product. Thus, this paper is based on information from the literature for both procedures combined with personal experience of using these technologies.

As outlined in the previous paper (by Wolters), in DBS micro-electrodes are inserted into the brain and used to deliver controlled electrical impulses to stimulate hyperexcited nuclei of the basal ganglia. In PD, the STN is the main target to regulate or normalise the basal ganglia motor loops and therefore DBS-STN treats mainly the motor symptoms of PD. To find the right location to implant the electrodes, most surgeons use microelectrode recording techniques: a small wire monitors the activity of nerve cells in the target area, measures the patterns and then identifies the precise region to be stimulated.

The operation to insert the electrodes is highly specialised; only experienced teams consisting of neurosurgeons and neurologists can undertake it. Depending on the centre, the implant procedure takes place on day one, then on day two the wires are connected to the stimulator implanted under the clavicula, and over the next week or two the pattern for the stimulation impulses is programmed. In other centres, the whole procedure is performed on the same day.

With Duodopa, a concentrated gel suspension of levodopa and carbidopa is delivered in a continuous manner to the duodenum via a catheter that passes through the skin into the stomach and descends past the sphincter into the small intestine. A programmable pump delivers an individualised dose to the patient. Duodopa requires a percutaneous endoscopic gastrostomy (PEG) to insert the tube, although prior to committing to surgery clinical response can be tested using a nasoduodenal tube. Once again, PEG is a specialised procedure that requires an experienced gastroenterology expert who is familiar with the device.

Comparison of Symptomatic Effects

Deep Brain Stimulation
The clinical and pathophysiological effects of DBS-STN have been extensively studied in the past years and as a result this surgical procedure is one of the best characterised treatment strategies. From our own experiences in Ulm and Dresden, patients who are receiving DBS spend less time in a dyskinetic state or in the ‘off’ state, and spend more time ‘on’ (Storch et al., unpublished observations). These changes remain strong over time, with evidence that DBS-STN is effective over several years. Figure 1 shows the trend to improvement in Unified Parkinson’s Disease Rating Scale (UPDRS III) score with DBS plus or minus medications. This improvement is beyond that achievable with medical management alone.

A 2006 study used matched pairs of PD patients with DBS or best medical management, all of whom kept daily diaries to record effects on motor functions: the number of hours in the day spent mobile (with or without dyskinesias), immobile, neither mobile nor immobile (‘neutral’) and sleeping. After six months the neurostimulation group showed significant improvements in all categories except for ‘neutral’ time, while the medication group had negligible changes (see Figure 2).
Treating Patients with Deep Brain Stimulation or Duodopa – Pros and Cons

DBS also has a positive effect on mood and quality of life (QoL). Looking at mood and QoL in our cohort of 46 patients undergoing STN-DBS, there were no incidents of depression. Activities of daily living showed a small but significant improvement, and QoL as measured by Short Form 36 (SF-36) had no major changes. Deuschl et al. found that DBS leads to improvements in all aspects of Parkinson’s Disease Questionnaire (PDQ)-39, and were particularly significant in the domains of mobility, activities of daily living, emotional wellbeing, stigma and bodily discomfort (see Figure 3).7

Therefore, it can be shown that DBS has excellent motor benefits on all symptoms – including tremors – for up to 10 years (with controlled data available for five years) in advanced PD.4–6 It leads to a large reduction in dyskinesias and motor fluctuations, and most patients require only half the amount of medication. DBS improves QoL compared with best medical treatment, although no comparisons with continuous subcutaneous apomorphine infusion or Duodopa are yet available.

Duodopa

Video scoring of 12 patients over two weeks of treatment in an open-label cross-over study of oral levodopa/carbidopa versus continuous dopaminergic stimulation (CDS) with levodopa/carbidopa, both without concomitant antiparkinson medication, showed a statistically significant difference between the two treatments in favour of Duodopa.8 Duodopa also shows longer-term benefits, reducing time with hyperkinesia and increasing time in a ‘normal’ state for at least seven years. The dosage of levodopa is similar in oral versus CDS administration, although there is a slight trend towards lowering the dose in the latter.8,9

To summarise the symptomatic effects, both treatments offer excellent improvement of all motor symptoms, and both reduce motor fluctuations. DBS definitely reduces dyskinesias, but data concerning the effect of Duodopa on dyskinesias are still limited. In our experience, however, the dose can be fine-tuned to help. Both treatments offer long-term benefits, but once again data are lacking concerning the effect of Duodopa on QoL.

Indications and Contraindications

There are many similarities in the indications for DBS and Duodopa, with a couple of exceptions (see Table 1). Most notably, Duodopa is suitable for a much wider age range of patients.

In terms of contraindications, there are many psychiatric restrictions for DBS, most notably dementia. Also included are:

- severe frontal executive dysfunction (Pillon score <20/50);
- psychosis (with paranoia and/or hallucinations);
- severe personality changes; and
- impaired co-operation/compliance.

Surgical contraindications include age (75 years is the currently recommended upper limit, although patients close to this figure should also be treated with caution), and more specifically:

- severe frontal executive dysfunction (Pillon score <20/50);
- psychosis (with paranoia and/or hallucinations);
- severe personality changes; and
- impaired co-operation/compliance.
Deep Brain Stimulation and Duodopa

Table 1: Indications of Deep Brain Stimulation versus Duodopa

<table>
<thead>
<tr>
<th></th>
<th>STN-DBS</th>
<th>Duodopa</th>
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<tbody>
<tr>
<td>Severe motor fluctuations</td>
<td></td>
<td>Severe motor fluctuations</td>
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<tr>
<td>Tried different oral drug (combinations)</td>
<td>Tried different oral drug (combinations)</td>
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<tr>
<td>Clear response to levodopa</td>
<td>Clear response to levodopa</td>
<td></td>
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<tr>
<td>Severe disabling medication-resistant tremor</td>
<td>No age limitations</td>
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<tr>
<td>Levodopa-induced psychosis (in particular in young patients without dementia)</td>
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STN-DBS = deep brain stimulation of the subthalamic nucleus.

Table 2: Side Effects of Deep Brain Stimulation of the Subthalamic Nucleus

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Patients Affected</th>
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<tbody>
<tr>
<td>Dysarthria</td>
<td>4–16%</td>
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<tr>
<td>Worsening of gait</td>
<td>3–15%</td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
<td>4–18%</td>
</tr>
<tr>
<td>Infection</td>
<td>4–5%</td>
</tr>
<tr>
<td>Eye opening apraxia</td>
<td>7%</td>
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<tr>
<td>Weight gain</td>
<td>Very frequent</td>
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<tr>
<td>Persistent paraesthesia</td>
<td>Rare</td>
</tr>
<tr>
<td>Depression</td>
<td>Moderate frequency</td>
</tr>
<tr>
<td>Other complex psychiatric side effects</td>
<td>Obsessive gambling</td>
</tr>
<tr>
<td></td>
<td>Suicides</td>
</tr>
<tr>
<td></td>
<td>Personality changes</td>
</tr>
<tr>
<td></td>
<td>Behavioural changes</td>
</tr>
</tbody>
</table>

- moderate to severe brain atrophy;
- moderate to severe white matter lesions;
- moderate to severe microangiopathy;
- severe general co-morbidities;
- therapy with anticoagulative drugs;
- immunosuppression; and
- bulbar paralysis.

For Duodopa there are far fewer contraindications. While previous surgery of the upper stomach is often considered a restriction, this depends on the centre and also on the nature of that surgery. It is preferable that the patient is free of dementia, although again this can depend on the care-giver who handles the pump. Otherwise, the typical contraindications of levodopa apply, including:

- hypersensitivity against levodopa or carbidopa;
- narrow-ankle glaucoma;
- acute stroke; and
- severe renal or liver failure.

Complications and Technical Issues

A study of 300 patients receiving STN-DBS, thalamus or globus pallidus internas (GPI) examined surgical complications of the procedures. Most commonly, electrode implantation caused confusion or bradyphrenia, affecting around 14% of patients. Following that, eyeld apraxia was fairly common, affecting 7% of patients. The electrode implantation also caused focal cerebral contusion, intracerebral haemorrhage or intra-cranial extra-cerebral haemorrhage in 3% of patients each. Infection is also a noticeable complication.10

Another survey of 319 patients reported similar results: intra-operative adverse events were rare and included vasovagal response in eight patients (2.5%) and syncope in four (1.2%). More common were peri-operative complications: 48 patients (15%) reported headache, 16 (5%) reported confusion and hallucinations affected nine (2.8%). However, these tended to be fairly tolerable. More severe complications such as bleeding affected a handful of patients.11 To date, a peri-operative complication rate of <1% (including all complications) should be considered the norm.

As with any procedure involving hardware, there are technical complications to contend with. The leads connecting the stimulator to the electrodes can fracture or migrate (around 3% of cases each), and 7.8% of cases need some form of revision or repair.10 In our experience at Dresden the figure for revisions was three in 46 (6.5%). Furthermore, the battery in the DBS pack needs to be changed every four to five years, and recipients should not subsequently be scanned with body magnetic resonance imaging (MRI), with only very limited head MRI possible.

Duodopa suffers from spontaneous catheter dislocation, apparently affecting around 10% of cases; however, we have not seen any examples of this in our patients at Dresden so far. There are other technical issues associated with this infusion: the gel can be stored at -20°C for two years, or refrigerated at 2–8°C for 15 weeks. It is stable for only 24 hours at room temperature.

Side Effects

In the Dresden cohort, in conjunction with the neuropsychology department we tested our STN-DBS patients for a variety of cognitive aspects (Junghanns and co-workers, unpublished observations). The parameters were stable from baseline through to the first assessment and second post-operative assessment (roughly two and four years) on:

- Mattis Dementia Rating Scale (MDRS);
- experience-dependent intelligence (Multiple Choice Word Test-B, MWT-B), ability to think (LPS-5);
- verbal-mnestic functions (Auditory Verbal Learning Test, AVLT);
- working memory (number series backwards, 100-7-test);
- sigural memory (Benton Test);
- phonematic word fluency; and
- flexibility and speed (Stroop Test).

There was evidence of impairment of semantic word fluency, tested using names and plants, but while statistically significant this
The side effects of Duodopa are well known as being the same as those of levodopa. Independent of the drug, the PEG procedure runs a 1–3% risk of infection of the gastroma.

Costs
There are German data for DBS covering treatment costs (i.e. costs for conservative pharmacological treatment and all inpatient admissions) of 46 PD patients for one year before and two years after STN-DBS. They show that total treatment costs were increased by 32% for the first year and decreased by 54% for the second year of STN-DBS compared with pre-operative values, and the UPDRS score was significantly improved. Specifically, medication costs – despite being reduced to nearly half the pre-operative value – were still a significant factor. The procedure itself is quite expensive (the German DRG list price is about €28,000) and the battery changes cost around €9,000 a time.12

With Duodopa, there are moderate costs of the operation (the DRG price is about €5,000); however, together the gel, pump and the supportive infrastructure for patients, doctors and hospitals are expensive and cost nearly €800 per week. Nevertheless, this cost can be largely offset by a reduction in or even elimination of the need for additional oral medication. There are as yet no data available on medical and non-medical indirect costs that are avoided through Duodopa treatment such as hospital admissions, dependence on nursing homes or home care.

Conclusions
Both STN-DBS and Duodopa have excellent effects on all motor symptoms of PD. Table 3 shows a summary of the comparison of the two treatments. DBS is efficient at reducing dyskinesias, has low costs after the initial operation, is easy for the patient to live with and has only a moderate complication rate. On the flip side, it is not suitable for all patients – particularly older patients and those with relevant co-morbidities. The programming can be time-consuming, there are frequent technical problems with the equipment and the battery needs to be changed every four to five years. Furthermore, it has a low but clear risk of severe complications such as haemorrhage, as well as neuropsychiatric issues.

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