

The Duodopa Debate

The effective treatment of motor complications is a challenge for all clinicians caring for patients with advanced Parkinson's disease (PD). During the XVIIth World Congress on Parkinson's Disease and Related Disorders (9-13 December 2007, Amsterdam, the Netherlands), delegates to a stand-alone meeting met to debate the place in therapy of Duodopa (co-careldopa) intestinal gel. This recently available treatment is indicated in the UK for patients with advanced levodopa-responsive PD with severe motor fluctuations and dyskinesia that do not respond to other medical treatments.

The Faculty

Chairman: Professor Andrew Lees, Consultant Neurologist, London

"This house believes that Duodopa should be used prior to deep brain stimulation in advanced Parkinson's disease patients"

For the motion

- Professor Anthony Schapira, Consultant Neurologist, London
- Dr David Stewart, Consultant Physician, Medicine for the Elderly, Glasgow
- Dr K Ray Chaudhuri, Consultant Neurologist, London

Against the motion

- Dr Donald Grosset, Consultant Neurologist, Glasgow
- Dr Doug MacMahon, Consultant Physician, Medicine for the Elderly, Redruth
- Dr Paul Worth, Consultant Neurologist, Norwich

For the motion

It is true that, compared with oral PD medication, deep-brain stimulation (DBS) improves motor control and reduces dyskinesia in advanced PD.¹ However, the treatment has important limitations. Older people form the majority of the PD population, but DBS may not be appropriate in this age group because, although DBS reduces motor complications in both older (mean age 69 years) and in younger (mean age 57) patients, post-operative quality of life improves only in younger people.²

DBS is generally well tolerated, but it is associated with important adverse effects. A recent wide-ranging, 10-year, retrospective meta-analysis of outcomes in 10,339 patients reported 6,573 device-related adverse events, including infection (16%), explantation (15%), lead fracture (14.7%) erosion (14%), battery failure (2.1%) and intracranial haemorrhage (2%). This study also drew attention to a risk of serious psychiatric adverse events, including completed suicide in 11 patients.³

Such retrospective analyses are open to reporting bias, but prospective studies also demonstrate a significant association between DBS and cognitive and psychiatric adverse events. These include significant declines in verbal memory,⁴ cognitive problems,⁵ and suicide or attempted suicide.⁶ There are many potential reasons why DBS might affect cognitive function; a recent study concluded that DBS selectively interferes with the normal ability to slow down when faced with decision conflict; indeed patients speed up their decision making when faced with high-conflict conditions. This impulsivity differs from that seen in association with dopamine agonists, which impair the ability to learn from negative experiences.⁷

Duodopa infusion is therefore an alternative to DBS for advanced PD patients with severe motor fluctuations and dyskinesia. Compared to conventional oral levodopa, Duodopa provides smoother levodopa plasma levels,⁸ resulting in an average increase in 'on' time without severe dyskinesia, greater overall improvement in Unified Parkinson's Disease Rating Scale (UPDRS) total scores and statistically significant improve-

ments in quality of life.⁸

Levodopa was introduced into clinical practice over 40 years ago, and there are 25 years' experience of levodopa infusion in patients with advanced PD. Treatment with Duodopa involves surgery for placement of the percutaneous endoscopic gastrostomy (PEG) tube but, unlike DBS, this is a common procedure that is reversible. Long-term costs are of course important and Duodopa infusion is more expensive than DBS. It is, however, important to bear in mind the continuing costs of oral PD medication following DBS. Treatment with Duodopa can potentially abolish the need for oral treatment and, since it is a treatment in evolution, we can expect to see improvements in the use of the product as clinical experience grows.

DBS is undoubtedly an excellent treatment for some patients with advanced PD, but it is essential to give patients an informed choice from among all appropriate treatments. In short, as doctors, we should consider and offer Duodopa to our patients, both in preference to and as an alternative to surgery.

Against the motion

Like levodopa, targeted brain lesioning has a long history. Earlier procedures such as pallidotomy, although destructive, involved tiny areas of targeted ablation. DBS as currently performed is not a lesion, but a non-destructive, programmable, technologically advanced intervention that specifically targets the site of the primary problem in advanced PD. Over 30,000 patients worldwide have undergone DBS. Its beneficial results are sustained in the long-term whether stimulation is targeted to the subthalamic nucleus (STN) or the global pallidus internus (GPI), and there is added improvement in symptoms when DBS is combined with oral medication.⁹

There is some long-term experience with Duodopa in a small series of 28 patients, albeit with a total infusion time of 87 patient years (median 44 months, range 2-83 months). The authors reported that mean daily levodopa was reduced by a median of 1% and at the end of the study 12 patients were taking oral anti-parkinsonian drugs. Like any surgery, including DBS, Duodopa is associated with adverse effects and the need for further intervention, including in this series transient post-operative infections in six patients, 162 X-ray and fluoroscopic examinations, and 35 gastroscopic changes or catheter adjustments. After a median of 33 months (range 13-67), six patients had returned to oral therapy: two reported decreasing effect (both developed symptoms of multiple system atrophy), three encountered problems in handling the infusion system after developing dementia, and one experienced no improvement in symptoms.¹⁰

DBS is not appropriate for all patients with advanced PD, but neither is Duodopa. DBS smoothes out, but does not cure, motor fluctuations, and bilateral surgery is often required. Surgery improves tremor, rigidity, bradykinesia and dyskinesia, but it does not eliminate these symptoms. It will not improve symptoms that are unresponsive to anti-parkinsonian medication. Many, but not all, patients need less oral anti-parkinsonian medication, but they do need to attend frequent programming visits during the first six months after surgery, with subsequent follow-up visits and multiple adjustments in the stimulator and medication.¹¹

In the UK, the costs of DBS surgery itself, follow-up visits and probable continuing need for medication amounts to £25,000-£30,000 over five years¹². This sum is, however, equivalent to the cost of the first year's treatment with Duodopa, taking into account initial placement of the PEG, follow-up visits and the cost of the drug itself³. This debate concerns the order of treatment, rather than a choice between Duodopa and surgery. DBS is worth considering before Duodopa on grounds of its cost implications as well as its proven effectiveness in treating the motor symptoms of advanced PD.

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**Professor Andrew Lees:
Chairman's Summary**

"The more options available to deal with the motor problems of advanced PD, the better. Duodopa and DBS are both important, and my concern is not which to use, but that patients may not be considered for either therapy. I hope that this debate will help to highlight the potential roles of both Duodopa and DBS in people with advanced PD."

Questions from the Audience

Q "I am concerned about the timing of surgery, given the comparatively brief follow-up to date and the very narrow two year window of opportunity for referral."

Answer 1:

"In my experience, two years usually allows sufficient time in which to make a decision about surgery. I would not recommend earlier referral until there is strong evidence of a good and sustained effect from the intervention." (Dr Grosset)

Answer 2:

"Patients who are relatively young – for example, in their 50s – do ask about DBS when they are still well controlled on oral therapy, and at present surgery is inappropriate in such patients. When patients develop advanced PD and oral therapy no longer controls their motor symptoms, the issues then concern when to perform surgery, its limited availability in the UK and the risk of cognitive problems associated with DBS." (Professor Schapira)

Q "Most PD patients will develop motor complications if they live long enough, so why is it not appropriate to refer them for surgery before they experience these symptoms?"

Answer:

"It is very difficult to refer a patient, who is well controlled on oral medication, for a procedure that is associated with a finite, albeit low, risk of significant morbidity and mortality. For this reason, surgery is at present only appropriate in patients with advanced PD. Furthermore, there are some data indicating that stimulation of the STN and GPI is no better than maximised oral therapy. DBS is a good therapy and a major advance, but we should carefully consider the sequencing of treatment and offer an alternative – that is, we should insert Duodopa into our and our patients' paradigm." (Professor Schapira)

Q "I believe that we should remember the significant risk of irreversible complications with DBS. Duodopa complications are relatively rare and the therapy derives from an alteration in the pharmacokinetics of a familiar drug. Based on current evidence, we should follow the standard therapeutic model in which a medical therapy like Duodopa is used before surgery."

Answer:

"There are other important issues such as operator dependence. Gastroenterologists regularly perform gastrostomies, and so it should be straightforward to find a skilled and experienced surgeon to reproduce the results with Duodopa seen in the literature. This contrasts with DBS, and I question whether it is possible to generalise results reported from expert centres to the average neurosurgical unit." (Dr Stewart).

DBS in PD: a mnemonic for PD patients¹¹

Does not cure

Bilateral DBS is often required to improve gait, although sometimes unilateral DBS has a marked effect on walking

Smooths out on/off fluctuations

Improves tremor, stiffness (rigidity), bradykinesia and dyskinesia in most cases, but may not completely eliminate them

Never improves symptoms that are unresponsive to your best 'on'. For example, if gait or balance does not improve with best medication response, it is very unlikely to improve with surgery

Programming visits are likely to occur many times during the first six months and then follow-up visits as frequently as every six months. There will be multiple adjustments to the stimulator and in the medication

Decreases medication use in many, but not all patients

Comparison of Duodopa and deep-brain stimulation

Duodopa infusion

Improves motor control
Reduces dyskinesias
Well tolerated with good side-effect profile
Widely available technique

PEG reversible
Long-term economics?

Deep-brain stimulation

Improves motor control
Reduces dyskinesias
Mostly well tolerated, but some serious morbidity/mortality
Limited availability confined to Tertiary specialist neurosurgical centres
Lesion not reversible
Long-term economics?

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Discussions from this meeting were recorded and written up by Sue Lyon, medical freelance writer

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DUODOPA intestinal gel▼ (co-careldopa):**ABBREVIATED PRESCRIBING INFORMATION**

Presentation: Intestinal gel containing 20mg/ml levodopa and 5mg/ml carbidopa

Basic NHS price 7 x 100ml cassettes: £539 PL 05727/0016

Legal Category: POM

Indication: Advanced levodopa-responsive Parkinson's disease with severe motor fluctuations and hyper/dyskinesia when available combinations of Parkinson medicinal products are unsatisfactory. A positive clinical response to Duodopa administered via a temporary nasoduodenal tube is required before a permanent tube is inserted.

Dosage and Administration: The Summary of Product Characteristics (SPC) should be read thoroughly for full prescribing information. *Adults/Elderly:* Administration by portable pump directly into the duodenum via a percutaneous endoscopic gastrostomy (PEG) or radiological gastrojejunostomy tube. Initially a nasoduodenal tube is used to determine patient's response and to adjust dose before fitting a permanent tube. Duodopa is given initially as monotherapy and dose adjusted to optimal response for the individual patient. Total dose/day is composed of three individually adjusted doses: morning bolus, continuous maintenance and extra bolus doses. Total morning dose is usually 5-10ml (100-200mg levodopa) but not exceeding 15ml (300mg levodopa). Continuous maintenance dose should be between 1-10ml/hour (20-200mg levodopa) but usually 2-6ml/hour (40-120mg levodopa/hour). Extra bolus doses (if patient becomes hypokinetic during the day) are normally 0.5-2.0ml. Increase maintenance dose if more than 5 extra bolus doses/day are needed. Fine adjustments to the morning bolus, maintenance and extra bolus doses should be made over a few weeks after the initial dose setting. Sudden deterioration in response with recurring motor fluctuations indicates the tube may have moved from the duodenum into the stomach and needs repositioning. Drug cassettes are for single use only and should not be used for longer than one day. *Children:* There is no relevant indication for use in children and adolescents.

Contraindications, Warnings etc: *Contraindications:* Hypersensitivity to ingredients, narrow-angle glaucoma, severe liver and renal insufficiency, severe heart failure or cardiac arrhythmia, acute stroke. Conditions where adrenergics are contraindicated (e.g. pheochromocytoma, hyperthyroidism, Cushing's syndrome). Non-selective MAO-inhibitors and selective MAO type A inhibitors must not be given concomitantly and should be withdrawn at least two weeks before starting Duodopa. *Warnings:* Not recommended for drug-induced extrapyramidal reactions. Caution in severe pulmonary or cardiovascular disease, bronchial asthma, renal, hepatic or endocrine disease, or history of peptic ulcer disease or of convulsions, past or current psychosis, chronic wide-angle glaucoma, co-administration with antipsychotics with dopamine receptor blocking properties or with medicines which may cause orthostatic hypotension. In patients with a history of myocardial infarction who have residual nodal or ventricular arrhythmias, cardiac function should be monitored with care during initial dose adjustments. Monitor all patients for mental changes, depression with suicidal tendencies and other serious mental changes. Neuroleptic malignant like syndrome with secondary rhabdomyolysis has not been reported with Duodopa but may occur on abrupt withdrawal. Periodically evaluate hepatic, haematopoietic, cardiovascular and renal function during extended therapy. Pathological gambling, increased libido and hypersexuality have been reported. Dose may need to be adjusted downwards to avoid levodopa induced dyskinesia. Sudden or gradual worsening of bradykinesia may indicate an obstruction in the device and should be investigated. For patients with reduced ability to handle the system, refer to full SPC. *Drug Interactions:* Antihypertensives, tricyclic antidepressants, anticholinergics, dopamine receptor antagonists, benzodiazepines, isoniazide, phenytoin, papaverine, sympathomimetics, iron, protein-rich diet. COMT inhibitors (e.g. tolcapone, entacapone) can increase the bioavailability of levodopa and amantadine acts synergistically and may increase levodopa related adverse events. Duodopa dose adjustment may be needed when used with these drugs. Duodopa can be taken with MAO type B inhibitors (e.g. selegiline) although serious orthostatic hypotension may occur.

Pregnancy and Lactation: Potential risk in pregnancy is not known. Women should not breast feed.

Ability to Drive and Operate Machinery: Caution. Refrain if somnolence or sudden sleep onset occur.

Side Effects: *Common:* Anorexia, hallucinations, confusion, nightmares, sleepiness, fatigue, sleeplessness, depression, euphoria, dementia, psychotic episodes, feeling of stimulation, dyskinesias, choreatic movements and dystonia, "ON-OFF" episodes, dizziness, palpitations, irregular heartbeat, orthostatic hypotension, fainting, syncope, nausea, vomiting, dry mouth, bitter taste. *Uncommon:* weight changes, ataxia, tremor, hypertension, hoarseness, chest pain, constipation, diarrhoea, sialorrhoea, dysphagia, flatulence, oedema, muscle spasm, dark urine, weakness, malaise, flare ups. Laboratory values may change. See SPC for details of rare and very rare side effects and for details of complications with the device.

Name and Address of Marketing Authorisation Holder:

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Further information is available in the UK from:

Solvay Healthcare Ltd, West End, Southampton, SO18 3JD

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Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk. Adverse events should also be reported to Solvay Healthcare.

The Parkinson's Disease Nurse Specialist Association

The Parkinson's Disease Nurse Specialist Association, [PDNSA] is a professional organisation with membership throughout the UK and overseas.

The objective of the Association is to act as a national resource and network for nurses and other healthcare professionals to share knowledge, expertise and best practice about Parkinson's disease and its management locally, nationally and internationally. It represents a body of healthcare professionals with an interest in Parkinson's and works in collaboration with the Department of Health, the Parkinson's disease society, The Royal College of Nursing, The British geriatric Society and the British and Irish Neurologists Movement disorders group.

Full membership of the PDNSA is available to Parkinson's Disease Nurse Specialists who are employed primarily in the practice of Parkinson's disease in primary and secondary care in the United Kingdom. Associate membership is open to any person who wishes to join the Association and is not eligible for full membership. Overseas Membership is open to any person who wishes to join the PDNSA and is not resident in the UK. Overseas members assume the same status as associate members. Honorary membership is awarded to individuals who have made a considerable contribution to the advancement of Parkinson's Disease Nurse Specialists. The PDNSA Committee are responsible for awarding honorary membership.

Membership entitles you to;

- 'Transmitter' our newsletter, which is published three times per year. This is an excellent forum to share best practice, experience, and inform others of current issues and developments.
- Any relevant documents published with support from the PDNSA.
- Reduced rate at our annual conference.

Professor Sir George Castledine has recently become the associations president and will be the keynote speaker at our annual conference which this year is being held on Monday 6th October and Tuesday 7th October. It is being held at the Scarman centre at Warwick University, the programme will be available very soon. The conference covers both clinical and professional issues and is an excellent opportunity for networking. We welcome new members.



To find out more about the association visit www.pdnsa.net