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Practical approaches to commencing device-assisted therapies for Parkinson's disease in Australia

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Running head: DAT for PD in Australia

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Practical approaches to commencing device-assisted therapies for Parkinson's disease in Australia

ABSTRACT:

Background: In Australia 1% of individuals aged over 50 years have Parkinson's disease (PD).

Aims: Guidance for commencing device-assisted therapies (DATs) for PD in Australia was developed based on a review of European recommendations and their relevance to the local clinical setting.

Methods: An online survey and teleconference discussions were held by a group of eight local movement disorder experts to develop consensus.

Results: Referral to a movement disorder specialist and consideration of DAT is appropriate when motor fluctuations cause disability or reduced quality of life, response to treatment is inconsistent or motor fluctuations and dyskinesias require frequent treatment adjustment without apparent benefit and levodopa is required four or more times daily. Three types of DAT are available in Australia for patients with PD: continuous subcutaneous apomorphine; continuous levodopa-carbidopa intestinal gel infusion; and deep brain stimulation. All improve consistency of motor response. The most important aspects when considering which DAT to use are the preferences of the patient and their carers, patient co-morbidities, age, cognitive function and neuropsychiatric status. Patients and their families need to be provided with treatment options that are suitable to them, with adequate explanations regarding the recommendations and comparison of potential device-related complications. DATs are best managed, where possible, in a specialist centre with experience in all three types of therapy.

Conclusion: Proactive and early management of symptoms during disease progression is essential to optimally maintain motor responses and quality of life in patients with PD.

KEYWORDS:

Parkinson's Disease; Dyskinesias; Carbidopa, levodopa drug combination; Apomorphine; Deep Brain Stimulation.

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BACKGROUND:

Parkinson's disease (PD) is the second most common neurodegenerative disorder in Australia, exceeded only by dementia.¹ The estimated prevalence is close to 1% in those aged over 50, and about 11 500 individuals were newly diagnosed in 2014.¹ Of the approximately 69 000 people in Australia who have PD, a substantial proportion (about 20%) have disabling disease requiring continuous care.¹

Oral or transdermal dopaminergic replacement therapies offer a remarkably efficacious treatment in the earlier stages of disease, but as PD progresses symptom control from these approaches deteriorates. In most patients dyskinesias and motor fluctuations emerge leading to shorter periods of satisfactory symptom control.² Proactive management of symptom progression is essential to maintain patients' quality of life, and referral to a movement disorder specialist for assessment and consideration of device-assisted therapies (DATs) is important when initial therapies no longer adequately control symptoms.^{3,4}

Evidence-based guidelines regarding the different treatment options for patients whose symptoms are no longer adequately controlled with oral or transdermal therapies are sparse and, where available, tend not to bridge the gap between clinical trial data and practical approaches in the real-life clinical setting.⁵⁻⁸ A recent European survey of movement disorder specialists – the Navigate PD program – aimed to supplement existing guidelines and provide recommendations around the commencement of DAT in patients with PD in Europe.⁴

AIMS:

The current document aims to provide guidance for Australian non-movement disorder specialists treating patients with PD to recognise when symptoms are no longer adequately controlled with oral/transdermal therapies, know when to refer their patient to a movement disorder specialist, and better understand the therapeutic management of PD with DAT. It builds on the European recommendations,⁴ with discussions around their relevance in the local clinical setting.

METHODS:

Guidance on practical approaches for commencing DAT for PD in Australia was developed by a group of eight local movement disorder experts. An online survey and teleconference discussions were held to develop consensus, based on a review of the European Navigate PD program recommendations⁴ and an analysis of their relevance in the local clinical setting.

RESULTS:

Basic principles

Definition

The term 'advanced PD' is commonly used to describe the phase of disease when referral to a movement disorder specialist and consideration of DAT is appropriate. However, the term 'advanced PD' is problematic. Patients may find it pejorative and suggestive of irreversibility. The term lacks clarity for physicians, leading to delays in referral for consideration of DAT. It may also incorrectly suggest that this stage of disease relates solely to the patient's age or to disease duration. The natural history of PD shows that the disease in its genuinely advanced stage usually entails a range of disabling and minimally treatment-responsive complications, such as cognitive impairment, swallowing and speech disturbance, dementia, gait dysfunction, loss of postural reflexes, and the need for residential care.⁹ In most patients, disabling motor response fluctuations precede these late stage complications and are amenable to treatment interventions such as DAT.

Our suggested working definition for the stage of PD when referral to a movement disorder specialist and consideration of DAT is appropriate is 'an inconsistent or unreliable medication response resulting in motor fluctuations, progression of disability and impairment despite optimised initial therapies'. During this phase of the disease, troublesome fluctuations and dyskinesias occur despite optimised oral or transdermal treatments, but many symptoms are still treatment-responsive.

When to refer

Main points on when to refer are listed in Box 1.

Box 1. When to refer

- Motor fluctuations cause disability or reduced quality of life
- Response to treatment is inconsistent
- Dyskinesias or motor fluctuations require frequent treatment adjustment without apparent benefit
- Levodopa required four or more times daily

The European PD program recommends referral when quality of life becomes inadequate due to motor fluctuations with or without dyskinesia and oral/transdermal therapy alone is no longer effective.⁴ We agree that DAT needs to be considered when motor fluctuations are causing disability or reduced quality of life; this may be recognised as inconsistent medication responses and a reduced capacity to participate in normal social and community activities. It may also be reasonable to consider DAT in patients with the primary problem of a reduced quality of life where there are also motor fluctuations refractory to standard therapeutic approaches. Early referrals are recommended if progression to this state is inevitable, so that long-term planning for DAT can be initiated.

DAT can minimise motor fluctuations, reduce 'off' time and reduce severity of dyskinesias, leading to an increased quality of life. Consideration should be given to the trajectory of the disease progression, rate of decline and realistic remaining treatment options when thinking of timeliness of referrals for DAT.

To ensure that PD treatments achieve maximum benefit and result in the best quality of life for affected patients, we would favour recommendation for referral if levodopa is required four or more times per day, rather than the five or more times per day suggested by the European PD program.⁴ Likewise, although the European program recommends referral for patients using amantadine for dyskinesias when symptoms are not controlled with this treatment, we suggest that patients whose dyskinesias are sufficiently severe to require treatment with amantadine be routinely referred for consideration of DAT.

The European program recommends considering DAT for patients who have more than 1–2 hours 'off' time during the day. We agree that the severity and quality of 'off' time is as important as the overall duration when considering referral for DAT.⁴ It is possible to establish this through careful history-taking and symptom review, without the need for complex questionnaires or detailed measurement of symptoms (e.g. using wearable devices).

Efficacy of DAT for motor symptoms and dyskinesias

Three types of DAT are available in Australia for patients with PD: continuous subcutaneous (SC) apomorphine, administered by a mini-pump or syringe driver; continuous levodopa-carbidopa intestinal gel (LCIG) infusion, delivered into the jejunum via a pump; and deep brain stimulation (DBS), via a surgically implanted neurostimulator.³ All three DATs provide consistency of motor response; however, if the relevant symptoms are non-responsive to dopaminergic therapies, then DAT will not provide extra benefit and should not be considered.

The evidence base to guide selection and timing of DAT initiation is limited and no randomised controlled trial (RCT) directly compares the three available therapies. Data from separate studies suggest similar improvements in 'off' time, motor fluctuations and dyskinesia with LCIG infusion, subthalamic nucleus (STN) DBS and SC apomorphine, although for SC apomorphine no RCT data are available.⁴ Across individual studies identified by the European program (including small, open-label, observational studies),⁴ the reported ranges in improvement of motor fluctuations and time with dyskinesias were: 49–64% and 47–59%, respectively, for LCIG;^{10,11} 50–85% and 43–64%, respectively, for SC apomorphine;¹²⁻²³ and 25–68% and 31–68% respectively, for STN-DBS.²⁴

Each DAT has its advantages as well as disadvantages. In general, motor improvements are similar across different DATs, so selection primarily depends on individual circumstances and patient choices. In our clinical experience, continuous apomorphine may not be as effective as LCIG infusion or DBS in reducing dyskinesias, as the magnitude of dyskinesia reduction after starting SC apomorphine is mostly dependent on the degree to which intermittent oral levodopa can be reduced.

Adverse events and complications

Data on the prevalence of adverse events and complications come from separate studies, with different methodologies and patient eligibility criteria, so direct comparisons cannot be made between the three available DATs. Table 1 summarises the most common adverse events and complications in relation to DAT from the European program publication.⁴

There is very little overlap in the device-related complication categories between the three DATs (Table 1). For LCIG infusion, surgical/device-related complications can occur, but can be minimised by involving an experienced gastroenterologist familiar with the infusion system.⁴ Published data are limited for SC apomorphine, with available information showing adverse events related to the device and to the drug; these can be minimised by optimal care of skin-related issues, correct use of cannulas and monitoring of patient behaviour for potential development of dopamine-agonist-related behavioural problems.⁴ When considering DBS, the patient's age, psychiatric history and cognitive status may influence the choice of surgical target. For example, compared with stimulation of the STN, DBS of the globus pallidus (GPi) may have a lower risk of adverse effects on executive and neuropsychiatric function.²⁵ There is ongoing controversy with respect to whether or not the differences in adverse effect profile of STN versus GPi are clinically significant.

Selection of therapy

The most important aspects when considering which DAT to use are the patient's age, cognitive function and neuropsychiatric status (e.g. presence of severe depression), and the personal preferences of the patient and their family. Geographical considerations, availability of carer or nursing support and cost may be relevant factors in selecting DATs. Starting DAT assumes that the symptoms respond to oral or transdermal medications, but that the response is inconsistent and with motor fluctuations that cause disability.

Table 2 shows criteria for the selection of a specific DAT according to the presence of disease-related or therapy-related symptoms from the European program,⁴ but with some recommendations changed in accordance with local experience where indicated in the table. The European program recommends that any DAT can be considered in patients who are younger than 70 years and who have motor fluctuations or dyskinesia but are otherwise healthy.⁴ For patients aged 70 years or older, the European program recommends that DBS should be considered second-line DAT (although patients can be operated on if MRI results are normal and cognitive function is not impaired); however, we think that age 70 years should not necessarily render DBS second-line and that age over 75 years may be a more appropriate cut-off. If patients are aged 70 years and older and have mildly or moderately impaired cognition (or other contraindications to DBS), the European program recommends considering LCIG infusion or SC apomorphine with cessation or reduction of oral therapy.⁴ However, in our clinical experience, it can be challenging to decide what constitutes mild cognitive impairment for the purposes of excluding a patient from DBS. For example, it may be difficult to decide whether mild mental inflexibility or executive dysfunction in an otherwise healthy patient aged 70 years or older should exclude consideration of DBS, especially GPi DBS, where the post-operative cognitive impact may be less than with STN DBS.

Information for patients and caregivers

It is important to discuss DATs with patients and their families, and to include a detailed disease management pathway. Early discussion of DAT is helpful, particularly in younger patients with expected long disease duration. The right time to inform patients about DAT options depends on the individual and their family, but is usually when inconsistency in response becomes evident. It is usually best to discuss all DAT options and referral should ideally be to a centre where all three DATs are available. In many patients it is appropriate to discuss DAT even if they are not deemed likely to be suitable, because it helps patients understand the goals of therapy in their particular circumstance.

Patients and their families need to be provided with treatment options that are suitable to them, with adequate and repeated explanations regarding the recommendations. We recommend emphasising the following key points to patients: DAT is not disease-modifying; it requires commitment (e.g. increased follow-up); it will largely maintain but will not improve the patient's previous best 'on' response; there is the possibility of troublesome side-effects. The following aspects should also be discussed: how the goals of each therapy are achieved (e.g. titration strategies, stimulation programming); anticipated time to achievement; and troubleshooting options. Information regarding cost and logistics of follow-up should be conveyed.

A stepwise approach is recommended when discussing DAT with patients and their families, first introducing the idea, and then going into more detail and providing examples. An opportunity to speak to other patients who have had similar treatments helps people understand the positive and negative aspects better. Repeated discussions are often necessary with demonstration of equipment and its use. Sources of information (e.g. videos, websites) can be provided. Technical aspects of the machinery should be discussed, and patients should be given the opportunity to handle the devices and understand their operations. For pump therapies, we would suggest that patients and carers be shown each device, and perhaps even given an opportunity to wear them, to establish whether they feel that the weight or size of the device would be burdensome.

Practical management issues

Patients who should not be considered

Contraindications to each DAT are listed in Table 3, adapted from the European program,⁴ the advice from which is generally appropriate for the Australian setting.

Cognitive dysfunction and postural instability

In patients who have cognitive dysfunction and postural instability, caution is advised and particular therapies may not be recommended because the risks outweigh the benefits. In accordance with the European program, we advise caution regarding DBS in patients showing signs of cognitive decline. At least some of our group would not use DBS when there is cognitive impairment. In our experience, infusion-based DAT still has a role in patients with cognitive impairment who have significant levodopa

responsiveness, although caregiver support is usually required. With the infusion therapies, postural hypotension can be exacerbated.

DAT should be considered if gait dysfunction is responsive to oral levodopa (i.e. freezing occurs only during 'off' periods). In patients with gait dysfunction or freezing that is resistant to oral levodopa but in whom poor oral absorption is suspected, LCIG infusion may still be a treatment option, because of its superior bioavailability over oral levodopa. In this situation, a naso-intestinal trial of LCIG can be justified to determine whether or not the gait dysfunction is genuinely levodopa-resistant.

Worsening motor fluctuations can be a consequence of poor adherence with medication schedules or dietary protein interactions. Patients with impaired ability to manage self-medication – a measure of early cognitive decline – might be particularly suitable for infusion therapy that does not rely on the frequent, accurately-timed dosing required with oral medications. This is also relevant to patients in residential care, where the requirement for frequent, accurately-timed doses is not practical because of staffing limitations.

Efficacy for non-motor symptoms

Published data are sparse for the efficacy of DATs for non-motor symptoms in PD and supporting information comes mostly from anecdotal clinical evidence,⁴ which is in agreement with our experience. Treatment decisions need to be made on a case-by-case basis. A recent open-label study showed improvements in non-motor symptoms with bilateral STN DBS.²⁶

Management of concomitant therapies

All DATs are best managed in a specialist centre, preferably with experience in all three types of DAT. Over the first few months of DAT, treatment-related issues are mostly handled within the specialist centre team and thereafter shared care arrangements can be made with the referring specialist. All patients and referring neurologists should be provided with an alternative medication plan should any of the devices fail. In Australia, a shared-care model (e.g. nursing help, percutaneous endoscopic gastrostomy clinics, support with device-related issues) is preferable for access to support services. The aim of DAT is to make life easier for the patient and family. The simpler the medical approach the better.

It is important to avoid rapid reduction or cessation of other Parkinson's disease treatments – including amantadine – before commencing DAT, because of the risk of exacerbating dyskinesias as a result of amantadine withdrawal and the risk of dopamine agonist withdrawal syndrome. In our experience, patients usually neither tolerate nor require cessation of levodopa therapy when receiving DBS or SC apomorphine. This may be related to the non-motor effects of levodopa on mood and motivation as much as its motor effects. It would be typical to aim for a 30% reduction in levodopa dose with SC apomorphine, rather than monotherapy, although monotherapy is achieved in some patients. In our clinical practice, following initiation of SC apomorphine or DBS, we tend to gradually reduce dopaminergic therapies and amantadine, while up-titrating apomorphine or DBS settings over weeks or months. Ultimately, we aim to minimise oral medications in conjunction with all DATs and can often achieve

monotherapy in patients receiving LCIG. We find that controlled-release oral or transdermal medications are often required at night-time in patients receiving infusional therapies.

We recommend monitoring of homocysteine, Vitamin B12 and Vitamin B6 levels in patients receiving treatment with LCIG. If the homocysteine levels become elevated, and Vitamin B12 or Vitamin B6 levels are found to be low, supplementation with parenteral vitamin B12 or oral Vitamin B6 is advised. Ongoing monitoring is required to avoid subsequent vitamin B6 toxicity. Full blood count and Coombs antiglobulin should be monitored periodically in patients being treated with SC apomorphine.

CONCLUSION:

The practical approaches presented in this document are intended to assist Australian non-movement disorder specialists with the proactive management of disease progression in patients with PD. Early referral to a movement disorder specialist is important to maintain patients' quality of life when initial therapies no longer adequately control symptoms. All three types of DAT available in Australia improve the consistency of motor response, and treatment decisions need to be made on a case-by-case basis, taking into account individual circumstances.

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Table 1 Adverse events reported relatively frequently ($\geq 10\%$) in relation to device-assisted therapies in patients with Parkinson's disease in clinical studies

Device-assisted therapy	
Levodopa-carbidopa intestinal gel infusion	
<i>General complications</i>	<i>Surgical/device-related complications</i>
Abdominal pain [†]	Complications of device insertion [†]
Flatulence	Procedural pain [†]
Constipation	Post-operative wound infection [†]
Nausea [†]	Incision site erythema [†]
Excessive granulation tissue [†]	Procedural site reaction [†]
Fall	Post-procedural discharge [†]
Dyskinesia [†]	
Insomnia	
Anxiety	
Pneumoperitoneum	
Subcutaneous apomorphine	
<i>Apomorphine-related complications</i>	<i>Administration/device-related complications</i>
Nodules [‡]	Needle/injection-site pain
Weight gain	
Neuropsychiatric adverse events [‡]	
Daytime somnolence [‡]	
Nausea [‡]	
Orthostatic hypotension	
Coombs antiglobulin positive	
Deep brain stimulation	
<i>Post-surgical complications</i>	
Balance and gait problems	

Depression

Dysarthria

Dyskinesias increased

Freezing/worsening of mobility

Pain

Weight change

[†]Listed as a frequent adverse effect in the Duodopa[®] Product Information, with most reported during the first 28 days after the percutaneous endoscopic gastronomy procedure.²⁷

[‡]Listed as an adverse effect in the Apomine™ Injection Product Information.²⁸

Table 2 Selection of a specific device-assisted therapy according to presence of symptoms

Symptom	LCIG infusion	SC apomorphine	STN DBS
Dyskinesias	+	+	+ [†]
Failure to adequately absorb oral medications [‡]	+	+	+
Non-motor fluctuations	+	+	+
Maintenance insomnia	+	+	+
Slight ongoing hallucinations	+/-	+/-	+/-
Dysphagia	+/-	+/-	+/- [§]
History of drug-related hallucinations and/or delusions	+	+/-	+
Marked ongoing hallucinations/psychosis (delirium)	+/-	-	-
Impulse control disorders	+/- [¶]	-	+
Drug-related daytime somnolence	+/-	-	+/-
Mild cognitive impairment	+	+/-	+/-
Dementia	+/-	-	-
Pronounced therapy-refractory depression	+/- [¶]	+	-
Dysarthria	+	+	-
L-dopa unresponsive postural and gait problems, falls	+/-	+/-	-
Restless legs	+/- [¶]	+	+/-
Orthostatic hypotension	+/-	-	+/-

+, presence of symptom strengthens the decision to select the DAT.

+/-, needs further investigation.

-, presence of symptom speaks against selecting the DAT.

[†]Recommendation changed from ‘++’ in European program publication.

[‡]Category added.

[§]Recommendation changed from ‘-’ in European program publication.

[¶]Recommendation changed from '+' in European program publication.

DAT, device-assisted therapy; DBS, deep brain stimulation; LCIG, levodopa-carbidopa intestinal gel; SC, subcutaneous; STN, subthalamic nucleus.

Table adapted from Odin et al. 2015.⁴

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Table 3 Contraindications to device-assisted therapies for Parkinson's disease[†]

Device-aided therapy	Relative contraindication/increased risk	Absolute contraindication
LCIG infusion	<ul style="list-style-type: none">• Non-adherence with oral/transdermal therapies• Pre-existing peripheral neuropathies[‡]• Previous or current dopamine dysregulation or punning• Moderate-to-severe dementia• Patient frailty (unable to support device weight)	<ul style="list-style-type: none">• Lack of levodopa response• Inability of patient and caregiver to handle medication and device• Relative or absolute contraindication to abdominal surgery
SC apomorphine	<ul style="list-style-type: none">• Non-adherence with oral/transdermal therapies• MCI or moderate-to-severe dementia• Previous or current dopamine dysregulation, punning or impulse control disorder	<ul style="list-style-type: none">• Lack of levodopa response• Inability of patient and caregiver to handle medication and device
DBS	<ul style="list-style-type: none">• Non-adherence with oral/transdermal therapies• Patient's age >70-75 years[§]• Severe depression• Condition that increases surgical risk, including cardiomyopathy	<ul style="list-style-type: none">• Lack of levodopa response, with the exception of rest tremor• Dementia• Severe brain atrophy or lesions interfering with trajectory planning

DBS, deep brain stimulation; LCIG, levodopa-carbidopa intestinal gel; MCI, mild cognitive impairment; SC, subcutaneous.

[†]Please refer to the manufacturers' product information for a list of all DAT-related absolute contraindications.

[‡]Reason for neuropathy should be determined (i.e. whether it is clinically relevant/symptomatic).

⁵The frailty of the patient and other comorbidities should be taken into account.

Table adapted from Odin et al. 2015.⁴

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