ARTICLE

Device-assisted therapies for Parkinson disease

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Keywords
apomorphine, deep brain stimulation, device-assisted therapies, intestinal infusions, levodopa, Parkinson disease, subcutaneous infusions

Aust Prescr 2025;48:10–7
https://doi.org/10.18773/austprescr.2025.003

SUMMARY

Device-assisted therapies for Parkinson disease include apomorphine continuous subcutaneous infusion, levodopa continuous intestinal gel infusion, levodopa continuous subcutaneous infusion and deep brain stimulation.

These therapies have a role in managing motor fluctuations and dyskinesias in people with advanced Parkinson disease when symptoms are inadequately controlled with oral and transdermal treatments.

Subcutaneous infusion of apomorphine or levodopa are the least invasive device-assisted therapies. Levodopa intestinal infusion is delivered via a surgically placed intestinal tube. Deep brain stimulation involves implanting electrodes into specific target regions of the basal ganglia to modulate brain activity.

Selecting an appropriate device-assisted therapy depends on individual factors such as age, comorbidities, symptom severity and patient preferences. Initiation and management require neurologist and multidisciplinary involvement, typically in a specialist movement disorder centre.

Primary care clinicians play a crucial role in ongoing support and management for people using these therapies, including monitoring and managing adverse effects and communicating with movement disorder services.

Introduction

Parkinson disease is a complex, progressive neurodegenerative disorder characterised by motor and non-motor symptoms.[1] It typically progresses slowly over years, with patients transitioning from early to mid to late stages of disease.[2] There are no disease-modifying treatments for Parkinson disease, so management focuses on symptom relief to improve quality of life and minimise disability.[3]

Most people with Parkinson disease are managed with levodopa and other oral or transdermal drug therapies, but in people with difficult-to-manage symptoms in the later stages of the disease, device-assisted therapies are sometimes beneficial. Device-assisted therapies available in Australia include apomorphine continuous subcutaneous infusion, levodopa continuous intestinal gel infusion, and deep brain stimulation.[1,2,4] Levodopa continuous subcutaneous infusion has been approved by the Therapeutic Goods Administration (TGA) but is not yet available in Australia at the time of writing.

This article provides a brief overview of oral and transdermal therapies for Parkinson disease, then describes the device-assisted therapies, and when and how they are used.

Oral and transdermal therapies

Early motor symptoms usually respond well to oral levodopa (with benserazide or carbidopa to reduce peripheral conversion of levodopa to dopamine, thus reducing peripheral side effects). This is typically the first-line therapy.

Over time, patients often experience fluctuations in their motor response to levodopa.[3] These fluctuations can manifest as a decline in motor response before the next dose ('wearing-OFF' phenomenon), a delayed response ('delayed ON'), or a failure of response ('no ON'). 'ON' periods may be accompanied by abnormal, involuntary movements (dyskinesias), usually occurring as a peak-dose effect.[1,3]

Several pharmacokinetic factors contribute to these fluctuations, such as delayed gastric emptying and competition from dietary amino acids that impede levodopa absorption.[1] Pharmacodynamic factors, including progressive neuron loss, can result in pulsatile dopamine release, leading to overstimulation of receptors (causing peak-dose dyskinesias) and rapid dopamine clearance (causing 'OFF' periods).[1]

To manage fluctuations, adjunctive therapies like dopamine agonists, catechol-O-methyltransferase

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inhibitors and monoamine oxidase type B inhibitors can be added to levodopa therapy.[3,5] Other strategies include shortening levodopa dose intervals, or dividing daily doses into smaller, more frequent administrations. Controlled-release levodopa formulations have a longer half-life and could theoretically improve fluctuations; however, erratic gastrointestinal absorption leads to inconsistent efficacy.[1,3,5] Amantadine can be used to treat dyskinesias but has short-lasting efficacy.[3,6]

A summary of oral and transdermal treatments currently available in Australia is provided in the Appendix. In most patients, motor fluctuations and dyskinesias are relatively mild and can be managed with these therapies. However, in some patients, symptoms persist, causing worsening disability despite optimised medical therapy.[1] In these patients, device-assisted therapies may be helpful.

Device-assisted therapies

Device-assisted therapies for Parkinson disease are a group of specialised treatments used to manage complex and disabling motor fluctuations and dyskinesias that cannot be adequately managed by oral or transdermal therapies alone.[1,7,8] Use of device-assisted therapies is typically reserved for those with advanced, complicated disease.

Initiation requires neurologist involvement, usually in a specialist movement disorder centre. Referral criteria for device-assisted therapies have been proposed by Australian movement disorder experts, based on European recommendations (Box 1).[4,7,8]

Each therapy has unique complexities and advantages, discussed below and summarised in Table 1.[7,8] Device selection depends on individual patient factors such as age, comorbidities, therapy-specific risks and patient preferences.[8,9] For device-assisted therapy to be effective the patient should retain a response to levodopa, except for deep brain stimulation which can be used for medication-refractory tremor.

Box 1 Criteria for referring patients with Parkinson disease for consideration of device-assisted therapies[5,8] [NB1]

- motor fluctuations causing disability or reduced quality of life
- inconsistent response to oral and transdermal therapies
- motor fluctuations or dyskinesias requiring frequent treatment adjustments without apparent benefit
- oral levodopa required 4 or more times a day
- severe medication-refractory tremor

NB1: Patients experiencing one or more criteria should be referred for further evaluation.

Apomorphine continuous subcutaneous infusion

Apomorphine is a subcutaneously administered dopamine agonist with rapid absorption and a short half-life. It can be given as intermittent bolus injections for rescue therapy, or as a continuous infusion via portable mini-pumps for severe fluctuations.[7] Continuous apomorphine infusions have been shown to be effective in improving motor function, significantly reducing daily OFF time and increasing ON time with minimal dyskinesia.[13,14]

Among the currently available device-assisted therapies, continuous apomorphine infusion is considered the most straightforward to initiate and discontinue (typically done in an outpatient setting), and may be the preferred choice in older patients where other devices may be contraindicated.[1,7,9,15]

Continuous apomorphine infusions are typically added to oral dopaminergic treatments. Following infusion commencement, other dopamine agonists are usually discontinued, and daytime levodopa is gradually reduced based on symptoms.[4,8,14] Use as monotherapy is rarely achieved.[8]

Dosing and administration

When commencing apomorphine therapy, a trial ('apomorphine challenge') is often conducted to confirm dopaminergic responsiveness and help estimate the dose needed.[10] Some patients may initially use intermittent subcutaneous bolus dosing as needed, for on-demand rescue therapy, while in others it may be more appropriate to directly commence a continuous infusion.[16] Infusions are typically continued for 12 to 16 hours during waking hours, with a usual dose range of 2 to 7 mg/hr.[6,16] Troublesome nocturnal OFF symptoms may benefit from an overnight rotigotine transdermal patch, or in rare cases a 24-hour apomorphine infusion.[10,17] Most pumps include a bolus function which enables patients to administer additional rescue doses during OFF periods. Frequent bolus use (over 3 times daily) may suggest the continuous hourly rate should be increased, although many patients maintain stable doses for years.[10,16,18]

Long-term adherence can be challenging and patients often require daily support to initialise the pump.[1,9] Training for patients and caregivers is crucial for compliance and preventing adverse events.

Complications and adverse effects

Panniculitis (subcutaneous nodules, erythema and needle-site tenderness) is a common adverse

Table 1 Device-assisted therapies for Parkinson disease[2,7-12]

Therapy	Route of administration	Advantages	Disadvantages	Side effects
Apomorphine continuous subcutaneous infusion (Apomine, Movapo)	Subcutaneous continuous infusion via portable pump	Less invasive than intestinal levodopa infusion and deep brain stimulation Easy to discontinue if response insufficient or poor tolerance	Patient usually requires assistance to prepare pump Pumps must be carried during the day Pumps are not water resistant, requiring disconnection prior to showers	Infusion-site skin reactions, nausea, orthostatic hypotension, neuropsychiatric effects, haemolytic anaemia (rare), prolonged QT interval (rare)
Levodopa+carbidopa continuous intestinal gel infusion (Duodopa) Levodopa+carbidopa+entacapone continuous intestinal gel infusion (Lecigon) [NB1]	Continuous infusion to jejunum via PEG-J tube	Can completely replace oral levodopa therapy	Moderately invasive (requires surgical PEG-J tube insertion) Complications such as infection, bezoar, intestinal obstruction, tube dislodgement or obstruction are common and may cause sudden clinical deterioration Patient usually requires assistance to prepare daily infusions Medication cassettes must be stored in the fridge before use Pumps require frequent battery changes (weekly)	Abdominal pain, surgical site reactions, flatulence, constipation, nausea, neuropathy, peritonitis, aspiration, malabsorption including vitamin B_{12} deficiency (associated with long-term use)
Foslevodopa+foscarbidopa continuous subcutaneous infusion (Vyalev) [NB1]	Subcutaneous continuous infusion via portable pump	Less invasive than intestinal levodopa infusion and deep brain stimulation Easy to discontinue if response insufficient or poor tolerance Can completely replace oral levodopa therapy	Patient usually requires assistance to prepare pump Pumps must be carried during the day	Infusion-site reactions and infection, nausea, neuropsychiatric effects
Deep brain stimulation	Surgical implantation	May be the preferred option in severe levodopa-induced dyskinesia and severe medication-refractory tremor Less reliant on daily assistance and may be the preferred option when no family support available	Highly invasive, requiring neurosurgery Risks of surgical complication such as intracranial haemorrhage, infection and seizures Ongoing programming required to optimise response Device-related problems (e.g. lead migration and disconnection) can occur Higher risk of adverse effects in older patients	Dysarthria, apathy, cognitive decline, depression, headache

PEG-J = percutaneous endoscopic gastrojejunostomy
NB1: Approved but not yet marketed in Australia at the time of writing

effect associated with apomorphine injection but can be minimised through skin care, rotation of injection site and correct use of cannulas. Nausea is common during initiation but can be minimised with pretreatment domperidone (dosed 10 mg three times a day). Tolerance to nausea develops rapidly, allowing gradual withdrawal of domperidone.[6] Rarer side effects include autoimmune haemolytic anaemia and prolonged QT interval (Table 1).[6]

Levodopa+carbidopa continuous intestinal gel infusion

Levodopa+carbidopa continuous intestinal gel infusion offers consistent drug delivery for patients with advanced Parkinson disease experiencing severe motor complications. Delivering the medication directly to the small intestine bypasses gastric emptying to ensure more stable plasma levodopa levels than may be achieved with oral dosing.[19] An intestinal gel containing levodopa+carbodopa+entacapone was also recently approved in Australia for advanced Parkinson disease with severe motor fluctuations unresponsive to optimised treatments.

These treatments involve surgical placement of a percutaneous endoscopic gastrostomy tube with jejunal extension (PEG-J tube) connected to a portable programmable pump worn by the patient. The procedure is invasive, typically requiring hospital admission for tube insertion and dose titration.

Improvement in motor symptoms from intestinal infusions are well-documented in several prospective trials.[20-22] A double-blind randomised controlled study showed significant reductions in OFF time and increased ON time without troublesome dyskinesia in levodopa intestinal gel-treated patients.[20]

Continuous intestinal infusions usually replace oral levodopa, but other oral dopaminergic therapies are often continued.

Dosing and administration

Prior to PEG-J tube insertion, intestinal gel clinical responsiveness may be established via a temporary nasointestinal tube. Following PEG-J tube placement, initial dosing is usually calculated from the total oral levodopa dose prior to infusion commencement and titrated according to response.

Infusions usually run continuously during waking hours and stop overnight to minimise tolerance development. Pumps are typically programmed to deliver a morning bolus dose (usually 100 to 200 mg levodopa) to achieve a quick therapeutic level, followed by a continuous infusion of the maintenance dose (usually 20 to 200 mg per hour). Extra bolus doses (usually 10 to 40 mg per dose) can be administered as required during OFF periods. If more than 5 bolus doses are needed per day, the continuous maintenance dose should be increased. Rarely, infusions may be extended for continuous 24-hour use, usually in patients with significant nocturnal symptoms.

Pump doses are pre-programmed and typically cannot be adjusted by patients or carers. Patients can prepare the levodopa intestinal pump each day, but many need carer assistance. Medication cassettes are single-use and should not be used for longer than 16 hours. Due to poor drug stability, cassettes require refrigeration and have a short expiry.

Complications and adverse effects

Adverse events associated with intestinal levodopa infusions are common. They are usually mild to moderate in severity and predominantly related to surgical complications or device-related problems, such as procedural pain, abdominal pain and infection (Table 1).[23] Serious adverse events can occur in up to 50% of individuals and include peritonitis, pneumoperitoneum and pneumonia.[21,22] Prolonged exposure has been associated with peripheral neuropathy.[24] Adverse event rates decrease over time, and despite the initial high rate, the overall benefit–risk profile remains favourable for long-term use.[21]

Foslevodopa+foscarbidopa continuous subcutaneous infusion

A continuous subcutaneous infusion containing foslevodopa+foscarbidopa (prodrugs converted to levodopa+carbidopa in vivo) has been approved but is not available in Australia at the time of writing. A potential advantage over intestinal levodopa+carbidopa infusion is that it does not require a hospital admission and surgical procedure for initiation.[12]

Deep brain stimulation

Deep brain stimulation is an invasive neurosurgical procedure delivering high-frequency electrical currents to specific brain regions. Electrodes are implanted into target regions of the basal ganglia such as the subthalamic nucleus, posterior subthalamic area, globus pallidus interna or occasionally the ventral intermediate nucleus of the thalamus.[11] The electrodes connect to a pulse generator implanted under the skin, typically near the collarbone with pulses controlled by an external remote.

The effectiveness of deep brain stimulation in Parkinson disease is well established, with substantial benefits in reducing OFF time and dyskinesias, and improving motor function, daily functioning and quality of life. Deep brain stimulation has been found to be superior to medical treatment in several

randomised controlled trials.[25-27] It is typically used in conjunction with oral therapies but often allows for reduced medication dosages.

Eligibility and device management

Access to deep brain stimulation involves referral to a specialist movement disorder clinic and extensive multidisciplinary evaluation. Eligibility is based on factors such as age, levodopa responsiveness and medical comorbidities including cognitive or psychiatric problems.[28,29] The surgery is performed by a neurosurgeon and requires hospital admission. Postoperative care involves programming and adjusting the stimulator settings by a neurologist or specialist nurse. Ongoing follow-up is essential to optimise device settings and address complications.

Complications and adverse effects

Potential complications include intracranial haemorrhage, seizures and infection (Table 1). Hardware-related issues, including lead migration or disconnection, can lead to sudden loss of stimulation and acute worsening of motor symptoms. Cognitive and psychiatric side effects, such as depression, anxiety or cognitive decline, can also occur, often limiting use of deep brain stimulation in older people.[30]

Comparison of device-assisted therapies

The evidence base to guide selection of device-assisted therapies in Parkinson disease is limited. No randomised controlled trials have directly compared the 4 device-assisted therapies. Separate studies suggest similar improvements in OFF time, motor fluctuations and dyskinesia.[1,8,9] One systematic review found that levodopa intestinal infusions and deep brain stimulation provided superior efficacy over oral and transdermal therapies, but were associated with significantly higher costs.[9] Continuous apomorphine infusions were found to be more cost-effective than levodopa intestinal infusions and deep brain stimulation.[9,31,32] The costs to patients for apomorphine and levodopa intestinal infusion are similar, as both are subsidised in Australia through the Pharmaceutical Benefits Scheme. Deep brain stimulation surgery costs are covered by Medicare and private health insurers, but there may be out-of-pocket costs in private hospital settings.

Management of device-assisted therapies

Device-assisted therapies are usually managed in specialist movement disorder clinics, typically involving a multidisciplinary team including neurologists, nurses, neurosurgeons, neuropsychologists, psychiatrists and physiotherapists.[1,7] Access to movement disorder clinics in Australia can be difficult, particularly in regional and rural areas. Movement disorder nurse specialists are available through these specialist clinics and may provide outreach consultation, education and training. Nurse specialists from pharmaceutical companies are also available to provide community support for patients, caregivers and clinicians, offering education and assistance with the administration and use of equipment.

Before commencing device-assisted therapy, patients should be thoroughly informed about the treatment process and potential outcomes. Collaborative decision-making involving the patient and their carers is essential.[7]

Regular review by the movement disorder clinic is crucial for dosage adjustments, monitoring side effects, addressing device-related issues and providing ongoing education.[7]

Ensuring adequate supply of medications is essential, as they may not be readily available in community pharmacies.

Primary care clinicians, particularly general practitioners and pharmacists, play a crucial role in ongoing support and management, including monitoring side effects, communicating with the movement disorder clinic or nurse specialist, and ensuring correct device use (Table 2).

Conclusion

Device-assisted therapies for Parkinson disease, including apomorphine or foslevodopa continuous subcutaneous infusion, levodopa continuous intestinal gel infusion and deep brain stimulation, offer effective management for complex motor fluctuations and dyskinesias. Selection of these therapies should be tailored to individual patient needs and managed in specialist movement disorder clinics. Regular review and patient education are crucial for optimising treatment outcomes. <

This article was finalised on 11 December 2024.

Conflicts of interest: Nadia Mouchaileh has no conflicts to declare. Jill Cameron received support from Abbvie to attend a conference in 2023, previously received honoraria from Abbvie, CSL Seqirus and Stada for involvement in educational seminars and presentations, and has been on advisory boards for Abbvie and Stada.

Table 2 Considerations for primary care clinicians caring for patients with Parkinson disease using device-assisted therapies

Consideration	Details
Adverse effects and complications to monitor	*Apomorphine continuous subcutaneous infusion*: Regularly assess for injection-site reactions, QT prolongation, nausea and orthostatic hypotension, especially during dose titration. Use domperidone for nausea management (preferred antiemetic in Parkinson disease). If nausea persists, consider referral to the patient's neurologist for apomorphine dose re-evaluation. *Levodopa continuous intestinal gel infusions*: Watch for surgical complications (e.g. infection at PEG-J tube site) and abdominal symptoms. Severe complications like peritonitis, bezoar, or tube dislodgement may require urgent attention. *Deep brain stimulation*: Monitor for postsurgical complications (e.g. intracranial haemorrhage, infection and seizures). Look for early signs of device malfunction (e.g. sudden worsening of symptoms); refer to the patient's neurologist if any signs of neurological deterioration. Monitor for signs of depression, apathy, or cognitive decline.
Movement disorder specialist support	Contact movement disorder clinic or nurse specialist for urgent issues. Some pharmaceutical companies offer after-hours hotline support for users of these therapies.
Device management	Monitor for signs of under- or overdosing and liaise with movement disorder clinic for device and dose adjustments.
Education and support	Ensure the patient and caregiver understand how to manage devices, recognise signs of complications, and attend scheduled specialist appointments.

PEG-J = percutaneous endoscopic gastrojejunostomy

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See Appendix on next page.

Appendix Oral and transdermal treatments for Parkinson disease[1,6]

Drug class	Generic (brand) name	Advantages	Disadvantages
Levodopa with benserazide or carbidopa [NB1]	levodopa+carbidopa IR (Sinemet, Kinson, Sinadopa) levodopa+benserazide IR (Madopar) levodopa+carbidopa SR (Sinemet SR) levodopa+benserazide SR (Madopar HBS)	Most potent dopaminergic effect Peripheral dopa-decarboxylase inhibition reduces peripheral dopamine effects (e.g. nausea, vomiting, hypotension) Dispersible tablets may be useful for rapid response	Frequent dosing required with disease progression Delayed gastric emptying and dietary amino acids can impair absorption Long-term use associated with increased motor fluctuations and dyskinesias SR preparations exhibit erratic and unpredictable absorption
Dopamine agonists	pramipexole IR (Sifrol, Simpral, Simipex) pramipexole SR (Sifrol ER, Simipex XR) rotigotine transdermal patch (Neupro) *Ergot derivatives*: bromocriptine (Parlodel) cabergoline (Dostinex, Cabaser)	Improve motor fluctuations when used as adjunctive therapy to levodopa Can be used as monotherapy in younger people with early disease to delay levodopa use Patches useful in people with nocturnal symptoms, swallowing difficulties or when unable to take oral therapy (e.g. fasting states)	Risk of impulse control disorders, excessive daytime somnolence and sudden sleep attacks Risk of confusion and hallucinations greater than levodopa, especially in older people Application-site reactions associated with patch use *Ergot derivatives*: Risk of cardiac, pulmonary and retroperitoneal fibrosis (rarely used; neurologist input required)
Monoamine oxidase type B inhibitors	rasagiline (Azilect, Alziras) selegiline (Eldepryl) safinamide (Xadago)	May be better tolerated than levodopa and dopamine agonists Rasagiline can be used as monotherapy in mild disease Improve motor fluctuations when used as adjunctive therapy to levodopa	Less effective than levodopa and dopamine agonists Associated with serotonin toxicity Avoid night-time dosing due to risk of insomnia Safinamide contraindicated in patients with retinal problems (retinal degeneration reported in animal studies)
Catechol-O-methyltransferase inhibitors	entacapone (Comtan) opicapone (Ongentys)	Improve motor fluctuations when used as adjunctive therapy to levodopa Once-daily dosing option available with opicapone Available as carbidopa+levodopa+entacapone formulation (Stalevo)	Urine, skin, hair and nail discolouration associated with entacapone use Opicapone may reduce levodopa absorption if administered simultaneously, separate by at least 1 hr
Anticholinergics	benzatropine (Benztrop) trihexyphenidyl, also known as benxhexol (Artane)	May improve tremor symptoms Can be useful as adjunctive therapy in dystonia management	Rarely used due to anticholinergic side effects Risk of cognitive impairment in older patients
Other	amantadine (Symmetrel, Amantamed)	Useful as adjunctive therapy for treatment of levodopa-induced dyskinesias	Efficacy reduced with long-term use Risks of gastrointestinal and neuropsychiatric side effects

IR = immediate release; SR = sustained release

NB1: Benserazide and carbidopa are peripheral dopa-decarboxylase inhibitors. They reduce peripheral conversion of levodopa to dopamine, thus reducing adverse effects (e.g. nausea, vomiting, hypotension) and improving central bioavailability.