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CLINICAL PERSPECTIVES

Deep brain stimulation for Parkinson disease in Australia: current scientific and clinical status

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Abstract

There is currently no cure for Parkinson disease (PD). Disease management is directed primarily at motor symptom relief, but the impact of non-motor symptoms associated with PD should not be underestimated. Medical and surgical treatment options aim to increase functional independence and quality of life. Deep brain stimulation (DBS) has proven to be a safe, effective and cost-efficient surgical treatment option. In 2009, the Australian referral guidelines, developed to provide a synopsis of DBS therapy for PD, were introduced, and since then novel findings have been reported regarding the timing of intervention, target selection and symptom management. Our aim is to provide an update of DBS for PD in Australia. Intervention at earlier stages of the disease can potentially improve quality of life over a longer period with greater possibilities for meaningful social and professional contributions. For less responsive motor symptoms (e.g. freezing of gait, postural instability), the pedunculopontine nucleus has emerged as a promising new surgical target. Traditional PD treatment is focused on improvement of motor symptoms, but the disorder is also characterised by non-motor symptoms, often undiagnosed or undisclosed, that have the potential to impact quality of life to a greater extent than motor symptoms. It is essential to identify and routinely monitor for non-motor symptoms as they can emerge at all stages of the disease or can result from treatment. Many of these current advances require long-term monitoring of treatment outcomes to improve future clinical practice, refine patient selection and ensure best patient outcomes.

Introduction

Parkinson disease (PD) is a progressive, neurodegenerative disorder, resulting in tremor, rigidity and bradykinesia as well as causing postural and gait disturbances. As such, PD reduces quality of life and functional status and increases dependence on care and assistance.[1] Although commonly considered primarily a movement disorder, several significant non-motor symptoms are associated with the primary disease or are therapy induced, which collectively may impact on patient health and functional status. Prevalence reports of PD vary considerably, possibly due to a lack of definitive diagnostic tools and consequent underreporting of the disorder or differences in methodological estimation approaches. The latest report from 2011 estimated that around 64 000 Australians were affected by PD (approximately one in every 350 people) of which the majority (80%) were aged over 65 years.[1] This number is predicted to double over the next two decades with the ageing Australian population. Even though PD is associated with older age, up to 19% of affected individuals were diagnosed between the working ages of 15 to 64 years, which led to a high risk of premature withdrawal from the workforce due to the increasing disease burden.[1]

Many of the cardinal symptoms of PD can be reduced by pharmacological or surgical treatment, thus greatly improving functional status and quality of life. Although dopaminergic medications have proven to be effective,

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Table 1 The financial cost of Parkinson disease in 2011 by barer of the cost[2]

Barer	% of total financial cost
Federal government	39
State government	16
Employers	2
Society	22
Household	21

long-term treatment is associated with motor fluctuations, characterised by unpredictable responsiveness to medication (e.g. end of dose wearing off, longer 'off' times and delays in 'on' response), which may limit the therapeutic window and the eventual development of non-motor and motor complications as well as dyskinesias.[2] These disabling effects not only affect the quality of life and wellness of the patient, but also have a significant impact on the caregiver as well as the community, due to the increasing dependence and need of care. In 2011, the total economic burden of disease was valued at $8.3 billion per year.[2] For an overview of these costs by barer, see Table 1.

Introduced in Australia in 2001 as a non-destructive and reversible stereotactic procedure, deep brain stimulation (DBS) has evolved as a well-established, safe and effective surgical treatment option for advanced stage PD.[2,3] The procedure consists of implantation of electrodes into specific uni- or bilateral deep brain targets, through which electrical stimulation is delivered (Fig. 1). The strength and frequency of stimulation can be flexibly programmed to the individual needs of the patient, to optimise treatment efficacy. Worldwide, DBS has proven effective for treatment of several disorders, including PD, and is under investigation as a treatment option for various novel indications by targeting different brain structures (Table 2). Most recently, DBS has received regulatory approval in Australia for refractory epilepsy and in most, but not all states for treatment-resistant obsessive-compulsive disorder. Since DBS for psychiatric disorders is considered psychosurgery under the state-based mental health legislation, it is prohibited in New South Wales and strictly regulated in Victoria for these purposes.[4]

In 2009, a panel of Australian neurosurgeons and neurologists developed the Australian referral guidelines for DBS, providing assistance for identification of potential patients with PD for DBS treatment.[2] Several studies have since reported novel findings regarding new targets, timing of intervention and symptom management. Our aim is to provide an update of the current clinical status of DBS for the treatment of PD in Australia that considers recent scientific advances.

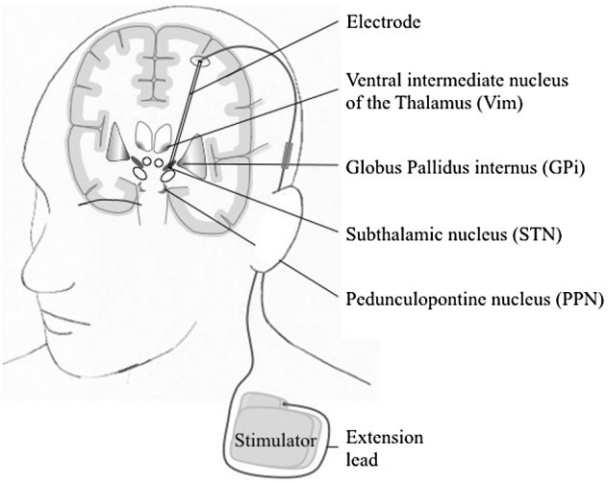

Figure 1 The implanted deep brain stimulation system, consisting of stimulator, extension lead and electrode. Also highlighted are the ventral intermediate nucleus of the thalamus, globus pallidus internus, subthalamic nucleus and pedunculopontine nucleus currently used as targets for Parkinson disease treatment.

Current status of DBS in Australia

Over 100 000 people have received DBS worldwide for a variety of indications,[5] with growth projections for the global DBS market estimating that it will nearly double to $800 million from 2012 to 2016.[6] In 2013, between 300 and 350 Australians were estimated to have received DBS for a variety of indications, although, at present PD remains the most common disorder for DBS intervention. Compared to conventional medical treatment, the initial cost of DBS treatment might seem substantial due to the cost of the surgical procedure and implanted device. However, Class 1 evidence has demonstrated that long-term DBS treatment for PD is more cost-effective than standard long-term medical treatment due to

Table 2 Overview of currently approved and novel indications for treatment with deep brain stimulation (DBS)

Approved indications	Emerging indications
Parkinson disease	Depression
Essential tremor	Cluster headache
Dystonia	Chronic pain syndromes
Obsessive compulsive disorder	Obesity
Epilepsy	Anorexia nervosa
	Tourette's syndrome

a decrease or discontinuation of PD medication and a reduction in symptoms and comorbidities leading to a decreased reliance on care, assistance and hospitalisation.[7] There are currently 16 DBS clinics across Australia responsible for over 3000 DBS procedures since 2001.[3] Many of the procedures are performed bilaterally with most implantations (including the pulse generators) performed during a single procedure.

Advances in DBS over the last five years

Patient selection: intervention at earlier stages of the disease

Although accuracy of electrode placement is necessary for the success of DBS treatment, it is alone insufficient for beneficial treatment outcomes. As indicated by the Australian referral guidelines, patient selection criteria are perhaps the first and the most crucial step in determining the success of DBS treatment for improving quality of life and alleviating symptoms.[2] There are no age standards for DBS treatment; however, studies investigating intervention outcomes commonly report a mean patient age of 60 years and a mean disease duration of 12 years. Seminal studies reported successful outcomes of patients with advanced PD presenting with reduced responsiveness to medications, considerable fluctuations in 'on-off' times and severe motor complications.[8,9] Furthermore, cognitive state and neuropsychological functioning, which can be more affected in older rather than younger patients, are routinely considered in the selection process.[2] In addition, patients must be willing and able to attend regular clinical consultations for monitoring/programming of stimulation settings to optimise treatment efficacy. Patients are generally assessed on an individual basis to provide a tailored approach in maximising treatment outcomes and minimising (post) operative risks or negative outcomes.[2] In general terms, potential candidates are considered for DBS when symptoms and/or quality of life are inadequately improved by medications, but are excluded when cognitive or psychiatric impairments or uncontrolled significant medical or surgical comorbidities are present.

One of the most important recent advances in DBS for PD is the shift to earlier stages of the disease. Recent Class 1 trials have reported beneficial patient outcomes when treated with DBS in the earlier stages of the disorder (mean age 52.5 years, disease duration >4 years).[8–10] The rationale for a shift to earlier intervention is that patients benefit longer before the disease reaches a state in which neither DBS nor medications can improve symptoms.[10] Further, earlier intervention could allow patients and their caregivers to return to meaningful social and productive professional participation.[1] DBS has already proven to be a cost-effective treatment for advanced PD, and scenario analyses have shown that intervention at earlier stages could result in even greater cost-effectiveness due to reductions in pharmaceutical costs, reliance on professional care, therapy and specialist consultations.[11] Long-term data from early-phase intervention are lacking, and therefore patients need to be monitored over prolonged periods to assess the long-term therapeutic outcomes in relation to quality of life and financial benefit.[9,11]

Identification of new target structures

The 2009 referral guidelines highlight that the decision to target a specific structure largely depends on the disease, type of symptoms and comorbidities.[2] Three well-established targets were described for implantation of DBS electrodes in PD (Fig. 1). These include the subthalamic nucleus (STN), the globus pallidus internus (GPi) and the ventral intermediate nucleus of the thalamus (VIM). Some of these targets have proven more beneficial in effectively treating PD symptoms, resulting in fewer adverse treatment effects and/or reduced requirements for additional medication, For instance, the VIM has been used successfully to alleviate tremor dominant PD, but is less suitable as a target for bradykinesia and rigidity. Further, medication is rarely reduced with VIM DBS.[2] Reduction in medication is advantageous when patients present with persistent medically refractory symptoms and/or medically induced adverse effects (e.g. dyskinesias, motor fluctuations, disabling 'off' periods and/or a variety of non-motor symptoms) despite optimal medical therapy. In a randomised control trial, STN stimulation was shown to be superior to standard medical PD therapy alone, reducing many symptoms with a concurrent significant reduction or even discontinuation of medications.[12] There has been an ongoing debate whether GPi or STN is the more preferable target for treatment of PD symptoms, and several small studies have reported results favoring either target. Recently, results from three large randomised controlled trials have shown comparable maintained improvements of motor function as assessed by the Unified Parkinson Disease Rating Scale (UPDRS)[13,14] and a generic disability scale (Academic Medical Center Linear Disability Score)[15] when directly comparing bilateral stimulation for both targets. In addition, no difference in adverse events was observed between targets. Differences between targets were mainly observed in secondary outcomes, with two studies reporting significant reductions in medication, as

well as lower stimulation settings (amplitudes and pulse widths) following STN DBS,[13,15] while dyskinesias were more effectively reduced following 1 year of GPi DBS without change to medication.[15] Further, the risk of neuropsychological complications was reported no worse[15] or slightly higher[13,14] for STN DBS than GPi DBS after 2 years. However, after 3 years, no differences between targets were observed.[14] In general, the results from these three studies show that both STN and GPi are effective targets for improving motor outcomes. However, the selection of one or the other depends on the combination of symptoms, their impact on quality of life, the desired treatment goals and long-term disease management plan.[13–15] In Australia, STN is the preferred target for treatment of many of the symptoms of PD.

Although effective for many symptoms, both DBS and medications have shown variable effectiveness for treatment of freezing of gait and falls.[16] A fourth structure, the pedunculopontine nucleus (PPN; Fig. 1), was also mentioned in the 2009 referral guidelines as possible target for symptoms of postural instability and freezing of gait.[17,18] To date, the PPN is the deepest part of the brain targeted for DBS stimulation. The indistinct borders of this structure and the lack of a characteristic neurophysiological activity make this structure a particularly challenging target.[19] In 2009, studies investigating the effects of stimulating this target had not been completed, but several studies have since reported on the effects of PPN stimulation for these difficult to treat symptoms. Double-blinded objective assessments of freezing of gait, start hesitancy and gait and falls showed significant improvements in both studies. These improvements were more pronounced with bilateral than unilateral stimulation. The effects of PPN stimulation were not directly reflected in changes in motor assessment scores (Movement Disorder Society (MDS)-UPDRS) and medication levels over a 2-year follow up[20] nor in improved step length and step variability when comparing 'on' and 'off' DBS states.[18] It is important to mention that although the MDS-UPDRS is suitable to assess motor function, it is less sensitive to detect subtle changes in gait and posture. Another distinction that sets this target apart from the other three targets is that low rather than high frequency stimulation seems to be more beneficial in improving motor activity.[19] To date, complete elimination of freezing of gait and start hesitancy following PPN stimulation have not been reported, and the impact of the reported improvements on quality of life remains to be determined. However, initial results from the recent small studies are promising, and more extensive studies are required to understand the full potential of PPN as a new individual target or as a supplementary target.

Table 3 Non-motor symptoms associated with Parkinson disease[8]

Behavioural dysfunction	Autonomic dysfunction
Depression†,§	Dysphagia
Anxiety†,§	Gastric dysfunction† (dribbling, nausea, reflux, vomiting)
Apathy§	Intestinal dysfunction†,‡ (constipation, fecal incontinence)
Obsessive behaviour§	Urological dysfunction‡ (bladder urgency, frequency, nocturia)
Impulse control disorders†,§	Impaired sexual function‡
Cognitive impairment (dementia)§	Cardiovascular autonomic dysfunction
Hallucinations†,§, psychosis§, delusions§	Thermoregulatory dysfunction
Panic attacks§	Respiratory dysfunction
Sleep-related dysfunction	**Sensory dysfunction**
Insomnia†	Visual dysfunction (blurred vision, diplopia)‡
REM sleep behaviour disorder†	Pain
Excessive daytime sleepiness†,‡	Olfactory dysfunction
Sleep apnoea	Sensorimotor dysfunction
Restless legs syndrome‡	Fatigue (central and peripheral)

†Potentially treatable. ‡Showed improvement. §Potentially worsen. REM, rapid eye movement.

Focus on non-motor symptoms

While traditional PD treatment has mainly focused on improvement of the overt motor symptoms, the disorder is characterised by at least one (90% of patients) and often more non-motor symptoms (Table 3), depending on the disease duration. Although only briefly mentioned in the 2009 referral guidelines, it is now internationally recognised that non-motor symptoms can potentially have a greater impact on quality of life than motor symptoms.[21] Identification of these non-motor symptoms is therefore essential, especially since some non-motor symptoms can emerge well before any motor symptoms, and their numbers increase as the disease advances. Furthermore, non-motor symptoms can be attributed to or worsened by the actual treatment (e.g. by high doses of medications and/or potential unwanted electrical stimulation of surrounding brain tissues with DBS) adversely affecting patient treatment and quality of life (Table 3).[21,22]

Many of the non-motor symptoms are often inappropriately identified or unidentified in routine clinical evaluations and therefore are not always included in treatment considerations.[23] Further, identification of non-motor symptoms can be challenging since patients do not always relate their non-motor symptoms to PD or are embarrassed to address their symptoms during clinical visits.[21] However, several non-motor symptoms are

treatable (Table 3) or at least manageable if properly identified.[24] It is therefore important to provide a clinical environment in which patients and their caregiver(s) are educated and informed about all symptoms, and communication between clinicians and patients is facilitated. Long-term management of PD requires a multidisciplinary approach involving routine patient assessments to monitor changes in or emergence of a broad range of associated symptoms. In recent years, several clinical tools have been adapted to accommodate identification of non-motor symptoms, such as the MDS-UPDRS and the Scales for Outcomes in PD. Several other tools have been developed and validated in recent years capable of measuring the impact of non-motor symptoms on quality of life. Aimed at subjective symptom detection (e.g. the Non-Motor Symptoms Questionnaire)[25] and objective rating of symptom severity and frequency (the Non-Motor Symptoms Scale),[26] both tools have been used in several recent studies and were successful in identifying and assessing changes in non-motor symptoms in patients following DBS surgery targeting the STN.[27–29] The results showed a significant reduction in the number and/or severity of several non-motor symptoms following DBS (Table 3), which was related to increased quality of life. Several reasons were proposed for the observed improvements following DBS, including direct stimulation effects on non-motor symptoms, increased mobility and sense of well-being and also significant reductions in medication.[28]

No current data are available for the extent of assessment of non-motor symptoms in the Australian PD population, nor is there evidence of clinical consideration of these symptoms as standard practice in DBS treatment plans. It is essential to keep in mind that for patients, functional status and independence are important treatment outcomes, and quality of life also involves non-motor, social and emotional factors that can outweigh the motor factors in DBS outcomes.[30] Clinical awareness of the broad range of motor and non-motor symptoms associated with PD is important, but the priorities for long-term management of PD and improvement of quality of life are early identification and appropriate consideration in subsequent treatment plans.

The efficacy and safety of DBS as treatment for PD as well as other indications is well established. Advances in the past 5 years have seen a shift to DBS intervention at early stages of the disease, investigation of new targets for less responsive symptoms and the recognition that PD is more than just a movement disorder and consequent treatment has to take into consideration a range of motor and non-motor symptoms. Long-term monitoring of symptom changes or emergence and their impact on quality of life is essential for increasing our understanding of the effects of DBS and improving clinical practice for treatment of PD and many emerging indications.[31]

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