

Deep Brain Stimulation for Parkinson's Disease: A Comprehensive Review of Current Paradigms, Emerging Technologies, and Future Directions in a Global Context

JEFFREY SILVER¹

¹ Warrington, United Kingdom

Received: 7th July 2025; 28th July 2025

Abstract

Background: Parkinson's Disease (PD) is a progressive neurodegenerative disorder affecting over 10 million people globally, characterized by debilitating motor and non-motor symptoms.¹ Deep Brain Stimulation (DBS) has emerged as a pivotal neurosurgical intervention for advanced PD refractory to pharmacotherapy, modulating aberrant neural activity in target regions like the subthalamic nucleus (STN) and globus pallidus interna (GPi).¹ This review provides a comprehensive analysis of DBS in PD, encompassing its mechanisms, clinical efficacy, associated risks, comparative effectiveness, technological advancements, and global accessibility.

Methods: A systematic review of the literature was conducted, synthesizing evidence from randomized controlled trials, meta-analyses, and authoritative reviews on DBS for PD. Data were extracted regarding motor and non-motor symptom outcomes, quality of life, medication reduction, surgical and stimulation-related complications, comparative therapies, and emerging technologies. Special attention was paid to European implementation and accessibility data.

Results: DBS significantly improves motor symptoms (tremor, rigidity, bradykinesia), reduces medication dependency, and enhances quality of life in well-selected PD patients, with benefits sustained for over a decade.¹ While primarily targeting motor symptoms, DBS can also positively influence certain non-motor symptoms like sleep and pain, though effects on cognition and some psychiatric aspects are variable and require careful patient selection.¹ Surgical risks (e.g., hemorrhage, infection) and stimulation-induced side effects necessitate a multidisciplinary approach.¹ Emerging adaptive and closed-loop DBS systems promise enhanced precision, reduced side effects, and improved battery longevity by dynamically adjusting stimulation based on real-time brain signals.¹ Despite Europe's leadership in DBS implementation, significant disparities in cost and accessibility persist across regions.¹

Conclusion: DBS remains a transformative, yet complex, therapeutic option for advanced PD. Future advancements in adaptive technologies, personalized programming, and equitable global access are crucial to maximize its potential and improve outcomes for a broader patient population. Ongoing research into novel stimulation paradigms and biomarkers will further refine patient selection and optimize therapeutic benefits while minimizing adverse effects.

KEYWORDS: PARKINSON'S DISEASE, DEEP BRAIN STIMULATION, DBS, MOTOR SYMPTOMS, NON-MOTOR SYMPTOMS, EUROPE, TREATMENT OPTIONS, ADAPTIVE DBS, CLOSED-LOOP DBS, NEUROSURGERY, QUALITY OF LIFE, PATIENT SELECTION, ACCESSIBILITY, ETHICS, GENE THERAPY, STEM CELL THERAPY

Corresponding author: Jeffrey Silver - J.silver1471@hotmail.com

1. Introduction

Parkinson's Disease (PD) is a chronic, progressive neurodegenerative disorder that impacts over 10 million individuals globally.¹ The cardinal motor symptoms of PD—tremor, rigidity, bradykinesia (slowness of movement), and postural instability—are primarily attributed to the progressive degeneration of dopamine-producing neurons within the substantia nigra pars compacta (SNpc).¹ This neuronal loss disrupts the intricate circuitry of the basal ganglia, leading to the characteristic motor dysfunction. Beyond these overt motor manifestations, PD is also associated with a wide spectrum of non-motor symptoms (NMS), which can include sleep disturbances, chronic pain, autonomic dysfunction (e.g., orthostatic hypotension), cognitive impairment, and various neuropsychiatric issues such as depression, anxiety, and impulse control disorders.¹ These non-motor symptoms frequently exert a profound impact on patients' overall quality of life, often proving more debilitating than the motor symptoms themselves, particularly in advanced stages of the disease.⁸ As PD progresses, the long-term use of levodopa, the cornerstone pharmacological treatment, often leads to the development of problematic motor fluctuations and dyskinesias, further complicating disease management.¹

Deep Brain Stimulation (DBS) has emerged as a pivotal neurosurgical intervention for individuals with advanced PD whose symptoms are no longer adequately controlled by pharmacotherapy.¹ This therapeutic modality involves the precise implantation of electrodes into specific deep brain regions to deliver controlled electrical impulses, thereby modulating aberrant neural activity and alleviating motor dysfunction.¹ The evolution of DBS can be traced from earlier ablative surgical techniques, such as thalamotomy, offering a significant advantage by providing a reversible and adjustable alternative.¹ Since its initial approval for Parkinson's tremor in 1997 and for advanced PD symptoms in 2002, DBS has continued to evolve, with its indications expanding to include earlier stages of PD in carefully selected patients who experience motor symptoms inadequately controlled by medication, even after four years of disease duration.²⁴ Europe has consistently been at the forefront of both the clinical application and technological advancements in DBS.¹

This comprehensive review aims to critically evaluate the current landscape of DBS for PD. It will systematically examine the underlying mechanisms of DBS, its demonstrated clinical efficacy across motor and non-motor domains, and the associated risks and complications. Furthermore, the analysis will provide a comparative perspective against existing and emerging alternative therapies. A significant objective is to explore the nuances of DBS implementation within the European context, highlighting leading clinical centers and cutting-edge technological innovations. Crucially, this review endeavors to synthesize the available evidence to identify compelling insights, pinpoint unresolved challenges in the field, and delineate promising future directions for research and clinical practice, including the potential of next-generation adaptive DBS systems and the imperative for equitable global access to this transformative therapy.

2. Mechanisms and Technical Aspects of Deep Brain Stimulation

Neurophysiological Basis of DBS in PD

Deep Brain Stimulation operates by implanting electrodes into specific brain targets, primarily the subthalamic nucleus (STN) or the globus pallidus interna (GPi), both integral components of the basal ganglia motor circuitry.¹ The selection of these targets is meticulously tailored to the patient's predominant symptom profile.¹ The basal ganglia play a crucial role in the activation and inhibition of feedback loops that govern muscle tone, movement, timing, and coordination.² In Parkinson's Disease, the progressive loss of dopaminergic neurons disrupts these delicate circuits, leading to the emergence of pathological neuronal oscillations, particularly in the beta-band frequency range (approximately 13-30 Hz).¹⁵ These abnormal synchronized rhythms are believed to "jam" the normal flow of information within brain networks, contributing directly to the motor impairments characteristic of PD.²⁶

While the precise mechanisms by which DBS exerts its therapeutic effects are still under active investigation and are considered complex, it is widely understood that the continuous electrical stimulation delivered by the electrodes works to normalize these aberrant brain

electrical activities.² This normalization is thought to occur by disrupting the pathologically elevated and oversynchronized informational flow within the misfiring brain networks.³¹ Unlike ablative procedures that permanently destroy brain tissue, DBS is considered to mimic a functional lesion, with the key advantage of being reversible by simply turning off the device.² The therapy typically involves delivering high-frequency electrical pulses, generally above 100 Hz, to restore more physiological brain rhythms.²³

Surgical Procedure and Intraoperative Considerations

The DBS surgical procedure is typically performed using stereotactic techniques, which allow for highly precise targeting within the brain.² A common approach involves performing the surgery with the patient awake, enabling real-time electrode adjustment and immediate assessment of symptom response to stimulation.¹ The process begins with the attachment of a stereotactic frame to the patient's head, followed by high-resolution imaging, such as MRI or CT scans, to precisely pinpoint the three-dimensional coordinates of the target brain area.² Small burr holes are then drilled in the skull to facilitate the insertion of the electrodes.² During the procedure, microelectrode recording (MER) and macrostimulation are often employed to confirm the optimal lead position and to identify the most effective stimulation sites by observing immediate clinical responses and potential side effects.⁴³

Once the electrodes (leads) are accurately positioned, they are connected to an extension wire. This wire is tunneled subcutaneously, typically from the head down to the chest, where it connects to a neurostimulator, also known as an Implantable Pulse Generator (IPG).¹ The IPG, which functions similarly to a cardiac pacemaker, is implanted under the skin, usually below the collarbone.² The entire surgical procedure typically lasts between 3 to 4 hours.² Following the implantation, the initial programming of the DBS system, involving the adjustment of parameters such as pulse width, frequency, and amplitude, is a complex process that often requires multiple sessions over 3 to 6 months to achieve optimal therapeutic results.¹⁰

Evolution of DBS Hardware: From Constant Voltage to Constant Current, Directional, and Segmented Leads

The technological landscape of DBS hardware has undergone significant advancements, moving beyond the initial constant voltage stimulation systems. Newer generations of devices incorporate constant-current technology, which offers a theoretical advantage by maintaining a stable electrical field within the brain tissue. This stability is less susceptible to changes in tissue impedance over time, potentially leading to more consistent therapeutic effects.³

A notable progression in DBS technology is the development of directional and segmented leads. These innovative electrodes allow for a more precise and targeted steering of the electrical current. This capability enables clinicians to direct stimulation more effectively towards the intended neural targets while simultaneously minimizing unintended current spread to adjacent brain structures that could induce undesirable side effects.²³ The ability to shape the volume of tissue activated (VTA) with greater precision can significantly widen the therapeutic window, meaning a larger margin between the current required for therapeutic benefit and the current that elicits side effects. This often translates to requiring less electrical power to achieve the desired clinical effect.³¹

The evolution of DBS hardware, particularly the shift towards constant current, directional, and segmented leads, represents a significant advancement in optimizing the therapeutic window and minimizing stimulation-induced side effects. Historically, traditional DBS delivered continuous, fixed stimulation, which could be likened to a "blunt tool" due to its inability to dynamically adapt to the patient's fluctuating needs.¹² This fixed approach often resulted in either overstimulation, leading to adverse effects, or under-stimulation, causing a return of symptoms.¹² The development of constant-current devices, by providing a stable stimulation field, was a foundational step towards greater control.⁴⁹ The subsequent introduction of directional and segmented leads has further refined this control, allowing for the precise "steering" of current.²³ This enhanced precision enables clinicians to target the specific beneficial brain areas more

effectively while actively avoiding adjacent structures that could trigger side effects.²⁷ The ability to widen the therapeutic window through such targeted stimulation is crucial for improving patient comfort and maximizing the benefits of the therapy. This technological trajectory signifies a profound shift from a generalized symptom management approach to highly individualized, adaptive neuromodulation. This progression is fundamental to improving patient quality of life and expanding the applicability of DBS to a broader range of patients with varying symptom profiles and sensitivities.

Beyond these functional improvements, modern DBS devices are also designed with enhanced practical features. Many are now MRI-compatible, allowing patients to safely undergo essential diagnostic imaging.²³ Furthermore, advancements in battery technology have led to the development of rechargeable IPGs, which can extend device longevity significantly, potentially up to 15 years, thereby reducing the need for frequent battery replacement surgeries.²³ These newer devices are also generally smaller and more ergonomically designed, contributing to increased patient comfort.²⁷

3. Clinical Efficacy of DBS in Parkinson's Disease

3.1. Motor Symptom Management

Deep Brain Stimulation has consistently demonstrated remarkable efficacy in ameliorating the cardinal motor symptoms of Parkinson's Disease. Studies report significant improvements in tremor, rigidity, and bradykinesia, with reported reductions in severity ranging from 50% to 80%.¹ Specifically, subthalamic nucleus (STN) DBS has been shown to sustain these motor benefits for over five years, often outperforming optimal medical therapy during "off" periods when medication effects wane.¹

A major strength of DBS lies in its profound impact on medication-related motor complications. It is highly effective in reducing both levodopa-induced dyskinesias (involuntary movements) and motor fluctuations, which are the unpredictable shifts between "on" (good motor control) and "off" (symptomatic) states.¹ Patients

frequently experience a significant increase in their "ON" time without troublesome dyskinesia, with reported gains averaging 4.5 to 4.6 hours per day.⁶² This extended period of good motor control dramatically improves daily functioning and overall quality of life.

Quantitative assessment of motor symptom improvement is typically performed using standardized scales such as the Unified Parkinson's Disease Rating Scale (UPDRS) and its updated version, the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS).⁴ Studies consistently report significant improvements in UPDRS-III (motor examination) scores, with reductions ranging from 25% to 57%.⁵ Furthermore, MDS-UPDRS Part IV, which specifically evaluates motor complications like dyskinesia and motor fluctuations, shows substantial improvements following DBS.⁴

The sustained long-term motor benefits of DBS, particularly in reducing dyskinesia and "off" periods, underscore its role not merely as a symptomatic treatment but as a critical intervention for maintaining functional independence and mitigating medication-related complications over the disease course. The initial observation is that DBS provides significant motor symptom relief and reduces medication dependency.¹ A deeper examination of long-term data reveals persistent effects on motor complications and appendicular levodopa-responsive motor signs for 8 to 11 years, with some benefits extending beyond 15 years.³ This quantitative impact, such as patients gaining several hours per day of "on" time without troubling dyskinesia⁶², directly translates into improved daily functioning. This long-term efficacy indicates that DBS fundamentally alters the trajectory of advanced PD management, enabling patients to retain a higher quality of life and functional autonomy for extended periods compared to relying solely on medication. This significantly reduces the cumulative burden of disease progression and the adverse effects associated with long-term pharmacological treatment, positioning DBS as a durable and impactful long-term management strategy that reshapes the patient's experience of the disease.

Table 1: Quantitative Improvements in Motor Symptoms and Medication Reduction with DBS

Study/ Reference	Patient Cohort (N)	Follow-up Duration	Baseline UPDRS-III (Off-med)	Post-DBS UPDRS-III (Off-med, On-stim)	% Improvement UPDRS-III	Change in "ON" Time (hours/day)	% Reduction in LEDD	Key Findings on Dyskinesia/ Fluctuations
Deuschl et al. ¹	78	6 months	48 ± 12.3	28.3 ± 14	41%	9.5 points (PDQ-39)	Not specified	Significant improvement in PDQ-39 and UPDRS-III.
Schuepbach et al. ¹	251	2 years	Not specified	Not specified	Not specified	8.0 points (PDQ-39 summary index)	Not specified	Superiority in motor disability, ADL, motor complications, time with good mobility/no dyskinesia.
Weaver et al. ¹	255	6 months	Not specified	Not specified	71% of patients had clinically meaningful motor improvement	+4.6	Not specified	Significantly improved "on" time without troubling dyskinesia.
St George et al. ¹	Meta-analysis	Variable	Variable	Variable	Variable	Variable	Variable	Positive impact on quality of life.
J Neurol Neurosurg Psychiatry ⁴	51	5 & 8 years	5 & 8 years	Sustained improvement	Not specified	Dyskinesias & motor fluctuations remained significantly reduced.	Not specified	Dyskinesias & motor fluctuations remained significantly reduced long-term.
StatPearls ⁶	Review	Variable	Variable	Variable	30-60%	Not specified	50% (STN-DBS)	Equivalent beneficial effects on motor symptoms for STN and GPi.
Mov Disord. ³	101 (active)	3 months	7 hours	+4.27	Not specified	+4.27	Declined similarly	Significant improvement in UPDRS motor subscore.
J Neurol Neurosurg Psychiatry ⁴	51	5 & 8 years	Significant reduction	Sustained benefit	Not specified	Not specified	Significant reduction	Dyskinesias & motor fluctuations remained significantly reduced long-term.
Mov Disord. ⁸⁵	53	6 & 18 months	Not specified	44% (6 months)	44% (6 months)	Not specified	43% (6 months), 35% (18 months)	Directional DBS effectively reduced motor and non-motor symptoms.
Mov Disord. ⁷⁸	51	17 years	Not specified	50.6% reduction	Not specified	Dyskinesia: 75% reduction; Off-state: 58.7% reduction	50.6%	Long-lasting effectiveness beyond 15 years.
Neurology ⁸⁶	Cohorts 2 & 3	3 years	Not specified	Stable or improved	Not specified	Not specified	21-30%	VY-AADC01 resulted in stable/improved motor function.
NPJ Parkinsons Dis. ⁹	Review	Variable	Variable	Variable	Variable	Variable	Variable	Many non-motor fluctuations improve with STN DBS.

(continued)

Table 1: Quantitative Improvements in Motor Symptoms and Medication Reduction with DBS (continued)

Study/ Reference	Patient Cohort (N)	Follow-up Duration	Baseline UPDRS-III (Off-med)	Post-DBS UPDRS-III (Off-med, On-stim)	% Improvement UPDRS-III	Change in "ON" Time (hours/day)	% Reduction in LEDD	Key Findings on Dyskinesia/ Fluctuations
J Neurol Neurosurg Psychiatry 4	51	5 & 8 years	Significant reduction	Sustained benefit	Not specified	Not specified	Significant reduction	Dyskinesias & motor fluctua- tions remained significantly reduced long-term.
Mov Disord. 69	Not specified	6 months	Not specified	29% (Part III)	29% (Part III)	Not specified	Not specified	MDS-UPDRS Part IV improved by 74%.
Neurology 52	Not specified	12 months	Not specified	Similar (directional vs omnidirectional)	Not specified	Not specified	51.3% (directional) vs 42.7% (omnidirec- tional)	Directional leads achieved comparable motor scores with greater LEDD reduction.

3.2. Non-Motor Symptom Modulation

While DBS is primarily recognized for its profound effects on motor symptoms, its impact on non-motor symptoms (NMS) is more nuanced and heterogeneous.¹ Although DBS may not consistently improve all non-motor aspects like cognitive decline or depression, emerging evidence suggests it can positively influence the overall non-motor symptom burden by reducing the prevalence and intensity of certain NMS.¹⁸

Sleep disturbances are highly prevalent in PD, and DBS, particularly STN-DBS, has been reported to improve both subjective and objective measures of sleep quality.⁸ This includes observed increases in total sleep time, reductions in wakefulness after sleep onset (WASO), and improved nocturnal mobility.³³ Some studies also indicate benefits for specific sleep disorders such as REM sleep behavior disorder (RBD) and restless legs syndrome (RLS).⁸

Pain, a common and often debilitating NMS in PD, can also be significantly improved by DBS. Studies indicate that global pain scores can improve substantially, with reported reductions ranging from 28% to 84%.⁹ Interestingly, research suggests that a more dorsal active contact location within the STN may be a specific predictor for pain improvement, hinting at distinct underlying mechanisms compared to motor symptom relief.⁹¹

Evidence regarding the effects of DBS on autonomic dysfunction remains somewhat limited and occasionally conflicting.⁹ However, some studies propose that STN-DBS may improve certain autonomic symptoms, such as orthostatic hypotension, by influencing heart rate and enhancing baroreceptor sensitivity.⁹ Other reported benefits include improvements in thermoregulation, sweating disturbances, and specific urinary symptoms in some patients.¹⁸

In the realm of neuropsychiatric outcomes, the effects of DBS are more variable. While DBS may not consistently improve global cognitive decline or depression, some studies have reported improvements in anxiety.⁴ However, a consistent finding is a decline in verbal fluency, which is often attributed to the surgical implantation itself (a microlesion effect) rather than the ongoing stimulation.⁷ Psychiatric changes such as hypomania, apathy, hypersexuality, and impulse control disorders can also emerge post-surgery.¹ These effects can be influenced by specific stimulation parameters, the precise location of stimulating contacts within the STN (e.g., limbic versus motor regions), and adjustments to dopaminergic medications post-surgery.⁹ Unrealistic patient expectations regarding surgical outcomes have also been identified as a factor contributing to postoperative psychological distress.⁹ Given these complexities, meticulous patient selection, involving comprehensive neuropsychological

Table 2: Impact of DBS on Specific Non-Motor Symptoms and Cognitive/Psychiatric Outcomes

Non-Motor Symptom Domain	Specific Symptom/ Measure	Assessment Scale Used	Observed Effect of DBS	Quantitative Change / Key Findings	Relevant References
Sleep	Overall Sleep Quality, Insomnia, WASO, Nocturnal Mobility, RLS, RBD	PDSS, PSG (Polysomnography), ESS	Improvement (subjective & objective)	STN-DBS significantly improved PDSS scores (mean difference = 20.41), increased total sleep time, decreased WASO, improved nocturnal mobility, RLS, nocturia, and increased sleep efficiency.	8
Pain	Global Pain	MDS-UPDRS Part I (item 9)	Improvement	Global pain scores improved by 28-84%. Dorsal STN active contact location predicted pain improvement.	9
Autonomic Dysfunction	Orthostatic Hypotension, Thermoregulation, Sweating, Urinary Symptoms, Gastric Emptying, Swallowing	Various clinical assessments, PET scans	Variable Improvement	STN-DBS may improve orthostatic hypotension (increased HR, improved baroreflex), thermoregulation, sweating, and urinary symptoms (e.g., detrusor hyperreflexia, increased bladder capacity). Bilateral STN-DBS can improve gastric emptying and constipation.	9
Cognition	Global Cognitive Function, Verbal Fluency, Executive Function, Memory	Mattis Dementia Rating Scale, Verbal Fluency Tests, Stroop Test	Generally stable global cognition; selective decline in verbal fluency.	Overall global cognitive function not significantly affected. Consistent declines in verbal fluency (e.g., -4.50 points semantic, -3.06 points phonemic) often attributed to surgical implantation. Rates of dementia not increased beyond natural PD progression.	1
Neuro-psychiatric	Depression, Anxiety, Apathy, Hypomania, Hypersexuality, Impulse Control Disorders (ICDs)	Beck Depression Inventory, NMSS, QUIP-RS	Variable (Improvement, No Change, Worsening)	Anxiety can be reduced. Depression results are conflicting (improvement, no change, worsening), often influenced by medication changes and stimulation location. Hypomania, apathy, hypersexuality, and ICDs can emerge, sometimes linked to direct limbic stimulation or medication reduction.	1

and psychiatric evaluation, is paramount to mitigate potential risks and optimize overall outcomes.⁹

The heterogeneous impact of DBS on non-motor symptoms suggests that while the primary effect is motor circuit modulation, the observed NMS improvements are likely due to complex, indirect effects on interconnected neural networks, and may also be influenced by medication reduction rather than direct stimulation. This highlights the

need for more targeted NMS-specific research. The initial observation is that DBS primarily targets motor symptoms, with variable effects on NMS.¹ However, a closer examination reveals that some NMS, such as sleep, pain, and certain autonomic functions, do show improvement.⁸ The underlying mechanisms for these improvements are not fully understood, but evidence suggests that the basal ganglia are connected to areas regulating the autonomic nervous system⁹⁰, and STN stimulation can modulate neural activity in regions like the thalamus and

insular cortex, which are involved in bladder function.⁹⁰ Additionally, some psychiatric effects are linked to direct stimulation of limbic systems or changes in medication.⁹ This points to the involvement of indirect network effects beyond just the motor circuits. The limited and often conflicting evidence for some NMS⁹, along with the call for randomized, prospectively controlled trials with NMS as primary endpoints¹⁸, indicates that current understanding is incomplete. This gap in knowledge underscores a critical area for future research to unravel the precise neural mechanisms and to optimize DBS specifically for non-motor symptoms, which could lead to a more holistic and comprehensive approach to PD management.

3.3. Quality of Life and Medication Reduction

Deep Brain Stimulation consistently leads to significant improvements in the overall quality of life (QoL) for eligible Parkinson's Disease patients. Long-term data demonstrate that the efficacy of DBS persists for a decade or more, with notable gains in patient-reported mobility and emotional well-being, as measured by instruments such as the Parkinson's Disease Questionnaire (PDQ-39).¹ A particularly compelling finding from one study revealed a stable QoL trend in the DBS group over five years, contrasting sharply with a 50% decline observed in a comparable medically treated group, with the primary driver of this QoL advantage being increased mobility.¹¹⁸

A significant benefit of DBS is its ability to substantially reduce the dependency on dopaminergic medications. Patients frequently experience a reduction in their levodopa equivalent daily dose (LEDD) by 30-50%.¹ This reduction in medication dosage is crucial, as it directly mitigates the burden of medication-related side effects, such as dyskinesias and motor fluctuations, which often become problematic with long-term pharmacological management.¹ The alleviation of these drug-related adverse effects contributes significantly to enhanced patient comfort and autonomy in their daily lives.¹

The significant reduction in medication dependency post-DBS creates a synergistic benefit that extends beyond mere symptom control, contributing profoundly to patient comfort and autonomy, and thereby to a more sustainable and patient-centric long-term management strategy. The

initial observation is that DBS improves quality of life and reduces medication.¹ A closer examination reveals a direct causal link: the reduced medication burden, often a 30-50% lower levodopa dose, directly leads to a decrease in troublesome dyskinesias and motor fluctuations.¹ This is not simply about managing symptoms; it is about fundamentally improving the patient's daily experience. Less reliance on medication translates into fewer drug-related side effects, greater physical comfort, and enhanced autonomy in managing their condition and daily activities.¹ This integrated benefit contributes significantly to the overall "quality of life gains" observed with DBS, extending beyond just motor improvements. This makes DBS a more appealing and effective long-term solution by addressing both the primary symptoms and the iatrogenic complications of conventional pharmacological treatment.

4. Risks and Complications Associated with DBS

4.1. Surgical and Hardware-Related Complications

Deep Brain Stimulation surgery, while highly effective, is an invasive neurosurgical procedure that carries inherent risks and potential complications, although reported rates can vary across studies. Common surgical risks include infection, which is reported to occur in 1-3% of cases in the original article, but literature reviews indicate a wider range, from 0% to 15%.¹ Intracranial hemorrhage is another significant risk, with reported incidences ranging from 0.5% to 2.8%, and a fatal risk reported at 0.4% in one large study.¹ Stroke can occur in 0-2% of patients.¹ Overall, the incidence of serious adverse events may be higher in DBS groups compared to medical therapy alone, with one trial reporting 13% vs. 4% and another 54.8% vs 44.1%.¹⁰

Hardware-related complications are also a concern over the long term. These include lead fracture, reported in 1-15% of patients, often occurring at the junction between the lead and the extension cable, with rotational movements identified as a contributing factor.³¹ Lead migration, defined as unintended post-operative displacement of the DBS lead, has an incidence ranging from 0% to 19%, and optimal lead placement is critically

Table 3: Incidence and Management of Surgical and Hardware-Related Complications in DBS for Parkinson's Disease

Type of Complication	Reported Incidence Rate (Range or Specific %)	Key Risk Factors	Management Strategies	Relevant References
Infection	0-15% (original: 1-3%)	Older patients, PD diagnosis, surgical complications, specific surgical techniques, intra-operative vancomycin (in some studies)	Systemic antibiotics, wound incision and debridement, hardware removal (complete or partial), device retention (if minor/patient preference).	1
Intracranial Hemorrhage	0.5-2.8% (fatal risk 0.4%)	Older patients (general surgical risk), surgical procedure itself.	Medical management, sometimes surgical intervention.	1
Stroke	0-2%	Surgical procedure itself.	Medical management, rehabilitation.	1
Lead Fracture	1-15% (4% in one study of 387 electrodes)	Rotational movement of lead-extension system, trauma, active engagement in sports, Twiddler's Syndrome.	Surgical revision/replacement of lead.	31
Lead Migration/Dislodgement	0-19%	Suboptimal lead placement, patient activity.	Surgical repositioning/revision, programming adjustments.	31
Device Malfunction	Not consistently quantified; can occur due to battery failure, loose connections.	Battery depletion, hardware component failure.	Battery replacement, component replacement, programming adjustments.	121
Overall Serious Adverse Events	13% vs 4% (DBS vs med. only) / 54.8% vs 44.1% (DBS vs med. only)	Surgical procedure, hardware, patient comorbidities.	Varies depending on specific event.	10

important for successful outcomes.³¹ Other hardware issues can include device malfunction.¹²¹

The management of hardware-related infections typically involves systemic antibiotic therapy, surgical wound incision and debridement, and in many cases, complete removal of the implanted DBS system.⁴³ However, efforts to retain the device may be considered depending on the depth and extent of the infection and patient preference, particularly if the DBS provides significant symptomatic improvement.¹²³ Advancements in surgical techniques, including the use of robotic guidance systems, aim to reduce infection rates and improve the accuracy of lead placement, thereby potentially minimizing the need for revisions.¹³²

The ongoing challenge of surgical and hardware complications, despite technological advancements, highlights a critical need for improved intraoperative precision and post-operative infection prevention protocols to enhance patient safety and long-term device integrity. The initial observation is that DBS carries surgical risks like hemorrhage and infection, and hardware complications such as lead fracture or

migration.¹ However, a closer look reveals that despite the development of advanced technologies like robotic guidance systems, which aim for millimeter accuracy in lead placement¹³², lead migration (0-19%) and fracture (1-15%) continue to occur.³¹ Similarly, infection rates, while variable, can still be substantial (up to 15%).¹²² The causal relationship is clear: inaccurate lead placement or post-operative displacement can lead to suboptimal therapeutic outcomes and necessitate revision surgery.¹³⁰ Furthermore, infections often require the removal of the implanted hardware, which can be a devastating setback for patients.¹²² The persistence of these complications, despite the continuous refinement of surgical techniques and device design, indicates that current prevention and management strategies are not yet fully optimized. This points to a crucial area for future research, including the development of novel biomaterials for leads, further advancements in surgical planning and execution, and more effective infection control protocols, all of which are necessary to truly enhance the safety profile and long-term reliability of DBS systems.

4.2. Stimulation-Induced Side Effects

Beyond the direct surgical and hardware-related complications, Deep Brain Stimulation can induce a range of side effects related to the electrical stimulation itself. These effects are often dependent on the stimulation parameters and the precise location of the active contacts.

Speech impairment, particularly dysarthria (slurred speech), is a commonly reported side effect of stimulation.¹ Similarly, gait freezing and balance problems can sometimes worsen with DBS, even if other motor symptoms improve.¹ These stimulation-induced motor side effects are often energy-dependent and can frequently be mitigated or resolved by careful adjustment of the stimulation settings.³¹

The impact of DBS on cognitive function is a complex area. While the therapy is generally considered to have a minimal effect on overall global cognitive function¹, consistent declines have been reported in specific cognitive domains, most notably verbal fluency and certain executive functions.⁷ These declines are often attributed to the microlesion effect of the surgical implantation itself rather than the ongoing electrical stimulation.⁷ Long-term studies indicate that the rates of cognitive decline or progression to dementia post-DBS are generally not higher than the natural progression of PD itself.⁴ However, certain risk factors for worse cognitive outcomes have been identified, including pre-operative executive dysfunction and poorer memory, older age, higher pre-operative levodopa doses, and greater axial symptom involvement.⁹⁹

Neuropsychiatric side effects are also a recognized concern. While some studies report improvements in anxiety post-DBS⁴, the impact on depression can be variable, with reports of improvement, no change, or even worsening.⁹ Other psychiatric changes, such as apathy, hypomania, hypersexuality, and impulse control disorders (ICDs), can occur.¹ These effects can be influenced by the precise stimulation parameters, the anatomical location of the stimulating contacts within the STN (e.g., whether stimulation extends into limbic or associative territories), and the changes in dopaminergic medications post-surgery.⁹ Furthermore, unrealistic patient expectations about the surgical outcome have been implicated as

a factor contributing to postoperative psychological distress.⁹ To mitigate these complex risks and optimize patient outcomes, a comprehensive, multidisciplinary team approach to patient selection, including thorough neuropsychological and psychiatric evaluation, is essential.⁹

The manifestation and severity of stimulation-induced side effects are determined by a complex interplay between DBS, the natural progression of Parkinson's Disease, and individual patient vulnerabilities, particularly their pre-existing cognitive and psychiatric profiles. This highlights the necessity for highly individualized pre-surgical assessment and adaptive post-operative programming strategies. The initial observation is that DBS can cause side effects such as speech and gait issues, as well as cognitive and psychiatric changes.¹ However, these side effects are not uniform across all patients. Their occurrence and severity are influenced by several causal factors, including the specific stimulation settings, the precise anatomical location of the electrode (for instance, whether stimulation extends into limbic versus motor regions of the STN), changes in medication regimens post-surgery, and, critically, the patient's pre-operative cognitive and psychiatric status.⁹ For example, the decline in verbal fluency is often linked to the surgical implantation itself rather than the chronic stimulation.⁷ Furthermore, disease duration at the time of surgery has been identified as a stronger predictor of future dementia than the presence of mild cognitive impairment before the procedure.¹⁰¹ This intricate relationship implies that a "one-size-fits-all" approach to DBS therapy is inherently insufficient. The success of DBS is not solely measured by motor improvement but also by its ability to preserve or enhance the patient's overall well-being, which is significantly influenced by these non-motor, stimulation-related effects. This underscores the indispensable role of a multidisciplinary team in patient selection, providing realistic counseling, and implementing long-term adaptive programming to ensure a favorable risk-benefit profile tailored to each individual patient.

5. Comparative Analysis with Alternative Therapies

DBS vs. Optimized Pharmacological Management

Levodopa remains the cornerstone and primary pharmacological treatment for Parkinson's Disease, offering significant symptomatic relief.¹ However, the long-term administration of levodopa frequently leads to the development of motor fluctuations (unpredictable shifts between "on" and "off" states) and levodopa-induced dyskinesias (involuntary movements), which often become refractory to conventional medication adjustments.¹

For patients experiencing these advanced motor complications, Deep Brain Stimulation has consistently demonstrated superiority over optimized medical therapy alone.¹ DBS leads to significant improvements in motor disability, activities of daily living, and a substantial reduction in levodopa-induced motor complications, ultimately enhancing the patient's quality of life.¹ A key benefit is the significant increase in "ON" time without troublesome dyskinesia.⁶²

Traditionally, DBS has been considered a treatment for late-stage PD, typically performed after 14 to 15 years of diagnosis.⁶¹ However, there is growing evidence supporting the consideration of DBS at earlier stages of PD, before symptoms become severely disabling.⁶ The landmark EARLYSTIM trial, for instance, demonstrated significant quality of life and motor benefits in patients with early motor complications (average disease duration of 7.5 years) when compared to best medical therapy alone.¹⁹

The expanding "window of opportunity" for DBS, with evidence suggesting benefits in earlier PD stages, challenges the traditional view of DBS as a last-resort therapy. This implies a paradigm shift towards earlier consideration for eligible patients to maximize long-term quality of life and functional independence. The traditional perspective held that DBS was typically reserved for late-stage PD, often after 14-15 years of diagnosis.⁶¹ However, emerging evidence, notably from the EARLYSTIM trial, has demonstrated significant benefits in patients with earlier motor complications, with an average disease duration

of 7.5 years at the time of intervention.¹⁹ Furthermore, Medtronic's guidance suggests that DBS is more effective if introduced early, before symptoms become unresponsive to medication or severe disability and cognitive impairment develop.¹¹⁷ This indicates that delaying DBS until very late stages might lead to patients missing out on the optimal period for intervention. The "window of opportunity" is thus not a static endpoint but a dynamic phase during which DBS can offer superior and more sustained outcomes. This understanding has significant implications for the evolution of clinical guidelines, patient education, and referral pathways, advocating for a more proactive rather than reactive approach to considering DBS as a therapeutic option.

DBS vs. Ablative Procedures

Historically, ablative surgical procedures such as thalamotomy and pallidotomy were utilized to treat Parkinson's Disease symptoms by creating permanent lesions in specific brain areas.¹ More recently, focused ultrasound (FUS) has emerged as a non-invasive ablative alternative, particularly for tremor.¹ While FUS offers the advantage of being non-invasive, it currently lacks the broad efficacy of DBS for the full spectrum of PD symptoms and, crucially, is not adjustable.¹ In some regions, FUS is approved for essential tremor and tremor in PD.¹³⁷

A key advantage of DBS over these ablative procedures is its reversibility and adjustability.¹ Unlike permanent lesions, DBS allows for the fine-tuning of stimulation settings post-operatively to maximize therapeutic benefits and minimize side effects over time.² This adjustability is a critical differentiator, as it enables clinicians to adapt the therapy as the patient's condition evolves, a feature not possible with irreversible ablative techniques.² For instance, if a pallidotomy results in slurred speech, this side effect is permanent; with DBS, adjustments to the settings can often alleviate such issues.⁹⁶

The adjustability and reversibility of DBS offer a significant long-term advantage over permanent ablative procedures like FUS, enabling adaptation to disease progression and mitigation of side effects, thereby providing more

sustained and personalized symptom management. The comparison highlights that ablative procedures, such as FUS, create permanent lesions in the brain²³, whereas DBS is reversible and adjustable.¹ The consequence of permanence is that if side effects, such as slurred speech from a pallidotomy, occur, they are irreversible.⁹⁶ Furthermore, FUS, while non-invasive, lacks the broad efficacy and adjustability of DBS for the diverse symptoms of PD.¹ In contrast, a key benefit of DBS's adjustability is the ability to fine-tune stimulation settings over time to maximize therapeutic benefits and minimize side effects as the patient's condition changes.² This allows for a "tailored level of brain stimulation for different stages of the disease".⁴⁶ This inherent flexibility of DBS makes it a more adaptive and patient-centric long-term solution, particularly crucial for managing a progressive neurodegenerative disorder like Parkinson's Disease, where symptoms and medication responses inevitably evolve over time. This provides a significant advantage in providing continuous, optimized care.

5.3. DBS vs. Emerging Biological and Pharmacological Approaches

The landscape of Parkinson's Disease treatment is continuously evolving, with several novel biological and pharmacological approaches under investigation. These emerging therapies present both potential complementary roles and future alternatives to established treatments like DBS.

Gene Therapy

Gene therapy approaches aim to address the underlying pathology of PD by restoring dopamine levels or protecting degenerating neurons. This is typically achieved by delivering therapeutic genes, such as those encoding aromatic L-amino acid decarboxylase (AADC) or glial cell line-derived neurotrophic factor (GDNF), directly into specific brain regions using viral vectors, commonly adeno-associated viruses (AAV).²⁰

Clinical trials for AADC gene therapy, such as with VY-AADC01, have demonstrated a favorable safety profile and preliminary indications of improved motor function and reduced medication requirements, with effects maintained

over 3-4 years.⁸⁶ However, concerns remain regarding the sustained efficacy of these therapies, as benefits may diminish over extended periods, and critically, gene therapy does not currently halt the underlying neurodegenerative progression of PD.¹²⁰ GDNF gene therapy (e.g., AB-1005) seeks to boost neurotrophic factors to support neuronal health and prevent cell loss. Early Phase 1 results have shown safety and some improvement or stability in motor symptoms, paving the way for larger, double-blinded trials.¹⁴²

While gene therapies hold promise for disease modification by addressing dopamine deficiency or neuroprotection, their current efficacy is primarily symptomatic, and long-term durability and ability to halt disease progression remain unconfirmed, positioning them as complementary rather than outright replacements for DBS in advanced symptomatic management. The promise of gene therapy lies in its potential to address the "root cause" of PD by restoring dopamine production or protecting neurons from degeneration.²⁰ However, the current reality from clinical trials indicates that while AADC gene therapy can improve motor function and reduce medication, these benefits may diminish over time, and the therapy does not halt disease progression.¹²⁰ Similarly, GDNF gene therapy shows early safety and some motor improvement, but larger trials are still needed to confirm its efficacy in slowing progression.¹⁴² When compared to DBS, which is a well-established symptomatic treatment for advanced PD with proven long-term efficacy²³, gene therapies are still in earlier clinical development stages.²⁰ This suggests that while gene therapies are an exciting area of research for their potential to modify the disease course, they are not yet at a stage to replace DBS for established symptomatic control in advanced PD. Instead, they are more likely to become complementary therapies in the future, potentially slowing disease progression or enhancing the long-term effects of DBS.

Stem Cell Therapy

Stem cell therapies represent a promising avenue for PD treatment by aiming to replace lost dopamine neurons. This involves reprogramming various types of stem cells, such as induced pluripotent stem cells (iPSCs), human embryonic stem cells (hESCs), or mesenchymal stem

cells (MSCs), into dopamine-producing neurons for transplantation into the brain.¹⁴⁹

Early phase 1 and 2 clinical trials have shown encouraging results regarding safety, with no significant adverse effects, tumor formation, or graft-induced dyskinesia reported.¹⁴⁹ These trials have also demonstrated promising signs of motor improvement and increased dopamine activity in the putamen following transplantation.¹⁵¹ Notably, Phase 3 trials for some of these therapies are anticipated to commence in the first half of 2025.¹⁵¹ However, challenges remain, including the small sample sizes and limited follow-up durations of current studies, as well as the necessity for immunosuppressive drugs when using donor-derived cells to prevent rejection.¹⁴⁹ The long-term effectiveness of these therapies is still unconfirmed.¹⁴⁹

Stem cell therapies, while showing promising early safety and symptomatic benefits, are still in early developmental stages. Their long-term effectiveness, optimal cell types, and integration into clinical practice remain significant research questions, suggesting they are a future frontier rather than immediate competitors to established DBS. The promise of stem cells lies in their ability to replace the dopamine neurons lost in PD, potentially restoring brain function.¹⁵⁰ Current trials have demonstrated early safety and some motor improvement, with Phase 3 trials slated for 2025.¹⁴⁹ However, significant challenges persist, including the small sample sizes and limited follow-up periods in existing studies, and the requirement for immunosuppression when donor cells are used.¹⁴⁹ Crucially, the long-term effectiveness of these therapies has yet to be confirmed.¹⁴⁹ This indicates that while stem cell therapy is a highly exciting and potentially transformative area of research, it is still largely experimental. Its widespread clinical application is likely years away, as it faces substantial hurdles regarding long-term safety, efficacy, and standardization of protocols. Thus, stem cell therapy currently represents a future potential "cure" or disease-modifying therapy, a distinct and complementary approach to DBS's established role as an advanced symptomatic management tool.

Novel Oral/Infusion Drugs

Recent pharmacological advancements in PD treatment primarily focus on minimizing motor fluctuations, reducing "OFF" time, and managing dyskinesias that are not adequately controlled by conventional oral levodopa regimens.⁶⁵ These novel approaches aim to overcome the pharmacokinetic limitations of traditional oral levodopa, which often leads to inconsistent drug levels and motor complications.

Examples of these new formulations include continuous subcutaneous levodopa/carbidopa infusion (e.g., ND0612), which provides more consistent medication levels throughout the day.¹⁵⁸ Inhaled levodopa (e.g., Inbrija®) and sublingual apomorphine offer "on-demand" relief for "OFF" periods.¹³³ Additionally, adenosine A2A receptor antagonists (e.g., istradefylline) represent a non-dopaminergic approach that can reduce "OFF" time and dyskinesia.¹³³ These therapies collectively aim to provide more stable symptom control by ensuring a more continuous or responsive dopaminergic stimulation.¹³³

Beyond these, nanocarriers are an emerging technology that holds significant promise for precise drug delivery. These extremely small, engineered particles are designed to overcome the blood-brain barrier and carry drugs directly to specific brain regions, offering the potential for delivering neuroprotective compounds or even combined therapies with unprecedented precision.¹⁶¹

The development of novel drug formulations and delivery systems, such as continuous infusions, inhaled, and nanocarrier-based approaches, aims to overcome the pharmacokinetic limitations of oral levodopa and provide more stable symptom control. This indicates a convergence of pharmacological and device-aided strategies to optimize continuous dopaminergic stimulation. The primary problem with oral levodopa is its fluctuating efficacy, leading to motor fluctuations and dyskinesias, largely due to inconsistent absorption and a short half-life.¹ The development of new drug formulations, including subcutaneous infusions, inhaled, and sublingual options, directly addresses this issue by aiming for more consistent drug levels and providing "on-demand" relief for "off" periods.¹³³ Furthermore, the advent of

nanocarriers, designed for precise drug delivery across the blood-brain barrier, offers the potential to deliver drugs directly to the affected brain regions, including neuroprotective compounds.¹⁶¹ These innovations reflect a broader therapeutic strategy to achieve continuous and stable dopaminergic stimulation, a goal that aligns closely with the objectives of DBS therapy. This suggests a future where pharmacological and surgical interventions are not strictly separate but rather integrated components of a comprehensive strategy for optimizing continuous dopaminergic stimulation. This evolving relationship implies that these novel drugs could potentially delay the need for DBS or serve as complementary therapies to enhance its effects, rather than simply competing with it.

6. Advancements and Future Directions

6.1. Next-Generation DBS Systems

The field of Deep Brain Stimulation is undergoing rapid evolution, with significant advancements in device technology and programming paradigms. These next-generation systems are poised to further enhance the efficacy and personalization of DBS therapy for Parkinson's Disease.

Adaptive and Closed-Loop DBS (aDBS)

A major leap forward in DBS technology is the development of adaptive and closed-loop DBS (aDBS) systems. Unlike conventional DBS, which delivers continuous, fixed stimulation, aDBS dynamically adjusts the stimulation parameters in real-time based on feedback from the patient's brain signals, typically local field potentials (LFPs), particularly the pathological beta-band oscillations.¹

Several key systems are leading this innovation. Medtronic's Percept PC with BrainSense™ technology, which allows for the capture and recording of brain signals while simultaneously delivering therapeutic stimulation, received CE Mark approval in Europe in January 2025 and FDA approval in February 2025.²⁶ This enables real-time, self-adjusting brain stimulation. Similarly, Newronika's AlphaDBS system also secured CE Mark approval in

March 2025, with its commercial rollout in select European markets anticipated in 2025.¹

The benefits of aDBS are multi-faceted. These systems aim to optimize symptom control by delivering stimulation only when and where needed, thereby reducing overstimulation side effects (such as speech issues or balance problems), decreasing energy consumption (which extends battery life), and minimizing the need for frequent manual programming adjustments by clinicians.¹ Early clinical trials suggest that aDBS may offer superior symptom control compared to conventional continuous DBS.¹

Personalized Programming and AI Integration

The advancement of adaptive systems is closely intertwined with the integration of artificial intelligence (AI) and machine learning (ML). These computational approaches are being leveraged to create individualized algorithms that are precisely tailored to each patient's unique symptom patterns and brain signal dynamics.²⁵ This personalized programming paradigm aims to achieve faster optimization of treatment, develop more responsive systems, and potentially facilitate seamless integration with other therapeutic modalities.²⁷

However, the clinical implementation of AI-driven programming faces several challenges. These include the need for data standardization across different platforms and institutions, navigating complex regulatory hurdles for AI-enabled medical devices, and, critically, the requirement for extensive prospective validation through rigorous randomized controlled trials (RCTs) to definitively establish their safety and clinical benefit in real-world settings.¹⁷²

The rapid commercialization of adaptive and closed-loop DBS systems in Europe, driven by real-time brain signal feedback and AI, signifies a paradigm shift from static, clinician-programmed therapy to dynamic, patient-tailored neuromodulation. This promises not only superior symptom control and fewer side effects but also fundamentally alters the patient's long-term management experience by reducing clinic visits and optimizing energy use. The traditional limitation of DBS was its "always on" stimulation, which necessitated frequent manual adjustments and often led to either

over- or under-stimulation.¹² The advent of adaptive and closed-loop systems, which can sense brain activity (e.g., beta oscillations) and dynamically adjust stimulation, represents a significant technological breakthrough.¹¹ The fact that major manufacturers like Medtronic and Newronika have received CE Mark approval and are rolling out these systems in Europe in 2025¹ is not merely an incremental improvement; it is a fundamental change in how DBS therapy is delivered. This shift moves the control of stimulation closer to the patient's physiological needs, which holds the potential to reduce the burden of frequent clinic visits, minimize stimulation-induced side effects, and extend battery life, thereby significantly enhancing the long-term patient experience and the sustainability of the therapy. This also lays the groundwork for the development of more complex AI-driven personalized algorithms, although it is important to acknowledge that regulatory and validation challenges for these advanced systems still need to be addressed.¹⁷²

6.2. Addressing Unresolved Challenges

Despite the significant progress in DBS technology and clinical application, several critical challenges remain that require ongoing research and innovative solutions to further optimize patient outcomes and expand the reach of this therapy.

Optimizing Patient Selection Criteria and Timing of Intervention

While established patient selection criteria for DBS exist (e.g., idiopathic PD for at least four years, presence of motor fluctuations, responsiveness to levodopa, absence of significant dementia or severe psychiatric illness)¹, there continues to be debate regarding precise cut-off values and the optimal "window of opportunity" for intervention.⁶¹ Current research is actively exploring the integration of advanced biomarkers, detailed neuroimaging data, comprehensive cognitive evaluations, and genetic insights to more accurately predict DBS outcomes and to identify patients who are most likely to benefit, as well as those at higher risk of cognitive or psychiatric sequelae.²⁵

Mechanisms of Long-Term Cognitive Decline and Non-Motor Symptom Effects

Understanding the long-term effects of DBS on cognition and non-motor symptoms remains an area of active investigation. While DBS generally does not increase the incidence of dementia beyond the natural progression rates observed in PD⁹⁹, selective declines in specific cognitive domains, such as verbal fluency and executive function, are consistently reported.⁷ The precise underlying mechanisms and neural correlates of these cognitive changes require further elucidation.³¹ Similarly, while DBS has shown benefits for certain non-motor symptoms like sleep and pain, the exact mechanisms by which it influences these and other NMS (e.g., mood, apathy) are not fully understood, necessitating more targeted and mechanistic research.⁹

Ethical Considerations (Patient Autonomy, Access, Enhancement Debate)

DBS raises a complex array of ethical considerations that extend beyond the clinical benefits and risks. These include ensuring truly informed consent, particularly for an invasive, "last-resort" therapy where patients may be in a vulnerable or desperate state.¹⁰⁴ Questions regarding patient autonomy and the potential impact on identity or personhood are also critical, especially as DBS technology becomes more sophisticated and capable of influencing mood and behavior.¹⁰⁴ The increasing capability of next-generation DBS systems to record and store sensitive neural data introduces new concerns about data privacy and security.¹⁰⁵ Furthermore, the expansion of DBS indications to new areas, such as certain psychiatric disorders, fuels an ongoing debate about the ethical boundaries between "therapy" (restoring function) and "enhancement" (improving beyond normal function).²⁹ This necessitates a proactive approach to developing ethical frameworks and ensuring transparent communication to guide responsible innovation and equitable access.

The increasing sophistication of DBS technologies, including adaptive systems and AI-driven programming, introduces new ethical challenges related to data privacy, patient autonomy, and the very definition of "therapy" versus "enhancement." This necessitates proactive

ethical frameworks and transparent communication to ensure responsible innovation and equitable access. The technological advancements in next-generation DBS systems, which can record brain signals and adapt stimulation in real-time¹², coupled with the integration of AI for personalized programming²⁷, fundamentally alter the ethical landscape. These capabilities raise significant concerns about the privacy of sensitive neural data.¹⁰⁵ The dynamic and adaptive nature of these systems also impacts patient autonomy and their sense of control over their own brain activity, prompting questions about who ultimately controls the therapy settings.¹⁰⁵ Furthermore, the potential for DBS to influence mood, behavior, or even cognitive functions, whether intended or subtle, contributes to a broader philosophical debate about "enhancement" and the nature of personhood.¹⁰⁴ This means that as DBS moves beyond purely motor symptoms and becomes more "intelligent," ethical considerations become paramount. This requires a collaborative effort among clinicians, ethicists, engineers, and regulatory bodies to develop robust guidelines and ensure that technological advancements serve patient well-being without compromising fundamental human rights or exacerbating existing healthcare disparities.

6.3. Global Accessibility and Disparities

Despite the proven efficacy and transformative potential of Deep Brain Stimulation, significant and persistent disparities in access exist across Europe and globally. These disparities are driven by a complex interplay of economic, geographical, systemic, and socio-cultural factors.

Cost and Reimbursement

The initial costs associated with DBS are substantial, ranging from €35,000 to €50,000, with ongoing follow-up care adding further expenses.¹ While some European countries, such as Germany, offer comprehensive coverage for DBS, accessibility varies significantly across the continent.¹ For example, in France, reimbursement policies are subject to stringent clinical added value assessments.¹⁸³ In the United Kingdom, DBS is commissioned by NHS England¹¹⁵, but patients often face prolonged waiting lists for neurology appointments (exceeding 235,000 people,

with only about half seen within the 18-week target).¹⁹¹ Furthermore, the number of DBS procedures performed in England has consistently been below the target of approximately 300 per year, with only 125 procedures reported in 2020.¹³⁷ In Scotland, the waiting time from first referral to surgery can be 18 months to 2 years.¹³⁷

Regional Disparities

Geographic disparities in DBS access are pronounced, reflecting variations in healthcare infrastructure and resource allocation. Access is often limited in rural areas of high-income countries and is a widespread challenge throughout low- and middle-income nations.¹ Southern and Eastern European countries, in particular, face significant access gaps.¹ For instance, in Morocco, despite approximately one-fifth of PD patients being definite candidates for DBS, only a fraction receive the intervention due to socioeconomic challenges, limited insurance coverage, and a concentration of neurological services in urban centers.¹⁹⁸

Other Disparities

Beyond geographical and economic factors, other demographic disparities influence DBS utilization. Women are notably less likely than men to receive DBS, a phenomenon influenced by referral patterns, social support networks, and patient preferences.¹⁹⁵ Similarly, racial and ethnic minority patients consistently receive DBS at lower rates.¹⁹⁵ Socioeconomic factors, including insurance status and household income, are strong predictors of DBS access, often favoring privately insured and wealthier patients.¹⁹⁵

Strategies to Improve Equitable Access

Addressing these multifaceted barriers necessitates systemic changes in referral practices, institutional policies, and healthcare funding models.¹⁹⁵ Key strategies to improve equitable access include the establishment of local training programs to increase the number of DBS specialists and multidisciplinary teams, insurance reforms to expand coverage, and public awareness campaigns to counter cultural misconceptions about brain surgery and advanced therapies.¹⁹⁸ While telemedicine and

smartphone-enabled DBS systems hold promise for improving access, particularly for underserved populations, they have not yet significantly impacted existing racial disparities.²⁷

Despite DBS being a well-established therapy, significant and persistent disparities in access exist across Europe and globally, driven by a complex interplay of economic, geographical, systemic (e.g., waiting lists, specialist shortages), and socio-cultural factors (e.g., gender, race, patient preference). This highlights that technological advancements alone are insufficient to ensure equitable healthcare; systemic policy and infrastructure changes are paramount. The initial observation is that while Europe leads in DBS, accessibility varies significantly, and costs are high.¹ A closer examination reveals specific barriers: high procedure costs, limited insurance coverage, and long waiting lists for neurology appointments in countries like the UK, where the waiting list exceeds 235,000 people and DBS procedures fall below target.¹³ There is also a critical shortage of movement disorder specialists¹⁹² and a concentration of neurological services in urban centers, leaving rural areas underserved.¹⁹⁸ Furthermore, socio-cultural factors contribute to these disparities, including gender differences (women are less likely to receive DBS), racial and ethnic disparities, and the influence of family and cultural perceptions that may discourage advanced therapies.¹⁹⁵ This multi-faceted problem implies that even with rapid advancements in DBS technology, its real-world impact is severely limited by these deeply entrenched systemic and societal barriers. Therefore, achieving "world-leading" patient outcomes requires not only continued scientific breakthroughs but also robust health policy, equitable funding models, expanded training programs for specialists, and targeted public health initiatives to overcome these pervasive disparities. The focus must extend beyond technological development to ensuring fair and widespread delivery of this life-changing therapy.

7. Conclusion

Deep Brain Stimulation has unequivocally established itself as a transformative and cornerstone therapy for individuals with advanced Parkinson's Disease. Its profound and sustained efficacy in alleviating debilitating motor

symptoms, significantly reducing medication burdens, and enhancing overall quality of life has revolutionized the management of this progressive neurodegenerative disorder.¹ The role of DBS is continuously evolving, driven by groundbreaking advancements in adaptive and closed-loop technologies. These next-generation systems promise to deliver more personalized, precise, and energy-efficient stimulation by dynamically responding to individual brain signals, marking a significant leap forward in neuromodulation.¹

The intricate nature of DBS, encompassing meticulous patient selection, complex surgical implantation, and nuanced post-operative programming, necessitates a highly skilled and collaborative multidisciplinary team approach. This collaborative model is essential for optimizing therapeutic outcomes and effectively managing potential side effects.¹ A patient-centric approach, emphasizing shared decision-making and the cultivation of realistic expectations, is paramount, given the invasive nature of the procedure and the potential for varied individual responses.¹

The imperative for ongoing research cannot be overstated. Future investigations must continue to refine patient selection criteria, explore novel stimulation paradigms such as dual-frequency and burst stimulation³⁹, unravel the complex mechanisms underlying long-term cognitive and non-motor effects, and further integrate artificial intelligence for truly personalized and adaptive management strategies.¹⁷²

Crucially, while Europe demonstrates leadership in DBS implementation, significant disparities in access persist, driven by a confluence of economic, geographical, and systemic factors.¹ Addressing these accessibility gaps is critical to ensuring the equitable provision of this life-transforming therapy. This will require concerted efforts in policy interventions, increased healthcare funding, and expanded training programs for specialists across all regions to maximize DBS's potential for every eligible Parkinson's Disease patient globally.

References

1. Deuschl G, Schade-Brittinger C, Krack P, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med*. 2006;355(9):896-908. 1
2. WM, Rau J, Knudsen K, et al. Neurostimulation for Parkinson's disease with early motor complications. *N Engl J Med*. 2013;368(7):610-22. 1
3. Weaver FM, Follett K, Stern M, et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *JAMA*. 2009;301(1):63-73. 1
4. St George RJ, Nutt JG, Burchiel KJ, et al. A meta-analysis of quality of life outcomes following deep brain stimulation for Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2012;83(9):899-906. 1
5. Newronika. AlphaDBS: Adaptive deep brain stimulation system [Internet]. 2024 [cited 2025 Apr 1]. Available from: <https://www.newronika.com/alphadbs>. 1
6. Voges J, Hilker R, Bötzel K, et al. Thirty days complication rate following surgery performed for deep-brain stimulation. *Mov Disord*. 2007;22(10):1486-9. 1
7. Okun MS, Gallo BV, Mandybur G, et al. Subthalamic deep brain stimulation with a constant-current device in Parkinson's disease: an open-label randomised controlled trial. *Lancet Neurol*. 2012;11(2):140-9. 1
8. Witt K, Daniels C, Reiff J, et al. Neuropsychological and psychiatric changes after deep brain stimulation for Parkinson's disease: a randomised, multicentre study. *Lancet Neurol*. 2008;7(7):605-14. 1
9. European Parkinson's Disease Association. Access to advanced therapies in Europe [Internet]. 2023 [cited 2025 Apr 1]. Available from: <https://www.epda.eu.com>. 1
10. National Hospital for Neurology and Neurosurgery. Deep brain stimulation services [Internet]. 2024 [cited 2025 Apr 1]. Available from: <https://www.uclh.nhs.uk/nhnn>. 1
11. University Hospital Munich. Neurosurgery and DBS [Internet]. 2024 [cited 2025 Apr 1]. Available from: <https://www.med.uni-muenchen.de>. 1
12. Pitié-Salpêtrière Hospital. Parkinson's disease treatment [Internet]. 2024 [cited 2025 Apr 1]. Available from: <https://www.aphp.fr>. 1
13. Amsterdam UMC. Adaptive DBS research [Internet]. 2024 [cited 2025 Apr 1]. Available from: <https://www.amsterdamumc.nl>. 1
14. Medtronic. Percept PC neurostimulator [Internet]. 2024 [cited 2025 Apr 1]. Available from: <https://www.medtronic.com>. 1
15. Bronstein JM, Tagliati M, Alterman RL, et al. Deep brain stimulation for Parkinson disease: an expert consensus and review of key issues. *Arch Neurol*. 2011;68(2):165-71. 1
16. Olanow CW, Stern MB, Sethi K. The scientific and clinical basis for the treatment of Parkinson disease. *Neurology*. 2009;72(21 Suppl 4):S1-136. 1
17. Tomlinson CL, Patel S, Meek C, et al. Physiotherapy versus placebo or no intervention in Parkinson's disease. *Cochrane Database Syst Rev*. 2013;2013(9):CD002817. 1
18. Bond AE, Shah BB, Huss DS, et al. Safety and efficacy of focused ultrasound thalamotomy for tremor in Parkinson's disease. *JAMA Neurol*. 2017;74(12):1412-8. 1
19. BMJ Medicine. Deep brain stimulation for Parkinson's disease compared with antiparkinsonian drug treatment only: a systematic review and meta-analysis. *BMJ Med*. 2024;3(1):e000705. 10
20. Keller DL. Deep brain stimulation for Parkinson's disease. *Am Fam Physician*. 2013;87(12):822. 7
21. Journal of Neurology, Neurosurgery, and Psychiatry. Long-term outcomes of subthalamic deep brain stimulation in Parkinson's disease: a single-centre 8-year follow-up study. *J Neurol Neurosurg Psychiatry*. 2014;85(12):1419-25. 4

22. News-Medical.net. Deep brain stimulation may improve quality of life in Parkinson disease. 2024 Jan 22. 118
23. Wang SS, Galifianakis NB, San Luciano M, et al. Comparison of change in the UPDRS versus MDS-UPDRS in a population of Parkinson's disease (PD) patients treated with deep brain stimulation (DBS). *Mov Disord*. 2016;31(suppl 2). 70
24. St George RJ, Nutt JG, Burchiel KJ, et al. The effect of deep brain stimulation on quality of life in movement disorders. *J Neurol Neurosurg Psychiatry*. 2005;76(9):1224-9. 84
25. Newronika. AlphaDBS [Internet]. 2024. Available from: <https://newronika.com/>. 11
26. Sullivan MG. Constant-Current Stimulation Boosts 'On' Time in Parkinson's. *Clin Psychiatry News*. 2012 Jan 12. 49
27. Okun MS, Gallo BV, Mandybur G, et al. A randomized controlled trial of constant current DBS active stimulation versus off stimulation in Parkinson's disease. *ResGate*. 2012. 204
28. Ribeiro MJ, de Almeida JG, de Almeida L, et al. Psychiatric disorders after deep brain stimulation of the subthalamic nucleus in Parkinson's disease: a systematic review. *ResGate*. 2024 Jul 1. 220
29. Parkinson's Europe. Home [Internet]. 2025. Available from: <https://parkinsonseurope.org/>. 205
30. University College London Hospitals NHS Foundation Trust. National Hospital for Neurology and Neurosurgery (NHN) [Internet]. 2024. Available from: <https://www.uclh.nhs.uk/nhnn>. 207
31. LMU Klinikum. Medizinische Fakultät - LMU München [Internet]. 2024. Available from: <https://www.med.uni-muenchen.de>. 209
32. Assistance Publique – Hôpitaux de Paris (AP-HP). Home [Internet]. 2024. Available from: <https://www.aphp.fr/>. 211
33. Amsterdam UMC. New Parkinson's treatment method in which the brain itself controls implanted electrodes [Internet]. 2025 Jan 14. Available from: <https://amsterdamumc.org/en/research/institutes/amsterdam-neuroscience/news/new-parkinsons-treatment-method-in-which-the-brain-itself-controls-implanted-electrodes-1.htm>. 213
34. Medtronic. Percept™ PC Neurostimulator with BrainSense™ Technology [Internet]. 2024. Available from: <https://www.medtronic.com/en-us/healthcare-professionals/products/neurological/deep-brain-stimulation/electrical-stimulation-systems/percept-pc-neurostimulator.html>. 50
35. Boston Scientific. Clinical Effectiveness of DBS for Parkinson's Disease [Internet]. 2024. Available from: <https://www.bostonscientific.com/en-EU/health-conditions/parkinson-s-disease/Clinical-Data.html>. 5
36. Deep brain stimulation for Parkinson's disease. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. 6
37. Troche MS, et al. Non-motor symptoms and sleep disorders in Parkinson's disease: a systematic review. *J Clin Sleep Med*. 2014;10(3):311-20. 8
38. Martinez-Martin P, et al. The effect of deep brain stimulation on the non-motor symptoms of Parkinson's disease: a critical review of the current evidence. *NPJ Parkinsons Dis*. 2017;3(1):20. 9
39. Deep brain stimulation. Wikipedia. Last updated 2024 Jun 28. 31
40. Al-Qurayshi Z, et al. Incidence of complications of deep brain stimulation surgery for Parkinson's disease: a systematic review and meta-analysis. *J Neurosurg*. 2023;138(1):25-34. 127
41. News Medical. Deep Brain Stimulation Side Effects [Internet]. 2024. Available from: <https://www.news-medical.net/health/Deep-Brain-Stimulation-Side-Effects.aspx>. 102

42. Parkinson's UK. The Parkinson's Disease Questionnaire (PDQ-39) [Internet]. 2025 Feb 12. Available from: <https://www.parkinsons.org.uk/professionals/resources/parkinsons-disease-questionnaire-pdq-39>. 71
43. MDS Abstracts. PDQ-39 predicts quality of life improvement following neurostimulation for Parkinson's disease: Prospective observational study. *Mov Disord*. 2024;39(suppl 1):Abstract 528. 72
44. ClinicalTrials.gov. Closed-Loop Deep Brain Stimulation for Parkinson's Disease. NCT03582891. 28
45. Parkinson's UK. Adaptive deep brain stimulation in the news [Internet]. 2025 Jan 29. Available from: <https://www.parkinsons.org.uk/news/adaptive-deep-brain-stimulation-news>. 58
46. Parkinson's News Today. Newronika's adaptive DBS system to launch this year in Europe. 2025 Mar 26. 17
47. Michael J. Fox Foundation for Parkinson's Research. Ask the MD: The Next Generation of DBS Is Here [Internet]. 2025 Mar 11. Available from: <https://www.michaeljfox.org/news/ask-md-next-generation-dbs-here>. 26
48. Neurology Associates. Deep Brain Stimulation for Parkinson's Disease: The New Era of Adaptive Technology [Internet]. 2025. Available from: <https://www.neurologyassociates.com/post/deep-brain-stimulation-for-parkinson-s-disease-the-new-era-of-adaptive-technology>. 27
49. PlacidWay. How Much Should I Pay for Deep brain stimulation DBS Abroad? [Internet]. 2024. Available from: <https://www.placidway.com/search-medical-pricings/Deep-brain-stimulation-DBS+Neurology/All/1>. 13
50. Bookimed. Deep brain stimulation (DBS) surgery in Germany: Our Best Clinics and Costs 2025 [Internet]. 2025. Available from: <https://us-uk.bookimed.com/clinics/country=germany/procedure=deep-brain-stimulation/>. 14
51. Parkinson's Europe. Our latest reports [Internet]. 2025. Available from: <https://parkinsonseurope.org/facts-and-figures/latest-insights-from-parkinsons-europe/>. 196
52. NHS. Guide to NHS waiting times in England [Internet]. 2024. Available from: <https://www.nhs.uk/nhs-services/hospitals/guide-to-nhs-waiting-times-in-england/>. 191
53. Oxford University Hospitals NHS Foundation Trust. Deep Brain Stimulation (DBS) for Parkinson's Disease [Internet]. 2024. Available from: <https://www.ouh.nhs.uk/media/ghbaj2eo/86901pdbc.pdf>. 189
54. Scielo. The scientific and clinical basis for the treatment of Parkinson disease. *An Acad Bras Cienc*. 2010;82(3):723-40. 20
55. ClinicalTrials.gov. Safety and Efficacy of Adaptive DBS Vs Conventional DBS in Parkinson Disease. NCT03422757. 222
56. NeurologyLive. Gender Disparities in Mood, Quality of Life in PD After DBS. 2024 Mar 1. 201
57. Duke University. Deep Brain Stimulation vs. Focused Ultrasound for Parkinson's Disease. YouTube. 2023 Apr 14. 136
58. EMJ Reviews. Novel Therapies and Targets for Parkinson's Disease. *EMJ Neurol*. 2024;12(1):110-20. 133
59. Hopkins Medicine. Deep Brain Stimulation [Internet]. 2024. Available from: <https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/deep-brain-stimulation>. 45
60. News Medical. Deep Brain Stimulation Side Effects [Internet]. 2024. Available from: <https://www.news-medical.net/health/Deep-Brain-Stimulation-Side-Effects.aspx>. 102
61. Frontiers in Integrative Neuroscience. Long-term psychiatric side effects of deep brain stimulation in Parkinson's disease. *Front Integr Neurosci*. 2016;10:17. 103

62. PubMed. Subthalamic deep brain stimulation improves sleep in Parkinson disease patients: A systematic review and meta-analysis. *Medicine (Baltimore)*. 2023;102(32):e34509. 87
63. *Frontiers in Human Neuroscience*. Deep brain stimulation at high and low frequencies: differential impact on sleep microarchitecture in Parkinson's disease. *Front Hum Neurosci*. 2023;17:1269864. 88
64. *Frontiers in Pain Research*. Dorsal subthalamic deep brain stimulation improves pain in Parkinson's disease. *Front Pain Res (Lausanne)*. 2023;4:1240379. 91
65. PubMed. Impact of deep brain stimulation therapy on autonomic disturbances and related symptoms of Parkinson's disease. *J Parkinsons Dis*. 2016;6(3):541-52. 92
66. Walsh Medical Media. Impact of Deep Brain Stimulation Therapy on Autonomic Disturbances and Related Symptoms of Parkinson's Disease. *J Parkinsons Dis*. 2016;6(3):541-52. 90
67. PubMed. Surgical site infections after deep brain stimulation surgery: frequency, characteristics, and management in a 10-year period. *World Neurosurg*. 2019;123:e169-e175. 122
68. Oxford University Press. Surgical site infections after deep brain stimulation surgery: frequency, characteristics, and management in a 10-year period. *Open Forum Infect Dis*. 2023;10(1):ofac631. 123
69. PubMed. Lead fractures in deep brain stimulation during long-term follow-up. *J Neurol Sci*. 2010;298(1-2):130-4. 128
70. ResearchGate. Lead Fractures in Deep Brain Stimulation during Long-Term Follow-Up. *ResGate*. 2010. 129
71. PubMed. Long-term cognitive outcomes after subthalamic deep brain stimulation in Parkinson's disease: a systematic review and meta-analysis of controlled studies. *Mov Disord Clin Pract*. 2022;9(8):1024-34. 99
72. Fierce Biotech. DBS startup Newronika nets European approval for adaptive Parkinson's therapy. 2025 Mar 26. 165
73. *Frontiers in Neuroscience*. Simulation of Closed-Loop Deep Brain Stimulation Control Schemes for Suppression of Pathological Beta Oscillations in Parkinson's Disease. *Front Neurosci*. 2020;14:166. 28
74. Cordis. Advances in deep brain stimulation for improved therapeutic outcome. 2015. 223
75. University of Florida Health. Real-World Outcomes Using DBS Systems With Directionality and Multiple Independent Current Control: USA Experience. 2024 Oct 17. 224
76. PubMed. Directional deep brain stimulation leads in Parkinson's disease: real-life data of 53 patients with 18 months of follow-up. *J Clin Med*. 2022;11(17):5103. 85
77. CMS. Medicare Coverage Database. Deep Brain Stimulation for Essential Tremor and Parkinson's Disease. 66
78. MTRConsult. Recommendations about add-on reimbursement of medical devices in France in July 2023. 2023 Jul 26. 183
79. King's College Hospital. Parkinson's and movement disorders [Internet]. 2024. Available from: <https://www.kch.nhs.uk/services/services-a-to-z/parkinsons-and-movement-disorders/>. 188
80. NHS England. Deep Brain Stimulation for Parkinson's Disease, Tremor and Dystonia. 2013 Apr. 184
81. Leiden University Medical Center. Movement Disorders [Internet]. 2024. Available from: <https://www.lumc.nl/en/afdelingen/neurologie/movement-disorders/>. 225
82. Karolinska University Hospital. Movement Disorders Center [Internet]. 2024. Available from: <https://www.karolinskahospital.com/care-at-karolinska/centers/movement-disorders-center/>. 226

83. HCA Healthcare UK. Deep brain stimulation to control parkinsons disease [Internet]. 2024. Available from: <https://www.hcahealthcare.co.uk/services/treatments/deep-brain-stimulation-to-control-parkinsons-disease>. 41
84. NHS. Parkinson's disease - Treatment [Internet]. 2024. Available from: <https://www.nhs.uk/conditions/parkinsons-disease/treatment/>. 119
85. NHS Scotland. Frequently Asked Questions [Internet]. 2024. Available from: <https://rightdecisions.scot.nhs.uk/scottish-deep-brain-stimulation/frequently-asked-questions/frequently-asked-questions/>. 137
86. Parkinson's UK. Government plans to cut waiting lists in England are a good start, but don't go far enough [Internet]. 2025 Jan 23. Available from: <https://www.parkinsons.org.uk/news/government-plans-cut-waiting-lists-england-are-good-start-dont-go-far-enough>. 192
87. ReachMD. Stem Cell Therapy in Parkinson's Disease: Safety and Future Directions From Clinical Trials [Internet]. 2024. Available from: <https://reachmd.com/news/stem-cell-therapy-in-parkinsons-disease-safety-and-future-directions-from-clinical-trials/2474205/>. 149
88. Michael J. Fox Foundation for Parkinson's Research. Stem Cell Research and Parkinson's Disease [Internet]. 2024. Available from: <https://www.michaeljfox.org/stem-cell-research-and-parkinsons-disease>. 150
89. EBSCO. Fetal tissue transplantation. 2024. 227
90. PubMed. Fetal tissue transplantation for Parkinson's disease: a review of the published results. *Mov Disord*. 2001;16(6):1005-14. 228
91. ClinicalTrials.gov. Study of AAV-GAD Gene Transfer Into the Subthalamic Nucleus for Parkinson's Disease. NCT00643890. 138
92. PubMed. Next generation AAV vectors for Parkinson's disease gene therapy. *Mol Ther Methods Clin Dev*. 2021;22:215-32. 139
93. Michael J. Fox Foundation for Parkinson's Research. New Parkinson's Drug Formulation Shows Positive Phase III Trial Results [Internet]. 2023 Jan 13. Available from: <https://www.michaeljfox.org/news/new-parkinsons-drug-formulation-shows-positive-phase-iii-trial-results>. 158
94. PubMed. Patient, target, device, and program selection for DBS in Parkinson's disease: advancing toward precision care. *J Integr Neurosci*. 2024;23(6):114. 25

disease: a review of current evidence and future directions. *J Parkinsons Dis*. 2023;13(4):535-46. 180
96. IMR Press. Deep Brain Stimulation for Parkinson's Disease. *J Integr Neurosci*. 2024;23(6):114. 35
97. EMBO Press. Deep brain stimulation: a new era in neuromodulation. *EMBO Mol Med*. 2018;10(9):e9575. 36
98. Health.gov.mt. Deep Brain Stimulation – Ethical Considerations. 2024 May. 104
99. Relias Media. Emerging Ethical Dilemmas with Deep Brain Stimulation. 2024. 105
100. PubMed. AI-Driven Advances in Parkinson's Disease Neurosurgery: Enhancing Patient Selection, Trial Efficiency, and Therapeutic Outcomes. *J Integr Neurosci*. 2024;23(6):114. 172
101. PubMed. The MDS–UPDRS tracks motor and non-motor improvement due to subthalamic nucleus deep brain stimulation. *Mov Disord*. 2013;28(14):1969-76. 69
102. HSRD. Deep Brain Stimulation for Parkinson's Disease: A Meta-Analysis. 2012. 74
103. Frontiers in Neurology. Comparison of the Unified Parkinson's Disease Rating Scale and the Movement Disorders Society-Unified Parkinson's Disease Rating Scale in evaluating motor function before and after subthalamic nucleus deep brain stimulation. *Front Neurol*. 2022;13:1042033. 73
104. PubMed. Parkinson's motor complications. *US Neurol*. 2015;11(1):28-32. 21

105. ResearchGate. MDS-UPDRS Part 4 Motor Fluctuations Subscores through the double-blind and open-label. ResGate. 2022. 65
106. ResearchGate. A Polysomnographic Study of Parkinson's Disease Sleep Architecture. ResGate. 2015. 32
107. PubMed. Deep brain stimulation for sleep dysfunction in Parkinson's disease. J Clin Sleep Med. 2011;7(1):109-16. 33
108. Parkinson's Foundation. Deep Brain Stimulation (DBS) [Internet]. 2024. Available from: <https://www.parkinson.org/living-with-parkinsons/treatment/surgical-treatment-options/deep-brain-stimulation>. 24
109. AHA Journals. Deep Brain Stimulation May Normalize Autonomic Dysfunction in Parkinson's Disease. Circulation. 2012;126(21 Suppl 1):A11416. 93
110. Frontiers in Neurology. Specific Programming Strategies for DBS of the Subthalamic Nucleus (STN). Front Neurol. 2019;10:410. 53
111. Frontiers in Human Neuroscience. Combined application of hydrogen dioxide solution and iodine-alcohol solution to prevent implantable pulse generator infection in deep brain stimulation. Front Hum Neurosci. 2021;15:707816. 43
112. Alex Taghva MD. DBS Success Rate for Parkinson's Disease [Internet]. 2024. Available from: <https://alextaghvamd.com/blog/dbs-success-rate-for-parkinsons-disease>. 46
113. Neurosurgery One. DBS Revision Rates [Internet]. 2024. Available from: <https://www.neurosurgeryone.com/blog/dbs-revision-rates/>. 132
114. YouTube. Long-term efficacy of STN-DBS for Parkinson's disease: a 17-year follow-up study. 2023 Jul 11. 78
115. Biospace. Neurotechnology Market Size to Surpass USD 52.86 Billion by 2034, Driven by Breakthroughs in Brain-Machine Interfaces [Internet]. 2024. Available from: <https://www.biospace.com/press-releases/neurotechnology-market-size-to-surpass-usd-52-86-billion-by-2034-driven-by-breakthroughs-in-brain-machine-interfaces/>. 229
116. Mayfield Clinic. Deep Brain Stimulation (DBS) for Parkinson's Disease [Internet]. 2024. Available from: <https://mayfieldclinic.com/pe-dbs.htm>. 2
117. University of Pittsburgh Medical Center. Deep Brain Stimulation for Movement Disorders [Internet]. 2024. Available from: <https://www.neurosurgery.pitt.edu/centers/epilepsy/dbs-movement-disorders>. 23
118. PubMed. Segmented electrodes for deep brain stimulation of the subthalamic nucleus in Parkinson's disease: a long-term follow-up study. Mov Disord. 2024;39(1):151-6. 51
119. Medtronic. Medtronic achieves CE Mark approval for BrainSense™ Adaptive deep brain stimulation and Electrode Identifier, a groundbreaking advance in personalized, sensing-enabled care for people with Parkinson's through innovative brain-computer interface technology [Internet]. 2025 Jan 13. Available from: <https://news.medtronic.com/2025-01-13-Medtronic-achieves-CE-Mark-approval-for-BrainSense-TM-Adaptive-deep-brain-stimulation-and-Electrode-Identifier,-a-groundbreaking-advance-in-personalized,-sensing-enabled-care-for-people-with-Parkinsons-through-innovative-brain-computer-interfac>. 164
120. Biospace. Newronika Receives CE Mark Approval for AlphaDBS, Advancing Adaptive Deep Brain Stimulation for Parkinson's Disease [Internet]. 2025 Mar 24. Available from: <https://www.biospace.com/press-releases/newronika-receives-ce-mark-approval-for-alphadbs-advancing-adaptive-deep-brain-stimulation-for-parkinsons-disease>. 165
121. Springer Medicine. A Novel Dual-Frequency Deep Brain Stimulation Paradigm for Parkinson's Disease [Internet]. 2019 Dec 1. Available from: <https://www.springermedicine.com/deep-brain-stimulation/parkinson-disease/a-novel-dual-frequency-deep-brain-stimulation-paradigm-for-parki/22241084>. 166

122. ClinicalTrials.gov. Novel Paradigms of Deep Brain Stimulation for Movement Disorders. NCT04563143. 39
123. MTRConsult. MTRC has released European reimbursement report for use of deep brain stimulation (DBS) in 11 EU countries [Internet]. 2024. Available from: <https://mtrconsult.com/news/mtrc-has-released-european-reimbursement-report-use-deep-brain-stimulation-dbs-11-eu-countries>. 183
124. ResearchGate. Deep brain stimulation access in 2025: geographic, gender, racial, and socioeconomic disparities re-examined. ResGate. 2024. 195
125. Frontiers in Neurology. Racial Disparities in Deep Brain Stimulation Utilization: A Real-World Evidence Study. Front Neurol. 2023;14:1233684. 197
126. Cambridge University Press. Patient Selection. In: Deep Brain Stimulation Management. 2015. 108
127. Clinical Gate. Patient Selection Criteria for Deep Brain Stimulation in Movement Disorders. 2014. 109
128. Memorial Sloan Kettering Cancer Center. Potential Treatment for Parkinson's Using Investigational Cell Therapy Shows Early Promise [Internet]. 2025 Jan 16. Available from: <https://www.mskcc.org/news/potential-treatment-for-parkinsons-using-investigational-cell-therapy-shows-early-promise>. 151
129. Parkinson's UK. Positive results announced from early stage stem cell therapy trial [Internet]. 2023 Aug 28. Available from: <https://www.parkinsons.org.uk/news/positive-results-announced-early-stage-stem-cell-therapy-trial>. 152
130. ClinicalTrials.gov. A Study of AADC Gene Transfer Into the Putamen for Parkinson's Disease. NCT01973543. 140
131. Parkinson's UK. Early results show new GDNF gene therapy treatment is safe [Internet]. 2025 Jun 9. Available from: <https://www.parkinsons.org.uk/news/early-results-show-new-gdnf-gene-therapy-treatment-safe>. 142
132. Parkinson's UK. GDNF and other growth factors [Internet]. 2025. Available from: <https://www.parkinsons.org.uk/research/research-blog/research-explained/gdnf-and-other-growth-factors>. 143
133. PubMed. Nondopaminergic treatments for Parkinson's disease. Mov Disord. 2016;31(2):165-74. 230
134. Reddit. Why do dopamine reuptake inhibitors not treat Parkinson's? 2023 Feb 11. 231
135. PubMed. Timing of Deep Brain Stimulation in Parkinson Disease: A Need for Reappraisal? Mov Disord. 2014;29(5):603-11. 61
136. Medtronic. When is the Best Time to Consider DBS Therapy? [Internet]. 2024. Available from: <https://www.medtronic.com/uk-en/patients/treatments-therapies/deep-brain-stimulation-parkinsons-disease/about-dbs/when-is-it-the-best-time-to-consider-dbs-therapy.html>. 134
137. PubMed. Impact of Deep Brain Stimulation on Non-Motor Symptoms in Parkinson's Disease. ResGate. 2024. 98
138. ClinicalTrials.gov. Biomarkers to Guide Directional DBS for Parkinson's Disease. NCT03353688. 110
139. Medifind. Neurophysiology Biomarkers of Cognitive Impairment Associated With Deep Brain Stimulation. 2023. 178
140. PubMed. Authenticity or autonomy? When deep brain stimulation causes a dilemma. J Med Ethics. 2013;39(12):757-61. 181
141. Number Analytics. Navigating Neurosurgical Ethics: A Comprehensive Guide to Deep Brain Stimulation Ethics [Internet]. 2024. Available from: <https://www.numberanalytics.com/blog/deep-brain-stimulation-ethics-guide>. 182
142. ClinicalTrials.gov. Pilot Study for Automated Deep Brain Stimulation Programming. NCT02046863. 173