

ECONOMIC EVALUATION OF THERAPIES
FOR THE TREATMENT OF MOTOR FLUCTUATIONS
IN ADVANCED STAGE PARKINSON'S DISEASE

By

QUỐC AN TĂNG

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College of Pharmacy
Rady Faculty of Health Sciences
University of Manitoba
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Thesis Abstract

Background: Up to half of all patients with Parkinson's Disease (PD) will progress to its advanced stage, when quality of life is severely hampered and treatment costs escalate. Advanced, device-assisted therapies are usually considered in these patients. Existing surgical interventions, including deep brain stimulation (DBS) and levodopa-carbidopa intestinal gel (LCIG), are invasive and difficult to access in the United States. Subcutaneous infusion therapies, namely continuous subcutaneous apomorphine infusion (CSAI) and continuous subcutaneous foslevodopa-foscarbidopa infusion (LDp/CDp) are the latest advanced therapies approved by the US Food and Drug Administration in October 2024 and February 2025, respectively. They promise to be minimally invasive alternatives to existing surgical interventions and alleviate access issues plaguing the advanced PD treatment landscape in the US. However, there is no direct efficacy comparison between subcutaneous infusions and surgical interventions. These new therapies are also costly, raising questions about their cost-effectiveness. My thesis provides the first evidence to address these questions.

Methods: First, we conducted a systematic review and Bayesian network meta-analysis of randomized clinical trials studying advanced therapies to estimate the comparative efficacy and safety of these treatments. We further evaluated whether the differences between the treatments, if there are any, are clinically meaningful. Next, we performed a cost-effective analysis to assess whether the new subcutaneous infusions offer good value for money and whether they are more economically efficient than surgical interventions.

Results: In the systematic review and network meta-analysis, we identified and analyzed 13 randomized controlled trials with a combined 2,069 participants. We found that the newly approved therapies generally fall behind existing treatments, most notably DBS. Foslevodopa-foscarbidopa is less effective than DBS at improving OFF time [mean difference (MD) vs. DBS, +1.13 hours (95% CrI: -0.01 to +2.29)] and clinical motor functions [UPDRS-III, MD vs. DBS, +2.36 points (95% CrI: -0.10 to +4.89)]. Similarly, CSAI is less effective than DBS at improving quality of life [PDQ-39, MD vs. DBS, +5.09 points (95% CrI: -0.37 to +10.67)]. However, the differences between therapies at improving OFF time and motor functions are not clinically important. In terms of safety, the risk of serious adverse effects is elevated with DBS. In the cost-effective analysis, we found that the newly approved subcutaneous infusions are not cost-effective compared with existing surgical therapies. DBS is the optimal therapy from a cost-effectiveness perspective, costing less but providing more quality-adjusted life

years (QALYs) compared to all other treatments. Infusion therapies are not cost-effective versus best medical therapy (BMT) at a willingness-to-pay threshold of \$100,000/QALY. LDp/CDp and CSAI have incremental cost-effectiveness ratios of \$1.69 million and \$1.98 million per QALY compared to BMT, respectively. Their prices would have to be reduced by 82-83% for them to be cost-effective versus BMT. However, in cases where infusion therapies are used as intermediate treatment before DBS, the novel therapies only need price reductions of 4-20% to be the best infusion option.

Conclusion: The findings of my thesis provide the first evidence on the economic value of LDp/CDp. It, also provides evidence on the value of subcutaneous infusions vs existing treatments for advanced PD in the United States. The systematic review and network meta-analysis highlighted the lower efficacy of subcutaneous infusions but also the small comparative differences between therapies. Furthermore, the cost-effectiveness analysis indicated that using DBS is cost-saving, while LDp/CDp and CSAI are not cost-effective, mainly due to high drug acquisition prices. At the same time, a modest price reduction can make subcutaneous infusions valuable options amidst limited DBS access. Altogether, the findings provided insights into the worth of eliminating barriers to accessing DBS, the economic value of novel infusion therapies as bridging treatments, and the need to negotiate price discounts for these therapies.

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CHAPTER 1

INTRODUCTION

Epidemiology of Parkinson's Disease in the United States

Parkinson's Disease (PD) is a progressive and debilitating disorder of the central nervous system. It is the second-most common age-related neurodegenerative diseases globally, only after Alzheimer's Disease (1). The disease is characterized by a continual drop in dopamine levels in the brain due to the degeneration of dopaminergic neurons in the substantia nigra (2). Clinically, it manifests as motor impairments, including bradykinesia, rigidity, resting tremors, and postural instability, as well as non-motor symptoms such as sleep disorder, cognitive impairment, or autonomic and sensory dysfunction (3).

Globally, PD is among the fastest growing neurological conditions. A March 2025 modelling study projected there would be 25.2 million PD patients worldwide in 2050, which is more than doubling 2021 figures (4). Approximately 90,000 Americans are newly diagnosed with PD each year, and this incidence rate is rising (5). In the United States, it is estimated that 1.1 million Americans are living with PD in 2024, with projections suggesting a figure of over 1.2 million patients by 2030, and a staggering 1.7 million by 2045 (5–7). Prevalence is higher in men, among those aged 65 or older, and in the White population (8). Access to healthcare is a major theme in PD treatment in the US, underscored by rising mortality among non-White populations and higher PD-related mortality in rural areas (9,10).

The physical and cognitive decline associated with PD progression inevitably leads to severe socioeconomic burden that impacts patients, their caregivers, and healthcare budgets. An April 2026 report revealed that in 2024, the annual economic impact of PD and atypical parkinsonism in the US has reached an astronomical \$82.2 billion, far exceeding a previous estimate of \$51.9 billion in 2017, and already surpassed the \$79 billion figure only expected to be reached by 2030 (7,11). The toll of PD is now expected to balloon to \$112.4 billion by 2045 (7).

Of the \$82.2 billion societal cost in 2024, \$23.8 billion was attributed to direct medical costs. This figure is comparable to 2017 estimates, and the excess medical cost (difference in medical expenses by those with PD compared to those without) decreased to \$19,644 per patient. This decrease, unfortunately, is likely due to rapid cost inflation in the non-PD comparison group (hypothesized to be from the rising popularity of high-cost treatments such as GLP-1 agonists), and not a result of a drop in PD management costs (7). On the other hand, indirect and non-medical costs (such as lost productivity or daily caregiving) accounted for the other \$58.4 billion, which nearly doubled 2017 figures. Per capita, \$40,301 was spent on each patient, while their care partners shouldered another \$6,800. These numbers are far higher than the indirect

costs of several other major diseases such as diabetes, which was estimated to be approximately \$4,200 per patient in 2022 (7,12).

Appropriately described as a “pandemic [that is] experiencing exponential growth, and no one is immune to the condition”, the shifting epidemiology of PD globally as well as in the US highlights a major public health challenge (13). At the same time, skyrocketing economic costs underscores the urgent need to review how healthcare systems should approach a chronic neurodegenerative condition such as PD. As PD progresses, costs escalate quickly. Early intervention, as well as newer therapies that better control and potentially slow disease progression, will be key to any mitigation strategies to ease future socioeconomic strain (14).

Pathogenesis and Advanced Stage Parkinson’s Disease

The transition of PD from a localized motor deficit into a debilitating, multi-system syndrome is associated with the deposition of aggregated alpha-synuclein throughout the central and peripheral nervous system (15). Under Braak’s “dual hit” hypothesis, a pathogen triggers the initial protein misfolding in the enteric or olfactory nervous systems, which then ascends to the central nervous system. As the aggregation reaches the midbrain, the loss of dopaminergic neurons triggers disease onset (15,16).

Approximately 50-60% of the neurons in the substantia nigra pars compacta (SNc) are lost by the time the first symptoms of PD emerge (17). Levodopa, a dopamine-replacing drug, is recommended as monotherapy to control motor symptoms in early-stage PD (18). Underlying progression is masked at this point, as dopaminergic therapies help stabilize motor symptoms. However, motor deterioration will continue to progress at an annual rate of approximately 2% of the maximum motor disability score, which closely mirrors the rate of SNc cell loss (16). As a consequence, the neurons’ ability to store and release levodopa continue to diminish, shortening the duration of response to levodopa and eventually mirroring its short half-life of around 90 minutes (19). The results are alterations in motor function caused by a rapid change between a therapeutic response (the ON state) and an absence of response (the OFF state), as well as larger differences in the magnitude of response between the ON and OFF state because of the lower trough levodopa concentration (19). This is motor fluctuations, a clinical feature of advanced stage PD, and an important motor complication that arises in almost 40% of PD patients after five years of first-line levodopa therapy (20).

Levodopa-induced dyskinesia (LID), the involuntary movement induced by levodopa use, is another common complication of long-term dopamine replacement therapy (21). The

pathogenesis of LID involves a combination of pre- and post-synaptic alterations. Pre-synapse, the degeneration of dopaminergic neurons in the SNc impairs its ability to buffer dopamine. As such, exogenous levodopa is converted to dopamine not only by dopaminergic neurons but also by serotonergic neurons (22). However, the latter type lacks regulatory receptors that control dopamine release. This leads to unstable levels of extracellular dopamine in the SNc (23). Post-synapse, dopamine spikes cause dopamine receptors to be hypersensitive, leading to abnormal molecular signaling and thus disrupt the SNc's ability to gate motor commands. This clinically presents as dyskinesia, and is another clinical feature of advanced stage PD (24,25). Postural instability, freezing of gait, and falls, together with several non-motor symptoms such as cognitive decline, psychosis and hallucinations are also associated with advanced stage PD (24).

Several studies have been conducted in an attempt to build a consensus on the characteristics that define advanced stage PD, however their findings have not been incorporated to clinical treatment guidelines (26,27). As such, clinical trials studying therapies for advanced stage PD often define advanced PD using a combination of motor symptoms such as motor fluctuations, dyskinesia, OFF duration, or Hoehn-Yahr (HY) staging, but the specific thresholds and criteria differs between trials (24). Notwithstanding this lack of concrete definition, studies have estimated the prevalence of advanced stage PD, ranging from 18.8% to 48.5% (28–30).

Advanced Therapies for Managing Motor Symptoms

As PD progresses, the initial therapeutic benefit of oral dopaminergic medications becomes increasingly diminished by a narrowing therapeutic window (19). This clinical transition is marked by the onset of motor fluctuations and dyskinesia. In clinical practice, one way to identify advanced disease is the “5-2-1” rule, which describes patients who take at least five daily doses of levodopa, spend at least two hours per day in the OFF state, and experience disruptive dyskinesia for at least one hour per day (31,32). The addition of further oral medications such as monoamine oxidase-B inhibitors (selegiline, rasagiline), catechol-O-methyltransferase inhibitors (entacapone), dopamine agonists (pramipexole, ropinirole, and rotigotine), or extended-release levodopa formulations may temporarily mitigate symptoms (33). For some patients, these strategies eventually fail to provide adequate symptom control (34,35). Advanced therapies, also known as device-assisted therapies, can be utilized to deliver targeted surgical neuromodulation or continuous dopaminergic stimulation (27).

Surgical neuromodulation and thermal ablation bypass pharmacotherapy by directly targeting the dysregulated SNc. Surgical options such as deep brain stimulation (DBS) and unilateral radiofrequency pallidotomy are the oldest procedures for advanced PD patients, though DBS is highly preferred due to its reversibility and has effectively superseded pallidotomy (36). Usual targets for DBS are the subthalamic nucleus (STN) and the globus pallidus internus (GPi). The INTREPID trial illustrates the long-term therapeutic efficacy of STN-DBS and showed a 36% improvement in motor function and a 22% improvement in daily living activities at five years (37). Dyskinesia scores were reduced by 70%, and medication usage decreased by 28% (37). Recently, a new approach has emerged, called adaptive deep brain stimulation, which uses real-time closed-loop sensing to dynamically modulate stimulation (38). This personalized approach aims to correct brain arrhythmias only when needed, potentially reducing side effects and increasing efficiency (38). Another option is MRI-guided focused ultrasound, which is non-surgical and involves transcranial thermal ablation of a brain target. Unlike DBS, this procedure is irreversible and mostly helps with tremor (39).

In addition to surgery, device-assisted pharmacological options can be considered. Levodopa-carbidopa intestinal gel (LCIG) or levodopa-carbidopa-entacapone intestinal gel (LECIG) provides a continuous infusion through a percutaneous tube directly into the duodenal or jejunal sections of the intestine via a portable pump, serving as an alternative to DBS (40). The latter therapy has not been marketed in the US. A meta-analysis showed LCIG significantly decreases “OFF” time (reduction of ~1.19 hours) and increases “ON” time without troublesome dyskinesia (~0.55 hours) (41).

In October 2024, foslevodopa-foscarbidopa (LDp/CDp) was approved by the US FDA, becoming the first 24-hour subcutaneous infusion therapy for the treatment of motor fluctuations in adults with advanced PD. It has been shown to improve motor fluctuations and offer potential quality of life (QoL) benefits, while maintaining a favorable safety profile (42). For the first time, US patients with advanced PD could benefit from a minimally invasive treatment without the need for surgery. Shortly thereafter, in February 2025, the US FDA also approved continuous subcutaneous apomorphine infusion (CSAI) – a therapy administered similarly to LDp/CDp. Despite having numerous important safety considerations, CSAI has been in use in Europe for over 20 years (43). In April 2026, the European Commission also approved continuous subcutaneous levodopa-carbidopa infusion, with a similar mode of administration to LDp/CDp (44).

In general, clinicians can consider advanced therapies for patients who retain a response to levodopa and lack cognitive deficits (such as dementia). Although these therapies are efficacious in reducing motor fluctuations and improving both motor symptoms and quality of life, they remain symptomatic treatments with no evidence of a disease-modifying effect (45). Considerations for patients with medical comorbidities also involve added complexity due to their increased surgical risk (34).

Although all advanced therapies are available for most patients, clear preference patterns exist among both patients and clinicians. A 2017 discrete choice experiment (DCE) survey of US patients revealed a preference for non-surgical interventions, showing that patients prefer LCIG over DBS when choosing between the two options (46). Moreover, a 2022 DCE survey of Japanese neurologists reported similar results, with a strong preference for treatments that do not require surgery (47). These suggest that the newer non-surgical treatments may be more desirable therapeutic choices.

Continuous Subcutaneous Apomorphine Infusion

While CSAI was only recently approved, the history of apomorphine itself goes back to the 19th century. It was first suggested as a possible treatment for PD in 1884 (48). However, it took nearly a century for its mechanism to be better understood, until Cotzias first demonstrated that oral apomorphine exerted powerful anti-tremor properties in parkinsonian patients and, unlike levodopa, was capable of alleviating LID (49). Early oral trials were subsequently abandoned because oral apomorphine undergoes near-complete first-pass hepatic metabolism, requiring high doses that induced reversible, dose-dependent elevations in blood urea and creatinine (49). In 1985, apomorphine demonstrated benefits when it was administered subcutaneously as a rescue therapy, which bypasses hepatic metabolism (50). Following this breakthrough, the continuous subcutaneous infusion of apomorphine got in focus.

Similar to other advanced therapies, CSAI is indicated for management of severe, persistent motor fluctuations in adult patients with advanced-stage Parkinson's disease whose symptoms cannot be adequately controlled by optimized oral or transdermal therapies (51).

Motor Efficacy

The clinical efficacy of CSAI has been established through randomized controlled trials and long-term open-label studies. In the TOLEDO trial, the primary endpoint of daily "OFF" time was evaluated using patient diaries (52). After 12 weeks of double-blind treatment, patients

randomized to CSAI experienced an absolute reduction in daily “OFF” time of –2.47 hours compared to –0.58 hours in the placebo group, representing a treatment difference of –1.89 hours per day (95% CI, –3.16 to –0.62; $p=0.0025$). Post-hoc analyses of diary data reported a reduction of –2.6 hours of “OFF” time per day for apomorphine compared to –0.9 hours for placebo ($p=0.0114$). This was accompanied by a significant daily increase in “Good” ON time of +2.8 hours for the apomorphine group versus +1.1 hours for placebo ($p=0.0188$).

The open-label, Phase 3 InfusON trial evaluated the long-term durability of this effect in a United States clinical setting (53). Reductions in “OFF” time were observed at the first titration visit, with a mean decrease of –0.9 hours per day. By the end of titration, daily “OFF” time had decreased by a mean of –2.8 hours (39% reduction from baseline). At the primary maintenance endpoint of 12 weeks, patients experienced a mean reduction in “OFF” time of –3.0 hours per day and an increase in “Good” ON time of +3.1 hours per day. These clinical benefits were sustained through 52 weeks of maintenance and remained stable throughout the 3-year extension period (53,54).

A post-hoc heat map diary analysis of 65 evaluable patients in the InfusON trial demonstrated that the longest single interval of uninterrupted “Good” ON time more than doubled, increasing from a baseline of 4.4 hours to 9.6 hours at maintenance week 12 (55). Total daily “Good” ON time increased from a mean of 9.3 hours to 12.0 hours, while total daily OFF time fell from 6.6 hours to 3.5 hours. On the Patient Global Impression of Change (PGIC) scale, 97% of patients reported clinical improvement, with 75% rating their condition as “much improved” or “very much improved” (55).

Safety

Pre-treatment is needed before initiating CSAI. Because apomorphine is a powerful dopamine agonist, especially the receptors within the medullary chemoreceptor trigger zone, starting CSAI is likely to cause nausea and vomiting (56). As such, it is necessary to first treat patients with a peripheral dopamine receptor antagonist. In the US, guidelines call for 300mg trimethobenzamide three times a day for three days before the first apomorphine dose (56). An “apomorphine challenge” test is then performed to confirm that the patient is responsive and to establish a therapeutic dose for the patient (57). Treatment can be initiated either via an inpatient stay or in an outpatient setting (51).

CSAI is associated with several systemic and localized adverse events (AEs). Apomorphine may cause dose-dependent prolongation of the QTc interval, and thus patients should be

monitored for orthostatic hypotension, particularly if they are taking concomitant hypertensive medication (56). Dopaminergic stimulation can also trigger hallucinations, confusion, and psychotic symptoms, particularly in patients with pre-existing cognitive impairment (58).

With regards to local AEs, in the InfusON trial, 93% of patients experienced at least one treatment-emergent AE, most of which were mild-to-moderate and occurred primarily during the acute titration phase (53). Dermatological complications at the infusion site represent the single most common localized AE associated with CSAI, affecting a large number of patients (44% in the TOLEDO trial and up to 63.6% in the InfusON trial) (52–54). The mechanism driving this reaction is not well understood. While mild nodules are primarily a cosmetic and comfort concern, severe, chronic nodule formation carries significant clinical risk. The development of hardened, fibrotic tissue severely limits the anatomical surface area available for needle insertion, leading to patient anxiety and the painful necessity of injecting into already tender or inflamed tissue (59). Injecting into fibrotic or severely inflamed nodules also impairs local capillary perfusion, resulting in erratic, unpredictable absorption kinetics. This erratic absorption limits the therapeutic predictability of the infusion, resulting in sudden, unexplained OFF periods and a perceived loss of efficacy (58). In severe, unmanaged cases, localized tissue trauma can progress to necrotic skin changes, ulceration, and secondary bacterial infections (such as abscesses or cellulitis) requiring surgical debridement or systemic antibiotic therapy (58,59).

Foslevodopa/Foscarbidopa: A New Non-Surgical Therapy for Advanced PD

The development of continuous subcutaneous levodopa-based infusions has gone through over two decades of research and navigating regulations. While both LCIG and LDp/CDp received orphan designation from the US FDA in 2000 for the treatment of late-stage PD, only LCIG received approval in 2015, while it took until 2024 for LDp/CDp to be marketed in the European Union and the US (60). Nevertheless, LDp/CDp is the first and currently the only 24-hour subcutaneous infusion approved for use in the US.

LDp/CDp is delivered via an ambulatory infusion pump, utilizing single-use syringes to deliver a constant medication infusion over a 24-hour period (61). Initiating therapy requires converting all oral levodopa-containing formulations and COMT inhibitors to an equivalent dose of subcutaneous foslevodopa (62). An analysis of discontinuation patterns highlight the importance of structured, conservative titration (63). Pharmacokinetic evaluations comparing patients who successfully maintained therapy against those who discontinued revealed a

distinct pattern of rapid, non-optimized rate escalations in the discontinuation group (63). Despite these higher doses and elevated blood levels, this cohort showed no corresponding improvement in motor symptoms (63). The difference between OFF- and ON-state MDS-UPDRS part III scores was lower in the discontinuation group (mean 21.1) compared to the continuation group (mean 30.4), indicating that rapid rate escalations during the optimization phase do not resolve underlying motor symptoms but significantly increase the risk of systemic side effects, ultimately leading to early treatment discontinuation (63).

Motor Efficacy

The safety and efficacy of foslevodopa-foscarbidopa have been established through a clinical trial program consisting of the M15-736 and M15-741 phase III studies, alongside real-world evidence from the observational ROSSINI study (42,64,65).

The pivotal M15-736 study was a 12-week, randomized, double-blind, double-dummy, active-controlled trial designed to compare the efficacy and safety of continuous subcutaneous infusion of foslevodopa-foscarbidopa against oral immediate-release carbidopa-levodopa (IR LD/CD). The trial randomized 141 patients with advanced Parkinson's disease across 80 sites in the United States and Australia (42). Motor states were assessed using patient-maintained home diaries normalized to a typical 16-hour waking day (42). Treatment with LDp/CDp demonstrated statistically significant increases in “Good” ON time (MD +1.75 hours, 95% CI +0.46 to +3.05) and reductions in daily “off” time (MD -1.79 hours, 95% CI -3.03 to -0.54). Statistically significant improvements were also observed in health-related quality of life (PDQ-39, MD -4.1 points, $p=0.047$) and sleep quality (PDSS-2, MD -5.4 points, $p \leq 0.001$), however only sleep quality improvements reached its minimally clinical important difference threshold (66). Differences in the motor examination scores (MDS-UPDRS Part III) also did not reach statistical significance between the arms, as both groups showed similar motor improvements during ON states (42).

The M15-741 study is a single-arm trial that evaluated the 52-week safety, tolerability, and clinical durability of 24-hour daily continuous subcutaneous infusion of foslevodopa-foscarbidopa in 244 patients with advanced Parkinson's disease (64). Key clinical outcomes at 52 weeks included a 3.5-hour reduction in OFF time, a 3.8-hour increase in “Good” ON time, and a decrease in proportion of patients experiencing morning akinesia from 77.7% to 27.8% (64).

Interim data of the ongoing observational ROSSINI study provided real-world validation of the trials (65). At 6 months of follow-up, patients treated in routine clinical practice experienced a mean reduction in "off" time of −2.7 hours and a reduction in dyskinesia duration of −1.7 hours (65). In contrast to the M15-736 trial, the ROSSINI study recorded a significant real-world improvement in the acute motor examination, with a mean improvement of −5.3 points on the MDS-UPDRS part III (65). Patients also reported improvements in sleep symptoms (PDSS-2 improved by −6.0 points), pain scores, freezing of gait, and gastrointestinal dysfunction (65).

Safety

In the M15-736 trial, the rate of localized infusion-site reactions was significantly higher in the subcutaneous infusion arm than in the oral therapy arm, with reactions reported in 62.2% vs. 7.5% of patients, and infections in 28.4% vs. 3.0% of patients (42). Among patients who discontinued the trial due to adverse events (21.6% in the active arm vs. 1.5% in the oral arm), the most common causes were localized site issues: infusion-site cellulitis (5.4%), infusion-site pain (4.1%), and infusion-site bruising, hemorrhage, or edema (each 2.7%) (42). Interestingly, the frequency of falls was lower in the infusion arm compared to the control arm. Finally, there is an increased risk for hallucinations and psychosis, consistent with high-dose dopaminergic therapy (42).

Recently, the FDA has mandated updated safety warnings for all levodopa-carbidopa formulations regarding the risk of vitamin B6 (pyridoxine) deficiency and associated seizures (67). The risk of seizures appears dose-dependent: all reviewed seizure cases involved daily levodopa doses exceeding 1,000 mg, with doses above 1,500 mg associated with a faster onset of deficiency symptoms. Because advanced Parkinson's patients on subcutaneous infusion often receive doses well above these thresholds, clinicians must evaluate baseline vitamin B6 levels before starting therapy, monitor them periodically during treatment, and prescribe pyridoxine supplements as needed (67).

Potential Economic Impacts of Newly Approved Therapies

Historically, progressing to advanced stage disease required invasive surgical procedures to manage, such as the neurosurgical implantation of a DBS device or the surgical placement of a percutaneous endoscopic gastrostomy with a jejunal tube LCIG infusion (68). Access to these therapies in the US, however, is limited. Between 2018 and 2020, less than 2,500 (or 2%) of the 110,000 patients with advanced PD under Medicare received surgical therapies (69).

Continuous subcutaneous infusions offer an effective, non-surgical intermediate step in the advanced therapeutic pathway, bridging the gap between oral therapeutics and invasive surgical procedures (70,71). Access to LDp/CDp, in particular, is being pushed across the world (72,73).

However, in spite of the promised benefits, from a cost perspective, the new infusion therapies involve high ongoing medication costs, while using DBS requires high upfront costs but is amortized by relatively lower recurring treatment costs (69,74). This is especially acute in the US where brand-name drug prices are usually unattainable out-of-pocket for patients. With ballooning healthcare costs, payers must also evaluate the economic value of these therapies against existing surgical options. The introduction of subcutaneous infusions therefore raises the question of whether these new therapies are cost-effective. Despite the importance of developing strategies to ease financial strain on patients and healthcare budgets, there is no established evidence on the economic value of subcutaneous infusions for advanced PD.

Thesis Objectives

My thesis had two objectives. First, I performed a systematic review and network meta-analysis of clinical trials studying advanced therapies to examine the comparative efficacy and safety of these therapies. Second, I conducted a cost-effectiveness analysis to examine whether the health benefits of CSAI and LDp/CDp would justify their costs when compared with existing surgical options.

CHAPTER 2
ECONOMIC EVIDENCE
ON ADVANCED PARKINSON'S THERAPIES

A total of 33 economic evaluations of advanced therapies for PD were identified and synthesized in this literature review (**Table 1**). The earliest analysis dated back to 2001, with a cluster of activity in the mid-2010s. Starting from 2020, more geographically diverse analyses appeared, reflecting the implementation of advanced therapies into practice and the maturation of health-technology assessment requirements across jurisdictions.

Overview of Included Studies

Eighteen out of 33 studies analyzed DBS, representing a majority of the existing literature (75–92). This reflects both its longer clinical usage and the volume of randomized evidence available. LCIG, sometimes reported as intrajejunal levodopa infusion (IJLI), duodenal or intraduodenal levodopa infusion (DLI/IDL), and, in the United States, as carbidopa-levodopa enteral suspension (CLES), is the subject of nine evaluations (93–101). CSAI is the main focus of one evaluation (74), and it is additionally a comparator within four multi-therapy analyses that compared two or more advanced therapies against one another (74,102–104). Two analyses looked at LDp/CDp, although both are only cost analyses (105,106).

The patient cohorts modelled or observed are consistent in their clinical disease state. The majority target advanced PD, characterized by Hoehn and Yahr (HY) stages 3-5, levodopa-refractory motor fluctuations, and a substantial proportion of the waking day spent in the OFF state, with mean baseline ages in the late fifties to mid-sixties. Two analyses looked at earlier intervention, using population from the EARLYSTIM trial (mean age 52 years) to test the value of DBS before the disease progressed to the advanced stage (85,86).

On the other hand, methodological quality and study design are heterogeneous, which affects the interpretation of results. This review comprises (i) model-based cost-utility analyses, which constitutes the majority and provides the most decision-relevant estimates for long-term treatment; (ii) trial-based evaluations conducted alongside randomized or prospective studies, which have strong internal validity but short follow-up (81,87); (iii) small real-life or before-and-after empirical studies, they are valuable as a source of real-world evidence but can be statistically fragile due to small sample sizes (78,82,97,98); (iv) cost analyses without a cost-per-benefit ratio, which helps inform the cost landscape but cannot evaluate the value for money (76,77,104,106). The majority of the evidence base is sponsored by industry, and there is a lack of true head-to-head device comparisons. As such, the overall quality of evidence is best described as moderate and heterogeneous, and results should be interpreted as guiding posts rather than precise conclusions.

Overview of Models Used

A majority of evaluations used the Markov state-transition model (79,80,83–86,88,91–93,96,99,102,103). Several analyses adopted alternative structures suited to their decision problem or data. Decision-tree models are used to compare discrete treatment pathways over a short horizon (89,90), or where the source evidence is a two-year decision-analytic dataset (94). A semi-Markov process is employed in the 2001 evaluation to capture duration-dependent transitions into nursing homes and mortality (75). An expert panel-driven cost model supports the SCOPE cost analysis (104). A cost-minimization analysis underpins the LDp/CDp reimbursement review by Canada's Drug Agency (CDA, previously CADTH), in which efficacy equivalence to LCIG is assumed and only differential costs are compared (106). A group of evaluations used no model and instead derive incremental costs and benefits by direct empirical calculations from prospective studies or trial patient-level data (78,81,82,87,97,98). Three studies are cost comparisons (76,77,106), and one is a review of HTA submissions based on a manufacturer's Markov model (95).

Despite the diversity in authorships, there is a recurrence of a small number of model lineages. The Markov structure accepted by the UK National Institute for Health and Care Excellence (NICE) – defined by the classification of both HY stages and percentage OFF time – can be traced back from many evaluations of DBS and infusions alike. Over time, it expanded from twelve health states (96) to twenty-one (80,83,91), and finally to twenty-five health states plus an absorbing death state (93,99–101). There is also an UPDRS-based algorithm developed by Fundament et al. (85), which is later applied in an Egyptian setting (92). Finally, a 6-state Markov model was first used in a German setting (79), which was later adapted in an early-stage PD analysis (86) and also modified in a Japanese evaluation (84). The prevalence of only a handful of structures enhances comparability across jurisdictions, but at the same time propagates structural assumptions, and, where the underlying cost and utility inputs are also shared (as with the Adelphi-DSP regression values used across many manufacturer-funded infusion studies), sources of bias may be correlated across supposedly independent analyses.

Modelling Approaches

Two complementary scales are used to define health states. First, disease progression is mapped to HY staging. Second, clinical severity is represented by the proportion of the waking day spent in the OFF state, which is typically partitioned into OFF 0 through OFF IV (corresponding to 0%, 1-25%, 26-50%, 51-75%, and 76-100% of waking hours) and adjusted

to a 16-hour waking day. Most models combine these two scales, classifying each HY stage by its OFF time partition to generate state structures containing 12 to 26 health states. Utilities are most commonly derived from the EQ-5D, generally obtained by mapping disease-specific Parkinson's Disease Questionnaire-39 scores (PDQ-39) onto the generic EQ-5D index. Scandinavian evaluations prefer the 15D instrument (94,98), while the US Veteran Affairs study used the Quality of Well-Being scale (81). Several LCIG evaluations also used the Adelphi-DSP data to calculate the utility decrement in each step increase in HY stage and OFF partition (93,99,101).

Cycle lengths range from quarterly (88) to annual cycles (93), but the most common length is six months. Discounting practices are consistent with national conventions: 3.5% per annum for both costs and benefits in the UK (80,85,96,100,101), 3% in German, Swedish, and US analyses (79,83,86,93,94). The Irish evaluation used a 4% discount (99), while the DBS and focused ultrasound comparison in the Canadian setting used a 1.5% rate (90). Sensitivity analyses typically vary this rate from 0-7%.

Choice of time horizons is the most influential structural decision, and the literature is clear on its consequences. Horizons span an order of magnitude, from one year in the prospective Spanish and Norwegian studies (78,98), through two to three years in the Hong Kong, US VA, and Swedish decision-tree analyses (81,82,94), to five years (80,103–105), ten to fifteen (85,88,91,92), and twenty-year or lifetime horizons (75,79,83,93,96,99–101). Because the cost of DBS is especially front-loaded, there is a consistent inverse relationship between horizon length and the incremental cost-effectiveness ratio (ICER) of DBS. This is most visible in the PD SURG trial-based analysis, where the ICER fell from £468,582 per QALY at one year to £45,180 at five years before rising again to £70,537 at ten years as device-replacement costs recur (87).

Interventions and Comparators

This review focuses on four main interventions. DBS is the most extensively studied, and analyses predominantly examine STN-DBS, with GPi-DBS examined only in the US VA study (81). LCIG, CSAI, and the most recent LDp/CDp comprises the other three interventions. This review also includes two ablative procedures as comparators against DBS: radiofrequency ablation (89) and magnetic-resonance-guided focused ultrasound (MRgFUS) thalamotomy (90).

In the vast majority of studies, the comparator is best medical therapy (BMT), or the equivalent standard of care (SoC) or optimized oral pharmacotherapy. In smaller empirical studies,

patients act as their own controls and pre-initiation BMT is compared to post-initiation advanced therapy (76,77,82,98). This within-patient design helps control for individual heterogeneity, however it also confounds the treatment effect with disease progression. A recurring assumption in the infusion analyses is that BMT patients can derive no further improvement from treatment on the rationale that they have already exhausted oral options (93). This leads to an asymmetrical structure that favors the active arm and thus should draw attention.

True head-to-head comparisons between competing advanced therapies remain the principal evidence gap. Only a handful of analyses compared two or more active therapies: the US VA study contrast STN with GPi-DBS (81); Walter and Odin model CSAI against LCIG and DBS (74); while Vivancos-Matellano et al. and Norlin et al. analyzed DBS, LCIG, and CSAI simultaneously against BMT (102,103); the procedural decision-tree analyses pit DBS against ablation (89,90); and the Canadian reimbursement review sets LDp/CDp against LCIG by cost-minimization, although the agency cautioned that omitting both DBS and BMT as comparators leaves the broader cost-effectiveness of LDp/CDp undetermined (106). Even so, these comparisons are indirect, as each active therapy is evaluated separately based on their pairwise efficacy with BMT, rather than on a common efficacy background. Thorlund et al. have shown that just relying on pairwise efficacy comparisons can exacerbate uncertainty in cost-effectiveness estimates and recommend using estimates from a network meta-analysis (107). As such, any existing ranking of the advanced therapies against one another are made uncertain.

Results

Deep Brain Stimulation

Among model-based evaluations conducted over long horizons, the cost-effectiveness of DBS versus BMT is remarkably stable and favorable. The foundational 2001 US semi-Markov analysis reported an ICER of \$49,194 per QALY (75); the subsequent Medicare-perspective Markov model returned a substantially lower \$23,404 per QALY and remained below \$50,000 across every scenario examined (83). The two UK analyses produced close figures of £20,678 (for advanced-stage PD) (80) and £19,887 per QALY (for early complications PD) (85), both comfortably within the NICE £20,000–£30,000 range. The German models were the most favorable of all, at €6,700 per QALY with DBS dominating medical therapy under several sensitivity assumptions (79) and €22,700 per QALY when intervention was modelled at an earlier disease stage (86). The Asian evaluations reinforced this pattern, with Japan at

approximately JPY 3.1 million (~\$25,600) per QALY (84), Taiwan at \$69,033 per QALY over a ten-year horizon (88), and China at CNY 213,544 (~\$32,550) per QALY, the latter sitting marginally above the national threshold but within its 95% confidence interval and therefore judged broadly cost-effective (91).

Trial-based and short-horizon evaluations temper this optimism. The PD SURG analysis found DBS not cost-effective at one year (£468,582 per QALY), with cost-effectiveness becoming plausible only on five-year extrapolation (£45,180) before deteriorating again to £70,537 at ten years (87). The Hong Kong prospective study likewise found the first-year ratio prohibitive, improving to a two-year figure of \$62,846 per EQ-5D unit (82). The US Veterans Affairs analysis, uniquely a target comparison rather than a comparison against BMT, found GPi and STN stimulation economically similar, supporting the view that surgical target should be selected on clinical rather than economic grounds (81). Procedural decision-tree analyses positioned DBS favorably against ablative alternatives, with bilateral DBS dominating radiofrequency ablation and identified as the most cost-effective procedure overall (89). Meanwhile, in tremor-dominant PD, DBS remains competitive with MRgFUS thalamotomy, with an ICER of \$56,503 per QALY (90). The Egypt analysis, performed in a lower-middle income setting, stands apart in the evidence base, with DBS returning an ICER of EGP 830,726 (~ \$18,322) per QALY which, while modest by high-income standards, exceeded the national cost-effectiveness threshold and rendered DBS not cost-effective (92).

Taken together, the DBS evidence indicates a therapy whose high front-loaded costs of implantation and pulse-generator are progressively offset by sustained utility gains from OFF-time and H&Y improvement and by reductions in dopaminergic drug expenditure, over a sufficiently long horizon. Cost-effectiveness is therefore most sensitive to horizon length, device replacement frequency, and patient age at implantation, with the EARLYSTIM-based analyses extending the favorable conclusion to earlier intervention (85,86).

Levodopa-Carbidopa Intestinal Gel

The economic profile of LCIG is sharply polarized in the literature. Long-horizon evaluations cluster around or within conventional thresholds: the original UK analysis reported an ICER of £36,024 per QALY, modestly above the NICE ceiling (96); the updated English NHS model returned £23,649 per QALY, placing the therapy within the NICE range (101). The Irish evaluation reported €26,944 per QALY, within the higher Irish drug threshold of €45,000 (99). The UK cost-utility analysis by Kalabina et al. reported LCIG to have an ICER of £52,110 per

QALY, which is above the standard threshold, but the cost-effectiveness conclusion was on the basis of an orphan-drug threshold framework, which allowed the ICER to fall within this relaxed threshold (100). The most favorable result is the US evaluation, which adapted the English model to the US payer setting and populating it with real-world registry and physician-survey data. It reported an incremental cost of only \$6,611 against a QALY gain of 0.86, yielding an ICER of \$7,711 per QALY, with LCIG dominant in a more severe (HY3+/OFF 51%+) population, and a 92% probability of cost-effectiveness at a \$100,000 WTP threshold (93).

By contrast, independent and real-life evaluations place LCIG well beyond any conventional threshold. The Swedish decision-analytic model derived from the DIREQT dataset reported an ICER of approximately SEK 6.1 million (~ \$816,000 in 2004 USD) per QALY (94); the Norwegian real-life prospective study returned NOK 9.2 million (~ \$1.65 million in 2008 USD) per QALY and concluded the therapy was not cost-effective despite genuine functional improvement (98); and the Swedish value-based-pricing case study documented an ICER of roughly SEK 1 million per QALY across iterative HTA submissions, with the therapy ultimately judged not cost-effective at the requested price (95). The small Bulgarian within-patient study is the outlier in the favorable direction, but its conclusion rests on annual per-patient cost falling below national GDP per capita in a cohort of only twelve patients with a rare akinetic phenotype and so is of limited generalizability (97).

The contrast between an ICER of \$7,711 per QALY in the manufacturer-funded US model (93) and figures of SEK 1-6 million or NOK 9.2 million per QALY in the independent and real-life European analyses (94,95,98) is a striking discrepancy in this review, and it cannot be explained by clinical efficacy alone. It is driven instead by the high recurring cost of the levodopa-carbidopa cassette, which the long-horizon models offset against substantial modelled reductions in emergencies, hospitalization and professional-care costs, which the shorter, observed data analyses cannot. The high recurring medication costs are also offset against sustained OFF time benefit, which is a highly influencing and difficult-to-substantiate assumption. The choice to fall back to orphan-drug reasoning and modified thresholds could be an acknowledgement that, without such offsets and cost discounts, the therapy sits at or beyond the margin of conventional cost-effectiveness (100).

Subcutaneous infusions (CSAI and LDp/CDp)

The subcutaneous infusion evidence is sparse. It suggests that CSAI is economically favorable. The single dedicated cost-utility analysis reported an ICER of £6,440 per QALY for CSAI vs

BMT in the UK, which is the lowest incremental ratio for any infusion therapy in the entire review. The study also found that CSAI dominated DBS, while LCIG was the least cost-effective comparator, with an LCIG vs CSAI ratio of £244,685 per QALY (74). The Spanish disease-history model corroborated the favorability of CSAI, reporting €38,249 per QALY, between DBS (€31,956) and LCIG (€75,206) (102). CSAI is attractive due to its comparatively low incremental cost, its lesser invasiveness relative to DBS and its lower medication cost relative to LCIG. However, this favorable picture is supported by essentially one manufacturer-funded study and should be independently corroborated in further evaluations.

The subcutaneous foslevodopa/foscarbidopa (LDp/CDp) evidence is even more recent and methodologically distinct. A 2025 societal impact analysis built upon the NICE-accepted cost-utility Markov structure reports net societal savings rather than an ICER. The study notes that NICE and the Scottish Medicines Consortium had already accepted LDp/CDp as cost-effective under a confidential commercial arrangement (105). The economic value of LDp/CDp in the study is expressed in terms of avoided OFF-time months and societal cost offsets, which cannot yet be compared with the QALY-based ratios reported for the established therapies. A 2023 independent appraisal comes from the Canadian reimbursement review, which is a cost-minimization analysis comparing LDp/CDp with LCIG over a twenty-year horizon from the public payer perspective (106). Because the two products are priced identically and the sponsor assumed equivalent efficacy, the subcutaneous formulation emerged as modestly cost saving by C\$2,453 per patient in the first year, which was driven entirely by its avoidance of the LCIG surgery, with no further cost difference thereafter. The CDA accepted this direction but emphasized that a cost-minimization framework is uninformative if the therapies differ in efficacy or safety, and that the cost-effectiveness of LDp/CDp against both DBS and BMT remains unknown (106).

In aggregate, the literature supports the conclusion that advanced therapies, in particular DBS, are generally cost-effective relative to BMT in high-income settings when evaluated over long horizons. DBS emerges as the most consistently favorable therapy, with lifetime ICERs clustering well within accepted thresholds across the US, the UK, Germany and several Asian systems. LCIG occupies a more polarized position: long-horizon model-based analyses funded by the manufacturer resulted in ICERs within thresholds, whereas independent and real-life evaluations, particularly the Scandinavian studies, place it far beyond any conventional threshold. The CSAI evidence is favorable, though it is sparse and only in European settings. LDp/CDp evidence remains nascent and is framed around cost savings rather than an ICER.

Across therapies, three main drivers of value emerge: the time horizon adopted, the magnitude of utility gain from OFF-time reduction, and the upfront and recurring costs. Small-sample, real-life, and trial-based evaluations consistently return less favorable ICERs than long horizon models, reflecting both the front-loading of costs and the uncertainty in extrapolating observed efficacy data. Also, a therapy deemed cost-effective throughout the high-income world can fall outside the local cost-effectiveness threshold, as demonstrated by a DBS analysis in the Egyptian setting (92). This exposes an affordability gap that must be closed not by clinical evidence, but by pricing policy.

Knowledge Gap and Thesis Contribution

My literature review identified several previous studies that examined aspects of costs related to treatment with advanced therapies for PD. No study has examined the economic value of newly approved subcutaneous infusions, CSAI and LDp/CDp, compared to existing surgical therapies, DBS and LCIG. Furthermore, no studies have looked at the economic positioning of infusion therapies in a treatment landscape with numerous barriers to access surgery. My thesis aims to provide the first evidence to address this knowledge gap. Chapter 3 contains a systematic review and network meta-analysis of trials studying advanced therapies, in order to assess their comparative efficacy and safety, as well as providing a common efficacy base to compare their economic value. Chapter 4 is a cost-effectiveness analysis that assesses the value of newly approved subcutaneous infusions to each other and to surgical therapies in the treatment of advanced PD, and also the value of infusion therapies in an environment where access to surgery is limited.

Table 1. Cost studies of advanced therapies for PD

First author's name, year of publication	Target Population	Analysis Type	Perspective, Time horizon	Model Type	Interventions vs Comparators	ICERs	WTP threshold	Conclusion	Funding Source
Tomaszewski and Holloway 2001 (75)	Advanced PD	CUA	US society, lifetime	Semi-Markov decision model	DBS vs BMT	\$49,194/QALY, can dominate or be over WTP in scenarios	US\$50,000-100,000 per QALY	DBS may be cost-effective	No funding
Gerzeli et al., 2002 (76)	Advanced PD	Cost analysis	Italian society, post-implant follow-up	Cost comparison; no model used	DBS vs pre-DBS BMT (within-patient)	Post-implant cost offsets reported	Not applicable	DBS is economically advantageous	Industry
Meissner et al., 2005 (77)	Advanced PD	Cost analysis	German public payer, 02 years	Retrospective cost analysis	DBS vs pre-DBS BMT (within-patient)	Small utility difference	Not applicable	DBS cheaper from 2 nd year, long-term value uncertain	Industry
Valledeoriola et al., 2007 (78)	Advanced PD	CEA + CUA	Spanish healthcare system, 01 year	Direct calculation; no model used	STN-DBS vs BMT	€34,389/QALY	€30,000 per QALY	DBS efficient as ICER within acceptable limit	Not stated
Dams et al., 2013 (79)	Advanced PD	CUA	German public payer, lifetime	Markov, 6 states (HY-off)	STN-DBS + BMT vs BMT	€6,700/QALY, DBS dominates in some scenarios	€32,000 per QALY	DBS cost-effective, better with longer horizons	Public
Egginton et al., 2014 (80)	Advanced PD	CUA	UK NHS, 5 years	Markov, 21 states (HY + OFF)	DBS + BMT vs BMT	£20,678/QALY	£30,000 per QALY	DBS cost-effective	Industry
Stroupe et al., 2014 (81)	Advanced PD	CEA	US VA + society, 03 years	Trial-based evaluation	GPI-DBS vs STN-DBS	Societal: \$100,355/QALY Payer: \$54,129/QALY	US\$100,000 per QALY	Costs and QALYs similar between DBS surgical sites	Public
Zhu et al., 2014 (82)	Advanced PD	CEA	Hong Kong public payer, 02 years	Direct calculation; no model used	DBS vs pre-DBS BMT (within-patient)	\$62,846/EQ-5D unit	US\$50,000 per QALY	DBS cost-effective as result is in upper end of threshold	Public
Pietzsch et al., 2016 (83)	Advanced PD	CUA	US Medicare, 10 years	Markov, 21 states (HY + OFF)	DBS + BMT vs BMT	\$23,404/QALY; <\$50k in all scenarios	US\$50,000 per QALY	DBS cost-effective; better with younger age	Industry

First author's name, year of publication	Target Population	Analysis Type	Perspective, Time horizon	Model Type	Interventions vs Comparators	ICERs	WTP threshold	Conclusion	Funding Source
								or longer horizons	
Kawamoto et al., 2016 (84)	Advanced PD	CUA	Japanese public payer, 10 years	Markov, 6 states (HY)	DBS vs BMT	JPY 3.1M/QALY (~\$25,600)	£30,000 per QALY (\$46,200)	DBS cost-effective, better at HY 4	No conflicts declared
Fundament et al., 2016 (85)	PD, early motor complications	CUA	UK NHS, 15 years	Markov, trial-based evaluation	DBS vs BMT	£19,887/QALY (99% cost-effective at threshold)	£30,000 per QALY	DBS cost-effective in early-complication PD	Industry
Dams et al., 2016 (86)	PD, early motor complications	CEA + CUA	German public payer, lifetime	Markov, 6 states (HY-off)	DBS vs BMT	€22,700/QALY	€50,000 per QALY	DBS in early stage is cost-effective	Not stated, authors report industry ties
McIntosh et al., 2016 (87)	Advanced PD	CUA	UK NHS, 01-05-10 years	Trial-based evaluation	DBS + BMT vs BMT	01-yr: £468,582/QALY 05-yr: £45,180/QALY 10-yr: £70,537/QALY	£30,000 per QALY	DBS NOT cost-effective at 01 year, long-term value uncertain	Public
Fann et al., 2020 (88)	PD, older adults	CEA + CUA	Taiwanese society, 03 years + 10 years	Markov, 5 states (HY)	DBS vs BMT	3-yr: \$123,436/QALY 10-yr: \$69,033/QALY	~US\$75,000 per QALY (3x GDP per capita)	DBS cost-effective over a 10-year horizon	No conflicts declared
Mahajan et al., 2020 (89)	Advanced PD	CEA + CUA	US society, 02-05-10 years	Decision tree	DBS vs RF ablation	DBS dominates RF ablation	US\$50,000 per QALY	DBS cost-effective	No funding, authors disclose industry grants
Meng et al., 2021 (90)	Tremor-dominant PD, eligible for DBS	CUA	Canadian society, 03 years	Decision tree	MRgFUS thalamotomy vs BMT; DBS vs MRgFUS	MRgFUS vs BMT: \$30,078/QALY DBS vs MRgFUS: \$56,503/QALY	US\$50,000 per QALY	MRgFUS cost-effective vs BMT, competitive with DBS	No industry funding, senior author discloses public funds and industry ties

First author's name, year of publication	Target Population	Analysis Type	Perspective, Time horizon	Model Type	Interventions vs Comparators	ICERs	WTP threshold	Conclusion	Funding Source
Guo et al., 2023 (91)	Advanced PD	CUA	Chinese patient payer, 15 years	Markov, 21 states (HY + OFF)	DBS vs BMT	CNY 213,544/QALY (~\$32,550)	CNY 212,676 per QALY	DBS cost-effective, better with younger age	No funding
Radwan et al., 2026 (92)	Advanced PD	CUA	Egypt society, 15 years	Markov, UPDRS-based	DBS vs BMT	EGP 830,726/QALY (~\$18,322)	EGP 782,460 per QALY	DBS NOT cost-effective	No funding
Kristiansen et al., 2009 (94)	Advanced PD	CUA	Swedish payer, 02 years	Decision tree	LCIG vs BMT	SEK 6.1M/QALY	SEK 500,000 per QALY	LCIG improves QoL but NOT cost-effective	Industry
Willis et al., 2010 (95)	Advanced PD	Review of HTA submissions	Swedish society, up to 10 years	Markov	LCIG vs BMT	SEK 1M/QALY	SEK 500,000 per QALY	LCIG NOT cost-effective	Industry
Lowin et al., 2011 (96)	Advanced PD	CUA	UK NHS, lifetime	Markov, 12 states	LCIG vs BMT	£36,024/QALY	£30,000 per QALY	LCIG may be cost-effective	Industry
Kamusheva et al., 2013 (97)	PD with prolonged akinesia	CEA	Bulgarian payer, diagnosis to LCIG initiation	Direct calculation; no model used	LCIG vs BMT	BGN 1,903/patient/year in added cost (below annual GDP per capita)	Annual GDP per capita	LCIG cost-effective	No funding
Lundqvist et al., 2014 (98)	Advanced PD	CUA	Norwegian payer and society, 01 year	Direct calculation; no model used	LCIG vs pre-LCIG BMT (within-patient)	NOK 9.2M/QALY (€1.18M)	NOK 500,000 per QALY	LCIG NOT cost-effective	Industry
Lowin et al., 2017 (99)	Advanced PD	CUA	Irish healthcare system, lifetime	Markov, 26 states (HY + OFF)	LCIG vs BMT	€26,944/QALY	€45,000 per QALY	LCIG cost-effective	Industry
Kalabina et al., 2019 (100)	Advanced PD	CUA	UK NHS, lifetime	Markov, 26 states (HY + OFF)	LCIG vs BMT (CSAI maybe included in BMT)	£52,110/QALY	£30,000 per QALY £50,000 per QALY argued for orphan drug	LCIG NOT cost-effective at standard threshold, have value as orphan drug	Industry
Chaudhuri et al., 2022 (101)	Advanced PD	CUA	UK NHS, 20 years	Markov, 26 states (HY + OFF)	LCIG vs BMT (CSAI maybe included in BMT)	£23,649/QALY	£30,000 per QALY	LCIG cost-effective	Industry

First author's name, year of publication	Target Population	Analysis Type	Perspective, Time horizon	Model Type	Interventions vs Comparators	ICERs	WTP threshold	Conclusion	Funding Source
Pahwa et al., 2023 (93)	Advanced PD	CUA	US payer, lifetime	Markov, 26 states (HY + OFF)	LCIG vs BMT (CSAI maybe included in BMT)	\$7,711/QALY	US\$100,000 per QALY	LCIG cost-effective	Industry
Valledeoriola et al., 2013 (104)	Advanced PD	Cost analysis	Spanish payer, 05 years	Expert panel questionnaire	DBS vs LCIG vs CSAI	Per patient: DBS €90,251 CSAI €149,932 LCIG €247,645	Not applicable	DBS least costly over 5 years	Industry
Walter and Odin, 2015 (74)	Advanced PD	CUA	UK & German healthcare provider, lifetime	Markov, 12 states	CSAI vs LCIG CSAI vs DBS CSAI vs BMT	CSAI vs SoC: £6,440/QALY CSAI dominates DBS LCIG vs CSAI £244,685/QALY	£30,000 per QALY	CSAI cost-effective	Industry
Vivancos-Matellano et al., 2016 (102)	Advanced PD	CUA	Spanish payer, 05 year costs, lifetime utilities	Markov, HY-based	DBS vs BMT CSAI vs BMT LCIG vs BMT	DBS €31,956/QALY CSAI €38,249/QALY LCIG €75,206/QALY	Not stated	DBS most cost-effective of the three therapies	Not stated
Norlin et al., 2021 (103)	Advanced PD	CUA	Swedish society, 05 years	Markov, 21 states	DBS vs BMT CSAI vs BMT LCIG vs BMT	DBS lowest ICER, cost-saving in some analyses	SEK 100k – 1M/QALY	All three therapies cost-effective, underused	Industry
CADTH, 2023 (106)	Advanced PD, ineligible for DBS	CMA	Canadian health system, 20 years	Cost comparison; no model used	LDp/CDp vs LCIG	Cost savings of CAD 2453	Not applicable	LDp/CDp generates savings	Public re-analysis of industry submission
Chaudhuri et al., 2025 (105)	Advanced PD	Societal impact	UK society, 05 years	Markov, 5 OFF states	LDp/CDp + BMT vs BMT	Not applicable	Not applicable	LDp/CDp generates savings	Industry

ICER, incremental cost-effectiveness ratio; WTP, willingness-to-pay; QALY, quality-adjusted life year; HY, Hoehn and Yahr stage; RF, radiofrequency; MRgFUS, MRI-guided focused ultrasound; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; CMA, cost-minimization analysis.

CHAPTER 3
COMPARATIVE EFFICACY AND SAFETY
OF ADVANCED THERAPIES FOR PARKINSON'S DISEASE:
A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

ABSTRACT

Background: In patients with Parkinson's Disease (PD) and medication-resistant motor fluctuations, advanced therapies are usually considered. Evidence on the comparative efficacy and safety between the newly approved continuous subcutaneous foslevodopa-foscarbidopa infusion (LDp/CDp), and existing therapies – deep brain stimulation (DBS), levodopa-carbidopa intestinal gel (LCIG), and continuous subcutaneous apomorphine infusion (CSAI), is lacking.

Methods: We searched Ovid MEDLINE, Embase, CINAHL, and Cochrane Library for randomized controlled trials published from inception until April 2025. We performed a Bayesian network meta-analysis. Primary outcomes included OFF time, clinical motor functions (UPDRS/MDS-UPDRS part III), and PD-related quality of life (PDQ-39/PDQ-8). Assessments of risk of bias and evidence certainty were completed.

Results: We included 13 trials with 2069 participants. Against best medical therapy, DBS ranked first at improving OFF time [MD, -2.59 hours (-3.61 to -1.57)] and clinical motor functions [-4.09 points (-5.43 to -2.75)], while gains in quality of life were highest with LCIG [-8.78 points (-13.96 to -3.67)] and DBS [-7.54 points (-9.57 to -5.52)]. LDp/CDp is less effective than DBS at improving OFF time and clinical motor functions, however these differences are not clinically important. Risk of SAEs is elevated with DBS. [RR, 1.93 (1.10 to 3.44)].

Conclusions: This systematic review and network meta-analysis found that DBS is generally the most efficacious among all advanced therapies considered but carries significant risk of SAEs. LDp/CDp might be less effective than DBS or LCIG. Our evidence certainty assessments indicated that further evidence on the effects and treatment costs of CSAI and foslevodopa-foscarbidopa is needed to facilitate informed decision-making by clinicians and patients.

Introduction

Parkinson's Disease (PD) is among the fastest growing neurological conditions globally. It is projected that there would be 25.2 million PD patients worldwide in 2050, more than double that in 2021 (4). Motor symptoms are a defining characteristic of PD. Managing motor fluctuations in PD typically begins with modifying the frequency and/or dose of levodopa. Further antiparkinsonian medications may be added as PD progresses. For patients whose motor fluctuations are no longer sufficiently controlled by optimized oral therapy, clinicians can consider several advanced therapies, including surgical and infusion options (27).

Deep brain stimulation (DBS) is among the oldest procedures for advanced PD patients, which involves the implantation of an electrode to stimulate a particular brain region, usually the subthalamic nucleus or the globus pallidus internus (108). Device-assisted pharmacological options are also available, which involve the continuous infusion of an antiparkinsonian drug. Levodopa-carbidopa intestinal gel (LCIG) uses a jejunal or duodenal tube to deliver the levodopa-carbidopa gel, and it is considered an alternative to DBS (40).

In October 2024, foslevodopa-foscarbidopa (LDp/CDp) was approved by the US FDA, becoming the first subcutaneous 24-hour infusion therapy for the treatment of motor fluctuations in adults with advanced PD. It was shown to improve motor fluctuations and potentially has quality of life (QoL) benefits, without elevated risk of SAEs while possibly having lower falls risk (42). For the first time, patients in the US with advanced PD had the potential to benefit from a minimally invasive treatment without the need for surgery. Shortly afterwards, in February 2025, the US FDA also approved continuous subcutaneous apomorphine infusion (CSAI) – a therapy administered similarly to LDp/CDp. There are numerous important safety issues with CSAI, but nonetheless it has been in use in Europe for over 20 years (43).

Although all existing therapies have been proven to be efficacious in reducing motor fluctuations, improving motor symptoms as well as QoL, to date, there have been no head-to-head randomized controlled trials comparing the relative efficacy and safety of these advanced therapies. Without direct comparative evidence, there is no clear answer to the question of which therapy should be used. The decision-making process regarding the choice of treatment has to take into account clinical features, treatment preferences, applicability as well as the economic costs of the therapy under consideration (45). Previous systematic reviews and meta-analyses have compared the efficacy and safety of DBS, LCIG, and CSAI. However, barring

the effect on risk of falls, the relative treatment efficacy of LDp/CDp in improving other disease outcomes compared to these established therapies has not been investigated (109–112). By including the newly approved LDp/CDp and expanding the outcomes studied, this systematic review and network meta-analysis aims to provide a comprehensive comparison of LDp/CDp with other existing interventions to aid decision-making by clinicians, patients and policymakers.

Methods

Search strategy

A comprehensive search strategy was developed using subject headings and keywords based on PICO characteristics (Supplementary Table 12) in collaboration with a health sciences librarian (ML). The search was run in MEDLINE (Ovid), Embase (Ovid), CINAHL (EBSCO) and the Cochrane Library (Wiley) from inception until April 24, 2025. Results were limited to randomized controlled trials. We also examined the reference lists of previously published systematic reviews on device-assisted treatments for PD.

Eligibility criteria

We included randomized controlled trials of patients with advanced-stage PD with uncontrolled motor symptoms using oral medications alone. Studies must have compared the efficacy of either DBS, LCIG, CSAI, or LDp/CDp versus another listed intervention, immediate-release levodopa, best medication therapy (BMT), placebo, or sham stimulation. We included studies reporting at least one of the following outcomes: i) motor functional disability clinically evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS/MDS-UPDRS) part III in both the ON- and OFF-medication states; ii) time spent in the OFF-medication state assessed via diary or the UPDRS/MDS-UPDRS part IV; iii) QoL assessed using the Parkinson's Disease Questionnaire (PDQ-39/PDQ-8); iv) time spent in the ON-medication state without troublesome dyskinesia assessed via diary (also called “good” ON time); v) motor impairment in daily activities assessed using the UPDRS/MDS-UPDRS part II in the ON-medication state; and vi) rate of falls. We restricted our search to peer-reviewed articles only, without any language restrictions. Only studies with a follow-up duration of 12 weeks or more were included.

Study selection

We imported identified articles from each database to Covidence, a web-based platform to screen and extract data (113). Duplicates were removed via Covidence upon importing. The

Cochrane RCT classifier – a machine learning tool for systematic reviews integrated into Covidence – then eliminated records that it deemed to be “not RCT” with high accuracy (114). One author (AT) screened the titles and abstracts of the eliminated records to verify the accuracy of the classifier.

Two authors (AT, NN) independently screened the titles and abstracts of all remaining records and subsequently screened the full text of potentially eligible articles. Any disagreements were discussed and resolved through mutual consent. In cases of uncertainty, a third author (SM) was consulted.

Data collection

Two authors (AT, NN) independently extracted data from each included study. Any discrepancies were discussed and resolved through mutual consent.

We extracted study information, including the study setting, study duration, trial design, population inclusion and exclusion criteria, interventions being compared, total sample size of each study arm, number and reason for withdrawals, baseline characteristics including mean age, gender proportion, and mean disease duration.

We categorized outcomes into the following domains: i) clinical motor functions, ii) OFF time, iii) ON time, iv) quality of life, v) daily motor functions, vi) levodopa-equivalent daily dose (LEDD), vii) adverse events. For clinical motor functions, we included mean UPDRS or MDS-UPDRS scores in either the ON or OFF medication states. OFF time captured the mean time spent in the OFF-medication state. For ON time, we included the mean time spent in the ON-medication state with or without either non-troublesome or troublesome dyskinesia. Quality of life comprised of mean PDQ-39 or PDQ-8 scores. LEDD consists of the daily dose of levodopa and dopaminergic drugs converted to mean levodopa-equivalent dose. For adverse events, we included the number and proportion of falls and dyskinesia. We also collected information on serious adverse events (SAEs). While SAEs may include different case-mixes across therapies, these have a common definition and reporting standards as outlined by the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (115,116). We collected outcomes at all time points from 12 weeks and beyond.

Risk of bias assessment

We assessed risk of bias in the included studies using the revised Cochrane risk-of-bias tool for randomized controlled trials (RoB 2) (117). RoB 2 assesses five domains of bias, including i)

bias arising from the randomization process, ii) deviations from intended interventions, iii) missing outcome data, iv) measurement of the outcome, and v) selection of the reported result. Two authors (AT, NN) independently assessed bias in each included study using the tool and recorded justifications for the assessment. Any disagreements in judgement or justifications were discussed and resolved through mutual consent. In cases of uncertainty, a third author (SM) was consulted. The overall risk of bias for each study was determined by the highest RoB level across all domains.

Data analysis

For each pairwise comparison between continuous outcomes, we calculated the mean difference of treatment effects (MD) and the 95% credible interval (95% CrI). Differences in treatment effects were assumed to be comparable between studies that used UPDRS III and MDS-UPDRS III; UPDRS II and MDS-UPDRS II; and PDQ-39 and PDQ-8. The comparability between these measures have previously been examined and reported (118,119). For comparisons between dichotomous outcomes, we used risk ratios (RR) and the 95% CrI. We handled studies with zero-event arm(s) using treatment arm continuity correction (120). Pairwise comparisons were presented in league tables. To rank treatments and assess result uncertainty, we also used the Surface Under the Cumulative Ranking Curve (SUCRA), which shows the relative probability of an intervention being among the best options.

Treatment differences higher than the minimal clinically important difference (MCID) – defined by Jaeschke et al. as “the smallest difference in score in the domain of interest which patients perceive as beneficial” – were considered superior/inferior, and differences less than MCID were considered trivial (121). We used MCID values published in the literature. MCID for OFF time was –1.3 hours (122). For clinical/daily motor functions, we used –3.25 points for MDS-UPDRS part III and –3.05 points for MDS-UPDRS part II (123,124). For quality of life, the MCID for PDQ-39 was –4.72 points (125). MCID for “good” ON time was +1 hour (112). Lastly, MCID for falls was a 25% reduction in the number of falls (126).

Certainty assessment

One author (AT) assessed the certainty of the results. We followed Izcovich et al. for applying the GRADE approach to a network meta-analysis (127). We considered four aspects in our assessment of the direct estimates, namely, risk of bias, inconsistency, indirectness, and imprecision. We further considered intransitivity when assessing the indirect estimates. Wherever possible, we considered the MCID to assess imprecision. We presented our results

using the Summary of Findings table proposed by Yepes-Nuñez et al (128). We followed guidance from GRADE to interpret our results using the MCID values and CrI thresholds (129).

Sensitivity analyses

We examined the impact of excluding the cZi DBS study and the levodopa-carbidopa subcutaneous infusion study on our results. We also examined excluding the Schuepbach et al. study from the LEDD analysis as the study reports a much narrower confidence interval for this outcome compared to others. Lastly, we conducted additional meta-regression analyses to examine the transitivity assumption.

Results

Study characteristics

Our search identified 1,287 records, and titles and abstracts of 796 studies were screened after removal of duplicates. After screening, we reviewed 51 full-text papers and finally included 13 studies with a total of 2,069 randomized participants (**Figure 1**).

All included studies were parallel group randomized controlled trials (**Table 2**). Seven studies investigated the efficacy of DBS, including two comparing STN DBS to BMT, two comparing STN or GPi DBS to BMT, two comparing active stimulation to sham stimulation (on top of usual care), and one comparing cZi DBS to BMT. Meanwhile, six studies investigated the efficacy of infusion therapies, including three studying LCIG, one studying CSAI, one looking at foslevodopa/foscarbidopa, and one studying levodopa/carbidopa subcutaneous infusion.

Across DBS trials, the mean age of participants ranged from 52.6 to 62.4 years. The reported age in studies investigating infusion therapies was higher, with means ranging from 63.3 to 69 years. The mean disease duration varied across studies from 7.5 to 13.4 years. All studies were conducted in the United States, UK, or European countries, and only two studies had an Asian site. Five out of 13 studies reported the race and ethnicity of participants, and the study populations overwhelmingly comprised of White participants, ranging from 79.1 to 96.7 percent. Most studies had more male than female participants, with the proportion of male participants ranging from 47.2 to 81.6 percent.

Figure 1. PRISMA flowchart for study identification and selection

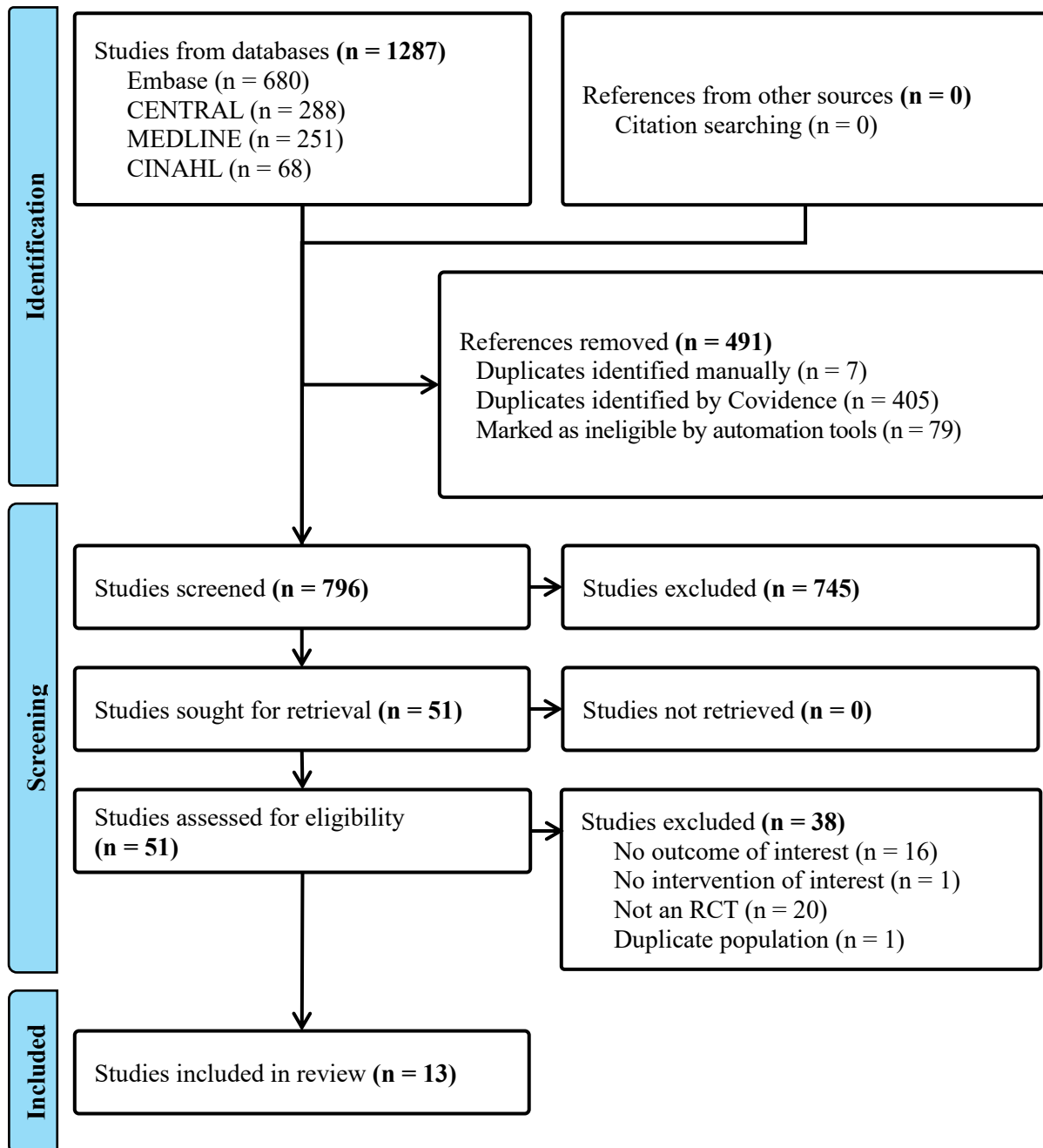


Table 2. Summary of included studies

<i>Study</i>	<i>Follow-up, weeks</i>	<i>Study setting</i>	<i>Arms</i>	<i>Sample size</i>	<i>Age, years</i>	<i>White, %</i>	<i>Male sex, %</i>	<i>Disease duration, years</i>	<i>Baseline OFF time, hours</i>	<i>Baseline “Good” ON time, hours</i>	<i>Baseline UPDRS III (ON)</i>	<i>Baseline MDS-UPDRS III (ON)</i>	<i>Baseline PDQ-39 SI</i>
<i>DBS versus BMT or sham stimulation</i>													
Deuschl 2006 (130)	24	Germany, Austria	STN DBS	78	60.5 (7.4)	—	64	13.0 (5.8)	—	—	18.9 (9.3)	—	41.8 (13.9)
			BMT	78	60.8 (7.8)	—	64	13.8 (5.6)	—	—	17.3 (9.6)	—	39.6 (16.0)
Weaver 2009 (131)	12, 24	USA	DBS (STN, GPi)	121	62.4 (8.8)	95.5	81.0	10.8 (5.4)	5.9 (2.6)	6.4 (2.7)	22.6 (12.6)	—	44.9 (13.2)
			BMT	134	62.3 (9.0)	96.7	82.1	12.6 (5.6)	5.6 (2.9)	7.0 (2.9)	23.4 (11.1)	—	44.3 (13.1)
Williams 2010 (132)	52	UK	DBS (STN, GPi)	183	59 (37-79)	—	68	11.5 (2.0-32.2)	—	—	18.9 (11.4)	—	37.5 (14.6)
			BMT	183	59 (36-75)	—	74	11.2 (1.0-30.0)	—	—	20.1 (11.4)	—	38.7 (13.7)
Okun 2012 (133)	12	USA	STN DBS	101	60.6 (8.3)	90	62	12.1 (4.9)	—	6.7 (3.1)	18.3 (9.5)	—	—
			Sham stimulation	35	59.5 (8.2)	89	60	11.7 (4.1)	—	7.4 (2.5)	17.8 (10.1)	—	—
Schuepbach 2013 (134)	24	Germany, France	STN DBS	124	52.9 (6.6)	—	75.8	7.3 (3.1)	—	10.3	12.5 (16.57)	—	30.2 (14.48)
			BMT	127	52.2 (6.1)	—	66.9	7.7 (2.7)	—	10.3	12.1 (16.90)	—	30.2 (14.65)
Blomstedt 2018 (135)	24	Sweden	cZi DBS	9	57 (11.4)	—	78	6.4 (3)	—	—	19.4 (12.5)	—	22.8 (13.2)
			BMT	10	60.9 (9.2)	—	80	10.3 (5.6)	—	—	20.6 (11.9)	—	25.0 (8.3)
Vitek 2020 (37)	12	USA	STN DBS	121	60.7 (7.9)	—	74	10.0 (3.6)	—	7.78 (3.65)	20.28 (9.28)	—	26.87 (12.89)
			Sham stimulation	39	57.5 (7.7)	—	67	10.2 (3.6)	—	8.08 (2.92)	20.44 (12.14)	—	25.13 (9.95)

<i>Study</i>	<i>Follow-up, weeks</i>	<i>Study setting</i>	<i>Arms</i>	<i>Sample size</i>	<i>Age, years</i>	<i>White, %</i>	<i>Male sex, %</i>	<i>Disease duration, years</i>	<i>Baseline OFF time, hours</i>	<i>Baseline “Good” ON time, hours</i>	<i>Baseline UPDRS III (ON)</i>	<i>Baseline MDS-UPDRS III (ON)</i>	<i>Baseline PDQ-39 SI</i>
<i>Infusion therapy versus BMT</i>													
Olanow 2014 (136)	12	Germany, USA, New Zealand	LCIG	37	63.7 (9.5)	95	65	10.0 (4.6)	6.3 (1.7)	8.7 (2.0)	18.1 (9.9)	—	35.1 (18.0)
			IR Levodopa	34	65.1 (6.8)	91	65	11.8 (5.6)	7.0 (2.1)	7.8 (2.5)	22.5 (11.7)	—	38.6 (17.9)
Freire-Alvarez 2021 (137)	12	USA, 6 EU countries	LCIG	28	69.3 (6.99)	—	42.9	12.67 (4.159)	4.8 (2.41)	8.8 (2.88)	26.30 (6.66)	—	45.1 (20.46)
			BMT	33	68.7 (7.20)	—	51.5	12.77 (6.370)	4.0 (2.99)	9.7 (3.57)	25.40 (10.91)	—	43.4 (15.81)
Chung 2022 (138)	24	USA, Canada, Australia, Korea, 5 EU countries	LCIG	43	66.9 (7.3)	79.1	67.4	11.7 (4.9)	—	—	—	—	39.7 (17.3)
			BMT	44	68.6 (6.2)	79.5	54.5	11.9 (6.0)	—	—	—	—	44.5 (17.3)
Katzen-schlager 2018 (52)	12	UK, 6 EU countries	CSAI	53	63.6 (9.3)	—	64	11.8 (5.6)	6.69 (2.23)	8.52 (2.36)	—	30.60 (13.65)	32.67 (15.03)
			Usual care	53	63.0 (8.3)	—	60	10.6 (4.3)	6.76 (2.51)	8.56 (2.39)	—	28.02 (15.25)	31.01 (12.66)
Soileau 2022 (42)	12	USA, Australia	CSCI (LDp/CDp)	67	66.3 (9.2)	95	68	8.38 (4.22)	6.34 (2.27)	9.2 (2.42)	—	29.47 (14.97)	30.68 (16.05)
			IR Levodopa	74	66.6 (9.8)	91	73	8.79 (5.49)	5.91 (1.88)	9.49 (2.62)	—	28.23 (13.67)	26.15 (14.46)
Espay 2024 (139)	12	USA, Israel, Russia, Ukraine, UK, 11 EU countries	CSCI (LD/CD)	128	63.5 (9.5)	—	66	9.3 (3.8)	6.1 (1.6)	9.4 (1.7)	—	—	—
			IR Levodopa	131	63.5 (8.5)	—	61	9.9 (4.7)	6.1 (1.9)	9.4 (1.9)	—	—	—

The assessment and reporting of outcomes varied across studies and are summarized in **Table 3**.

Table 3. Summary of reported outcomes

<i>Study</i>	<i>Clinical motor functions</i>	<i>OFF time</i>	<i>ON time*</i>	<i>Quality of Life</i>	<i>Daily motor functions</i>	<i>Disease severity</i>	<i>Key Adverse Events**</i>
<i>DBS versus BMT or sham stimulation</i>							
Deuschl 2006	✓	—	—	✓	✓	—	✓
Weaver 2009	✓	✓	✓	✓	—	—	✓
Williams 2010	✓	—	—	✓	✓	—	Some
Okun 2012	✓	—	✓	—	✓	—	✓
Schuepbach 2013	✓	—	✓	✓	—	—	Some
Blomstedt 2018	✓	—	—	✓	—	—	—
Vitek 2020	✓	—	✓	✓	✓	✓	✓
<i>Infusion therapy versus BMT</i>							
Olanow 2014	✓	✓	✓	✓	✓	✓	✓
Freire-Alvarez 2021	✓	✓	✓	✓	—	✓	Some
Chung 2022	—	—	—	✓	✓	✓	Some
Katzenschlager 2018	✓	✓	✓	✓	—	—	Some
Soileau 2022	✓ [†]	✓	✓	✓	✓	—	✓
Espay 2024	✓	✓	✓	✓	✓	✓	✓

✓: Outcome reported, —: Outcome not reported, Some: Some outcomes reported.

* Only ON-time without troublesome dyskinesia (Good ON-time) is of interest.

** Key adverse events include falls or dyskinesia, or any type of site infection. All studies reported serious adverse events.

[†] Outcome not reported in journal article; data gathered from CADTH reimbursement recommendation document for foslevodopa-foscarbidopa (106)

Risk of bias assessment

Regarding efficacy outcomes, most studies were judged to have some concerns or at high risk of bias. This is mainly due to the trials having non-trivial numbers of follow-up losses which led to at least a judgement of “some concerns” in the missing outcome domain. Furthermore, most studies were also unblinded while several outcomes including QoL, OFF/ON time, and daily motor functions were patient-reported. This resulted in all open-label trials being assessed to have a high risk of bias in the outcome measurement domain for these patient-reported outcomes. The risk of bias for safety outcomes was generally low. Traffic light plots for individual outcomes are presented in the **Supplementary Figures 1c–9c**.

Syntheses of results

OFF time

OFF time at baseline ranged from 4.0 to 7.0 hours per day on average. All advanced therapies reduced time spent in the OFF state by more than MCID compared to BMT. Specifically, DBS produced the greatest reduction in OFF time with a mean of –2.59 hours (95% CrI, –3.61 to –1.57), followed by LCIG (mean difference (MD): –2.18 hours; 95% CrI, –3.32 to –1.08) (**Table 4**). LDp/CDp was not inferior to DBS and other therapies, with a mean OFF time difference of +1.13 hours (95% CrI, –0.01 to +2.29) compared to DBS (**Supplementary Table 3a**). Across therapies, DBS had a 61% chance to be the best intervention, but it was unlikely to be clinically different from other advanced therapies at reducing OFF time, with only a 12.7% to 38.8% probability of being better by more than MCID compared to LCIG and LDp/CDp, respectively (**Supplementary Tables 4b–c**).

Clinical motor functions (UPDRS part III in ON state)

DBS was the only intervention that was better than BMT at improving clinical motor functions, with a mean change of –4.09 points (95% CrI, –5.43 to –2.75) (**Table 4**). It also ranked first with an 83% probability of being the best intervention at improving clinical motor function score (**Supplementary Table 5c**). The efficacy of the remaining interventions were similar to each other (**Supplementary Figure 2b**). Moreover, DBS had the highest probability (89.1%) of being clinically better than BMT, although it was still unlikely to be clinically different from other advanced therapies; the probability that DBS was better than CSAI, LDp/CDp, and LCIG was only 21.9%, 24.3%, and 25.9%, respectively (**Supplementary Table 5b**). LDp/CDp was not inferior to other therapies (MD vs. DBS: +2.36 points; 95% CrI, –0.10 to +4.89; MD vs. BMT: –1.73 points; 95% CrI, –3.81 to +0.40) (**Supplementary Table 3b**).

QoL

The mean PDQ score at baseline ranged from 22.8 to 45.1 points. DBS and LCIG were better than BMT at improving QoL, producing a mean change of -7.54 (95% CrI, -9.57 to -5.52) and -8.78 (95% CrI, -13.96 to -3.67) points, respectively. LDp/CDp was also better than BMT (MD: -2.90 points; 95% CrI, -4.88 to -0.91), however the difference did not reach clinical importance (**Table 4**). LDp/CDp was also clinically and statistically inferior to LCIG (MD vs. LCIG: $+5.88$ points; 95% CrI, $+0.40$ to $+11.43$) (**Supplementary Table 6a**). DBS and LCIG were both superior to CSAI and were likely to be better than BMT by MCID at improving QoL (99.7 and 93.9%, respectively). LCIG had a 67% chance of being the first-ranked intervention at improving QoL (**Supplementary Tables 6b–c**).

Daily motor functions (UPDRS part II in ON state)

Three therapies (DBS, LCIG, LDp/CDp) produced trivial improvements compared to BMT, with DBS at -0.93 points (95% CrI, -1.82 to -0.05), LCIG at -2.90 points (95% CrI, -4.97 to -0.84), and LDp/CDp at -2.70 points (95% CrI, -3.79 to -1.61) (**Table 5**). LDp/CDp had similar efficacy to LCIG and had a 43% chance of being the first-ranked intervention (this probability for LCIG was 56%) (**Supplementary Table 7c**). CSAI was not studied for this outcome due to a lack of data.

ON time without troublesome dyskinesia

The baseline means of “good” ON time ranged from 6.4 to 10.3 hours across studies. All therapies were better than BMT with mean gains ranging from $+1.72$ hours (95% CrI, $+1.14$ to $+2.30$) with LDp/CDp to $+3.33$ hours (95% CrI, $+2.61$ to $+4.06$) with DBS (**Table 5**). DBS had a 79% probability of being the best intervention at improving “good” ON time, whereas LCIG was most likely to be the second-best intervention (**Supplementary Table 8c**). DBS appears to be better than CSAI, and it was also superior to LDp/CDp (MD vs. CSAI: $+1.36$ hours; 95% CrI, -0.01 to $+2.72$; vs. LDp/CDp: $+1.61$ hours; 95% CrI, $+0.68$ to $+2.54$) and the probabilities of being better by MCID were 70.1% and 89.9%, respectively (**Supplementary Tables 8a–b**).

Table 4. Summary of Findings – Primary outcomes

Outcome	Effects (95% CrI) and confidence in the estimates of effects							
	DBS		LCIG		CSAI		LDp/CDp	
Baseline effect	Relative effect	Absolute effect	Relative effect	Absolute effect	Relative effect	Absolute effect	Relative effect	Absolute effect
OFF time								
BMT Comparator –0.18 hours	MD –2.59 (–3.61 to –1.57)	–2.77 hours (–3.79 to –1.75 hours)	MD –2.18 (–3.32 to –1.08)	–2.36 hours (–3.50 to –1.26 hours)	MD –1.88 (–3.11 to –0.62)	–2.06 hours (–3.29 to –0.80 hours)	MD –1.46 (–2.01 to –0.91)	–1.64 hours (–2.19 to –1.09 hours)
	⊕○○○ Very low confidence in estimate due to risk of bias ² and imprecision ¹ based on 255 patients (1 study)		⊕⊕○○ Low confidence in estimate due to risk of bias ¹ and imprecision ¹ based on 130 participants (2 studies)		⊕⊕⊕○ Moderate confidence in estimate due to imprecision ¹ based on 106 participants (1 study)		⊕⊕○○ Low confidence in estimate due to risk of bias ¹ and imprecision ¹ based on 400 participants (2 studies)	
Rank 5 th (5 th – 5 th)	Rank 1 st (1 st – 3 rd)		Rank 2 nd (1 st – 4 th)		Rank 3 rd (1 st – 4 th)		Rank 4 th (2 nd – 5 th)	
Interpretation (vs. BMT)	DBS might be superior		LCIG is possibly superior		CSAI is probably superior		LDp/CDp is possibly superior	
Clinical motor functions (UPDRS part III in ON state)								
BMT Comparator –1.93 points	MD –4.09 (–5.43 to –2.75)	–6.02 points (–7.36 to –4.68 points)	MD –1.85 (–4.90 to 1.22)	–3.78 points (–6.83 to –0.71 points)	MD –2.09 (–5.23 to 0.73)	–4.02 points (–7.16 to –1.20 points)	MD –1.73 (–3.81 to 0.40)	–3.66 points (–5.74 to –1.53 points)
	⊕⊕○○ Low confidence in estimate due to risk of bias ² and imprecision ¹ based on 1304 patients (7 studies)		⊕⊕○○ Low confidence in estimate due to imprecision ² based on 131 participants (2 studies)		⊕○○○ Very low confidence in estimate due to risk of bias ¹ and imprecision ² based on 106 participants (1 study)		⊕⊕○○ Low confidence in estimate due to risk of bias ¹ and imprecision ¹ based on 400 participants (2 studies)	
Rank 5 th (4 th – 5 th)	Rank 1 st (1 st – 2 nd)		Rank 3 rd (1 st – 5 th)		Rank 2 nd (1 st – 5 th)		Rank 4 th (2 nd – 5 th)	
Interpretation (vs. BMT)	DBS is possibly superior		LCIG possibly have trivial to no effect		CSAI might have trivial to no effect		LDp/CDp possibly have trivial to no effect	
Quality of Life (PDQ-39)								
BMT Comparator +0.07 points	MD –7.54 (–9.57 to –5.52)	–7.47 points (–9.50 to –5.45 points)	MD –8.78 (–13.96 to –3.67)	–8.71 points (–13.89 to –3.60 points)	MD –2.45 (–7.53 to 2.67)	–2.38 points (–7.46 to +3.08 points)	MD –2.90 (–4.88 to –0.91)	–2.83 points (–4.81 to –0.84 points)
	⊕⊕⊕○ Moderate confidence in estimate due to risk of bias ¹ based on 1197 patients (6 studies)		⊕⊕○○ Low confidence in estimate due to risk of bias ¹ and imprecision ¹ based on 217 participants (3 studies)		⊕○○○ Very low confidence in estimate due to risk of bias ¹ and imprecision ² based on 106 participants (1 study)		⊕⊕○○ Low confidence in estimate due to risk of bias ¹ and imprecision ¹ based on 400 participants (2 studies)	
Rank 5 th (4 th – 5 th)	Rank 2 nd (1 st – 3 rd)		Rank 1 st (1 st – 2 nd)		Rank 4 th (2 nd – 5 th)		Rank 3 rd (3 rd – 4 th)	
Interpretation (vs. BMT)	DBS is probably superior		LCIG is possibly superior		CSAI might have trivial to no effect		LDp/CDp possibly have trivial to no effect	
Footnotes								
Baseline effect calculated from control group results in the studies. The absolute effect is based on the baseline effect and the relative effect.								
Relative effects are presented in the left cell and are reported as mean difference (MD) and 95% credible interval (CrI). Absolute effects are presented in the right cell as absolute change and 95% CrI.								
Superscripts ^{1,2,3} denote the number of certainty levels downgraded due to a specific reason. See Supplementary Tables 3a-i for detailed explanation.								

Table 5. Summary of Findings – Secondary efficacy outcomes

Outcome	Effects (95% CrI) and confidence in the estimates of effects							
	DBS		LCIG		CSAI		LDp/CDp	
Baseline effect	Relative effect	Absolute effect	Relative effect	Absolute effect	Relative effect	Absolute effect	Relative effect	Absolute effect
Daily motor functions (UPDRS part II in ON state)								
BMT Comparator −0.37 points	MD −0.93 (−1.82 to −0.05)	−1.30 points (−2.19 to −0.42 points)	MD −2.90 (−4.97 to −0.84)	−3.27 points (−5.34 to −1.21 points)	No information for analysis		MD −2.70 (−3.79 to −1.61)	−3.07 points (−4.16 to −1.98 points)
	⊕⊕⊕○ Moderate confidence in estimate due to risk of bias ¹ based on 1043 patients (5 studies)		⊕○○○ Very low confidence in estimate due to risk of bias ¹ and imprecision ² based on 158 participants (2 studies)				⊕⊕○○ Low confidence in estimate due to risk of bias ¹ and imprecision ¹ based on 400 participants (2 studies)	
	Rank 4 th (4 th − 4 th)	Rank 3 rd (2 nd − 3 rd)	Rank 1 st (1 st − 2 nd)	Rank 2 nd (1 st − 2 nd)				
Interpretation (vs. BMT)	DBS probably have trivial to no effect		LCIG might have trivial to no effect				LDp/CDp possibly have trivial to no effect	
“Good” ON time								
BMT Comparator +0.40 hours	MD +3.33 (+2.61 to +4.06)	+3.73 hours (+3.01 to +4.46 hours)	MD +2.64 (+1.27 to +4.02)	+3.04 hours (+1.67 to +4.42 hours)	MD +1.96 (+0.80 to +3.14)	+2.36 hours (+1.20 to +3.54 hours)	MD +1.72 (+1.14 to +2.30)	+2.12 hours (+1.54 to +2.70 hours)
	⊕⊕⊕○ Moderate confidence in estimate due to risk of bias ¹ based on 766 patients (4 studies)		⊕⊕○○ Low confidence in estimate due to risk of bias ¹ and imprecision ¹ based on 130 participants (2 studies)		⊕⊕⊕○ Moderate confidence in estimate due to imprecision ¹ based on 106 participants (1 study)		⊕⊕⊕○ Moderate confidence in estimate due to imprecision ¹ based on 400 participants (2 studies)	
	Rank 5 th (5 th − 5 th)	Rank 1 st (1 st − 2 nd)	Rank 2 nd (1 st − 4 th)	Rank 3 rd (2 nd − 4 th)	Rank 4 th (2 nd − 4 th)			
Interpretation (vs. BMT)	DBS is probably superior		LCIG is possibly superior		CSAI is probably superior		LDp/CDp is probably superior	
Levodopa-equivalent daily dose								
BMT Comparator +40 mg	MD −577 (−626 to −528)	−537 mg (−586 to −488 mg)	MD −155 (−418 to +107)	−115 mg (−378 to +147 mg)	MD −326 (−518 to −136)	−286 mg (−478 to −96 mg)	No information for analysis	
	⊕⊕⊕○ Moderate confidence in estimate due to risk of bias ¹ based on 778 patients (5 studies)		⊕⊕○○ Low confidence in estimate due to risk of bias ¹ and imprecision ¹ based on 71 participants (1 study)		⊕⊕○○ Low confidence in estimate due to risk of bias ² based on 106 participants (1 study)			
	Rank 4 th (3 rd − 4 th)	Rank 1 st (1 st − 1 st)	Rank 3 rd (2 nd − 4 th)	Rank 2 nd (2 nd − 3 rd)				
Interpretation (vs. BMT)	DBS is probably superior		LCIG is possibly superior		CSAI is possibly superior			
Footnotes								
Baseline effect calculated from control group results in the studies. The absolute effect is based on the baseline effect and the relative effect.								
Relative effects are presented in the left cell and are reported as mean difference (MD) and 95% credible interval (CrI). Absolute effects are presented in the right cell as absolute change and 95% CrI.								
Superscripts ^{1,2,3} denote the number of certainty levels downgraded due to a specific reason. See Supplementary Tables 3a-i for detailed explanation.								

Table 6. Summary of Findings – Safety outcomes

Outcome	Effects (95% CrI) and confidence in the estimates of effects							
	DBS		LCIG		CSAI		LDp/CDp	
Baseline effect	Relative effect	Absolute effect	Relative effect	Absolute effect	Relative effect	Absolute effect	Relative effect	Absolute effect
Risk of falls								
BMT Comparator 61 per 1000	RR 1.12 (0.70 to 1.80)	7 more per 1000 (18 fewer to 49 more)	RR 1.59 (0.62 to 4.11)	36 more per 1000 (23 fewer to 190 more)	No information for analysis		RR 0.52 (0.29 to 0.94)	29 fewer per 1000 (43 fewer to 4 fewer)
	⊕⊕○○ Low confidence in estimate due to imprecision ² based on 1073 patients (5 studies)		⊕○○○ Very low confidence in estimate due to imprecision ³ based on 219 participants (3 studies)				⊕⊕⊕○ Moderate confidence in estimate due to imprecision ¹ based on 400 participants (2 studies)	
	Rank 2 nd (2 nd – 4 th)		Rank 4 th (2 nd – 4 th)				Rank 1 st (1 st – 2 nd)	
Interpretation (vs. BMT)	DBS possibly have trivial to no effect		LCIG might be inferior				LDp/CDp is probably superior	
Risk of dyskinesia								
BMT Comparator 54 per 1000	RR 0.63 (0.43 to 0.92)	20 fewer per 1000 (31 fewer to 4 fewer)	RR 1.14 (0.33 to 3.95)	8 more per 1000 (36 fewer to 160 more)	RR 17.11 (1.03 to 289.06)	Inestim-able	RR 1.17 (0.48 to 2.84)	9 more per 1000 (28 fewer to 100 more)
	⊕⊕⊕⊕ High confidence in estimate based on 922 patients (5 studies)		⊕○○○ Very low confidence in estimate due to imprecision ³ based on 71 participants (1 study)		⊕⊕○○ Low confidence in estimate due to imprecision ² based on 106 participants (1 study)		⊕○○○ Very low confidence in estimate due to imprecision ³ based on 400 participants (2 studies)	
	Rank 2 nd (2 nd – 4 th)		Rank 1 st (1 st – 2 nd)		Rank 3 rd (1 st – 4 th)		Rank 5 th (4 th – 5 th)	
Interpretation (vs. BMT)	DBS is definitely superior		LCIG might be inferior		CSAI is possibly inferior		LDp/CDp might be inferior	
Risk of serious adverse events								
BMT Comparator 96 per 1000	RR 1.93 (1.10 to 3.44)	90 more per 1000 (10 more to 235 more)	RR 1.36 (0.47 to 4.17)	35 more per 1000 (51 fewer to 305 more)	RR 2.45 (0.33 to 18.61)	139 more per 1000 (Inestim-able)	RR 1.41 (0.42 to 4.67)	39 more per 1000 (56 fewer to 353 more)
	⊕⊕⊕○ Moderate confidence in estimate due to imprecision ¹ based on 1343 patients (7 studies)		⊕○○○ Very low confidence in estimate due to imprecision ³ based on 219 participants (3 studies)		⊕○○○ Very low confidence in estimate due to imprecision ³ based on 107 participants (1 study)		⊕○○○ Very low confidence in estimate due to imprecision ³ based on 400 participants (2 studies)	
	Rank 1 st (1 st – 3 rd)		Rank 5 th (2 nd – 5 th)		Rank 2 nd (1 st – 5 th)		Rank 4 th (1 st – 5 th)	
Interpretation (vs. BMT)	DBS is probably inferior		LCIG might be inferior		CSAI might be inferior		LDp/CDp might be inferior	
Footnotes								
Baseline effect calculated from control group results in the studies. The absolute effect is based on the baseline effect and the relative effect.								
Relative effects are presented in the left cell and are reported as risk ratio (RR) and 95% credible interval (CrI). Absolute effects are presented in the right cell as absolute change and 95% CrI.								
Superscripts ^{1,2,3} denote the number of certainty levels downgraded due to a specific reason. See Supplementary Tables 3a-i for detailed explanation.								

Levodopa-equivalent daily dose

Three therapies (DBS, LCIG, CSAI) reduced the daily dose of levodopa compared to BMT, with DBS at −577 mg (95% CrI, −626 to −528), LCIG at −155 mg (95% CrI, −418 to +107), and CSAI at −326 mg (95% CrI, −518 to −136) (**Table 5**). Quantitatively, DBS has a 99% probability of being the first-ranked intervention, although the qualitative evidence certainty assessment yielded very low confidence in the relative effect estimate between therapies due to risk of bias and transitivity issues (**Supplementary Tables 3f, 9c**).

Falls

LDp/CDp showed a decreased risk of falls (RR, 0.52; 95% CrI, 0.29 to 0.94] (**Table 6**). LCIG might elevate the risk of falls (RR, 1.59; 95% CrI, 0.62 to 4.11). The risk of falls associated with DBS was similar to that of BMT (**Supplementary Figure 7b**).

Dyskinesia

Compared to BMT, the risk of dyskinesia was elevated with CSAI, while it decreased with DBS (RR: 0.63; 95% CrI, 0.43 to 0.92) (**Table 6**). There was also a 73% chance that DBS is the best intervention (**Supplementary Table 11c**). LCIG and LDp/CDp had similar risks of dyskinesia compared with BMT (**Supplementary Figure 8b**).

Serious adverse events

The risk of SAEs was increased with DBS vs BMT (RR: 1.93; 95% CrI, 1.10 to 3.44). The risk of SAEs with CSAI was estimated to be higher than DBS, although the coefficient is imprecisely estimated as demonstrated by the wide credible interval (RR: 2.45; 95% CrI, 0.33 to 18.61). Other infusion therapies (LCIG and LDp/CDp) might also elevate SAE risk compared to BMT (LCIG RR: 1.36; 95% CrI, 0.47 to 4.17; LDp/CDp RR: 1.41; 95% CrI, 0.42 to 4.67) (**Table 6**).

Sensitivity analyses

Network meta-regression revealed a possible effect interaction between age and DBS, where a 1-year increase in age was associated with a 0.24-hour increase (95% CrI, +0.06 to +0.43) in “good” ON time, a 16.37-mg LEDD increase (95% CrI, +3.58 to +29.25), and an 86% increase (95% CrI, +19% to +194%) in the risk of falls (**Supplementary Tables 10e–g**).

Sensitivity analyses that used different model types, different priors, or excluded studies with a high risk of bias yielded results that were consistent with the main analysis. Excluding the

cZi DBS study had negligible impact on the results but excluding the levodopa-carbidopa subcutaneous infusion study led to marked change in the LDp/CDp estimates for OFF time, clinical motor functions, and daily motor functions (**Supplementary Figures 11a, b, d**). Excluding Schuepbach et al. (134) also led to change in the DBS estimate for LEDD (**Supplementary Figure 11f**). Results for other outcomes and therapies remained similar.

Discussion

This network meta-analysis revealed that, for patients with advanced PD, DBS is effective at reducing time spent in the OFF-medication state and improving clinical motor functions as well as QoL. Infusion therapies, especially the newly approved CSAI and LDp/CDp, are generally not as efficacious as DBS. However, the differences across all therapies were small and did not reach clinical significance in several efficacy outcomes. Regarding safety, we found a reduction in the risk of falls with LDp/CDp and an elevated risk of SAE with DBS.

For clinical motor functions and PD-related QoL, our results regarding DBS, LCIG, and CSAI are in line with previous reviews by Antonini et al., Rajan et al., and Nijhuis et al. (109,111,112). We additionally found that LDp/CDp is similar to other infusion therapies at improving clinical motor functions, and this new therapy is also potentially inferior to LCIG at improving QoL.

It may be noted that QoL gains recorded in some studies included in our review, especially those studying invasive therapies, may not translate to real-world contexts. Open-label trial designs evidently lead to biases in patient-reported outcomes such as QoL. However, double-blinded studies necessitate the use of invasive procedures in the control arm. These procedures inherently entail risks and can lower QoL, and thus the control arm may no longer be representative of normal patients on medical therapy. It is possible that these issues in trial design drive QoL gains in a more positive direction. A study by Ramirez-Zamora et al. has looked at the real-world impact of DBS or LCIG on QoL of PD patients (140). After 12 months, patients transitioning to DBS or LCIG had a 5-point reduction in PDQ-39 score compared to baseline (mean change: -5.0; 95% confidence interval, -5.9 to -4.2). This is noticeably less of a QoL gain than our absolute effect estimates of DBS and LCIG at -7.47 and -8.71 points respectively.

Meanwhile, we found all advanced therapies to be superior to BMT at reducing OFF time. This is in contrast with results from Rajan et al., which among DBS (STN and GPi), LCIG, and CSAI, did not find any therapy to be significantly better than BMT (111). This difference could

be due to the additional information from three recent studies in our network. Furthermore, Rajan et al. used a random-effects model which led to wide confidence intervals and non-significance. We employed a fixed-effect model as our model selection process did not support the added complexity in a random-effects model. Our ON time estimates are also more positive than previous reviews for similar reasons as our OFF time analysis.

In terms of safety, our finding that LDp/CDp infusion reduces the risk of falls corroborates with that in Rajalingam et al., although we urge readers to exercise caution while interpreting this result, as falls can be multifactorial in PD patients. In the pivotal LDp/CDp trial where this effect was identified, authors did not explain the reasons for this outcome (42). Subsequent studies have hypothesized better management of nocturnal symptoms due to 24-hour infusion duration of LDp/CDp (110), reduction in peak-dose dyskinesia and smoother dopaminergic stimulation (141), and improved vitamin metabolism as possible mechanisms (110,142). Several of these arguments could, however, also apply to other therapies and the reason for reduced risk of falls with LDp/CDp remains mechanistically unclear.

We did not see an increase in the risk of falls for DBS, a key difference compared to Rajalingam et al. This could be explained by our decision to retain the study by Williams et al (132). Rajalingam et al. excluded Williams et al. in their analysis due to having a high risk of bias and causing large heterogeneity (110,132). However, we did not judge Williams et al. to have a high risk of bias in the falls outcome. To patients, we believe falls are conspicuous accidents, and for clinicians, falls are clearly defined events, thus there is unlikely to be bias in the process of recording falls events. We also performed a sensitivity analysis without the Williams study and did not obtain a substantially better model fit, which further strengthened our decision to retain Williams et al. Our results further showed that DBS decreases the risk of dyskinesia adverse events, reinforcing findings previously demonstrated by Yan et al. (143). We also agree with Petersen et al. who calculated a similar estimate for the risk of SAE with DBS (144). Notably, our analysis did not detect an increase in SAE risk with other therapies.

The therapies considered in our analysis have existed for varied lengths of time. While DBS is well-established and has been iteratively optimized since the days of its pivotal trials, LDp/CDp has been only recently approved. Early trials for new therapies often have selective centers, optimized protocols, and short follow-up. As more real-world evidence on the newer therapies is generated, it would be worth revisiting the comparative effectiveness of these therapies although we note that numerous trials have demonstrated similar efficacy of DBS approaches

such as automated stimulator programming or directional stimulation and adaptive DBS on a number of outcomes compared with standard DBS (38,145–147).

Findings from our study can be useful in clinical decision-making. While DBS may be the most effective intervention, our results suggest it may not be clinically different from other advanced therapies and carries a significantly higher safety risk. As barriers to accessing DBS remain for patients in the United States and elsewhere, clinicians may contemplate whether to prescribe other available therapies that might reduce wait times for patients, be less invasive, and alleviate the need for frequent travelling (148,149). For patients and clinicians considering the latest treatment, LDp/CDp, our results as well as our evidence certainty assessment can help decide whether to trade-off the small potential efficacy gains of other therapies for a possibly better risk profile. Policymakers may also consider whether to expand reimbursement for newer, less invasive therapies that may be preferred by patients and clinicians but also have limited efficacy evidence and potentially inferior efficacy, or to focus more resources on addressing barriers to DBS access (46,47).

Our study has several strengths. This is the first study to compare all US-approved advanced therapies across multiple outcome domains. Uniquely, we further assessed the certainty of our results, providing critical contextual information for clinicians. Our study also has some limitations, which stem primarily from inadequacies in the randomized controlled trials in this field. First, many of our results had wide credible intervals due to limited evidence in the literature. This evidence gap highlights the need for further studies, especially into the newer therapies such as CSAI and LDp/CDp to fully ascertain their therapeutic benefits. Second, we were unable to assess network coherence as no study directly compared two advanced therapies, thereby resulting in a lack of a closed loop in the network meta-analysis. Third, while we limited our analysis to studies of patients with medication-refractory motor fluctuations, trials of infusion therapies could have included patients who were also ineligible for DBS. However, to the extent that the baseline population characteristics across therapies in the included trials were similar (**Table 2**), the transitivity assumption of in our network meta-analysis would hold. Fourth, while our study compared only motor outcomes across therapies, non-motor outcomes such as cognitive change or neuropsychiatric outcomes may also be of interest to clinicians and patients. While these outcomes were beyond the scope of our study, these could be considered in future meta-analyses. Finally, among studies that reported race and ethnicities distributions, the majority of participants were White. Thus, our results may not be readily generalizable to other populations. Further studies that compare between advanced

therapies, such as an ongoing trial comparing DBS and LCIG (150), as well as trials conducted among diverse populations will be useful.

Conclusion

We performed a systematic review and network meta-analysis to compare multiple aspects of efficacy and safety between all available advanced therapies used in advanced-stage Parkinson's Disease. We found that DBS is generally the most efficacious. However, with few exceptions, it is generally not clinically different from other advanced therapies. DBS also carries a significant risk of SAEs compared with other therapies. Using foslevodopa-foscarbidopa infusion might be less effective than DBS or LCIG. Our evidence certainty assessments will aid clinicians and patients in making informed decisions regarding their care. Our analysis identified a need for further studies examining the effects of CSAI and foslevodopa-foscarbidopa, as well as analyses of treatment costs to provide a comprehensive evidence base for decision makers.

CONTRIBUTION STATEMENT

The candidate has co-authored this paper with his supervisor – Dr. Shweta Mital; his advisory committee members – Dr. Jamie Falk and Dr. Dung Nguyen; a health science librarian – Mrs. Mê-Linh Lê; and his colleague – Ms. Ha Nhi Nguyen. He conceptualized the idea, collected data, led statistical analysis and data interpretation, wrote the first draft of the paper, and contributed to subsequent revisions.

CHAPTER 4
COST-EFFECTIVENESS OF ADVANCED THERAPIES
FOR PARKINSON'S DISEASE

ABSTRACT

Background

Patients with advanced-stage Parkinson's Disease with motor fluctuations that can no longer be controlled by oral medications may be eligible for advanced therapies. Foslevodopa/foscarbidopa (LDp/CDp) and apomorphine (CSAI) subcutaneous infusion are two newly approved, minimally invasive therapies. While both have been shown to be efficacious at improving ON time, they are expensive. The economic value of LDp/CDp compared to CSAI or other advanced therapies is unknown.

Methods

We used a Markov microsimulation model to compare the cost-effectiveness of LDp/CDp and CSAI vs three alternative treatments, namely, deep brain stimulation (DBS), levodopa-carbidopa intestinal gel, and best medical therapy (BMT). Treatment efficacy was based on a network meta-analysis of clinical trials. Effectiveness was measured in quality-adjusted life years (QALYs). Costs were estimated in 2026 US dollars from a third-party payer perspective.

Results

Among all strategies, DBS was the optimal therapy from a cost-effectiveness perspective. It costed less but generated more QALYs than all other treatments. Infusion therapies, including LDp/CDp and CSAI, were not cost-effective versus BMT at a willingness-to-pay threshold of \$100,000/QALY. Compared to BMT, LDp/CDp provided more QALYs, but the higher cost resulted in an ICER of \$1,695,815/QALY. Similarly, CSAI had an ICER of \$1,979,480/QALY compared to BMT.

Conclusion

At current prices, LDp/CDp and CSAI are not cost-effective compared with existing therapies. The price of LDp/CDp and CSAI would need to be reduced by 4% (to \$323 per unit) and 20% (to \$270 per unit) compared to base-case, respectively, for these therapies to be cost-effective against LCIG.

Introduction

Parkinson's Disease (PD) is one of the most common neurodegenerative diseases in the United States, with a projected 1.2 million Americans suffering from the disease in 2030 (6). The economic burden of PD in the US is estimated at a staggering \$51.9 billion (11). This cost is increasingly felt by patients and their caregivers as worsening motor and mental symptoms impact daily life and oral medications prove less effective over time. In advanced PD, optimized oral therapy is no longer able to control motor fluctuations.

Prior to 2024, deep brain stimulation (DBS) and levodopa-carbidopa intestinal gel (LCIG) were the only advanced therapy options approved by the US Food and Drug Administration (FDA). In 2024 and 2025, the FDA approved two new treatments, namely, continuous subcutaneous infusion of foslevodopa/foscarbidopa (LDp/CDp) and continuous subcutaneous apomorphine infusion (CSAI). As these therapies are relatively non-invasive alternatives to DBS or LCIG, they provide options for patients unwilling or unable to undergo surgery (45).

Compared with DBS and LCIG, LDp/CDp and CSAI are either similarly or less efficacious in measures of motor function and quality of life (42,52,131,136). In their respective trials, DBS decreased OFF time by 2.6 hours, while other therapies lowered this outcome by 1.8-1.9 hours (42,52,131,136). With regards to quality of life measured using the Parkinson's Disease Questionnaire (PDQ), DBS improved the PDQ-39 score by 8.1 points, LCIG by 7.0 points, while LDp/CDp and CSAI only recorded a 4.1-point and 2.5-point improvement, respectively (42,52,131,136).

However, access to DBS and LCIG in the US is limited. Between 2018 and 2020, less than 2,500 (or 2%) of the 110,000 patients with advanced PD under Medicare received these therapies (69). Further, from a cost perspective, using DBS requires high upfront costs while the new infusion therapies have relatively lower initial treatment costs but involve high ongoing medication costs (151–154).

It is therefore unclear whether the new interventions, LDp/CDp and CSAI, deliver the best value for money. Previous studies have looked at the economic value of DBS, LCIG, and CSAI in the treatment of advanced PD. While these therapies were individually shown to be cost-effective in the long-term compared to oral therapy, when considering shorter time horizons, DBS and LCIG yielded too little benefit in exchange for their high upfront costs (74,78,87,94,96,98,99). However, most studies only made comparisons between individual

therapies versus optimized oral therapy. Moreover, analyses of LCIG and CSAI have only been conducted in the European and UK contexts (74,101); studies for the US are lacking.

There is also no evidence on the cost-effectiveness of LDp/CDp versus existing therapies. Compared to other infusion therapies, LDp/CDp requires a comparatively smaller pump and is approved for 24-hour deliveries instead of just 16 hours, which adds comfort and ease of use for patients (34,155). As such, LDp/CDp is now available and reimbursed in multiple countries, including the US, and calls have been made across the world to expand access to LDp/CDp (72,73). Given the high medication costs, however, it is unknown whether its cost would be justified by its benefits. This was echoed in a report by the Canadian Drug Agency, which noted that current economic evidence was insufficient to determine “whether [LDp/CDp] represents good value to the health care system” (106).

This study fills these gaps by estimating the cost-effectiveness of LDp/CDp and CSAI compared with existing advanced therapies available in the US. To our knowledge, this study is also the first economic evaluation of advanced PD therapies that utilizes network meta-analytic evidence on the comparative efficacy between these treatments. Findings from this study will be useful to inform reimbursement decisions. In particular, studies have consistently demonstrated a wealth disparity in the utilization of DBS or LCIG for PD in the US (69,148,156). Payers and policymakers are faced with deciding between allocating resources towards addressing barriers to DBS and LCIG versus expanding access to the newer LDp/CDp and CSAI options. Our findings will aid their decisions.

Methods

Strategies under comparison

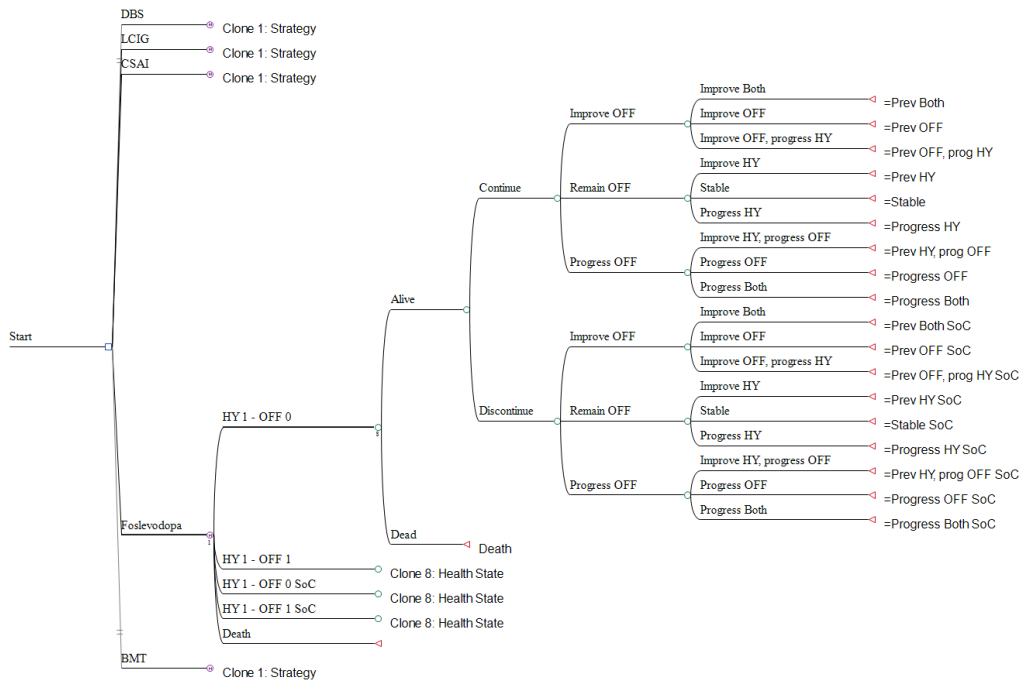
Our analysis compared five alternative treatments: undergoing surgery for i) DBS, or ii) LCIG; or using a continuous subcutaneous infusion of iii) apomorphine (CSAI), or iv) foslevodopa/foscarbidopa (LDp/CDp); or v) remaining on optimized oral regimens (e.g. levodopa, MAO-B inhibitors, COMT inhibitors, etc.), also called best medical therapy (BMT).

Model Structure

We followed a previously published Markov microsimulation model to compare the costs and effectiveness of each treatment strategy. The model consisted of 25 disease-specific health states and a death state (**Figure 2**) (99,101,157). The disease-specific states were defined by a combination of five Hoehn and Yahr (HY) stages and five different proportions of waking day

spent in the “off-medication” state (OFF time) evaluated using part IV of the Unified Parkinson’s Disease Rating Scale (UPDRS) or Movement Disorder Society-sponsored revision of the UPDRS (MDS-UPDRS) (0% ~ OFF 0; 1-25% ~ OFF 1; 26-50% ~ OFF 2; 51-75% ~ OFF 3; 76-100% ~ OFF 4). We followed simulated patients over a lifetime, with a cycle length of 3 months. Patients could remain or move to a worse health state in each cycle, except for the first cycle.

Figure 2: Model structure



Patient may enter “Improve OFF” or “Improve HY” branches only in the first cycle. Patients receiving BMT automatically enters the “Discontinue” branch in the first cycle. Patients receiving advanced therapies may discontinue treatment and enter “SoC” health states. For brevity, not all health states are shown.

Population

Our model simulated a hypothetical cohort of 10,000 patients. We pooled the baseline characteristics of patients reported in clinical trials of each therapy to obtain the baseline distribution of age, sex, OFF time, and UPDRS/MDS-UPDRS part III scores of our simulated patients. UPDRS/MDS-UPDRS III scores were categorized into HY stages using reported distribution of these scores across HY stages in the literature (158–160). OFF times were categorized into OFF states assuming a 16-hour waking day. As the therapies are indicated for patients with advanced PD, we only include patients with a starting health state of HY 3/OFF 2 or worse. Our model population thus include patients with a mean age of 63.4 years, with 71% being male, 60% starting in HY 3, and 72% starting in OFF 2.

Model Inputs

We provide an overview of the model inputs below. Further details can be found in **Tables 7–8**.

Treatment Efficacy

Treatment efficacy of each therapy was determined by improvements in UPDRS/MDS-UPDRS part III and OFF time at 3-month follow-up and was obtained from a network meta-analysis of randomized controlled trials (161). Our model captured the initial treatment effect by patients receiving therapies other than BMT to improve to a better health state in the first cycle of the model. Starting from the second cycle, patients in all treatment strategies moved through the model based on the reported HY and OFF state transition probabilities reported in the literature (162–164). Improvements in the first cycle helped delay progression to worse health states, which informed long-term treatment effects.

Adverse Events and Discontinuation

Using network meta-analytic estimates, our model accounted for risk of falls and dyskinesia with each therapy. Additionally, we considered the risk of infection and device complication related to DBS and adverse events leading to tube replacement for LCIG (165–167). Treatment discontinuation rates in the first cycle were estimated from clinical trials (42,52,131,136). As adverse events and discontinuation are more likely to occur during the initial treatment period, those who remained on treatment at the end of cycle 1 were assumed to continue treatment thereafter.

Costs

We captured costs of medication acquisition, devices and supplies, surgery, quarterly follow-up, adverse events, and health state-specific costs. For DBS, costs of electrodes/device implantation surgery, management of complications post-surgery, device replacement, and concomitant antiparkinsonian medication were included (83). For LCIG, we included costs of purchasing LCIG cassettes, tube insertion surgery and management of complications post-surgery, tube replacement, and concomitant medication (101,151). For CSAI and LDp/CDp, we captured drug and concomitant medication costs (151,168). BMT medication costs were acquired from the literature (83). Finally, in all strategies, we also accounted for costs of follow-up visits to the neurologist, adverse events (including falls and dyskinesia) and health state-specific costs (83,101,169).

Mortality and Quality of Life

Effectiveness was measured in quality-adjusted life years (QALY) and health-state specific quality of life was obtained from a previous cost-effectiveness analysis (101). Mortality rates were specific to age and gender, and were based on the US Life Tables (170). PD-specific mortality was captured by applying HY stage-specific hazard ratios (164).

Cost-Effectiveness Analysis

We calculated the costs and QALYs that a patient accrues on average over their lifetime with each therapy. We then determined if any therapies were dominated, i.e. more costly but less effective than another therapy or a combination of different therapies. Finally, the difference in costs and benefits between two undominated strategies was used to calculate the incremental cost-effectiveness ratio (ICER). In our analysis, a therapy was of good value if its ICER was below the conventional US willingness-to-pay (WTP) threshold of \$100,000 per QALY. The primary analysis was conducted under a US third party payer perspective. All costs and utilities were discounted at 3%. Analyses were done in TreeAge Pro Healthcare 2026 R1.1 (171).

Analyses of Uncertainty

We performed one-way sensitivity analyses in which input parameters were varied between –25% and +25% for most parameters, except for treatment efficacy parameters which were varied between –50% and +100%, as these network meta-analytic values had wide credible intervals. We performed additional price threshold analyses to determine the prices at which LDp/CDp and CSAI would become cost-effective compared to BMT at the conventional WTP threshold of \$100,000/QALY. We then conducted various scenario analyses to further test our assumptions. As PD hampers patients' activities and requires significant caregiver support, we considered a societal perspective, wherein we took into account caregiver cost and disutility as well as costs due to lost productivity (14). We also considered a starting population consisting entirely of HY3-OFF2 patients, representing the earliest state patients can be indicated for advanced therapies. To investigate the impact of upfront costs on the cost-effectiveness of therapies, we looked at shorter time horizons from 01 to 10 years. We further investigated parameter uncertainty by testing alternative sets of additional mortality rate and health state transition probabilities reported in the literature. As there is uncertainty around long-term treatment benefit and discontinuation, we considered long-term treatment benefit expressed as a reduction in OFF state transition probabilities (instead of as a downstream consequence of the initial treatment benefit in the base case analysis) and allowed for long-term treatment discontinuation. Finally, as only LDp/CDp was reported to decrease the risk of falls, we considered a lower rate of falls exclusively for LDp/CDp. We also performed a probabilistic sensitivity analysis to assess the robustness of the model.

Table 7. Input parameters in the base case analysis

Parameter	Value	Sources
Costs (2026 US\$)		
Medications		
LCIG	\$243.79 per cassette	(151)
LDp/CDp	\$336.96 per vial	(151)
CSAI	\$336.96 per vial	Assumption, (168)
Additional medication usage	10% extra	Assumption, (172)
Concomitant oral medications (per cycle)		
DBS	\$784– \$1,244 after 11 years	Calculated, (83,173)
LCIG	\$46.05	Calculated, (136,174)
CSAI	\$143.53	Calculated, (52,174)
LDp/CDp	\$77.62	Calculated, (106,174)
BMT	\$1834.94	(83)
Surgery and start-up supplies		
DBS neurostimulator + implantation	\$47,077.84	(83)
LCIG surgery	\$5,664.03	(101)
LCIG tube	\$2,970.05	(101)
Replacements		
DBS neurostimulator	\$37,177.14	(83)
LCIG tube	\$1,363.98	(101)
Monitoring		
Neurologist visit	\$210.19	(169)
Checkup frequency	BMT: 04 per year Other: 06 per year	Assumption
Adverse events		
Falls	\$7,016.13	(83)
Dyskinesia	\$420.38	(175)
DBS infection management	\$32,696.86	(83)
DBS device complication	\$22,181.02	(83)
DBS explantation	\$6,859.91	(83)
LCIG tube removal	\$1,032.37	(101)
Mortality	US Life Table	(170)
Mortality hazard ratios		
HY 1–3	1.18	(164)
HY 4	2.37	(164)
HY 5	3.34	(164)
Increased falls hazard ratios		
HY 1–3	1.00	(176)
HY 4	1.72	(176)
HY 5	2.96	(176)
Probabilities (per cycle)		
DBS neurostimulator replacement	0.0625	(83)

LCIG tube replacement	0.128		Calculated, (167,177)
DBS infection	0.0318 in first cycle; 0.0025 in subsequent cycles		(83)
DBS device complication	0.05 in first cycle		Assumption
Falls	BMT	0.061	NMA results (161), Assumed for CSAI
	DBS	0.068	
	LCIG	0.097	
	CSAI	0.061	
	LDp/CDp	0.032	
	Increases to 0.125 after 5 years		Assumption
Dyskinesia	BMT	0.054	NMA results (161)
	DBS	0.044	
	LCIG	0.062	
	CSAI	0.283	
	LDp/CDp	0.063	
Discontinuation (first cycle only)	DBS	0.091	(42,52,131,136)
	LCIG	0.054	
	CSAI	0.189	
	LDp/CDp	0.351	
Falls requiring hospitalization	62%		(83)
Dyskinesia requiring intervention	15%		Assumption
Transition probabilities (per cycle)			
HY 1 → HY 2	0.062		(162)
HY 2 → HY 3	0.033		(162)
HY 3 → HY 4	0.047		(162)
HY 4 → HY 5	0.076		(162)
OFF 0 → OFF 1	0.212		(164)
OFF 1 → OFF 2	0.066		(164)
OFF 2 → OFF 3	0.038		(164)
OFF 3 → OFF 4	0.022		(164)
Health state costs & Utilities (annually)			
HY 1 – OFF 0	0.818	\$1,579.44	(101)
HY 1 – OFF 1	0.748	\$5,102.76	(101)
HY 1 – OFF 2	0.677	\$13,446.54	(101)
HY 1 – OFF 3	0.607	\$28,338.15	(101)
HY 1 – OFF 4	0.536	\$49,526.40	(101)
HY 2 – OFF 0	0.709	\$4,201.78	(101)
HY 2 – OFF 1	0.638	\$11,628.54	(101)
HY 2 – OFF 2	0.568	\$25,718.84	(101)
HY 2 – OFF 3	0.497	\$46,027.09	(101)
HY 2 – OFF 4	0.427	\$69,649.27	(101)
HY 3 – OFF 0	0.599	\$9,982.13	(101)
HY 3 – OFF 1	0.528	\$23,049.61	(101)
HY 3 – OFF 2	0.458	\$42,780.98	(101)
HY 3 – OFF 3	0.387	\$65,805.56	(101)
HY 3 – OFF 4	0.317	\$88,213.94	(101)
HY 4 – OFF 0	0.489	\$20,419.64	(101)

HY 4 – OFF 1	0.419	\$39,457.07	(101)
HY 4 – OFF 2	0.348	\$62,421.27	(101)
HY 4 – OFF 3	0.278	\$84,531.72	(101)
HY 4 – OFF 4	0.207	\$103,509.69	(101)
HY 5 – OFF 0	0.379	\$35,876.70	(101)
HY 5 – OFF 1	0.309	\$58,957.23	(101)
HY 5 – OFF 2	0.238	\$81,529.51	(101)
HY 5 – OFF 3	0.168	\$100,269.92	(101)
HY 5 – OFF 4	0.097	\$115,778.81	(101)
AE utility decrement			
Falls	–0.02		(178)
Dyskinesia	–23.3%		(175)
Other inputs			
Cohort age (mean ± SD, years)	63.4 ± 8.45		Calculated
Male proportion	0.7112		Calculated
Starting patient distribution			
HY 1–2	0		Starting criteria
HY 3	0.6042		Calculated
HY 4	0.3105		Calculated
HY 5	0.0853		Calculated
OFF 0–1	0		Starting criteria
OFF 2	0.7201		Calculated
OFF 3	0.2693		Calculated
OFF 4	0.0106		Calculated
Efficacy			
OFF time improvement (hours)	DBS	–2.77	NMA results (161)
	LCIG	–2.36	
	CSAI	–2.06	
	LDp/CDp	–1.64	
UPDRS III improvement (points)	DBS	–6.02	NMA results (161)
	LCIG	–3.78	
	CSAI	–4.02	
	LDp/CDp	–3.66	
Duration of the waking day (hours)	16		Assumption

Table 8. Input parameters in sensitivity analyses

Parameter	Value		Sources
Societal perspective			
Caregiving costs (per year)	HY 1–2	\$1,359.44	(14)
	HY 3	\$7,048.82	
	HY 4–5	\$30,583.92	
Lost productivity (per year)	HY 1–2	\$9,416.23	(14)
	HY 3	\$8,560.40	
	HY 4–5	\$3,858.62	
Caregiver disutility	HY 1	−0.014	(101)
	HY 2	−0.035	
	HY 3	−0.061	
	HY 4	−0.087	
	HY 5	−0.114	
Alternate mortality hazard ratio			
HY 1	1.00		(179)
HY 2	2.03		(179)
HY 3	2.16		(179)
HY 4	4.99		(179)
HY 5	4.99		(179)
Alternate HY stage transition probabilities			
HY 1 → HY 2	0.099		(180)
HY 2 → HY 3	0.020		(180)
HY 3 → HY 4	0.082		(180)
HY 4 → HY 5	0.077		(180)
Alternate OFF stage transition probabilities			
OFF 0 → OFF 1	0.162		(101)
OFF 1 → OFF 2	0.067		(101)
OFF 2 → OFF 3	0.067		(101)
OFF 3 → OFF 4	0.067		(101)
Alternate long-term benefit expression			
OFF stage transition risk ratio	DBS	0.63	(74), Assumed for LDp/CDp
	LCIG	0.6	
	CSAI	0.65	
	LDp/CDp	0.65	
Long-term discontinuation rate (per cycle)	DBS	0.01	Assumption
	LCIG	0.015	
	CSAI	0.025	
	LDp/CDp	0.02	
Lower risk of falls for LDp/CDp			
Probability of falls	0.032 in all cycles		

Results

Base Case Analysis

Across all five strategies, DBS was the best strategy from a cost-effectiveness perspective. It dominated BMT and the three infusion therapies (**Panel A, Table 9**). Using DBS costed \$2,300 less than BMT but provided an additional 0.80 QALYs over a lifetime. Compared to the infusion options, DBS costed \$740,000 to \$930,000 less and gave an extra 0.10 to 0.36 QALYs.

Among the infusion options, LCIG costed \$1,691,554 to provide 2.79 QALYs over a lifetime. It dominated the newer subcutaneous infusions – LDp/CDp and CSAI – costing \$10,000 to \$186,000 less and providing an additional 0.24 to 0.26 QALYs (**Panel B, Table 9**).

When comparing individual advanced therapies to BMT, the infusion therapies were more costly but also provided more QALYs, with ICERs ranging from \$1.05 million to \$1.98 million (**Panel C, Table 9**). LDp/CDp costed an extra \$751,826 while giving 0.44 more QALYs compared to BMT, for an ICER of \$1.69 million per QALY. Meanwhile, CSAI costed an extra \$927,913 while giving 0.47 more QALYs, leading to an ICER of nearly \$1.98 million per QALY.

Table 9. Base case Cost-effectiveness Results

<i>Strategy</i>	<i>Cost</i>	<i>Δ Cost</i>	<i>QALY</i>	<i>Δ QALY</i>	<i>ICER</i>
<i>Panel A: Comparison across all strategies[†]</i>					
<i>DBS</i>	947,814		2.89		
<i>BMT</i>	950,134	2,319	2.09	−0.80	Dominated
<i>LCIG</i>	1,691,554	743,740	2.79	−0.10	Dominated
<i>LDp/CDp</i>	1,701,960	754,146	2.53	−0.36	Dominated
<i>CSAI</i>	1,878,046	930,232	2.56	−0.33	Dominated
<i>Panel B: Comparison between infusion therapies[†]</i>					
<i>LCIG</i>	1,691,554		2.79		
<i>LDp/CDp</i>	1,701,960	10,406	2.53	−0.26	Dominated
<i>CSAI</i>	1,878,046	186,492	2.56	−0.24	Dominated
<i>Panel C: Comparison versus best medical therapy</i>					
<i>DBS</i>	947,814	−2,319	2.89	0.80	Dominating
<i>LCIG</i>	1,691,554	741,420	2.79	0.70	1,052,246
<i>LDp/CDp</i>	1,701,960	751,826	2.53	0.44	1,695,815
<i>CSAI</i>	1,878,046	927,913	2.56	0.47	1,979,480

Analyses conducted over a lifetime horizon. Costs are in 2026 US dollars.

[†]*Each strategy compared to the next less costly strategy, excluding any dominated strategies.*

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years; BMT, best medical therapy; DBS, deep brain stimulation; LDp/CDp, continuous subcutaneous foslevodopa-foscarbidopa infusion; LCIG, levodopa-carbidopa intestinal gel; CSAI, continuous subcutaneous apomorphine infusion.

Sensitivity Analyses and Price Thresholds

For all values in the range of $\pm 25\%$ of base case for key parameters (and -50% to $+100\%$ of baseline efficacy), the ICER for DBS compared to BMT remained below the conventional WTP threshold of \$100,000/QALY (**Figure 4a**). LCIG will no longer be cost-effective versus LDp/CDp if LDp/CDp can reduce OFF time by at least 3.2 hours (95% increase in efficacy from base case), or if LCIG only reduces OFF time by 1.9 hours (19% decrease), or if LCIG costs \$254 per unit or more (4% price increase). Similarly, LCIG will no longer be cost-effective versus CSAI if LCIG costs \$301 per unit or more (23% price increase) (**Figures 4b–c**).

Cost-effectiveness acceptability curves revealed that at a WTP threshold of \$100,000/QALY, DBS has a 97% probability of being cost-effective. (**Figure 5**).

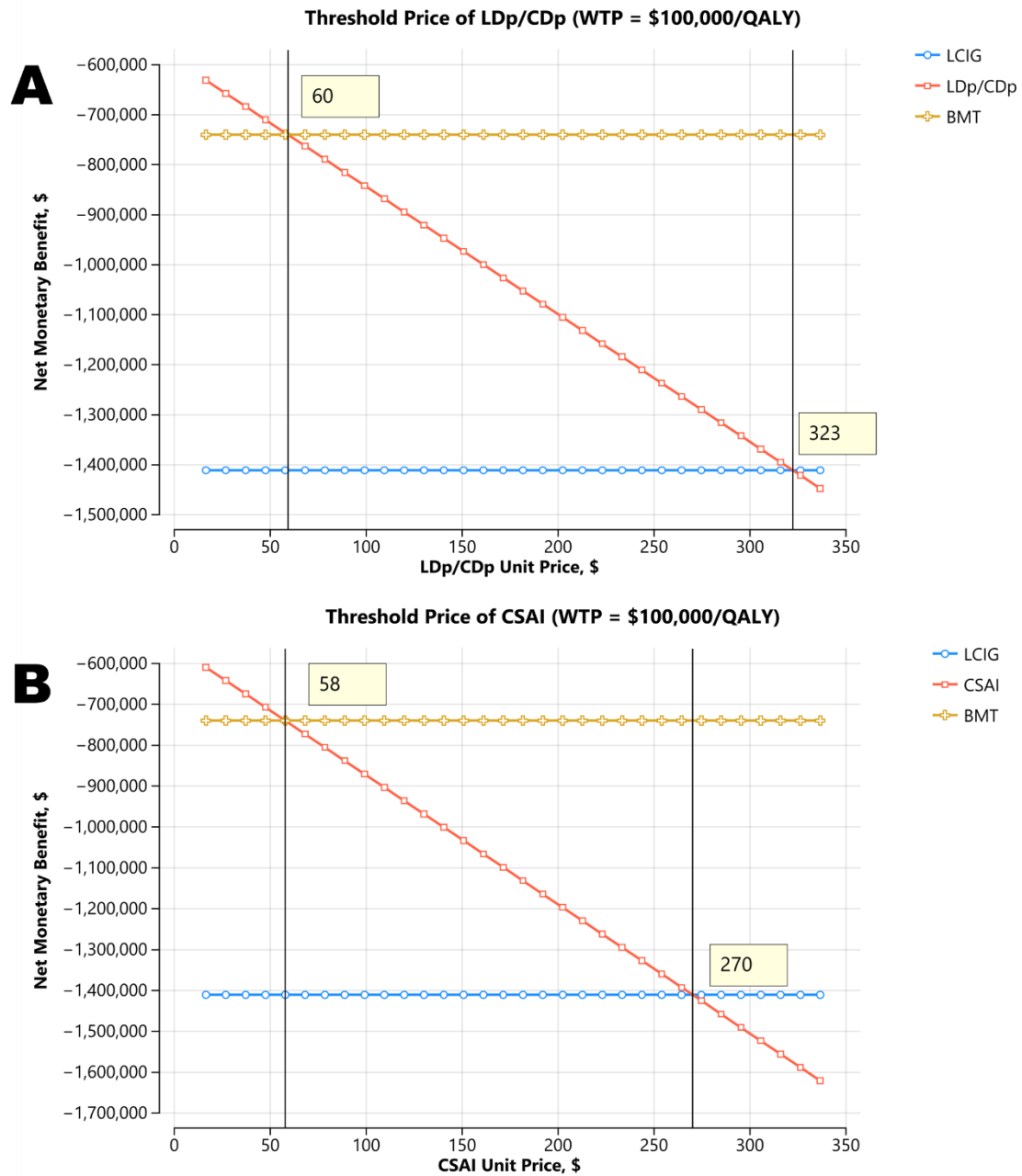
If the price of LDp/CDp was reduced by 4% to \$323, it would become the most cost-effective among the three infusion therapies (**Figure 3a**). At this price, while LCIG would be more effective than LDp/CDp, its higher cost would not justify the additional benefits. Similarly, pricing CSAI at \$270 per unit or below (a 20% reduction from base case), would make it the most cost-effective infusion therapy (**Figure 3b**).

Scenario Analyses

DBS remained the most cost-effective option across all specified scenarios, except for the 1-year horizon case where it is not cost-effective versus BMT (**Table 8**). The infusion therapies remained dominated by DBS across all scenarios.

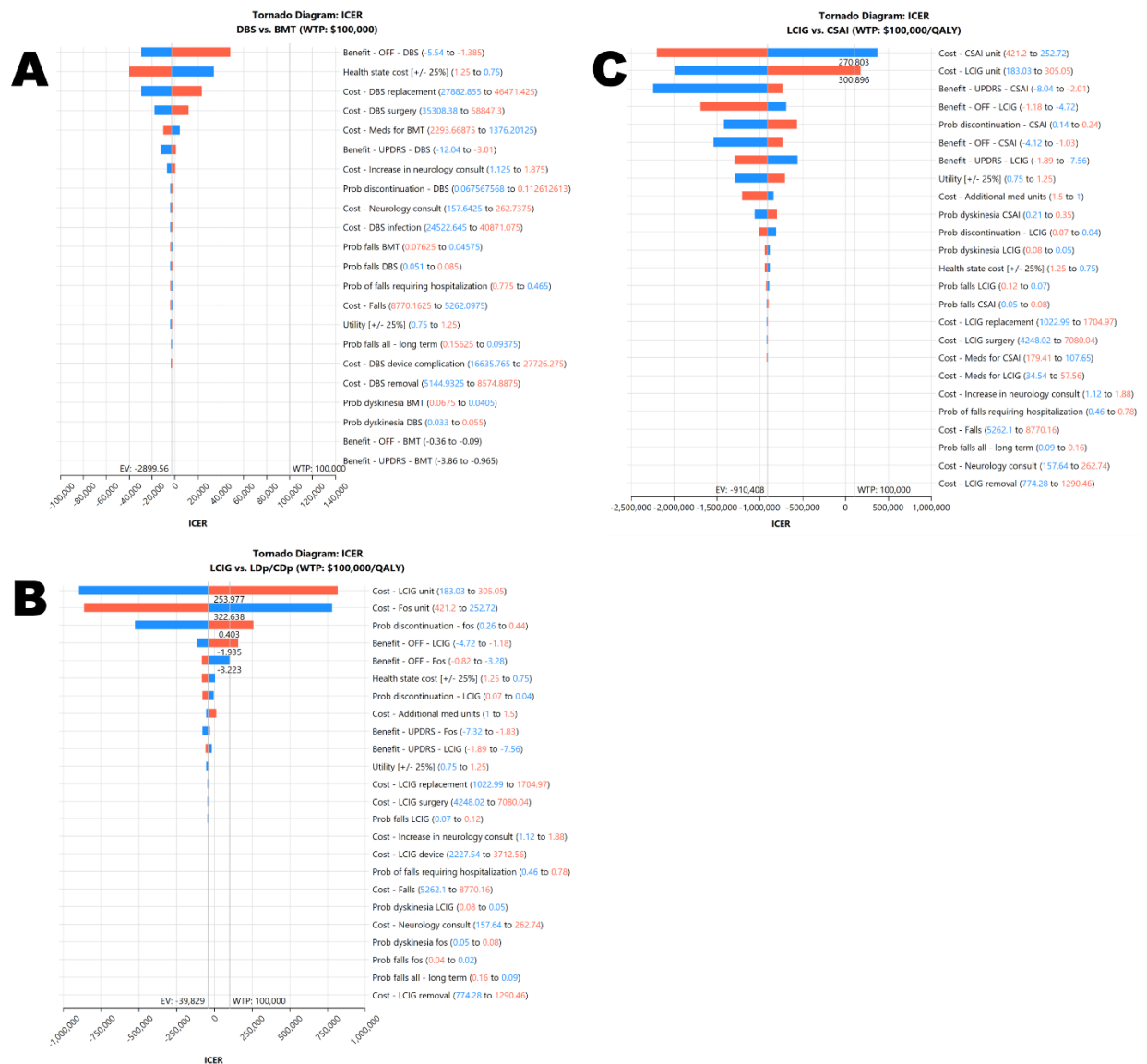
When considering only the infusion therapies, results remained similar to the base case. However, if long-term treatment benefit was expressed as a reduction in OFF state transition probabilities rather than as a downstream consequence of the initial treatment benefit, LDp/CDp could become the most cost-effective option among the infusion therapies (**Supplementary Table 15**). CSAI remained dominated by LCIG in all cases.

Figure 3: Threshold Prices



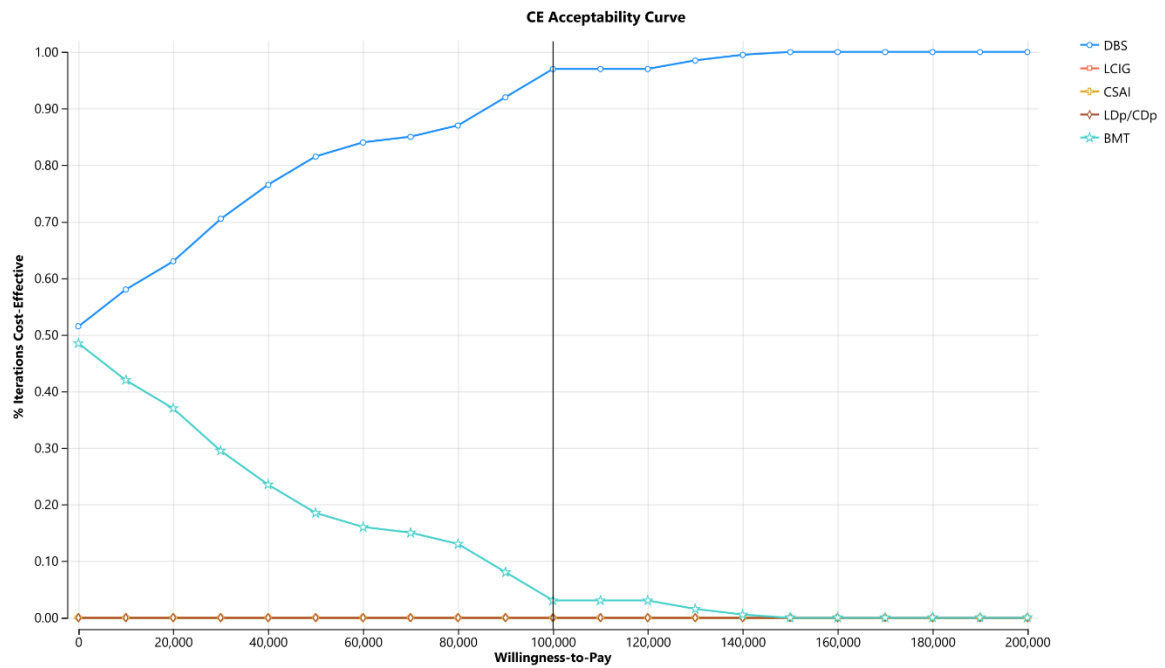
WTP, willingness-to-pay; LCIG, levodopa-carbidopa intestinal gel; LDp/CDp, continuous subcutaneous foslevodopa/foscarbidopa infusion; CSAI, continuous subcutaneous apomorphine infusion; BMT, best medical therapy.

Figure 4. One-way Sensitivity Analyses



ICER, incremental cost-effectiveness ratio; WTP, willingness-to-pay; EV, expected value; DBS, deep brain stimulation; LCIG, levodopa-carbidopa intestinal gel; LDp/CDp, continuous subcutaneous foslevodopa/foscarbidopa infusion; CSAI, continuous subcutaneous apomorphine infusion; BMT, best medical therapy.

Figure 5. Cost-effectiveness acceptability curve



CE, cost-effectiveness; DBS, deep brain stimulation; LCIG, levodopa-carbidopa intestinal gel; LDp/CDp, continuous subcutaneous foslevodopa/foscarbidopa infusion; CSAI, continuous subcutaneous apomorphine infusion; BMT, best medical therapy.

Table 10: Results of Scenario Analyses

<i>Strategy</i>	<i>Cost</i>	<i>Δ Cost</i>	<i>QALY</i>	<i>Δ QALY</i>	<i>ICER</i>
<i>Societal perspective</i>					
<i>DBS</i>	1,214,067		2.04		
<i>BMT</i>	1,227,886	13,818	1.21	−0.83	Dominated
<i>LCIG</i>	1,959,341	745,274	1.95	−0.10	Dominated
<i>LDp/CDp</i>	1,972,407	758,340	1.68	−0.37	Dominated
<i>CSAI</i>	2,147,691	933,623	1.74	−0.30	Dominated
<i>Alternate starting population: 100% HY 3 – OFF 2</i>					
<i>BMT</i>	899,224		2.68		
<i>DBS</i>	906,228	7,004	3.49	0.81	8,644
<i>LCIG</i>	1,691,445	785,218	3.37	−0.12	Dominated
<i>LDp/CDp</i>	1,698,707	792,479	3.11	−0.38	Dominated
<i>CSAI</i>	1,887,502	981,274	3.11	−0.38	Dominated
<i>1-year horizon</i>					
<i>BMT</i>	68,111		0.36		
<i>DBS</i>	108,378	40,266	0.42	0.06	633,136
<i>LCIG</i>	148,596	40,218	0.41	−0.01	Dominated
<i>LDp/CDp</i>	151,399	43,022	0.39	−0.03	Dominated
<i>CSAI</i>	163,654	55,277	0.38	−0.04	Dominated
<i>5-year horizon</i>					
<i>DBS</i>	345,982		1.67		
<i>BMT</i>	347,203	1,221	1.31	−0.36	Dominated
<i>LCIG</i>	653,747	307,765	1.61	−0.05	Dominated
<i>LDp/CDp</i>	668,038	322,056	1.50	−0.17	Dominated
<i>CSAI</i>	735,939	389,957	1.50	−0.17	Dominated
<i>10-year horizon</i>					
<i>DBS</i>	617,039		2.41		
<i>BMT</i>	635,127	18,088	1.81	−0.60	Dominated
<i>LCIG</i>	1,144,313	527,274	2.34	−0.08	Dominated
<i>LDp/CDp</i>	1,162,702	545,663	2.14	−0.27	Dominated
<i>CSAI</i>	1,282,026	664,988	2.15	−0.26	Dominated
<i>Alternate mortality</i>					
<i>DBS</i>	832,508		2.65		
<i>BMT</i>	846,454	13,945	1.93	−0.71	Dominated
<i>LCIG</i>	1,493,990	661,482	2.56	−0.09	Dominated
<i>LDp/CDp</i>	1,508,931	676,422	2.32	−0.32	Dominated
<i>CSAI</i>	1,660,963	828,455	2.34	−0.30	Dominated
<i>Alternate HY transition probabilities</i>					
<i>DBS</i>	942,422		2.74		
<i>BMT</i>	952,420	9,998	1.86	−0.88	Dominated
<i>LCIG</i>	1,670,184	727,762	2.63	−0.10	Dominated
<i>LDp/CDp</i>	1,681,873	739,451	2.35	−0.39	Dominated
<i>CSAI</i>	1,852,818	910,396	2.39	−0.34	Dominated
<i>Alternate OFF transition probabilities</i>					
<i>BMT</i>	995,959		1.93		
<i>DBS</i>	1,008,981	13,022	2.66	0.74	17,662
<i>LCIG</i>	1,753,574	744,593	2.56	−0.10	Dominated
<i>LDp/CDp</i>	1,760,693	751,712	2.32	−0.35	Dominated
<i>CSAI</i>	1,938,841	929,860	2.34	−0.32	Dominated

<i>Strategy</i>	<i>Cost</i>	<i>Δ Cost</i>	<i>QALY</i>	<i>Δ QALY</i>	<i>ICER</i>
<i>Alternate long-term benefit: Reduced OFF stage transition, linear decay in 5 years</i>					
<i>DBS</i>	927,206		2.90		
<i>BMT</i>	950,134	22,927	2.09	−0.82	Dominated
<i>LDp/CDp</i>	1,397,029	469,823	2.52	−0.38	Dominated
<i>LCIG</i>	1,427,518	500,311	2.80	−0.10	Dominated
<i>CSAI</i>	1,445,537	518,331	2.58	−0.32	Dominated
<i>Alternate long-term benefit: Reduced OFF stage transition, sustained for 5 years</i>					
<i>DBS</i>	902,791		2.99		
<i>BMT</i>	950,134	47,342	2.09	−0.90	Dominated
<i>LDp/CDp</i>	1,385,943	483,152	2.56	−0.43	Dominated
<i>LCIG</i>	1,403,817	501,026	2.89	−0.10	Dominated
<i>CSAI</i>	1,432,623	529,832	2.63	−0.36	Dominated
<i>Alternate long-term benefit: Reduced OFF stage transition, linear decay in 5 years + Societal perspective</i>					
<i>DBS</i>	1,193,459		2.06		
<i>BMT</i>	1,227,886	34,426	1.21	−0.85	Dominated
<i>LDp/CDp</i>	1,667,476	474,017	1.67	−0.39	Dominated
<i>LCIG</i>	1,695,305	501,846	1.95	−0.10	Dominated
<i>CSAI</i>	1,715,182	521,722	1.75	−0.31	Dominated
<i>Alternate long-term benefit: Reduced OFF stage transition, linear decay in 10 years</i>					
<i>DBS</i>	919,286		2.93		
<i>BMT</i>	950,134	30,848	2.09	−0.84	Dominated
<i>LDp/CDp</i>	1,393,184	473,899	2.54	−0.40	Dominated
<i>LCIG</i>	1,419,276	499,991	2.83	−0.10	Dominated
<i>CSAI</i>	1,440,874	521,588	2.60	−0.33	Dominated
<i>Lower long-term falls rate for LDp/CDp</i>					
<i>DBS</i>	947,814		2.89		
<i>BMT</i>	950,134	2,319	2.09	−0.80	Dominated
<i>LCIG</i>	1,691,554	743,740	2.79	−0.10	Dominated
<i>LDp/CDp</i>	1,692,355	744,540	2.58	−0.31	Dominated
<i>CSAI</i>	1,878,046	930,232	2.56	−0.33	Dominated

Analyses conducted over a lifetime horizon. Costs are in 2026 US dollars. Each strategy compared to the next less costly strategy, excluding any dominated strategies. ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years; BMT, best medical therapy; DBS, deep brain stimulation; LDp/CDp, continuous subcutaneous foslevodopa-foscarbidopa infusion; LCIG, levodopa-carbidopa intestinal gel; CSAI, continuous subcutaneous apomorphine infusion; HY, Hoehn and Yahr stage.

Table 11: Results of Scenario Analyses, Considering only Infusion Therapies.

Strategy	Cost	Δ Cost	QALY	Δ QALY	ICER
Societal perspective					
LCIG	1,959,341		1.95		
LDp/CDp	1,972,407	13,066	1.68	−0.27	Dominated
CSAI	2,147,691	188,349	1.74	−0.21	Dominated
Alternate starting population: 100% HY 3 – OFF 2					
LCIG	1,691,445		3.37		
LDp/CDp	1,698,707	7,262	3.11	−0.26	Dominated
CSAI	1,887,502	196,057	3.11	−0.26	Dominated
1-year horizon					
LCIG	148,596		0.41		
LDp/CDp	151,399	2,803	0.39	−0.02	Dominated
CSAI	163,654	15,059	0.38	−0.03	Dominated
5-year horizon					
LCIG	653,747		1.61		
LDp/CDp	668,038	14,290	1.50	−0.11	Dominated
CSAI	735,939	82,191	1.50	−0.12	Dominated
10-year horizon					
LCIG	1,144,313		2.34		
LDp/CDp	1,162,702	18,389	2.14	−0.20	Dominated
CSAI	1,282,026	137,713	2.15	−0.18	Dominated
Alternate mortality					
LCIG	1,493,990		2.56		
LDp/CDp	1,508,931	14,941	2.32	−0.23	Dominated
CSAI	1,660,963	166,973	2.34	−0.21	Dominated
Alternate HY transition probabilities					
LCIG	1,670,184		2.63		
LDp/CDp	1,681,873	11,689	2.35	−0.29	Dominated
CSAI	1,852,818	182,634	2.39	−0.24	Dominated
Alternate OFF transition probabilities					
LCIG	1,753,574		2.56		
LDp/CDp	1,760,693	7,119	2.32	−0.25	Dominated
CSAI	1,938,841	185,267	2.34	−0.22	Dominated
Alternate long-term benefit: Reduced OFF stage transition, linear decay in 5 years					
LDp/CDp	1,397,029		2.52		
LCIG	1,427,518	30,489	2.80	0.28	109,344
CSAI	1,445,537	18,020	2.58	−0.22	Dominated
Alternate long-term benefit: Reduced OFF stage transition, sustained for 5 years					
LDp/CDp	1,385,943		2.56		
LCIG	1,403,817	17,874	2.89	0.32	55,200
CSAI	1,432,623	28,806	2.63	−0.26	Dominated
Alternate long-term benefit: Reduced OFF stage transition, linear decay in 5 years + Societal					
LDp/CDp	1,667,476		1.67		
LCIG	1,695,305	27,829	1.95	0.29	96,944
CSAI	1,715,182	19,876	1.75	−0.21	Dominated
Alternate long-term benefit: Reduced OFF stage transition, linear decay in 10 years					
LDp/CDp	1,393,184		2.54		
LCIG	1,419,276	26,092	2.83	0.29	88,661
CSAI	1,440,874	21,597	2.60	−0.23	Dominated
Lower long-term falls rate for LDp/CDp					
LCIG	1,691,554		2.79		
LDp/CDp	1,692,355	801	2.58	−0.22	Dominated
CSAI	1,878,046	186,492	2.56	−0.24	Dominated

Discussion

This study found that DBS is the least costly and most effective treatment option among the currently approved advanced therapies for PD in the US. Among the three infusion therapies, LCIG is the best strategy. The current lack of cost-effectiveness for the infusion options are mainly explained by the high ongoing medication costs (\$24,000–33,000 every 3 months). Our analysis indicates that a 4-20% reduction in medication price, however, can make LDp/CDp and CSAI the best infusion therapy from a cost-effectiveness perspective.

These results corroborate several studies which found DBS to be cost-effective versus BMT (79,80,83). However, our findings contrast with previous analyses of infusion therapies, where LCIG and CSAI were also found to be cost-effective (74,96,99,101). Several factors explain these differences. First, previous studies of infusion therapies were performed in European contexts, where medication acquisition costs are much lower compared to the US. Medicare reimbursement prices for LCIG are 1.5-2x higher than costs used in previous studies, adjusted for inflation (74,96,99,101). Since CSAI has not been reimbursed by Medicare, we assumed CSAI acquisition costs to be the same as LDp/CDp (168). This price is 6-8x more than the values used by the previous cost-effectiveness analysis of CSAI in the European context (74).

Second, differences in the way long-term treatment benefits are modelled can also explain the differences in findings. Previous analyses modelled both a short-term benefit and a long-term reduction in probability of transitioning to a worse OFF state. However, there is little evidence to determine the exact reduction in OFF state progression in the long-term. The sensitivity analyses in both our study and Chaudhuri et al (101) showed that results can be sensitive to the trajectory of long-term benefit. Walter and Odin too showed that their ICERs were sensitive to the risk ratios capturing treatment benefits (74).

A cost-minimization analysis submitted by the sponsor of LDp/CDp and reanalysed by the Canadian Drug Agency found that LDp/CDp was associated with a minor cost saving after 01 year and was cost neutral to LCIG after 20 years (106). In our analysis, LDp/CDp was dominated by LCIG across all studied time horizons. This difference arises due to different drug unit costs used in the two analyses (LDp/CDp cost ~1.4 times than LCIG in the US-context, while they cost the same in the Canadian-context (106)). Furthermore, we found that reducing LDp/CDp price by only 4% makes LCIG no longer cost-effective.

Our study has several clinical and policy implications. First, as DBS has been shown to be the most effective among all therapies for advanced PD and cost-saving, expanding access to DBS is prudent. Second, in current real-world clinical situations where lack of access and long wait

times for DBS remain issues, if prices of LDp/CDp and CSAI were even slightly lower than their list prices, these therapies – which can potentially serve as intermediate treatments– could be economically valuable for clinicians and patients (70). Third, our analysis indicated that the lack of cost-effectiveness of new infusion therapies was driven by high drug acquisition costs. Payer negotiated price discounts will not only allow access to less invasive and potentially life altering therapies for patients but could also expand the market for manufacturers.

Our study has some limitations. First, our model structure assumes that HY and OFF stages are independent from each other. However, modelling this interplay between clinical symptoms within a Markov model is challenging and the model used in our study is a validated and the most commonly used PD progression model in the literature (79). Second, our analysis could not account for the costs of the infusion pumps as information was not available on the agreement between the Medicare and the manufacturers on the provision of these pumps in the United States, and existing economic studies of infusion therapies in other countries were mixed. We note that in Canada, the pump used to administer LDp/CDp is provided free of cost by the manufacturer (106). Nonetheless, adding pump costs would make infusion therapies even more costly and our estimates are therefore conservative. Moreover, data on long-term drug usage for infusion therapies are lacking. The dosage required to control symptoms may increase over time as PD progresses, thus per-patient costs to acquire infusion medications may continue to rise. Third, given insufficient evidence on the long-term discontinuation of advanced therapies, our analysis assumed treatment discontinuation occurred only in the first cycle. Similarly, our analysis relied on 3-month trial efficacy results as 12 weeks was the longest endpoint reported in trials of LDp/CDp. However, RCTs of DBS and LCIG indicate stable efficacy with 24- and 52-week results similar to 12-week results. Future studies could re-evaluate the cost-effectiveness of these therapies as longer term evidence becomes available.

Conclusion

DBS is the least costly and most effective treatment option among the currently approved advanced therapies for PD in the US. However, as barriers to DBS access remain, the FDA approval of CSAI and LDp/CDp opens opportunities for patients to benefit from non-invasive alternatives to existing surgical options. At current prices, these therapies are not cost-effective compared with DBS, LCIG and BMT. However, if the price of LDp/CDp and CSAI is reduced by 82-83%, these therapies could become the most cost-effective. Reducing their price by only 4-20% would make LDp/CDp and CSAI the best infusion therapy from a cost-effectiveness perspective.

CONTRIBUTION STATEMENT

The candidate has co-authored this paper with his supervisor – Dr. Shweta Mital, and his advisory committee members – Dr. Jamie Falk and Dr. Dung Nguyen. He conceptualized the idea, collected data, built and analyzed the model, interpreted the results, wrote the first draft of the paper, and contributed to subsequent revisions.

CHAPTER 5

CONCLUSIONS

With a projected 1.7 million patients and economic impact of \$112.4 billion dollars by 2045 in the United States alone, Parkinson's Disease presents a major public health challenge globally. Policymakers must not only strive to keep patients healthy, but also to suppress costs from going out of control. One-fifth to nearly half of all patients with Parkinson's Disease will progress to its advanced stage, when quality of life is severely compromised and the cost of disease is at its highest. Treatment historically depended on capacity-constrained, surgical deep brain stimulation (DBS) or levodopa-carbidopa intestinal gel (LCIG). Barriers to access remained severe, with wait times counted in years and 98% of patients not getting treatment. Newly approved subcutaneous infusions, namely continuous subcutaneous apomorphine infusion (CSAI) and continuous subcutaneous foslevodopa-foscarbidopa infusion (LDp/CDp) can help fill this unmet medical need.

Findings from my systematic review and network meta-analysis from Chapter 3 showed that DBS is the most effective treatment among the advanced therapies at reducing time spent in the OFF medication state, as well as improving clinical motor functions and quality of life. Meanwhile, the newly approved subcutaneous infusions are not as effective as DBS. However, with few exceptions, the differences in therapeutic effect are small and not clinically important. On the other hand, subcutaneous infusions have lower risk of serious adverse events (SAEs) and falls compared to the surgical counterparts.

These results helped inform my cost-effectiveness analysis in Chapter 4. The analysis revealed that the subcutaneous infusions have limited economic value. LDp/CDp costed an extra \$751,826 when compared to BMT, while giving 0.44 more QALYs for an ICER of \$1.69 million per QALY. At the same time, CSAI costed \$927,213 compared to BMT while giving 0.47 more QALYs, leading to an ICER of nearly \$1.98 million per QALY. Notably, DBS dominates all other therapies and is even likely to be cost saving compared to BMT, while LCIG also dominates the new subcutaneous infusions. Against a background of limited DBS access, however, the subcutaneous infusions gain value. LDp/CDp and CSAI can become the best infusion therapy from a cost-effectiveness perspective with only a minor price reduction of 4-20%. Drug unit cost is the main cost driver for subcutaneous infusions.

For policymakers, these findings highlight the need to tackle access barriers to DBS, being the most cost-effective treatment for advanced PD, and may even be cost saving in the long term. From a clinical perspective, these findings help clinicians and patients make their clinical decisions. Efficacy differences between therapies are small and may not be noticeable. For patients waiting for DBS, the new subcutaneous infusions, CSAI and LDp/CDp, can be economically and clinically valuable as intermediate therapies. Payers should also enter price

negotiations, which will allow more patients to access these therapies and potentially expand the market for manufacturers.

There were some challenges and limitations. First, existing randomized trial evidence base is relatively lacking and reports numerous outcome values judged to be at risk of bias. This led to higher-than-expected uncertainty in the efficacy values used to inform the economic model. A probabilistic sensitivity analysis was conducted to evaluate parameter uncertainty, which resulted in a 97% probability that DBS is cost-effective. The economic conclusion is thus reliable. Second, implementing long-term treatment efficacy in the model was more complex than initially expected. Trials examining advanced therapies report their efficacy as mean differences (MD) between treatment arms. MD can be used quite simply to inform short-term efficacy, however it is not immediately apparent how to implement MD in a Markov state transition model, which usually relies on a risk or hazard ratio to capture long-term efficacy using differences in transition probabilities between health states. Previous studies modelled both a short-term benefit and a long-term reduction in the probability of transitioning to a worse OFF state (using a risk ratio). However, there is little evidence to determine the exact reduction in OFF state progression in the long term, and previous studies used highly variable risk ratios. Furthermore, this risk ratio is highly influential on economic results and can easily be used to change conclusions. My analysis implemented long-term benefits as downstream effects from short-term benefits. This ensures the relative rankings of therapies are consistent. Third, both long-term treatment efficacy and long-term drug usage patterns are lacking. As PD continues to progress, treatment benefit is expected to diminish, while patients may need higher doses of infusion medications which increases costs. The exact long-term trajectory is not determined, and so my results, which extrapolated short-term trial data, may have higher uncertainty. To address this, numerous scenario analyses were performed, and all gave similar results to the base case. The economic conclusion is thus robust.

Future economic evaluations of advanced therapies for PD should look to more sources to inform model inputs, in particular, real-world evidence and patient-level data. Furthermore, with even newer, potentially disease-modifying therapies on the horizon such as gene therapies or neural stem cell transplantation, interests will be focused on the economic value of these therapies, especially against the existing “conventional” treatments.

In summary, my thesis provided relevant comparative efficacy and economic evidence that can inform clinicians and payers in treatment and reimbursement decisions around advanced PD therapies in general and the newly approved subcutaneous infusions.

CHAPTER 6

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APPENDIX

In the network meta-analysis, we considered DBS to be a single comparator that included stimulation of the subthalamic nucleus (STN), globus pallidus internus (GPi), and caudal zona incerta (cZi). Existing direct comparative RCT evidence shows that STN and GPi DBS are similar in terms of improving motor symptoms and QoL, as well as safety (165,181). When compared with best medication therapy, cZi DBS has also shown effects on motor symptoms comparable to that of STN and GPi DBS (135). We also considered LDp/CDp to be a single comparator that included the continuous subcutaneous infusion of foslevodopa-foscarbidopa as well as levodopa-carbidopa. The subcutaneous infusion of either foslevodopa-foscarbidopa or levodopa-carbidopa has been individually shown to have pharmacokinetic properties similar to that of LCIG (182,183). For our analyses, we considered BMT to be a single comparator that included optimized medication treatment, immediate-release levodopa-carbidopa, placebo, usual care, or sham stimulation.

We conducted the network meta-analysis using a contrast-based Bayesian three-level hierarchical model, which incorporates class effects. Treatments were nested within two classes: surgical (DBS) and infusion (LCIG, CSAI, LDp/CDp). Following recommendations by NICE Decision Support Unit, we used vaguely informative priors for all treatment effects and study-specific intercept parameters (184). For binary outcomes, we used $\log-N(-2.01, 1.64^2)$ for the between-trial heterogeneity parameter τ^2 , according to guidance by Turner et al (185). Details of prior distributions used in the main analysis can be found in Supplementary Table 2.

For each outcome, we fitted up to four types of models: fixed-effects, random-effects, both with and without exchangeable class effects. The deviance information criterion (DIC) was used to compare models, and a $\Delta DIC \leq -2$ was needed to select a more complex model. Based on the DIC, we selected and reported results from fixed-effects models for OFF-time, quality of life, daily motor functions, “good” ON time, risk of falls, and risk of dyskinesia; from fixed models with class effects for clinical motor functions; and from random-effects models for risk of SAEs. Sensitivity analyses showed consistent estimates between different model types, with the only notable difference being wider CrIs for random-effects models.

The models were fitted using Markov Chain Monte Carlo simulation. We used four chains of 10,000 iterations with the first 5,000 discarded as burn-in. We assessed convergence using the Gelman-Rubin (R-hat) statistic and deem convergence to be achieved if this value is less than 1.01 for all model parameters. Analyses were conducted using R 4.5.1 and package *multinma* version 0.8.1 (186).

Supplementary Table 1. PRISMA-NMA Checklist

Section/Topic	Item #	Checklist Item	Reported on section
TITLE			
Title	1	Identify the report as a systematic review <i>incorporating a network meta-analysis (or related form of meta-analysis)</i> .	Title
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: Background: main objectives Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and <i>synthesis methods, such as network meta-analysis</i> . Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; <i>treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.</i> Discussion/Conclusions: limitations; conclusions and implications of findings. Other: primary source of funding; systematic review registration number with registry name.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, <i>including mention of why a network meta-analysis has been conducted</i> .	Introduction
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	Not reported (no registration)
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. <i>Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification)</i> .	Methods, sections “Search strategy” and “Eligibility criteria”
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Methods, section “Search strategy”

Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary Table 12
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Methods, section “Study selection”
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Methods, section “Data collection”
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Methods, section “Eligibility criteria”
Geometry of the network	S1	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	Table 4-6 footnotes
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Methods, section “Risk of bias assessment”
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). <i>Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.</i>	Methods, section “Data analysis”
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • <i>Handling of multi-arm trials;</i> • <i>Selection of variance structure;</i> • <i>Selection of prior distributions in Bayesian analyses; and</i> • <i>Assessment of model fit.</i>	Methods, section “Data analysis”
Assessment of Inconsistency	S2	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	Not performed, star-shaped network
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Not performed, insufficient studies

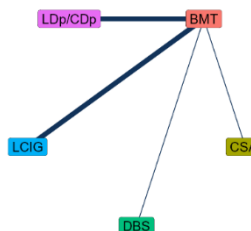
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • <i>Alternative formulations of the treatment network; and</i> • <i>Use of alternative prior distributions for Bayesian analyses (if applicable).</i>	Methods, sections “Certainty assessment” and “Sensitivity analyses”
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Results, section “Study characteristics”, Figure 2
Presentation of network structure	S3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	Supplementary Tables 3a-i
Summary of network geometry	S4	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	Results, section “Study characteristics”, Table 3
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	Results, section “Risk of bias assessment”, Supplementary Figures 1c-9c
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. <i>Modified approaches may be needed to deal with information from larger networks.</i>	Supplementary Figures 1a-9a
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. <i>In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.</i> If additional summary measures were explored (such as treatment rankings), these should also be presented.	Results, section “Syntheses of results”, Tables 4-6, Supplementary Tables 3a-i, Supplementary Tables 4-12, Supplementary Figures 1b-9b

Exploration for inconsistency	S5	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, <i>P</i> values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	Not performed, star-shaped network
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	Not performed, insufficient studies
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, <i>alternative network geometries studied</i> , <i>alternative choice of prior distributions for Bayesian analyses</i> , and so forth).	Results, section “Sensitivity analyses”, Supplementary Figures 10-11
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	Discussion
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). <i>Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).</i>	Discussion
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Conclusion
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	Reported

Supplementary Table 2. Prior distribution used in the main analysis

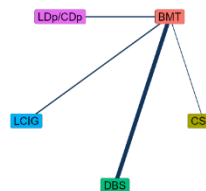
Outcome	Treatment effects	Between-trial heterogeneity	Class effects	Within-class variance
OFF time	N(0, 10 ²)	half-N(0, 5 ²)	N(0, 10 ²)	half-N(0, 5 ²)
Good ON time				
UPDRS III	N(0, 50 ²)	half-N(0, 5 ²)		
PDQ-39				
UPDRS II				
Falls	N(0, 100 ²)	log-N(−2.01, 1.64 ²)		
Dyskinesia				
SAE				
LEDD	N(0, 1000 ²)	half-N(0, 5 ²)	N(0, 100 ²)	

Supplementary Table 3a. Summary of Findings: Estimates of effects, credible intervals, and certainty of evidence for advanced therapies in patients with advanced Parkinson's Disease – OFF time

Efficacy							
OFF-time							
Population: Patients with advanced stage Parkinson’s Disease							
Interventions: Deep brain stimulation (DBS), Levodopa/carbidopa intestinal gel (LCIG), Continuous subcutaneous apomorphine infusion (CSAI), Continuous foslevodopa-foscarbidopa infusion (LDp/CDp)							
Comparator (reference): Best medical therapy (BMT)							
Outcome: Duration of waking day spent in OFF-medication state, range of follow-up between 12 to 24 weeks							
Total studies: 6 RCTs Total participants: 891		Relative Effect (hours) (95% CrI)	Anticipated absolute effects		Certainty of Evidence	Ranking (95% CrI)	Interpretation of Findings
			Without intervention	With intervention (95% CrI)			
●	DBS 1 RCT; 255 participants	−2.59 (−3.61 to −1.57)	−0.18 hours	−2.77 hours (−3.79 to −1.75 hours)	⊕○○○ Very low ^{1,2}	1 st (1 st – 3 rd)	Might be superior
●	LCIG 2 RCT; 130 participants	−2.18 (−3.32 to −1.08)	−0.18 hours	−2.36 hours (−3.50 to −1.26 hours)	⊕⊕○○ Low ^{3,4}	2 nd (1 st – 4 th)	Possibly superior
●	CSAI 1 RCT; 106 participants	−1.88 (−3.11 to −0.62)	−0.18 hours	−2.06 hours (−3.29 to −0.80 hours)	⊕⊕⊕○ Moderate ⁵	3 rd (1 st – 4 th)	Probably superior
●	LDp/CDp 2 RCT; 400 participants	−1.46 (−2.01 to −0.91)	−0.18 hours	−1.64 hours (−2.19 to −1.09 hours)	⊕⊕○○ Low ^{6,7}	4 th (2 nd – 4 th)	Possibly superior
●	BMT	Reference	N/A	N/A	N/A	5 th (5 th – 5 th)	Reference comparator
Explanatory Footnotes							
¹ Very serious risk of bias. Evidence provided by a single unblinded trial with substantial losses to follow-up.							
² Serious imprecision. Sample size < 50% of optimal information size.							
^{3,6} Serious risk of bias. 53/132 participants from high RoB trials, and 79/132 participants from trials with “some concerns” for RoB.							

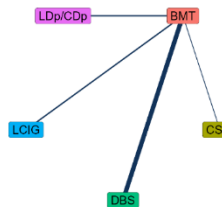
4,5,7 Serious imprecision. Credible interval crosses MCID.				
Indirect comparisons				
Intervention	Comparator	Relative Effect (hours) (95% CrI)	Certainty of Evidence	Interpretation of Findings
 DBS	 LCIG	−0.41 (−1.93 to 1.09)	⊕○○○ Very low ^{1,2}	Might have trivial to no difference
Indirect evidence only				
 DBS	 CSAI	−0.72 (−2.34 to 0.88)	⊕○○○ Very low ^{3,4}	Might have trivial to no difference
Indirect evidence only				
 DBS	 LDp/CDp	−1.13 (−2.29 to 0.01)	⊕○○○ Very low ^{5,6}	Might have trivial to no difference
Indirect evidence only				
 LCIG	 CSAI	−0.30 (−2.00 to 1.36)	⊕○○○ Very low ^{7,8}	Might have trivial to no difference
Indirect evidence only				
 LCIG	 LDp/CDp	−0.72 (−1.96 to 0.52)	⊕○○○ Very low ^{9,10}	Might have trivial to no difference
Indirect evidence only				
 CSAI	 LDp/CDp	−0.42 (−1.78 to 0.96)	⊕⊕○○ Low ^{11,12}	Possibly have trivial to no difference
Indirect evidence only				
Explanatory Footnotes				
1,3,5 DBS evidence has a very serious risk of bias.				
7,9 LCIG evidence has a serious risk of bias.				
11 LDp/CDp evidence has a serious risk of bias.				
2,12 Serious imprecision. Credible interval suggests possibility of substantial benefit.				
4,6,10 Very serious imprecision. Credible interval suggests possibility of substantially large benefit.				
8 Very serious imprecision. Credible interval suggests possibility of both substantial harm and substantial benefit.				

Supplementary Table 3b. Summary of Findings: Estimates of effects, credible intervals, and certainty of evidence for advanced therapies in patients with advanced Parkinson's Disease – Clinical motor functions

Efficacy							
Clinical motor functions							
Population: Patients with advanced stage Parkinson’s Disease							
Interventions: Deep brain stimulation (DBS), Levodopa/carbidopa intestinal gel (LCIG), Continuous subcutaneous apomorphine infusion (CSAI), Continuous foslevodopa-foscarbidopa infusion (LDp/CDp)							
Comparator (reference): Best medical therapy (BMT)							
Outcome: Clinical motor functions in the ON-medication state assessed via UPDRS part III, range of follow-up between 12 to 52 weeks							
Total studies: 12 RCTs Total participants: 1941		Relative Effect (points) (95% CrI)	Anticipated absolute effects		Certainty of Evidence	Ranking (95% CrI)	Interpretation of Findings
			Without intervention	With intervention (95% CrI)			
	DBS 7 RCT; 1304 participants	−4.09 (−5.43 to −2.75)	−1.93 points	−6.02 points (−7.36 to −4.68 points)	⊕⊕○○ Low ^{1,2}	1 st (1 st – 2 nd)	Possibly superior
	LCIG 2 RCT; 131 participants	−1.85 (−4.90 to 1.22)	−1.93 points	−3.78 points (−6.83 to −0.71 points)	⊕⊕○○ Low ³	3 rd (1 st – 5 th)	Possibly have trivial to no effect
	CSAI 1 RCT; 106 participants	−2.09 (−5.23 to 0.73)	−1.93 points	−4.02 points (−7.16 to −1.20 points)	⊕○○○ Very low ^{4,5}	2 nd (1 st – 5 th)	Might have trivial to no effect
	LDp/CDp 2 RCT; 400 participants	−1.73 (−3.81 to 0.40)	−1.93 points	−3.66 points (−5.74 to −1.53 points)	⊕⊕○○ Low ^{6,7}	4 th (2 nd – 5 th)	Possibly have trivial to no effect
	BMT	Reference	N/A	N/A	N/A	5 th (4 th – 5 th)	Reference comparator
Explanatory Footnotes							
¹ Serious risk of bias. 274/1304 participants from high RoB trials, and 621/1304 participants from trials with “some concerns” for RoB.							
⁴ Serious risk of bias. Evidence provided from a single trial with substantial losses to follow-up.							
⁶ Serious risk of bias. 141/400 participants from high RoB trials, and 259/400 participants from trials with “some concerns” for RoB.							
² Serious imprecision. Credible interval crosses MCID.							
^{3,5} Very serious imprecision. Credible interval suggests possibility of substantially large benefit.							
⁷ Serious imprecision. Credible interval suggests possibility of substantial benefit.							

Indirect comparisons				
Intervention	Comparator	Relative Effect (points) (95% CrI)	Certainty of Evidence	Interpretation of Findings
 DBS	 LCIG	−2.24 (−5.58 to 1.11)	⊕○○○ Very low ^{1,2}	Might have trivial to no difference
Indirect evidence only				
 DBS	 CSAI	−2.01 (−5.23 to 1.40)	⊕○○○ Very low ^{3,4}	Might have trivial to no difference
Indirect evidence only				
 DBS	 LDp/CDp	−2.36 (−4.89 to 0.10)	⊕○○○ Very low ^{5,6}	Might have trivial to no difference
Indirect evidence only				
 LCIG	 CSAI	0.23 (−3.37 to 4.26)	⊕○○○ Very low ^{7,8}	Might have trivial to no difference
Indirect evidence only				
 LCIG	 LDp/CDp	−0.12 (−3.51 to 3.14)	⊕⊕○○ Low ^{9,10}	Possibly have trivial to no difference
Indirect evidence only				
 CSAI	 LDp/CDp	−0.36 (−3.84 to 2.66)	⊕⊕○○ Low ^{11,12}	Possibly have trivial to no difference
Indirect evidence only				
Explanatory Footnotes				
^{1,3,5} DBS evidence has a serious risk of bias.				
^{7,11} CSAI evidence has a serious risk of bias.				
⁹ LDp/CDp evidence has a serious risk of bias.				
^{2,4,6} Very serious imprecision. Credible interval suggests possibility of substantially large benefit.				
⁸ Very serious imprecision. Credible interval suggests possibility of both substantial harm and substantial benefit.				
^{10,12} Serious imprecision. Credible interval suggests possibility of substantial benefit.				

Supplementary Table 3c. Summary of Findings: Estimates of effects, credible intervals, and certainty of evidence for advanced therapies in patients with advanced Parkinson's Disease – Quality of Life

Efficacy							
Quality of Life							
Population: Patients with advanced stage Parkinson’s Disease							
Interventions: Deep brain stimulation (DBS), Levodopa/carbidopa intestinal gel (LCIG), Continuous subcutaneous apomorphine infusion (CSAI), Continuous foslevodopa-foscarbidopa infusion (LDp/CDp)							
Comparator (reference): Best medical therapy (BMT)							
Outcome: Quality of life assessed via PDQ-39, range of follow-up between 12 to 52 weeks							
Total studies: 12 RCTs Total participants: 1920		Relative Effect (points) (95% CrI)	Anticipated absolute effects		Certainty of Evidence	Ranking (95% CrI)	Interpretation of Findings
			Without intervention	With intervention (95% CrI)			
●	DBS 6 RCT; 1197 participants	−7.54 (−9.57 to −5.52)	+0.07 points	−7.47 points (−9.50 to −5.45 points)	⊕⊕⊕○ Moderate ¹	2 nd (1 st – 3 rd)	Probably superior
●	LCIG 3 RCT; 217 participants	−8.78 (−13.96 to −3.67)	+0.07 points	−8.71 points (−13.89 to −3.60 points)	⊕⊕○○ Low ^{2,3}	1 st (1 st – 2 nd)	Possibly superior
●	CSAI 1 RCT; 106 participants	−2.45 (−7.53 to 2.67)	+0.07 points	−2.38 points (−7.46 to +3.08 points)	⊕○○○ Very low ^{4,5}	4 th (2 nd – 5 th)	Might have trivial to no effect
●	LDp/CDp 2 RCT; 400 participants	−2.90 (−4.88 to −0.91)	+0.07 points	−2.83 points (−4.81 to −0.84 points)	⊕⊕○○ Low ^{6,7}	3 rd (3 rd – 4 th)	Possibly have trivial to no effect
●	BMT	Reference	N/A	N/A	N/A	5 th (4 th – 5 th)	Reference comparator
Explanatory Footnotes							
¹ Serious risk of bias. 1037/1197 participants from high RoB trials.							
² Serious risk of bias. 151/217 participants from high RoB trials, and 66/217 participants from trials with “some concerns” for RoB.							
⁴ Serious risk of bias. Evidence from a single trial with substantial losses to follow-up.							
⁶ Serious risk of bias. 141/400 participants from high RoB trials, and 259/400 participants from trials with “some concerns” for RoB.							
^{3,7} Serious imprecision. Credible interval crosses MCID.							
⁵ Very serious imprecision. Credible interval suggests possibility of both harmful effect and substantially large benefit.							

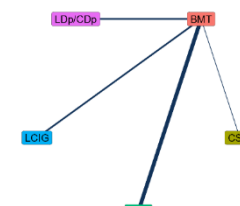
<i>Indirect comparisons</i>				
Intervention	Comparator	Relative Effect (points) (95% CrI)	Certainty of Evidence	Interpretation of Findings
 DBS	 LCIG	1.25 (−4.22 to 6.75)	⊕⊕○○ Low ^{1,2}	Possibly have trivial to no difference
<i>Indirect evidence only</i>				
 DBS	 CSAI	−5.09 (−10.67 to 0.37)	⊕⊕○○ Low ^{3,4}	DBS possibly superior to CSAI
<i>Indirect evidence only</i>				
 DBS	 LDp/CDp	−4.63 (−7.47 to −1.84)	⊕○○○ Very low ^{5,6}	Might have trivial to no difference
<i>Indirect evidence only</i>				
 LCIG	 CSAI	−6.34 (−13.45 to 0.78)	⊕⊕○○ Low ^{7,8}	LCIG possibly superior to CSAI
<i>Indirect evidence only</i>				
 LCIG	 LDp/CDp	−5.88 (−11.43 to −0.40)	⊕⊕○○ Low ^{9,10}	LCIG possibly superior to LDp/CDp
<i>Indirect evidence only</i>				
 CSAI	 LDp/CDp	0.46 (−4.95 to 5.85)	⊕○○○ Very low ^{11,12}	Might have trivial to no difference
<i>Indirect evidence only</i>				
Explanatory Footnotes ^{1,3,5} DBS evidence has a serious risk of bias. ^{7,9} LCIG evidence has a serious risk of bias. ¹¹ CSAI evidence has a serious risk of bias. ² Serious imprecision. Credible interval suggests possibility of substantial harm. ^{4,8,10} Serious imprecision. Credible interval crosses MCID. ¹² Very serious imprecision. Credible interval suggests possibility of both substantial harm and substantial benefit.				

Supplementary Table 3d. Summary of Findings: Estimates of effects, credible intervals, and certainty of evidence for advanced therapies in patients with advanced Parkinson's Disease – Daily motor functions

Efficacy							
Daily motor functions							
Population: Patients with advanced stage Parkinson’s Disease							
Interventions: Deep brain stimulation (DBS), Levodopa/carbidopa intestinal gel (LCIG), Continuous subcutaneous apomorphine infusion (CSAI), Continuous foslevodopa-foscarbidopa infusion (LDp/CDp)							
Comparator (reference): Best medical therapy (BMT)							
Outcome: Daily motor functions in the ON-medication state assessed via UPDRS part II, range of follow-up between 12 to 52 weeks							
Total studies: 9 RCTs Total participants: 1601		Relative Effect (points) (95% CrI)	Anticipated absolute effects		Certainty of Evidence	Ranking (95% CrI)	Interpretation of Findings
			Without intervention	With intervention (95% CrI)			
●	DBS 5 RCT; 1043 participants	−0.93 (−1.82 to −0.05)	−0.37 points	−1.30 points (−2.19 to −0.42 points)	⊕⊕⊕○ Moderate ¹	3 rd (2 nd – 3 rd)	Probably have trivial to no effect
●	LCIG 2 RCT; 158 participants	−2.90 (−4.97 to −0.84)	−0.37 points	−3.27 points (−5.34 to −1.21 points)	⊕○○○ Very low ^{2,3}	1 st (1 st – 2 nd)	Might have trivial to no effect
●	LDp/CDp 2 RCT; 400 participants	−2.70 (−3.79 to −1.61)	−0.37 points	−3.07 points (−4.16 to −1.98 points)	⊕⊕○○ Low ^{4,5}	2 nd (1 st – 2 nd)	Possibly have trivial to no effect
●	BMT	Reference	N/A	N/A	N/A	4 th (4 th – 4 th)	Reference comparator
Explanatory Footnotes							
¹ Serious risk of bias. 883/1043 participants from high RoB trials.							
² Serious risk of bias. 87/158 participants from high RoB trials, and 71/158 participants from trials with “some concerns” for RoB.							
⁴ Serious risk of bias. 141/400 participants from high RoB trials, and 259/400 participants from trials with “some concerns” for RoB.							
³ Very serious imprecision. Credible interval suggests possibility of substantially large benefit.							
⁵ Serious imprecision. Credible interval suggests possibility of substantial benefit.							

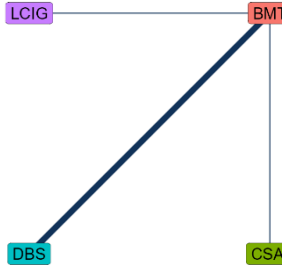
Indirect comparisons				
Intervention	Comparator	Relative Effect (points) (95% CrI)	Certainty of Evidence	Interpretation of Findings
 DBS	 LCIG	1.97 (−0.28 to 4.23)	⊕⊕○○ Low ^{1,2}	Possibly have trivial to no difference
Indirect evidence only				
 DBS	 LDp/CDp	1.77 (0.38 to 3.15)	⊕⊕○○ Low ^{3,4}	Possibly have trivial to no difference
Indirect evidence only				
 LCIG	 LDp/CDp	−0.20 (−2.51 to 2.10)	⊕⊕⊕○ Moderate ⁵	Probably have trivial to no difference
Indirect evidence only				
Explanatory Footnotes				
^{1,3} DBS evidence has a serious risk of bias.				
⁵ LCIG evidence has a serious risk of bias.				
^{2,4} Serious imprecision. Credible interval suggests possibility of substantial harm.				

Supplementary Table 3e. Summary of Findings: Estimates of effects, credible intervals, and certainty of evidence for advanced therapies in patients with advanced Parkinson's Disease – "Good" ON time

Efficacy							
“Good” ON time							
Population: Patients with advanced stage Parkinson’s Disease							
Interventions: Deep brain stimulation (DBS), Levodopa/carbidopa intestinal gel (LCIG), Continuous subcutaneous apomorphine infusion (CSAI), Continuous foslevodopa-foscarbidopa infusion (LDp/CDp)							
Comparator (reference): Best medical therapy (BMT)							
Outcome: Duration of waking day spent in the ON-medication state without troublesome dyskinesia, range of follow-up between 12 to 24 weeks							
Total studies: 9 RCTs Total participants: 1402		Relative Effect (hours) (95% CrI)	Anticipated absolute effects		Certainty of Evidence	Ranking (95% CrI)	Interpretation of Findings
			Without intervention	With intervention (95% CrI)			
●	DBS 4 RCT; 766 participants	+3.33 (+2.61 to +4.06)	+0.40 hours	+3.73 hours (+3.01 to +4.46 hours)	⊕⊕⊕○ Moderate ¹	1 st (1 st – 2 nd)	Probably superior
●	LCIG 2 RCT; 130 participants	+2.64 (+1.27 to +4.02)	+0.40 hours	+3.04 hours (+1.67 to +4.42 hours)	⊕⊕○○ Low ^{2,3}	2 nd (1 st – 4 th)	Possibly superior
●	CSAI 1 RCT; 106 participants	+1.96 (+0.80 to +3.14)	+0.40 hours	+2.36 hours (+1.20 to +3.54 hours)	⊕⊕⊕○ Moderate ⁴	3 rd (2 nd – 4 th)	Probably superior
●	LDp/CDp 2 RCT; 400 participants	+1.72 (+1.14 to +2.30)	+0.40 hours	+2.12 hours (+1.54 to +2.70 hours)	⊕⊕⊕○ Moderate ⁵	4 th (2 nd – 4 th)	Probably superior
●	BMT	Reference	N/A	N/A	N/A	5 th (5 th – 5 th)	Reference comparator
Explanatory Footnotes							
¹ Serious risk of bias. 606/766 participants from high RoB trials.							
² Serious risk of bias. 59/130 participants from high RoB trials, and 71/130 participants from trials with “some concerns” for RoB.							
⁵ Serious risk of bias. 141/400 participants from high RoB trials.							
³ Serious imprecision. Sample size < 50% of optimal information size.							
⁴ Serious imprecision. Credible interval crosses MCID.							

Indirect comparisons				
Intervention	Comparator	Relative Effect (hours) (95% CrI)	Certainty of Evidence	Interpretation of Findings
 DBS	 LCIG	0.68 (−0.87 to 2.24)	⊕○○○ Very low ^{1,2}	Might have trivial to no difference
Indirect evidence only				
 DBS	 CSAI	1.36 (−0.01 to 2.72)	⊕⊕○○ Low ^{3,4}	DBS possibly superior to CSAI
Indirect evidence only				
 DBS	 LDp/CDp	1.61 (0.68 to 2.54)	⊕⊕○○ Low ^{5,6}	DBS possibly superior to LDp/CDp
Indirect evidence only				
 LCIG	 CSAI	0.68 (−1.12 to 2.48)	⊕○○○ Very low ^{7,8}	Might have trivial to no difference
Indirect evidence only				
 LCIG	 LDp/CDp	0.92 (−0.56 to 2.41)	⊕○○○ Very low ^{9,10}	Might have trivial to no difference
Indirect evidence only				
 CSAI	 LDp/CDp	0.24 (−1.06 to 1.54)	⊕○○○ Very low ^{11,12}	Might have trivial to no difference
Indirect evidence only				
Explanatory Footnotes ^{1,3,5} DBS evidence has a serious risk of bias. ^{7,9} LCIG evidence has a serious risk of bias. ¹¹ LDp/CDp evidence has a serious risk of bias. ^{2,8,10} Very serious imprecision. Credible interval suggests possibility of substantially large benefit. ^{4,6} Serious imprecision. Credible interval crosses MCID. ¹² Very serious imprecision. Credible interval suggests possibility of both substantial harm and substantial benefit.				

Supplementary Table 3e. Summary of Findings: Estimates of effects, credible intervals, and certainty of evidence for advanced therapies in patients with advanced Parkinson's Disease – Levodopa-equivalent daily dose

Efficacy							
Levodopa-equivalent daily dose							
Population: Patients with advanced stage Parkinson’s Disease							
Interventions: Deep brain stimulation (DBS), Levodopa/carbidopa intestinal gel (LCIG), Continuous subcutaneous apomorphine infusion (CSAI), Continuous foslevodopa-foscarbidopa infusion (LDp/CDp)							
Comparator (reference): Best medical therapy (BMT)							
Outcome: Daily levodopa-equivalent dose, range of follow-up between 12 to 52 weeks							
Total studies: 7 RCTs Total participants: 1601		Relative Effect (mg) (95% CrI)	Anticipated absolute effects		Certainty of Evidence	Ranking (95% CrI)	Interpretation of Findings
			Without intervention	With intervention (95% CrI)			
	DBS 5 RCT; 778 participants	−577.25 (−626.18 to −527.99)	+39.8 mg	−537.45 mg (−586.38 to −488.19 mg)	⊕⊕⊕○ Moderate ¹	1 st (1 st – 1 st)	Probably superior
	LCIG 1 RCT; 71 participants	−154.54 (−418.38 to +106.90)	+39.8 mg	−114.74 mg (−378.58 to +146.70 mg)	⊕⊕○○ Low ^{2,3}	3 rd (2 nd – 4 th)	Possibly superior
	CSAI 1 RCT; 106 participants	−326.31 (−517.50 to −136.33)	+39.8 mg	−286.51 mg (−477.7 to −96.53 mg)	⊕⊕○○ Low ⁴	2 nd (2 nd – 3 rd)	Possibly superior
	BMT	Reference	N/A	N/A	N/A	4 th (3 rd – 4 th)	Reference comparator
Explanatory Footnotes							
¹ Serious risk of bias. 249/778 participants from high RoB trials, and 142/778 participants from trials with “some concerns” for RoB.							
² Serious risk of bias. All evidence from a trial with “some concerns” for RoB.							
⁴ Very serious risk of bias. 141/400 participants from high RoB trials, and 259/400 participants from trials with “some concerns” for RoB.							
³ Serious imprecision. Credible interval suggests possibility of both benefit and harm.							

Indirect comparisons				
Intervention	Comparator	Relative Effect (mg) (95% CrI)	Certainty of Evidence	Interpretation of Findings
 DBS	 LCIG	−422.70 (−688.81 to −153.78)	⊕○○○ Very low ^{1,2*}	DBS might be superior to LCIG
Indirect evidence only				
 DBS	 CSAI	−250.94 (−447.98 to −55.11)	⊕○○○ Very low ^{3,4*}	DBS might be superior to CSAI
Indirect evidence only				
 LCIG	 CSAI	171.76 (−157.63 to 497.15)	⊕○○○ Very low ^{5,6}	LCIG might be inferior to CSAI
Indirect evidence only				
Explanatory Footnotes				
* Certainty rated down one level due to possibility of intransitivity.				
^{1,3} DBS evidence has a serious risk of bias.				
^{2,5} LCIG evidence has a serious risk of bias.				
^{4,6} CSAI evidence has a very serious risk of bias.				
^{2,4} Serious imprecision. Credible interval suggests possibility of both benefit and harm.				

Supplementary Table 3g. Summary of Findings: Estimates of effects, credible intervals, and certainty of evidence for advanced therapies in patients with advanced Parkinson's Disease – Risk of falls

Safety								
<i>Risk of falls</i>								
Population: Patients with advanced stage Parkinson's Disease Interventions: Deep brain stimulation (DBS), Levodopa/carbidopa intestinal gel (LCIG), Continuous subcutaneous apomorphine infusion (CSAI), Continuous foslevodopa-foscarbidopa infusion (LDp/CDp) Comparator (reference): Best medical therapy (BMT) Outcome: Fall adverse events, range of follow-up between 12 to 52 weeks								
Total studies: 10 RCTs Total participants: 1692		Relative Effect (RR) (95% CrI)	Anticipated absolute effects			Certainty of Evidence	Ranking (95% CrI)	Interpretation of Findings
			Without intervention	With intervention	Difference (95% CrI)			
●	DBS 5 RCT; 1073 participants	1.12 (0.70 to 1.80)	61 per 1000	68 per 1000	7 more per 1000 (18 fewer to 49 more)	⊕⊕○○ Low ¹	3 rd (2 nd – 4 th)	Possibly have trivial to no effect
●	LCIG 3 RCT; 219 participants	1.59 (0.62 to 4.11)	61 per 1000	97 per 1000	36 more per 1000 (23 fewer to 190 more)	⊕○○○ Very low ²	4 th (2 nd – 4 th)	Might be inferior
●	LDp/CDp 2 RCT; 400 participants	0.52 (0.29 to 0.94)	61 per 1000	32 per 1000	29 fewer per 1000 (43 fewer to 4 fewer)	⊕⊕⊕○ Moderate ³	1 st (1 st – 2 nd)	Probably superior
●	BMT	Reference	N/A	N/A	N/A	N/A	2 nd (2 nd – 4 th)	Reference comparator
Explanatory Footnotes ¹ Very serious imprecision. Credible interval suggests possibility of both substantial harm and substantial benefit. ² Extremely serious imprecision. Credible interval suggests possibility of both substantially large harm and substantially large benefit. ³ Serious imprecision. Credible interval crosses MCID.								

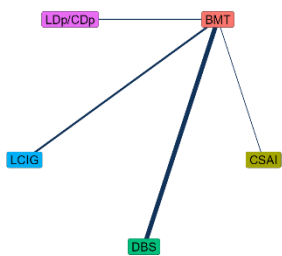
Indirect comparisons				
Intervention	Comparator	Relative Effect (RR) (95% CrI)	Certainty of Evidence	Interpretation of Findings
 DBS	 LCIG	0.70 (0.25 to 2.03)	⊕○○○ Very low ^{1*}	Might be superior to LCIG
Indirect evidence only				
 DBS	 LDp/CDp	2.15 (1.01 to 4.61)	⊕⊕○○ Low ^{2*}	DBS possibly inferior to LDp/CDp
Indirect evidence only				
 LCIG	 LDp/CDp	3.06 (1.02 to 9.52)	⊕○○○ Very low ³	LCIG might be inferior to LDp/CDp
Indirect evidence only				
Explanatory Footnotes				
* Certainty rated down one level due to possibility of intransitivity.				
¹ Extremely serious imprecision. Credible interval suggests possibility of both substantially large harm and substantially large benefit.				
² Serious imprecision. Credible interval crosses MCID.				
³ Extremely serious imprecision. Credible interval suggests possibility of implausibly large harm.				

Supplementary Table 3h. Summary of Findings: Estimates of effects, credible intervals, and certainty of evidence for advanced therapies in patients with advanced Parkinson's Disease – Risk of dyskinesia

Safety								
<i>Risk of dyskinesia</i>								
Population: Patients with advanced stage Parkinson's Disease Interventions: Deep brain stimulation (DBS), Levodopa/carbidopa intestinal gel (LCIG), Continuous subcutaneous apomorphine infusion (CSAI), Continuous foslevodopa-foscarbidopa infusion (LDp/CDp) Comparator (reference): Best medical therapy (BMT) Outcome: Dyskinesia adverse events, range of follow-up between 12 to 24 weeks								
Total studies: 9 RCTs Total participants: 1499		Relative Effect (RR) (95% CrI)	Anticipated absolute effects			Certainty of Evidence	Ranking (95% CrI)	Interpretation of Findings
			Without intervention	With intervention	Difference (95% CrI)			
	DBS 5 RCT; 922 participants	0.63 (0.43 to 0.92)	54 per 1000	34 per 1000	20 fewer per 1000 (31 fewer to 4 fewer)	⊕⊕⊕⊕ High	1 st (1 st – 2 nd)	Definitely superior
	LCIG 1 RCT; 71 participants	1.14 (0.33 to 3.95)	54 per 1000	62 per 1000	8 more per 1000 (36 fewer to 160 more)	⊕○○○ Very low ¹	3 rd (1 st – 4 th)	Might be inferior
	CSAI 1 RCT; 106 participants	17.11 (1.03 to 289.06)	54 per 1000	Inestimable	Inestimable	⊕⊕○○ Low ²	5 th (4 th – 5 th)	Possibly inferior
	LDp/CDp 2 RCT; 400 participants	1.17 (0.48 to 2.84)	54 per 1000	63 per 1000	9 more per 1000 (28 fewer to 100 more)	⊕○○○ Very low ³	4 th (1 st – 4 th)	Might be inferior
	BMT	Reference	N/A	N/A	N/A	N/A	2 nd (2 nd – 4 th)	Reference comparator
Explanatory Footnotes ^{1,3} Extremely serious imprecision. Credible interval suggests possibility of both large harm and large benefit. ² Very serious imprecision. Credible interval suggests possibility of implausible effect.								

Indirect comparisons				
Intervention	Comparator	Relative Effect (RR) (95% CrI)	Certainty of Evidence	Interpretation of Findings
 DBS	 LCIG	0.55 (0.15 to 2.02)	⊕○○○ Very low ¹	DBS might be superior to LCIG
Indirect evidence only				
 DBS	 CSAI	0.04 (0.00 to 0.64)	⊕⊕○○ Low ²	DBS possibly superior to CSAI
Indirect evidence only				
 DBS	 LDp/CDp	0.54 (0.20 to 1.40)	⊕○○○ Very low ³	DBS might be superior to LDp/CDp
Indirect evidence only				
 LCIG	 CSAI	0.07 (0.00 to 1.43)	⊕○○○ Very low ⁴	LCIG might be superior to CSAI
Indirect evidence only				
 LCIG	 LDp/CDp	0.97 (0.21 to 4.40)	⊕○○○ Very low ⁵	LCIG might be superior to LDp/CDp
Indirect evidence only				
 CSAI	 LDp/CDp	14.58 (0.76 to 286.54)	⊕○○○ Very low ⁶	CSAI might be inferior to LDp/CDp
Indirect evidence only				
Explanatory Footnotes ^{1,3,4,5} Extremely serious imprecision. Credible interval suggests possibility of both large harm and large benefit. ² Very serious imprecision. Credible interval suggests possibility of implausible effect. ⁶ Extremely serious imprecision. Credible interval suggests possibility of benefit and implausible harm.				

Supplementary Table 3i. Summary of Findings: Estimates of effects, credible intervals, and certainty of evidence for advanced therapies in patients with advanced Parkinson's Disease – Risk of SAEs

Safety								
<i>Risk of serious adverse events</i>								
Population: Patients with advanced stage Parkinson's Disease Interventions: Deep brain stimulation (DBS), Levodopa/carbidopa intestinal gel (LCIG), Continuous subcutaneous apomorphine infusion (CSAI), Continuous foslevodopa-foscarbidopa infusion (LDp/CDp) Comparator (reference): Best medical therapy (BMT) Outcome: Serious adverse events, range of follow-up between 12 to 52 weeks								
Total studies: 13 RCTs Total participants: 2069		Relative Effect (RR) (95% CrI)	Anticipated absolute effects			Certainty of Evidence	Ranking (95% CrI)	Interpretation of Findings
			Without intervention	With intervention	Difference (95% CrI)			
	DBS 7 RCT; 1343 participants	1.93 (1.10 to 3.44)	96 per 1000	186 per 1000	90 more per 1000 (10 more to 235 more)	⊕⊕⊕○ Moderate ¹	5 th (2 nd – 5 th)	Probably inferior
	LCIG 3 RCT; 219 participants	1.36 (0.47 to 4.17)	96 per 1000	131 per 1000	35 more per 1000 (51 fewer to 305 more)	⊕○○○ Very low ²	2 nd (1 st – 5 th)	Might be inferior
	CSAI 1 RCT; 107 participants	2.45 (0.33 to 18.61)	96 per 1000	235 per 1000	139 more per 1000 (Inestimable)	⊕○○○ Very low ³	4 th (1 st – 5 th)	Might be inferior
	LDp/CDp 2 RCT; 400 participants	1.41 (0.42 to 4.67)	96 per 1000	135 per 1000	39 more per 1000 (56 fewer to 353 more)	⊕○○○ Very low ⁴	3 rd (1 st – 5 th)	Might be inferior
	BMT	Reference	N/A	N/A	N/A	N/A	1 st (1 st – 3 rd)	Reference comparator
Explanatory Footnotes ¹ Serious imprecision. Wide credible interval. ^{2,3,4} Extremely serious imprecision. Credible interval suggests possibility of both large harm and large benefit.								

Indirect comparisons				
Intervention	Comparator	Relative Effect (RR) (95% CrI)	Certainty of Evidence	Interpretation of Findings
 DBS	 LCIG	1.42 (0.40 to 4.75)	⊕○○○ Very low ¹	DBS might be inferior to LCIG
Indirect evidence only				
 DBS	 CSAI	0.79 (0.09 to 6.28)	⊕○○○ Very low ²	DBS might be superior to CSAI
Indirect evidence only				
 DBS	 LDp/CDp	1.37 (0.36 to 5.16)	⊕○○○ Very low ³	DBS might be inferior to LDp/CDp
Indirect evidence only				
 LCIG	 CSAI	0.56 (0.06 to 5.63)	⊕○○○ Very low ⁴	LCIG might be superior to CSAI
Indirect evidence only				
 LCIG	 LDp/CDp	0.97 (0.20 to 5.08)	⊕○○○ Very low ⁵	LCIG might be superior to LDp/CDp
Indirect evidence only				
 CSAI	 LDp/CDp	1.74 (0.17 to 18.54)	⊕○○○ Very low ⁶	CSAI might be inferior to LDp/CDp
Indirect evidence only				
Explanatory Footnotes				
^{1,2,3,4,5,6} Extremely serious imprecision. Credible interval suggests possibility of both large harm and large benefit.				

Supplementary Table 4a. Pairwise comparative reduction in OFF time

		Comparator			
		BMT	CSAI	DBS	LCIG
Intervention	CSAI	−1.88 (−3.11 to −0.62)			
	DBS	−2.59 (−3.61 to −1.57)	−0.72 (−2.34 to 0.88)		
	LCIG	−2.18 (−3.32 to −1.08)	−0.30 (−2.00 to 1.36)	0.41 (−1.09 to 1.93)	
	LDp/CDp	−1.46 (−2.01 to −0.91)	0.42 (−0.96 to 1.78)	1.13 (−0.01 to 2.29)	0.72 (−0.52 to 1.96)

Data is reported as mean (95% CrI) in hours. BMT, best medical therapy; CSAI, continuous subcutaneous apomorphine infusion; DBS, deep brain stimulation; LCIG, levodopa-carbidopa intestinal gel; LDp/CDp; foslevodopa-foscarbidopa.

Supplementary Table 4b. Probability of comparative treatment effect being better than MCID – OFF time

		Comparator				
		BMT	CSAI	DBS	LCIG	LDp/CDp
Intervention	BMT	—	0%	0%	0%	0%
	CSAI	81.8%	—	0.6%	2.9%	10.0%
	DBS	99.3%	24.1%	—	12.7%	38.8%
	LCIG	93.8%	12.1%	1.3%	—	18.0%
	LDp/CDp	72.1%	0.7%	0%	0%	—

Comparative treatment effect is between the intervention versus the comparator. MCID for OFF time was set to −1.3 hour (122). MCID, minimum clinically important difference; BMT, best medical therapy; CSAI, continuous subcutaneous apomorphine infusion; DBS, deep brain stimulation; LCIG, levodopa-carbidopa intestinal gel; LDp/CDp; foslevodopa-foscarbidopa.

Supplementary Table 4c. Ranking probabilities – OFF time reduction

Treatment	Ranking probabilities – OFF time reduction					SUCRA
	1 st	2 nd	3 rd	4 th	5 th	
BMT	0	0	0	0	1.00	0.00
CSAI	0.13	0.27	0.35	0.25	0	0.57
DBS	0.61	0.28	0.10	0.02	0	0.87
LCIG	0.25	0.40	0.25	0.10	0	0.70
LCp/CDp	0	0.06	0.31	0.64	0	0.36

Ranking of treatment efficacy is based on the surface under the cumulative curve (SUCRA). Probabilities may not add up to 1 due to rounding.

Supplementary Table 5a. Pairwise comparative reduction in UPDRS part III score

		Comparator			
		BMT	CSAI	DBS	LCIG
Intervention	CSAI	−2.09 (−5.23 to 0.73)			
	DBS	−4.09 (−5.43 to −2.75)	−2.01 (−5.23 to 1.40)		
	LCIG	−1.85 (−4.90 to 1.22)	0.23 (−3.37 to 4.26)	2.24 (−1.11 to 5.58)	
	LDp/CDp	−1.73 (−3.81 to 0.40)	0.36 (−2.66 to 3.84)	2.36 (−0.10 to 4.89)	0.12 (−3.14 to 3.51)

Data is reported as mean (95% CrI) in points. BMT, best medical therapy; CSAI, continuous subcutaneous apomorphine infusion; DBS, deep brain stimulation; LCIG, levodopa-carbidopa intestinal gel; LDp/CDp; foslevodopa-foscarbidopa.

Supplementary Table 5b. Probability of comparative treatment effect being better than MCID – UPDRS III

		Comparator				
		BMT	CSAI	DBS	LCIG	LDp/CDp
Intervention	BMT	—	0.1%	0%	0.2%	0%
	CSAI	20.0%	—	0.2%	5.5%	4.4%
	DBS	89.1%	21.9%	—	25.9%	24.3%
	LCIG	16.0%	2.8%	0.1%	—	3.4%
	LDp/CDp	7.6%	1.3%	0%	2.2%	—

Comparative treatment effect is between the intervention versus the comparator. MCID for UPDRS part III was set to −3.25 points (123). MCID, minimum clinically important difference; BMT, best medical therapy; CSAI, continuous subcutaneous apomorphine infusion; DBS, deep brain stimulation; LCIG, levodopa-carbidopa intestinal gel; LDp/CDp; foslevodopa-foscarbidopa.

Supplementary Table 5c. Ranking probabilities – UPDRS III

Treatment	Ranking probabilities – UPDRS III reduction					SUCRA
	1 st	2 nd	3 rd	4 th	5 th	
BMT	0	0.01	0.03	0.14	0.82	0.06
CSAI	0.09	0.33	0.29	0.23	0.06	0.54
DBS	0.83	0.13	0.03	0.01	0	0.94
LCIG	0.07	0.28	0.30	0.27	0.09	0.49
LCp/CDp	0.02	0.25	0.36	0.34	0.04	0.47

Ranking of treatment efficacy is based on the surface under the cumulative curve (SUCRA). Probabilities may not add up to 1 due to rounding.

Supplementary Table 6a. Pairwise comparative reduction in PDQ-39 total score

		Comparator			
		BMT	CSAI	DBS	LCIG
Intervention	CSAI	−2.45 (−7.53 to 2.67)			
	DBS	−7.54 (−9.57 to −5.52)	−5.09 (−10.67 to 0.37)		
	LCIG	−8.78 (−13.96 to −3.67)	−6.34 (−13.45 to 0.78)	−1.25 (−6.75 to 4.22)	
	LDp/CDp	−2.90 (−4.88 to −0.91)	−0.46 (−5.85 to 4.95)	4.63 (1.84 to 7.47)	5.88 (0.40 to 11.43)

Data is reported as mean (95% CrI) in points. BMT, best medical therapy; CSAI, continuous subcutaneous apomorphine infusion; DBS, deep brain stimulation; LCIG, levodopa-carbidopa intestinal gel; LDp/CDp; foslevodopa-foscarbidopa.

Supplementary Table 6b. Probability of comparative treatment effect being better than MCID – PDQ-39

		Comparator				
		BMT	CSAI	DBS	LCIG	LDp/CDp
Intervention	BMT	—	0.3%	0%	0%	0%
	CSAI	19.1%	—	0%	0.1%	3.1%
	DBS	99.7%	55.0%	—	1.6%	47.3%
	LCIG	93.9%	67.0%	10.4%	—	65.9%
	LDp/CDp	3.6%	6.3%	0%	0%	—

Comparative treatment effect is between the intervention versus the comparator. MCID for PDQ-39 was set to −4.72 points (125). MCID, minimum clinically important difference; BMT, best medical therapy; CSAI, continuous subcutaneous apomorphine infusion; DBS, deep brain stimulation; LCIG, levodopa-carbidopa intestinal gel; LDp/CDp; foslevodopa-foscarbidopa.

Supplementary Table 6c. Ranking probabilities – PDQ-39

Treatment	Ranking probabilities – PDQ-39 improvement					SUCRA
	1 st	2 nd	3 rd	4 th	5 th	
BMT	0	0	0	0.17	0.83	0.04
CSAI	0.01	0.05	0.38	0.39	0.17	0.34
DBS	0.32	0.65	0.03	0	0	0.82
LCIG	0.67	0.28	0.04	0.01	0	0.90
LCp/CDp	0	0.01	0.56	0.43	0	0.39

Ranking of treatment efficacy is based on the surface under the cumulative curve (SUCRA). Probabilities may not add up to 1 due to rounding.

Supplementary Table 7a. Pairwise comparative reduction in UPDRS part II score

		Comparator		
		BMT	DBS	LCIG
Intervention	DBS	−0.93 (−1.82 to −0.05)		
	LCIG	−2.90 (−4.97 to −0.84)	−1.97 (−4.23 to 0.28)	
	LDp/CDp	−2.70 (−3.79 to −1.61)	−1.77 (−3.15 to −0.38)	0.20 (−2.10 to 2.51)

Data is reported as mean (95% CrI) in points. BMT, best medical therapy; DBS, deep brain stimulation; LCIG, levodopa-carbidopa intestinal gel; LDp/CDp; foslevodopa-foscarbidopa.

Supplementary Table 7b. Probability of comparative treatment effect being better than MCID – UPDRS II

		Comparator			
		BMT	DBS	LCIG	LDp/CDp
Intervention	BMT	—	0%	0%	0%
	DBS	0%	—	0%	0%
	LCIG	44.2%	17.1%	—	0.8%
	LDp/CDp	27.0%	3.6%	0.3%	—

Comparative treatment effect is between the intervention versus the comparator. MCID for UPDRS part II score was set to −3.05 points (124). MCID, minimum clinically important difference; BMT, best medical therapy; DBS, deep brain stimulation; LCIG, levodopa-carbidopa intestinal gel; LDp/CDp; foslevodopa-foscarbidopa.

Supplementary Table 7c. Ranking probabilities – UPDRS II

Treatment	Ranking probabilities – UPDRS II reduction				SUCRA
	1 st	2 nd	3 rd	4 th	
BMT	0	0	0.02	0.98	0.01
DBS	0	0.05	0.93	0.02	0.34
LCIG	0.56	0.39	0.04	0	0.84
LCp/CDp	0.43	0.56	0.01	0	0.81

Ranking of treatment efficacy is based on the surface under the cumulative curve (SUCRA). Probabilities may not add up to 1 due to rounding.

Supplementary Table 8a. Pairwise comparative improvement in “Good” ON time

		Comparator			
		BMT	CSAI	DBS	LCIG
Intervention	CSAI	1.96 (0.80 to 3.14)			
	DBS	3.33 (2.61 to 4.06)	1.36 (−0.01 to 2.72)		
	LCIG	2.64 (1.27 to 4.02)	0.68 (−1.12 to 2.48)	−0.68 (−2.24 to 0.87)	
	LDp/CDp	1.72 (1.14 to 2.30)	−0.24 (−1.54 to 1.06)	−1.61 (−2.54 to −0.68)	−0.92 (−2.41 to 0.56)

Data is reported as mean (95% CrI) in hours. BMT, best medical therapy; CSAI, continuous subcutaneous apomorphine infusion; DBS, deep brain stimulation; LCIG, levodopa-carbidopa intestinal gel; LDp/CDp; foslevodopa-foscarbidopa.

Supplementary Table 8b. Probability of comparative treatment effect being better than MCID – Good ON time

		Comparator				
		BMT	CSAI	DBS	LCIG	LDp/CDp
Intervention	BMT	—	0%	0%	0%	0%
	CSAI	94.8%	—	0.1%	3.3%	12.9%
	DBS	100.0%	70.1%	—	34.4%	89.9%
	LCIG	99.1%	36.0%	1.7%	—	45.9%
	LDp/CDp	99.3%	3.0%	0%	0.5%	—

Comparative treatment effect is between the intervention versus the comparator. MCID for “Good” ON time was set to +1 hour (112). MCID, minimum clinically important difference; BMT, best medical therapy; CSAI, continuous subcutaneous apomorphine infusion; DBS, deep brain stimulation; LCIG, levodopa-carbidopa intestinal gel; LDp/CDp; foslevodopa-foscarbidopa.

Supplementary Table 8c. Ranking probabilities – Good ON time

Treatment	Ranking probabilities – Good ON time improvement					SUCRA
	1 st	2 nd	3 rd	4 th	5 th	
BMT	0	0	0	0	1.00	0.00
CSAI	0.02	0.19	0.45	0.34	0	0.47
DBS	0.79	0.20	0.01	0	0	0.94
LCIG	0.19	0.55	0.18	0.08	0	0.71
LCp/CDp	0	0.06	0.36	0.58	0	0.37

Ranking of treatment efficacy is based on the surface under the cumulative curve (SUCRA). Probabilities may not add up to 1 due to rounding.

Supplementary Table 9a. Pairwise comparative reduction in LEDD

		Comparator		
		BMT	CSAI	DBS
Intervention	CSAI	-326.31 (-517.50 to -136.33)		
	DBS	-577.25 (-626.18 to -527.99)	-250.94 (-447.98 to -55.11)	
	LCIG	-154.54 (-418.38 to 106.90)	171.76 (-157.63 to 497.15)	422.70 (153.78 to 688.81)

Data is reported as mean (95% CrI) in points. BMT, best medical therapy; DBS, deep brain stimulation; LCIG, levodopa-carbidopa intestinal gel; LDp/CDp; foslevodopa-foscarbidopa.

Supplementary Table 9b. Probability of comparative treatment effect – LEDD

		Comparator			
		BMT	CSAI	DBS	LCIG
Intervention	BMT	—	0.1%	0%	13.0%
	CSAI	99.9%	—	0.6%	84.6%
	DBS	100.00%	99.4%	—	99.9%
	LCIG	87.0%	15.4%	0.1%	—

Comparative treatment effect is between the intervention versus the comparator. BMT, best medical therapy; DBS, deep brain stimulation; LCIG, levodopa-carbidopa intestinal gel; LDp/CDp; foslevodopa-foscarbidopa.

Supplementary Table 9c. Ranking probabilities – LEDD

Treatment	Ranking probabilities – LEDD reduction				SUCRA
	1 st	2 nd	3 rd	4 th	
BMT	0	0	0.13	0.87	0.04
CSAI	0.01	0.84	0.15	0	0.62
DBS	0.99	0.01	0	0	1.00
LCIG	0	0.15	0.72	0.13	0.34

Ranking of treatment efficacy is based on the surface under the cumulative curve (SUCRA). Probabilities may not add up to 1 due to rounding.

Supplementary Table 10a. Pairwise comparative risk of falls

		Comparator		
		BMT	DBS	LCIG
Intervention	DBS	1.12 (0.70 to 1.79)		
	LCIG	1.59 (0.62 to 4.11)	1.43 (0.49 to 4.07)	
	LDp/CDp	0.52 (0.29 to 0.94)	0.47 (0.22 to 0.99)	0.33 (0.11 to 0.98)

Data is reported as mean risk ratio (95% CrI). BMT, best medical therapy; DBS, deep brain stimulation; LCIG, levodopa-carbidopa intestinal gel; LDp/CDp; foslevodopa-foscarbidopa.

Supplementary Table 10b. Probability of comparative safety being better than MCID – Risk of falls

		Comparator			
		BMT	DBS	LCIG	LDp/CDp
Intervention	BMT	—	22.6%	64.4%	0.1%
	DBS	4.9%	—	54.9%	0.3%
	LCIG	6.0%	11.9%	—	0.6%
	LDp/CDp	88.6%	89.1%	92.7%	—

Comparative safety is between the intervention versus the comparator. MCID for risk of falls was set to a 25% reduction in risk (126). MCID, minimum clinically important difference; BMT, best medical therapy; DBS, deep brain stimulation; LCIG, levodopa-carbidopa intestinal gel; LDp/CDp; foslevodopa-foscarbidopa.

Supplementary Table 10c. Ranking probabilities – Risk of falls

Treatment	Ranking probabilities – Falls				SUCRA
	1 st	2 nd	3 rd	4 th	
BMT	0.01	0.55	0.38	0.05	0.51
DBS	0.02	0.28	0.48	0.22	0.36
LCIG	0.02	0.13	0.13	0.72	0.15
LCp/CDp	0.95	0.04	0.01	0.00	0.98

Ranking of treatment efficacy is based on the surface under the cumulative curve (SUCRA). Probabilities may not add up to 1 due to rounding.

Supplementary Table 11a. Pairwise comparative risk of dyskinesia

		Comparator			
		BMT	CSAI	DBS	LCIG
Intervention	CSAI	17.11 (1.03 to 289.06)			
	DBS	0.63 (0.43 to 0.92)	0.04 (0.00 to 0.64)		
	LCIG	1.14 (0.33 to 3.95)	0.07 (0.00 to 1.43)	1.82 (0.49 to 6.62)	
	LDp/CDp	1.17 (0.48 to 2.84)	0.07 (0.00 to 1.32)	1.87 (0.71 to 4.91)	1.03 (0.23 to 4.74)

Data is reported as mean risk ratio (95% CrI). BMT, best medical therapy; CSAI, continuous subcutaneous apomorphine infusion; DBS, deep brain stimulation; LCIG, levodopa-carbidopa intestinal gel; LDp/CDp; foslevodopa-foscarbidopa.

Supplementary Table 11b. Probability of better comparative safety – Dyskinesia

		Comparator				
		BMT	CSAI	DBS	LCIG	LDp/CDp
Intervention	BMT	—	97.6%	0.8%	58.5%	64.1%
	CSAI	2.4%	—	1.1%	4.2%	3.7%
	DBS	99.2%	98.9%	—	81.7%	90.0%
	LCIG	41.5%	95.8%	18.3%	—	51.1%
	LDp/CDp	35.9%	96.3%	10.0%	48.9%	—

Comparative safety is between the intervention versus the comparator. BMT, best medical therapy; DBS, deep brain stimulation; CSAI, continuous subcutaneous apomorphine infusion; LCIG, levodopa-carbidopa intestinal gel; LDp/CDp; foslevodopa-foscarbidopa.

Supplementary Table 11c. Ranking probabilities – Risk of dyskinesia

Treatment	Ranking probabilities – Dyskinesia					SUCRA
	1 st	2 nd	3 rd	4 th	5 th	
BMT	0	0.36	0.48	0.15	0	0.55
CSAI	0.01	0.01	0.01	0.03	0.94	0.03
DBS	0.73	0.24	0.03	0	0	0.92
LCIG	0.17	0.19	0.20	0.41	0.03	0.52
LCp/CDp	0.08	0.20	0.29	0.41	0.02	0.48

Ranking of treatment efficacy is based on the surface under the cumulative curve (SUCRA). Probabilities may not add up to 1 due to rounding.

Supplementary Table 12a. Pairwise comparative risk of serious adverse events

		Comparator			
		BMT	CSAI	DBS	LCIG
Intervention	CSAI	2.45 (0.33 to 18.61)			
	DBS	1.93 (1.10 to 3.44)	0.79 (0.09 to 6.28)		
	LCIG	1.36 (0.47 to 4.17)	0.56 (0.06 to 5.63)	0.70 (0.21 to 2.49)	
	LDp/CDp	1.41 (0.42 to 4.67)	0.57 (0.05 to 6.04)	0.73 (0.19 to 2.78)	1.03 (0.20 to 5.07)

Data is reported as mean risk ratio (95% CrI). BMT, best medical therapy; CSAI, continuous subcutaneous apomorphine infusion; DBS, deep brain stimulation; LCIG, levodopa-carbidopa intestinal gel; LDp/CDp; foslevodopa-foscarbidopa.

Supplementary Table 12b. Probability of comparative safety – Serious adverse events

		Comparator				
		BMT	CSAI	DBS	LCIG	LDp/CDp
Intervention	BMT	—	81.0%	98.6%	71.8%	71.8%
	CSAI	19.0%	—	41.3%	30.3%	31.8%
	DBS	1.4%	58.7%	—	26.8%	31.1%
	LCIG	28.2%	69.7%	73.2%	—	52.0%
	LDp/CDp	28.2%	68.2%	68.9%	48.0%	—

Comparative safety is between the intervention versus the comparator. BMT, best medical therapy; CSAI, continuous subcutaneous apomorphine infusion; DBS, deep brain stimulation; LCIG, levodopa-carbidopa intestinal gel; LDp/CDp; foslevodopa-foscarbidopa.

Supplementary Table 12c. Ranking probabilities – Serious adverse events

Treatment	Ranking probabilities – Serious adverse events					SUCRA
	1 st	2 nd	3 rd	4 th	5 th	
BMT	0.41	0.42	0.15	0.02	0	0.81
CSAI	0.15	0.08	0.11	0.14	0.51	0.31
DBS	0.01	0.07	0.26	0.43	0.24	0.29
LCIG	0.21	0.23	0.26	0.19	0.11	0.56
LCp/CDp	0.22	0.20	0.23	0.21	0.14	0.53

Ranking of treatment efficacy is based on the surface under the cumulative curve (SUCRA). Probabilities may not add up to 1 due to rounding.

Supplementary Table 13. Systematic Literature search strategy

<u>MEDLINE</u>	
#	Terms
1	(Parkinsonism or Parkinson* or Paralysis agitans or Shaking palsy).tw,kf.
2	exp Parkinson Disease/ or exp Parkinsonian Disorders/
3	or/1-2
4	Deep Brain Stimulation/
5	(deep brain stimulation* or DBS or subthalamic stimulation* or pallidal stimulation* or ventral intermediate nucleus stimulation* or thalamic stimulation* or (electric stimulation* adj3 brain)).tw,kf.
6	or/4-5
7	((levodopa* or dopaflex* or dopar* or larodopa* or levodopa* or levopa*).tw,kf. or levodopa/) and ((carbidopa* or lodosin* or lodosyn* or methyl dopahydrazine*).tw,kf,nm. or carbidopa/)
8	exp Intestines/ or (intestin* or jejun* or duoden* or intrainstestine* or intrajejun* or intraduoden* or enteral or intra intestin* or intra jejun* or intra duoden*).tw,kf.
9	LCIG.tw,kf.
10	(7 and 8) or 9
11	(apokinin* or apomorphin* or britaject*).mp. or Apomorphine/
12	(drug infusion system* or external infusion pump* or infusion pump* or infusor* or intravenous drug delivery system* or perfusion pump* or implantable medication system* or implantable perfusion pump* or implantable peristaltic pump* or programmable implantable medication system* or infusion system*).tw,kf.
13	exp Infusions, Subcutaneous/ or (Subcutaneous Infusion* or Hypodermoclysis* or Subcutaneous Hydrat*).tw,kf.
14	11 and (12 or 13)
15	((foscarbidopa* adj1 foslevodopa*) or Vyalev* or Produodopa).tw,kf.
16	3 and (6 or 10 or 14 or 15)
17	exp randomized controlled trial/
18	Clinical Trial, Phase I.pt.
19	case reports/
20	(16 and 17) not (18 or 19)
21	remove duplicates from 20

<u>EMBASE</u>	
#	Terms
1	(Parkinsonism or Parkinson* or Paralysis agitans or Shaking palsy).tw,kf.
2	exp Parkinson Disease/ or exp Parkinsonian Disorders/
3	or/1-2
4	Deep Brain Stimulation/
5	(deep brain stimulation* or DBS or subthalamic stimulation* or pallidal stimulation* or ventral intermediate nucleus stimulation* or thalamic stimulation* or (electric stimulation* adj3 brain)).tw,kf.
6	or/4-5
7	((levodopa* or dopaflex* or dopar* or larodopa* or levodopa* or levopa*).tw,kf. or levodopa/) and ((carbidopa* or lodosin* or lodosyn* or methyl dopahydrazine*).tw,kf. or carbidopa/)
8	exp Intestines/ or (intestin* or jejun* or duoden* or intrainstestine* or intrajejun* or intraduoden* or enteral or intra intestin* or intra jejun* or intra duoden*).tw,kf.

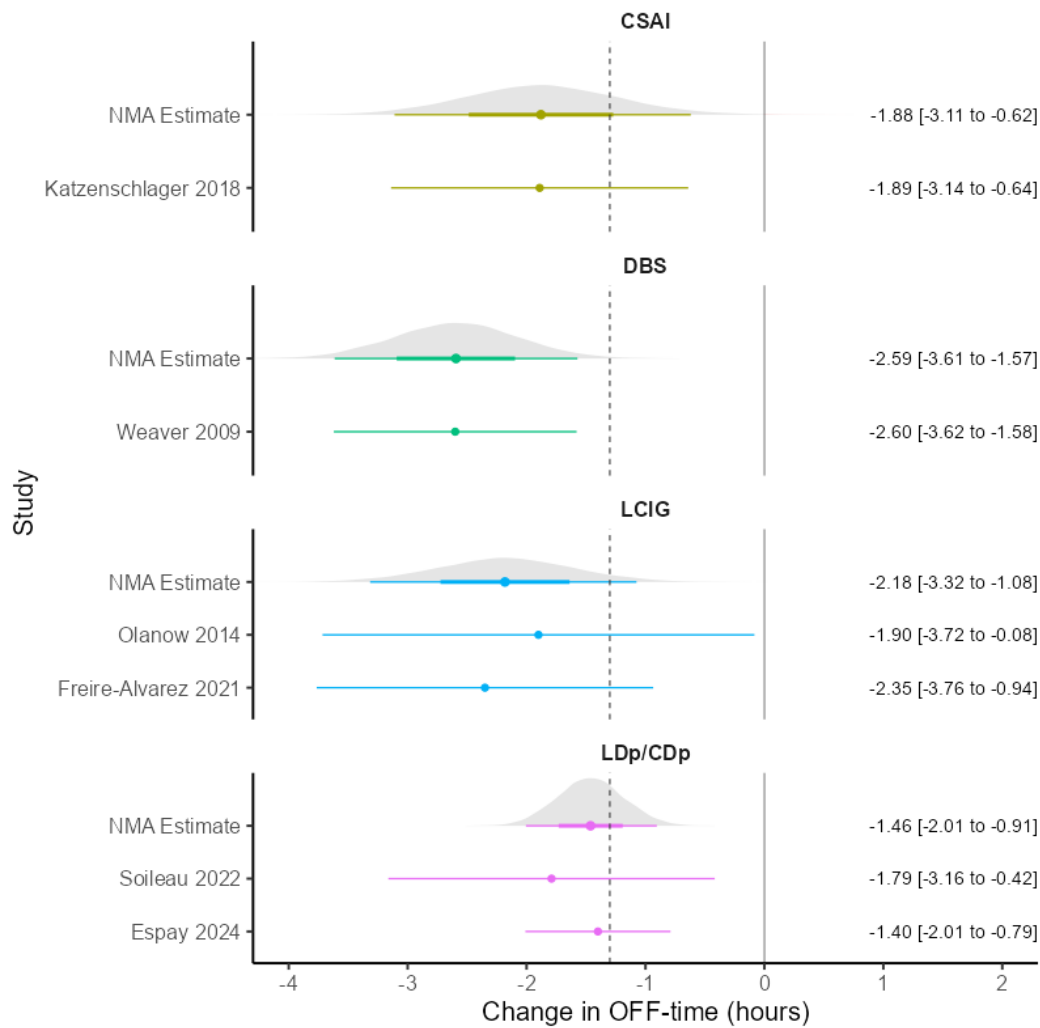
9	LCIG.tw,kf.
10	(7 and 8) or 9
11	(apokinin* or apomorphin* or britaject*).mp. or Apomorphine/
12	(drug infusion system* or external infusion pump* or infusion pump* or infusor* or intravenous drug delivery system* or perfusion pump* or implantable medication system* or implantable perfusion pump* or implantable peristaltic pump* or programmable implantable medication system* or infusion system*).tw,kf.
13	exp Infusions, Subcutaneous/ or (Subcutaneous Infusion* or Hypodermoclys* or Subcutaneous Hydrat*).tw,kf.
14	11 and (12 or 13)
15	((foscarnidopa* adj1 foslevodopa*) or Vyalev* or Produodopa).tw,kf.
16	3 and (6 or 10 or 14 or 15)
17	exp randomized controlled trial/
18	phase I clinical trial/
19	case reports/
20	(16 and 17) not (18 or 19)
21	remove duplicates from 20

Cochrane Library	
#	Terms
#1	(Parkinsonism or Parkinson* or Paralysis agitans or Shaking palsy).tw,kf.
#2	MeSH descriptor: [Parkinson Disease] explode all trees
#3	MeSH descriptor: [Parkinsonian Disorders] explode all trees
#4	#1 or #2 or #3
#5	MeSH descriptor: [Deep Brain Stimulation] explode all trees
#6	(deep brain stimulation* or DBS or subthalamic stimulation* or pallidal stimulation* or ventral intermediate nucleus stimulation* or thalamic stimulation* or (electric stimulation* adj3 brain)).tw,kf.
#7	#5 or #6
#8	(levodopa* or dopaflex* or dopar* or larodopa* or levodopa* or levopa*).tw,kf.
#9	MeSH descriptor: [Levodopa] explode all trees
#10	#8 or #9
#11	(carbidopa* or lodosin* or lodosyn* or methyl dopahydrazine*).tw,kf.
#12	MeSH descriptor: [Carbidopa] explode all trees
#13	#11 or #12
#14	#10 and #13
#15	(intestin* or jejun* or duoden* or intrainstest* or intrajejun* or intraduoden* or enteral or intra intestin* or intra jejun* or intra duoden*).tw,kf.
#16	MeSH descriptor: [Intestines] explode all trees
#17	#15 or #16
#18	(LCIG).tw,kf.
#19	(#14 and #17) or #18
#20	MeSH descriptor: [Apomorphine] explode all trees
#21	(apokinin* or apomorphin* or britaject*).mp.

#22	#20 or #21
#23	MeSH descriptor: [Infusions, Subcutaneous] explode all trees
#24	(Subcutaneous Infusion* or Hypodermoclysis* or Subcutaneous Hydrat*).tw,kf.
#25	#23 or #24
#26	(drug infusion system* or external infusion pump* or infusion pump* or infusor* or intravenous drug delivery system* or perfusion pump* or implantable medication system* or implantable perfusion pump* or implantable peristaltic pump* or programmable implantable medication system* or infusion system*).tw,kf.
#27	#22 and (#25 or #26)
#28	#23 or #26
#29	((foscarnidopa* adj1 foslevodopa*) or Vyalev* or Produodopa).tw,kf.
#30	#4 and (#7 or #19 or #28 or #29)
#31	#30 in Trials
#32	#31 NOT (phase I or phase 1)

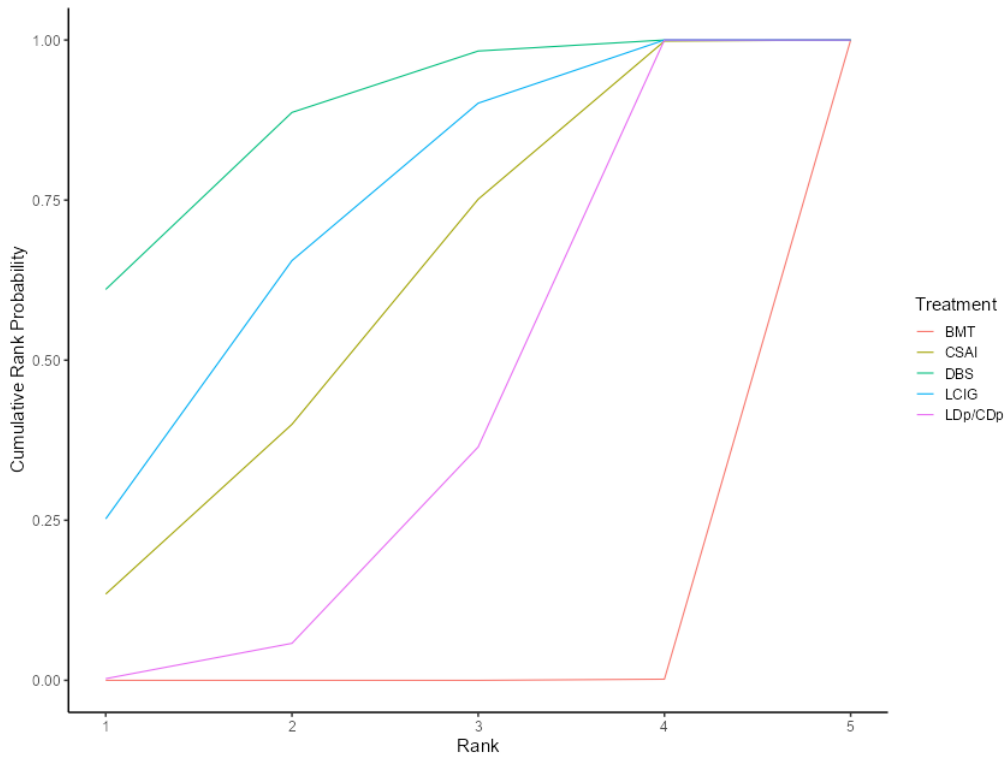
<u>CINAHL</u>	
#	Terms
S1	XB (Parkinsonism or Parkinson* or Paralysis agitans or Shaking palsy)
S2	MH Parkinson Disease OR MH Parkinsonian Disorders
S3	S1 or S2
S4	MH Deep Brain Stimulation
S5	XB (deep brain stimulation* or DBS or subthalamic stimulation* or pallidal stimulation* or ventral intermediate nucleus stimulation* or thalamic stimulation* or (electric stimulation* adj3 brain)
S6	S4 or S5
S7	XB (levodopa* or dopaflex* or dopar* or larodopa* or levodopa* or levopa*) OR MH levodopa
S8	XB (carbidopa* or lodosin* or lodosyn* or methyldopahydrazine*) OR MH carbidopa
S9	XB (intestin* or jejun* or duoden* or intrainstestine* or intrajejun* or intraduoden* or enteral or intra intestine* or intra jejun* or intra duoden*) OR MH intestines
S10	XB LCIG
S11	(S7 AND S8 AND S9) or S10
S12	TX (apokinin* or apomorphin* or britaject*) OR MH Apomorphine
S13	XB (drug infusion system* or external infusion pump* or infusion pump* or infusor* or intravenous drug delivery system* or perfusion pump* or implantable medication system* or implantable perfusion pump* or implantable peristaltic pump* or programmable implantable medication system* or infusion system*)
S14	XB (Subcutaneous Infusion* or Hypodermoclysis* or Subcutaneous Hydrat*) OR MH Infusions, Subcutaneous
S15	S12 and (S13 or S14)
S16	XB ((foscarnidopa* adj1 foslevodopa*) or Vyalev* or Produodopa)
S17	S3 and (S6 or S11 or S15 or S16) Limiters – Randomized Controlled Trials

Supplementary Figure 1a. Change in OFF time versus BMT



For the network estimate, the shaded area is the posterior distribution. The red shaded area represents the probability of a treatment being worse than BMT. The dashed line is the MCID value. The dot, thick band, and thin band signify the posterior mean, 66% CrI, and 95% CrI, respectively. For individual studies, the dot and band signify the mean and 95% confidence interval.

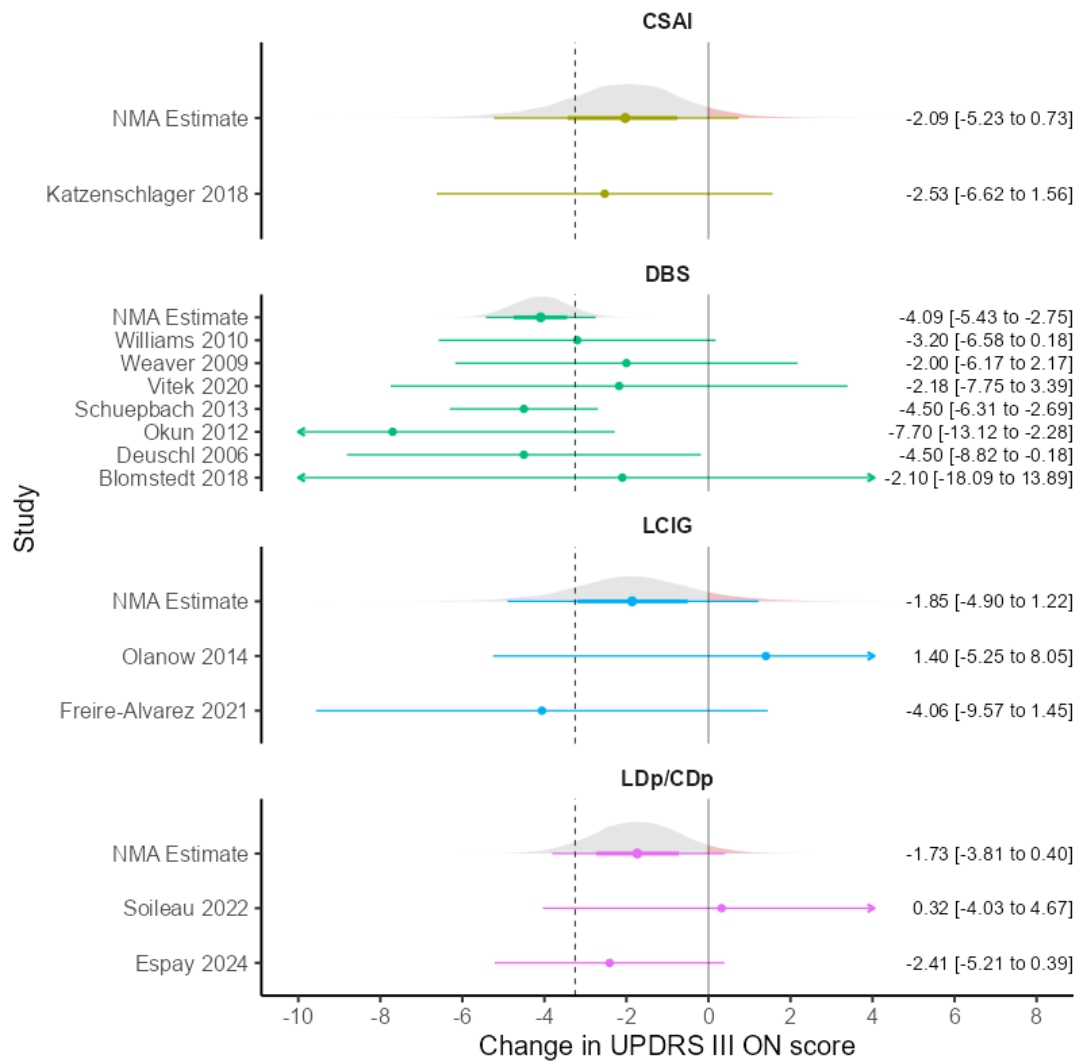
Supplementary Figure 1b. Ranking of advanced therapies and BMT based on OFF time reduction



Supplementary Figure 1c. Risk of bias assessment for OFF time

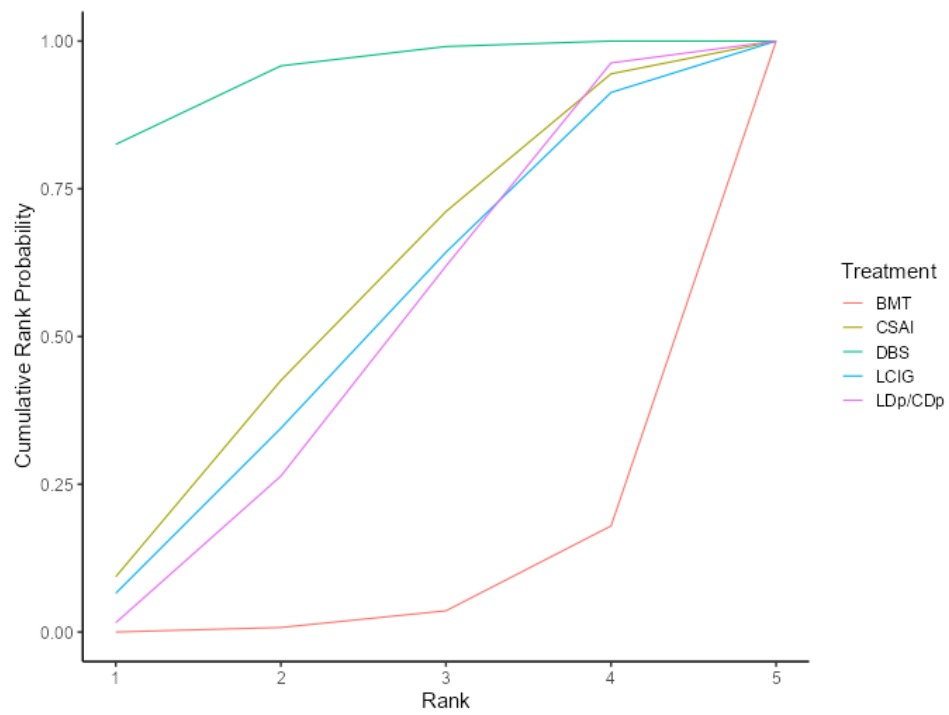
		Risk of bias domains					
		D1	D2	D3	D4	D5	Overall
Study	Weaver 2009	-	-	X	X	+	X
	Olanow 2014	+	+	-	+	-	-
	Alvarez 2021	+	-	-	X	+	X
	Katzenschlager 2018	+	-	+	+	-	-
	Soileau 2022	+	-	X	+	+	X
	Espay 2024	+	+	-	+	+	-
Domains:		D1: Bias arising from the randomization process. D2: Bias due to deviations from intended intervention. D3: Bias due to missing outcome data. D4: Bias in measurement of the outcome. D5: Bias in selection of the reported result.					
		Judgement					
		X High - Some concerns + Low					

Supplementary Figure 2a. Change in UPDRS part III score versus BMT



For the network estimate, the shaded area is the posterior distribution. The red shaded area represents the probability of a treatment being worse than BMT. The dashed line is the MCID value. The dot, thick band, and thin band signify the posterior mean, 66% CrI, and 95% CrI, respectively. For individual studies, the dot and band signify the mean and 95% confidence interval.

Supplementary Figure 2b. Ranking of advanced therapies and BMT based on UPDRS part III score reduction



Supplementary Figure 2c. Risk of bias assessment for UPDRS part III

	Risk of bias domains					
	D1	D2	D3	D4	D5	Overall
Study	Deuschl 2006					
	Weaver 2009					
	Williams 2010					
	Okun 2012					
	Schuepbach 2013					
	Blomstedt 2018					
	Vitek 2020					
	Olanow 2014					
	Alvarez 2021					
	Katzenschlager 2018					
	Soileau 2022					
	Espay 2024					

Domains:

D1: Bias arising from the randomization process.

D2: Bias due to deviations from intended intervention.

D3: Bias due to missing outcome data.

D4: Bias in measurement of the outcome.

D5: Bias in selection of the reported result.

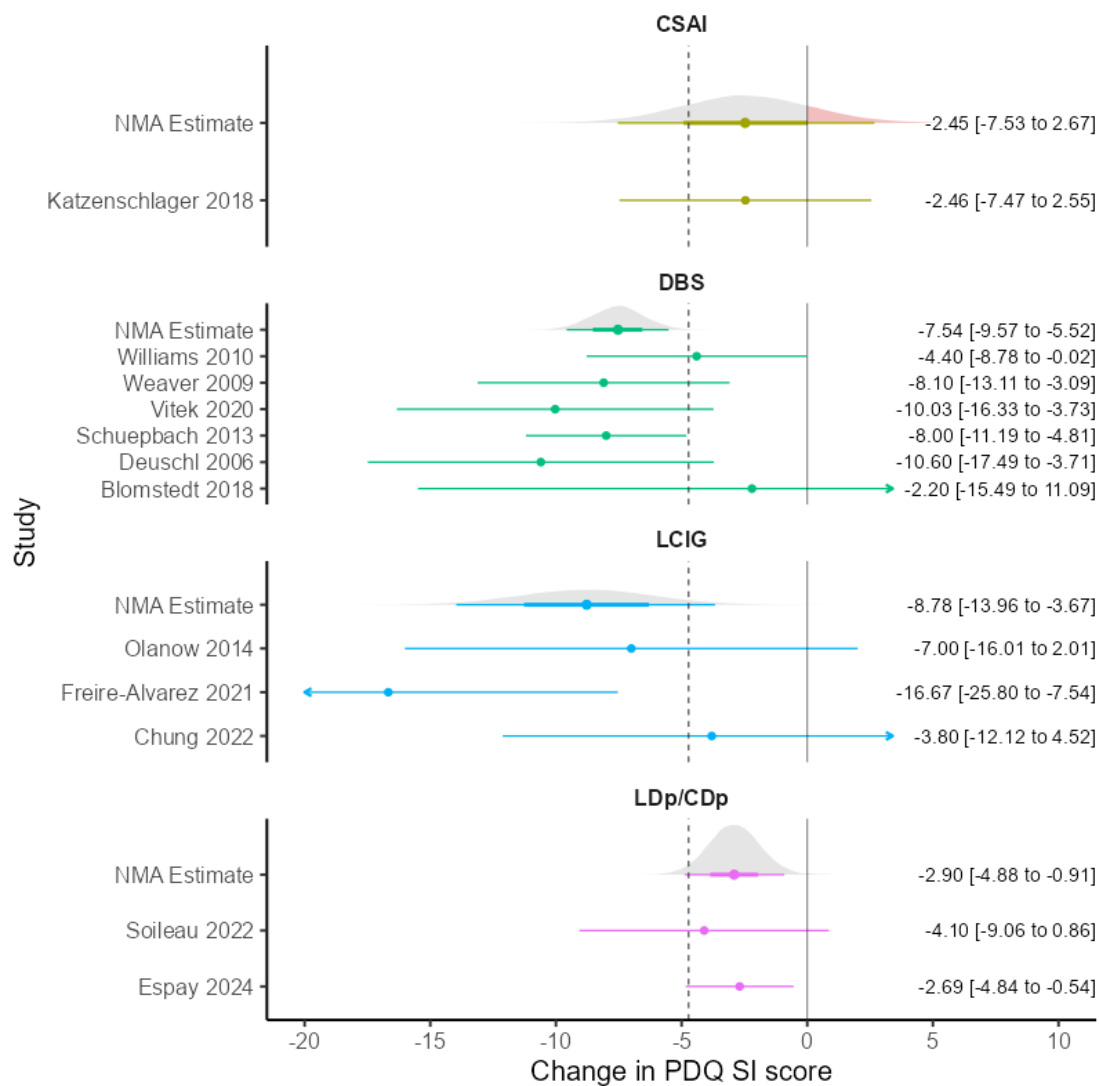
Judgement

High

Some concerns

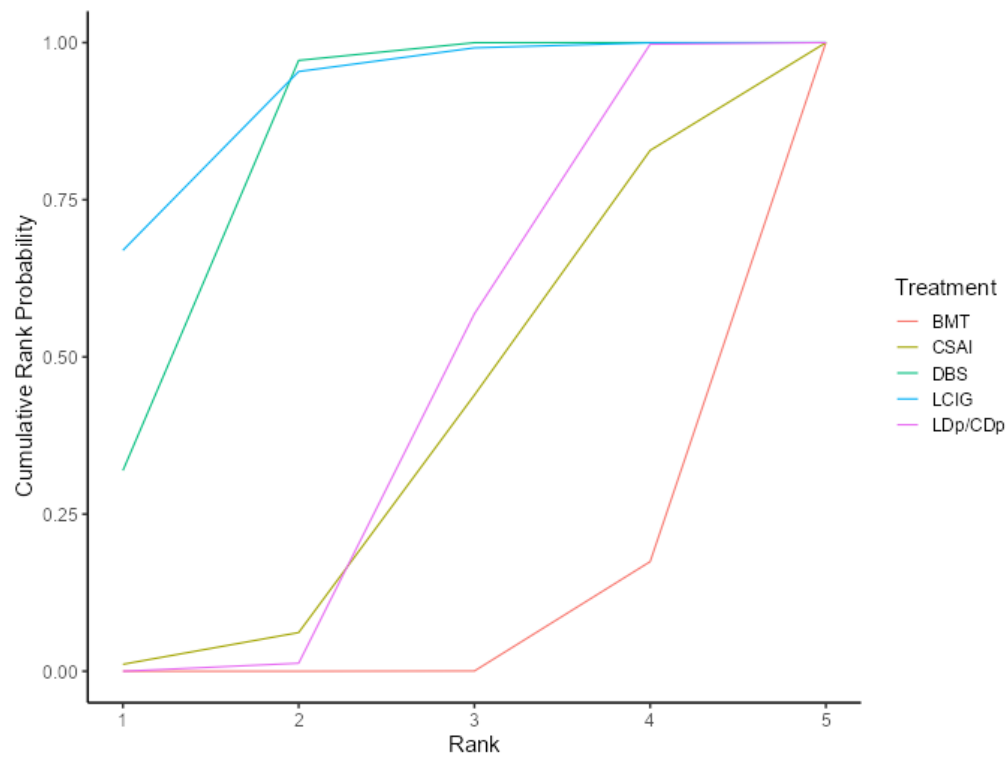
Low

Supplementary Figure 3a. Change in PDQ-39 score versus BMT



For the network estimate, the shaded area is the posterior distribution. The red shaded area represents the probability of a treatment being worse than BMT. The dashed line is the MCID value. The dot, thick band, and thin band signify the posterior mean, 66% CrI, and 95% CrI, respectively. For individual studies, the dot and band signify the mean and 95% confidence interval.

Supplementary Figure 3b. Ranking of advanced therapies and BMT based on PDQ-39 score reduction



Supplementary Figure 3c. Risk of bias assessment for PDQ

	Risk of bias domains					
	D1	D2	D3	D4	D5	Overall
Study	Deuschl 2006					
	Weaver 2009					
	Williams 2010					
	Schuepbach 2013					
	Blomstedt 2018					
	Vitek 2020					
	Olanow 2014					
	Alvarez 2021					
	Chung 2022					
	Katzenschlager 2018					
	Soileau 2022					
	Espay 2024					

Domains:

D1: Bias arising from the randomization process.

D2: Bias due to deviations from intended intervention.

D3: Bias due to missing outcome data.

D4: Bias in measurement of the outcome.

D5: Bias in selection of the reported result.

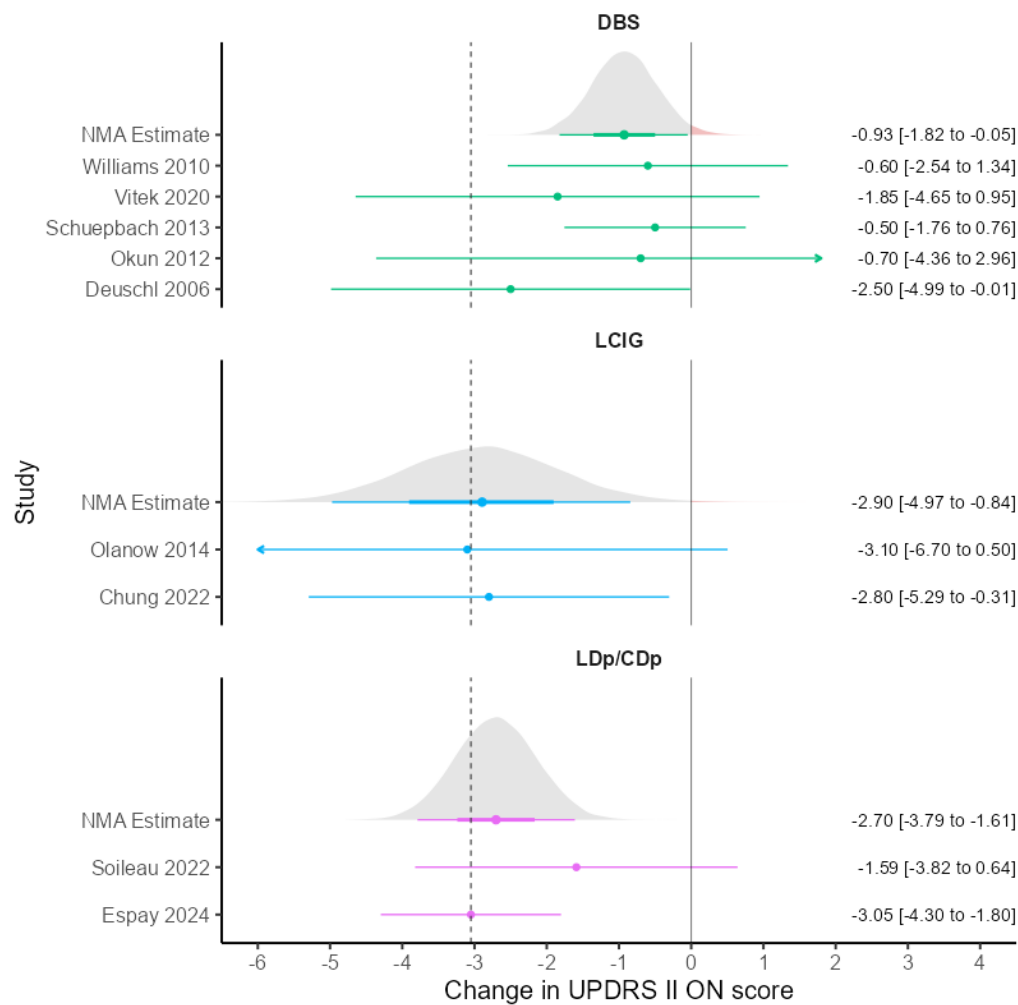
Judgement

High

Some concerns

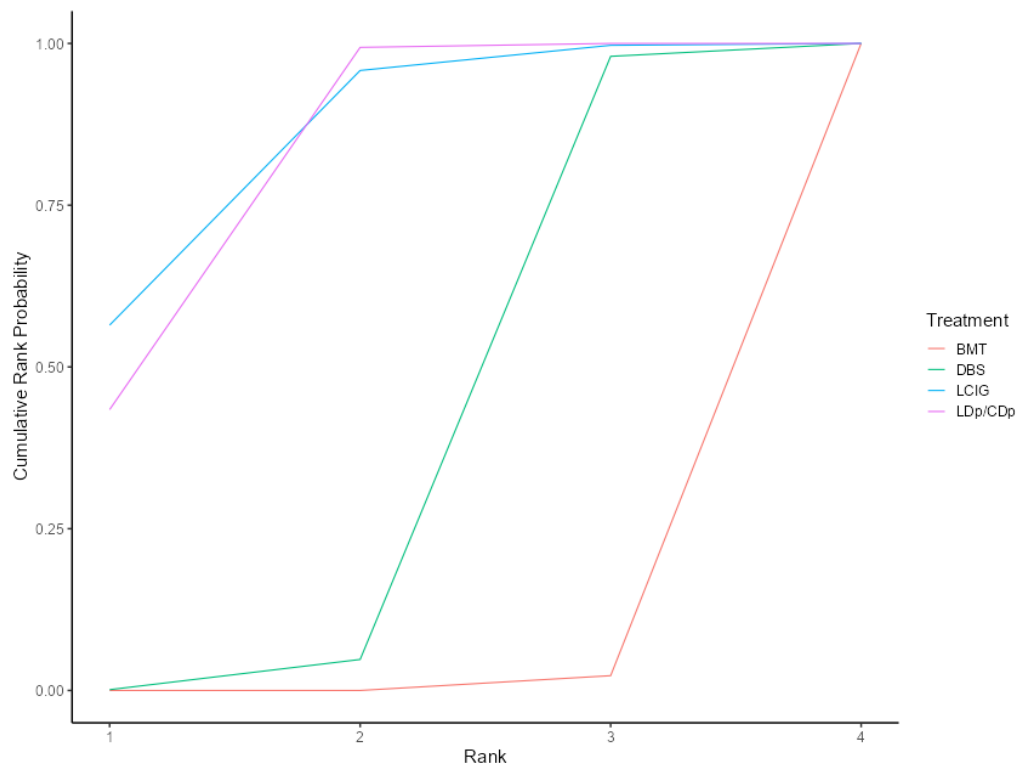
Low

Supplementary Figure 4a. Reduction in UPDRS part II score versus BMT



For the network estimate, the shaded area is the posterior distribution. The red shaded area represents the probability of a treatment being worse than BMT. The dashed line is the MCID value. The dot, thick band, and thin band signify the posterior mean, 66% CrI, and 95% CrI, respectively. For individual studies, the dot and band signify the mean and 95% confidence interval.

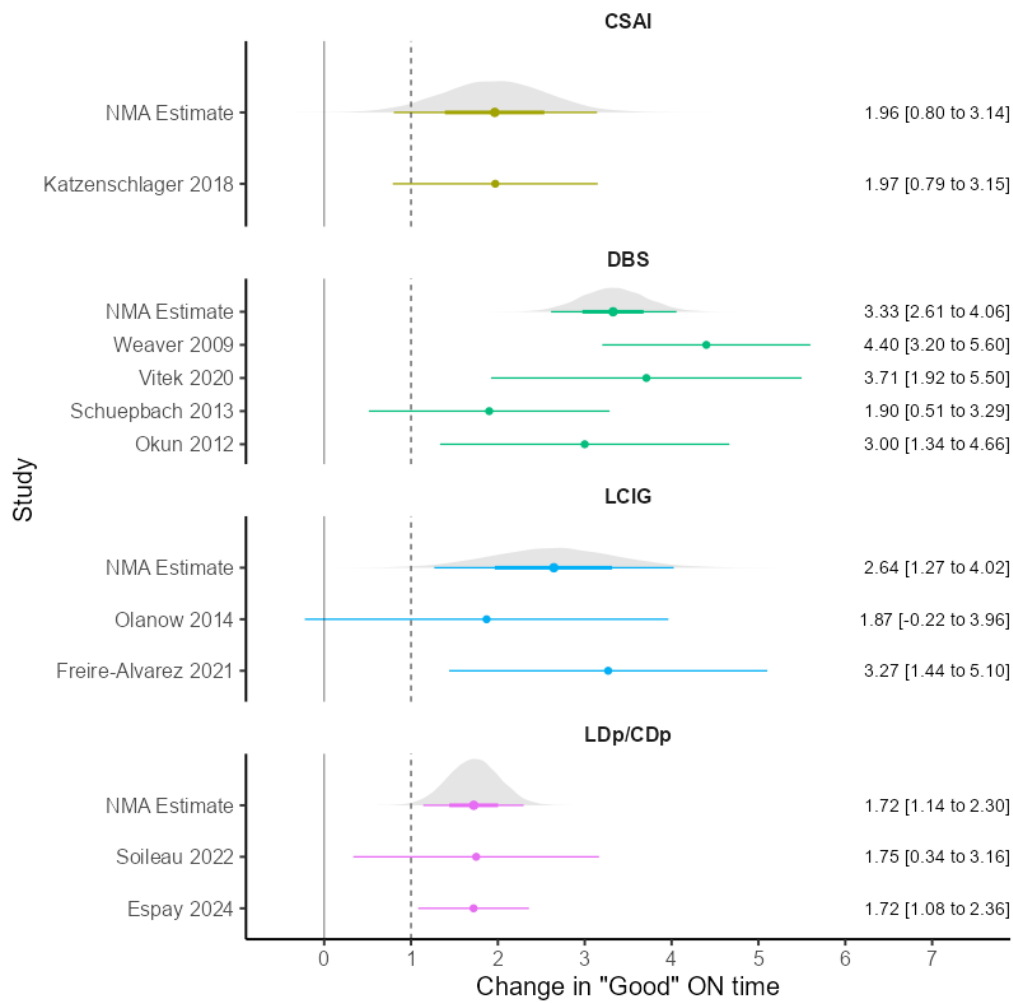
Supplementary Figure 4b. Ranking of advanced therapies and BMT based on UPDRS part II score reduction



Supplementary Figure 4c. Risk of bias assessment for UPDRS part II

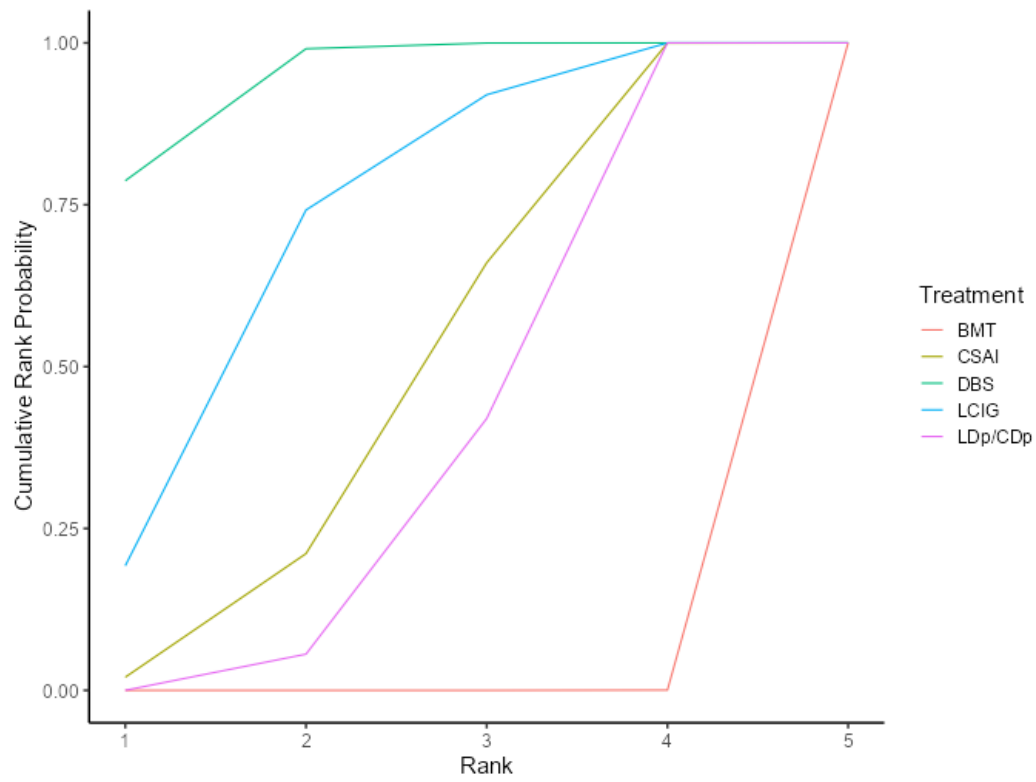
Study	Risk of bias domains					
	D1	D2	D3	D4	D5	Overall
Domains:						
D1: Bias arising from the randomization process.						
D2: Bias due to deviations from intended intervention.						
D3: Bias due to missing outcome data.						
D4: Bias in measurement of the outcome.						
D5: Bias in selection of the reported result.						
Judgement						
High						
Some concerns						
Low						

Supplementary Figure 5a. Change in Good ON time versus BMT



For the network estimate, the shaded area is the posterior distribution. The red shaded area represents the probability of a treatment being worse than BMT. The dashed line is the MCID value. The dot, thick band, and thin band signify the posterior mean, 66% CrI, and 95% CrI, respectively. For individual studies, the dot and band signify the mean and 95% confidence interval.

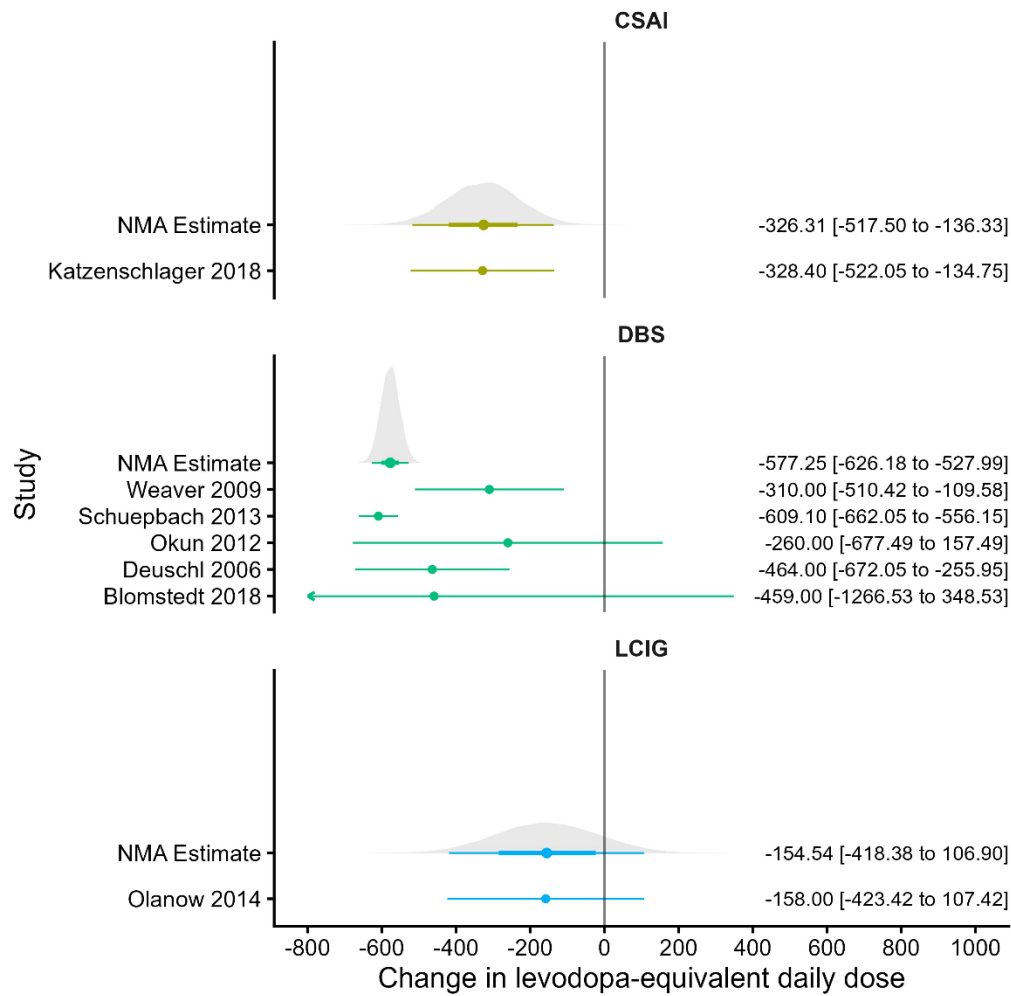
Supplementary Figure 5b. Ranking of advanced therapies and BMT based on Good ON time improvement



Supplementary Figure 5c. Risk of bias assessment for Good ON time

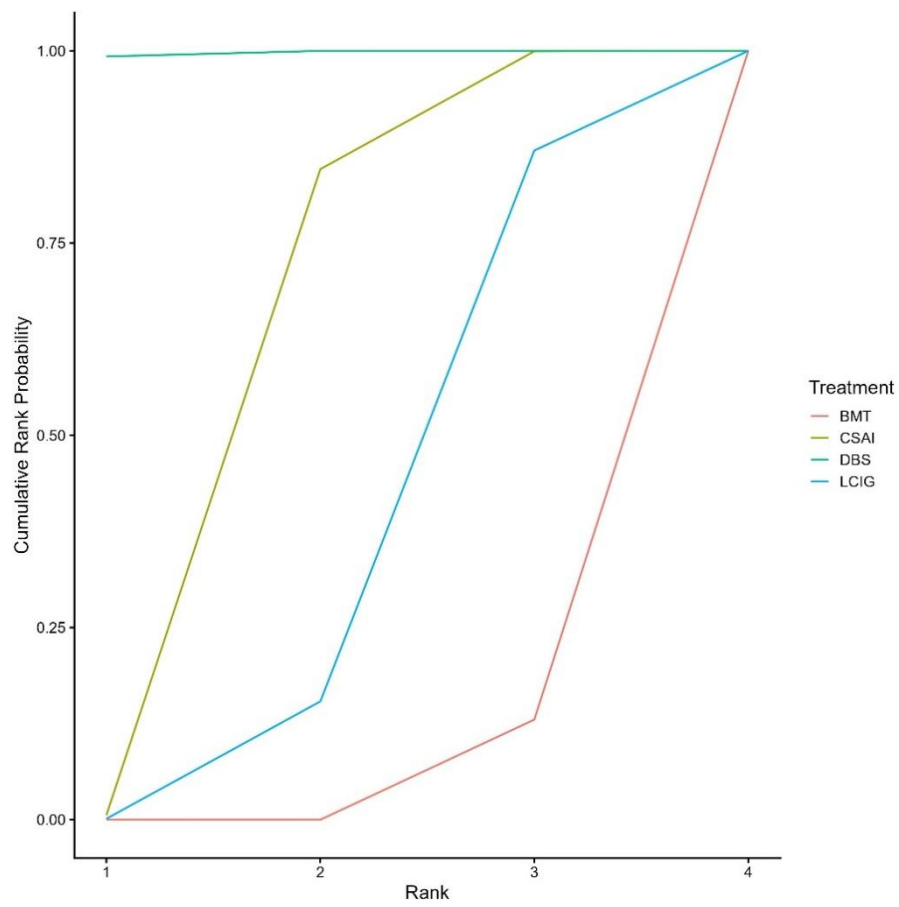
		Risk of bias domains					
		D1	D2	D3	D4	D5	Overall
Study	Weaver 2009	⊖	⊖	⊗	⊗	⊕	⊗
	Okun 2012	⊕	⊕	⊕	⊗	⊕	⊗
	Schuepbach 2013	⊕	⊕	⊖	⊗	⊕	⊗
	Vitek 2020	⊕	⊕	⊕	⊕	⊕	⊕
	Olanow 2014	⊕	⊕	⊖	⊕	⊖	⊖
	Alvarez 2021	⊕	⊖	⊖	⊗	⊕	⊗
	Katzenschlager 2018	⊕	⊖	⊖	⊕	⊖	⊖
	Soileau 2022	⊕	⊖	⊗	⊕	⊕	⊗
	Espay 2024	⊕	⊕	⊕	⊕	⊕	⊕
Domains:							Judgement
D1: Bias arising from the randomization process.							⊗ High
D2: Bias due to deviations from intended intervention.							⊖ Some concerns
D3: Bias due to missing outcome data.							⊕ Low
D4: Bias in measurement of the outcome.							
D5: Bias in selection of the reported result.							

Supplementary Figure 6a. Change in LEDD versus BMT



For the network estimate, the shaded area is the posterior distribution. The dashed line is the MCID value. The dot, thick band, and thin band signify the posterior mean, 66% CrI, and 95% CrI, respectively. For individual studies, the dot and band signify the mean and 95% confidence interval.

Supplementary Figure 6b. Ranking of advanced therapies and BMT based on LEDD improvement



Supplementary Figure 6c. Risk of bias assessment for LEDD

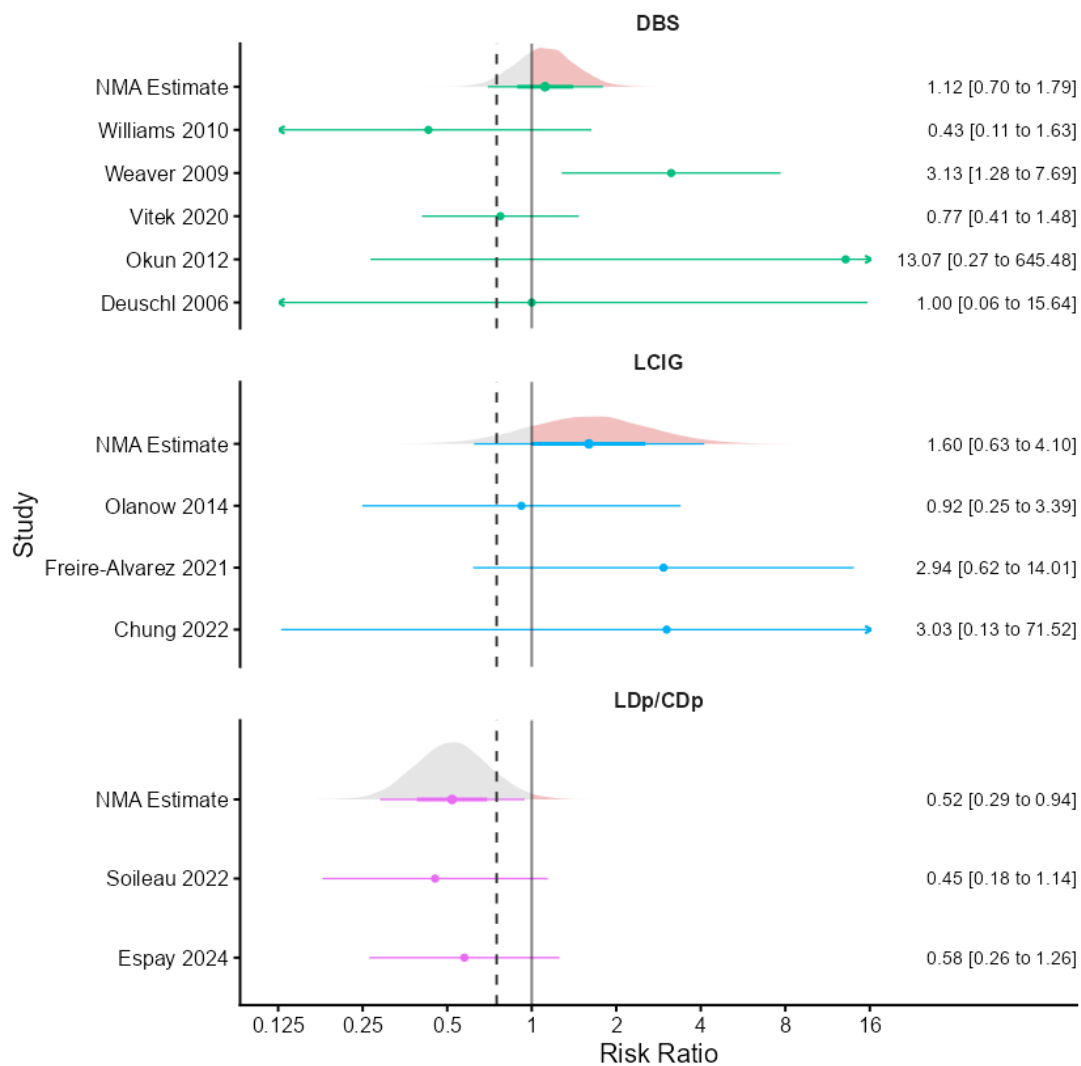
	Risk of bias domains					
	D1	D2	D3	D4	D5	Overall
Deuschl 2006						
Weaver 2009						
Okun 2012						
Schuepbach 2013						
Blomstedt 2018						
Olanow 2014						
Katzenschlager 2018						

Study

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

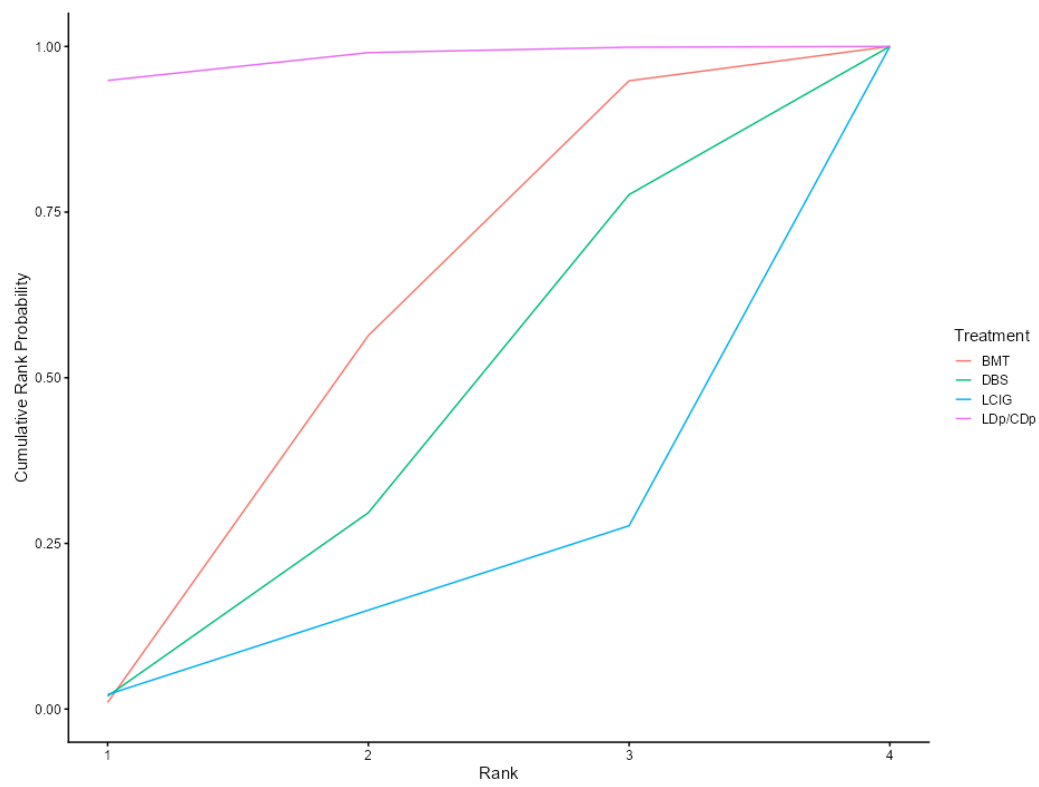
Judgement
 High
 Some concerns
 Low

Supplementary Figure 7a. Risk of falls versus BMT



For the network estimate, the shaded area is the posterior distribution. The red shaded area represents the probability of a treatment being worse than BMT. The dashed line is the MCID value. The dot, thick band, and thin band signify the posterior mean, 66% CrI, and 95% CrI, respectively. For individual studies, the dot and band signify the mean and 95% confidence interval.

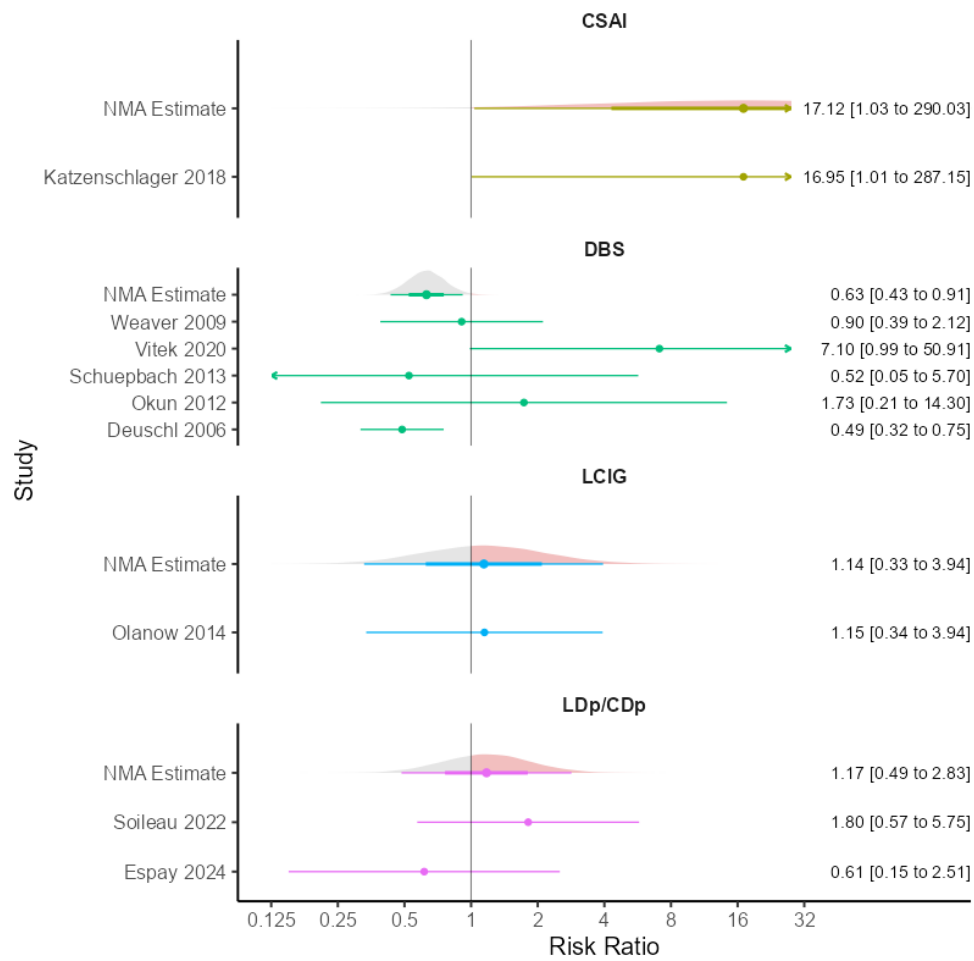
Supplementary Figure 7b. Ranking of advanced therapies and BMT based on risk of falls



Supplementary Figure 7c. Risk of bias assessment for falls events

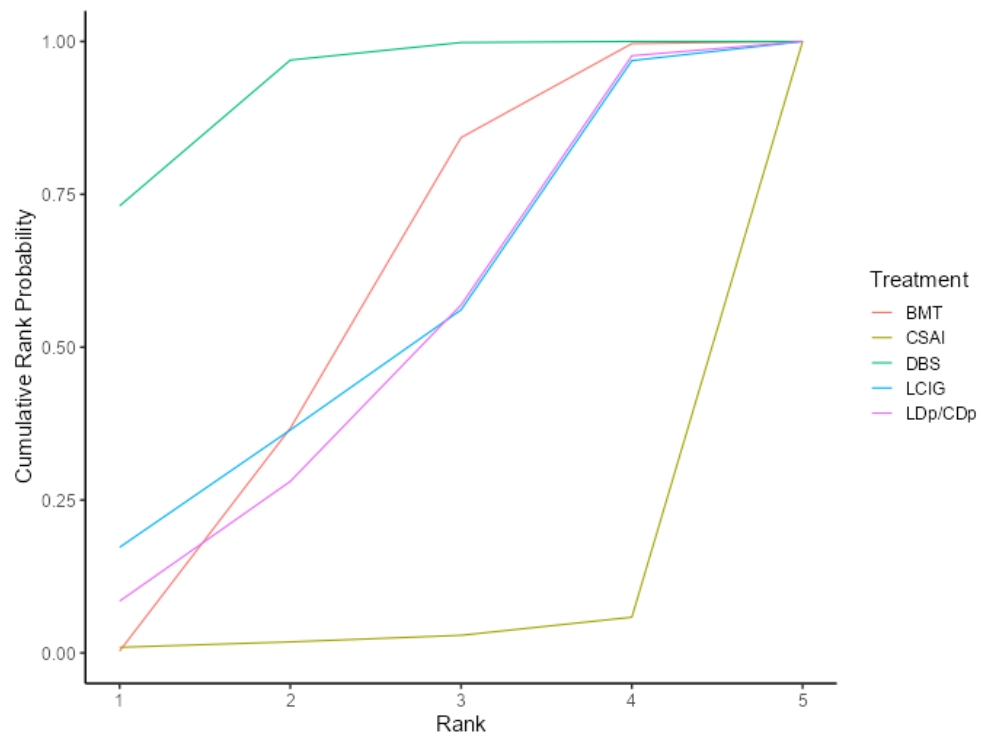
		Risk of bias domains					
		D1	D2	D3	D4	D5	Overall
Study	Deuschl 2006						
	Weaver 2009						
	Williams 2010						
	Okun 2012						
	Vitek 2020						
	Olanow 2014						
	Alvarez 2021						
	Chung 2022						
	Soileau 2022						
	Espay 2024						
Domains:		D1: Bias arising from the randomization process. D2: Bias due to deviations from intended intervention. D3: Bias due to missing outcome data. D4: Bias in measurement of the outcome. D5: Bias in selection of the reported result.					
		Judgement					
		Some concerns					
		Low					

Supplementary Figure 8a. Risk of dyskinesia versus BMT

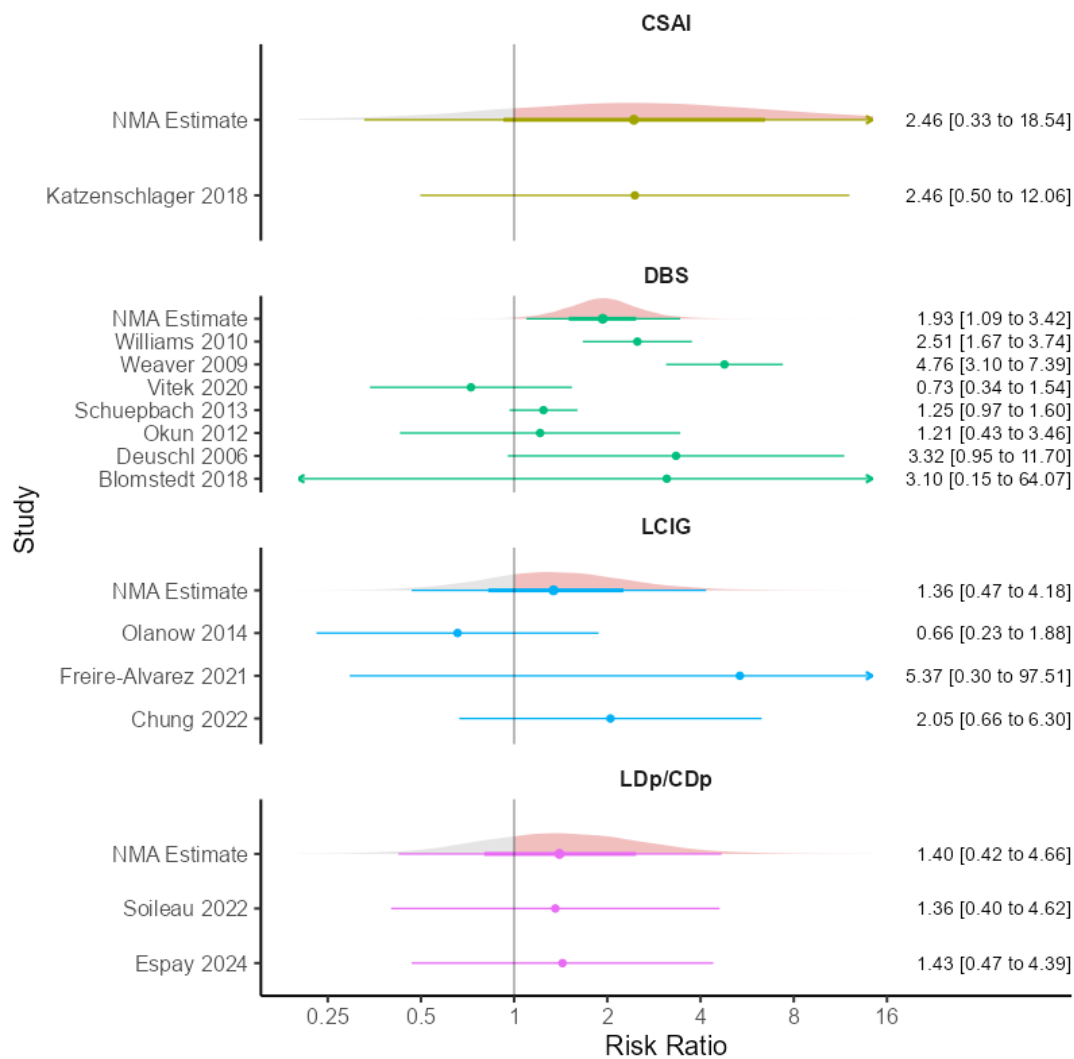


For the network estimate, the shaded area is the posterior distribution. The red shaded area represents the probability of a treatment being worse than BMT. The dashed line is the MCID value. The dot, thick band, and thin band signify the posterior mean, 66% CrI, and 95% CrI, respectively. For individual studies, the dot and band signify the mean and 95% confidence interval.

Supplementary Figure 8b. Ranking of advanced therapies and BMT based on risk of dyskinesia

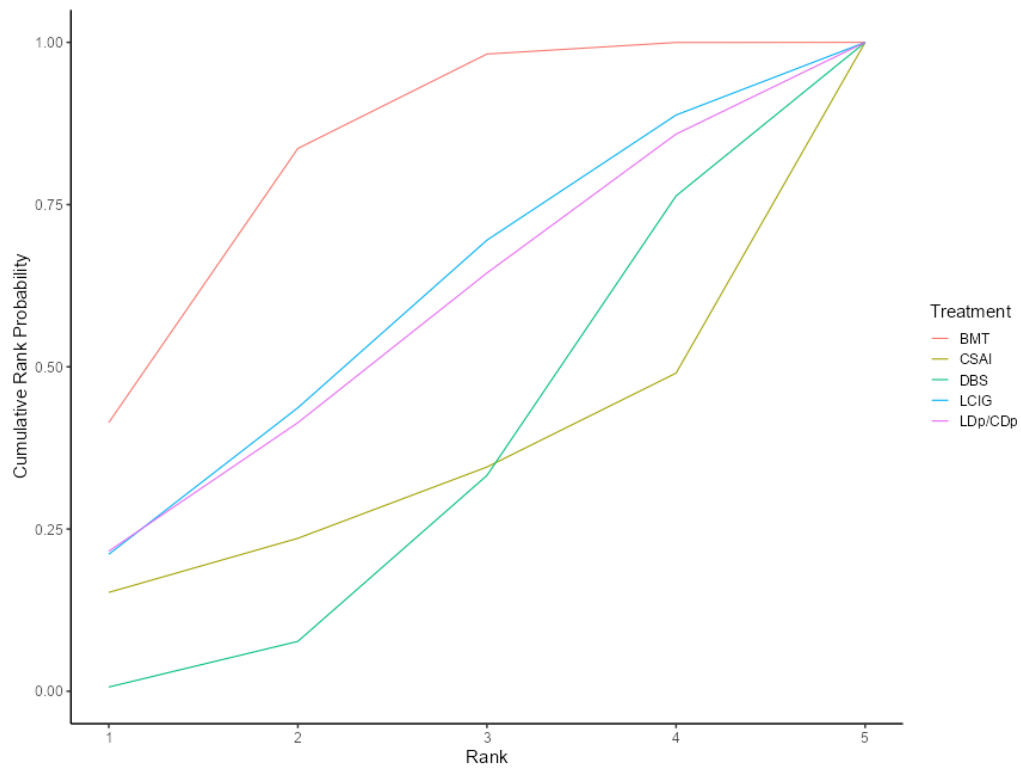


Supplementary Figure 9a. Risk of serious adverse event versus BMT



For the network estimate, the shaded area is the posterior distribution. The red shaded area represents the probability of a treatment being worse than BMT. The dashed line is the MCID value. The dot, thick band, and thin band signify the posterior mean, 66% CrI, and 95% CrI, respectively. For individual studies, the dot and band signify the mean and 95% confidence interval.

Supplementary Figure 9b. Ranking of advanced therapies and BMT based on risk of serious adverse event



Supplementary Figure 9c. Risk of bias assessment for serious adverse events

		Risk of bias domains					
		D1	D2	D3	D4	D5	Overall
Study	Deuschl 2006	+	-	+	+	+	-
	Weaver 2009	-	-	+	+	+	-
	Williams 2010	+	-	+	+	+	-
	Okun 2012	+	+	+	+	+	+
	Schuepbach 2013	+	+	+	+	+	+
	Blomstedt 2018	-	X	+	+	+	X
	Vitek 2020	+	+	+	+	+	+
	Olanow 2014	+	+	+	+	+	+
	Alvarez 2021	+	-	+	+	+	-
	Chung 2022	+	-	+	+	+	-
	Katzenschlager 2018	+	-	+	+	+	-
	Soileau 2022	+	-	+	+	+	-
	Espay 2024	+	+	+	+	+	+

Domains:

D1: Bias arising from the randomization process.

D2: Bias due to deviations from intended intervention.

D3: Bias due to missing outcome data.

D4: Bias in measurement of the outcome.

D5: Bias in selection of the reported result.

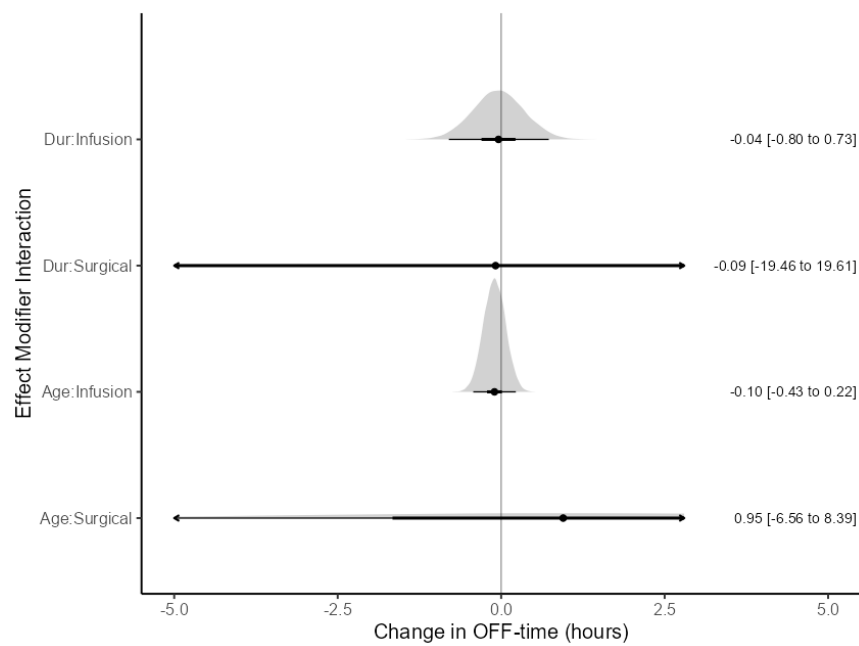
Judgement

X High

- Some concerns

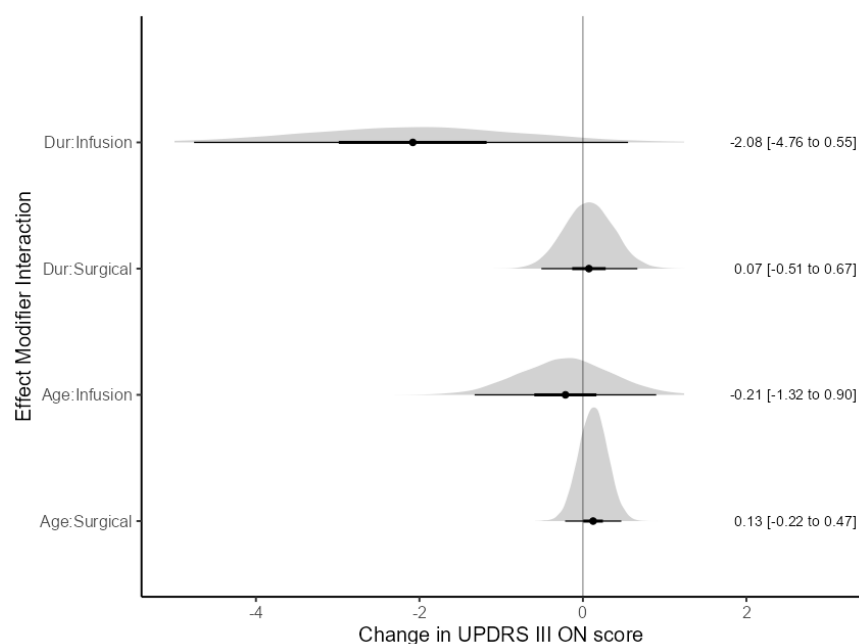
+ Low

Supplementary Figure 10a. Effect modification – OFF time



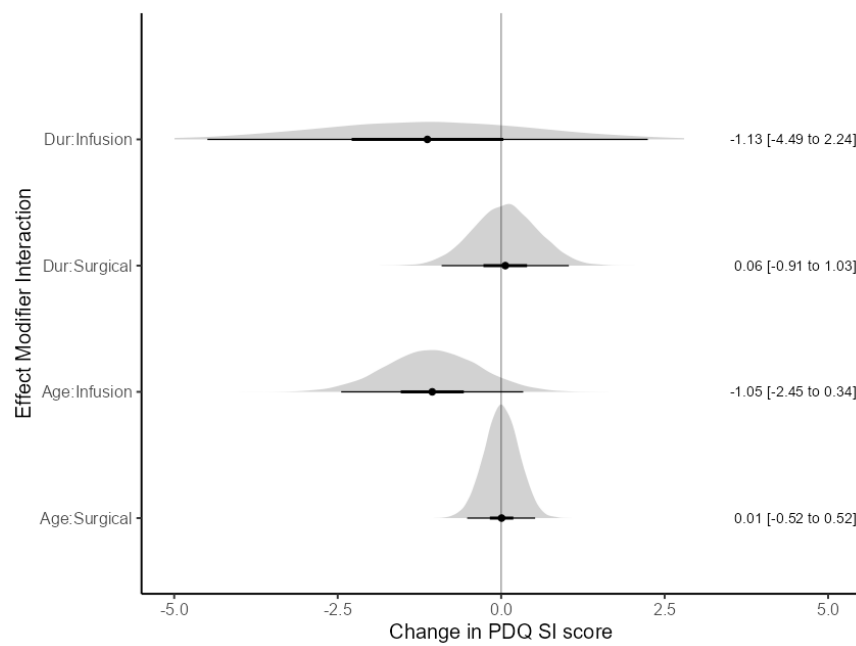
The shaded area is the posterior distribution. The dot, thick band, and thin band signify the posterior mean, 66% CrI, and 95% CrI, respectively.

Supplementary Figure 10b. Effect modification – UPDRS part III



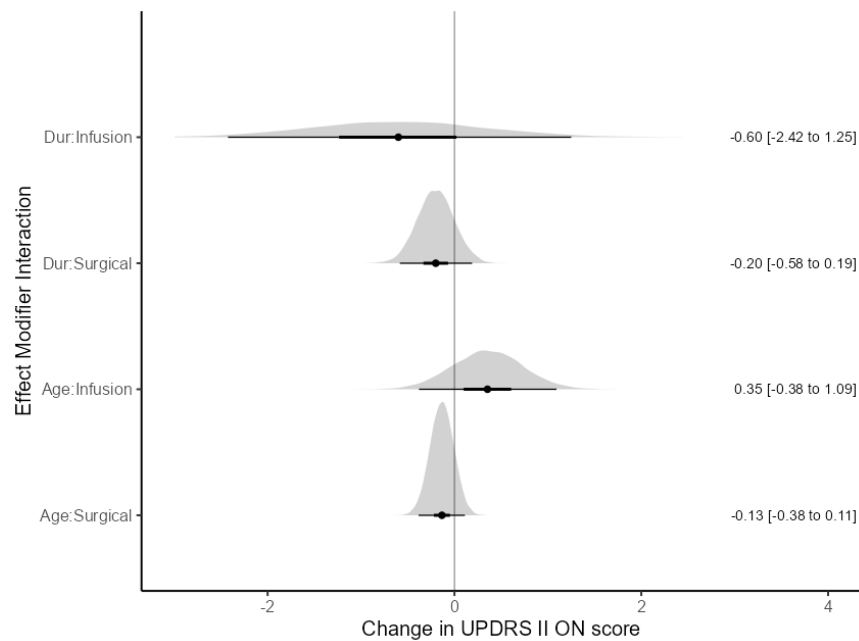
The shaded area is the posterior distribution. The dot, thick band, and thin band signify the posterior mean, 66% CrI, and 95% CrI, respectively.

Supplementary Figure 10c. Effect modification – PDQ score



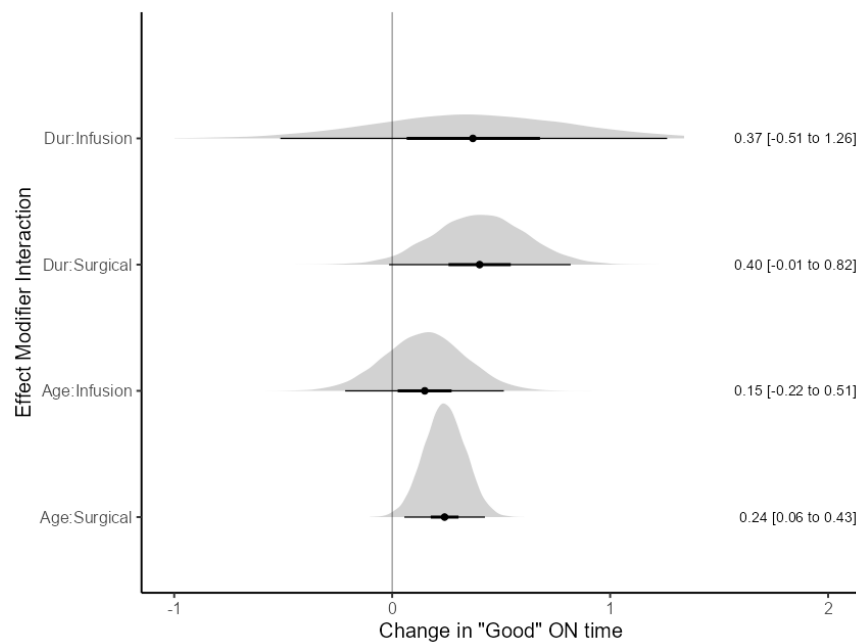
The shaded area is the posterior distribution. The dot, thick band, and thin band signify the posterior mean, 66% CrI, and 95% CrI, respectively.

Supplementary Figure 10d. Effect modification – UPDRS part II



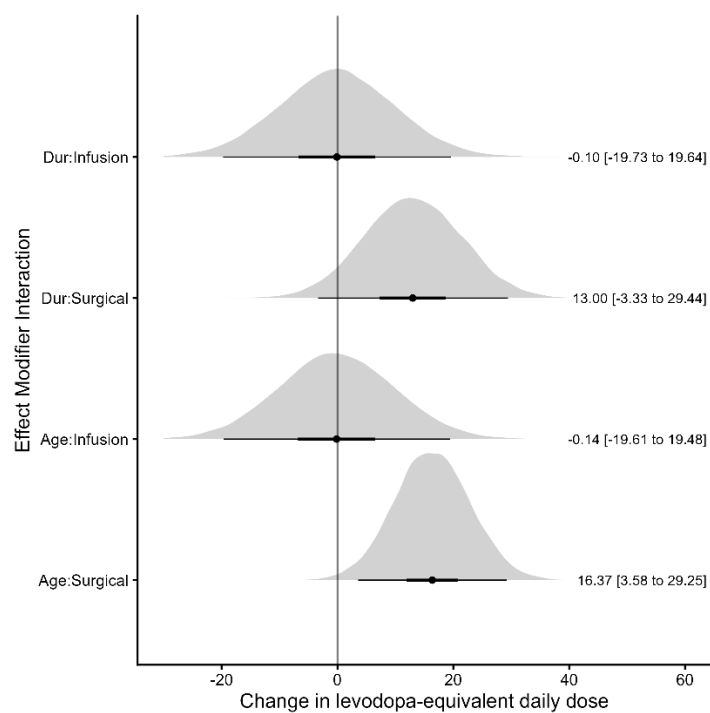
The shaded area is the posterior distribution. The dot, thick band, and thin band signify the posterior mean, 66% CrI, and 95% CrI, respectively.

Supplementary Figure 10e. Effect modification – “Good” ON time



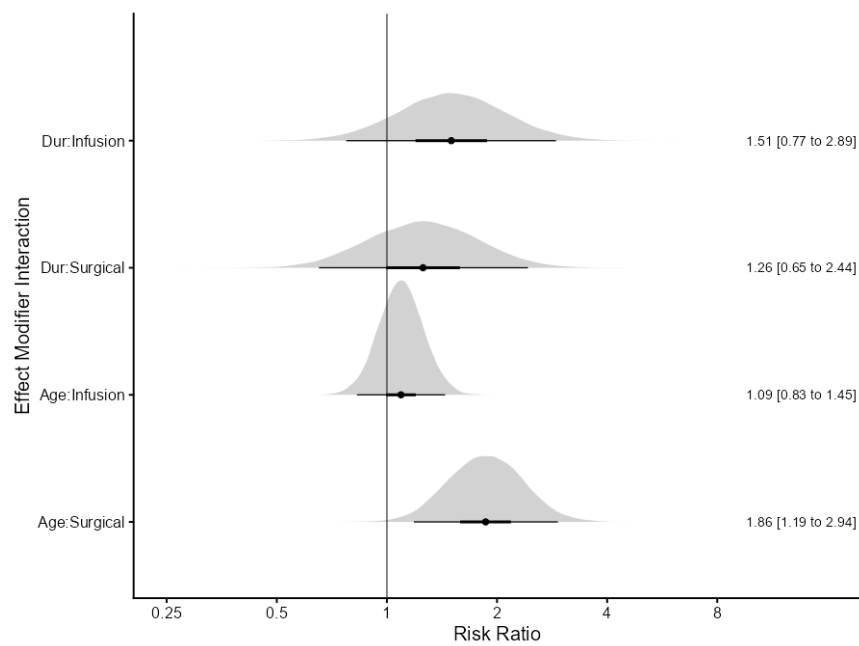
The shaded area is the posterior distribution. The dot, thick band, and thin band signify the posterior mean, 66% CrI, and 95% CrI, respectively.

Supplementary Figure 10f. Effect modification – LEDD



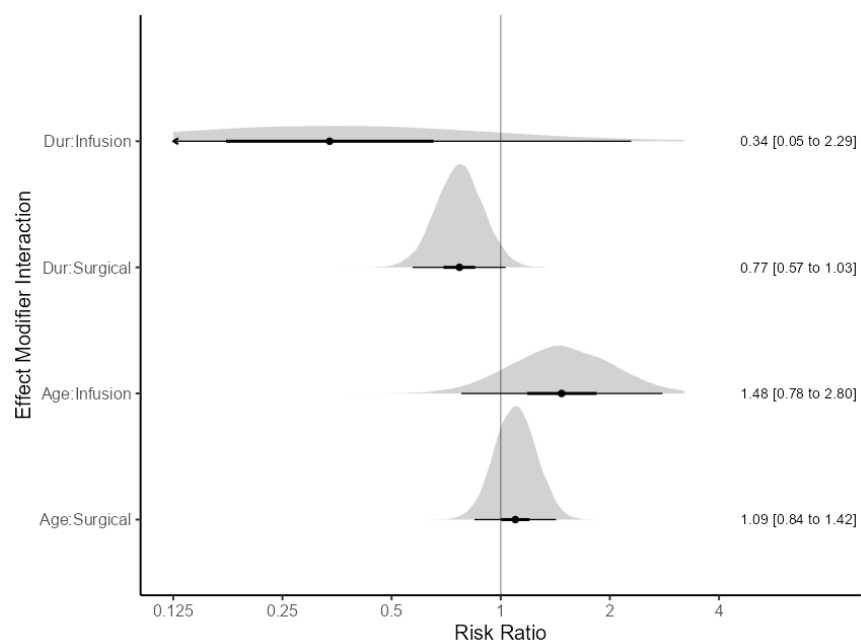
The shaded area is the posterior distribution. The dot, thick band, and thin band signify the posterior mean, 66% CrI, and 95% CrI, respectively.

Supplementary Figure 10g. Effect modification – Risk of falls



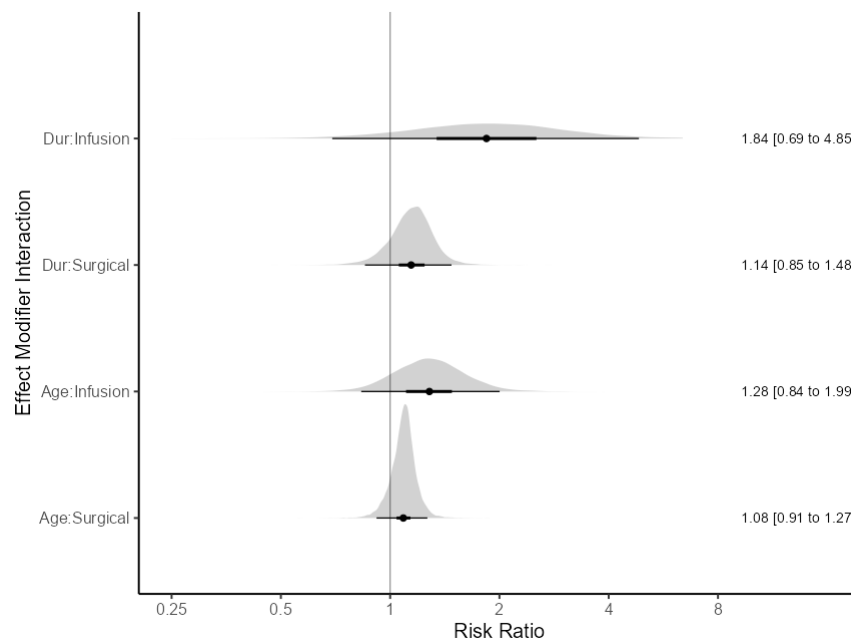
The shaded area is the posterior distribution. The dot, thick band, and thin band signify the posterior mean, 66% CrI, and 95% CrI, respectively.

Supplementary Figure 10h. Effect modification – Risk of dyskinesia



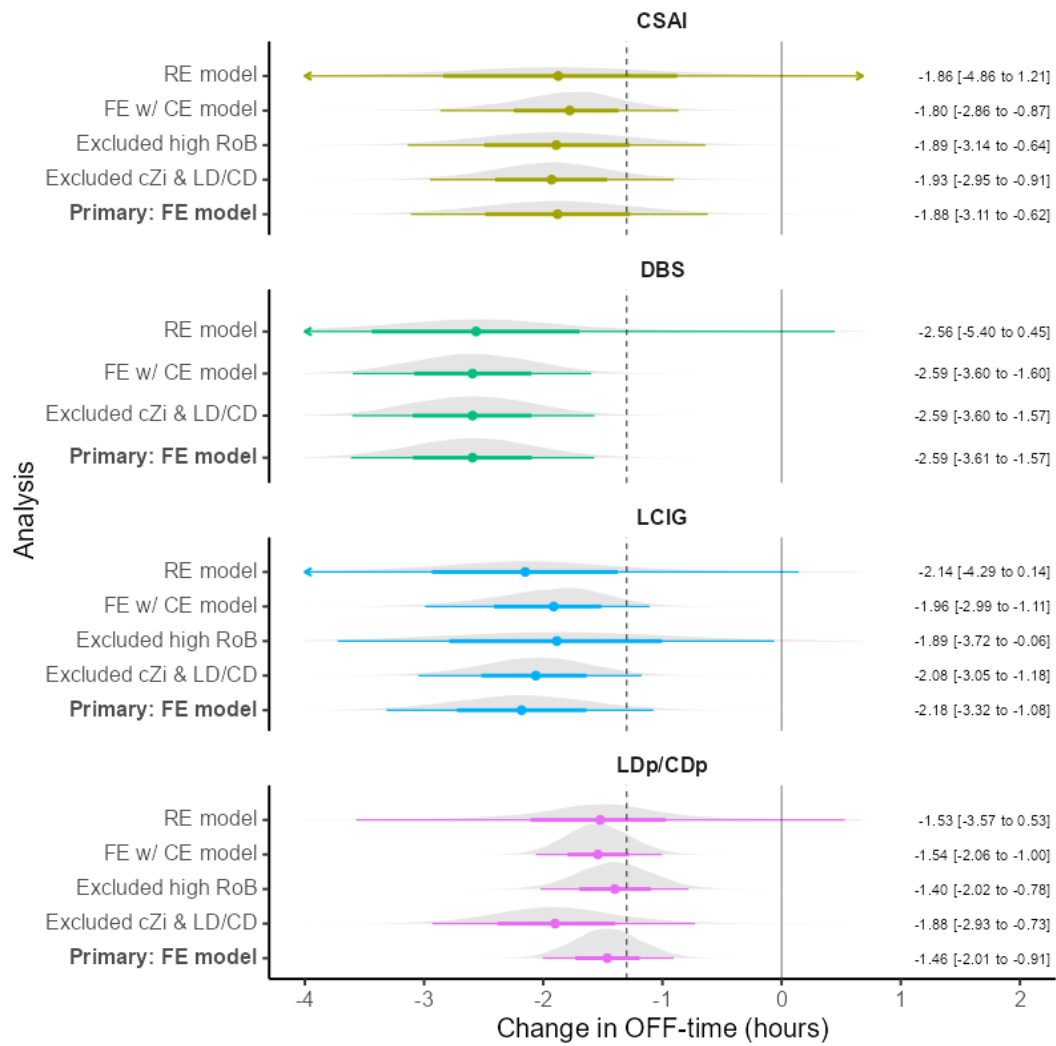
The shaded area is the posterior distribution. The dot, thick band, and thin band signify the posterior mean, 66% CrI, and 95% CrI, respectively.

Supplementary Figure 10i. Effect modification – Risk of SAEs



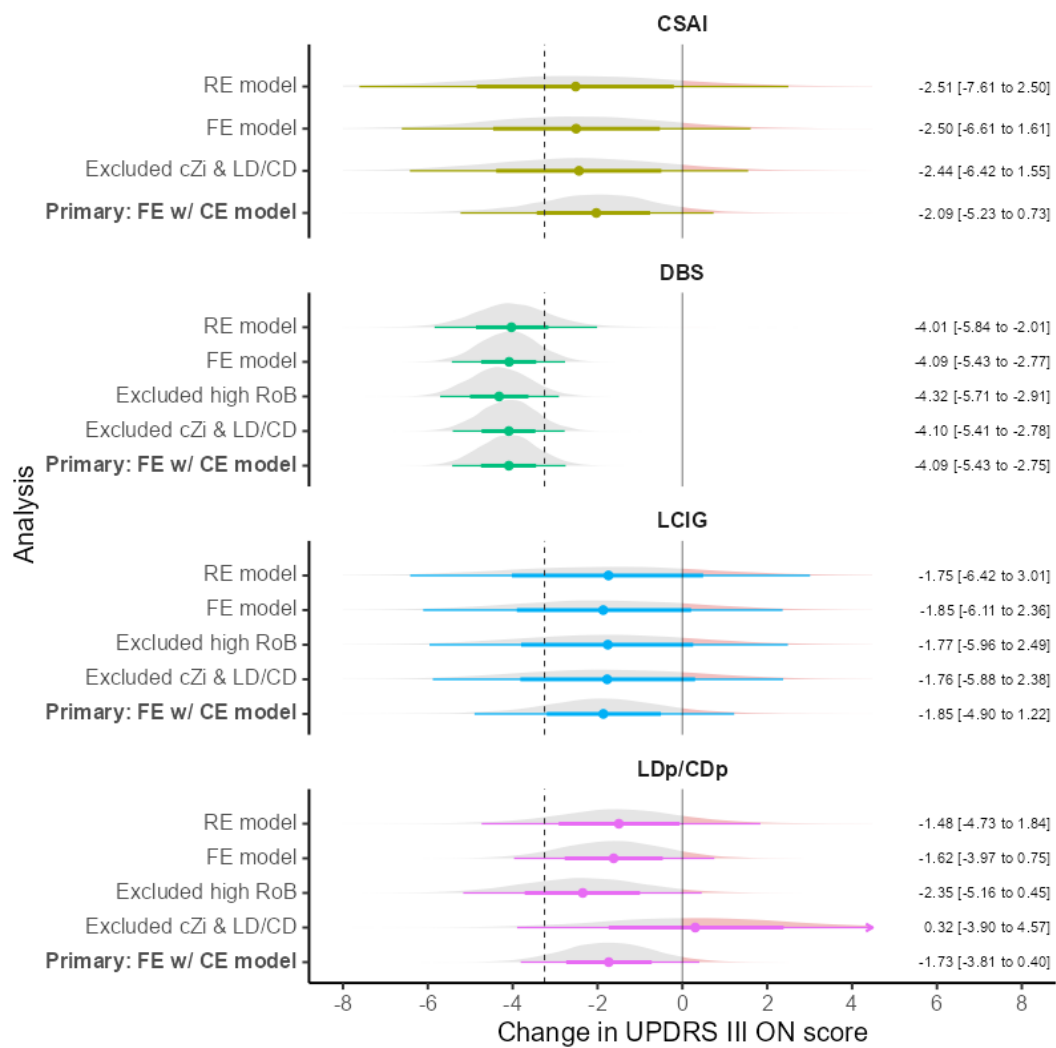
The shaded area is the posterior distribution. The dot, thick band, and thin band signify the posterior mean, 66% CrI, and 95% CrI, respectively.

Supplementary Figure 11a. Sensitivity analysis – OFF time



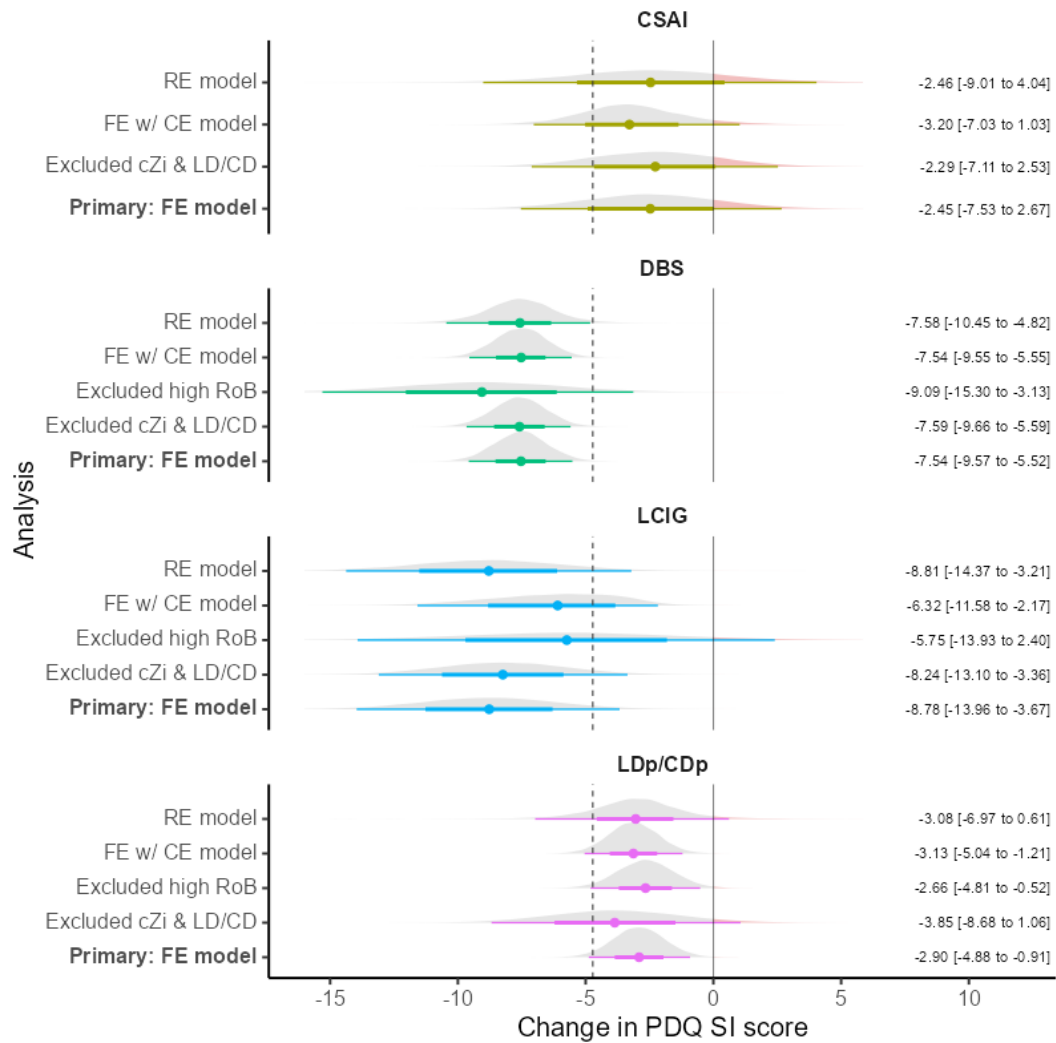
The shaded area is the posterior distribution. The red shaded area represents the probability of a treatment being worse than BMT. The dashed line is the MCID value. The dot, thick band, and thin band signify the posterior mean, 66% CrI, and 95% CrI, respectively.

Supplementary Figure 11b. Sensitivity analysis – UPDRS part III



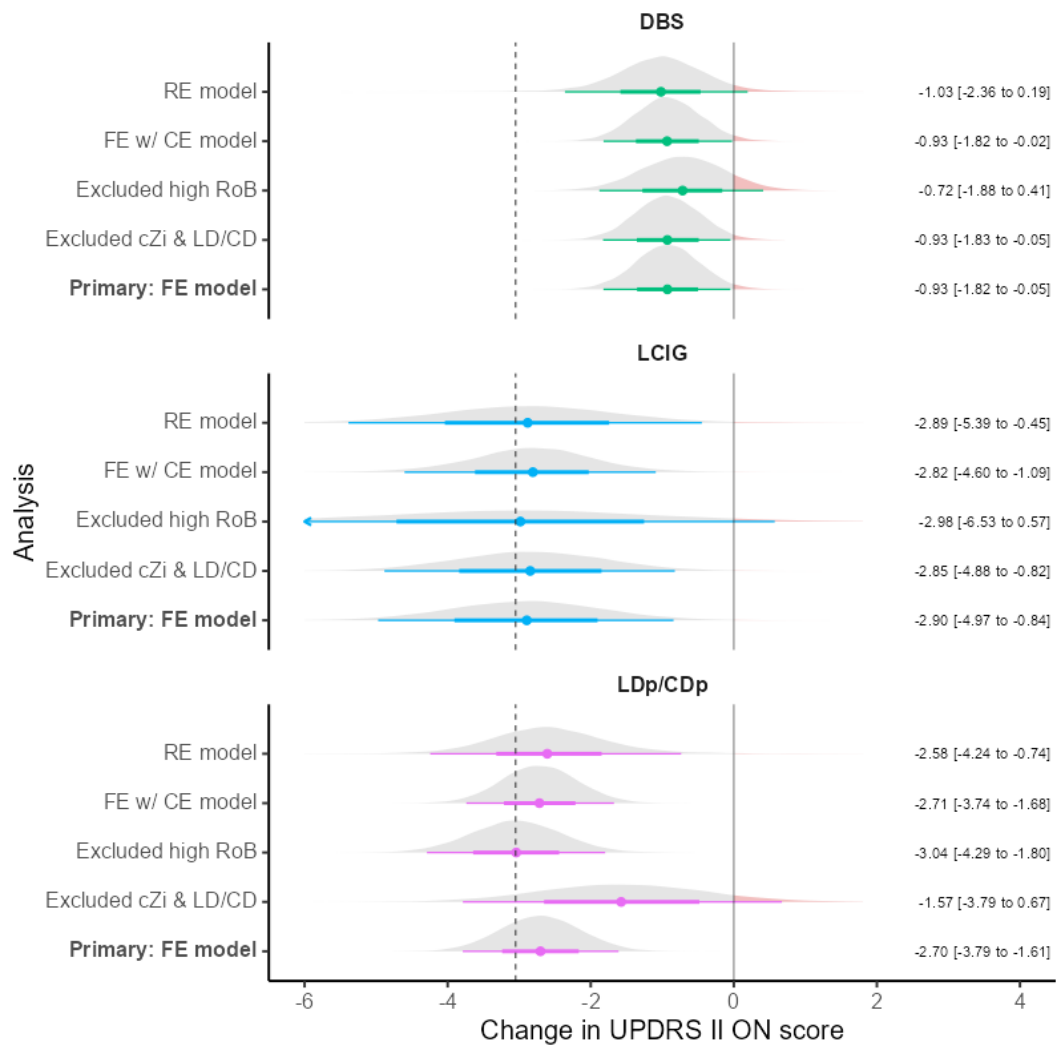
The shaded area is the posterior distribution. The red shaded area represents the probability of a treatment being worse than BMT. The dashed line is the MCID value. The dot, thick band, and thin band signify the posterior mean, 66% CrI, and 95% CrI, respectively.

Supplementary Figure 11c. Sensitivity analysis – PDQ score



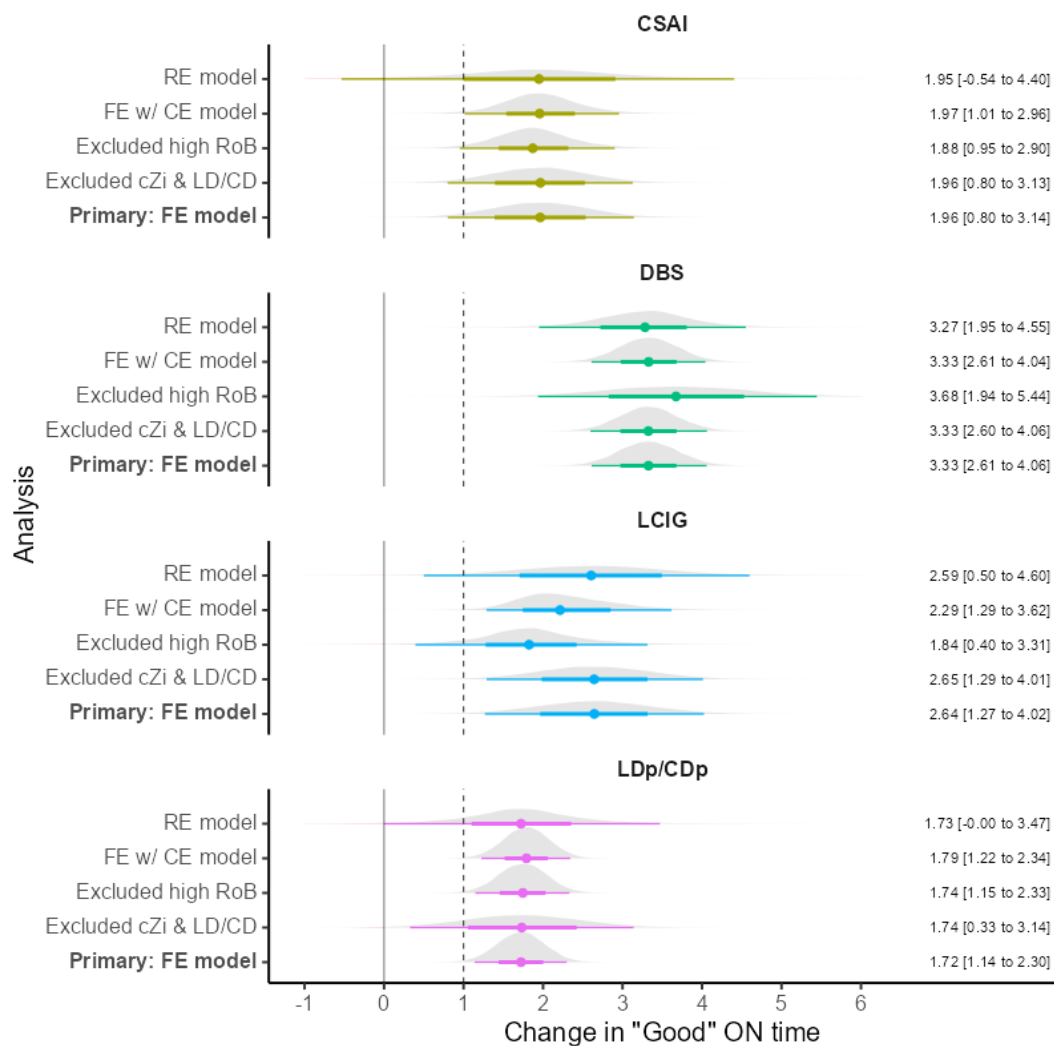
The shaded area is the posterior distribution. The red shaded area represents the probability of a treatment being worse than BMT. The dashed line is the MCID value. The dot, thick band, and thin band signify the posterior mean, 66% CrI, and 95% CrI, respectively.

Supplementary Figure 11d. Sensitivity analysis – UPDRS part II



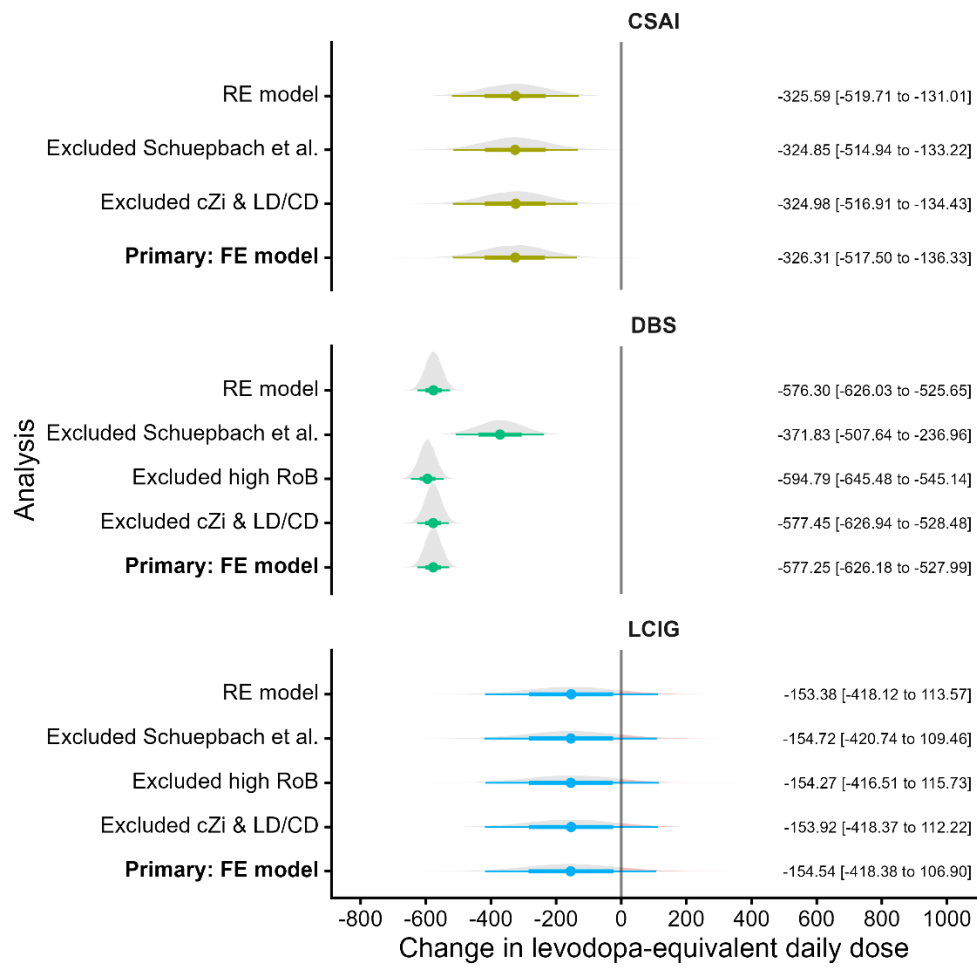
The shaded area is the posterior distribution. The red shaded area represents the probability of a treatment being worse than BMT. The dashed line is the MCID value. The dot, thick band, and thin band signify the posterior mean, 66% CrI, and 95% CrI, respectively.

Supplementary Figure 11e. Sensitivity analysis – “Good” ON time



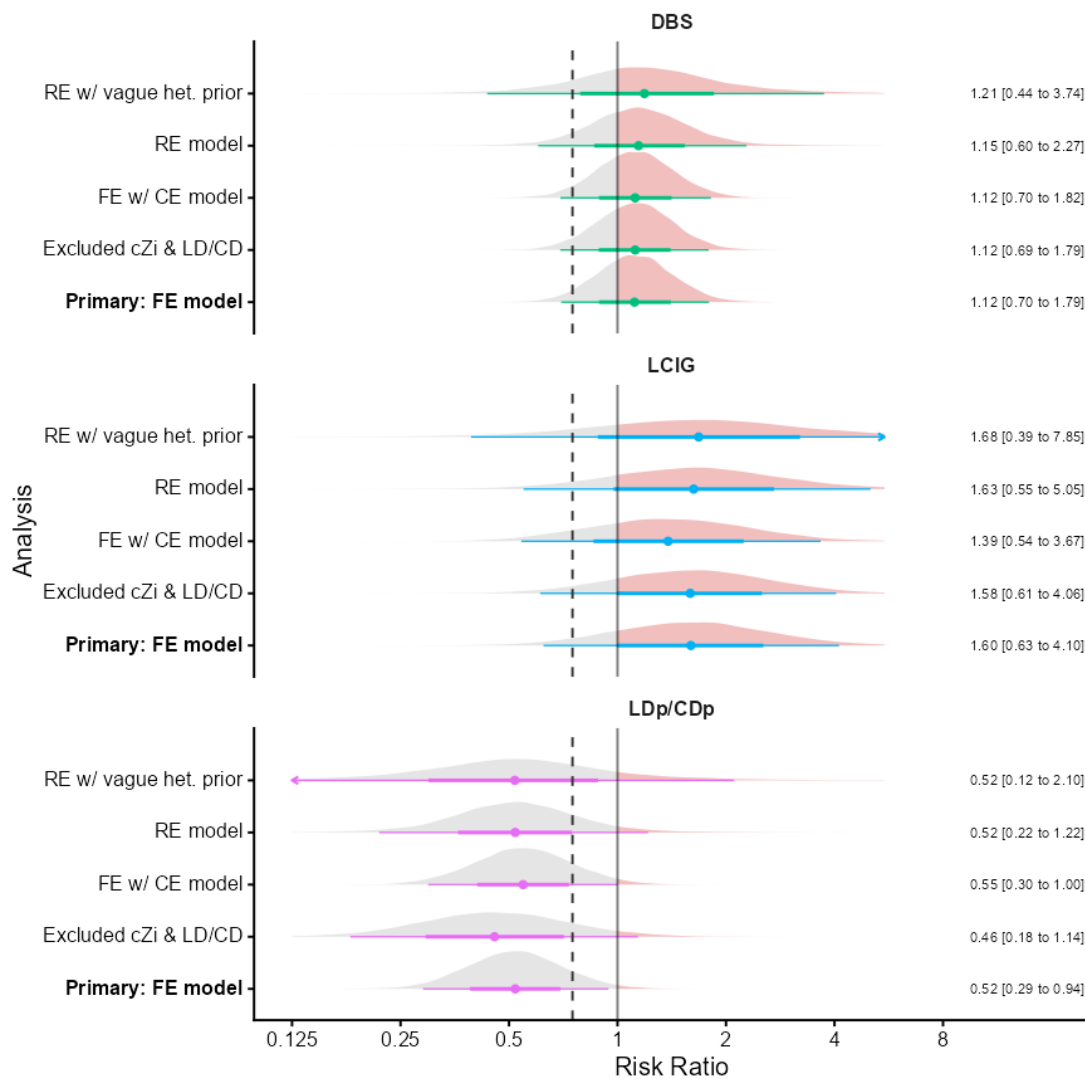
The shaded area is the posterior distribution. The red shaded area represents the probability of a treatment being worse than BMT. The dashed line is the MCID value. The dot, thick band, and thin band signify the posterior mean, 66% CrI, and 95% CrI, respectively.

Supplementary Figure 11f. Sensitivity analysis – LEDD



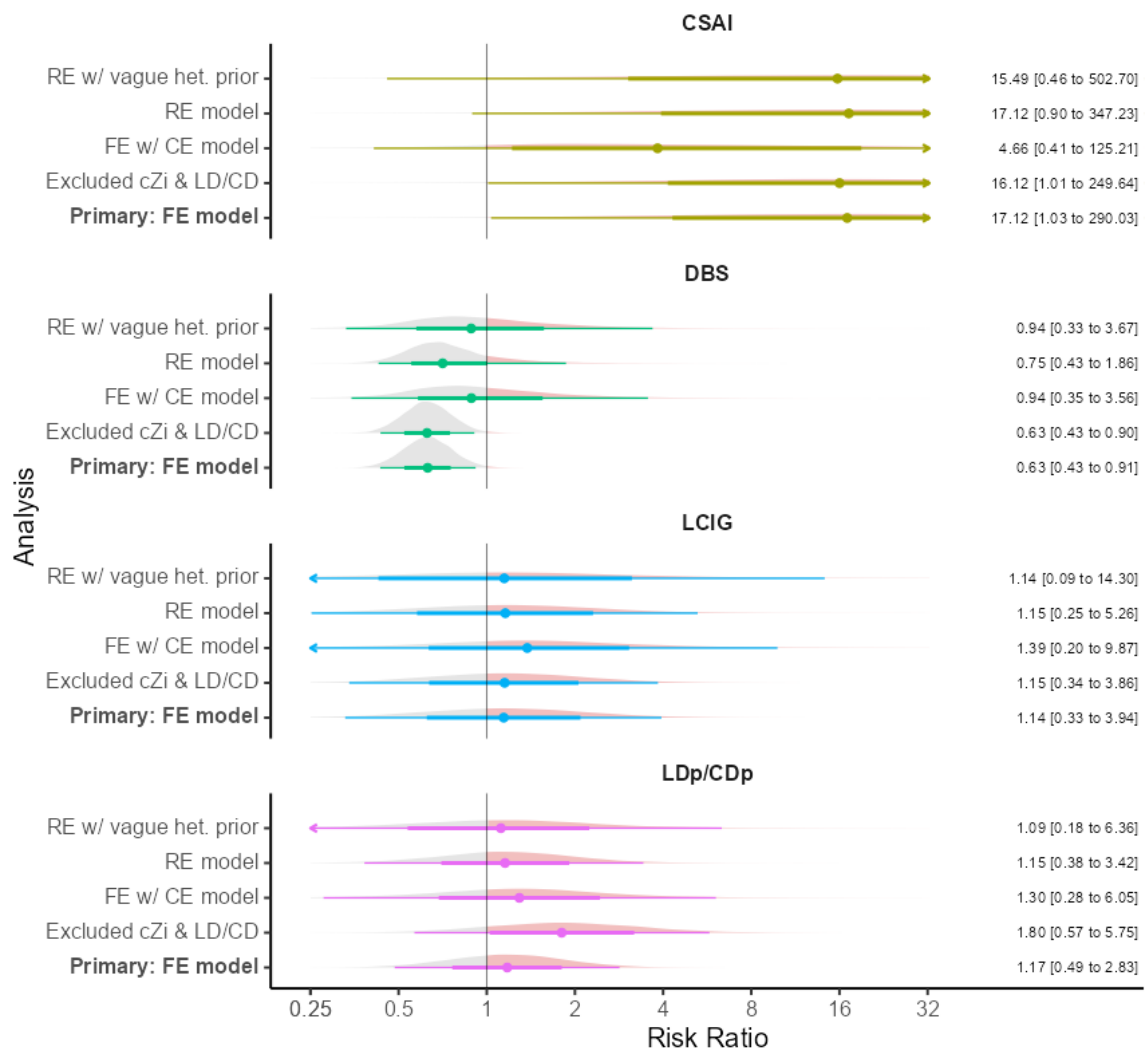
The shaded area is the posterior distribution. The dashed line is the MCID value. The dot, thick band, and thin band signify the posterior mean, 66% CrI, and 95% CrI, respectively.

Supplementary Figure 11g. Sensitivity analysis – Risk of falls



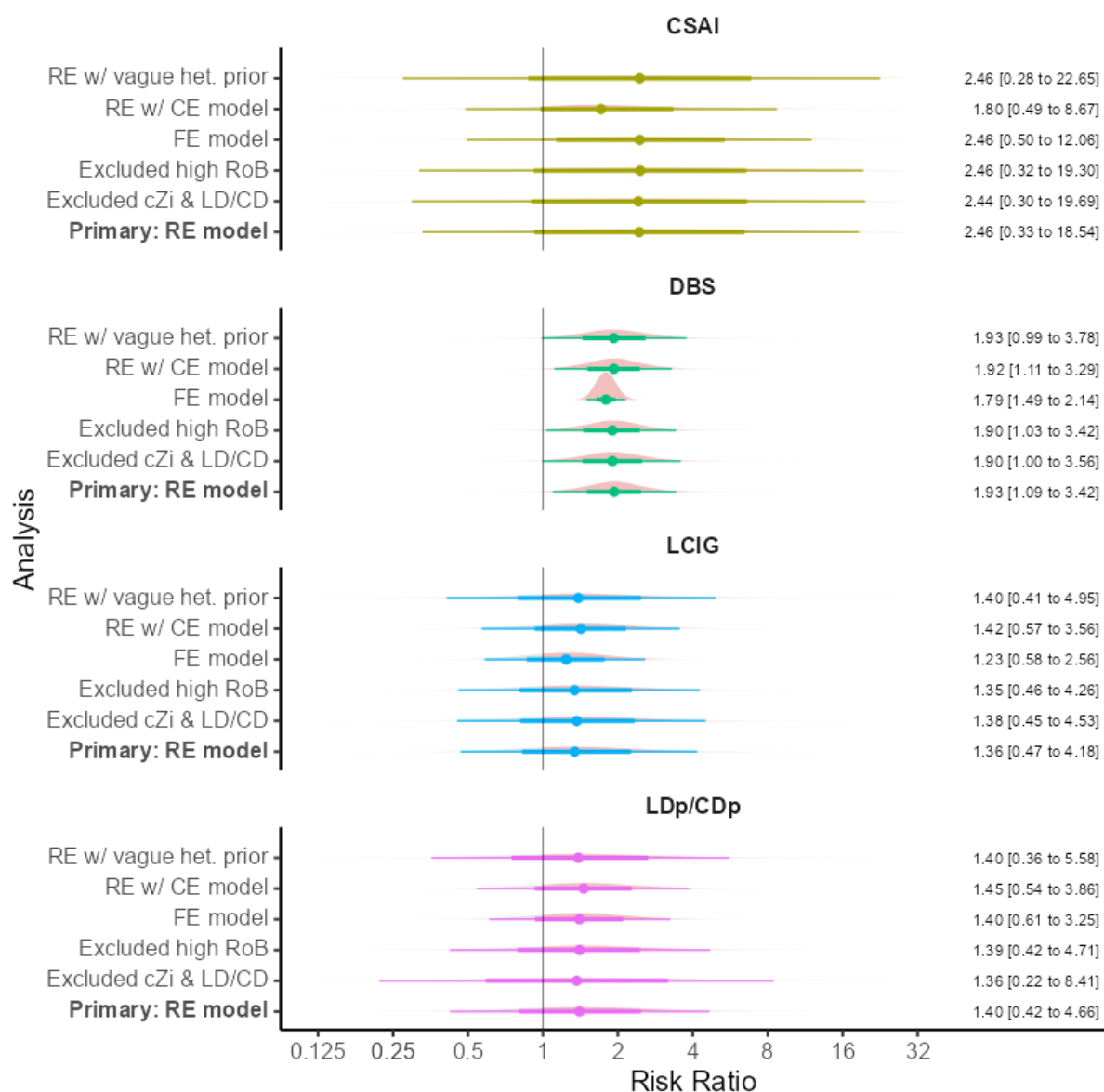
The shaded area is the posterior distribution. The red shaded area represents the probability of a treatment being worse than BMT. The dashed line is the MCID value. The dot, thick band, and thin band signify the posterior mean, 66% CrI, and 95% CrI, respectively.

Supplementary Figure 11h. Sensitivity analysis – Risk of dyskinesia



The shaded area is the posterior distribution. The red shaded area represents the probability of a treatment being worse than BMT. The dashed line is the MCID value. The dot, thick band, and thin band signify the posterior mean, 66% CrI, and 95% CrI, respectively.

Supplementary Figure 11i. Sensitivity analysis – Risk of SAE



The shaded area is the posterior distribution. The red shaded area represents the probability of a treatment being worse than BMT. The dashed line is the MCID value. The dot, thick band, and thin band signify the posterior mean, 66% CrI, and 95% CrI, respectively.