TECHNOLOGY REVIEW (MINI-HTA)

APOMORPHINE INJECTION AND SUBCUTANEOUS INFUSION THERAPY FOR ADVANCED PARKINSON'S DISEASE

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
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EXECUTIVE SUMMARY

Background

Parkinson's disease (PD) is a progressive neurodegenerative disorder with evolving layers of complexity, characterized by loss of dopaminergic neurons in the substantia nigra and its incidence is increasing globally. This debilitating progressive neurodegenerative disorder has wide range of motor and non-motor manifestations that result in significant morbidity and mortality, impacting mobility, mental health, mood and cognition, autonomic function, and a markedly decreased quality of life. PD was identified as the fastest growing neurological disorder when measured using death and disability. Its prevalence rate is approximately 0.3%, which increases to 1% in individuals over 60 years old. The prevalence of PD has doubled in the past 25 years. In 2017, PD was estimated to cost US$52 billion per year in the USA. As the incidence of PD is rising sharply, with prevalence that is expected to double within the next 25 years, this places an onerous economic burden on society. In Malaysia, there were about 15,000 to 20,000 Parkinson's patients and expected to increase by 9.5%. The prevalence of Parkinson's disease in Malaysia is expected to increase by five-fold over the next 20 years. There were approximately 2,121 Parkinson's disease patients discharged from hospitals in Malaysia (2020-2024), with an increase of patients reported from 2020(370) to 2023(563).

As the disease progresses, patients' quality of life is impaired, particularly by prolonged periods of restricted mobility, commonly referred to as ''off-time''. A reliable tool for distinguishing patients in the advanced stage of PD is the 5-2-1 criteria; patients with PD who take at least five oral doses of levodopa per day, have at least two hours of daily off-time, and have at least one hour of disruptive dyskinesia per day. Advanced PD (APD) is defined as a condition where periods of poor mobility with or without dyskinesia are present and impacting functional independence of the affected person.

Main therapeutic approach in Parkinson's disease is dopaminergic replacement therapy through the administration of levodopa. Although levodopa is the standard treatment for PD, the effects of levodopa therapy may subside, and patients can experience a return of symptoms during OFF* episodes. As PD advances, OFF episodes can impact up to 50% of a patient's waking hours, affecting a patient's ability to perform normal daily activities. There are distinct types of OFF episodes, including wearing OFF (wearing OFF of levodopa effect), delayed ON (delayed onset of levodopa effect), suboptimal ON, unpredictable OFF, morning akinesia and nocturnal akinesia.

Despite optimal dopaminergic treatment, most patients in moderate to advance stages of PD experience progressively increasing disabilities. At this stage, motor fluctuations are almost inevitable with levodopa treatment, and calls for the initiation of device-aided therapies (DAT). Motor fluctuations are often accompanied by non-motor fluctuations, adding to a separate complexity and the decline in perceived quality of life. When fluctuations occur, treatment aims shift from oral medication to continuous dopaminergic stimulation in the form of DAT. Available DAT includes deep brain stimulation (DBS) or infusion therapies including continuous subcutaneous apomorphine infusion (CSAI) and levodopa-carbidopa intestinal gel

(LCIG). CSAI is particularly valued for its non-invasive nature, as it requires no surgical intervention, compared to DBS or LCIG, as well as its compact design and its easy reversibility. Apomorphine is the only dopamine analogue with an equivalent efficacy to levodopa. The rationale for infusion therapies is to achieve continuous dopaminergic stimulation. Apomorphine minimize adverse events from polytherapy, improve treatment adherence, reduce dopaminergic hypersensitivity and minimize cardinal mechanisms underlying the pathophysiology of motor complications. Infusion therapies bypass problems related to irregular and often unpredictable intestinal absorption of oral levodopa, affecting its bioavailability.

In the Ministry of Health's setting, there is currently therapeutic gap for Parkinson's disease patients with motor fluctuation following levodopa treatment, or motor fluctuation due to the disease itself, or for patients with symptoms that could not be controlled by oral therapy. Concerns continue to exist on the cost implication associated with these DAT therapies. Hence, this necessitates the review of apomorphine injection and infusion as treatment modalities in patients with advanced Parkinson's disease. This review is conducted following the request from the Neurologist representing Head of Neurology Services, Ministry of Health to assess the evidence on apomorphine injection and subcutaneous infusion to be used in the treatment of patients with advanced Parkinson's disease.

Objective

The objective of this technology review is to assess the effectiveness, safety and cost-effectiveness of apomorphine injection and subcutaneous infusion therapy for the treatment of patients with advanced Parkinson's disease.

Results and conclusion

The review included 12 studies which consisted of SR (five), randomised controlled trials (three), non-randomised trial (one), cohort (two) and SR of CEA (one). The 11 included articles in this review were in the effectiveness and safety section, including one evidence retrieved in the cost-effectiveness section. The included articles were published between 2018 and 2025 The studies were conducted in the US, France, India, multicentres in Europe, Spain, Germany, UK. This review included a total of 12,696 patients with PD enrolled from all the studies. Sample size for each of the included studies ranged from 51 to 173 patients (primary studies), and from 220 to 6560 in the included review. Most of the studies were followed at six months and one year, the longest was two years. Most of the study participants were patients with advanced PD with motor fluctuations not adequately controlled on medical treatment, at stage 4 & 5 H&Y scale. Age range of the patients as reported was between 55.5 to 70.9 in the included studies.

Effectiveness

Based on the above review, there was fair level of evidences on apomorphine injection and subcutaneous infusion therapy to be used in the treatment of advanced Parkinson's disease.

Administration of apomorphine injection or infusion showed beneficial effect on motor function namely off time, functional impact of dyskinesia, ON time, improvement in H&Y scale; patient impression of change, quality of life, pain alleviation, reduction in LEDD and improvement in non-motor function in the patients with advanced Parkinson's disease.

Following apomorphine injection or infusion in patients with advanced Parkinson's disease, evidence demonstrated: -

Significant improvement in **motor function** was observed in the treated patients;

a) Reduction in 'off' time, with difference of 1.89h/day to 3.0±3.18 h/day (by maintenance week 12 and improvement maintained through week 52), compared to placebo. Reduction in daily OFF time was sustained for up to 64 weeks. Pooled data for week 64 showed a mean (SD) change from baseline in daily OFF time of − 3.66 (2.72) hours. Apomorphine ranked the highest in reducing OFF Time (SUCRA 77.2%), followed by ropinirole_PR, pramipexole_IR and other dopamine agonists.
b) Significant reduction in the functional impact of dyskinesia at 6 months and 12 months.
c) Increase in Good ON time (daily ON time without troublesome dyskinesia) of 3.1 ±3.35 h/day by maintenance week 12.. Improvement in ON time without troublesome dyskinesia was sustained for up to 64 weeks. Pooled data for week 64 showed a mean (SD) change from baseline in ON time without troublesome dyskinesia of 3.31 (3.12) hours. Apomorphine ranked the highest in increasing good ON time without troublesome dyskinesia (SUCRA 97.08%), followed by pramipexole_IR and ropinirole_PR.
d) Improvement in Hoehn and Yahr (H&Y) scores (scores of 2.5 or less) following CSAI (patients had H&Y score of 3.0 and above at baseline). The H&Y Scale was used to stage their functional disability.

Patient Global Impression of Change (PGI-C)

Significant improvement in PGIC scores, 68% of patients rated themselves as much or very much improved, 62% had at least a 2-hour reduction in daily OFF time by maintenance week 12.

Levodopa and levodopa equivalent daily doses (LEDD)

Significant reduction in levodopa equivalent dose in Apomorphine treated patients compared to placebo, mean concomitant oral levodopa and levodopa equivalent doses had been reduced by 198 mg/day and 283 mg/day, respectively. Improvements were maintained through week 52. LEDD scores significantly decreased from baseline at month 6. At week 64 post treatment, mean (±SD) daily levodopa-equivalent dose decreased from baseline by 543 mg (±674) and levodopa dose by 273 mg (±515) respectively.

Quality Of Life

All device-aided therapies demonstrated greater improvements in PD-specific QoL score than BMT at six months, for CSAI (3.61; 95%CI 0.55 to 6.68) LCIG (7.83;95%CI 5.15 to 10.51) and DBS (7.24; 95%CI 5.37 to 9.10). HRQoL remained stable of those who continued treatment 24 months after CSAI initiation, with Parkinson's Disease Questionnaire (PDQ)-39 was the only baseline predictor of HRQoL improvement after 2 years of treatment. The 8-item Parkinson's Disease Questionnaire (PDQ-8) improvement ranges between 11.3% and 41.9% at the 6-month follow-up. Based on a greater relative change, larger effect size, and smaller number needed to treat, an advantageous effect of apomorphine on QoL was observed in the real-life cohort.

Pain

Following subcutaneous apomorphine administration, significant improvement in nocturnal pain and orofacial pain was showed at 6 month and 12 month from baseline.

Non-motor function

Significant improvement in non-motor function was observed in the treated patients with apomorphine; Using the UPDRS III, the SUCRA values indicated that apomorphine had the best efficacy on the non-motor symptoms of PD (99.0%), followed by Bromocriptine (78.8%), and Piribedil MaHTAS Technology Review vi (75.9%). Significant improvement in Non-Motor Symptom Scale (NMSS) (improvement in various domains; mood/ cognition, perceptual problems/hallucinations, attention/ memory, and the miscellaneous domain), favorable for neuropsychological/ neuropsychiatric NMS. The preserved cognitive function observed over a 12- month follow-up (average 16 months follow up).

Safety

Apomorphine was well tolerated without unexpected safety signals. Treated patients reported one or more AEs, which were mostly mild to moderate in severity. Common treatment-related adverse events included infusion site nodules and erythema, nausea, somnolence, dyskinesia, which occurred more frequently during the titration period.

Injection or infusion apomorphine has been granted regulatory approval from the USFDA, indicated for the treatment of motor fluctuations (OFF episodes) in adults with advanced Parkinson's disease. Apomorphine is licensed in UK for use in refractory motor fluctuations in Parkinson's disease ('off' episodes) inadequately controlled by levodopa with dopa-decarboxylase inhibitor or other dopaminergics (for capable and motivated patients under specialist supervision), approved in Canada for the treatment of acute, intermittent hypomobility and "off" ("end-of-dose wearing off" and unpredictable "on/off") episodes in patients with advanced PD, in Ireland and Thailand. In Thailand, the initial use was on a compassionate basis for a group of patients (2013), followed by approval (2015).

Cost-effectiveness

A CEA conducted from the national healthcare providers showed this therapy was cost-effective in the UK, but not in Germany (compared to BMT), the direct lifetime costs of continuous apomorphine infusion was estimated at £78,251.49 (€57,123.59) (MYR275,332) and generated 2.85 QALYs in the United Kingdom, and €104,500.08 (MYR503,690) and 2.92 QALYs in Germany respectively. With an ICER of £6440.45 MYR36,772), CSAI is cost-effective against standard care in the UK. In Germany the ICER is several times higher (€74,695.62) (MYR360,029). LCIG is associated with the highest costs and an ICER of £244,684.69 (MYR1,397,145) in the UK and €272,914.58 (MYR1,315,445) in Germany compared to CSAI which exceeds established cost-effectiveness thresholds. CSAI is a cost-effective therapy and could be seen as an alternative treatment to LCIG or DBS for patients with advanced PD. The initial treatment effect and the discount rates exhibit the greatest cost influence. Another CEA demonstrated an ICER of €38,249 (MYR184,360) per QALY for CSAI compared to IJLI, which is above the GDP of Spain.

Organizational

The selection for all device-aided therapies in PD should carefully assess the following factors: disease duration, age, levodopa responsiveness, type and severity of levodopa unresponsive symptoms, cognitive and psychiatric issues and comorbid disorders. The European Academy of Neurology/Movement Disorder Society guidelines on the treatment of PD with invasive therapies recommend APO infusion for people with advanced PD in whom fluctuations are not satisfactorily controlled with medication. The UK's National Institute for Health and Care Excellence (NICE) guidelines recommended that it should be started before patients are considered for foslevodopa/foscarbidopa and prior to invasive DATs such as DBS or LCIG, while an APO PEN injection can be used even earlier for managing troublesome predictable OFF periods. The NICE recommendations stated that intermittent apomorphine injections may be used to reduce off-time in people with PD with severe motor complications; and continuous subcutaneous infusions of apomorphine may be used to reduce off-time and dyskinesias in people with PD with severe motor complications.

Apomorphine should be initiated in the controlled environment of a clinic. During the titration phase of apomorphine the patient should be supervised by a trained healthcare professional experienced in the treatment of Parkinson's disease. The patient's treatment with levodopa and/or other dopaminergic medications should be optimised before starting apomorphine treatment. Successful treatment requires commitment from patients and their families and continuing encouragement from their doctors and nurses, particularly in the early months of therapy.

Methods

Studies were identified by searching electronic databases. The following databases were searched through the Ovid interface: MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present. EBM Reviews-Cochrane Database of Systematic Reviews (2005 to March 2025), EBM Reviews-Cochrane Central Register of Controlled Trials (March 2025), EBM Reviews – Database of Abstracts of Review of Effects (1st Quarter 2025), EBM Reviews-Health Technology Assessment 1st Quarter 2025), EBM Reviews-NHS Economic Evaluation Database (1st Quarter 2025). Parallel searches were run in PubMed. Appendix 3 showed the detailed search strategies. No limits were applied to the search. The last search was run on 15 April 2025. Additional articles were identified from reviewing the references of retrieved articles. Among the tools used to assess the risk of bias and methodological quality of the articles retrieved is the Cochrane ROBIS, ROB-2 tool and ROBINS-I. All full text articles were then graded based on guidelines from the US/Canadian Preventive Services Task Force.

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ABBREVIATION

AE	Adverse event
BDI	Beck Depression Index
BMT	Best medical therapy
BPRS	Brief Psychiatric Rating Scale
CI	Confidence Interval
CrI	Credible Interval
CSAI	Continuous subcutaneous apomorphine infusion
DA	Dopamine agonist
HADS	Hospital anxiety and depression scale
HAMD-17	Hamilton Depression rating scale-17
HR	Hazard Ratio
HRQOL	Health related quality of life
IJLI	Intrajejunal Levodopa Infusion
KPPS	King's Parkinson's disease pain scale
LCIG	Levodopa carbidopa infusion gel
LEDD	Levodopa Equivalent Dose
MMSE	Mini-Mental State Examination
MOH	Ministry of Health
NMA	Network meta-analysis
NMSS	Non-Motor Symptoms Scale
NPI	Neuropsychiatric Inventory
PD	Parkinson's disease
PDQ	Parkinson's disease Questionnaire
PDSS	Parkinson's disease Sleep scale
PGIC	Patient Global Impression of Change
QOL	Quality of Life
RCT	Randomised controlled trial
RR	Relative risk
SE	Standard error
SR	Systematic review
STN-DBS	Subthalamic stimulation deep brain stimulation
SUCRA	Surface under the cumulative ranking curve
TEAE	Treatment emergent adverse events
UPDRS	Unified Parkinson's disease rating scale
vs	Versus
WMD	Weighted mean difference

1.0 BACKGROUND

Parkinson's disease (PD) is a progressive neurodegenerative disorder with evolving layers of complexity, characterized by loss of dopaminergic neurons in the substantia nigra and its incidence is increasing globally.[1] This debilitating progressive neurodegenerative disorder has wide range of motor and non-motor manifestations that result in impaired mobility, mental health disorders, mood and cognition issues, autonomic dysfunction, and a markedly decreased quality of life.[2] The characteristic motor symptoms of Parkinson's disease (PD) are bradykinesia, rigidity and tremor.[3] PD was identified as the fastest growing neurological disorder when measured using death and disability according to the Global Burden of Disease study conducted between 1990 and 2016. Most people affected by PD live in low- and middle-income countries (LMICs) and experience large inequalities in access to neurological care and essential medicines.[2] Its prevalence rate is approximately 0.3%, which increases to 1% in individuals over 60 years old.[4] The prevalence of PD has doubled in the past 25 years.[5] The numbers are likely even higher when the many people living with various forms of parkinsonism are included, such as those caused by degenerative conditions (atypical parkinsonism).[6,7] As the incidence of PD is rising sharply, with a continuous growth in prevalence that is expected to double within the next 25 years, costs associated with treatment and the burden this places on society is becoming increasingly relevant.[8] In 2019, PD resulted in 5.8 million disability-adjusted life years, an increase of 81% since 2000, and caused 329,000 deaths, an increase of over 100% since 2000.[13] In 2017, PD was estimated to cost US$52 billion per year in the USA, which will continue to increase as the incidence and prevalence of PD rise.[10] A European study estimated that PD associated costs reached €13.9 billion (US$14.9 billion) in 2010.[11]

In Malaysia, there were about 15,000 to 20,000 Parkinson's patients and expected to increase by 9.5% by 2020. The prevalence of Parkinson's disease in Malaysia is expected to further increase by five-fold over the next 20 years.[12] There were approximately 1,542 Parkinson's disease patients discharged from hospitals (2018 to 2022), with a total of 364 discharges reported in 2022 based on data obtained from the Health Informatic Centre, MOH.[13]

When the loss of nigrostriatal nerve terminals becomes severe, the neurotransmitter storage capacity diminishes and dopamine levels in the central nervous system are progressively dependent on the pharmacokinetics of exogenous levodopa.[14] Pulsatile stimulation of striatal dopamine receptors and changes in the basal ganglia, thalamus and cerebral cortex are key elements in the development of motor complications, such as fluctuations of clinical status, delayed-ON, wearing-OFF and dyskinesia.[14,15] As a result, the time spent in a good mobility (ON time) decreases and the time with inadequate clinical efcacy (OFF time) increases along with disease progression.[16] The complexity of Parkinson's disease is accompanied by clinical challenges, including an inability to make a definitive diagnosis at the earliest stages of the disease and difficulties in the management of symptoms at later stages. Parkinson's disease (PD) is a neurodegenerative disorder whose main therapeutic approach is dopaminergic replacement therapy through the administration of levodopa.[17] Although levodopa is the standard treatment for PD, the effects of levodopa therapy may subside, and patients can experience a return of symptoms during OFF* episodes. As PD advances, OFF episodes can impact up to 50% of a patient's waking hours, affecting a patient's ability to perform normal daily activities. There are distinct types of OFF episodes, including wearing OFF (wearing

OFF of levodopa effect), delayed ON (delayed onset of levodopa effect), suboptimal ON, unpredictable OFF, morning akinesia and nocturnal akinesia.[18]

As the disease progresses, patients' quality of life is impaired, particularly by prolonged periods of restricted mobility, commonly referred to as ''off-time''. A reliable tool for distinguishing patients in the advanced stage of PD is the 5-2-1 criteria; patients with PD who take at least five oral doses of levodopa per day, have at least two hours of daily off-time, and have at least one hour of disruptive dyskinesia per day.[19] Advanced PD (APD) is defined as a condition where periods of poor mobility with or without dyskinesia are present and impacting functional independence of the affected person.[19]

Despite optimal dopaminergic treatment most patients in moderate to advance stages of PD experience progressively increasing disabilities.[20] At this stage of the disease motor fluctuations are almost inevitable with levodopa treatment, and calls for the initiation of device-aided therapies once the criteria for these therapies are met.[21] Moreover, motor fluctuations are often accompanied by non-motor fluctuations, adding to a separate complexity and the decline in perceived quality of life. When fluctuations occur, treatment aims should shift from oral medication to more continuous dopaminergic stimulation in the form of device-aided therapies. Available DAT includes deep brain stimulation (DBS) or infusion therapies including continuous subcutaneous apomorphine infusion (CSAI) and levodopa-carbidopa intestinal gel (LCIG).[22]

CSAI is particularly valued for its relatively non-invasive nature, as it requires no surgical intervention, compared to DBS or LCIG, as well as its compact design and its easy reversibility.[17] Apomorphine is the only dopamine analog with an equivalent efficacy to levodopa.[23] The rationale for infusion therapies is to achieve continuous dopaminergic stimulation. Constant plasma levels of levodopa or of the DA apomorphine, minimize adverse events from polytherapy and improve treatment adherence, reduce dopaminergic hypersensitivity and minimize cardinal mechanisms underlying the pathophysiology of motor complications.[15] Infusion therapies bypass problems related to irregular and often unpredictable intestinal absorption of oral levodopa, affecting its bioavailability.[24] Infusion therapies can also provide greater improvement than oral medications in advanced PD patient with poor symptom control.[25]

In the Ministry of Health's setting, there is currently therapeutic gap for Parkinson's disease patients with motor fluctuation following levodopa treatment, or motor fluctuation due to the disease itself, or for patients with symptoms that could not be controlled by oral therapy. Concerns continue to exist on the associated cost implications of these DAT therapies. Hence, this necessitates the review of apomorphine injection and infusion as treatment modalities in patients with advanced Parkinson's disease. This review is conducted following request from the Neurologist representing Head of Neurology Services, Ministry of Health to assess the evidence on apomorphine injection and subcutaneous infusion to be used in the treatment of patients with advanced Parkinson's disease.

2. OBJECTIVE / AIM

The objective of this technology review is to assess the effectiveness, safety and cost-effectiveness of apomorphine injection and subcutaneous infusion to be used in the treatment of patients with advanced Parkinson's disease.

3.0 TECHNICAL FEATURES

Apomorphine is a non-ergoline dopamine D2 agonist indicated to treat hypomobility associated with Parkinson's. Apomorphine injection is distributed under the brand name Apokyn by MDD US Operations, LLC, Rockville.[2] Apokyn (apomorphine hydrochloride injection) contains apomorphine hydrochloride, a non-ergoline dopamine agonist, with a molecular formula of $C_{17}H_{17}NO_2$. Apokyn (apomorphine hydrochloride injection) is indicated for the acute, intermittent treatment of hypomobility, "off" episodes ("end-of-dose wearing off" and unpredictable "on/off" episodes) in patients with advanced Parkinson's disease.[2]

Apokyn is a non-ergoline dopamine agonist with high in- vitro binding affinity for the dopamine D4 receptor, and moderate affinity for the dopamine D2, D3, and D5, and adrenergic α1D, α2B, α2C receptors. The mechanism of action is stimulation of post-synaptic dopamine D2-type receptors within the caudate-putamen in the brain.[2]

Apomorphine is administered via subcutaneous injections (for intermittent therapy or titration) or infusions (for continuous infusion therapy). It can be delivered either as continuous SC infusion via a pump (APO-go® pre-filled syringe 50 mg/10 ml solution for infusion; Dacepton® vials 100 mg/20 ml solution for infusion;APO-go® POD 100mg/20ml solution for infusion in cartridge) or as an intermittent SC pen injection (APO-go® PEN 30 mg/3ml solution for injection; Dacepton® cartridge 30 mg/3 ml solution for injection). [4]

The recommended starting dose of Apokyn is 0.2mL(2mg). Titration is on the basis of effectiveness and tolerance, up to a maximum recommended dose of 0.6 mL(6mg). Blood pressure and pulse should be measured in the supine and standing position before and after dosing. The initial dose and dose titrations should be performed by a healthcare provider.[3]

The optimum dose of apomorphine needs to be determined on an individual patient basis. During treatment with a pen injector, the daily dose varies widely between patients and is typically within the range of 3 – 30 mg, with each dose administered at the start of an 'off' episode. Individual bolus injections and the total daily dose should not exceed 10mg and 100 mg respectively.

Apokyn is a clear, colorless, sterile solution comes in glass cartridge to use with injector pen for subcutaneous injection and is available in 3mL (30mg) multi-dose cartridges. The 3mL (30mg) glass cartridge for single-patient-use is used with a manual reusable pen (Apokyn Pen). A single cartridge, pen and needle can deliver doses up to 1 mL (10mg) in 0.02mL (0.2 mg) increments. The pen injector is provided in a package with six needles.[3]

Patients selected for a pen-injector should be able to recognise the onset of their 'off' symptoms and be capable of injecting themselves, or have a responsible carer able to inject for them when required.

Figure 1: Apokyn pen injector

For patients whose overall control remains unsatisfactory using intermittent injections, or who require many and frequent injections (> 6 per day), apomorphine can be administered as a continuous SC infusion via pump. Maximum daily apomorphine dose should not exceed 100 mg.

Continuous subcutaneous apomorphine infusion (CSAI) is administered via a portable pump system that delivers a continuous dose, with the possibility of releasing a rescue bolus if needed. (Figure 2-4). The duration of infusion is normally 12–16 hours (waking time), but a 24-h regimen can also be programmed for patients experiencing nocturnal hypokinesia. This infusion uses a small pump that works with batteries. It can give boosters of apomorphine to control symptoms. The pump can be carried in the patients' pocket or a small pouch. The pump delivers a continuous dose from a syringe. The syringe has a fine needle that is inserted under the skin, either in the lower stomach or on the outside of patients' thighs. This ís secured with dressing to hold it in place.[4]

For patients starting CSAI in the inpatient setting, domperidone 10 · mg (or trimethobenzamide in countries where domperidone is not available) three times daily from one day before initiation to three – seven days in total is strongly recommended to prevent nausea. On the first day, apomorphine treatment is started at a dose of 0.5 or 1mg/h. Uptitration is usually with 0.5 or 1mg/h daily increments, and the optimal infusion rate ranges from 4 to 7 · mg/h for most patients. Concomitantly, oral dopamine agonists and other antiparkinsonian drugs are gradually discontinued. During the titration phase, levodopa is

also usually reduced, and discontinued if possible in patients with dyskinesia. The same up-titration protocol should be used for outpatients but with a slower increase in infusion rates.[4]

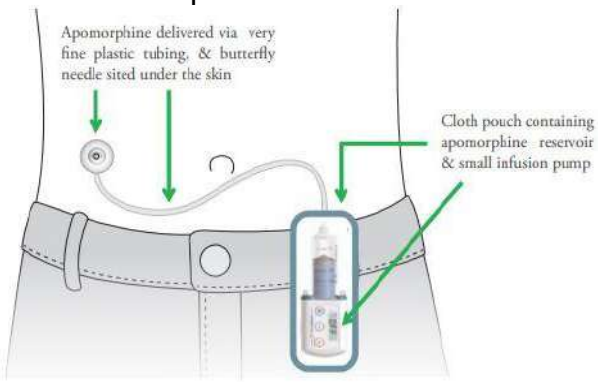

Figure 2: Apomorphine infusion set up (Source: Malaysian Consensus Guideline on PD)

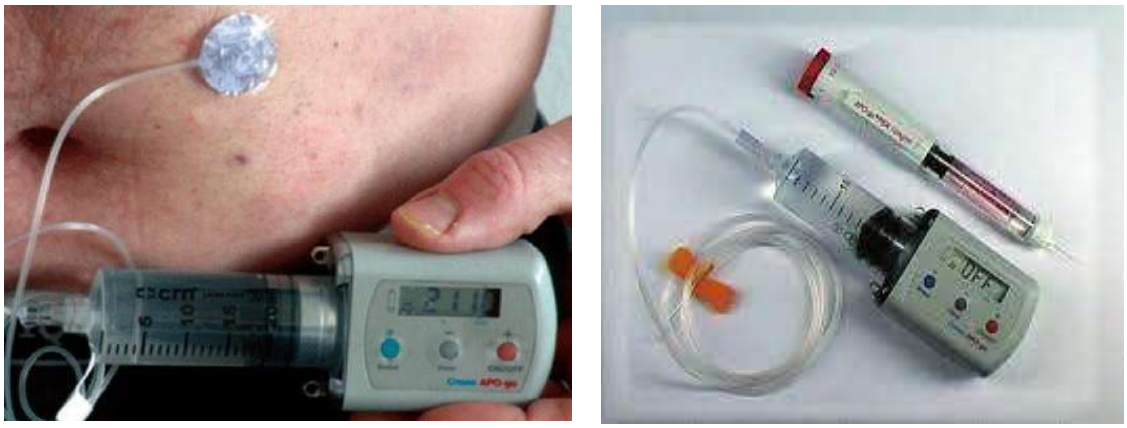

Figure 3: Apomorphine infusion in a patient (left) and the apomorphine infusion device
(Source: Lees A, Turner K. Apomorphine for Parkinson's Disease. Practical Neurology 2002;2:280-287)

Figure 4: Example of small size and light weight (127 g) infusion pump used for apomorphine

Apomorphine is contraindicated in patients with neuropsychiatric problems or dementia, hepatic impairment, respiratory or CNS depression and is not for use in patients under 18 years. Apokyn is contraindicated in patients:

i. Using concomitant drugs of the 5HT3 antagonist class including antiemetics (e.g., ondansetron, granisetron, dolasetron, palonosetron) and alosetron.

ii. With hypersensitivity/allergic reaction to apomorphine or to any of the excipients of apokyn, including a sulfite (i.e., sodium metabisulfite)[3]

Apokyn should not be administered intravenously, as serious adverse reactions including thrombus formation and pulmonary embolism due to intravenous crystallization of apomorphine have occurred.[3]

4.0 METHODS

4.1 SEARCHING

Electronic databases searched through the Ovid interface:

- MEDLINE(R) In-Process and Other Non-Indexed Citations and Ovid MEDLINE (R) 1946 to present
- EBM Reviews – Cochrane Central Registered of Controlled Trials – March 2025
- EBM Reviews – Database of Abstracts of Review of Effects – 1st Quarter 2025
- EBM Reviews – Cochrane Database of Systematic Reviews – 2005 to March 2025
- EBM Reviews – Health Technology Assessment – 1st Quarter 2025
- EBM Reviews - NHS Economic Evaluation Database – 1st Quarter 2025

Other databases:

- PubMed
- Horizon Scanning database (National Instutute of Health research (NIHR) Innovation Observatory, Euroscan International Network)
- Other websites: US FDA, INAHTA, MHRA, EMA

General databases such as Google and Yahoo were used to search for additional web-based materials and information. Additional articles retrieved from reviewing the bibliographies of retrieved articles or contacting the authors. The search was limited to articles on human. No limitation in the study design. There was no language limitation in the search. Appendix 1 showed the detailed search strategies. The last search was conducted on the 15 April 2025.

4.2 SELECTION

Two reviewers screened the titles and abstracts against the inclusion and exclusion criteria and then evaluated the selected full-text articles for final article selection. The inclusion and exclusion criteria were:

Inclusion criteria

Population	Patients with advanced Parkinson's disease
Interventions	Apomorphine (injection or subcutaneous infusion)
Comparators	Device aided therapies, deep brain stimulation, levodopa-carbidopa intestinal gel (LCIG), intrajejunal levodopa infusion

	(IJLI), best medical therapy or no comparator
Outcomes	Motor, non-motor symptom, quality of life, levodopa equivalent daily dose, perception of impact, ON" time without troublesome dyskinesia, "OFF" time, "ON" time, "UPDRS-III, "UPDRS-II" and adverse events
Study design	Systematic reviews (SR), randomised control trials (RCTs), cohort study, case control study
Type of publication	English, full text articles

Exclusion criteria

Study design	Survey, anecdotal, animal studies
Type of publication	Non-English
Setting	Studies evaluating apomorphine injection or infusion in clinical setting

Studies evaluating apomorphine in sublingual form were not within the scope of this review.

4.3 RISK OF BIAS ASSESSMENT

Relevant articles were critically appraised according to the study design. Systematic review was appraised using ROBIS tool, randomized controlled trial was appraised using ROB-2, cohort using CASP checklist, and non-randomized trials were appraised using ROBINS-I and evidences were graded according to the US/Canadian Preventive Services Task Force (See Appendix 2). Data were extracted from included studies using a pre-designed data extraction form (evidence table as shown in Appendix 6) and presented qualitatively in narrative summaries. No meta-analysis was conducted for this review.

5.0 RESULTS

A total of 336 titles were identified through the Ovid interface: MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present, EBM Reviews-Cochrane Database of Systematic Reviews (2005 to March 2025), EBM Reviews-Cochrane Central Register of Controlled Trials (March 2025), EBM Reviews-Database of Abstracts of Review of Effects (1st Quarter 2025), EBM Reviews-Health Technology Assessment (1st Quarter 2025), EBM Reviews-NHS Economic Evaluation Database (1st Quarter 2025) and PubMed.

Twenty-six articles were identified from references of retrieved articles. After removal of 38 duplicates, 362 titles were screened. A total of 362 titles were found to be potentially relevant and abstracts were screened using the inclusion and exclusion criteria. Of these, 341 abstracts were found to be irrelevant. Twenty-one potentially relevant abstracts were retrieved in full text. After applying the inclusion and exclusion criteria

and critical appraisal to the 31 full text articles, eleven full text articles were included and 20 full text articles were excluded. (Figure 5).

The review included eleven studies which were consisted of SR with and without network meta-analysis (five), randomized controlled trials (two), non-randomized trial (one), cohort (two), and SR of CEA (one).

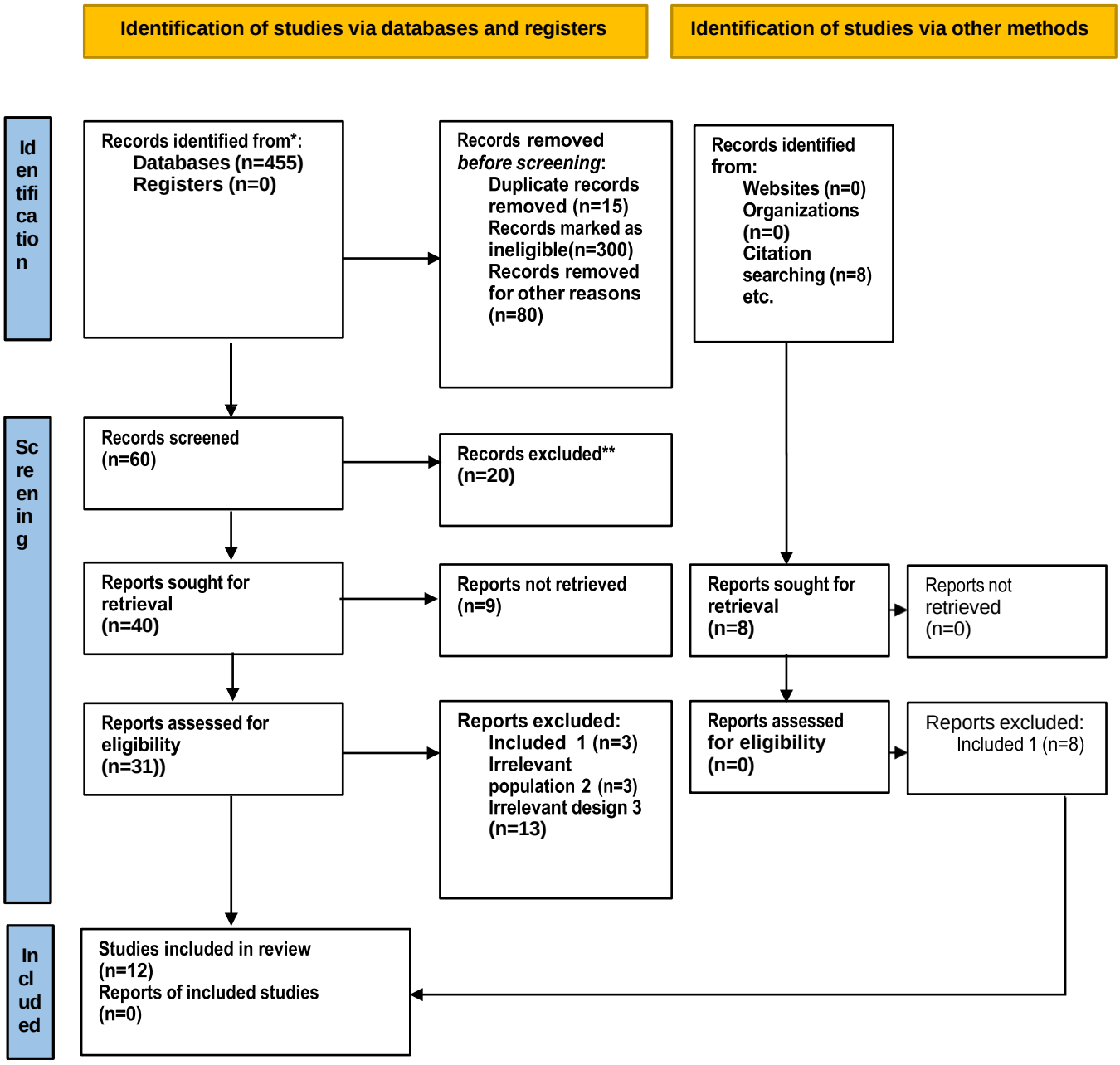

Figure 5: Flow chart of study selection in the review according to the PRISMA guidelines

The review included 12 studies which consisted of SR (five), randomised controlled trials (three), non-randomised trial (one), cohort (two) and SR of CEA (one). The 11 included articles in this review were in the effectiveness and safety section, including one evidence retrieved in the cost-effectiveness section. The included articles were published between 2018 and 2025 The studies were conducted in the US, France, India, multicentres in Europe, Spain, Germany, UK. This review included a total of 12,696 patients with PD enrolled from all the studies. Sample size for each of the included studies ranged from 51 to 173 patients (primary studies), and from 220 to 6560 in the included review. Most of the studies were followed at six months and one year, the longest was two years. Most of the study participants were patients with advanced PD with motor fluctuations not adequately controlled on medical treatment, at stage 4 & 5 H&Y scale. Age range of the patients as reported was between 55.5 to 70.9 in the included studies.The SR was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist guideline.

5.1 RISK OF BIAS ASSESSMENT OF INCLUDED STUDIES

Risk of bias was assessed using ROBIS for SR and Cochrane Risk of Bias (ROB) 2 for RCT. These assessments involved answering a pre-specified question of those criteria assessed and assigning a judgement relating to the risk of bias. The risk of bias of the included studies was assessed independently by two reviewers. Any disagreements were resolved through discussion until consensus was reached.

For RCT, assessment was done following the domain-based evaluation (RoB-2), addressing these domains: bias arising from randomization, deviation from intended intervention, missing outcome data, measurement of outcome and selection of reporting result. Trials having three or more high risk of bias were considered as having poor methodological quality. The plot of the domain-level judgements for each individual result was generated using robvis, a web app designed for visualizing risk-of-bias assessments. The results were illustrated in the figure as below.

Risk of bias assessment for included RCT

Katzenschlager et al (2018) was the landmark trial, that was mostly cited and referred, similarly the recent trial published by Isaacson et al (2025) (InfusON study). Both were judged as having overall low risk of bias on the domains assessed. In assessing randomisation process, random sequence generation or allocation concealment were not explicitly documented. Blinding was considered not relevant for objective measurements (efficacy and adverse events outcomes). Selective reporting was considered to have a low risk of bias as all prespecified outcomes were reported and analysed. (Figure 6).

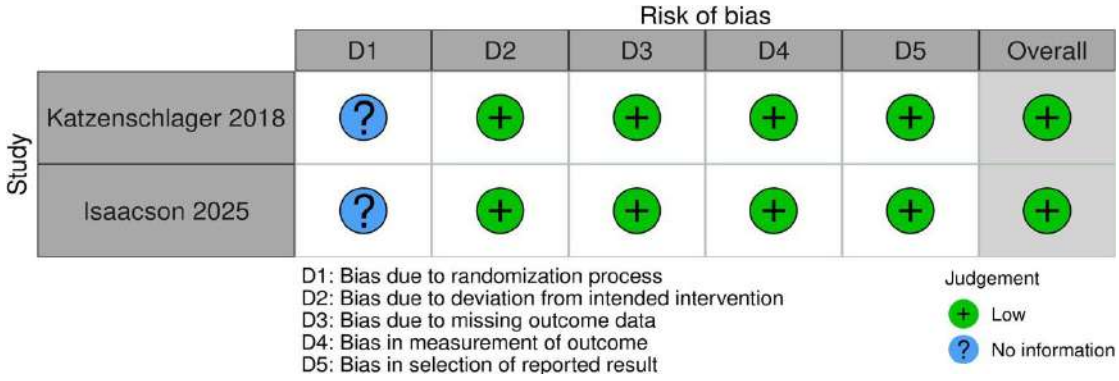

Figure 6: Summary of risk of bias assessment for RCT using ROB 2.0

Risk of bias assessment for included systematic review and meta-analysis

Five SR were included in this assessment. Using ROBIS, the risk of bias of each of the included study is displayed as in Figure 7 below. Three SR included in the review were judged as unclear for domain synthesis and finding. Otherwise, the rest of the SR were judged as having low risk of bias.

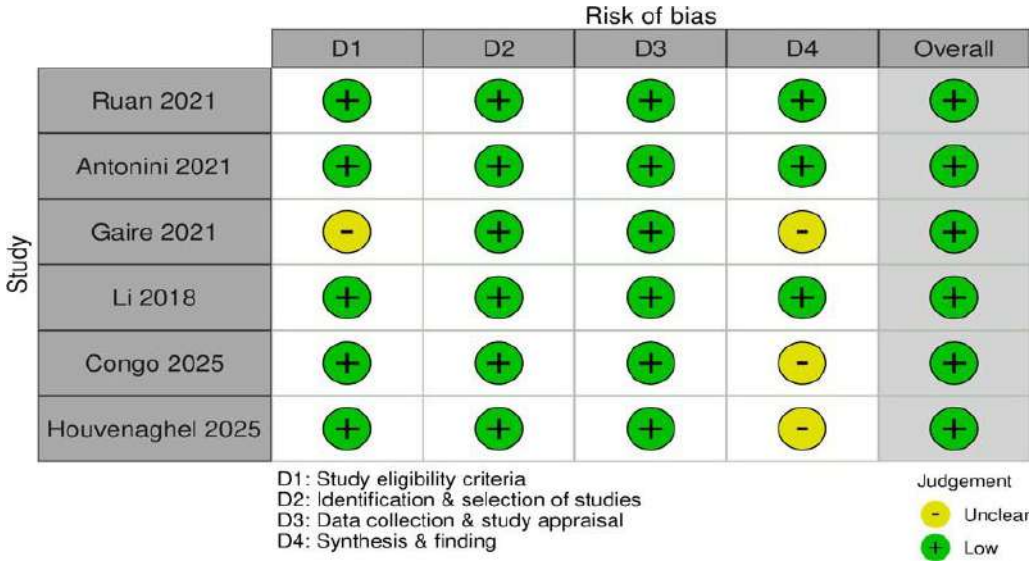

Figure 7: Summary of risk of bias assessment for SR using ROBIS

5.2 EFFECTIVENESS

There were ten studies retrieved on the effectiveness of apomorphine injection or infusion in the treatment of advanced PD, consisted of five SR, two RCTs, two cohort study and one non-randomized trial.

Table 1: Summary of effectiveness outcomes from the included studies

<table>
<tr><th>Study</th><th>Population</th><th>Intervention</th><th>Comparator</th><th>Outcome</th></tr>
<tr>
<td>Ruan et al 2021
NMA of RCT</td>
<td>N=20 RCTs (6,560 patients)
Advanced Parkinson’s Disease (stage 4 or 5 of the Hoehn and Yahr scale)</td>
<td>Dopamine agonist (DA)
• apomorphine
• pramipexole_IR
• pramipexole_ER
• ropinirole_IR
• ropinirole_PR
• rotigotine
• sumanirole
• cabergoline
IR: Immediate release
PR: Prolong release
ER: extended release</td>
<td>Placebo or others</td>
<td>Motor function –
“ON” time without troublesome dyskinesia, “OFF” time, “ON” time,
“UPDRS-III (scores in the on-medication state) and “UPDRS-II (scores in the on medication state)

ON” time without troublesome dyskinesia
<table>
<tr><th>DA</th><th>SUCRA</th><th>Md(Crl)</th></tr>
<tr><td>apomorphine</td><td>97.08%</td><td>1.97 (0.64,3.31)</td></tr>
<tr><td>pramipexole_IR</td><td>79.00%</td><td>1.04 (0.18, 1.86)</td></tr>
<tr><td>ropinirole_PR</td><td>63.92%</td><td>0.78 (0.34,1.18),</td></tr>
</table>
OFF’ Time Defined as the Return of Parkinson’s Symptoms
<table>
<tr><th>DA</th><th>SUCRA</th></tr>
<tr><td>apomorphine</td><td>77.2%</td></tr>
<tr><td>ropinirole_PR</td><td>69.89%</td></tr>
<tr><td>pramipexole_IR</td><td>67.83%</td></tr>
</table>
The mean changes from baseline to endpoint in patients with at least one treatment-emergent adverse event (TEAE) including dyskinetic, fall, hallucinosis, gastrointestinal response (vomiting, diarrhea, nausea, or constipation).

Unified Parkinson’s Disease Rating Scale (UPDRS)-III
<table>
<tr><th>DA</th><th>SUCRA</th></tr>
<tr><td>Pramipexole_IR</td><td>61.42%</td></tr>
<tr><td>rotigotine</td><td>59.13%</td></tr>
<tr><td>sumanirole</td><td>53.70%</td></tr>
</table>
UPDRS-II
<table>
<tr><th>DA</th><th>SUCRA</th></tr>
<tr><td>rotigotine</td><td>74.07%</td></tr>
<tr><td>cabergoline</td><td>57.10%),</td></tr>
<tr><td>ropinirole_PR</td><td>49.42%)</td></tr>
</table>
Safety [treatment-emergent adverse events (TEAE)
<table>
<tr><th>DA</th><th>SUCRA</th></tr>
<tr><td>placebo</td><td>74.49%</td></tr>
<tr><td>pramipexole_ER</td><td>63.6%</td></tr>
<tr><td>sumanirole</td><td>54.07%</td></tr>
<tr><td>rotigotine</td><td>53.84%</td></tr>
</table>
</td>
</tr>
<tr>
<td>Antonini et al. 2021
NMA of RCT and</td>
<td>22 studies included (n = 2063 patients):</td>
<td>Levodopa-carbidopa Intestinal Gel (LCIG), Deep</td>
<td>Best Medical Therapy</td>
<td>Off-time (reported by diary or Unified Parkinson’s Disease Rating Scale Part IV item 39)
10 studies (LCIG (five), CSAI (two) and DBS</td>
</tr>
</table>

<table>
<tr><td>observational studies</td><td>four RCTs, and 16 single-armed, one 2-armed and one 3-armed prospective studies. Baseline mean age was between 55.5 to 70.9 years</td><td>Brain Stimulation, Continuous Subcutaneous Apomorphine Infusion</td><td></td><td>(three))
• DBS (2.35 h/day; 95%CI 1.66 to 3.04), and LCIG (2.25 h/day; 95%CI 1.32 to 3.19) but not CSAI (0.90 h/day; 95%CI −0.08 to 1.88) produced significantly greater reductions in of-time compared with BMT. DBS
• DBS (1.45 h/day; 95%CI 0.29 to 2.61) and LCIG (1.35 h/day; 95%CI 0.11 to 2.60) resulted in greater improvements in of-time at 6 months compared with CSAI (pairwise comparisons).
• DBS ranked highest, and LCIG ranked second highest for of-time reduction (Based on 135,000 Bayesian iterations)

QoL (reported by Parkinson’s Disease Questionnaire (PDQ-39/PDQ-8)).
• All device-aided therapies demonstrated greater improvements in PD-specific QoL than BMT at 6 months, but with smaller estimated improvements for CSAI (3.61; 95% CI 0.55, 6.68) than for LCIG (7.83; 95%CI 5.15, 10.51) and DBS (7.24; 95% CI 5.37 to 9.10)
• LCIG ranked highest and DBS ranked second highest based on 135,000 Bayesian iterations.

LCIG and DBS significantly improved off-time and QoL at six months compared with CSAI and BMT</td></tr>
<tr><td>Li et al 2018 NMA of RCT</td><td>21 RCTs (4, 844 cases of PD patients above 50 years)</td><td>Dopamine agonist (Ropinirole, pramipexoleDopamine receptor agonist (rotigotine, apomorphine, sumanirole, bromocriptine, piribedil) , COMT inhibitor (entacapone), MAO inhibitor (rasagiline), and levodopa,

(11 drugs)
COMT: catechol-Omethyl transferase

MAO: monoamine oxidase</td><td>Placebo</td><td>Non-motor symptom
Using UPDRS III, the efficacies of placebo, ropinirole, rasagiline, rotigotine, entacapone, pramipexole, sumanirole and levodopa in treating PD were lower than apomorphine

<table><tr><th>Drugs</th><th>WMD (95%CI)</th></tr><tr><td>placebo</td><td>-10.90, (-16.12 to-5.48)</td></tr><tr><td>ropinirole</td><td>-11.85, 95%CI: -17.31 to -6.16;</td></tr><tr><td>rasagiline</td><td>-11.15, 95%CI: -16.64 to -5.04;</td></tr><tr><td>rotigotine</td><td>-11.70, 95% CI: -16.98 to -5.60;</td></tr><tr><td>entacapone</td><td>-11.04, 95% CI: -16.97 to -5.34;</td></tr><tr><td>pramipexole</td><td>-13.27, 95% CI: -19.22 to -7.40;</td></tr><tr><td>sumanirole</td><td>-10.25, 95% CI: -15.66 to -4.32; and</td></tr><tr><td>levodopa</td><td>-11.60, 95% CI: -17.89 to - 5.57,</td></tr></table>
SUCRA values indicated apomorphine had the best efficacy on the non-motor symptoms (99.0%), followed by Bromocriptine (78.8%), and Piribedil (75.9%).</td></tr>
<tr><td>Gaire S et al 2021
(SR)</td><td>8 studies (cohort studies and 1 RCT) (total of 477</td><td>CSAI</td><td>Deep brain stimulation, intestinal levodopa gel, and oral</td><td>Off-time
Significant decrease in off-time hours per day in the apomorphine infusion arm vs placebo arm, -1·89 (95%CI -3.16 to -0.62) hours.</td></tr>
</table>

	patients, 187 received CSAI, 290 alternative treatment or placebo		dopaminergic agents	**Non-motor functions** neuropsychiatric problems Significant improvement in Non motor Symptom Scale (NMSS) (calculated in various domains), PHQ-8 score, LEDD, and BDI in APO-treated patients. **Safety** Nausea, local site discomfort or subcutaneous nodules (most common side effects). Side effects like infusion site erythema (9/53), dyskinesia (8/53), headache (7/53), insomnia (6/53) were reported.
Katzenschlager R, et al 2018 (RCT) .	N=107 patients randomized(106 included in the full-analysis),from 23 European centres and had a diagnosis of PD of >3 years' duration with motor fluctuations not adequately controlled on medical treatment.	apomorphine infusion during waking hours (16±2 hours) at 3–8 mg/hour for 12 weeks (N=53)	Placebo (N=53)	**Change in daily 'off' time (based on patient diaries)** Apomorphine infusion (n=53; mean [±SD] final dose: 4.68±1.50 mg/hour) provided statistically significantly greater reduction in 'off' time compared with placebo (n=53); difference between treatment groups of -1.89 hours (95% CI: -3.16 to -0.62). **Safety** Apomorphine was well tolerated without unexpected safety signals.
Katzenschlager R, et al 2021	N=84 patients entered the OLP (40 previously on APO, 44 on placebo) and 59 patients (70.2%) completed the study. Objective: Evaluate long term safety of apomorphine – up to 64 weeks (safety and efficacy results including the 52-week open-label phase (OLP))	apomorphine infusion during waking hours	Placebo	**AE** Common **treatment-related adverse events** (AEs) were mild or moderate infusion site nodules, somnolence and nausea. Fourteen (16.7%) patients discontinued the OLP due to AEs, those involving >1 patient were infusion site reactions (n = 4) and fatigue (n = 2); haemolytic anaemia occurred in one case. **Off/On time without trouble dyskinesia, LEDD** Reduction in daily OFF time and improvement in ON time without troublesome dyskinesia were sustained for up to 64 weeks. Pooled data for week 64 (n = 55) showed a mean (SD) change from DBP baseline in daily OFF time of − 3.66 (2.72) hours and in ON time without troublesome dyskinesia of 3.31 (3.12) hours. Mean (±SD) daily levodopa-equivalent dose decreased from DBP baseline to week 64 by 543 mg (±674) and levodopa dose by 273 mg (±515).

Isaacson et al 2025 (RCT) Open label phase 3 trial, up to 52 weeks	N=99 patients treated, 85 completed the titration period, 69 completed maintenance week 12 and 48 completed maintenance week 52	CSAI was initiated with a 1 to 2 mg bolus followed by 1 mg/h infusion titrated to optimal efficacy and tolerability. Following titration, patients entered a 52-week maintenance period	-	**Treatment-related adverse events** included infusion site nodules and erythema, dyskinesia, nausea, and somnolence, each of which occurred more frequently during the titration period. **Off time** **Reduction in OFF time** began at CSAI initiation and reached a mean of 3.0 ±3.18 h/day by maintenance week 12 (primary efficacy endpoint), with a corresponding increase in Good ON time of 3.1 ±3.35 h/day. **By maintenance week 12,** • **68% of patients rated themselves as much or very much improved,** • 62% had at least a 2-hour reduction in daily OFF time, and • **mean concomitant oral levodopa and levodopa equivalent** doses (excluding CSAI) had been reduced by 198 mg/day and 283 mg/day, respectively. Improvements were maintained through week 52.
Houvenaghel et al 2025 SR	23 longitudinal studies evaluated the effect of CSAI on cognition and/or behavior.	CSAI	-	Overall, results were suggestive of positive effects, notably on executive functions and emotion recognition. At the behavioral level, no study showed significant AE of CSAI. Occasionally, a slight improvement of depression, anxiety, apathy, and neuropsychiatric fluctuations was reported. CSAI has no obvious negative effects on cognition and behavior in PD. This treatment shows promise in reducing certain symptoms such as neuropsychiatric fluctuations.
Longo et al 2025 SR	15 studies (cohort and case control) (7 APO and 8 LCIG studies). APO (193 patients, 27 controls, mean age 60.8 years) (8 LCIG studies involving 179 patients, 20 control)	Apomorphine, LCIG	STN-DBS	**Cognitive function** APO preserved cognitive function over a 12-month follow- up (average 16 months follow up), with some decreases in visuospatial memory and executive functions. LCIG, with a 28- month follow-up, showed more extensive cognitive decline, particularly in patients with pre-existing impairments. Variability in cognitive tests made direct comparisons difficult. . **Motor function** A motor improvement following APO were demonstrated (decrease of motor symptoms, reduction in OFF times, dyskinesias, and/or motor fluctuations, a significant decrease in the LEDD). General motor improvement and reduction in motor fluctuations were found following LCIG, however LEDD remained stable Cognitive test
Meira B, et al 2021	N=110 patients advanced Parkinson's disease	Continuous subcutaneous apomorphine infusion (CSAI)	-	**Health-related quality of life (HRQoL)** Of those who continued treatment, HRQoL remained stable with a sustained reduction in motor fluctuations.

	patients treated in routine care (data collected 24 months after CSAI initiation) Focus: 39-item Parkinson's disease questionnaire (PDQ-39			PDQ-39 was the only baseline predictor of HRQoL improvement after two years of treatment. **CSAI discontinuation & predictors** Of the 110 subjects evaluated over a 2-year period, 35% discontinued CSAI. The presence of dyskinesias, poorer psychological status, shorter disease duration, male sex, and worse OFF state were predictors of discontinuation. The observed effect on dyskinesias was mild and transient. Of note, patients with preexisting impulse control disorders showed an overall good tolerability. **Suggested candidates for CSAI:** (i) poor baseline HRQoL and (ii) marked motor fluctuations
Dafsari et al 2019 Cohort (prospective, multicenter, international, real-life cohort)	173 PD patients undergoing STN-DBS (n = 101), IJLI (n = 33), or APO (n = 39), The 173 patients in the final analysis were aged 62.3 years 9.5 with 12.1 years 5.3 disease duration.	STN-DBS, Intrajenunal levodopa infusion (IJLI), Apomorphine		**Motor** PDQuestionnaire-8, UPDRS-IV, and NMSS total scores improved significantly at follow-up following STN-DBS, IJLI and apomorphine. **NMSS domain analysis:** Apomorphine improved mood/ cognition, perceptual problems/hallucinations, attention/ memory, and the miscellaneous domain. Overall, APO favorable for neuropsychological/neuropsychiatric NMS and PDQuestionnaire-8 outcome. **Quality of life** In the STN-DBS group, QoL improved by approximately 27% in the STN-DBS group in the original cohort. 21% improvement of QoL in the IJLI group closely resembles the results from previous observational real-life studies, improvement may be considerably higher, up to 34% improvement as reported in this study. For APO, PDQ-8 improvement at the 6-month follow-up varies widely and ranges between 11.3%3 and 41.9%. **Adverse events** Overall, moderate and severe nonserious AE were observed more frequently in infusion therapies than in STN-DBS
Metta et al 2023 India	N=51 patients with APD, not responding to or with significant side effects from oral dopaminergic therapy, were assessed at	CSAI	-	**Motor** CSAI significantly reduced the functional impact of dyskinesia ($p< 0.01$ at 6 months and $p < 0.001$ at 12 months). There was a significant improvement in the OFF-state from baseline ($p < 0.01$ at 6 months and $p < 0.001$ at 12 months) All patients had H&Y scores of 2.5 or less following CSAI. LEDD scores significantly decreased from

	baseline and at month 6 and 12 following CSAI infusion.			baseline at month 6 (p<0.001) Significant improvement in UPDRS parts 3 and 4, NMSS total score, PDQ-8 summary index, depression and anxiety subdomains of HADS, KPPS and PFS-16 scores (p < 0.001). Following initiation of CSAI, all the clinical parameters showed a significant improvement from baseline at month-6 and month-12 (both p<0.05). **Adverse events** No discernible side effects were observed apart from mild site reaction (n = 7), nausea (n = 7) skin nodules (n = 2)

5.2.1 Motor function

Ruan et al. (2021) compared and ranked the efficacy and safety of dopamine agonists (DAs) with regard to motor fluctuations in Advanced Parkinson's Disease in a Bayesian network meta-analysis (NMA) of RCT. Electronic databases (PubMed, Embase and Cochrane Library) were systematically searched for relevant studies published until January 2021. Eligibility criteria for included studies were i) RCT, ii) Studies that included **advanced PD patients (PD patients classified as at stage 4 or 5 of the Hoehn and Yahr scale which is characterized by the presence of motor fluctuations) or PD patients with motor fluctuation**, iii) Studies that compared various curative measures with a placebo group or each other and iv) Studies that reported motor function, quality of life, and results of adverse events. Two reviewers independently extracted individual study data and evaluated risk of bias using the Cochrane Risk of Bias tool. Strength of the body of evidence for the primary outcome was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. Network meta-analyses using a Bayesian framework were used to calculate the related parameters. The pre-specified primary and secondary outcomes were efficacy ("ON" time without troublesome dyskinesia, "OFF" time, "ON" time, "UPDRS-III," and "UPDRS-II") and safety [treatment-emergent adverse events (TEAE) and other adverse events] of DAs. The results are presented as the surface under the cumulative ranking (SUCRA) curve. Higher SUCRA scores correspond to a higher ranking for reducing motor fluctuations and a lower risk of adverse events, compared with other interventions. A total of 20 RCTs assessing 6,560 patients were included. The included PD patients with motor fluctuations received eight different treatments. The review found the general DA effects were ranked from high to low with respect to the amount of "**ON" time without troublesome dyskinesia** as follows: apomorphine (SUCRA:97.08%), pramipexole_IR (SUCRA:79.00%), and ropinirole_PR (SUCRA:63.92%).(Figure 8).The top three ranked drugs were apomorphine (SUCRA:77.2%), ropinirole_PR (SUCRA:69.89%), and pramipexole_IR (SUCRA:67.83%) for '**OFF' Time Defined as the Return of Parkinson's Symptoms.** The general safety of DAs was ranked from high to low with respect to **TEAE** as follows: placebo (SUCRA:74.49%), pramipexole_ER (SUCRA:63.6%), sumanirole (SUCRA:54.07%), and rotigotine (SUCRA:53.84%). This NMA shows that apomorphine is one of the most effective agonists for motor

fluctuations, and can increase “ON” time without troublesome dyskinesia and decrease “OFF” time for advanced PD patients. The addition of pramipexole, ropinirole, or rotigotine to levodopa treatment in advanced PD patients with motor fluctuations increased “ON” time without troublesome dyskinesia, improved the UPDRS III scores, and ultimately improved the UPDRS II scores, thereby maximizing its benefit.[26] level I

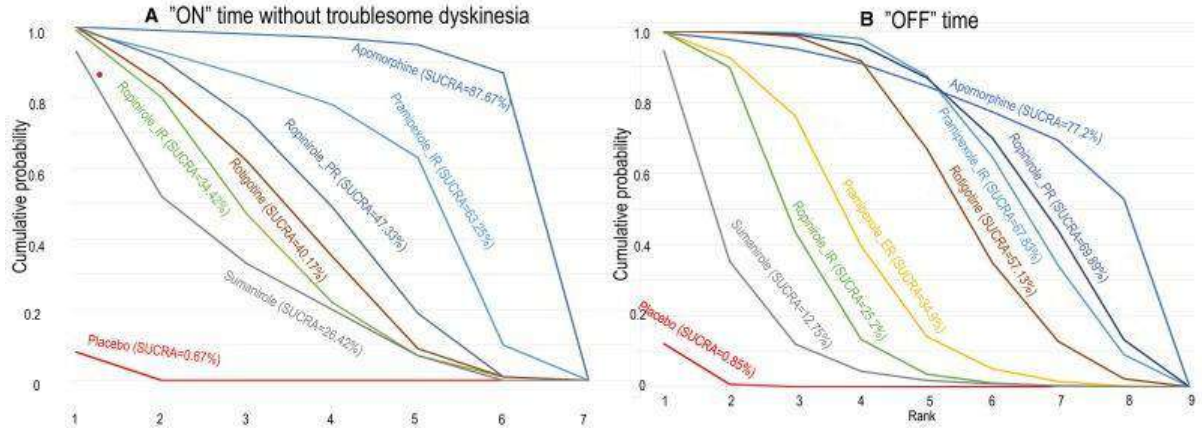

Figure 8: The surface under the cumulative ranking curve for competing interventions based on (A) “ON” time without troublesome dyskinesia, (B) “off” time

Antonini et al. (2021) in another NMA assessed the comparative effectiveness of **Levodopa-carbidopa Intestinal Gel (LCIG), Deep Brain Stimulation, Continuous Subcutaneous Apomorphine Infusion (CSAI) and best medical therapy (BMT)** in reducing of-time and improving quality of life (QoL) in patients with advanced PD.The systematic review included RCTs, observational and interventional studies from January 2003 to September 2019. Study bias was analyzed using the Cochrane Risk of Bias (RoB) tool to assess RCTs, ROBINS-I tool for non-randomized comparative studies, and the National Institutes of Health (NIH) Quality Assessment Tool for before-after (pre-post) studies with no control group or single-arm studies. Data extracted at **baseline and six months** were of-time, as reported by diary or Unified Parkinson’s Disease Rating Scale Part IV item 39, and QoL, as reported by Parkinson’s Disease Questionnaire (PDQ-39/PDQ-8). Bayesian NMA was performed to estimate pooled treatment effect sizes and to rank treatments in order of effectiveness. A total of 22 studies were included (n = 2063 patients): four RCTs, and 16 single-armed, one 2-armed and one 3-armed prospective studies. Of the study population, 908 patients were assigned to treatment with LCIG, 705 to DBS, and 322 to CSAI. Baseline mean age was between 55.5 to 70.9 years, duration of PD was 9.1 to 15.3 years, of-time ranged from 5.4 to 8.7 hour/day in nine studies, and PDQ scores ranged from 28.8 to 67.0 in 19 studies. Ten studies reported off time outcomes; LCIG (five), CSAI (two) and DBS (three). Deep brain stimulation (2.35 h/day; 95% CI 1.66 to 3.04), and LCIG (2.25 h/ day; 95% CI 1.32 to 3.19) but not CSAI (0.90 h/day; 95% CI – 0.08 to 1.88) produced significantly greater reductions in of-time compared with BMT. DBS (1.45 h/day; 95%CI 0.29 to 2.61) and LCIG (1.35 h/day; 95%CI 0.11 to 2.60) resulted in greater improvements in of-time at 6 months compared with CSAI (pairwise comparisons). Based on 135,000 Bayesian iterations, DBS ranked highest, and LCIG ranked second highest for of-time reduction. In terms of QoL, all device-

aided therapies demonstrated greater improvements in PD-specific QoL score than BMT at six months, for CSAI (3.61; 95%CI 0.55 to 6.68) than for LCIG (7.83; 95%CI 5.15 to 10.51) and DBS (7.24; 95%CI 5.37 to 9.10). Pairwise comparisons indicated that both LCIG (4.22, 95% CI 1.77 to 6.66) and DBS (3.63, 95% CI 0.74 to 6.50) resulted in significantly greater improvements in QoL at 6 months compared with CSAI. Levodopa/carbidopa intestinal gel and DBS demonstrated significantly greater improvement in off-time and QoL at six months compared with CSAI and BMT ($p<0.05$). Understanding the comparative benefits of each treatment provides additional information that can help the patient, caregiver, and provider in the selection of the most appropriate therapy to ensure optimal symptom control and improved QoL. Patient preference is essential to consider, as some patients may be unwilling to undergo invasive brain surgery for DBS or PEG surgery for LCIG, and would prefer the less invasive procedure of CSAI. Patients' treatment preferences must be part of the shared decision approach.[25 level I]

Gaire S et al. (2021) in another SR evaluated the effectiveness and safety of Continuous Subcutaneous Apomorphine Infusion (CSAI) in Advanced Parkinson's Disease. They conducted the study to review the available literature comparing the efficacy and safety of CSAI with other available treatment options like deep brain stimulation, intestinal levodopa gel, and oral dopaminergic agents. They searched PubMed, Embase, and Scopus databases using the appropriate search strategy. The studies which compared the safety and efficacy of CSAI to other available treatment options including placebo, oral dopaminergic agents, intestinal levodopa-carbidopa gel, or subthalamic deep brain stimulation in advanced Parkinson's disease were included. The bias assessment of the studies was done using Cochrane Risk of Bias 2.0 tool for RCT, Risk of Bias In Non-Randomized Studies - of Interventions (ROBINS-I) tool for non-randomized interventional studies, and Joanna Briggs Institute Critical Appraisal tools (JBI) for cohort studies. For studies assessing non-motor symptoms, various instruments were used including Mini-Mental State Examination (MMSE) score, Non-Motor Symptoms Scale (NMSS) Neuropsychiatric Inventory (NPI) score, Hamilton Depression rating scale-17 (HAMD-17), PHQ-8 score, Brief Psychiatric Rating Scale (BPRS), Patient Global Impression of Change (PGIC), Levodopa Equivalent Dose (LEDD) and Beck Depression Index (BDI).A total of eight studies were included in the SR comprised of cohort studies and a randomized controlled trial (total of 477 patients, out of which 187 received CSAI, and 290 received alternative treatment or placebo). Overall mean age and standard deviation (SD) of the people receiving CSAI is 61.3±10.5 years. None of the included studies had a high risk of bias. The duration of the studies varied from 12 weeks to five years. In all the included studies, apomorphine was given subcutaneously in continuous infusion form.

They found in patients with advanced Parkinson's, CSAI demonstrated definite improvement in off-time duration. Significant decrease in off-time hours per day in the apomorphine infusion arm compared to the placebo arm, the difference being -1.89 (95%CI -3.16 to -0.62) hours. CSAI has also been shown to improve various non-motor functions, including neuropsychiatric problems in these patients. The review found significant improvement in PGIC scores and reduction of levodopa equivalent dose in APO treated patients vs. placebo ($p<0.05$). Significant improvement in NMSS (calculated in various domains), PHQ-8 score, LEDD, and BDI in APO-treated patients. In terms of safety, nausea and local site discomfort or subcutaneous nodules

are the most common side effects observed among patients receiving apomorphine. Side effects like infusion site erythema (9/53), dyskinesia (8/53), headache (7/53), insomnia (6/53) were reported. They concluded CSAI has demonstrated safety and efficacy in patients with advanced Parkinson's disease. However, the decision-making is multifactorial. Hence, they suggested further studies required that directly compare the available treatment options with one another and study their overall effects on patients' quality of life.[27 level I]

Katzenschlager R et al. (2018) in a randomised, placebo-controlled, double-blind, multicentre trial (TOLEDO trial) investigated the efficacy and safety of apomorphine infusion over placebo in patients with Parkinson´s disease (PD) and persistent motor fluctuations despite optimized oral/transdermal treatment. Subjects were enrolled at 23 European centers and had a diagnosis of PD of >3 years' duration with motor fluctuations not adequately controlled on medical treatment. Subjects gave written informed consent; local ethics committees approved the study. Patients were randomised in a 1:1 ratio stratified by site to receive apomorphine or placebo saline infusion during waking hours (16±2 hours) at 3 to 8 mg/hour for 12 weeks. Based on individual efficacy and tolerability, the flow rate of the study drug and oral medication were adjusted during 4 weeks, followed by an 8-week maintenance period. The primary endpoint was the absolute change in daily 'off' time based on patient diaries (intention-to-treat analysis). A total of 107 patients were randomised and 106 included in the full-analysis set (one did not provide any post-baseline efficacy data). Apomorphine infusion (n=53; mean [±SD] final dose: 4.68±1.50 mg/hour) provided statistically significantly greater reduction in 'off' time compared with placebo (n=53); difference between treatment groups of -1.89 hours (95% CI: -3.16 to -0.62; p=0.0025). Apomorphine was well tolerated without unexpected safety signals. The TOLEDO study provides the level-1 evidence previously lacking. Apomorphine infusion resulted in statistically significant and clinically meaningful 'off' time reduction without increasing dyskinesias in PD patients with persistent motor fluctuations despite optimised oral/transdermal therapy.[28 level I]

Katzenschlager R et al. (2021) in the randomized, double-blind phase (DBP) of the TOLEDO study confirmed the efficacy of apomorphine infusion (APO) in reducing OFF time in PD patients with persistent motor fluctuations despite optimized oral/transdermal therapy. Subsequently, this study aimed to report safety and efficacy results including the 52-week open-label phase (OLP). In this study, all patients completing the 12-week DBP (including those switching early to open-label treatment) were offered OLP entry. The primary objective was the evaluation of long-term safety of APO. A total of 84 patients entered the OLP (40 previously on APO, 44 on placebo) and 59 patients (70.2%) completed the study. The safety profile of APO was consistent with experience from extensive clinical use. Common treatment-related adverse events (AEs) were mild or moderate infusion site nodules, somnolence and nausea. Fourteen (16.7%) patients discontinued the OLP due to AEs, those involving >1 patient were infusion site reactions (n = 4) and fatigue (n = 2); haemolytic anaemia occurred in one case. Reduction in daily OFF time and improvement in ON time without troublesome dyskinesia were sustained for up to 64 weeks. Pooled data for week 64 (n = 55) showed a mean (SD) change from DBP baseline in daily OFF time of – 3.66 (2.72) hours and in ON time without troublesome dyskinesia of 3.31 (3.12) hours. Mean (±SD) daily levodopa-equivalent dose decreased from DBP baseline to

week 64 by 543 mg (±674) and levodopa dose by 273 mg (±515). They concluded the safety and efficacy of APO infusion were demonstrated with long-term use up to 62 weeks for persistent motor fluctuations, allowing substantial reductions in oral PD medication.

Isaacson et al. (2025) in another RCT evaluated CSAI for motor fluctuations in the US setting. This prospective, 52-week open-label, phase 3, outpatient study was conducted at 19 US centers with expertise at treating motor fluctuations in PD. This open-label study (NCT02339064) enrolled patients with PD experiencing ≥3 hours (h) daily OFF time despite optimized levodopa and current/prior use of at least one other adjunctive therapy. The study involved several phases; the screening (including a baseline period), titration, and maintenance periods. Apomorphine for CSAI was provided in 20mL prefilled glass cartridges and delivered via a wearable (ambulatory) infusion device. Each mL of solution contained 5 mg apomorphine hydrochloride hemihydrate (equivalent to 4.27 mg apomorphine base).CSAI was initiated with a 1 to 2mg bolus followed by 1mg/h infusion titrated to optimal efficacy and tolerability. Following titration, patients entered a 52-week maintenance period. The primary efficacy endpoint was change from baseline to week 12 of the maintenance period in total daily OFF time, as recorded in the 24-hour motor-diaries. Secondary efficacy measures were the change from baseline to week 12 of the maintenance period in; Daily ON time without troublesome dyskinesia (commonly referred to as Good ON time), Patient Global Impression of Change (PGI-C), oral levodopa and levodopa equivalent dose (LED), and percentage of patients with response to therapy, defined as OFF time reduction of ≥2 h/day.

They found between 31 March 2014 and 26 July 2018, of the 99 patients treated, 85 completed the titration period, 69 completed maintenance week 12 and 48 completed maintenance week 52. All patients reported one or more AEs, which were mostly mild to moderate in severity. Common treatment-related adverse events included infusion site nodules and erythema, dyskinesia, nausea, and somnolence, each of which occurred more frequently during the titration period. Reduction in OFF time began at CSAI initiation and reached a mean of 3.0 ±3.18 h/day by maintenance week 12 (primary efficacy endpoint), with a corresponding increase in Good ON time of 3.1 ±3.35 h/day. By maintenance week 12, 68% of patients rated themselves as much or very much improved, 62% had at least a 2-hour reduction in daily OFF time, and mean concomitant oral levodopa and levodopa equivalent doses (excluding CSAI) had been reduced by 198 mg/day and 283 mg/day, respectively. Improvements were maintained through week 52. They concluded this study supported the clinical utility of CSAI to reduce OFF time and increase Good ON time in patients with motor fluctuations inadequately controlled with oral therapy. [29] level I

5.2.2 Non-motor function

Houvenaghel JF et al. 2021 in another SR evaluated the influence of continuous subcutaneous apomorphine infusion on cognition and behaviour in Parkinson's disease. The main objective of this systematic review was to describe the existing literature on the effects of CSAI on cognition and behaviour and to determine the quality for each study. PubMed/Medline, Embase, APA PsycInfo1, and Cochrane

Library databases were searched, following PRISMA recommendations. Only longitudinal studies evaluating the effect of CSAI on cognition (global cognition, executive functions, visuospatial abilities, language, memory, attention, social cognition) and/or behaviour (depression, anxiety, apathy, psychotic symptoms, impulse control disorders, neuropsychiatric fluctuations) in PD were included. The quality of the included studies was also assessed with a questionnaire. They included 23 longitudinal studies evaluated the effect of CSAI on cognition and/or behaviour. Overall, results were suggestive of positive effects, notably on executive functions and emotion recognition. However, there were some reports of cognitive slowing and long-term global cognitive deterioration. At the behavioural level, no study showed significant adverse effect of CSAI. Occasionally, a slight improvement of depression, anxiety, apathy, and neuropsychiatric fluctuations was reported. Nevertheless, only four studies met good quality criteria and controlled study regarding cognition were lacking. They concluded that CSAI has no obvious negative effects on cognition and behaviour in PD. This treatment even shows promise in reducing certain symptoms such as neuropsychiatric fluctuations. However, due to methodological limitations in many studies, no robust conclusions can be drawn. Further multicentre controlled trials are needed to confirm these results. [17] level I

Li B et al. (2018) in another NMA compared the efficacy of ropinirole, rasagiline, rotigotine, entacapone, apomorphine, pramipexole, sumanirole, bromocriptine, piribedil and levodopa, with placebo as a control, for non-motor symptoms in Parkinson's disease (PD). PubMed, Embase and the Cochrane Library were searched from their establishment dates up to January 2017 for RCTs investigating the efficacy of the above ten drugs on the non-motor symptoms of PD. A NMA combined the evidence from direct and indirect comparisons and evaluated the pooled weighted mean difference (WMD) values and surfaces under the cumulative ranking curves (SUCRA). Bayesian network meta-analysis was carried out to compare different interventions. The NMA included 21 RCTs (4,844 cases of PD patients). Among these 21 RCTs, 16 trials were performed in Caucasians, five trials were in Asians, 18 trials were two-arm, and three trials were three-arm. The results indicated that, using the United Parkinson's Disease Rating Scale (UPDRS) III, the efficacies of placebo, ropinirole, rasagiline, rotigotine, entacapone, pramipexole, sumanirole and levodopa in treating PD were lower than that of apomorphine (WMD = -10.90, 95% CI = -16.12 to-5.48; WMD: -11.85, 95% CI: -17.31 to -6.16; WMD: -11.15, 95% CI: -16.64 to -5.04; WMD: -11.70, 95% CI: -16.98 to -5.60; WMD: -11.04, 95% CI: -16.97 to -5.34; WMD: -13.27, 95% CI: -19.22 to -7.40; WMD: -10.25, 95% CI: -15.66 to -4.32; and WMD: -11.60, 95% CI: -17.89 to - 5.57, respectively). Treatment with ropinirole, rasagiline, rotigotine, entacapone, pramipexole, sumanirole, bromocriptine, piribedil or levodopa, with placebo as a control, on PD exhibited no significant differences on PD symptoms when the UPDRS II was used for evaluation. Moreover, using the UPDRS III, the SUCRA values indicated that apomorphine had the best efficacy on the non-motor symptoms of PD (99.0%), followed by Bromocriptine (78.8%), and Piribedil (75.9%). (Figure 9). Using the UPDRS II, the SUCRA values for ropinirole, rasagiline, rotigotine, entacapone, pramipexole, sumanirole, bromocriptine, piribedil and levodopa treatments, with placebo as a control, indicated that bromocriptine showed the best efficacy on the non-motor symptoms of PD (75.6%). They concluded among ropinirole, rasagiline, rotigotine, entacapone, apomorphine, pramipexole, sumanirole, bromocriptine, piribedil and levodopa, with placebo as a control, apomorphine

appeared as the most efficacious drug for therapy in treating the non-motor symptoms of PD.[30 level I]

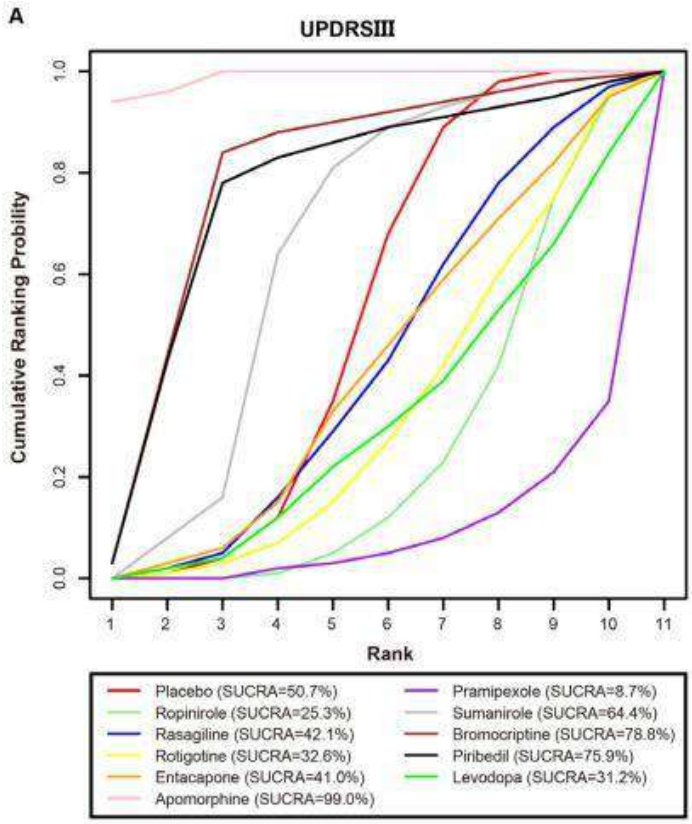

Figure 9: The cumulative ranking probability diagram of the efficacy of ten drugs for Parkinson's disease using the United Parkinson's Disease Rating Scale (UPDRS) III

Longo C et al (2025) in another SR evaluated the cognitive impact of APO and LCIG in PD patients. A SR was conducted following PRISMA guidelines, with searches in PubMed, Web of Science, Scopus and Embase. Two authors screened studies based on key inclusion criteria, including studies involving PD patients, focusing on cognitive outcomes following treatment with LCIG or APO, at least two cognitive tests, and a follow- up of 6 months or more. Citations were imported into the web- based systematic review software Rayyan. The risk of bias was evaluated using the Newcastle - Ottawa Scale (NOS). They included 15 studies cohort and case control (7 APO and 8 LCIG). The seven included studies for APO involved 193 patients and 27 controls, weighted mean age of 60.8 years, and mean of disease duration of 12.35 years; while the eight included studies of LCIG involved 179 patients and 20 control subjects, with weighted mean age of 65.1 years. Three out of seven studies for APO and three out of eight for LCIG were case-control studies. In both APO and LCIG studies, the control groups consisted of patients undergoing STN-DBS.

They found for cognitive outcomes; APO generally preserved cognitive function over a 12- month follow- up (average 16 months follow up), with some decreases in visuospatial memory and executive functions. LCIG, with a 28-month follow-up, showed more extensive cognitive decline, particularly in patients with pre-existing impairments. Variability in cognitive tests made direct comparisons difficult. For motor

outcomes, a motor improvement following APO were highlighted in the included studies, specifically, decrease of motor symptoms, reduction in OFF times, dyskinesias, and/or motor fluctuations, a significant decrease in the LEDD. General motor improvement and reduction in motor fluctuations were found following LCIG, however LEDD remained stable. In terms of cognitive test, for APO four out of five studies employed the Mini-Mental State Examination (MMSE) as a screening test, with a weighted mean score of 26.47 (range 0–30), other three studies used the Mattis Dementia Rating Scale. While for LCIG similarly, MMSE was the most used cognitive screening test reporting a weighted mean score of 26.17 (range 0 to 30). They concluded APO may have a more favorable cognitive profile than LCIG. However, differences in follow- up duration, moderate risk of bias, and inconsistent cognitive assessments warrant cautious interpretation. Improved patient selection and comprehensive cognitive evaluations are recommended for future practice. [31 level I]

Dafsari et al (2019) in a real-life observational study reported clinical efficacy of bilateral subthalamic stimulation (STN-DBS), apomorphine (APO), and intrajejunal levodopa infusion (IJLI) on quality of life, motor, and non-motor symptoms (NMS) in Parkinson's disease (PD). Study populations were enrolled in five movement disorders centers (Cologne, London, Venice, São Paulo, and Ljubljana). These centers were chosen based on their experience in using motor and non-motor scales, their expertise in surgical and device-aided medical therapies, and their ability to provide these treatment options under one roof without healthcare system restrictions/prerequisites. They conducted prospective, multicenter, international, real life cohort observation study of 173 PD patients undergoing STN-DBS (n = 101), IJLI (n = 33), or APO (n = 39), whom were followed-up using PDQuestionnaire-8, NMSScale (NMSS), Unified PD Rating Scale (UPDRS)-III, UPDRS-IV, and levodopa equivalent daily dose (LEDD) before and six months after intervention. The 173 patients in the final analysis were aged 62.3 years 9.5 with 12.1 years 5.3 disease duration. The therapeutic medical regimen was recorded calculating the levodopa equivalent daily dose (LEDD) according to the method of Tomlinson et al. The PD Questionaire-8 (PDQ-8) has previously been used in patients with PD and STN-DBS, APO, and IJLI.The PDQ is recommended for QoL assessments by the Movement Disorders Society Scales Committee and has been commonly used studies on invasive therapies of advanced PD; the results are reported as PDQ-8 Summary Index (PDQ-8 SI) to ease the interpretation. The NMSScale (NMSS) was used to survey the following nine domains of NMS: cardiovascular, sleep/fatigue, mood/cognition, perceptional problems/hallucinations, attention/memory, gastrointestinal, urinary, sexual function, and miscellaneous, which consists of items for pain, inability to smell or taste, weight change, and excessive sweating. As this was an analysis of observational, real-life data, they used propensity score matching to minimize selection bias and increase causal inference.

Outcome changes were analyzed with Wilcoxon signed-rank or paired t-test when parametric tests were applicable. Multiple comparisons were corrected (multiple treatments/scales). Effect strengths were quantified with relative changes, effect size, and number needed to treat. Analyses were computed before and after propensity score matching, balancing demographic and clinical characteristics. They found in all groups (the STN-DBS, IJLI, and APO groups), PDQuestionnaire-8, UPDRS-IV, and NMSS total scores improved significantly at follow-up. (Table 2) There was no

significant difference between continuous infusion times for IJLI (15.4 hours/day 1.3) and APO (15.4 hours/day 2.6; p=0.907; no 24-hour infusions in both groups). Hoehn and Yahr score improved significantly in the IJLI and APO groups (both p<0.005).

Levodopa equivalent daily dose (LEDD) was significantly reduced after STN-DBS. Explorative NMSS domain analyses resulted in distinct profiles for each intervention: STN-DBS improved urinary/ sexual functions, mood/cognition, sleep/fatigue, and the miscellaneous domain. IJLI improved the three latter domains and gastrointestinal symptoms. Apomorphine improved significantly the mood/ cognition, perceptual problems/hallucinations, attention/ memory, and the miscellaneous domain. Overall, STN DBS and IJLI seemed favorable for NMSS total score, and APO favorable for neuropsychological/neuropsychiatric NMS and PDQuestionnaire-8 outcome. Number needed to treat results were favorable for bilateral STN-DBS regarding LEDD reduction and UPDRS-III, for IJLI regarding UPDRS IV and NMSS total score, and for APO regarding Hoehn and Yahr scale and PDQ-8 SI**.** (Figure 10).

In terms of QoL, based on a greater relative change, larger effect size, and smaller number needed to treat, they observed an advantageous effect of APO on QoL in the real-life cohort. Meanwhile, adverse events following STN-DBS, IJLI and apomorphine was as illustrated in table 3 below. Overall, moderate and severe nonserious AE were observed more frequently in infusion therapies than in STN-DBS.

They highlighted that this was the first comparison of quality of life, non-motor and motor outcomes in PD patients undergoing STN-DBS, IJLI, and APO in a real-life cohort. Distinct effect profiles were identified for each treatment option. The results highlighted the importance of holistic non-motor and motor symptoms assessments to personalize treatment choices. [32] level II-2

Table 2: Relative change and effect size of original and matched cohort following STN-DBS, IJLI and Apomorphine

	Relative change			Effect size (CI)		
Original cohort	STN-DBS	IJLI	APO	STN-DBS	IJLI	APO
PDQ-8 SI	−26.9	−21.1	−30.3	*0.58* (0.37 to 0.79)	*0.55* (0.17 to 0.92)	*0.76* (0.40 to 1.12)
UPDRS-III	−3.7	−6.4	−5.8	0.10 (−0.10 to 0.30)	0.19 (−0.16 to 0.54)	0.13 (−0.19 to 0.45)
UPDRS-IV	−49.4	−45.3	−34.4	**0.85** (0.62 to 1.08)	**1.20** (0.74 to 1.65)	**0.80** (0.41 to 1.18)
H&Y	−5.6	−11.8	−16.1	0.19 (−0.01 to 0.39)	*0.61* (0.23 to 0.98)	*0.74* (0.38 to 1.10)
LEDD	−52.3	16.4	11.3	**1.18** (0.92 to 1.43)	0.34 (−0.03 to 0.70)	0.27 (−0.07 to 0.61)

Table 3: Adverse events

Event	STN-DBS No. of events	STN-DBS No. of patients with event (%)		IJLI No. of events	IJLI No. of patients with event (%)		APO No. of events	APO No. of patients with event (%)	
Serious adverse events	7[a]	7	(6.9)	4[b]	4	(12.1)	4[c]	4	(10.3)
Death	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)
Life-threatening event	1	1	(1.0)	0	0	(0.0)	0	0	(0.0)
Event related to oral/transdermal PD medication	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)
Event related to surgery or device	2	2	(2.0)	2	2	(6.1)	0	0	(0.0)
Wound healing disturbance	3	3	(3.0)	2	2	(6.1)	0	0	(0.0)
Event related to stimulation or infusion therapy	0	0	(0.0)	0	0	(0.0)	2	2	(2.6)
Depression	0	0	(0.0)	0	0	(0.0)	1	1	(2.6)
Event related to PD	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)
Other	1	1	(1.0)	0	0	(0.0)	1	1	(2.6)
Adverse events	214	75	(74.3)	93	28	(84.4)	79	31	(79.5)
Mild	132	72	(71.3)	55	26	(78.8)	41	28	(71.8)
Moderate	69	52	(51.5)	32	23	(69.7)	30	21	(53.8)
Severe	17	14	(13.8)	6	5	(15.2)	9	6	(15.4)

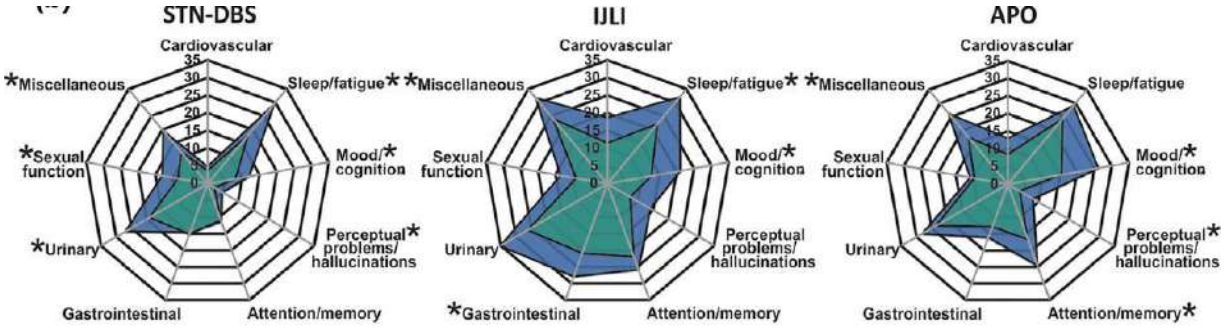

Figure 10: Non-motor Symptom Scale (NMSS) domains
at baseline (blue) and follow-up (green) in the original cohort for subthalamic stimulation, intrajejunal levodopa infusion, and apomorphine infusion in radar charts

Health Related Quality Of Life

Meira B et al. (2021) evaluated long-term effects of continuous subcutaneous apomorphine infusion (CSAI) on health-related quality of life (HRQoL) and predictors of CSAI discontinuation are poorly known. Data from consecutive advanced Parkinson's disease patients treated in routine care were retrospectively collected over 24 months after CSAI initiation, with a focus on the 39-item Parkinson's disease questionnaire (PDQ-39). We determined predictors of CSAI discontinuation and HRQoL improvement using multiple regression analysis. Of the 110 subjects evaluated over a 2-year period, 35% discontinued CSAI. Of those who continued treatment, HRQoL remained stable with a sustained reduction in motor fluctuations. The observed effect on dyskinesias was mild and transient. Of note, patients with preexisting impulse control disorders showed an overall good tolerability. PDQ-39 was the only baseline predictor of HRQoL improvement after 2 years of treatment. The presence of dyskinesias, poorer psychological status, shorter disease duration, male sex, and worse OFF state were predictors of discontinuation. Best candidates for CSAI are patients with: (i) poor baseline HRQoL and (ii) marked motor fluctuations.[33]
level II-2

Metta et al. (2023) studied the safety, tolerability and efficacy of CSAI in Indian patients with APD in a registry design to raise local awareness of this important treatment. Continuous Subcutaneous Apomorphine Infusion (CSAI), despite being approved for the treatment of APD since 1993, was approved in India only in 2019. They conducted a prospective registry-based observational audit at 10 centers across different states of India**.** Data was collected from the registries of the following centers: the Sri Ramaswamy Memorial Institute for Medical Sciences, Chennai; Radha Gobinda Kar Medical College and Hospital, Kolkata; Lady Hardinge Medical College, Delhi; Institute of Movement disorders and Parkinson's research centre Medanta, hospital Gurugram; Manipal Hospital, Bengaluru; Narayana Medical College, Nellore; Amrita Institute of Medical Science and Research Centre, Kochi; Nizam's Institute of Medical Sciences, Hyderabad; Institute of Movement Disorders Parkinson's Centre of Excellence, City Neurosciences, Hyderabad; and RM institute of Neurosciences, Kochi. Hoehn and Yahr (H&Y) Scale was used to stage their functional disability. The study included patients with advanced idiopathic PD (as per H&Y staging 2.5 and above) who did not respond to the conventional oral dopaminergic treatments or developed side effects. Each subject received 14 waking hours of CSAI from 8 am to 10 pm at the rate of 2 mg/h optimized to 3.0 mg/h at six months and 3.5 mg/h at 12 months. Titration was done by the treating PD specialist as driven by individual patients' clinical responsive ness. Levodopa equivalent daily dose (LEDD) was calculated to estimate the overall baseline intake of total oral dopaminergic medications. Motor and non-motor assessments were performed using the Movement Disorder Society unified Parkin son's disease rating scale (MDS-UPDRS) part 2, 3, 4, the non-motor symptom scale (NMSS), and the 8-item Parkinson's disease questionnaire (PDQ-8) on quality of life. Anxiety and depression were evaluated using the hospital anxiety and depression scale (HADS), cognition was evaluated using Montreal cognitive assessment (MoCA) scale and the severity of fatigue was assessed using Parkinson's disease fatigue scale (PFS-16).Parkinson's disease sleep scale (PDSS) was used to quantify the level of sleep disturbances. The King's Parkinson's disease pain scale (KPPS) was used to quantify and assess the different types of pain perceived by the study subjects.

In this study, patients with APD, not responding to or with significant side effects from oral dopaminergic therapy, were assessed at baseline and at month 6 and 12 following CSAI infusion. Fifty-one patients completed the study. The mean age of the participants was 64.59 ± 7.12 years (range 45 to 80 years), the average duration of PD was 7.43 ± 2.03 years. At baseline, most patients had H&Y scores of 3.0 or more, by month 12, all patients had H&Y scores of 2.5 or less. (Table 4). LEDD scores significantly decreased from baseline at month 6 ($p<0.001$) as CSAI was initiated and there was a significant improvement in UPDRS parts 3 and 4, NMSS total score, PDQ-8 summary index, depression and anxiety subdomains of HADS, KPPS and PFS-16 scores ($p<0.001$). Following initiation of CSAI, all the clinical parameters showed a significant improvement from baseline at month 6 and month 12 (both $p<0.05$), except in MoCA and PDSS. (Table 5)

CSAI significantly reduced the functional impact of dyskinesia ($p<0.01$ at 6 months and $p<0.001$ at 12 months). There was a significant improvement in the OFF-state from baseline ($p<0.01$ at 6 months and $p<0.001$ at 12 months).

Only two pain parameters, i.e., nocturnal pain and orofacial pain, showed significant improvement at month 6 and month 12 from baseline following subcutaneous apomorphine administration. ($p<0.05$, Table 6).

No discernible side effects were observed apart from mild site reaction (n = 7), nausea (n = 7) skin nodules (n = 2). CSAI demonstrated safety, efficacy, tolerability and improved quality of life in patients with APD, as shown in previous studies. Their study highlighted current existing inequalities in treatment availability, lack of awareness, knowledge gap, affordability and cost remain a concern regarding apomorphine use in Indian PD population. [34 level II-2]

Table 4: Hoehn and Yahr staging in patients with PD at baseline and during follow up following CSAI

HY stage*	Baseline n (%)	Month 6 n (%)	p[a]	Month 12 n (%)	p[b]
2.0	–	–		19 (37.3)	
2.5	2 (3.9)	3 (5.9)		32 (62.7)	
3.0	34 (66.7)	25 (49.0)	<0.001	–	0.013
3.5	13 (25.5)	21 (41.2)		–	
4	2 (3.9)	2 (3.9)		–	

Table 5: Changes following CSAI in the study population (n=51)

Time period	Baseline	Month 6		Month 12	
Measure	Mean ± SD (range)	Mean ± SD (range)	p[a]	Mean ± SD (range)	p[b]
Dose of medication					
LEDD	823.73 ± 267.17 (400–1800)	574.51 ± 169.52 (200–1000)	<0.001	407.84 ± 132.43 (200–800)	<0.001
Apomorphine	–	24.67 ± 4.19 (18–36)	–	36.00 ± 6.79 (24–60)	–
UPDRS					
Part 2[d]	30.18 ± 1.85 (27–33)	23.41 ± 2.30 (19–27)	<0.001	–	
Part 3	46.78 ± 4.21 (39–57)	34.96 ± 2.03 (30–39)	<0.001	34.43 ± 0.86 (33–36)	<0.001
Part 4	17.78 ± 2.33 (13–22)	14.02 ± 1.42 (12–18)	<0.001	11.98 ± 1.52 (9–15)	<0.001
NMSS total[e]	128.06 ± 18.33 (87–161)	95.51 ± 100.0 (68–118)	<0.001	78.00 ± 21.32 (46–124)	<0.001
PDQ-8 Summary index	59.56 ± 7.45 (43.75–75.0)	42.50 ± 5.54 (37.5–53.13)	<0.001	43.75 ± 5.56 (37.5–53.13)	<0.001
HADS-Depression	12.22 ± 2.06 (8–18)	10.51 ± 1.43 (6–14)	<0.001	10.51 ± 1.43 (6–14)	<0.001
HADS-Anxiety	13.02 ± 7.75 (9–18)	10.31 ± 1.53 (6–14)	<0.001	10.51 ± 1.43 (6–14)	<0.001
MOCA	24.55 ± 2.77 (20–30)	24.55 ± 2.77 (20–30)	n.s.	24.59 ± 2.66 (20–30)	n.s.
PFS-16	11.16 ± 3.66 (0–16)	9.33 ± 2.78 (0–12)	<0.001	9.82 ± 3.03 (0–16)	<0.001
PDSS	63.55 ± 18.07 (20–90)	66.18 ± 12.63 (30–90)	n.s.	66.18 ± 12.36 (30–90)	n.s.
KPPS	40.59 ± 8.56 (21–67)	33.69 ± 9.10 (20–60)	<0.001	33.29 ± 9.23 (20–60)	<0.001

Table 6: Changes in KPPS domain in patients with PD following CSAI

Timeline	Baseline	Month 6		Month 12	
Measure	Mean ± SD (range)	Mean ± SD (range)	p[a]	Mean ± SD (range)	p[b]
Musculoskeletal pain	2.65 ± 1.820 (0–6)	2.55 ± 1.689 (0–6)	n.s.	2.55 ± 1.689 (0–6)	n.s.
Chronic pain	2.31 ± 1.581 (0–4)	2.55 ± 1.689 (0–6)	n.s.	2.55 ± 1.689 (0–6)	n.s.
Fluctuation-related pain	2.51 ± 1.725 (0–6)	2.51 ± 1.725 (0–6)	n.s.	2.51 ± 1.725 (0–6)	n.s.
Nocturnal pain	16.27 ± 4.574 (11–24)	11.06 ± 1.363 (9–14)	< 0.001	10.18 ± 2.463 (2–14)	< 0.001
Oro-facial pain	11.16 ± 3.657 (0–16)	9.33 ± 2.783 (0–12)	< 0.001	9.82 ± 3.031 (0–16)	< 0.001
Discoloration, oedema/swelling	2.84 ± 2.336 (0–10)	2.84 ± 2.336 (0–10)	n.s.	2.84 ± 2.336 (0–10)	n.s.
Radicular pain	2.84 ± 2.336 (0–10)	2.84 ± 2.336 (0–10)	n.s.	2.84 ± 2.336 (0–10)	n.s.

5.3 SAFETY

There were three studies retrieved on the safety of apomorphine injection or infusion in the management of PD, and these studies measured effectiveness outcome as reported above.

Apomorphine was first approved in 2004 (US) under the brand name Apokyn, a non-ergoline dopamine agonist indicated for the acute, intermittent treatment of hypomobility, OFF episodes ("end-of-dose wearing off" and unpredictable "on/off" episodes) associated with advanced Parkinson's disease. Apokyn is administered by subcutaneous injection with a multiple-dose pen injector that can be used up to five times a day, with doses no less than two hours apart. Apokyn is available as injection: 30 mg/3 mL (10 mg/mL) of apomorphine hydrochloride solution, available in APOKYN single-patient-use cartridges and APOKYN NXT single-patient-use disposable prefilled pen. Treatment with trimethobenzamide is recommended, starting three days prior to the first dose of APOKYN. Most common adverse reactions (incidence at least 10% greater on APOKYN than on placebo) were yawning, drowsiness/somnolence, dyskinesias, dizziness/postural hypotension, rhinorrhea, nausea and/or vomiting, hallucination/confusion, and edema/swelling of extremities.[35]

Recently, in February 2025, the US Food and Drug Administration (FDA) approved Onapgo (apomorphine hydrochloride injection, previous name: SPN830). This approval makes Onapgo is the first infusion-based apomorphine therapy approved in the US for Parkinson's disease. ONAPGO is expected to be available in the US in the second quarter of 2025.[36]

ONAPGO (apomorphine hydrochloride) is indicated for the treatment of motor fluctuations (OFF episodes) in adults with advanced Parkinson's disease. It is indicated for subcutaneous use by infusion only. Patients selected for treatment with ONAPGO should be capable of understanding and trained on using the delivery system, either themselves or with the assistance of a caregiver. ONAPGO initiation and dose titrations should be done under medical supervision. [37] Onapgo is designed to provide more consistent control of OFF episodes, administered by delivering apomorphine continuously for up

to 16 hours during the waking day through a delivery device (ONAPGO pump). Because of the incidence of nausea and vomiting with ONAPGO, it is recommended that treatment with trimethobenzamide 300 mg three times a day start three days prior to the initial dose of ONAPGO. The daily dosage is determined by individualized patient titration and is composed of a continuous dosage and as needed extra dose(s).The maximum recommended total daily dosage of ONAPGO, including the continuous dosage and any extra dose(s), is 98mg per day, generally administered over the waking day (e.g., 16 hours). Most common adverse reactions were infusion site nodule, nausea, somnolence, infusion site erythema, dyskinesia, headache, and insomnia.[37]

In February 2022, the USFDA has approved the first generic of Apokyn (apomorphine hydrochloride injection) drug cartridges to treat hypomobility “off” episodes (“end-of-dose wearing off” and unpredictable “on/off” episodes) associated with advanced Parkinson’s disease. Prescribers and pharmacists should be aware that patients starting treatment with generic apomorphine hydrochloride injection will need to separately obtain the Apokyn Pen. This approval is for the application of the drug cartridges only, which are compatible for use with the Apokyn Pen. The Apokyn Pen is supplied by the brand manufacturer, is distributed and packaged separately, and is generally only dispensed through specialty pharmacies. Patients should first obtain the prescribed Apokyn Pen through a specialty pharmacy before being prescribed the generic apomorphine hydrochloride injection. [38]

On 16 February 2006, orphan designation (EU/3/06/349) was granted by the European Commission to Vectura Group plc, United Kingdom, for apomorphine hydrochloride (inhalation use) for the treatment of off-periods in Parkinson's disease not responding to oral treatment. On 5 December 2001, orphan designation (EU/3/01/072) was granted by the European Commission to Orion Corporation, Finland, for apomorphine (oromucosal use) for the treatment of off-periods in Parkinson's disease not responding adequately to other existing therapies.[39]

In UK, Apomorphine is licensed for use in refractory motor fluctuations in Parkinson’s disease (‘off‘ episodes) inadequately controlled by levodopa with dopa-decarboxylase inhibitor or other dopaminergics (for capable and motivated patients under specialist supervision).[40]

In Canada, apomorphine has a Health Canada–approved indication for the treatment of acute, intermittent hypomobility and “off” (“end-of-dose wearing off” and unpredictable “on/off”) episodes in patients with advanced PD. Apomorphine belongs to the class of post-synaptic dopamine agonists and is available in Canada as 3 mL pre-filled, disposable, multi-dose pens at a strength of 10 mg/mL. The Health Canada approved dosage is 0.2 mL (2 mg) to 0.6 mL (6 mg) per dose, to be administered subcutaneously as an adjunct to regular oral anti-PD medications.[41]

In Ireland, the HPRA has granted a marketing authorisation for APO-go POD 5 mg/ml solution for infusion in cartridge, from Stada Arzneimittel AG on

November 13, 2020 for the treatment of motor fluctuations ('on-off' phenomena) in patients with Parkinson's disease which are not sufficiently controlled by oral anti-Parkinson medication. The Health Product Regulatory Authority, on the basis of the data submitted, considered that APO-go POD 5 mg/ml solution for infusion in cartridge demonstrated adequate evidence of efficacy for the approved indication as well as a satisfactory risk/benefit profile and therefore granted a marketing authorization. [42]

Apomorphine injection has regulatory approval in Thailand for treating Parkinson's disease, specifically for managing motor fluctuations, as of 2015. While not initially approved in 2013, it was used on a compassionate basis for a small group of patients before its formal approval by the Thai FDA in 2015. The Chulalongkorn Center of Excellence for Parkinson's Disease and Related Disorders plays a key role in managing and monitoring apomorphine treatment in Thailand, including the establishment of the Thai Apomorphine Registry.[43]

5.4 ECONOMIC EVALUATION / FINANCIAL IMPLICATION

There was limited retrievable evidence on the cost-effectiveness of apomorphine injection or infusion in the management of patients with Parkinson's disease. One SR of CEA was retrieved on this intervention for patients with Parkinson's disease.

Table 6: Summary evidence on CE of apomorphine injection or infusion in PD

Study	Population	Intervention	Comparator	Outcome
Smilowskaa et al (2021) **SR of CEA**	30 studies were retrieved	Device aided therapies; deep brain stimulation (DBS), intrajejunal Levodopa-carbidopa infusion (IJLI) and continuous subcutaneous apomorphine infusion (CSAI)	**BMT, IJLI**	All device-aided therapies improved quality of life compared to best medical treatment, with improvements in QALYs between 0.88 and 1.26 in the studies with long temporal horizons. For infusion therapies **only three studies showed a cost per QALY below this threshold,** with several studies with long temporal horizons showing costs below or near the GDP threshold. This therapy was cost-effective in the UK, but not in Germany (vs BMT) CSAI vs IJLI showed ICER of €38,249 per QALY, above the GDP of Spain

Smilowskaa et al. (2021) conducted a systematic review on cost-effectiveness analyses (CEA) for device-aided therapies in PD. They identified references by performing a systematic search in the PubMed and Web of Science databases

in accordance with the PRISMA statement. They determined time horizon of the intervention of at least one year. The time span of the search ranged from 1988 to April 2020.In the absence of universal cost-effectiveness definitions, the gross domestic product per capita (GDP) in the country where a study was conducted, was used as a cut-off for cost-effectiveness based on cost per quality adjusted life year (QALY) gained. Information on GDP was downloaded from the Organization for Economic Co-operation and Development.

They found in total 30 studies were retrieved. All device-aided therapies (DAT) improved quality of life compared to best medical treatment, with improvements in QALYs between 0.88 and 1.26 in the studies with long temporal horizons. For DBS, nearly all studies showed that cost per QALY was below the GDP threshold. For infusion therapies only three studies showed a cost per QALY below this threshold, with several studies with long temporal horizons showing costs below or near the GDP threshold.

A CEA included in this review was by Walter & Per Odin (2015) whom evaluated cost-effectiveness of continuous subcutaneous apomorphine infusion (CSAI) in the treatment of Parkinson's disease in the UK and Germany. The purpose of this analysis was to estimate the cost-effectiveness of CSAI compared with Levodopa/carbidopa intestinal gel (LCIG), Deep-Brain-Stimulation (DBS) and Standard-of-care (SOC). A multi-country Markov-Model to simulate the longterm consequences, disease progression (Hoehn & Yahr stages 3–5, percentage of waking-time in the OFF-state), complications, and adverse events was developed. MonteCarlo simulation accounted for uncertainty. Probabilities werederived from RCT and open-label studies. Costs were estimated from the UK and German healthcare provider's perspective. QALYs, life-years (LYs), and costs were projected over a life-time horizon. They found the UK lifetime costs associated with CSAI amounts to £78,251.49 and generates 2.85 QALYs and 6.28 LYs (E104,500.08, 2.92 QALYs and 6.49 LYs for Germany). Costs associated with LCIG are £130,011.34, achieves 3.06 QALYs and 6.93 LYs (E175,004.43, 3.18 QALYs and 7.18 LYs for Germany). The incremental-cost per QALY gained (ICER) was £244,684.69 (E272,914.58). Costs for DBS are £87,730.22, associated with 2.75 QALYs and 6.38 LYs (E105,737.08, 2.85 QALYs and 6.61 LYs for Germany). CSAI dominates DBS. SOC associated UK costs are £76,793.49; 2.62 QALYs and 5.76 LYs were reached (E90,011.91, 2.73 QALYs and 6 LYs for Germany). CSAI dominates DBS in the UK and show comparable results for Germany. With an ICER of £6440.45 CSAI is cost-effective against SOC in the UK. In Germany the ICER for CSAI is several times higher (E74,695.62) vs SOC. LCIG is associated with the highest costs, with and an ICER of £244,684.69 (vs CSAI) in the UK and E272,914.58 in Germany which exceeds established cost-effectiveness thresholds. From a health care provider perspective, CSAI is a cost-effective therapy and could be considered as a cost-effective alternative to LCIG or DBS for patients with advanced PD.

In this review, Walter and Odin (2015) described that the direct lifetime costs of continuous apomorphine infusion was estimated at £78,251.49 (€57,123.59) and generated 2.85 QALYs in the United Kingdom, and €104,500.08 and 2.92

QALYs in Germany respectively (Table 7), showing this therapy was cost-effective in the UK, but not in Germany. With an ICER of £6440.45, CSAI is cost-effective against standard care in the UK. In Germany the ICER is several times higher (€74,695.62). LCIG is associated with the highest costs and an ICER of £244,684.69 in the UK and €272,914.58 in Germany vs CSAI which exceeds established cost-effectiveness thresholds. CSAI is a cost-effective therapy and could be seen as an alternative treatment to LCIG or DBS for patients with advanced PD. The initial treatment effect and the discount rates exhibit the greatest cost influence.

Another CEA included in the review was conducted by Vivancos-Matellano et al. (2014) in Spain, evaluating cost-effectiveness of the use of Subcutaneous Apomorphine Infusion (CSAI), with levodopa/carbidopa duodenal infusion (LDI) and DBS in Spain. Information on life years gained and quality adjusted life years (QALY) according to Hoehn and Yahr scale was obtained, as well as data on costs and resource use for each of the alternatives. The perspective of the analysis was the National Health System and the time horizon was 5 years for costs and patient´s lifetime for utilities. Outcome measures used were life years gained and QALYs, and incremental cost/utility ratio for comparison. These cost/utility ratios were obtained for each option: €31,956/QALY for DBS, €38,249/QALY for CAIS, and €75,206/QALY for LDI. After five years CSAI was associated with a cost reduction of €124,295 compared to LDI, and a cost increment of €20,871 compared to DBS, with an ICER of €38,249 per QALY, above the GDP of Spain. In the CEA by Vivancos-Matellano et al.(2016) in Spain it was showed that after five years CSAI was associated with a cost reduction of €124,295 compared to IJLI, and a cost increment of €20,871 compared to DBS, with an ICER of €38,249 per QALY, above the GDP of Spain. Future cost-effectiveness analyses should additionally look at non-motor effects and associated improvements in quality of life and reductions in both direct and indirect costs. [44]

Table 7: Cost-effectiveness of advanced therapies (CSAI) in Parkinson's disease (Smilowskaa 2021)

Study	Cost of intervention	QALYs intervention	Comparator	Cost comparator	QALYs comparator	ICER	Incremental cost	GDP/capita	C/E
Walter & Odin 2015	£78,251	2.85	BMT	£76,793	2.62	0.23	€8,822 ($9,792) (RM42,522)	$42,522 UK	Yes
	€104,500	2.92	BMT	€90,012	2.73	0.19	€74,696 ($82,912) (RM360,034)	$47,684 Germany	No
Vivancos-Matellano 2016	€110,348	2.89	IJLI DBS	€234,643 €89,477	3.12 2.80	-0.23 0.09	€38,249 ($42,456) (RM184,360)	$37,310 Spain	No

BMT: Best medical therapy, CSAI: Continuous subcutaneous apomorphine infusion, DBS: deep brain stimulation, IJLI: Intrajejunal levodopa infusion, CE: cost-effective

These were the estimated cost listed for each item relevant to the apomorphine injection or infusion procedure. [45]

- APO-go®1 Injection, apomorphine hydrochloride 10 mg/mL, net price 5-mL amp (£14.62).

- Injection (APO-go® Pen), apomorphine hydrochloride 10 mg/mL, net price 3-mL pen injector (£24.78).
- Injection (APO-go® PFS), apomorphine hydrochloride 5 mg/mL, net price 10-mL prefilled syringe (£14.62).
- APO-go® POD Infusion cartridges, apomorphine hydrochloride 5 mg/mL, net price 20-mL cartridge (£29.24).
- Dacepton®2 Injection cartridges (D-mine- Pen®), apomorphine hydrochloride hemihydrate 10 mg/mL, net price 3-mL cartridge (£24.60).
- Infusion vials (Dacepton®), apomorphine hydrochloride hemihydrate 5 mg/mL, net price 20mL vial (£29.00).

Note: Dacepton® brand of apomorphine pre-filled cartridges has chemical and physical stability for 15 days after first opening, compared to 48 hours for the APO-go® Pen. Dacepton® brand of vials of apomorphine solution for infusion has chemical and physical stability for 7 days after first opening, compared to 24 hours for the APO-go® Pen

According to the Nottinghamshire Area Prescribing Committee, below were the cost estimation of different apomorphine preparation. (Table 8)[40]

Table 8: Relevant apomorphine injection/infusion products for use and its cost

Product	Pack size	Cost	Expiry once in use
APO-go POD (apomorphine hydrochloride hemihydrate) 5mg/ml solution for infusion in cartridge	5	£146.22	48 hours
APO-go PFS 5mg/ml solution for infusion in cartridge	5	£73.11	Single use only
Dacepton 5mg/ml solution for infusion	5	£145.00	7 days
APO-go pen 10mg/ml solution for injection	5	£123.91	48 hours
Dacepton 10mg/ml solution for infusion	5	£123.00	15 days
APO-go ampoule 10mg/ml solution for injection or infusion	5	£73.11	Single use only

Table 9: Estimated cost implication following use of apomorphine injection and infusion

No.	Item	Price / Pack	Price / Unit	Maximum Dose	1 MONTH		1 YEAR	
					Utilization quantity per patient per month (Unit)	Cost per patient per month (RM)	Utilization quantity per patient per year (Unit)	Cost per patient per year (RM)
1	SC Apomorphine 10mg/ml (3ml) - Pen Max dose: 6mg 5 times/day			1 vial/day	30	RM5,202.00	365	RM62,424.00
	Medical Device (for intermittent subcutaneous injection) D'mine PEN			1 pen/ patient	1	RM1,981.20	1	RM1,981.20
	Total					**RM7,183.20**		**RM64,405.20**

2	SC Infusion Apomorphine 5mg/ml (20ml) Max dose: 6mg/hr for 16 hours	[redacted]	[redacted]	1 vial/day	30	RM5,202.00	365	RM62,424.00
	D'mine Pump	[redacted]	[redacted]	1 pump/ patient	1	RM9,144.00	1	RM9,144.00
	D'mine Pump Reservoir	[redacted]	[redacted]	1 reservoir/ day	30	RM1,676.40	365	RM20,116.80
	D'mine Catheter	[redacted]	[redacted]	1 catheter/ day	30	RM666.60	365	RM7,999.20
	Total					**RM16,689.00**		**RM99,684.00**

Using maximum dose of apomorphine, the estimated cost implication on the use of pen injection per patient per month is RM7,200; while for continuous apomorphine infusion per patient per month is around RM16,700. The cost of drug only is estimated [redacted] per month per patient. The cost of pen for injection and infusion pump is one off and the pump's lifespan can extend up to six years. Consumables including reservoir and catheter will be changed accordingly according to its in-use-stability. Nevertheless, this estimation does not take into account calibration/maintenance cost and inflation rate of the drugs and devices. In short, apomorphine injection or infusion, while offering a valuable treatment option for advanced PD, can have significant cost implications. These costs need to be carefully considered in the context of overall PD treatment strategies, individual patient circumstances, and the potential benefits of apomorphine in reducing motor fluctuations and improving quality of life.

5.5 ORGANISATIONAL

A pragmatic and evidence-based clinical pathway, recently published as stepped care for PD, includes firstly confirmation of a diagnosis of APD, a process that can be aided by various screening tools, and then a decision as to which is the best DAT option based on the clinical profile supported by appropriate biomarkers where required (e.g. wearable sensors), patient choice, side effects profile, age, stage of PD, the motor and non-motor burden, and patient lifestyle. The patient's own viewpoint is critical in making any therapeutic choice and their preference for, particular DATs need to be considered and discussed.[46]

To assist clinicians in correctly diagnosing APD, several validated screening tools are available for use in clinical practice.[46] Commonly used tools are the 5-2-1 criteria (≥ 5 doses of oral levodopa per day and/or ≥ 2 hours of OFF time per day and/or ≥ 1 hour of troublesome dyskinesia) which is based a consensus statement of European PD experts along with several non-motor symptoms such as non-motor fluctuations and sleep dysfunction as well as functional

consequences affecting quality of life. The MANAGE-PD is an online tool which can help determine whether current treatment needs further optimisation or if a device-aided option should be considered. The Dutch DAT Screening tool (D-DATS) has also been developed and helps in promoting timely referral and appropriate treatment with DAT in APD.[46]

Needles, Tubing, Pump

Although the manufacturers loan infusion pumps to patients on apomorphine, the tubing and needles for infusion must be prescribed separately. The Neria® lines made by Unomedical have been stability tested with APO-go®, APO-go® POD and Dacepton®. These lines have an attached needle with an adhesive patch, which makes it easy for patients to insert the needle at the correct angle. The GP will need to prescribe apomorphine, lines and sharps bin (the specialist will list the drugs, ancillaries, and consumables to be prescribed in primary care). Batteries for APO-go pumps should be changed approximately every 6 months. The expected battery life for APO-go® POD is approximately 100 infusions, one 3V lithium battery. All new pumps come with a spare battery. [40]

Selection of Patients

The selection for all device-aided therapies in PD should carefully assess the following factors: disease duration, age, levodopa responsiveness, type and severity of levodopa-unresponsive symptoms, cognitive and psychiatric issues and comorbid disorders.

Patients who have shown a good 'on' period response during the initiation stage of apomorphine therapy, but whose overall control remains unsatisfactory using intermittent injections, or who require many and frequent injections, may be transferred to continuous subcutaneous infusion by minipump. Patients who have frequent 'off' periods not controlled by oral/transdermal medication may also be commenced on continuous subcutaneous infusion by minipump without prior use of intermittent injections. Patients selected for treatment with APO-go POD should be capable of setting up an infusion system themselves or else have a responsible carer able to set up an infusion system for them when required. Patients treated with apomorphine will usually need to start domperidone at least two days prior to initiation of therapy. The domperidone dose should be titrated to the lowest effective dose and discontinued whenever possible. Before the decision to initiate domperidone and apomorphine treatment, risk factors for QT interval prolongation in the individual patient should be carefully assessed to ensure that the benefit outweighs the risk. Apomorphine should be initiated in the controlled environment of a clinic. During the titration phase of apomorphine the patient should be supervised by a trained healthcare professional experienced in the treatment of Parkinson's disease (e.g., neurologist). The patient's treatment with levodopa, with or without dopamine agonists, should be optimised before starting APO-go POD treatment.[42]

Guidelines

According to the Polish expert consensus guideline (2024), normally, patients under the age of 70 are eligible for DBS if there is insufficient response to conventional pharmacological therapies and the emergence of clinically relevant motor fluctuations and dyskinesias along with a lack of significant cognitive impairment (excluding mild cognitive impairment), moderate-to-severe depression, significant white matter hyperintensities, or other vascular changes on brain MRI scan. Many patients who do not fulfil these criteria could potentially benefit from the available infusion-based advanced therapies, including apomorphine and LCIG infusion. If patients are older than 70 and not eligible for DBS, then subcutaneous apomorphine infusion is considered the least invasive of all advanced therapies at this stage and can be used. Selecting who is suitable for which therapeutic option is, therefore, a complex challenge. As of July 2024, the Poland's Specialized Treatment Programme (STP) for PD has been updated to include equal access to subcutaneous APO infusion, LCIG infusion and subcutaneous foslevodopa/foscarbidopa infusion.[46]

The European Academy of Neurology/Movement Disorder Society guidelines on the treatment of PD with invasive therapies recommend APO infusion for people with APD in whom fluctuations are not satisfactorily controlled with medication. [47]

The National Institute for Health and Care Excellence (NICE) recommendations for the use of apomorphine in Parkinson's disease conclude that; intermittent apomorphine injections may be used to reduce off- time in people with PD with severe motor complications; continuous subcutaneous infusions of apomorphine may be used to reduce off- time and dyskinesias in people with PD with severe motor complications. Apomorphine should be initiated in the controlled environment of a specialist clinic. Its initiation should be restricted to expert units with facilities for appropriate monitoring. The patient's treatment with levodopa and/or other dopaminergic medications should be optimised before starting apomorphine treatment.[40]

The UK's (NICE) guidelines recommended that it should be started before patients are considered for foslevodopa/foscarbidopa and prior to invasive DATs such as DBS or LCIG, while an APO PEN injection can be used even earlier for managing troublesome predictable OFF periods.[46,48] The National Institute for Health and Care Excellence (NICE) guideline recommends DBS for advanced PD patients, and highlight apomorphine infusion therapy as one of the treatments under BMT.[48]

Initiation of treatment should be performed by consultant neurologist / specialist experienced in the management of PD. Patients should be established on Domperidone. The first dose of apomorphine should be given in the controlled environment of a specialist clinic to establish efficacy, tolerability and appropriate dosage for an adequate patient response. The threshold dose will be determined by the specialist, using incremental dosing schedules. Typically, this can be performed day care unit. For patients requiring continuous

subcutaneous infusions, a specialist nurse will assist in the initiation and titration of the patient's dose and train the patient and / or carer / district nurse on how to set up the infusion.[40]

According to the Malaysian Guideline on PD, patients who experience severe and prolonged "OFF" periods and/or dyskinesia despite optimization of their oral PD medications can be considered for deep brain stimulation (DBS) surgery or pump (infusion) therapy using apomorphine (APO-go®) or jejunal L-dopa (Duodopa®). [49]

Reimbursement

The CADTH Canadian Drug Expert Committee (CDEC) recommends that apomorphine hydrochloride (apomorphine) be reimbursed for the acute, intermittent treatment of hypomobility "off" episodes ("end-of-dose wearing off" and unpredictable "on/off" episodes) in patients with advanced Parkinson's disease (PD), if the following criterion and conditions are met:[41]

Criterion

- Apomorphine should only be used as adjunctive therapy in patients who are receiving optimized PD therapy (levodopa and derivatives and dopaminergic agonists) and still experiencing "off" episodes.

Conditions

- Patients treated with apomorphine should be under the care of a physician with experience in the diagnosis and management of PD.
- Reduction in price.

Registry

The efforts at creating an Indian registry of apomorphine use in PD patients is directed towards raising awareness of this important therapy among neurologists, patient groups and industry who need to ensure that therapies such as apomorphine infusion need to be made available to bespoke populations where a large number of PD patients would be diagnosed.[34]

Barriers

Limited decision-making capabilities in PD patients is an additional barrier in patients with advanced PD, where increasing disease severity and associated cognitive deficits further complicate these capabilities. Other factors of influence include the patient's place of residence, where, for example, patients in rural areas often have limited access to specialised centres providing device-aided therapies for PD. [44]

Implementation facilitators

One of the key factors for successful implementation of device-aided infusion therapies, such as APO and LECIG, in other European countries has been the comprehensive education of PD Nurse Specialists (PDNS) about the products and their use, which allows them to feel empowered and confident when managing these treatment options. The Polish exert consensus guide also highlighted the use and availability of the most up-to-date versions of APO

formulations i.e. an APO PEN injection that can be used for rescue therapy or an APO infusion using a modern POD system. This include the new development for APO infusion, i.e. the APO-go® POD system (Britannia Pharmaceuticals Ltd., Reading, UK) which extends the benefits of the currently pre-filled syringe, which has been designed to support patient autonomy as there is no liquid transfer required and set-up time is reduced. [46]

5.6 SOCIAL

There was no retrievable evidence on apomorphine injection or infusion in Parkinson's disease. A detailed discussion needs to take place with the patient and their family/carer(s) regarding the pros and cons of apomorphine infusion to determine whether it would fit their personal circumstances. Good communication greatly improves the likelihood of successful outcomes and patients should be encouraged to take control of the management of their pump, including inserting the needle under the skin of the abdominal wall. An advantage of apomorphine infusion therapy over other device-aided treatments such as gastro-jejunostomies, is that it can be discontinued much more easily if results are unsatisfactory. Successful treatment requires commitment from patients and their families and continuing encouragement from their doctors and nurses, particularly in the early months of therapy. [50]

5.7 LIMITATION

Our review has several limitations. Although there was no restriction in language during the search, only English full text articles were included in the report. Very few RCT compared head-to-head between the device aided therapies in patients with advanced Parkinson's disease. Many of the studies involved limited or small study population, with lack of long-term data on the measure of effectiveness in the included studies. Heterogeneity of outcomes measured limiting quantitative summary of results. Most of the studies were followed up to one year, hence sustain or long-term improvement in motor or non-motor function following the intervention need to be ascertained. Included studies with high risk of bias may affect methodological quality of this review. Lack of local data on cost and utility of the interventions and comparator in the population of interest prohibit the generation of local cost-utility analysis.

6.0 CONCLUSION

Based on the above review, there was good level of evidences retrieved on apomorphine injection and subcutaneous infusion therapy to be used in the treatment of patients with advanced Parkinson's disease.

Administration of apomorphine injection or infusion showed beneficial effect on motor function namely off time, functional impact of dyskinesia, ON time, improvement in H&Y scale; patient impression of change, quality of life, pain

alleviation, reduction in LEDD and improvement in non-motor function in the patients with advanced Parkinson's disease.

Following apomorphine injection or infusion in patients with advanced Parkinson's disease, evidence demonstrated: -

Motor function

Significant improvement in motor function was observed in the treated patients;

e) Reduction in 'off' time, with difference of 1.89h/day to 3.0±3.18 h/day (by maintenance week 12 and improvement maintained through week 52), compared to placebo. Reduction in daily OFF time was sustained for up to 64 weeks. Pooled data for week 64 showed a mean (SD) change from baseline in daily OFF time of − 3.66 (2.72) hours. Apomorphine ranked the highest in reducing OFF Time (SUCRA 77.2%), followed by ropinirole_PR, pramipexole_IR and other dopamine agonists.
f) Significant reduction in the functional impact of dyskinesia at 6 months and 12 months.
g) Increase in Good ON time (daily ON time without troublesome dyskinesia) of 3.1 ±3.35 h/day by maintenance week 12.. Improvement in ON time without troublesome dyskinesia was sustained for up to 64 weeks. Pooled data for week 64 showed a mean (SD) change from baseline in ON time without troublesome dyskinesia of 3.31 (3.12) hours.
   Apomorphine ranked the highest in increasing good ON time without troublesome dyskinesia (SUCRA 97.08%), followed by pramipexole_IR and ropinirole_PR.
h) Improvement in Hoehn and Yahr (H&Y) scores (scores of 2.5 or less) following CSAI (patients had H&Y score of 3.0 and above at baseline). The H&Y Scale was used to stage their functional disability.

Patient Global Impression of Change (PGI-C)

Significant improvement in PGIC scores, 68% of patients rated themselves as much or very much improved, 62% had at least a 2-hour reduction in daily OFF time by maintenance week 12.

Levodopa and levodopa equivalent daily doses (LEDD)

Significant reduction in levodopa equivalent dose in Apomorphine treated patients compared to placebo, mean concomitant oral levodopa and levodopa equivalent doses had been reduced by 198 mg/day and 283 mg/day, respectively. Improvements were maintained through week 52. LEDD scores significantly decreased from baseline at month 6. At week 64 post treatment, mean (±SD) daily levodopa-equivalent dose decreased from baseline by 543 mg (±674) and levodopa dose by 273 mg (±515) respectively.

Quality of Life

All device-aided therapies demonstrated greater improvements in PD-specific QoL score than BMT at six months, for CSAI (3.61; 95%CI 0.55 to 6.68) LCIG (7.83;95%CI 5.15 to 10.51) and DBS (7.24; 95%CI 5.37 to 9.10). HRQoL remained stable of those who continued treatment 24 months after CSAI initiation, with Parkinson's Disease Questionnaire (PDQ)-39 was the only

baseline predictor of HRQoL improvement after 2 years of treatment. The 8-item Parkinson's Disease Questionnaire (PDQ-8) improvement ranges between 11.3% and 41.9% at the 6-month follow-up. Based on a greater relative change, larger effect size, and smaller number needed to treat, an advantageous effect of apomorphine on QoL was observed in the real-life cohort.

Pain

Following subcutaneous apomorphine administration, significant improvement in nocturnal pain and orofacial pain was showed at 6 month and 12 month from baseline.

Non-motor function

Significant improvement in non-motor function was observed in the treated patients with apomorphine; Using the UPDRS III, the SUCRA values indicated that apomorphine had the best efficacy on the non-motor symptoms of PD (99.0%), followed by Bromocriptine (78.8%), and Piribedil MaHTAS Technology Review vi (75.9%). Significant improvement in Non-Motor Symptom Scale (NMSS) (improvement in various domains; mood/ cognition, perceptual problems/hallucinations, attention/ memory, and the miscellaneous domain), favorable for neuropsychological/ neuropsychiatric NMS. The preserved cognitive function observed over a 12- month follow-up (average 16 months follow up).

Apomorphine was well tolerated without unexpected safety signals. Treated patients reported one or more AEs, which were mostly mild to moderate in severity. Common treatment-related adverse events included infusion site nodules and erythema, nausea, somnolence, dyskinesia, which occurred more frequently during the titration period.

Injection or infusion apomorphine has been granted regulatory approval from the USFDA, indicated for the treatment of motor fluctuations (OFF episodes) in adults with advanced Parkinson's disease. Apomorphine is licensed in UK for use in refractory motor fluctuations in Parkinson's disease ('off' episodes) inadequately controlled by levodopa with dopa-decarboxylase inhibitor or other dopaminergics (for capable and motivated patients under specialist supervision), approved in Canada for the treatment of acute, intermittent hypomobility and "off" ("end-of-dose wearing off" and unpredictable "on/off") episodes in patients with advanced PD, in Ireland and Thailand. In Thailand, the initial use was on a compassionate basis for a group of patients (2013), followed by approval (2015).

A CEA conducted from the national healthcare providers showed this therapy was cost-effective in the UK, but not in Germany (compared to BMT), the direct lifetime costs of continuous apomorphine infusion was estimated at £78,251.49 (€57,123.59) and generated 2.85 QALYs in the United Kingdom, and €104,500.08 and 2.92 QALYs in Germany respectively. With an ICER of £6440.45, CSAI is cost-effective against standard care in the UK. In Germany the ICER is several times higher (€74,695.62). LCIG is associated with the highest costs and an ICER of £244,684.69 in the UK and €272,914.58 in

Germany vs CSAI which exceeds established cost-effectiveness thresholds. CSAI is a cost-effective therapy and could be seen as an alternative treatment to LCIG or DBS for patients with advanced PD. The initial treatment effect and the discount rates exhibit the greatest cost influence. Another CEA demonstrated an ICER of €38,249 per QALY for CSAI compared to IJLI, which is above the GDP of Spain.

The selection for all device-aided therapies in PD should carefully assess the following factors: disease duration, age, levodopa responsiveness, type and severity of levodopa-unresponsive symptoms, cognitive and psychiatric issues and comorbid disorders.

The European Academy of Neurology/Movement Disorder Society guidelines on the treatment of PD with invasive therapies recommend APO infusion for people with advanced PD in whom fluctuations are not satisfactorily controlled with medication. The UK's National Institute for Health and Care Excellence (NICE) guidelines recommended that it should be started before patients are considered for foslevodopa/foscarbidopa and prior to invasive DATs such as DBS or LCIG, while an APO PEN injection can be used even earlier for managing troublesome predictable OFF periods. The NICE recommendations stated that intermittent apomorphine injections may be used to reduce off-time in people with PD with severe motor complications; and continuous subcutaneous infusions of apomorphine may be used to reduce off-time and dyskinesias in people with PD with severe motor complications.

Apomorphine should be initiated in the controlled environment of a clinic. During the titration phase of apomorphine the patient should be supervised by a trained healthcare professional experienced in the treatment of Parkinson's disease. The patient's treatment with levodopa and/or other dopaminergic medications should be optimised before starting apomorphine treatment. Successful treatment requires commitment from patients and their families and continuing encouragement from their doctors and nurses, particularly in the early months of therapy.

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APPENDIX 1: HIERARCHY OF EVIDENCE FOR EFFECTIVENESS

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

APPENDIX 2: SEARCH STRATEGY

Ovid MEDLINE® In-Process & Other Non-indexed Citations and Ovid MEDLINE® 1946 to present

1	apomorphine.tw.	12762
2	apomorphine injection.tw.	128078
3	apomorphine infusion.tw.	42857
4	parkinson's disease.tw.	8015
5	advanced parkinson's disease.tw.	33
6	1 or 2 or 3	5858
7	4 or 5	10421
8	6 and 7	882
10	Limit 8 (human and English)	312

OTHER DATABASES	
EBM Reviews – Cochrane Central Registered of Controlled Trials	Similar MeSH, keywords, limits used as per MEDLINE search
EBM Reviews – Database of Abstracts of Review of Effects	
EBM Reviews – Cochrane database of systematic reviews	
EBM Reviews – Health Technology Assessment	
NHS economic evaluation database	
PubMed	Similar MeSH, keywords, limits used as per MEDLINE search
INAHTA	
US FDA	

APPENDIX 3: EVIDENCE TABLE

Only available upon request.

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