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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, this places an onerous economic burden on society. 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. 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/ aim

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.

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 (1 st Quarter 2025), EBM Reviews-Health Technology Assessment 1 st Quarter 2025), EBM Reviews-NHS Economic Evaluation Database (1 st 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.

Results and conclusion

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: -

Motor function

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

- 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.
- Significant reduction in the functional impact of dyskinesia at 6 months and 12 months.
- 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.
- 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 (75.9%). Significant improvement in Non-Motor Symptom Scale (NMSS) was demonstrated (improvement in various domains; mood/ cognition, perceptual problems/hallucinations, attention/memory, and the miscellaneous domain), favourable for neuropsychological/ neuropsychiatric NMS. The preserved cognitive function demonstrated was 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 dopadecarboxylase 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 apomorphine 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.