CHAPTER FIVE

Subcutaneous foslevodopa/foscarbidopa: A novel 24 h delivery option for levodopa

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1. Introduction

1.1 The need for non oral levodopa based therapies

From the 1960s levodopa has remained the best symptomatic treatment for Parkinson's disease (PD) since its discovery and was even called a "miracle drug," because of its dramatic effect on untreated Parkinsonian patients as immortalized by Ronin Williams in the film "Awakenings." (Website

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Accessed April 2, 2024). The combination of levodopa with peripheral dopa decarboxylase (DDC) inhibitors allowed a fourfold reduction of levodopa dosing and consequentially peripheral and central side effects and conventional levodopa therapy is now administered with either carbidopa or benserazide unless in specific circumstances *Mucuna pruriens* is used (Ray Chaudhuri & Batzu, 2024). However, almost invariably, even 9 months after initiation of treatment with levodopa, fluctuations start (Stocchi et al., 2014) and mild to severe (troublesome) dyskinesias develop. To combat this, in the 1990s and early 2000s several oral levodopa vs dopamine agonist (pramipxole, ropinirole, cabergoline, pergolide) trial were undertaken showing some sparing of dyskinesias with agonist initiation although quality of life and motor scores were better with levodopa. The recognition of impulse control disorders (ICD) and neurosychiatric problems severely limited the use of dopamine agonists from the 2010 onwards. The increased impetus to use levodopa even as initiating therapy for PD was also boosted by the publication of the PDMED study data which showed better benefit with levodopa in terms of motor function and dyskinesias compared to agonists at 7 years follow-up (Gray et al., 2022).

1.1.1 Non oral levodopa therapy and 24 h treatment

Inspite of the often dramatic effects of oral levodopa on motor and nonmotor states in PD (Ray Chaudhuri, Poewe, & Brooks, 2018) problems of absorption exists because of an almost ubiquitous gastrointestinal absorption "block" (Leta et al., 2023). The consequent pulsatile delivery of levodopa to brain is postulated to be the chief cause for the emergence of dyskinesia's and motor and nonmotor fluctuations which continue to pose a huge therapeutic challenge to clinicians and patients. Pulsatile stimulation of the basal ganglia pathways occur secondary to fluctuating plasma levels of levodopa which has a short half-life (approximately 90 min) with a dose-dependent peak and trough pattern during the waking day and flat hypodominergic levels at night. 24 h continuous dopaminergic stimulation (CDS) has been widely proposed to be the best solution to combat the fluctuations and several oral long acting levodopa preparations have been developed and yet not been widely adopted in clinical practice as the gastrointestinal blocks to oral delivery continue to be a problem. Non oral levodopa based 24 h treatment strategies delivering CDS therefore, is a major unmet need and in the wishlist of "ideal" therapy in advanced PD (Fig. 1).

Usually treatment is started with three doses of levodopa per day but the short half-life of levodopa soon necessitates augmentation of therapy. Oral

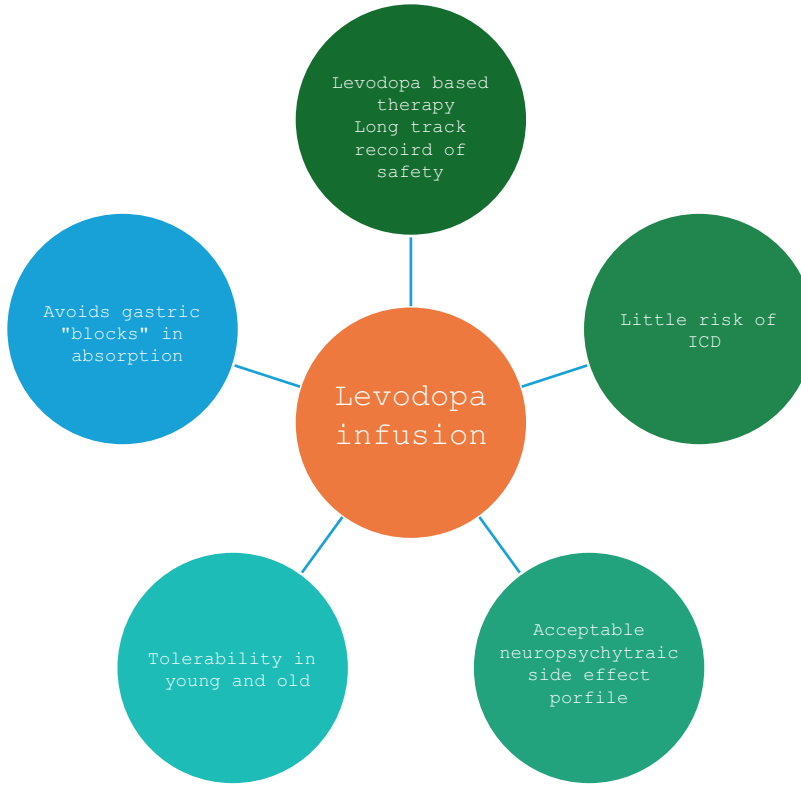

Fig. 1 Potential advantages of levodopa infusion in Parkinson's disease. ICD, impulse control disorder.

dosing of levodopa is often not feasible beyond 4–5 doses/day and compliance becomes an issue and gastric "blocks" to oral levodopa can lead to "no on" or "delayed on" periods. Long acting oral formulations of levodopa have been marketed but not widely available and face the same issues regarding gastric block (Leta et al., 2023).

1.1.2 Non oral levodopa based continuous drug delivery systems

Currently several non-oral levodopa based treatment options are in clinical use or in development as below (Fig. 2)

- Intrajejunal levodopa-carbidopa infusion (duodopa or duopa)
- Lecig: Intrajejunal levodopa-entacapone-carbidopa infusion (lecigon)
- Subcutaneous foslevodopa-foscarbidopa infusion (recent release in Europe, United Kingdom and Japan)

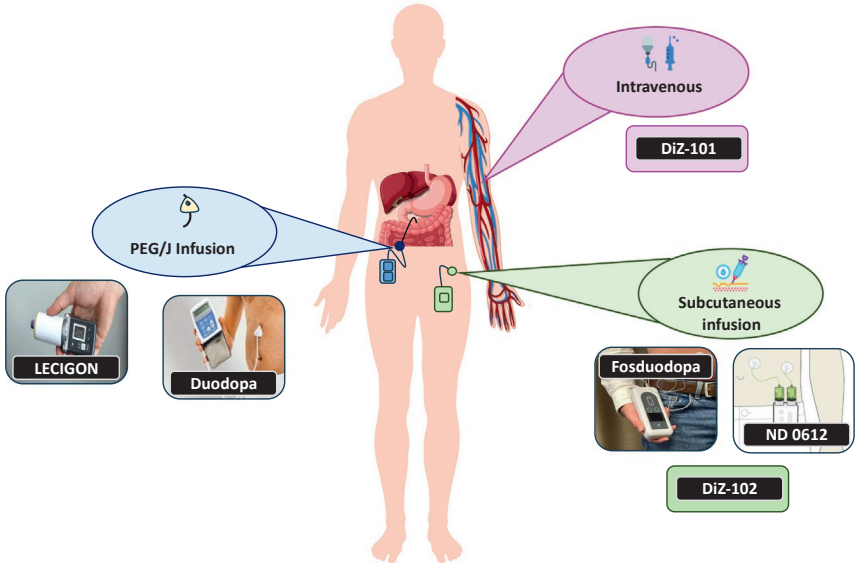

Fig. 2 A figure illustrating currently available or "in trial" levodopa infusion options for Parkinson's disease. PEG, Pecutaneous endoscopic gastrostomy; J, Jejunal. Acknowledgment (Dr Mubasher Qamar).

- Subcutaneous levodopa infusion ND0612 (In development)
- Subcutaneous levodopa (DIZ 101, in development)
- Intravenous levodopa infusion (DIZ 102, In development)

A comparative current analysis of the subcutaneous and intravenous option for levodopa delivery is shown in Table 1. In this review we focus on LDp/CDp as a clinical option to manage advanced PD.

2. Subcutaneous foslevodopa and foscarbidopa

24 h infusion of levodopa remains a key unmet need in real life therapy of PD till the recent licensing of **foslevodopa/foscarbidopa (**LDp/CDp) and publication of a positive trial using subcutaneous levodopa (ND 0612, Espay et al., 2024). In an effort to bridge this gap, Abbvie developed ABBV-951 to provide continuous subcutaneous infusion of LD/CD prodrug which is a solution of prodrugs that are rapidly converted to levodopa and carbidopa upon subcutaneous administration in the skin. This product is now marketed as produodopa (Foslevodopa/foscarbidopa).

Table 1 Comparative analysis foslevodopa/foscarbidopa, ND-0612 (Neuroderm) and DIZ 101/102.

Delivery method	**SC**	**SC**	**SC**	**IV**
Molecule	Levodopa prodrug converted to levodopa in skin	Levodopa	Levodopa	Levodopa
Technology	Vyafuser pump, single needle infusion	ND0612 belt pump, 2 needles and 2 sites infusion	2 Braun space infusion pumps 2 infusion catheters	Venous catheter in arm
pH	7.4 SmPC—take this info from SmPS	NA	Around 5	NA
Dosing	Foslevodopa/ Foscarbidopa	ND 0612	DIZ 102	DIZ 101
Clinical trials	Pivotal randomized double blind, double dummy licensing study	Pivotal randomized double blind, double dummy study	Open label cross over study for pharmacokinetics	
No of patients	174 enrolled	259 randomized	20	
Long-term data	1 year follow-up open label published	Extension phase a multicenter, international, open-label study is ongoing to provide further information on the long-term efficacy and safety of treatment (NCT02726386)	NA	
Nonmotor efficacy	Efficacy on sleep, early morning akinesia and sleep disruption published Significant beneficial effect on PDSS 2 total score and nocturia item	No change in PDSS 2 scores between the groups Daytime sleepiness rates (assessed by ESS,PDSS-2) remained low and comparable between treatment groups	NA	
Skin reaction	Infusion site events 72%	Infusion site events 83%	Skin and subcutaneous tissue disorders—11%	Skin and subcutaneous tissue disorders—5%

Continued

Table 1 Comparative analysis foslevodopa/foscarbidopa, ND-0612 (Neuroderm) and DIZ 101/102.—cont'd

Delivery method	SC	SC	SC	IV
Cost benefit	The societal cost impact of adoption of LDp/CDp if all 17,505 eligible patients in the UK receive treatment is estimated at net savings of £314 M after 2 years, and £953 M after 5 years[a]	Nil	Nil	
Licensing	EMA and NICE approved For European Union (EU) and the UK	III phase	I phase	

[a]From Chaudhuri et al. Foslevodopa/foscarbidopa (LDp/CDp) in advanced Parkinson's Disease (aPD) Demonstration of savings from a societal perspective in the UK. To be presented European Academy of Neurology, 2024.
SmPC, Summary of product characteristics; PDSS-2, Parkinson's disease sleep scale version 2; ESS, Epworth sleepiness scale; EMA, European Medicines Agency; NICE, National Institute of Clinical Excellence.

3. Pharmacokinetics

Ideally an effective "prodrug" that works via subcutaneous (SC) route requires three basic characteristics which include excellent aqueous solubility, chemical stability as well as an efficient and reliable conversion of the prodrug to the active pharmaceutical ingredient which in this case is levodopa. Preclinical studies of foslevodopa/foscarbidopa showed that this drug met the above three criteria with aqueous solubility at physiological pH (>1 g/mL at pH 7.4) and an exceptional chemical stability (<2% decomposition in solution for 1 year) while there is rapid conversion to levodopa carbidopa after SC administration (Cardinal-David et al., 2016). Studies were performed in rats and minipigs where a range of formulation was used and data suggested that a therapeutically relevant levodopa levels can be attained at a range of ratios from 4:1 to 15:1 (Rosebraugh et al., 2021). A highly concentrated (20:1) solution of levodopa/carbidopa prodrugs for s.c. delivery was developed after a range of concentrations (4:1, 10:1, 20:1) were used and showed stability at almost a near normal pH. When a loading dose of foslevodopa/foscarbidopa is used followed by a continuous SC infusion a levodopa steady state is attained in 2 h suggesting the ability of SC foslevodopa/foscarbidopa to maintain a stable levodopa PK profile similar to levodopa/carbidopa intestinal gel infusion (Othman, Rosebraugh,

Chatamra, Locke, & Dutta, 2017). Studies also showed that after SC infusion of foslevodopa there is a reproducible and rapid distribution of active levodopa in the systemic circulation. The pharmacokinetic studies show that a full range of levodopa doses can be delivered to advanced PD patients over a 24 h period using a specially designed 24 h portable pump in much smaller volumes compared to intrajejunal levodopa infusion. Absorption profile of SC foslevodopa/foscarbidopa has been studied in healthy subjects at three different skin sites and data suggest that there is similar levodopa exposure and overlapping pharmacokinetic profile overlapping at the three different sites (Thakkar et al., 2021). In an open-label, 2-way crossover study with randomized sequence in 20 healthy subjects, 24-h levodopa/carbidopa (LDP/CDP) SC abdominal infusion was compared to a 16-h LCIG intrajejunal infusion supplemented by two separate nighttime oral LD/CD doses (Rosebraugh, Stodtmann, Liu, & Facheris, 2022). The data from this study showed that foslevodopa/foscarbidopa SC infusion generated similar levodopa levels to LCIG infusion over the 16-h interval but also maintained levodopa levels throughout the nighttime period thus providing real 24 h cover.

4. Clinical trials

Several phase 1 and phase 3 clinical trials in PD patients have been performed to address and assess the PK, safety profile as well as clinical efficacy of foslevodopa/foscarbidopa (clinicaltrials.gov NCT03033498, NCT03374917, NCT03781167, NCT04379050, and NCT04380142) (Rosebraugh et al., 2021). Two main trials have been reported thus far with foslevodopa/foscarbidopa in PD. The licensing trial of foslevodopa/foscarbidopa was a 12 week randomized, double-blind, double-dummy, active-controlled study with centers in the United States and Australia (NCT04380142) and enrolled 174 patients of whom 141 was randomized to continuous subcutaneous infusion of foslevodopa/foscarbidopa plus oral placebo capsules ($n = 74$) or oral encapsulated immediate-release levodopa-carbidopa plus continuous subcutaneous infusion of placebo solution ($n = 67$ (Soileau et al., 2022). Primary outcome measures was the change from baseline to week 12 of the double-blind treatment period in hours of average daily normalized on time without troublesome dyskinesia which was defined by using the Parkinson's disease diary. Several secondary endpoints were used in an hierarchical order of analysis and included change of daily normalized off time from baseline to week 12, motor aspects of experiences of daily living and the presence of morning akinesia. Morning

akinesia was defined by patient reported off state in the Parkinson's disease diary during the first half-hour period on waking. In addition, Parkinson's disease Sleep Scale-2 (PDSS-2) total score, Parkinson's disease Questionaire-39 (PDQ-39) summary index, EQ-5D-5L summary index were also assessed.

Foslevodopa-foscarbidopa infusion showed a significantly greater increase in on time without troublesome dyskinesia (Good on) of 1.75 h, $P = 0.0083$) and a significantly greater reduction in off time (−1.79 h, $P = 0.0054$). Importantly data also showed that the foslevodopa-foscarbidopa ambulatory drug-device was able to deliver a range of therapeutically effective doses of foslevodopa (approximately 600–4250 mg/day levodopa equivalents) while infusion rates could be adjusted in small increments (approximately 1.7 mg of levodopa per h) allowing for personalized medicine delivery (Soileau et al., 2022). The study also reported a lower incidence of falls in the foslevodopa/foscarbidopa arm compared to the oral levodopa-carbidopa arm. A post hoc analysis of single items related to gait and freezing (UPDRS items 2.12, 2.13, 3.10–3.13) from LDp/CDp registration trials was reported by Odin et al. and significant improvements from baseline to week 12 in walking and balance, freezing and gait compared to oral levodopa therapy was reported in the double blind trials. Analysis of the open label trial also indicated a significant improvements from baseline in walking and balance and freezing at weeks 13 and 52 but gait, postural stability, and posture worsened vs baseline at week 52. The implications of this data is therefore uncertain and further studies addressing gait and the effect of foslevodopa/foscarbidopa are warranted (Odin et al., 2023).

In an open label long-term study, Aldred et al. (2023) reported data from a 52-week, open label international phase 3 registrational trial (NCT03781167) which evaluated safety/tolerability and long-term and efficacy of 24-h/day SC foslevodopa/foscarbidopa in advanced PD (Aldred et al., 2023. Study demographics indicated a 13.9% Asian PD patient recruitment but only 1 black subject. 244 patients were enrolled and 137 completed treatment. The data at 52 weeks follow-up mirrored the pivotal licensing trial and there was significant improvement in "On" time without troublesome dyskinesia (3.8 [3.3] h) as well as reduction in "Off" time (−3.5 [3.1]) compared to baseline. There was improvement in quality of life (QoL) and motor complications noted at week 1 after foslevodopa/foscarbidopa and sustained throughout the 52-week treatment period. Improvements in the PDQ-39 Summary Index included domains of mobility, activities of daily living, stigma, and bodily discomfort and was

accompanied by improvements in the EQ-5D-5L summary index and visual analog scale scores at all study time points ($P = 0.001$ for all). In patients initiated on foslevodopa/foscarbidopa over 30% could achieve monotherapy with LDP/CDP by week 52 with a 10.3% reduction in the number of patients taking ≥3 PD medications with maintenance of a stable levodopa equivalent dosing over time (range, 1621.9–1847.0 mg/day).

5. Foslevodopa/foscarbidopa specific effects: Early morning off related akinesia (EMO) and effect on sleep

EMO leads to morning akinesia and can occur in over 60% of levodopa treated PD patients and is often associated with severe nonmotor fluctuations such as pain, anxiety, urinary urgency (Rizos et al., 2014). Aldred et al. studied nighttime effect of foslevodopa/foscarbidopa and morning akinesias was defined by patient reported "Off" as the main motor status during the first half hour period on awakening. At 52 weeks there were approximately 50% fewer patients who reported early morning akinesia compared to baseline and overall there was a significant reduction in the percentage of patients experiencing EMO, which was reduced from 77.7% at baseline to 27.8% at week 52 with a sharp drop noted at week 1 (77.7–31%) Fig. 3. The improvement in EMO and akinesia time was associated with patients who reported a good on time on waking (62.2% at week 52).

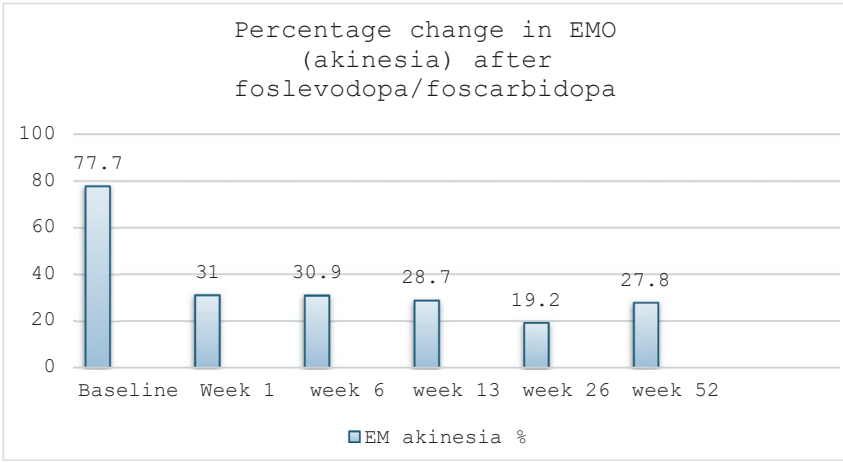

Fig. 3 Percentage change in early morning off period (akinesia) as reported from Parkinson's diary in the study by Aldred et al., 2023.

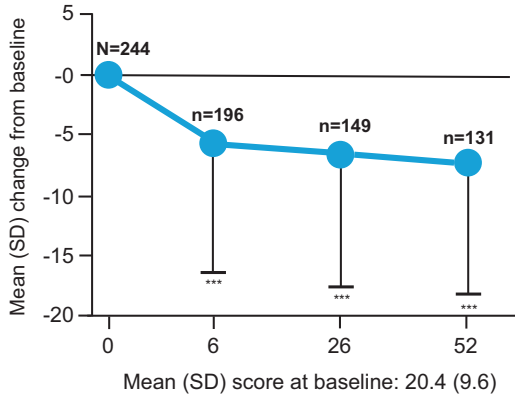

Fig. 4 Sleep quality report using PDSS 2 scale total score in 244 subjects on Foslevodopa/foscarbidopa (Ray Chaudhuri, Bergmann, et al. (2024) and Ray Chaudhuri, Facheris, et al. (2024)). PDSS, Parkinson's disease sleep scale; N, Number of patients at weeks 0, 6, 26 and 52.

Ray Chaudhuri, Bergmann, et al. (2024) and Ray Chaudhuri, Facheris, et al. (2024) reported an interim post hoc analysis from the Aldred et al. study using the Parkinson's Disease Sleep Scale-2, the Parkinson's Disease Questionnaire-39 [PDQ-39] and m-EDL (Movement Disorder Society-Unified Parkinson's Disease Scale Part II (Ray Chaudhuri, Bergmann, et al., 2024; Ray Chaudhuri, Facheris, et al., 2024). At baseline, the PDSS-2 and PDQ-39 scores were correlated ($r = 0.44$; $P < 0.001$; $n = 222$) which suggested that impaired sleep was associated with negative QoL. Following foslevodopa/foscarbidopa, PDSS-2 scores improved (Fig. 4) and the improvements from baseline to week 26 showed a weak but significant positive correlation with both improvements in "Off" time ($r = 0.37$; $P < 0.001$; $n = 88$) as well as quality of life as measured by PDQ-39 scores ($r = 0.36$; $P < 0.001$; $n = 104$).

6. Nocturia

In PD, bladder function is in part mediated through dopamine D1 receptor activity and levodopa exerts a dopamine D1 effect (Sakakibara et al., 2011). It is attractive therefore, to address if foslevodopa/foscarbidopa could have an effect on nocturia which is widely prevalent nonmotor symptoms of PD causing nocturnal sleep disruption. A post hoc data analysis from the 12-week pivotal trial (NCT04380142) and 52-week open-label safety study of fospevodopa/foscarbidopa (NCT03781167) in PD has been

reported in an abstract form by Ray Chaudhuri, Bergmann, et al. (2024) and Ray Chaudhuri, Facheris, et al. (2024) using a mixed effects regression model and analysis of covariance. Mean changes in nocturia (the item 8 score of the Parkinson's Disease Sleep Scal—2 over time was measured and significant improvement in nocturia symptoms (a reduction in mean PDSS-2 item 8 score) from BL to week 12 ($P < 0.01$) compared to oral levodopa was reported. Furthermore, in the open-label study of Aldred et al. (2023), a significant reduction in the mean PDSS-2 item 8 score were noted at weeks 6, 13, 26, and 52, compared with BL ($P < 0.001$ for all comparisons). These data are intriguing and should prompt further trials to explore whether the D1 agonism effect of foslevodopa/foscarbidopa combined with a robust nighttime dopaminergic stimulation may be a beneficial way to tackle nocturia.

The above post hoc data analysis strengthens the 24 h role of foslevodopa/foscarbidopa and shows efficacy on sleep maintenance in PD by addressing troublesome EMO with akinesia and also improvement in nocturia. Further focused prospective focused trial are now required.

7. Cost benefit analysis

Chaudhuri et al. have recently reported evidence from clinical trials data and also real-world evidence to drive a cost-utility model comparing LDp/CDp with reasonable best medical treatment (BMT) as accepted by the UK National Institute of Health and Care Excellence. A state-specific cost estimates were applied to the modeled aPD patient population taking into account direct medical, direct non-medical and indirect costs. The authors estimate that the use of LDp/CDp in the toal UK advanced PD population would amount to a net saving in LDp/CDp-treated patients of £73.1 million in year 1 which can rise to a saving of £95.4 million in year 5 (Ray Chaudhuri, Bergmann, et al., 2024).

8. Safety

In the pivotal licensing double dummy study of LDp/CDp vs oral levodopa, adverse events were reported in 63 (85%) foslevodopa-foscarbidopa participants and in 42 (63%) levodopa-carbidopa participants. Importantly the incidences of serious adverse events were similar between the groups. Major side effects were related to infusion site adverse events

in the foslevodopa/foscarbidopa with erythema [27%], local site pain [26%], cellulitis [19%] and skin oedema [12%]. Most adverse events were non-serious and mild or moderate in severity and serious adverse events were noted in 9% of the LDp/CDp arm and included hallucinations and psychosis in 15% as reported in the 12 week trial (Soileau et al., 2022). It is worth noting that the trial regime was fixed and did not allow any nighttime dose-modifications which could have contributed to the reported hallucinations. One anticipates that in real life, dosing can be adjusted with the commercially available pump. In the 12 months open label phase 3 study (Aldred et al., 2023), there were serious adverse events reported in 25.8% of patients and included infusion site cellulitis (4.1%) and infusion site abscess (3.3%) and these were in line with the pivotal studies. Majority of AEs were nonserious, mild or moderate in severity, and resolved with appropriate care and time. It is envisaged that personalized dosing of foslevodopa/foscarbidopa using the porgrammable portable pump system as well as nursing and home care could substantially reduce the problems of skin reactions.

9. Conclusions

Levodopa remains the gold standard of symptomatic treatment of PD and nonoral delivery with intrajejunal levodopa infusion showed significant advantages over oral delivery in advanced PD in terms of long-term control of motor and nonmotor symptoms. However, surgical side effects as well as device related issues complicate delivery of the intrajejunal levodopa in some patients and as such subcutaneous delivery to achieve true 24 h continuous levodopa delivery has been the subject of clinical development for many years. Subcutaneous foslevodopa/foscarbidopa has become the first such prodrug of levodopa/carbidopa to be licensed in several European countries, UK and Japan and represent a major advancement in the medical device aided therapy for advanced PD. Pivotal and open label long-term studies show continued efficacy with increase of good on as well as reduction of motor off periods and a substantial improvement in time to on waking as well as improvement in early morning akinesia and Parkinson's disease sleep scale scores. Further studies are now under way and preliminary data from the United Kingdom also suggest substantial cost savings. Subcutaneous foslevdopa/foscarbidopa therefore, represents a major therapeutic advance in the pathway of care for advanced PD.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

K. P. D. and K. R. C. conceptualized and designed and wrote the review.

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