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Review

Levodopa-Carbidopa Intestinal Gel may improve treatment-resistant freezing of gait in Parkinson's disease

Melanie R. Shackleford [a], Virendra Mishra [b], Zoltan Mari [b]

[a] Kirk Kerkorian School of Medicine at University of Nevada, 2040 W Charleston Blvd 3rd Floor, Las Vegas, NV 89102, United States
[b] Cleveland Clinic Lou Ruvo Center for Brain Health, 888 W Bonneville Ave, Las Vegas, NV 89106, United States

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ABSTRACT

Introduction: Freezing of gait (FOG) is a highly disabling symptom in Parkinson's Disease (PD) with varying degree of benefits from oral dopaminergic medications and several subtypes that present with different medication states (e.g., off FOG, on FOG, pseudo-on FOG, supra-on FOG). Levodopa-Carbidopa Intestinal Gel (LCIG) greatly reduces the variability of cerebral dopamine replacement inherent to oral therapies by continuous levodopa intestinal infusion. While LCIG may be superior to oral therapy in its ability to treat motor fluctuations and minimize off-time, there is no consensus regarding the overall effectiveness of LCIG specifically for the treatment of FOG in PD patients.

Methods: A systematic literature review was conducted to understand the efficacy of LCIG to treat FOG in PD patients. A PubMed search was conducted using the search query "Intestinal AND (Levodopa OR L-dopa) AND Freezing of Gait AND Parkinson." Additional eligibility criteria included articles written in English and currently published journal articles. Articles were excluded if they did not have a clinical design or if they did not yield reportable data on FOG.

Results: The literature search yielded 16 articles, of which 10 articles were included. Of the 10 studies included, there were 3 retrospective studies, 6 case reports or case series, and 1 open-label study. (n = 449 patients total and 318 FOG patients). Nine of the 10 studies concluded that LCIG has a favorable effect on FOG, though the metrics to evaluate benefits of LCIG on FOG varied among the articles.

Conclusion: LCIG may be an effective treatment for PD patients suffering from FOG including those with poor response to oral medication, likely because of its ability to maintain steadier dopamine levels. Further research is necessary on LCIG as a therapy for refractory FOG, with particular attention to the different subtypes of FOG.

1. Introduction

Parkinson's Disease (PD) is the second most common neurodegenerative disorder with overwhelming public health impact. [1] The cardinal motor symptoms of PD are resting tremor, bradykinesia, and rigidity. [2–5] Additionally, advanced PD patients often experience freezing of gait (FOG) which is a particularly disabling symptom as it is relatively resistant to traditional treatments that are usually more effective for other motor symptoms in PD [6,7]. FOG is a significant cause of falls, loss of autonomy, and decreased quality of life in PD patients and poses a major challenge for caregivers.[8] FOG is characterized by the acute, intermittent inability to walk despite the intention to move forward. [6,9] Patients with FOG report feeling as if they are stuck to the ground and exhibit short, rapid steps without forward locomotion as they attempt to overcome FOG. [10] Despite its increased prevalence in later disease stages, [11,12] multiple studies suggest that the pathophysiology of FOG is different from that of other motor symptoms, which typically worsen with disease progression [12–14]. The development of FOG in advanced disease is often associated with symptoms in non-motor domains [15], including executive functioning [16], while its severity does not necessarily correlate closely with the progression of motor symptoms [7,12]. Additionally, FOG has been observed in other neurological conditions including normal pressure hydrocephalus, vascular parkinsonism, and progressive supranuclear palsy, further suggesting that its pathophysiology is not specifically connected to classic motor symptoms of PD [9].

Abbreviations: LCIG, Levodopa-Carbidop Intestional Gel; FOG, Freezing of Gait; PD, Parkinson's Disease.

E-mail address: mariz@ccf.org (Z. Mari).

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1.1. Freezing of Gait and Levodopa: A historical perspective

The relationship between FOG and levodopa therapy is debated. While levodopa therapy has been shown to improve a multitude of motor symptoms in PD including tremor, bradykinesia, and rigidity, FOG is generally known to have a less consistent and predictable response to levodopa. It has even been suggested that FOG is a levodopa-resistant symptom. [6] Moreover, some studies suggested that long-term levodopa use contributes to the pathogenesis of FOG [7,17–19]. A study by Ambani et al. described patients who developed difficulties initiating gait as a side effect of long-term levodopa therapy.[19] This was labeled as "long-term levodopa syndrome," "akinesia paradoxica," or "start hesitation."[19] Similar conclusions were derived by a study by Giladi et al. that levodopa and dopamine agonists are responsible for the development of FOG in patients on long-term therapy.[7] In a recent historical review of films and medical textbooks [17], the prevalence of FOG in PD patients was found to be increased after the introduction of levodopa, which was further supported by a case series on a group of patients with MPTP-induced parkinsonism, in which none of the drug-naïve patients developed FOG, but one patient developed FOG after 6 years of levodopa therapy.[20] However, this historical review was refuted with the arguments that i) cinematography was not sensitive enough to detect FOG episodes, and ii) FOG was indeed prevalent in the pre-levodopa era.[21] Additionally, cohort studies of PD patients show the presence of FOG in drug-naïve patients[22,23], which further suggests that levodopa does not induce FOG.[21] Further, the presence of FOG during on-states may be a result of increased mobility overall [13].

1.2. Freezing of Gait and Levodopa: Current opinions

Levodopa is arguably the most potent and most commonly used medication for the symptomatic treatment of PD, but not all symptoms of PD respond to the same dosage of levodopa. The subtypes of FOG (off-FOG, on-FOG, pseudo-on FOG) have different responses to levodopa therapy. [24] Off-freezing occurs during the off-state and commonly accompanies other motor symptoms of PD including bradykinesia and rigidity. [24] Levodopa is generally effective for treating off-freezing because it reduces time spent in the off-state. [25,26] On the other hand, on-freezing responds poorly to and may even be exacerbated by oral levodopa. [24–29] On-freezing poses therapeutic challenges; reducing the dosage of levodopa may alleviate the severity of FOG episodes but may not be optimal for other motor syptoms or minimizing adverse effects. [24,30] However, the relationship between FOG and levodopa remains incompletely understood. [27,29,31].

1.3. LCIG treatment

L-dopa levels in PD patients must be carefully maintained within a progressively narrowing therapeutic window to maximize on-time and minimize dyskinesias and wearing-off effects. [27] Oral administration of levodopa can create further challenges to managing its narrowing therapeutic window: gastrointestinal factors such as rate of gastric emptying [27,32], intestinal motility, or presence of dietary amino acids which may compete with levodopa for absorption and transport [33] may influence the on and off states in PD patients. The LCIG pump was designed to deliver continuous intra-jejunal infusion of L-dopa-carbidopa and is administered via percutaneous endoscopic gastrostomy with jejunal extension (PEG-J) connected to a portable infusion pump. [34,35] The LCIG pump bypasses the stomach and administers small, frequent doses of the drug directly into the proximal jejunum, thereby maintaining a constant plasma levodopa level and minimizing dopamine fluctuations in the brain. [35–37] The ability of LCIG to improve motor features of PD by increasing on-time, decreasing off-time, and reducing dyskinesias are well-characterized. [36–39] LCIG may also improve the overall quality of life and non-motor symptoms (autonomic functions, fatigue, somnolence), although the association is weaker. [36,38].

Since FOG is a PD symptom that may be exacerbated by routine fluctuations in dopamine levels secondary to oral levodopa administration, LCIG may be a promising treatment because it maintains stable dopamine levels throughout the day. Additionally, many patients have difficulty tolerating high oral doses of levodopa due to adverse effects (nausea, vomiting, etc.) [27] and as a result may be taking a dose that may be insufficient to control their FOG. LCIG may provide a solution to this by bypassing the upper gastrointestinal tract. However, the effects of LCIG on managing FOG are currently poorly understood. This systematic literature review focuses on assessing current findings on the effects of LCIG administration on PD-FOG.

2. Methods

A systematic literature review was conducted to identify relevant articles. A PubMed search was conducted on January 11, 2022 using the search query "Intestinal AND (Levodopa OR L-dopa) AND Freezing of Gait AND Parkinson." (Fig. 1) Additional eligibility criteria included articles written in English and currently published journal articles. Articles were excluded if they did not have a clinical design or if they did not yield reportable data relevant to LCIG and FOG. Abstracts were screened for inclusion and exclusion criteria, followed by assessment of the full text of the remaining articles. The literature search and selection of papers was performed by MS and independently verified by VM and ZM. Only data pertaining to FOG as reported by the UPDRS II or UPDRS III [40], Freezing of Gait Questionnaire (FOG-Q) [41], or New Freezing of Gait Questionnaire (NFOG-Q) [42] were collected in this systematic review. The data extracted from each study were the type of study, sample size, year, treatment duration, FOG metric, number of improved patients, and FOG subtypes. Data on other motor and non-motor symptoms of PD were not collected because the authors believe these are already well-characterized in the literature on LCIG, and we direct the readers to other systematic reviews [36–38] for more information pertaining to this.

A Q-test for heterogeneity was performed as outlined in Wang 2018. [43] We analyzed the number of patients who had reduced FOG to a significant degree compared to the number of FOG patients enrolled in the studies. Case studies were excluded from statistical tests due to lack of power. The data was transformed using the double-arcsine transformation and the summary effect size was calculated according to the random-effects model and Restricted Maximum Likelihood Method (REML).

3. Results

The search yielded 16 articles, of which we included 10. Thakkar et al. [44] was excluded because it was a literature review on 24-hour LCIG compared to 16-hour LCIG without reportable data relevant to FOG. Vijiaratnam et al. [45] was excluded because it examined patient outcomes following a modification to standard LCIG procedure, but did not evaluate the effectiveness of LCIG on FOG. Katoaka et al. [46] was excluded because it was a case report that did not discuss the FOG outcomes following LCIG administration. Chang et al. [47] was excluded because it reported the effects of switching from 16-hour to 24-hour LCIG in patients with unresponsive FOG. Morgante et al. [48] was excluded because it primarily examined the role of advanced age in LCIG therapy; they compared "late elderly" (>80 years old) PD patients who had received LCIG to matched controls who were < 75 years old and received LCIG. Both groups of subjects received LCIG, so there was no metric of comparing LCIG to refractory oral therapy. Okajima et al. [49] was not an eligible study because it is not written in English.

Of the 10 studies included, there were 3 retrospective studies, 6 case reports or case series, and 1 open-label study. (n = 449 patients total, n = 318 FOG patients). (Table 1).

FOG effect was measured by responses on the Freezing of Gait

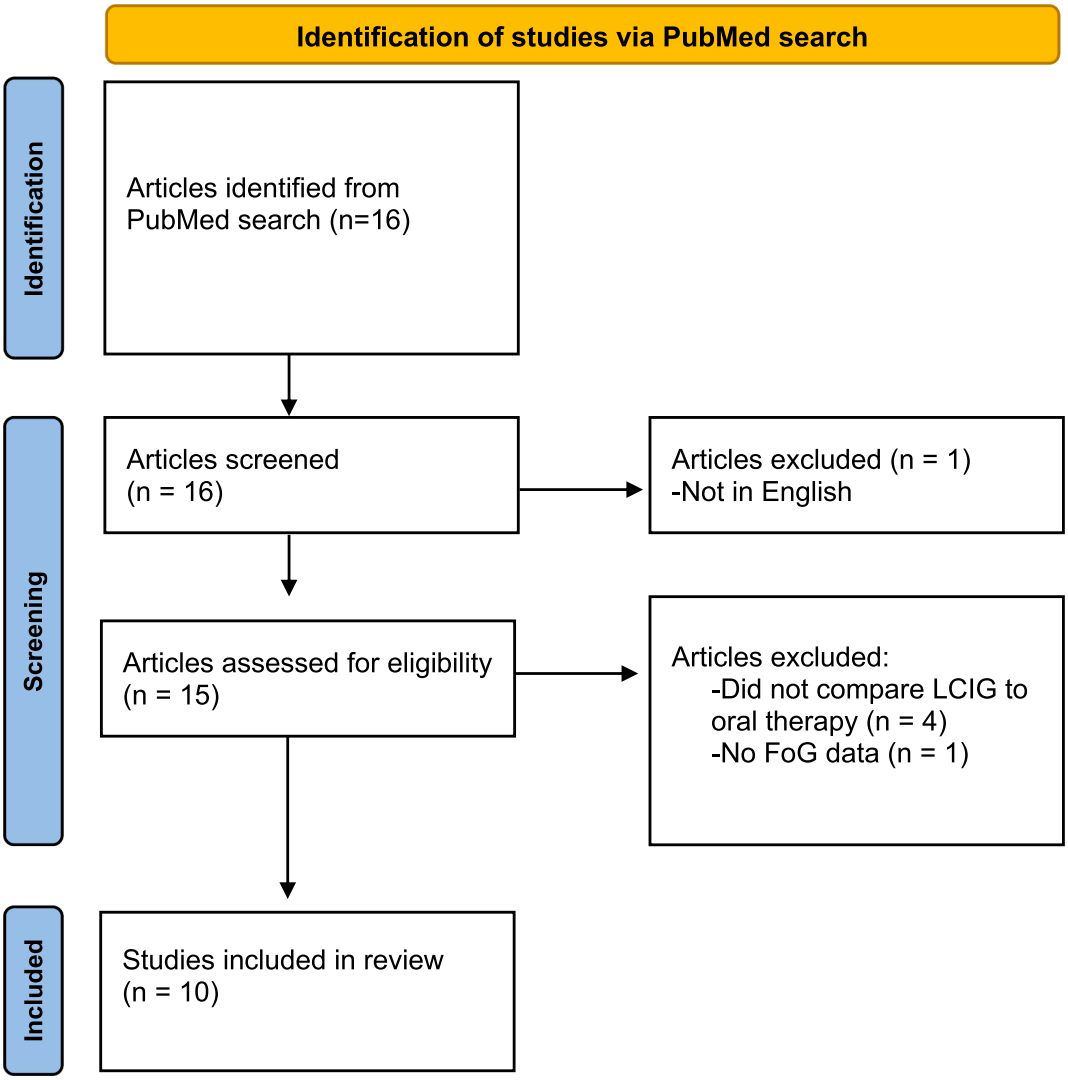

Fig. 1. Literature flow diagram depicting the identification of appropriate studies via PubMed search. In the Screening phase, articles were excluded if they were not in English, if they did not compare LCIG to oral therapy, and if they did not report data on freezing of gait. 10 of 16 studies were ultimately included in this review.

Questionnaire (FOG-Q) [41], New Freezing of Gait Questionnaire (NFOG-Q)[42], UPDRS [40], or by clinician assessment.

The Q-test for heterogeneity yielded a Q-statistic of 12.4372 ($p = 0.0293$) and an I-squared value of 68.91%. This indicates a high degree of heterogeneity between the studies. A forest plot of the summary proportions are reported in Fig. 2. Fabbri et al. [50] was excluded from the statistical analysis because they did not report the total number of patients whose FOG improved. Because of the high degree of heterogeneity, the studies were not sufficiently uniform to arrive at a pooled summary estimate. [51] A *meta*-analysis was therefore not possible. Additionally, a moderator analysis to determine the degree to which certain study characteristics contributed to the heterogeneity was not possible because of the small number of studies (<10) in this review. [43,51].

The remainder of this Results section will be a descriptive analysis of the included studies. Each article is categorized below according to study design.

3.1. Observational Open-Label studies

Rispoli et al. [52] conducted an observational, open-label study of fifteen patients receiving LCIG. They used FOG classification outlined in Espay et al.[24] to categorize patients as off FOG, pseudo-on FOG, and on FOG. The researchers conducted a follow-up at fifty-two weeks and found that all three subtypes (off FOG, pseudo-on FOG, and on FOG) saw an improvement in FOG.

3.2. Retrospective studies

Fabbri et al. [50] performed a retrospective study on the effects of LCIG on axial signs and FOG. The researchers found that FOG remains stable for about one year compared to the patients' baseline off-states, but subsequently deteriorates, especially after four years of treatment.

Antonini et al. [53] performed a twelve-month retrospective and prospective investigation on 159 patients who received LCIG. They found a significant reduction in frequency of FOG following LCIG that was sustained during a 12-month follow-up period.

Valldeoriola et al. [54] performed an observational, cross-sectional, retrospective study of 177 Spanish patients from 18 Movement Disorder centers. They found that LCIG improved FOG and tremor, as well as various nonmotor symptoms. The mean treatment duration was 34.7 months with 80.8% of patients treated for at least twelve months.

3.3. Case series

Cossu et al. [55] performed a retrospective chart review on seven

Table 1
summarizes the studies that evaluated FOG outcomes following LCIG therapy.

Title	Authors	Design	FOG Metric	Findings
1. Intestinal Levodopa/Carbidopa Infusion as a Therapeutic Option for Unresponsive Freezing of Gait after Deep Brain Stimulation in Parkinson's Disease	González-Herrero et al.	Retrospective case series of 5 patients who received STN DBS stimulation, developed unresponsive FOG, and received intestinal levodopa as an alternative therapy.	UPDRS item 14 score before and after LCIG infusion	Administration of intestinal levodopa caused improvement of FOG in the "ON" state in 4/5 patients (80%). The improvement was maintained for at least 12 months.
2. The TANDEM investigation: efficacy and tolerability oflevodopa-carbidopa intestinal gel in (LCIG) advanced Parkinson's disease patients	Antonini et al.	Retrospective and prospective study of 159 PD patients who were already being treated with LCIG. The efficacy and safety of LCIG treatment in routine medical care were retrospectively collected at baseline and prospectively assessed and two follow-up visits within the first 12 months following PEG-J placement.	UPDRS II	Freezing of gait was reduced ($p < 0.001$) at the 2 follow-up visits following PEG-J placement.
3. "On–State" Freezing of Gait: Insights and Treatment With Levodopa Intestinal Gel Infusion	Morales-Briceño H, Tsui D, Griffith J, Martin AJ, Mahant N, Fung VSC.	Case report on a 61F PD patient with on-state FOG who received LCIG.	Investigator assessment, number of falls	The patient exhibited supra-on FOG following LCIG, which improved after titration.
4. Levodopa/carbidopa intestinal gel infusion can improve camptocormia in Parkinson's disease	Morales-Briceño H, Mahant N, Duma S, Martin A, Griffith J, Tsui D, Fung VS.	Case report on 2 patients who received LCIG.	New Freezing of Gait Questionnaire (NFOG-Q)	Both patients exhibited a reduction in freezing of gait.
5. Long-term effect of levodopa-carbidopa intestinal gel on axial signs in Parkinson's disease	Fabbri et al.	Retrospective study on 49 PD patients treated with LCIG.	UPDRS-II Item 14	FOG improved compared to baseline off-state, and remained stable up to 1 year ($p < 0.05$) but subsequently deteriorated.
6. Levodopa/Carbidopa Intestinal Gel Infusion Therapy: Focus on Gait and Balance	Rispoli et al.	Observational open-label study. Motor status and FOG of 15 PD patients were followed for 52 weeks of LCIG infusion. Subjects were classified as having off-FOG, on-FOG, and pseudo-on-FOG according to the classification outlined in Espay et al. [29]	Freezing of Gait Questionnaire (FOG-Q), New Freezing of Gait Questionnaire (NFOG-Q),	LCIG had a beneficial effect on all FOG subtypes ($p < 0.001$).
7. Effects of intestinal Levodopa infusion on freezing of gait in Parkinson disease	Zibetti et al.	Case series on 32 PD patients with FOG who received LCIG. Subjects were classified into 4 subtypes of FOG: off-FOG, pseudo-on FOG, unresponsive FOG, true-on FOG.	UPDRS item 14	FOG improved after LCIG compared to baseline off-state ($p < 0.05$) and baseline on-state ($p < 0.05$).
8. Long-term effectiveness of levodopa-carbidopa intestinal gel in 177 Spanish patients with advanced Parkinson's disease	Valldeoriola et al.	Retrospective study of 177 patients who received LCIG	UPDRS III, investigator assessment	FOG improved in 76.2% of patients ($p < 0.05$).
9. Levodopa-carbidopa intrajejunal gel in advanced Parkinson disease with "on" freezing of gait	Cossu et al.	Chart review of 7 patients who presented with on-FOG before switching from levodopa to LCIG therapy.	UPDRS II and III; FOG-Q	Subjects significantly improved UPDRS item 14 scores ($p = 0.026$) and FOG-Q ($p = 0.017$)
10. Levodopa-carbidopa intestinal gel therapy may cause "Supra-ON freezing of gate" in patients with Parkinson's disease with diphasic dyskinesia	Oshiro S, Baba T, Takeda A	2 case reports on 2 patients with diphasic dyskinesia who received LCIG.	UPDRS III, investigator assessment	Both subjects developed supra-on FOG following LCIG, which improved after titration.

patients who received LCIG who previously presented with on-FOG refractory to oral therapy. The median LCIG treatment duration was twelve months. All seven patients saw an improvement in FOG after initiation of LCIG therapy. This study concluded that LCIG was an effective therapy for patients with on-FOG or pseudo-on FOG.

Zibetti et al. [56] performed a retrospective case series of thirty-two FOG patients who received LCIG. LCIG improved FOG in patients with off-FOG by reducing off-time. LCIG also improved FOG in patients with pseudo-on FOG, which was attributed to reduced dopamine fluctuations. [56] These results were measured at a mean follow-up time of 30 months.

González-Herrero et al. [57] found that LCIG was effective in patients who had previously received deep brain stimulation of the subthalamic nucleus (STN-DBS) and later developed FOG refractory to levodopa therapy. They performed a retrospective case series on five patients who had received STN-DBS and subsequently developed levodopa-unresponsive FOG that appeared in both off and on-states.[57] These patients received LCIG as an alternative therapy; DBS was switched off to better isolate the effects of LCIG. Effects were measured for twelve months following LCIG. Three of the five patients saw significant improvement in FOG following LCIG therapy. One patient continued to have on-freezing and discontinued LCIG. Two patients remained on dual therapy following the study with both LCIG and STN-DBS. Four of the five patients had improved FOG with LCIG.

3.4. Case reports

Morales-Briceño et al. 2020 [58] is a case report on a 61-year-old

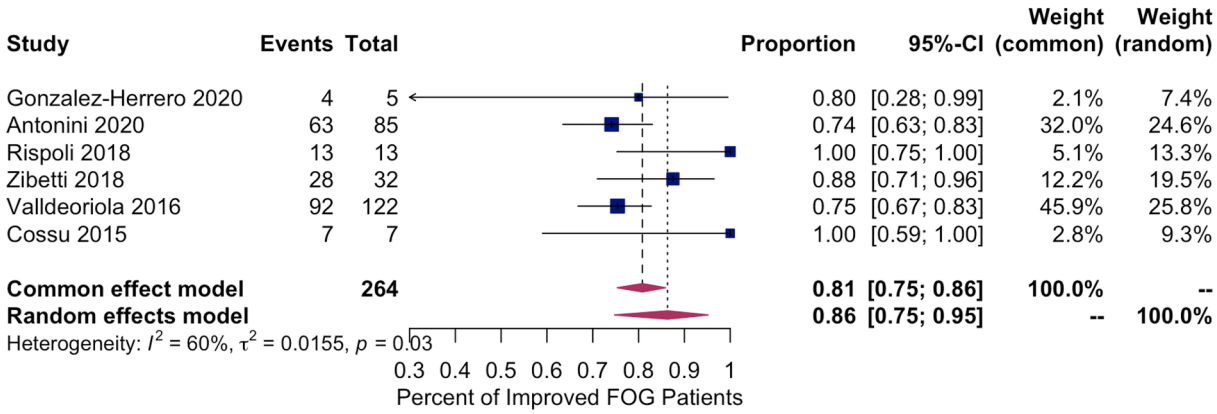

Fig. 2. Forest plot showing pooled effect sizes and percent of improved FOG patients in six studies. Heterogeneity between studies was statistically significant (p = 0.03). FOG improvement in the studies included in this forest plot were calculated according to different scales (FOG-Q, NFOG-Q, UPDRS). This likely contributed to the heterogeneity between studies and greatly limits the ability to compare their effect sizes.

female with PD who exhibited on-state FOG after acute levodopa challenge. She was started on 16-hour LCIG therapy. She exhibited supra-on FOG following LCIG infusion at twice her usual levodopa dose, but her FOG improved after titration. The patient had sustained improvement for twelve months and experienced significant reduction in falls and disability.

Morales-Briceño et al. 2019 [59] is a case report on two patients who received LCIG. These patients saw subsequent improvement in camptocormia (Bent Spine Syndrome) and FOG compared to baseline. Patient 1 was assessed after twelve months and patient 2 was assessed after ten months of LCIG therapy. It is unspecified which type of FOG was present in either patient or whether their FOG was previously responsive to oral medication.

A case report recently published by Oshiro et al. [60] describes two patients with diphasic dyskinesia who developed supra-ON FOG after initiating LCIG therapy. Supra-on FOG resolved in both patients in this study after titrating down the LCIG dose. However, these patients experienced increased wearing-off effects after decreasing the LCIG dose. One patient's wearing-off symptoms were alleviated by adjusting the dosage of ropinirole. The duration of LCIG treatment is unclear in either patient.

4. Discussion

This systematic literature review identified ten articles pertaining to the effect of LCIG on PD-FOG. These articles included retrospective studies, open-label studies, case series, and case reports. While the current body of literature was insufficient to conduct a *meta*-analysis, our descriptive analysis of these studies warrants further investigation into the effect of LCIG on FOG. Our findings provide insight into the pharmacologic responsiveness of FOG to levodopa therapy.

Freezing of Gait (FOG) is often refractory to oral levodopa therapy. [6,7] Historically, FOG has been thought to be a result of long-term levodopa treatment. [6,7,17–19] This is now recognized as a misconception; [21] rather, FOG has been shown to be highly sensitive to fluctuations in dopamine levels.[24,30] In patients who are minimally or partially responsive to oral levodopa therapy, higher dosages of levodopa may be needed to improve FOG. [24,30] However, oral levodopa is often poorly tolerated and affected by gastrointestinal factors such as variable gastric emptying. [27,32,33] This may limit the ability to titrate to a high enough dose to reach FOG improvement in patients with a narrow therapeutic window. The advantage of LCIG over oral levodopa-carbidopa is it allows for more consistent plasma L-dopa concentration and avoids wearing-off effects. [35–37] This may treat FOG by allowing titration of levodopa to higher overall doses and maintaining stable dopamine levels while avoiding adverse effects.

Multiple articles in this review support this hypothesis. González-Herrero et al. [57] showed that FOG may exhibit "pseudo-resistance," in which the patient's FOG is associated with an insufficient dose of levodopa but is alleviated by increasing the dose appropriately. [32] Morales-Briceño 2020 [58] presented a case report in which the patient exhibited on-freezing that resolved after titrating their LCIG infusion to the appropriate therapeutic window, which may show preliminary evidence that patients with on-FOG can respond to LCIG. Oshiro et al. [60] present two case reports where LCIG caused, rather than alleviated FOG symptoms. However, these case reports also show that careful titration of medication dose can avoid supra-on FOG while also improving wearing-off effects and other symptoms of PD. The findings in these case studies are consistent with Cossu et al. [55] and Zibetti et al. [56]; continuous levodopa administration was effective in reducing on or pseudo-on FOG by reducing dopamine fluctuation.

The small number of studies is a significant limitation of this review. While multiple case reports show that LCIG improved FOG in their subjects, [58–60] these have a low level of evidence. These findings warrant further investigation by larger studies. This is necessary to provide sufficient power to conduct *meta*-analytic statistical tests. [51] The larger observational and open-label studies in this systematic review were not sufficiently homogenous to pool their results. The small number of studies prevented a moderator analysis from being performed to determine which study characteristics contributed to their heterogeneity. The studies included also used different metrics for assessing FOG severity (FOG-Q, NFOG-Q, UPDRS). This likely contributed to the heterogeneity of studies and impedes comparison of patient outcomes.

Another limitation of this review is the varied treatment durations of each study. Six studies in this review followed subjects [52,53,55,57–59] for twelve months or fewer. Three studies reported data spanning a longer time period. Fabbri et al. [50] in a four-year retrospective study found that FOG improvements began to wear off after one year, and largely were not sustained after four years. Zibetti et al. [56] in a retrospective case series reported that LCIG improved pseudo-on FOG and off-FOG for a mean time period of thirty months. Valldeoriola et al. [54] in their cross-sectional, retrospective study reported sustained improvement in FOG for six years. These three studies show mixed evidence that LCIG may provide sustained improvement in FOG. This indicates the need for prospective, longitudinal studies with longer treatment durations. [54].

FOG is a highly disabling symptom of PD that is associated with increased falls and loss of autonomy. [8] While this review paper did not systematically examine the effects of LCIG on falls and loss of autonomy, these are relevant and clinically significant outcomes for FOG patients. Investigators conducting future research on LCIG and FOG should strongly consider including these patient outcomes in their analysis.

Future studies should also categorize subjects according to subtypes of FOG [24] to further understand the pathophysiology underlying levodopa responsiveness and resistance.[26] Multiple studies in this review [52,55,57,58,60] attributed the improvements in FOG to reduced dopamine fluctuation as a result of LCIG. Several of these show that LCIG may treat FOG that was previously unresponsive to oral levodopa therapy and occurred in the on-states.[52,55,56,58] Three studies in this review did not differentiate different subtypes of FOG but instead reported generalized improvement in FOG.[53,54,59] Given that much of the FOG literature indicates that different subtypes have different pathophysiologies and therapeutic approaches [24,32,61,62], these studies are limited in their ability to elucidate the mechanisms of FOG.

The effect of LCIG on FOG remains an open question; additional research is needed to confirm the findings of the studies included in this review. Although these findings are preliminary, they provide important directions for future research and emphasize the need for larger studies.

A potential challenge for research surrounding FOG is patients often do not exhibit FOG episodes in the clinical setting.[26] Assessment of FOG in these studies is therefore predominantly based on responses to subjective historical questionnaires such as the FOG-Q.[41] While these assessments are useful in that they are easy to administer, retrospection on past FOG episodes may be inaccurate.[26] Several studies have attempted to solve this problem by assessing FOG through video analysis [26], wearable wireless systems[63], a virtual reality gait task[64], and other methods. However, to this date there are no studies that assess FOG via any of these methods in the context of patients receiving LCIG therapy. Using these metrics to assess FOG may provide additional insight regarding the effects of LCIG on FOG.

CRediT authorship contribution statement

Melanie R. Shackleford: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing, Data curation, Visualization. **Virendra Mishra:** Writing – review & editing, Supervision, Funding acquisition, Project administration, Data curation. **Zoltan Mari:** Writing – review & editing, Funding acquisition, Supervision, Project administration.

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.

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