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Review

Subcutaneous Apomorphine Infusion Effects on OFF Time and Motor Symptoms in Individuals with Parkinson's Disease: A Systematic Review and Meta-Analysis

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Abstract: Background: Parkinson's Disease (PD) is a progressive neurodegenerative disorder characterized by motor fluctuations and dyskinesias that become increasingly challenging to manage in advanced stages. Continuous subcutaneous Apomorphine infusion offers a less invasive alternative to device-aided therapies such as deep brain stimulation and Levodopa-Carbidopa intestinal gel. This systematic review and meta-analysis aimed to evaluate the efficacy of Apomorphine infusion in reducing OFF time and motor symptom severity, focusing on Unified Parkinson's Disease Rating Scale (UPDRS) Part III scores in individuals with advanced PD. Objectives: A systematic search of PubMed, Cochrane, and EBSCO Megafile databases was conducted through April 16, 2025, according to PRISMA guidelines. Randomized controlled trials (RCTs) evaluating Apomorphine infusion and reporting outcomes on OFF time and UPDRS Part III were included. Risk of bias was assessed using the Cochrane RoB 2 tool, and certainty of evidence was evaluated with GRADE. Meta-analyses were performed using a random effects model. Result: Eight studies (n = 458) met the inclusion criteria, of which five were eligible for meta-analysis. Apomorphine infusion significantly reduced OFF time compared to placebo (MD = -1.93 hours; 95% CI: -2.91 to -0.95; low-certainty evidence), with minimal heterogeneity (I^2 = 0%). A significant reduction was also observed in UPDRS Part III scores (MD = -19.11; 95% CI: -25.54 to -12.68; very low-certainty evidence), although substantial heterogeneity was present (I^2 = 67.93%). Conclusion: This systematic review supports the efficacy of Apomorphine infusion in reducing OFF time and improving motor symptoms in individuals with advanced PD. Apomorphine infusion represents a treatment option, particularly for patient's ineligible for surgical interventions. However, the overall certainty of evidence is limited by methodological heterogeneity and a small number of high-quality trials. Future studies should aim for standardized outcome measures, long-term comparisons with other device-aided therapies, and exploration of patient-centered outcomes to enhance clinical integration.

Keywords: Parkinson's Disease; Apomorphine; OFF time; motor symptoms; dyskinesia

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1. Introduction

Parkinson's disease (PD) is a progressive chronic neurodegenerative disorder characterized primarily by bradykinesia, rigidity, tremors, and postural instability, resulting from the degeneration of dopaminergic neurons in the substantia nigra part of the brain [1]. As PD progresses, motor fluctuations and dyskinesias become more common, often representing a significant therapeutic challenge [2]. These motor complications and dyskinesias typically emerge after prolonged use of Levodopa. They are marked by unpredictable

OFF periods during which the effect of oral medications diminishes, leading to transient worsening of motor symptoms [3].

The management of motor fluctuations and dyskinesias has evolved to include various strategies, such as adjusting the timing and dosage of Levodopa, and incorporating adjunctive therapies like monoamine oxidase-B (MAO-B) inhibitors, catechol-O-methyltransferase (COMT) inhibitors, and dopamine agonists. However, in many individuals with PD, these strategies fail to provide consistent symptom control [4]. Device-aided therapies, including deep brain stimulation and continuous dopaminergic medication delivery systems, have emerged as alternatives for managing motor complications and fluctuations associated with advanced PD [5]. Among these, continuous subcutaneous Apomorphine infusion offers a less invasive option compared to deep brain stimulation, or intrajejunal Levodopa-Carbidopa intestinal gel provides a more stable dopaminergic activation than intermittent oral therapies [6].

Apomorphine is a potent dopamine receptor agonist with affinity for both D1 and D2 receptor families [8]. Although its efficacy has been well established in open-label and observational studies since its clinical introduction, robust randomized controlled trial (RCT) evidence has historically been limited. The TOLEDO trial, conducted in 2016, was the first large-scale, multicenter, double-blind, placebo-controlled RCT to confirm the efficacy of continuous subcutaneous infusion of Apomorphine in reducing the OFF time in individuals with persistent motor fluctuations [8]. The open label extension of the study further demonstrated the long-term safety and tolerability of apomorphine infusion, as well as its sustained benefits in the treatment of motor symptoms management [9].

Despite these encouraging findings, the clinical acceptance of continuous subcutaneous Apomorphine infusion remains variable between regions and patient populations, in part due to concerns about side effects, the need for infusion devices, and the limited generalizability of existing trial data [10]. Although several RCTs have explored different dosing regimens, titration protocols, and the role of antiemetic co-medication, it remains necessary to synthesize the available high-quality evidence to evaluate the overall efficacy of continuous subcutaneous Apomorphine infusion in individuals with PD [11,12].

This systematic review aims to critically evaluate and synthesize data from RCTs evaluating the effects of continuous subcutaneous Apomorphine infusion on motor symptoms severity, specifically focusing on results measured by the Unified Parkinson's Disease Rating Scale (UPDRS) Part III scores and the duration of the OFF time. By synthesizing data from rigorously designed studies, we seek to provide a comprehensive overview of the therapeutic potential and limitations of continuous subcutaneous infusion of Apomorphine.

2. Materials and Methods

2.1. Source of Data and Search Strategy

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [13]. The review protocol was registered on PROSPERO: CRD420251013826 and vetted by a professional research librarian. An extensive literature search on subcutaneous Apomorphine infusion was performed using PubMed, Cochrane, and EBSCO Megafile electronic databases and manual searches. They were searched from inception to April 16th, 2025. Searches were restricted to articles in the English language and RCTs. Appendix 1 provides a detailed list of search terms utilized.

2.2. Outcome Measures

The UPDRS is a frequently used outcome measure to quantify the severity and progression of PD. The UPDRS includes four sections that assess: (1) mentation, behavior, and

mood (UPDRS I), (2) activities of daily living (UPDRS II), (3) motor symptoms (UPDRS III), and (4) complications of therapy in patients with PD (UPDRS IV). Clinicians and researchers use the sectional and total scores to assess the status of PD symptoms and monitor disease progression [14]. Estimates of minimal, moderate, and large clinically important differences (CID) for the UPDRS section and total scores have been determined. On the UPDRS motor score, a minimal CID is 2.3 to 2.7 points, a moderate CID is 4.5 to 6.7 points, and a large CID is 10.7 to 10.8 points [15]. OFF time is a frequently used outcome measure to quantify the time when the motor symptoms of individuals with PD return between medication doses. OFF time can occur in the morning before the first dose of medication or during the day between scheduled doses of medication [16]. Estimates of minimal, moderate, and large CID for OFF time have not been determined. However, others have utilized a 1-hour reduction in OFF time as a benchmark for meaningful CID [17]. UPDRS Part III scores and OFF time were used to assess the progression of motor symptoms in individuals with PD.

2.3. Inclusion and Exclusion Criteria

Studies were included with the following criteria: female and male individuals aged 30 or over with a clinical diagnosis of PD consistent with the UK Brain Bank criteria [18] who have been diagnosed with PD for 8-15 years. The intervention studied is subcutaneous Apomorphine infusion. The outcomes assessed are UPDRS Part III scores and/or OFF time. The study design search was limited to RCTs published in English (Table 1). Studies were excluded with the following criteria: individuals with a mini-mental state examination score of 24 or less. Studies were also excluded if the outcomes assessed were not UPDRS Part III scores or OFF time, or if the study design was expert opinion, editorial, case report, abstracts without full results, or preprints.

2.4. Study Selection

Two reviewers (PA, BW) independently screened all titles and abstracts of the identified studies. Full texts were obtained for the studies deemed eligible from the initial screening. Two reviewers (PA, BW) independently reviewed full texts. Any discrepancies were discussed and resolved through discussion with a third reviewer (MW).

2.5. Data Extraction

Data were extracted into a standardized form that included lead author, publication date, country, study design, intervention type, sample size, age, and results of UPDRS Part III scores and OFF time outcome measures by one independent reviewer (PA). A second reviewer (BW) conducted a reliability check. No discrepancies in data extraction were identified between the reviewers. If there was missing data, the authors were contacted for additional information.

2.6. Risk of Bias

Methodological quality was examined using the Cochrane Risk of Bias 2 (RoB 2) tool [19]. The RoB 2 is structured into five domains of bias: (1) randomization process, (2) deviations from the intended interventions (effect of assignment and adhering to intervention), (3) missing outcome data, (4) measurement of the outcome, and (5) selection of the reported result. The results in each domain determined an overall risk of bias. The overall risk of bias was judged as high risk of bias, some concerns, or low risk of bias. Two reviewers (PA, BW) independently conducted the risk of bias analysis. Any discrepancies were discussed and resolved through discussion with a third reviewer (MW).

2.7. Data Analysis

We performed a random effects meta-analysis using the DerSimonian and Laird method to calculate the mean difference (MD) and 95% confidence interval (CI) of subcutaneous Apomorphine infusion compared to placebo on UPDRS Part III scores and OFF time. The MD and 95% CI were estimated when at least two or more studies included the same outcome measure. We assessed heterogeneity using Q, p, and The I^2 values and the 95% prediction interval (PI). The I^2 value of 0%-40% was interpreted as small heterogeneity, 30%-60% as moderate heterogeneity, 50%-90% as substantial heterogeneity, and 75%-100% as considerable heterogeneity [20]. The 95% PI was estimated when the meta-analysis included more than two studies. Publication bias was assessed in meta-analyses with at least ten studies [21]. To assess the robustness of the pooled effect size and detect any potential undue influence from individual studies, we performed a leave-one-out sensitivity analysis. To account for clinical and methodological variability, studies were categorized based on treatment context into acute and maintenance groups as separate meta-analyses. Acute studies were defined as those evaluating the short-term motor response to a single dose of subcutaneous Apomorphine, typically measured within minutes post-administration. Maintenance studies assessed the longer-term effects of subcutaneous Apomorphine treatment over days to weeks. This classification guided the structure of the meta-analyses. All statistical analyses were conducted using STATA 18 (StataCorp. 2023. Stata Statistical Software: Release 18. College Station, TX: StataCorp LLC.).

Some studies identified during the review were not included in the quantitative meta-analysis due to limitations in data reporting or study design. Specifically, studies that lacked reported outcomes in non-standardized formats (e.g., duration of OFF time response per dose instead of daily OFF time) or used open-label, non-randomized designs without a comparator group were excluded from pooled analyses. These studies were instead evaluated qualitatively to provide context and support for the meta-analytic findings and to illustrate the broader clinical experience with Apomorphine treatment.

2.8. Certainty of Evidence

Two reviewers (PA, MW) independently assessed the certainty of evidence using the GRADE approach for each meta-analysis (GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University and Evidence Prime, 2022. Available from gradepro.org) [23]. Each meta-analysis was classified as very low, low, moderate, or high-quality certainty of evidence.

3. Results

3.1. Study Selection

The electronic search of databases yielded 266 articles. Two hundred and thirty-five articles were excluded after reviewing titles and abstracts. Seventeen duplicate articles were excluded. Five articles were excluded because they were abstracts only. The remaining nine articles were retrieved and assessed for eligibility via full-text review. One article was excluded because it did not meet the inclusion criteria. The remaining eight articles [8,9,23–28] were found eligible and included in the review (Figure 1). Five [8,23–25,27] of the articles were included in the meta-analyses. Three articles could not be included in the meta-analysis. For two articles [9,28] , it was due to the open-label design and lack of a comparator group, whereas for one article [26], it was due to the lack of reporting outcomes in standardized formats.

Table 1. Flowchart of the systematic literature search on four electronic databases according to the PRISMA guidelines.

Parameter	Inclusion Criteria	Exclusion Criteria
Population	Female and male individuals over the age of 18 with a clinical diagnosis of PD consistent with the UK Brain Bank criteria who have been diagnosed with PD for 8-15 years.	Individuals with a mini-mental state examination score of 24 or less
Intervention	Subcutaneous Apomorphine infusion	Other types of PD medication
Comparator	Placebo or no comparator	Comparator other than placebo or other than no comparator
Outcome	UPDRS Part III scores and/or OFF time as efficacy endpoints	UPDRS Part III scores and/or OFF time not included as efficacy endpoints
Study Design	Randomized Controlled Trials published in English	Expert opinions, editorials, case reports, abstracts without full reports, and preprints. Published in any other language than English

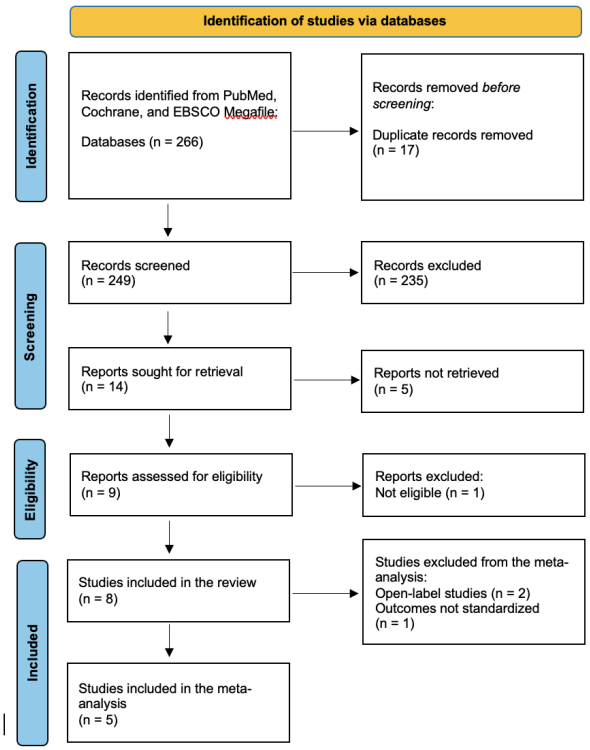

Figure 1. PRISMA Flow Diagram for Systematic Searches.

3.2. Characteristics of Selected Studies

As summarized in Table 2, 458 participants were assessed in studies across the United States [23,24,26,28], Austria [8,9], Denmark [8,9], France [8,9], Germany [8,9], Spain [8,9], Netherlands [8,9,25], the United Kingdom [8,9], and Japan [27]. The duration of the studies ranged from a single dose to 52 weeks. The studies included varying doses of Apomorphine, determined individually for each patient. In six studies, a placebo was included as the control [8,23–27]. Two studies were open-label studies and had no control [8,28].

Table 2. Summary of the Studies on Subcutaneous Apomorphine Infusion Retrieved from the Literature.

Authors	Number of Participants at Baseline	Gender Allocation	Mean Age of Participants in the Apomorphine Group	Group Allocation	Intervention Duration
Katzenschlager et al. (2018, TOLEDO) [8]	107	61.7% male, 38.3% female	63.6 ± 9.3	53 Apomorphine, 53 Placebo	12 weeks
Katzenschlager et al. (2020, TOLEDO extension) [9]	84	Not specified	64.3 ± 8.2	All Apomorphine (open-label)	52 weeks
Pahwa et al. (2007) [23]	56	58.9% male, 41.1% female	Not specified	Crossover: 26 Apomorphine/ Placebo, 25 placebo/apomorphine	Single dose
Pfeiffer et al. (2007) [24]	62	72.6% male, 27.4% female	64.8 ± 1.5	19 Apomorphine typical dose, 16 Apomorphine 0.2 mL greater than typical dose, 13 placebo at typical dose, and 14 placebo at 0.2 mL greater than typical dose	Single dose
van Laar et al. (1993) [25]	5	60% male, 40% female	54.2	Apomorphine vs Placebo (n=1 design, where each patient was their own control)	Single dose
Dewey et al. (2001) [26]	29	69% male, 31% female	66 ± 2.0	20 Apomorphine, 9 Placebo	One month
Nomoto et al. (2015) [27]	16	31.3% male, 68.7% female	57.7 ± 11.4	10 Apomorphine, 6 placebo	Single-day, three repeated doses
Isaacson et al. (2025, InfusON) [28]	99	69.7% male, 30.3% female	61.6 ± 9.41	All Apomorphine (open-label)	52 weeks

Four were acute studies [23–25,27] and three were maintenance studies [8,9,28]. One study included both acute and maintenance phases [26].

3.3. Characteristics of Participants

The mean age of individuals ranged from 54.2 to 66.7 years in the Apomorphine groups and from 54.2 to 66.5 years in the placebo groups. The mean duration of PD in individuals ranged from 9.2 to 14.7 years in the Apomorphine groups and from 10.6 to 16.1 years in the placebo groups. The mean percentage of female individuals ranged from 27.4 to 68.7%.

3.4. Study Quality

The overall risk of bias was low for five included studies [23–27], some concerns for one included study [8], and high for two included studies [9,28] (Figure 2). In one study [8], the cause of some concerns was missing outcome data due to 34% of participants discontinuing before week 12. Discontinuation rates were higher in the placebo group (43%) compared to the Apomorphine group (23%). In two studies [9,28], the cause of high risk was the open-label design. In both studies, no randomization occurred, and the open-label design led to no blinding among both the patients and the investigators. In both studies, there was a high rate of discontinuation with 30% of participants discontinued from one study [9] and 52% of patients discontinued from the other study [1].

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Figure 2. Traffic Light Plot of Risk of Bias.

3.5. 3.5 Study Outcomes

The eight included studies [8,9,23–28] assessed outcomes immediately following the intervention. In four studies [8,9,26,28], OFF time was an efficacy endpoint. One study [25], only reported the mean duration of OFF time per Apomorphine infusion, not the reduction in daily OFF time. In seven studies [8,9,23,24,26–28], UPDRS Part III scores were an efficacy endpoint. The included studies varied in terms of treatment duration and timing of outcome assessment. Four studies [23–25,27] evaluated the acute effects of subcutaneous Apomorphine, measuring motor response (UPDRS Part III scores) within 20 to 40 minutes after a single infusion, while three studies [8,9,28]investigated the maintenance effects of subcutaneous Apomorphine over longer periods, such as 12 weeks in one study [8] and up to 52 weeks in open-label studies [9,28]. One study [26] included both acute and maintenance phases.

3.6. Meta-Analysis: Motor Symptoms

3.6.1. OFF Time

Two studies [8,26] (n = 136) investigated the effect of subcutaneous Apomorphine infusion compared to placebo on OFF time in the longer-term (maintenance phase). The overall effect size was significant (MD = -1.93, p < 0.01; 95% CI -2.91, -0.95). This effect size is a meaningful CID for OFF time [17]. There was a small and statistically non-significant degree of heterogeneity identified in the meta-analysis (Q = 0.01, p = 0.91, I^2 = 0.00%; Figure 3).

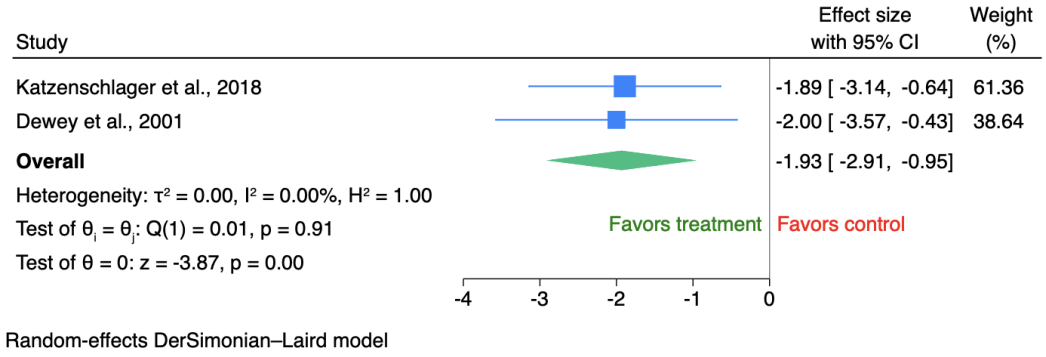

Figure 3. Forest plot OFF Time.

3.6.2. Study Outcomes

Four studies [23,24,26,27] (n = 163) investigated the effect of subcutaneous Apomorphine infusion compared to placebo on UPDRS Part III scores directly after injection (acute phase). The overall effect size was significant (MD = -19.11, p < 0.01; 95% CI -25.54, -12.68). This effect size is beyond the threshold for a large CID for UPDRS scores [15]. There was a substantial and statistically significant degree of heterogeneity identified in the meta-analysis (Q = 9.35, p = 0.02, The I^2 = 67.93%; 95% PI -45.49, 7.28; Figure 4).

The results of the leave-out-one sensitivity analysis demonstrated that the overall effect remained statistically significant across all analyses, with effect sizes ranging from -15.86 (95% CI -21.47, -10.25) to -22.20 (95% CI -26.39, -18.02; Figure 5). The exclusion of any single study did not substantially alter the magnitude or direction of the pooled estimate, indicating that no individual study had a disproportionate influence on the overall findings.

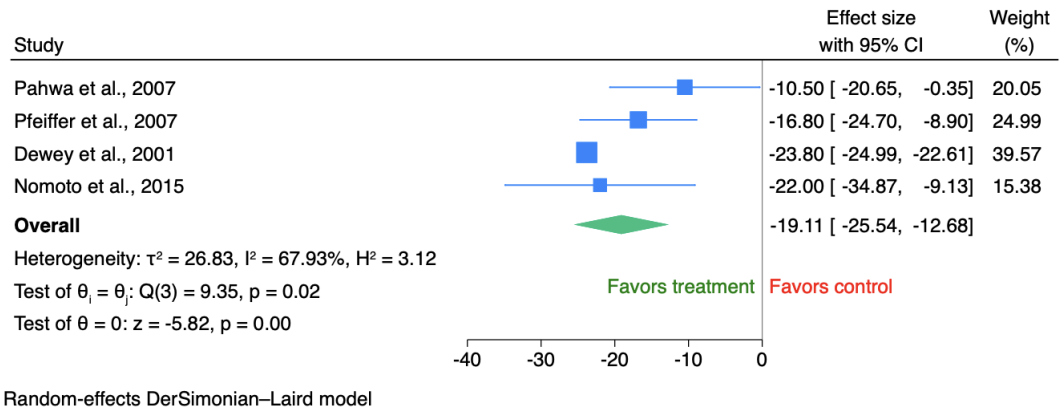

Figure 4. Forest plot UPDRS Part III Scores.

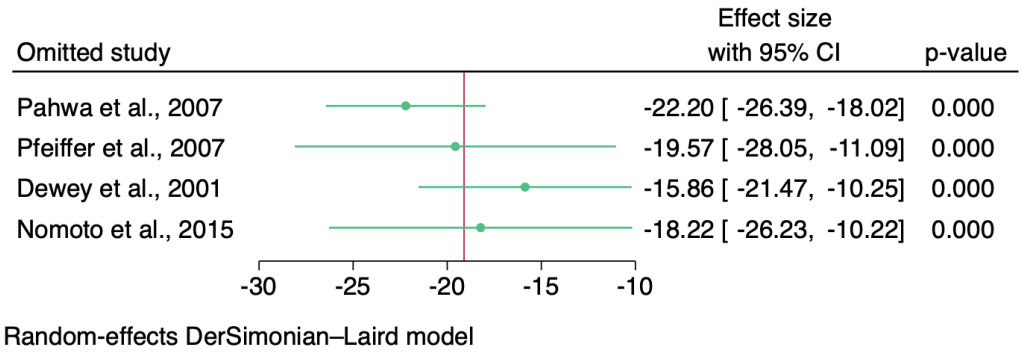

Figure 5. UPDRS Part III Scores Leave-One-Out Analysis.

3.7. Descriptive

3.7.1. OFF Time

One study reported findings from the open-label phase of the TOLEDO study, assessing long-term apomorphine infusion in Parkinson's patients with persistent motor fluctuations. Among 84 patients, the mean reduction in daily OFF time from double-blind phase baseline to week 64 was -3.66 hours (SD 2.72), indicating a sustained and clinically meaningful benefit over a one-year treatment period [9]. Another study conducted the InfusON open-label study in the United States, enrolling 99 patients with 3 hours of daily OFF time. By week 12 of the maintenance period, participants experienced a mean reduction of 3.0 hours (SD 3.18) in daily OFF time, with corresponding increases in Good ON time (ON without troublesome dyskinesia) of 3.1 hours (SD 3.35). These improvements were maintained through the 52-week duration [28]. A randomized, double-blind, placebo-controlled crossover study in five idiopathic PD patients using apomorphine injections during OFF periods was also performed. The treatment led to rapid onset of action (mean 7.3 minutes) and average duration of response of 96 minutes, with all five patients showing significant reductions in OFF symptoms during apomorphine administration, although exact daily OFF hour changes were not quantified due to the short-term nature and small sample size of the study [25].

3.7.2. UPDRS Part III

One open-label study [9] evaluated changes in UPDRS Part III scores during ON periods over the 52-week open-label phase. Although exact change values were not detailed in the main text, the study stated that UPDRS III motor scores improved and remained stable, supporting sustained motor benefits from continuous apomorphine infusion [9]. Another open-label study [28] included UPDRS Part III as a secondary outcome. Over the 52-week maintenance period, patients demonstrated improvements in UPDRS III scores, with details collected at multiple timepoints (weeks 2, 12, and every 8 weeks thereafter). While the exact mean change was not stated in the summary, the study emphasized that improvements were sustained and paralleled OFF time reduction, supporting clinical efficacy [28]. A randomized, double-blind, placebo-controlled crossover study [25] assessed motor function using the Columbia rating scale, which includes tremor, rigidity, gait, bradykinesia, and stability, conceptually overlapping with UPDRS III. Apomorphine resulted in statistically significant improvements across all domains, with $p < 0.001$ for individual items. The sum of Columbia items and the sum of quantitative assessments (e.g., tapping, walking) both improved significantly, reinforcing apomorphine's robust motor efficacy [25].

3.8. Overall Quality of Evidence

Using the Cochrane GRADE approach, the level of evidence was downgraded by two levels for the OFF time meta-analysis as risk of bias was deemed serious (risk of bias, -1) and publication bias was strongly suspected (other considerations, -1) due to the low number of studies included. The level of evidence was downgraded by three levels for the UDPRS Part III scores meta-analysis as risk of bias was deemed serious (risk of bias, -1), the heterogeneity The I^2 was deemed serious (inconsistency, -1), and publication bias was strongly suspected (other considerations, -1) due to the low number of studies included. The overall quality was deemed low for OFF time and very low for UPDRS Part III (Appendix 2).

4. Discussion

Continuous subcutaneous Apomorphine infusion serves a specific function in the management of advanced PD. It offers a less invasive alternative to deep brain stimulation and can be preferable for individuals ineligible for surgery or those desiring reversible interventions [5]. When compared to Levodopa-Carbidopa intestinal gel, subcutaneous Apomorphine presents logistical advantages in terms of portability and setup but requires careful management of infusion site reactions and potential neuropsychiatric side effects [10]. Our findings reinforce this clinical positioning by providing low to very low certainty evidence that Apomorphine infusion significantly reduces OFF time and may meaningfully improve motor symptoms as measured by UPDRS Part III. These results align with established clinical practice recommendations, such as those from the Movement Disorder Society (MDS), which recognize Apomorphine infusion as an option for patients experiencing disabling motor fluctuations not controlled by oral medication [29].

4.1. Efficacy of Apomorphine in Reducing OFF Time

This systematic review and meta-analysis provide low-certainty evidence supporting the efficacy of continuous subcutaneous Apomorphine infusion in reducing OFF time among individuals with PD experiencing motor fluctuations. The observed statistically significant effect is aligned with findings from the TOLEDO open-label extension [9], which reported clinically meaningful reductions in OFF time. The minimal heterogeneity across the included studies suggests a relatively consistent reduction of OFF time across populations and trial settings. These findings support earlier observational and open-label studies that highlighted subcutaneous Apomorphine infusion's capacity to stabilize dopaminergic stimulation and bridge motor gaps between oral medication doses [6,24,28]. This reduction in OFF time is clinically relevant, particularly for individuals in advanced stages of PD who experience disabling motor fluctuations despite optimized oral therapy. By offering continuous dopaminergic stimulation, apomorphine infusion helps maintain motor stability throughout the day, potentially improving daily function, independence, and quality of life.

4.2. Efficacy of Apomorphine in Reducing UPDRS Part III Scores

The meta-analysis of UPDRS Part III scores revealed a statistically significant effect, which is beyond the threshold for a large CID. However, this finding is accompanied by substantial heterogeneity, and thus, the certainty of evidence is considered very low, due to inconsistency across studies. Despite the variability, the overall direction of effect suggests that continuous Apomorphine infusion may provide meaningful improvements in motor function, particularly in the early phase of treatment. This is supported by several acute studies that reported rapid reductions in UPDRS III scores following initiation of infusion therapy [23,26,27]. This variability could come from several sources, including differences

in Apomorphine dosage and titration schedules, varying baseline disease severity, heterogeneity in outcome assessment timing (acute vs. maintenance), and discrepancies in trial design. Moreover, some studies used ON-state vs. OFF-state assessments inconsistently, making cross-study comparisons difficult [23,27]. Differences in the use of rescue medications and comorbid non-motor symptom burden may also have influenced motor outcomes [24,26].

Several studies also failed to report standardization of motor assessment protocols, such as time since last oral dopaminergic dose, which is critical for reliable UPDRS scoring [23,25]. Furthermore, trial durations varied widely, with shorter studies potentially capturing acute effects [23,25] and longer ones reflecting sustained, but possibly attenuated, responses [9,28]. These methodological inconsistencies make it difficult to precisely determine the magnitude and durability of motor symptom improvement. The inconsistency observed highlights challenges reported in prior literature, where UPDRS III scores are sensitive to assessment timing and motor state fluctuations [30]. Despite these limitations, the potential for Apomorphine infusion to enhance motor control remains promising, particularly as an add-on strategy in patients inadequately managed with standard oral medications. Future studies with standardized protocols, stratified dosing, and longer follow-up periods are needed to confirm these findings and clarify sustained benefit.

4.3. Integration of Subcutaneous Apomorphine in Clinical Practice

Real-world registry data such as the EUROINF study have emphasized the utility of Apomorphine infusion in daily clinical practice, particularly for its rapid onset, flexibility in dosing, and favorable impact on non-motor symptoms [31]. Our synthesis contributes to this broader evidence by providing pooled estimates of effect size, highlighting both therapeutic potential and heterogeneity in outcomes. By integrating efficacy data with methodological critique, our work moves the conversation forward from isolated clinical impressions to a more structured, evidence-based framework for determining when and for whom Apomorphine infusion is appropriate. This is particularly relevant as treatment strategies shift toward personalized, stepwise strategies to advanced PD, balancing efficacy, tolerability, and patient preferences.

4.4. Study Limitations

Only two studies were eligible for the OFF time meta-analysis, limiting the generalizability and precluding the estimation of a prediction interval. The UPDRS Part III meta-analysis exhibited substantial heterogeneity, which reduced the certainty of the findings. The open-label studies, though presenting long-term safety and adherence data, could not be included in the meta-analyses due to a lack of comparator groups. The small number of RCTs and variability in trial methodologies (e.g., timing of outcome assessment, infusion duration) challenge the consistency of effect estimates. Finally, the exclusion of non-English studies and grey literature may have introduced publication bias.

4.5. Implications for Future Research

Future RCTs should aim for standardization in outcome reporting, including consistent timing for UPDRS III assessments and daily OFF time measurements. RCTs should also report subgroup analyses based on age, sex, disease duration, and co-medication use, which would facilitate precision in treatment recommendations. Furthermore, comparative effectiveness studies between subcutaneous Apomorphine infusion and other device-aided therapies, including deep brain stimulation and Levodopa-Carbidopa intestinal gel, are urgently needed. The exploration of patient-centered outcomes, such as quality of life, treatment satisfaction, and caregiver burden, would provide a more comprehensive picture of subcutaneous Apomorphine's clinical value. Finally, real-world observational studies

could offer insights into long-term treatment compliance, cost-effectiveness, and regional variations in clinical implementation.

5. Conclusions

This systematic review and meta-analysis provide low to very-low level of evidence that continuous subcutaneous Apomorphine infusion significantly reduces OFF time and UPDRS Part III scores in individuals with advanced PD, supporting its role as an effective treatment. While Apomorphine offers a less invasive alternative to surgical interventions, further high-quality RCTs are needed to strengthen the evidence base and guide clinical decision-making. Optimizing treatment protocols and addressing barriers to broader clinical integration is essential to maximizing its potential in routine PD care.

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Appendix A

Search Terms: The search terms for the PubMed database were: ("Parkinson's disease" OR "Parkinson" OR "Parkinson disease" OR "Parkinsonism" OR "PD" OR "idiopathic parkinsonism") AND ("subcutaneous apomorphine" OR "subcutaneous apomorphine infusion" OR "apomorphine infusion" OR "continuous apomorphine" OR "apomorphine pump" OR "CSAI" OR "dopamine agonist infusion" OR "apomorphine therapy") AND ("placebo" OR "placebo-controlled" OR "control" OR "sham treatment" OR "comparator" OR "no placebo" OR "no control" OR "no comparator") AND ("nonmotor" OR "non-motor" OR "motor" OR "mobility" OR "gait" OR "walking" OR "balance" OR "instability" OR "postural control" OR "postural instability" OR "falls" OR "falling" OR "slowness" OR "bradykinesia" OR "rigidity" OR "stiffness" OR "tremor" OR "shaking" OR "cognitive impairment" OR "cognitive decline" OR "cognitive problems" OR "cognitive symptoms" OR "cognitive dysfunction" OR "cognitive changes" OR "memory problems" OR "executive dysfunction" OR "attention deficits" OR "dementia" OR "depression" OR "anxiety" OR "mood disorders" OR "mood symptoms" OR "neuropsychiatric symptoms" OR "UPDRS" OR "Unified Parkinson's Disease Rating Scale" OR "motor scores" OR "OFF time" OR "wearing-off" OR "fluctuations" OR "symptom control" OR "daily functioning" OR "activities of daily living" OR "fatigue" OR "sleep problems" OR "sleep disturbances" OR "REM sleep behavior disorder" OR "pain" OR "apathy"), Filters: Randomized Controlled Trials.

The search terms for the Cochrane database were: ("Parkinson's disease" OR "Parkinson" OR "Parkinson disease" OR "Parkinsonism" OR "PD" OR "idiopathic parkinsonism") AND ("subcutaneous apomorphine" OR "subcutaneous apomorphine infusion" OR "apomorphine infusion" OR "continuous apomorphine" OR "apomorphine pump" OR "CSAI" OR "dopamine agonist infusion" OR "apomorphine therapy") AND ("placebo" OR "placebo-controlled" OR "control" OR "sham treatment" OR "comparator" OR "no placebo" OR "no control" OR "no comparator") AND ("nonmotor" OR "non-motor" OR "motor" OR "mobility" OR "gait" OR "walking" OR "balance" OR "instability" OR "postural control" OR "postural instability" OR "falls" OR "falling" OR "slowness" OR "bradykinesia" OR "rigidity" OR "stiffness" OR "tremor" OR "shaking" OR "cognitive impairment" OR "cognitive decline" OR "cognitive problems" OR "cognitive symptoms" OR "cognitive dysfunction" OR "cognitive changes" OR "memory problems" OR "executive dysfunction" OR "attention deficits" OR "dementia" OR "depression" OR "anxiety" OR "mood disorders" OR "mood symptoms" OR "neuropsychiatric symptoms" OR "UPDRS" OR "Unified Parkinson's Disease Rating Scale" OR "motor scores" OR "OFF time" OR "wearing-off" OR "fluctuations" OR "symptom

control" OR "daily functioning" OR "activities of daily living" OR "fatigue" OR "sleep problems" OR "sleep disturbances" OR "REM sleep behavior disorder" OR "pain" OR "apathy"), Filters: Trials, English.

The search terms for the EBSCO Megafile database were: ("Parkinson's disease" OR "Parkinson" OR "Parkinson disease" OR "Parkinsonism" OR "PD" OR "idiopathic parkinsonism") AND ("subcutaneous apomorphine" OR "subcutaneous apomorphine infusion" OR "apomorphine infusion" OR "continuous apomorphine" OR "apomorphine pump" OR "CSAI" OR "dopamine agonist infusion" OR "apomorphine therapy") AND ("placebo" OR "placebo-controlled" OR "control" OR "sham treatment" OR "comparator" OR "no placebo" OR "no control" OR "no comparator") AND ("nonmotor" OR "non-motor" OR "motor" OR "mobility" OR "gait" OR "walking" OR "balance" OR "instability" OR "postural control" OR "postural instability" OR "falls" OR "falling" OR "slowness" OR "bradykinesia" OR "rigidity" OR "stiffness" OR "tremor" OR "shaking" OR "cognitive impairment" OR "cognitive decline" OR "cognitive problems" OR "cognitive symptoms" OR "cognitive dysfunction" OR "cognitive changes" OR "memory problems" OR "executive dysfunction" OR "attention deficits" OR "dementia" OR "depression" OR "anxiety" OR "mood disorders" OR "mood symptoms" OR "neuropsychiatric symptoms" OR "UPDRS" OR "Unified Parkinson's Disease Rating Scale" OR "motor scores" OR "OFF time" OR "wearing-off" OR "fluctuations" OR "symptom control" OR "daily functioning" OR "activities of daily living" OR "fatigue" OR "sleep problems" OR "sleep disturbances" OR "REM sleep behavior disorder" OR "pain" OR "apathy"), Filters: English.

Appendix B

GRADE Approach for OFF Time and UPDRS Part III Scores Outcomes Subcutaneous Apomorphine Compared to Placebo for Parkinson's Disease.

Certainty assessment							Nr of patients		Effect		Certainty
Nr of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Subcutaneous Apomorphine	Placebo	Relative (95% CI)	Absolute (95% CI)	
2	randomised trials	serious	not serious	not serious	not serious	publication bias strongly suspected	73	62	-	MD 1.93 SD lower (2.91 lower to 0.95 lower)	⊕⊕◯◯ Low
4	randomised trials	serious	serious	not serious	not serious	publication bias strongly suspected	116	93	-	MD 19.11 SD lower (25.54 lower to 12.68 lower)	⊕◯◯◯ Very low

CI: confidence interval; MD: mean difference

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