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REVIEW

Continuous Dopaminergic Stimulation-Based Levodopa Treatment in Patients with Early to Mid-Stage Parkinson's Disease: A Systematic Review and Meta-Analysis

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ABSTRACT

***Introduction*:** Despite promising results from continuous dopaminergic stimulation (CDS)-based treatments, the effectiveness of sustained-release formulations of levodopa remains debated. This meta-analysis aims to assess the effectiveness of CDS-based levodopa treatment in patients with early to mid-stage Parkinson's disease (PD).

***Methods*:** Comprehensive searches were performed using PubMed, EMBASE, the Cochrane Library, Web of Science, and ClinicalTrials.gov. The clinical trials were included to compare CDS-based levodopa treatments with intermittent levodopa (IL) treatment in patients with early to mid-stage PD.

***Results*:** A total of 18 clinical trials involving 2208 patients were included in this meta-analysis. Results showed that CDS-based levodopa treatments were associated with a significant reduction in Unified Parkinson's Disease Rating Scale (UPDRS) II scores (mean difference (MD) – 0.79, 95% CI – 1.26, – 0.32) and UPDRS III scores (MD – 1.03, 95% CI – 1.98, – 0.08) compared to IL treatments. Additionally, CDS-based treatments increased ON time without troublesome dyskinesia (MD 0.63, 95% CI 0.35, 0.91) and decreased OFF time (MD – 0.60, 95% CI – 1.03, – 0.18). In the subgroup analysis of UPDRS II scores and UPDRS III scores, the MD were – 0.62 (95% CI – 1.27, 0.02) and – 1.20 (95% CI – 4.74, 2.34) for 200 mg and – 1.10 (95% CI – 1.88, – 0.32) and – 1.25 (95% CI – 3.26, 0.76) for a combination of levodopa and other drugs at varying dosages, respectively.

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Conclusion: Treatment with CDS-based levodopa offers significant benefits in managing motor symptoms and reducing complications in patients with early to mid-stage PD. These therapies provide a promising alternative to traditional IL treatments, potentially leading to improving patient outcomes and quality of life.

PLAIN LANGUAGE SUMMARY

Parkinson's disease is a chronic, progressive neurodegenerative disorder affecting millions of people worldwide. Promising results have been reported among studies of continuous dopaminergic stimulation-based treatments; however, the effectiveness of sustained-release formulations of levodopa remains debated. To address this controversy, we conducted a systematic review and meta-analysis of clinical trials to evaluate the effectiveness of continuous dopaminergic stimulation-based levodopa treatments in patients with early to mid-stage Parkinson's disease. Comprehensive searches were performed, and clinical trials were included to compare continuous dopaminergic stimulation-based levodopa treatments with intermittent levodopa treatment in patients with early to mid-stage Parkinson's disease. A total of 18 clinical trials involving 2208 patients were included in this meta-analysis, of which 14 were randomized controlled trials comprising 2133 patients. Results showed that continuous dopaminergic stimulation-based levodopa treatments were associated with a significant reduction in Unified Parkinson's Disease Rating Scale II scores (mean difference – 0.79, 95% confidence interval – 1.26, – 0.32) and Unified Parkinson's Disease Rating Scale III scores (mean difference – 1.03, 95% confidence interval – 1.98, – 0.08) compared to intermittent levodopa treatments. Additionally, continuous dopaminergic stimulation-based treatments increased ON time without troublesome dyskinesia (mean difference 0.63, 95% confidence interval 0.35, 0.91) and decreased OFF time (mean difference – 0.60, 95% confidence interval – 1.03, – 0.18). Treatment with continuous dopaminergic stimulation-based levodopa offers significant benefits in managing motor symptoms and reducing complications in patients with early to mid-stage Parkinson's disease. These therapies provide a promising alternative to traditional intermittent levodopa treatments, potentially leading to improving patient outcomes and quality of life.

Keywords: Continuous dopaminergic stimulation-based levodopa; Parkinson's disease; Meta-analysis; Clinical trial

Key Summary Points

Why carry out this study?
Parkinson's disease affects millions worldwide, causing significant economic burden and motor complications from long-term levodopa use that reduce quality of life
This study investigates if continuous dopaminergic stimulation (CDS)-based levodopa treatment outperforms intermittent levodopa (IL) in patients with early to mid-stage Parkinson's disease
What was learned from the study?
CDS-based levodopa treatment improved motor function, daily activities, and reduced complications compared to IL in early to mid-stage Parkinson's disease
Compared to IL, CDS-based levodopa significantly improved UPDRS II/III scores, increased ON time without troublesome dyskinesia, and reduced OFF time in patients with early to mid-stage PD, demonstrating superior efficacy in enhancing daily function and controlling motor function
These results position CDS-based levodopa as a promising option, suggesting better patient outcomes and warranting further research into long-term effects and optimization

INTRODUCTION

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder affecting millions of people worldwide. The global prevalence of PD is estimated to be around 0.3% in the general population, with a significantly higher incidence in older adults [1]. A previous systematic review indicated that the incidence of PD is approximately 37.55 per 100,000 person-years [2], and the prevalence is about 315 per 100,000 persons [3]. The disease burden is substantial, with significant impacts on both the individual and society. PD is associated with a reduced quality of life, increased mortality, and high healthcare costs [1]. The combined direct and indirect cost of PD in the USA alone is nearly $52 billion annually [4].

Current treatments for PD primarily focus on symptomatic relief. The main medications include levodopa, dopamine agonists, monoamine oxidase B inhibitors, and catechol-*O*-methyltransferase inhibitors. Among these, levodopa is considered the gold standard and recommended as a primary treatment option by several clinical guidelines and consensus statements for early PD, including those from both Chinese and US authorities [5–8]. However, long-term use of levodopa can lead to motor complications, such as dyskinesias and motor fluctuations, which can significantly impact the quality of life for patients with PD [2].

The emergence of these motor complications in PD may be due to long-term pulsatile, non-physiological stimulation of the dopamine receptors [9]. This intermittent stimulation contrasts with the continuous dopaminergic stimulation (CDS) that the brain would normally receive under physiological conditions. The CDS theory was first proposed by Thomas Chase in 1998, suggesting that continuous dopaminergic delivery could mitigate motor complications by providing a more stable dopaminergic environment [9]. Several studies have supported this theory, demonstrating improvements in daily living activities, motor scores, and reducing motor complications compared to traditional, pulsatile administration [10, 11].

Despite promising results from CDS-based treatments, the effectiveness of sustained-release formulations of levodopa remains debated. Some studies have reported similar effectiveness between immediate-release and sustained-release levodopa [12], while others have suggested the superiority of sustained-release formulations [13]. To address this controversy, we conducted a systematic review and meta-analysis of clinical trials to evaluate the effectiveness of CDS-based levodopa treatments in patients with early to mid-stage PD.

METHODS

Study Searches and Selection

Following the PRISMA guidelines and the registered protocol (PROSPERO registration number CRD42024501692), we conducted a comprehensive search for relevant studies up to October 23, 2023. Our electronic searches covered four databases: PubMed, EMBASE, the Cochrane Library, Web of Science, and ClinicalTrials.gov. No language restrictions were applied. The search terms encompassed various aspects, including levodopa, PD, controlled release, clinical trials, and MeSH terms. Detailed information about these search terms can be found in Supplementary Material.

After removing duplicate records, two independent reviewers screened the articles on the basis of their titles and abstracts. Discrepancies were addressed through discussion and, if needed, resolved by a third reviewer. Additionally, we used the latest information from multiple publications if possible. Our inclusion criteria encompassed clinical trials that compared CDS-based levodopa treatment with intermittent levodopa (IL) treatment among patients with early to mid-stage PD aged 18 years or older. CDS-based levodopa treatment, including levodopa controlled-release or sustained-release formulation, carbidopa/levodopa/entacapone, IPX203, IPX066, or IPX054.

Data Extraction and Quality Assessment

Data extraction was performed by one reviewer and double-checked by another using a predesigned data extraction form. Any disagreements were resolved through discussion, with a more experienced third-party consultation if necessary. The following information was extracted: baseline study characteristics, treatment group, Hoehn and Yahr stage, PD duration, intervention, dosage, treatment duration, treatment, and targeted outcomes. If relevant information was unclear or insufficient, attempts were made to contact the authors for additional data. If the information in the studies was not provided, data presented in graphs and figures were extracted whenever possible but only included when two reviewers independently obtained the same results.

Bias assessment followed the revised Cochrane risk of bias assessment tool for randomized controlled trials (RoB 2) [14]. Five domains were evaluated: the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results. Any discrepancies were resolved through discussion, with a third party consulted for judgment if necessary.

To evaluate the risk of bias in non-randomized trials, we employed the ROBINS-I tool (Risk Of Bias In Non-randomized Studies of Interventions) [15]. It evaluates potential bias across seven domains: (1) bias due to confounding, (2) bias in the selection of participants, (3) bias in the classification of interventions, (4) bias due to deviations from intended interventions, (5) bias due to missing data, (6) bias in the measurement of outcomes, and (7) bias in the selection of the reported result. Each study was judged on these domains and categorized as having a "low," "moderate," "serious," or "critical" risk of bias, following the detailed criteria provided by ROBINS-I [15].

Outcomes

In this meta-analysis, the comprehensive rating scales were analyzed to compare the clinical effectiveness between CDS-based and IL treatment in patients with early to mid-stage PD. The primary outcomes are comprehensive rating scales: Unified Parkinson's Disease Rating Scale (UPDRS) II and UPDRS III; the secondary outcomes are ON time without troublesome dyskinesia, and OFF time. In general, higher UPDRS II and III scores indicate increased severity.

Statistical Analysis

For continuous outcomes, we calculated the mean difference (MD) and corresponding 95% CIs for each study. If studies used the same measurement tool/scale, the mean changes from baseline data were combined in the analysis. For studies that did not report change values, change values were calculated from baseline and endpoint values by referring to the formulae in the Cochrane handbook [16].

Heterogeneity was assessed using the I^2 statistic [17]. To account for variations between studies, we applied a random effects model to calculate the overall MD for each outcome. Subgroup analyses were also conducted, considering different doses (i.e., 200 mg versus a mix of levodopa and other drugs) of levodopa and follow-up duration. To further test the robustness of the meta-analysis, sensitivity analysis of potential heterogeneity factors was used.

All statistical analyses were performed using Review Manager Software (RevMan version 5.4; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). If data were extracted from figures, the Web Plot Digitizer 4.7 software was used. Two-sided statistical tests were conducted, with significance level set at $P<0.05$, unless specified otherwise.

Ethical Approval

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

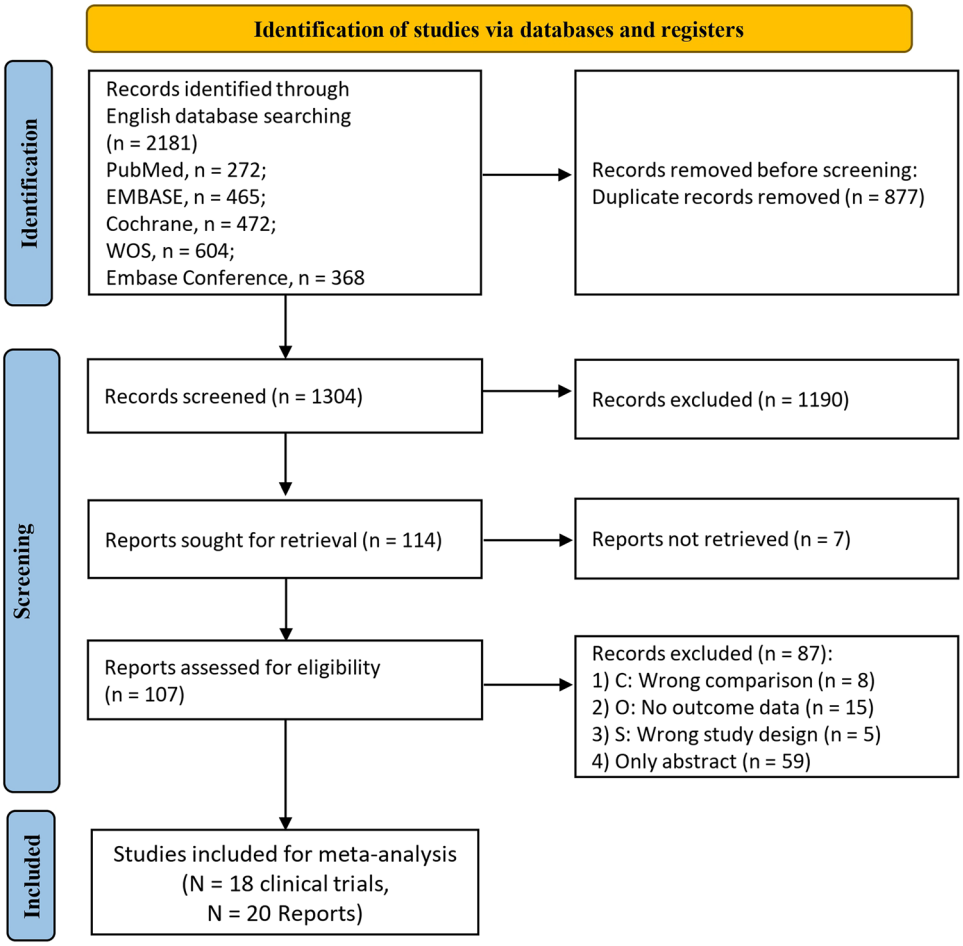

Fig. 1 Systematic identification of published literature on continuous dopaminergic stimulation (CDS)-based levodopa treatment of patients with early to mid-stage Parkinson's disease

RESULTS

Overview of Studies Included in the Meta-Analysis

After duplicates were eliminated, a total of 1304 articles were initially identified, and 1190 articles were excluded. Following a comprehensive review of 107 full-text articles, we ultimately selected 18 clinical trials, comprising 20 articles [18–37], for inclusion in this meta-analysis (Fig. 1). These clinical trials involve a total of 2208 patients with early to mid-stage PD, ranging in age from 30 to 84. Of these patients, 62.9% were male ($N = 1270$), while 37.1% were female ($N = 749$). Two studies did not provide gender information [22, 32]. The details of these studies are summarized in Table S1.

The quality assessment of randomized controlled trials is presented in Fig. S1. Notably, many studies show a low risk of bias related to the randomization process (11/14, 78.6%), deviations from the intended intervention (9/14, 64.3%), or missing outcome data (11/14, 78.6%). Only one study was deemed to exhibit some concerns regarding missing outcome data. For the domains of measurement bias and reporting bias, most studies showed some concerns. Overall, six studies demonstrated a high risk of bias, while the remaining eight studies exhibited some concerns regarding the risk of bias.

The quality assessment of non-randomized trials is presented in Table S2. Notably, all four

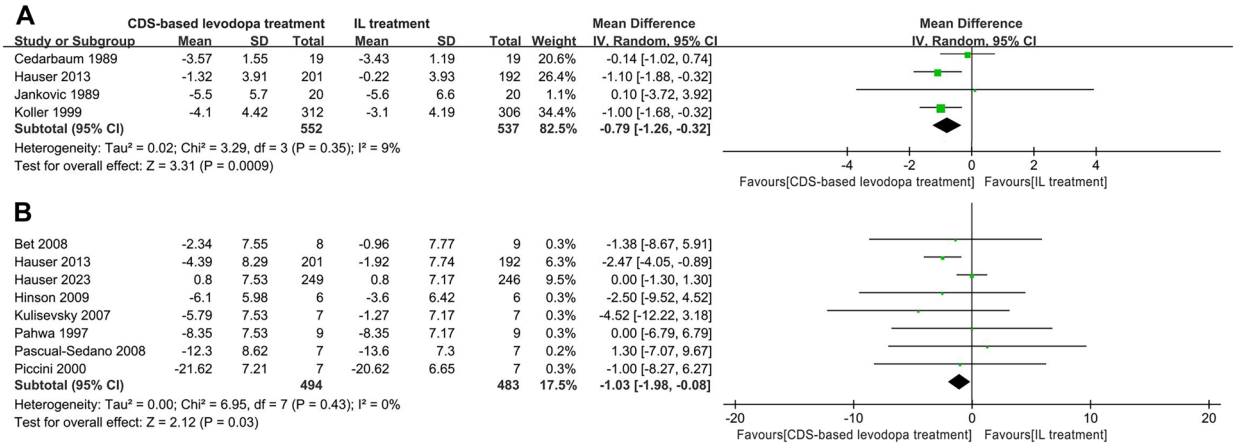

Fig. 2 Meta-analysis of UPDRS II (**a**) and UPDRS III scores (**b**) between continuous dopaminergic stimulation (CDS)-based levodopa treatment and intermittent levodopa (IL) treatment at the different dosing of levodopa

studies showed a moderate risk of bias related to the confounding, one study showed a serious bias in selection of participants into the study, two studies showed moderate bias in classification of interventions, and in other domains the four studies all showed low risk of bias. Overall, one study demonstrated a serious risk of bias, while the remaining three studies exhibited moderate risk of bias.

UPDRS II Scores

For the UPDRS II score, five studies were identified, comprising a total of 552 patients in the CDS-based levodopa treatment group and 537 patients in the IL treatment group (Fig. 2a). A low degree of heterogeneity was evident across these studies (I^2=9%). The mean difference in UPDRS II scores between CDS-based levodopa and IL use was – 0.79 (95% CI – 1.26, – 0.32; p=0.0009).

In a subgroup analysis based on the dosing of CDS-based levodopa, UPDRS II scores did not significantly differ between CDS-based levodopa and IL use, whether the dosage was 200 mg or a mix of levodopa and other drugs (Fig. S2). The mean differences were – 0.62 (95% CI – 1.27, 0.02; p=0.06) and – 1.10 (95% CI – 1.88, – 0.32; p=0.005), respectively.

Further subgroup analysis based on different follow-up periods revealed the mean difference in UPDRS II scores between CDS-based levodopa and IL treatments at the 3–12 months follow-up were –0.63 (95% CI – 1.37, 0.12; p=0.1) with little heterogeneity (I^2=27%). Another study [21] reported the data of 2, 3, 4, and 5 years, and all showed significant difference (Fig. S3).

Notably, this study included both randomized controlled trials and non-randomized trials. After non-randomized trials were excluded for sensitivity analysis, the overall mean difference in UPDRS II scores between CDS-based levodopa and IL use was – 1.02 (95% CI – 1.53, – 0.52; p<0.0001) in the meta-analysis of randomized controlled trials (Fig. S4).

UPDRS III Scores

Regarding the UPDRS III score, eight studies were identified, including 494 patients in the CDS-based levodopa group and 483 patients in the IL group (Fig. 2b). No heterogeneity was observed among the studies (I^2=0%). Overall, the mean difference in UPDRS III scores between CDS-based levodopa and IL use was – 1.03 (95% CI – 1.98, – 0.08; p=0.03).

For subgroup analysis based on the dosing of CDS-based levodopa, there were a total of 464 patients in the CDS-based levodopa group and 452 patients in the IL group. The UPDRS III scores did not significantly differ between CDS-based levodopa and IL use, regardless of whether the dosage was 200 mg (with levodopa

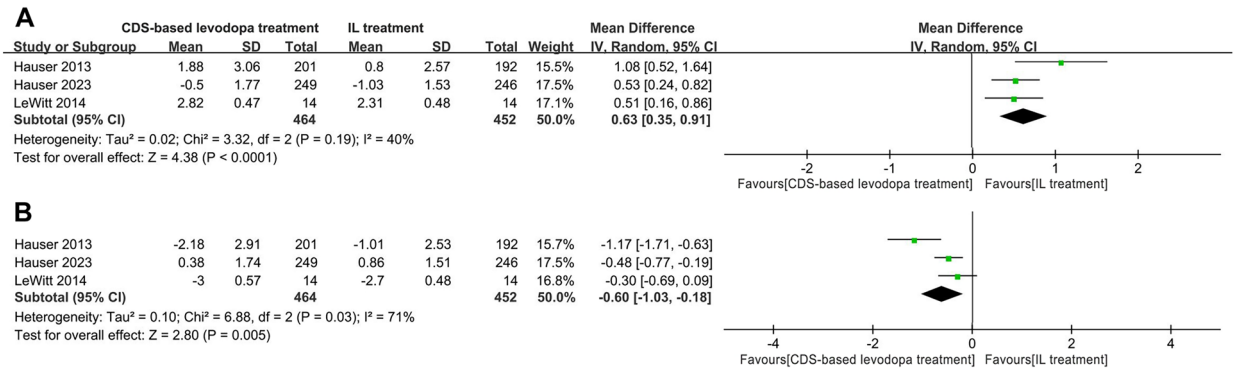

Fig. 3 Meta-analysis of ON time without troublesome dyskinesia (good ON time, **a**) and OFF time (**b**) between continuous dopaminergic stimulation (CDS)-based levodopa treatment and intermittent levodopa (IL) treatment

equivalent daily dose 150 mg vs. 166/266 mg or 300 mg vs. 400 mg among CDS-based levodopa group and IL group) or a combination of levodopa and other drugs at different dosages (Fig. S5). The mean differences were – 1.20 (95% CI – 4.74, 2.34; $p = 0.51$; $I^2 = 0\%$) and – 1.25 (95% CI – 3.26, 0.76; $p = 0.22$; $I^2 = 55\%$), respectively. There was either no or a moderate level of heterogeneity among these studies.

Further subgroup analysis based on different follow-up periods (< 3 months and 3–6 months) showed no significant differences in UPDRS III scores between CDS-based levodopa and IL use (Fig. S6). The mean differences were – 1.38 (95% CI – 4.39, 1.62; $p = 0.37$) and – 1.19 (95% CI – 3.61, 1.23; $p = 0.33$), respectively.

After non-randomized trials were excluded for sensitivity analysis, the mean difference in UPDRS III scores between CDS-based levodopa and IL use was – 1.24 (95% CI – 2.73, 0.26; $p = 0.11$) in the meta-analysis of randomized controlled trials (Fig. S7). This suggests no significant differences in UPDRS III scores between CDS-based levodopa and IL use when considering only randomized controlled trials.

ON Time Without Troublesome Dyskinesia

In terms of good ON time, three studies [23, 24, 28] were identified with a total of 464 patients in the CDS-based levodopa treatment group and 452 patients in the IL treatment group (Fig. 3a). A low degree of heterogeneity was evident across these studies ($I^2 = 40\%$). Overall, the mean difference in good ON time between CDS-based levodopa and IL use was 0.63 (95% CI 0.35, 0.91; $p < 0.0001$).

OFF Time

For OFF time, three studies [23, 24, 28] were identified, comprising a total of 464 patients in the CDS-based levodopa treatment group and 452 patients in the IL treatment group (Fig. 3b). A moderate degree of heterogeneity was evident across these studies ($I^2 = 71\%$). Overall, the mean difference in OFF time between CDS-based levodopa and IL use was – 0.60 (95% CI – 1.03, – 0.18; $p = 0.005$).

DISCUSSION

This systematic review and meta-analysis, involving 18 clinical trials with a total of 2208 patients, provides a comprehensive assessment of the effectiveness of the CDS-based levodopa treatments in patients with early to mid-stage PD. The analyses provide robust evidence for the potential benefits of CDS-based levodopa treatments in this patient population. We observed significant improvements in UPDRS II and III scores, as well as increased good ON time without troublesome dyskinesia and decreased OFF time.

To our knowledge, this is the first meta-analysis of clinical trials specifically evaluating the effectiveness of CDS-based levodopa treatments in patients with early to mid-stage PD. Our findings support previous research highlighting the effectiveness of CDS-based levodopa treatments in managing motor complications associated with PD [6, 38]. Furthermore, our study extends the existing evidence by focusing on patients with early to mid-stage PD, a cohort often underrepresented in previous meta-analyses [38].

The significant improvement in UPDRS II scores with CDS-based levodopa treatments suggests better motor experiences of daily living in patients with early to mid-stage PD. This improvement could be attributed to the more stable and continuous dopamine delivery to the brain, which potentially reduces the non-physiological, pulsatile stimulation of striatal dopamine receptors associated with IL administration [6, 39]. These findings are consistent with previous evidence, demonstrating improved motor control with CDS-based treatments [20]. Furthermore, the subgroup analysis did not show significant differences in UPDRS II scores based on the dosing of CDS-based levodopa, indicating that the protective impact is not dosage-dependent. However, the protective effect of CDS-based levodopa was more pronounced in the short term (3–6 months) but may appear to diminish over longer follow-up periods. This could be due to the progression of the disease, the rise in adverse effects, and the development of drug tolerance [9, 37].

Similarly, a significant improvement was observed in UPDRS III scores following CDS-based levodopa treatments, indicating enhanced management of motor functions in early to mid-stage PD. This improvement could be attributed to the sustained release feature of the drug, which ensures a steady and continuous dopamine supply to the brain. Previous research has validated the effectiveness of sustained-release formulations in improving motor symptoms [20, 33, 37]. However, subgroup analyses did not show significant differences in UPDRS III scores over shorter follow-up periods. This may be due to the unique attributes of the studies or the participants involved.

In terms of motor complications, CDS-based levodopa treatments significantly increased "good ON time" and decreased "OFF time," implying an improvement in motor complications. This benefit may be due to the continuous dopaminergic stimulation that stabilizes dopamine levels, thereby reducing fluctuations and the associated motor complications [33]. These findings in improving motor complications have been validated by previous studies [20, 40]. The source of heterogeneity in OFF time identified could be multifactorial, which may be due to the differences in baseline study characteristics, disease severity, or treatment adherence.

While the observed reductions in UPDRS II and III scores (approximately 1 point) and changes in ON time and OFF time (less than 1 h) are modest, their clinical relevance in patients with early to mid-stage PD should not be overlooked. In this population, where symptom burden is less pronounced, small improvements in motor function and daily activities may still enhance quality of life, particularly as the disease progresses. Notably, established minimum clinically important difference (MCID) values [41, 42] are often derived from advanced PD cohorts, suggesting a need for stage-specific MCID research.

Sustained-release levodopa formulations, while offering significant benefits, are not without limitations. Levodopa's primary absorption in the upper small intestine means prolonged release may deliver the drug beyond this optimal site, potentially reducing bioavailability and leading to inconsistent plasma concentrations [43]. Additionally, delayed onset of action [44]—particularly evident in the early morning—often necessitates adjunctive immediate-release levodopa, while dietary protein and interindividual variability further complicate absorption and dose titration. These factors may limit the ability of sustained-release formulations to achieve optimal CDS, potentially attenuating their clinical impact.

Our study focused on CDS-based levodopa treatments, whereas long-acting dopamine agonists represent another CDS strategy for early to mid-stage PD. These agents may offer advantages such as reduced pulsatile stimulation and fewer absorption-related issues compared to sustained-release

levodopa, though they are associated with distinct side-effect profiles (e.g., impulse control disorders) [45]. Direct comparisons between these approaches could elucidate their relative efficacy and tolerability in this population.

For patients with mid-stage PD where motor complications persist despite optimized oral therapies, advanced CDS options such as levodopa-carbidopa intestinal gel (LCIG) [46] or subcutaneously administered foslevodopa-foscarbidopa [47] may provide superior dopaminergic stability, potentially improving quality of life where sustained-release formulations fall short.

Given these limitations, future research should focus on developing novel levodopa formulations or delivery systems that enhance bioavailability, minimize variability, and ensure more consistent CDS, potentially amplifying the clinical benefits observed in our study.

One of the primary strengths of this study is its comprehensive inclusion of clinical trials that directly compare CDS-based levodopa treatments with traditional IL therapies in patients with early to mid-stage PD. This focus addresses a critical gap in the current literature and provides robust evidence for the clinical benefits of CDS-based treatments. Moreover, using the revised RoB 2 tool ensured a rigorous assessment of study quality. Our study not only evaluates the efficacy of CDS-based levodopa treatments in patients with early to mid-stage PD but also conducts subgroup and sensitivity analyses on other outcomes, further strengthening the robustness of our findings.

However, several limitations must be acknowledged in this study. The inclusion of both randomized controlled trials and non-randomized trials may introduce potential heterogeneity and bias. Although sensitivity analyses were performed to evaluate the robustness of our findings, the inherent limitations of non-randomized trials remain unavoidable. The variability in dosage regimens, follow-up periods, and patient baseline characteristics across the included trials further complicates the situation and potentially introduces additional bias. Moreover, the reliance on published data and potential publication bias are inherent limitations of meta-analysis. Lastly, the majority of studies included in our analysis had relatively small sample sizes, which may impact the reliability of our conclusions. To address this, larger-scale randomized controlled trials are required to generate more robust evidence.

CONCLUSIONS

This meta-analysis provides strong evidence supporting the advantages of CDS-based levodopa treatments in patients with early to mid-stage PD, particularly in improving motor functions and reducing complications. The findings underscore the significance of sustained dopaminergic stimulation in PD management and offer valuable insights into their potential advantages compared to traditional IL treatments. The results have important implications for clinical practice, suggesting that CDS-based levodopa may serve as a primary treatment option to improve patient outcomes and quality of life. Future research should prioritize investigating the long-term effects, optimal dosing methods, and the underlying mechanisms responsible for the benefits observed with CDS-based levodopa treatments. Additionally, studies establishing MCID values tailored to patients with early to mid-stage PD would better contextualize these findings. Comparative studies that evaluate the effectiveness of sustained-release levodopa, long-acting dopamine agonists, and advanced therapies like LCIG or foslevodopa-foscarbidopa in patients with PD could further optimize CDS strategies.

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Author Contributions. All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Rong Tang, Yunxing Hu, Sunying Zhang, Rui Sun, Jiacheng Xu and Hongyu Tan. The first draft of the manuscript was written by Ling Chen and Rong Tang, all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data Availability. All data generated or analyzed during this study are included in this published article and supplementary information files.

Declarations

Conflict of Interest. Yunxing Hu, Hongyu Tan and Ling Chen stated they have no conflicts of interest to disclose. Rong Tang, Sunying Zhang, Jiacheng Xu, and Rui Sun are employees of Organon (Shanghai) Pharmaceutical Technology Co., Ltd.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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