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# Continuous dopaminergic stimulation (CDS)-based treatment in Parkinson's disease patients with motor complications: A systematic review and meta-analysis

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A systematic review of the literature was conducted to identify randomized trials involving continuous dopaminergic stimulation (CDS) in PD patients with motor complications. Difference between n groups was assessed by partitioning heterogeneity and using the  $\chi^2$  distribution with n-1 degrees of freedom, where n equals the number of groups. We looked for publication bias using funnel plotting, Egger's test and Begg's test. Twenty Randomized Controlled Trials (RCTs) were included. The results showed that CDS could evidently improve the Unified Parkinson's Disease Rating Scale (UPDRS) Part II ( $p < 0.0001$ ), part III ( $P < 0.00001$ ) and UPDRS total score ( $p < 0.00001$ ). There was also a statistical discrepancy in off time reduction ( $p < 0.00001$ ) and prolongation of on time ( $p < 0.00001$ ) by the CDS therapy compared with control groups. Meanwhile, the results of this study showed obvious side effects in the CDS therapy compared with the placebo, especially at the expense of increased dyskinesia (23.4% vs 11.7%). The present study showed that CDS was beneficial in the treatment of PD patients with motor complications. But the incidence of the side events is more common than placebo.

Parkinson's disease (PD) is a progressive central nervous system disorder affecting at least six million people worldwide, making it being the second common neurodegenerative disease after Alzheimer's disease<sup>1</sup>. At the same time, with a growing elderly population and a reduction in other causes of mortality, the prevalence of PD is likely to increase<sup>2</sup>. The burden of PD is speculated to grow substantially over the next few decades as the size of the elderly population grows. Such projections give impetus to the need for innovative new treatments to prevent, delay onset, or alleviate symptoms of PD<sup>3</sup>. To our knowledge, the gold standard treatment for PD still is oral L-dopa because of its excellent efficacy and tolerability<sup>4</sup>. However, long-term use with oral L-dopa administration leads to various motor complications, including the "wearing-off" phenomenon and involuntary movements<sup>5</sup>. Motor complications occur in up to 50% of patients taking L-dopa more than 5 years and in as many as 100% of patients with young-onset PD, and are a dominating cause of disability. This presents a particular challenge to managing advanced PD patients. The motor complications are supposed to be the result of a combination of progressive denervation of the striatum and long-term abnormal, intermittent drug administration leading to pulsatile stimulation of dopaminergic neurons<sup>6,7</sup>. Over time, this pulsatile stimulation results in gene and protein changes in striatal dopaminergic neurons, affecting firing patterns in basal ganglia output neurons and ultimately leads to motor complications<sup>8</sup>. Moreover, in animal models of PD, intermittent but not continuous administration of L-dopa can lead to the wearing-off phenomenon and dyskinesia<sup>9</sup>. All of these results provide the rationale for treating patients with continuous dopaminergic stimulation (CDS) approach.

The concept of CDS has received considerable attention as a therapeutic approach to the treatment of Parkinson's disease<sup>10</sup>. Long-acting dopaminergic agents matched to provide comparable motor improvement to L-dopa treated animal models, but experience an evidently reduced frequency and severity of motor complications<sup>11</sup>. What is more, clinical studies of L-dopa/carbidopa intraduodenal gel infusion revealed marked reductions

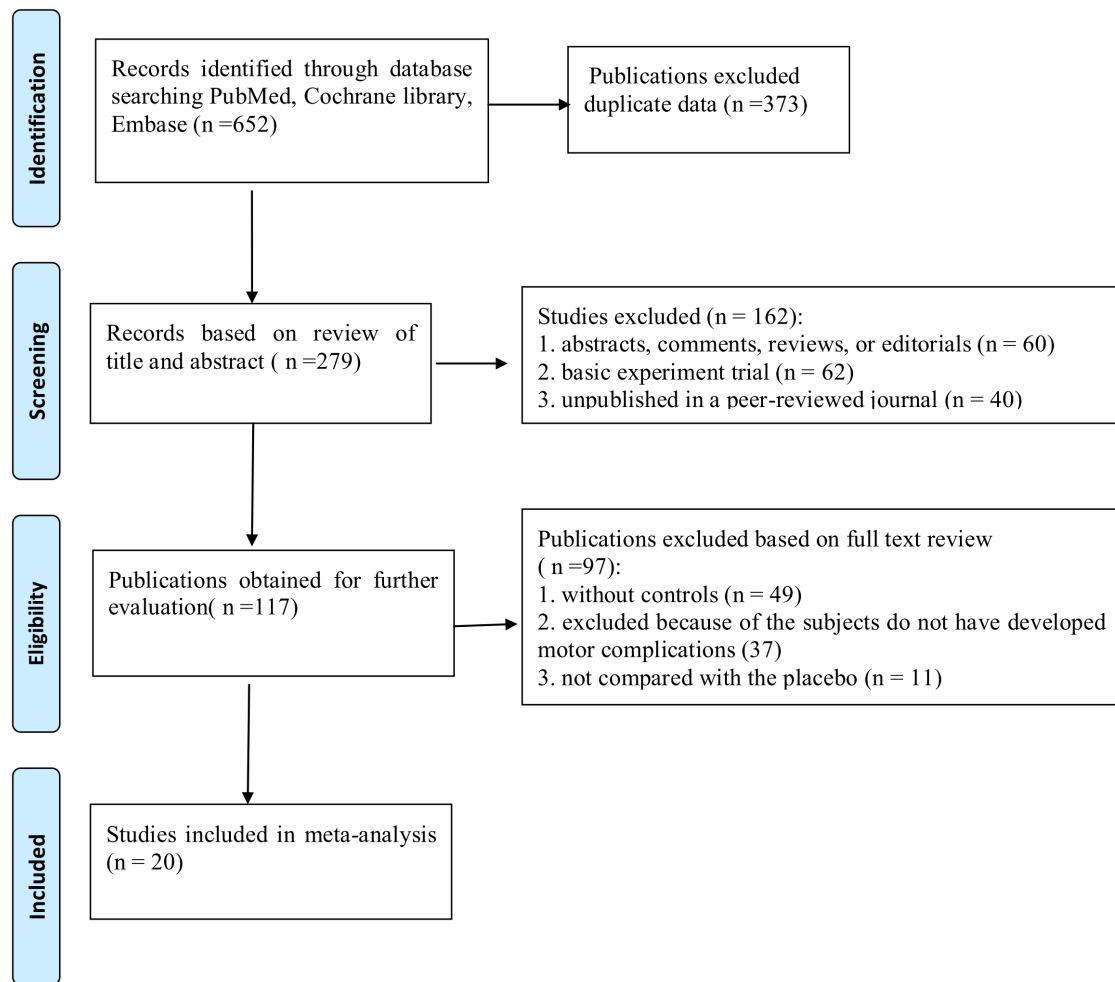


Figure 1 | PRISMA 2009 Flow Diagram.

in ‘off’ time along with improvement in ‘on’ time when compared with conventional treatment<sup>12</sup>. Recent numerous evidences suggest wide-ranging symptoms improvement with CDS in patients with severe motor complication, which has beneficial implications for the management of patients with advanced PD in clinical practice<sup>13</sup>. This theory proposes that CDS can provide more continuous stimulation of brain dopaminergic receptors than intermittent doses of oral L-dopa, which is indicate dyskinesia and motor fluctuations could be delayed even though prevented by realizing continuous stimulation of striatal dopamine receptors using long-acting medicines such as dopamine agonists<sup>14</sup>.

Nevertheless, the CDS theory has fallen out of favor for a variety of reasons. Some studies reported the incidence of dyskinesia had not been proven to be directly correlated with drug half-life<sup>15</sup>. In addition, many of these studies are of small sample size and thus cannot fully elucidate the efficacy and safety implications of the therapy. Hence, there is uncertainty whether CDS is more effective than another in the PD patients with motor complications. We therefore conducted the present meta-analysis by pooling the results of these trials in order to provide more useful information about efficacy and safety of CDS in the PD patients with motor complications.

## Results

This Meta-analysis is conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses<sup>16</sup>.

**Study inclusion.** We identified 652 potentially relevant articles from six databases. After removal of duplicates, 279 records remained.

After going through the titles and abstracts, 162 were excluded because they failed to meet the inclusion criteria. By reading the full text of the remaining 117 articles as possibly reporting the CDS for the PD patients with motor complications, 49 studies were excluded because a result of without control groups, 37 were excluded because of the subjects did not have developed motor complications, 11 studies were excluded due to not compared with the placebo. Ultimately, 20 eligible studies satisfied the pre-established inclusion criteria<sup>17–36</sup> (Figure 1).

**Characteristics of studies.** Twenty studies with 3234 PD patients with motor complications were retrieved based on the search criteria<sup>17–36</sup>. Among them, only 2 studies belong to L-dopa drug class, remaining 18 studies were dopamine agonist’s drug class. The number of participants randomised into the 20 trials included in this meta-analysis ranged from 24<sup>28</sup> to 393<sup>32</sup> participants. The mean age of the participants in the trials was approximately 64 years. Meanwhile, 64% of the participants were male and they had PD for approximately 8 years. The duration of treatment was varied from 6 weeks<sup>28</sup> to 32 weeks<sup>22</sup>. UPDRS as the outcome measure was observed in 15 studies, the change of the on/off time was observed in 12 studies, adverse effects were reported in 19 studies. Of the L-dopa drug class, L-dopa intraduode infusion and intrajejunal infusion of levodopa/carbidopa intestinal gel were administrated in 1 study, respectively<sup>28,36</sup>. In the dopamine agonists drug class, pramipexole were administrated in 8 studies (8/18, 44.4%), ropinirole were used in 3 studies (3/18, 16.7%), cabegoline and bromocriptine as the intervention therapy in 2 studies. What is more, lisuride infusion<sup>27</sup>,



rotigotine transdermal system<sup>30</sup> and subcutaneous apomorphine infusion<sup>34</sup> in 1 study, respectively. There were 3 three-arm trials comparing with the placebo. The basic characteristics of each case control study were listed in Table 1.

**Risk of bias in included studies.** We utilized the criteria recommended by Cochrane Handbook for Systematic Reviews to assess the risk of bias in the 20 articles included. Although all included studies claimed randomization, 11 articles described the method of random sequences generation (for example, random number generator, computer generated). But only 5 trials gave information that allowed the assessment of whether an adequate concealment of allocation procedure was used. All the studies reported the blinding of participants except two trials<sup>27,34</sup>. Non-selective reporting was found in 14 trials. Three studies existed certain degree other potential threats to validity. Therefore, all of the included trials were deemed to have a low risk of bias. The methodological quality of each study was summarized in Table 2.

**Meta analysis results.** *UPDRS.* Data on the clinician-rated UPDRS Part II scores were available from 8 trials with 1 trials of L-dopa drug class and 7 trials of dopamine agonist's drug class. For the UPDRS Part II score, there were 2034 participants included in the analysis. We pooled the whole data to process and found significant difference when CDS treatment compared with placebo ( $p < 0.0001$ , standard mean difference (SMD) =  $-3.04$ , 95% CI:  $-4.51$  to  $-1.57$ , Figure 2A). Nevertheless, there was severe heterogeneity for the analysis of UPDRS Part II between studies ( $\text{Tau}^2 = 4.46$ ,  $\text{Chi}^2 = 960.54$ ,  $p < 0.00001$ ,  $I^2 = 99\%$ , Figure 2A). Consequently, we should interpret the pool result prudently. The remaining three studies failed to pool analysis due to the raw data demonstrated in the form of percentage improvement (%) or missing, but all of them reported the significant effects of CDS for ameliorating the UPDRS Part II compared with the placebo group ( $p < 0.05$  or  $p < 0.01$ ). Compared to placebo treatment, ten independent studies showed significant effects of CDS therapy for improving the UPDRS Part III scores ( $P < 0.00001$ , SMD =  $-2.16$ , 95% CI  $-3.10$  to  $-1.23$ ; heterogeneity  $\text{Tau}^2 = 2.17$ ,  $\text{Chi}^2 = 632.53$ ,  $p < 0.00001$ ,  $I^2 = 99\%$ , Figure 2B), suggesting that CDS treatment could contribute to improving complications of treatment in patients with PD with motor complications, but the remaining two studies did not provide raw data and thus failed for meta-analysis. There were 3 studies included in the meta-analysis to comparing CDS with placebo according to the UPDRS total score as the outcome index. We pooled the trials and found significant difference between two groups ( $p < 0.00001$ , SMD =  $-0.63$ , 95%CI:  $-0.83$  to  $-0.44$ , Figure 2C) without heterogeneity ( $\text{Tau}^2 = 0.00$ ,  $\text{Chi}^2 = 2.13$ ,  $p = 0.34$ ,  $I^2 = 6\%$ , Figure 2C), indicating CDS could apparent ameliorate the symptoms of the PD patients with motor complications. The funnel plot was roughly symmetric for the effect of CDS on UPDRS score. Thus, funnel plots did not suggest an obvious publication bias (Figure 3A). Meanwhile, Egger's weighted regression ( $p = 0.246 > 0.05$ , Figure 3B) and Begg's test ( $p = 0.755 > 0.05$ , Figure 3B) both suggested low likelihood of publication bias for all analysis.

**Prolongation of on time and off time reduction.** A total of 3 trials evaluated CDS treatment versus placebo in patients of on time increase. Patients had greater response to CDS than placebo as evidenced by obvious significant effects of CDS for prolongation of on time compared with control groups ( $p < 0.00001$ , SMD =  $2.59$ , 95%CI:  $2.35$  to  $2.83$ , Figure 4A). The average on time increased by 2.3 hours for CDS treatment and by 0.7 hours for the placebo group, which was apparent statistical difference between CDS and placebo. Data on off-time reduction were available from 6 trials including 930 participants. Compared to placebo, CDS significant reduced off-time by approximately 2.0 hour a day ( $p < 0.00001$ , SMD =  $-4.34$ , 95%CI:  $-5.82$  to  $-2.86$ , Figure 3C). Nevertheless, there was severe

heterogeneity between trials ( $\text{Tau}^2 = 3.08$ ,  $\text{Chi}^2 = 157.33$ ,  $p < 0.00001$ ,  $I^2 = 97\%$ , Figure 4B). Some studies failed to pool analysis due to the aforementioned reasons.

**Adverse effects.** Adverse effects (AE) were reported in 20 studies. CDS in general showed statistically significant higher rates of AE than placebo (Data not showed). There was significant difference of adverse events including incidences of dyskinesia (23.4% vs 11.7%), nausea (14.7% vs 9.3%), dizziness (6.53% vs 4.5%), diarrhea (3.44% vs 1.6%) between the CDS and placebo. However, there was no obvious discrepancy of insomnia (4.7% vs 4.1%).

## Discussion

**Main findings.** Our meta-analysis found that CDS could evidently improve the UPDRS Part II, part III and UPDRS total score compared with placebo in PD patients with motor complications. There was also a statistical significance in off time reduction and prolongation of on time by the CDS therapy. These results displayed that patients receive CDS experienced significant improvement in both "off" and "on" time, as well as in improving the UPDRS subscale score in PD patients with motor complications. However, the results of this study showed obvious side effects in the CDS therapy compared to the placebo, especially at the expense of increased dyskinesia. Hence, it was necessary to detect the optimal therapeutic efficacy to balance the incidence of adverse events. To our best knowledge, it was no question that CDS was beneficial in the treatment of PD patients with motor complications. But it was less clear which class of drug therapy was more effective between L-dopa drug class and dopamine agonist drug class. We failed to draw conclusion which was more effective based on the present meta-analysis due to only two studies focused on the L-dopa drug class. In terms of AE, two kinds of drugs have a nearly similar incidence of AE, both higher rates than placebo.

**Interpretation of the results.** CDS has been influential in recent years and has lead to increased prevalence of dopamine agonists for PD<sup>37</sup>. Under normal physiologic condition, the dopamine concentration in the striatum is maintained at constant levels<sup>38</sup>. Therefore, continuous stimulation of postsynaptic receptors is thought to be essential for normal basal ganglia function<sup>39</sup>. Meanwhile, motor complications are associated with non-physiologic intermittent or pulsatile stimulation of dopamine receptors<sup>40</sup>. Based on such theory, CDS has been shown to reduce motor complications in advanced PD patients, and has been hypothesized to prevent their incidence when given as early therapy in PD<sup>13</sup>. Indeed, some basic researches showed treatment with intermittent injections of a short-acting dopamine agonist induced motor complications while continuous infusion of the same agent did not<sup>11</sup>. But, whether CDS can reduce the development of dyskinesia has yet to be studied. STRIDE-PD study reported initial therapy with carbidopa-levodopa-entacapone result in an increased frequency of dyskinesia compared to standard carbidopa/levodopa<sup>41</sup>. Moreover, laboratory and clinical studies have indicated that although dyskinesias are closely linked to the short serum half-life of levodopa, other factors may also play a pivotal role in the pathogenesis<sup>7</sup>. Consequently, CDS is no doubt effective to manage the PD patients with motor complications, but it may cause serious side effects, especially at the expense of increased dyskinesia.

**Limitations.** Several limitations of this study should be considered. Firstly, a large proportion of the studies included in this review are of six months or less in duration. Among the 20 studies, a very large proportion of studies treatment duration are less than one years, suggesting that there are insufficient data on the comparative efficacy and tolerability of these drugs beyond six months. In such a chronic long-term disease as PD, it would inevitable be valuable to know whether the drug actions persist for a much longer period. Secondly, The role of potentially useful CDS such as levodopa-



Table 1 | Basic characteristics of included studies

study	Basic data: Numbers, Male/Female, MA, DOD (y), MLD		Intervention#	Main outcomes
	Trial group	Control group		
<b>Toyokur 1985</b> <sup>17</sup>	114,59/55,62.5 ± 0.9 Y, NR, 418 ± 20.7 mg	108,50/58,63.2 ± 0.9 Y, NR,465 ± 22.3 mg	Bromocriptine (22.5 mg/d) for 18 w	1.AE
<b>Olanow 1994</b> <sup>18</sup>	189,116/73,62.5 ± 8 Y,11.4 ± 5.5 Y,891 ± 420 mg	189,123/64,63 ± 8 Y,10 ± 5.3 Y, 940 ± 496 mg	Pergolide(5 mg/d) for 24 w	1. UPDRSII-III (p1); 2.AE
<b>Steiger 1996</b> <sup>19</sup>	19,NR, 60.8 ± 9.1, 13.6 ± 7.5,NR	18,NR, 63.4 ± 7.2, 11.9 ± 7.2,NR	Cabergoline(5 mg/d) for 3 m	1.on/off time(p1), 2.AE
<b>Hutton 1996</b> <sup>20</sup>	123,83/40,63.4 ± 10 Y, 10.6 ± 5.9 Y,NR	65,42/23, 62.8 ± 8.9 Y, 10.5 ± 5.0 Y, NR	Cabergoline(1.0 mg/d) for 24 w	1. UPDRSII-III (p1); 2.AE
<b>Rascol 1996</b> <sup>21</sup>	23,14/9,62 ± 7 y,8 ± 2 y,663 ± 302 mg	23,14/9,63 ± 9 y,8 ± 3 y, 715 ± 353 mg	Ropinirole (8 mg/d) for 3 m	1.off time (p1); 2.AE
<b>Lieberman 1997</b> <sup>22</sup>	181,119/62, 63.4 y, 9.4 y, NR	179,116/63, 63.3 y, 9.0 y, NR	Pramipexole(4.5 mg/d) for 32 w	1.UPDRS(IP2),2.UPDRSII-IV(P1),3.AE
<b>Guttman 1997</b> <sup>23</sup>	FA:79,48/31,62.89 ± 10.02 y,6 y, NR SA:84,55/29,61.51 ± 9.48 y,7.17 Y, NR	83,53/30,63.72 ± 10.35 y, 7.58 Y, NR	FA: pramipexole(4.5 mg/d) for 10 m; SA: Bromocriptine (30 mg/d)	1.UPDRS-IV (p1); 2. AE
<b>Wermuth 1998</b> <sup>24</sup>	36,20/16, 63.2 ± 7.9 y, 10.1 ± 5.0 y, NR	33,20/13, 62.1 ± 9.9 y, 9.9 ± 4.1 y, NR	Pramipexole(5 mg/d) for 12 w	1.UPDRS total (p1); 2.AE
<b>Lieberman 1998</b> <sup>25</sup>	95,NR,NR,8.6 ± 4.7 y,759 ± 422 mg	54,NR,NR,9.4 ± 6.3 y,843 ± 517 mg	Ropinirole (24 mg/d) for 6 m	1.off time (p1); 2.AE
<b>Pinter 1999</b> <sup>26</sup>	34,20/14, 59.3 ± 8.3 y, 7.8 ± 4.3 y, NR	34,20/14, 59.3 ± 8.3 y, 7.8 ± 4.3 y, NR	Pramipexole(1.25 mg/d) for 12 w	1.UPDRS-IV (p1); 2. UPDRS total (p1); 3.AE
<b>Stocchi 2002</b> <sup>27</sup>	20,NR,10 ± 2.1,688.2 ± 133.4 mg	20,NR,8.8 ± 2.7,675 ± 180.6 mg	Lisuride infusion(1 mg/ml) for 4 y	1.Off time (p1); 2.UPDRS III (p2); 3. AE
<b>Nyholm 2005</b> <sup>28</sup>	12,9/3,64,NR,NR	12,9/3,68,NR,NR	Intraduode infusion Levodopa for 6 w	1.on/off time; 2.UPDRS; 3.AE
<b>Moller 2005</b> <sup>29</sup>	174,108/66, 63.4 y, 7.6 y, 637,7 mg	180,122/58,64.7 y, 7.9 y,648,8 mg	Pramipexole(3.7 mg/d) for 25 m	1.off time (p1); 2. UPDRSII-III, total (p1) 3.AE
<b>Peter 2007</b> <sup>30</sup>	FA:111,63/48,63.2 ± 9.7 y,NR,NR SA:120,71/49,64.3 ± 9.0 y,NR,NR	120,73/47,65 ± 10 y, NR,NR	FA: rotigotine TS(12 mg/d) for 24 w; SA: rotigotine TS(8 mg/d)	1. UPDRSII-III (p1); 2. off time (p1); 3.AE
<b>Poewe 2007</b> <sup>31</sup>	FA:200,112/88,63.2 ± 9.7 y,NR, 813 ± 459 mg SA:201,132/69,64.3 ± 9.0 y,NR, 795 ± 380 mg	100,71/29,65 ± 10 y, NR,814 ± 398 mg	FA: pramipexole(4.5 mg/d) for 6 m; SA: rotigotine(16 mg/d)	1.on/off time(p1); 2. UPDRSII (p1) 3. UPDRSIII(p1); 4.AE
<b>R. Pahwa, 2007</b> <sup>32</sup>	202,118/84,66.3 ± 9.2 y, 8.6 ± 4.8 y,824 ± 424.4 mg	191,129/61,66.0 ± 9.7 y, 8.6 ± 5.2 y,776 ± 357.3 mg	Ropinirole 24-hour (18.8 mg/d) for 24 w	1.on/Off time (p1); 2. UPDRS motor (p1) 3.UPDRS II(p1); 4.AE
<b>Hauser 2009</b> <sup>33</sup>	FA:24,19/5,64.3 ± 7.8 y,NA, 769.8 ± 284.9 mg SA:26,21/5,65.2 ± 9.3 y,NR, 775.0 ± 397.1 mg	11,6/5,65.1 ± 7.8 y,NA,638.6 ± 204.1 mg	Pramipexole(4.5 mg/d) for 7 w;	1.on/off time (p1); 2.AE
<b>Pablo 2011</b> <sup>34</sup>	17,NA,59.5 ± 11.7 Y,12.05 ± 4.2 Y, 1077.81 ± 446.26 mg	17,NA,66.4 ± 7.0 Y,13.23 ± 4.7 Y, 1028.18 ± 388.76 mg	Apomorphine (12–16 hrs/day) subcutaneous infusion	1. UPDRSIII (p1)
<b>Schapira 2011</b> <sup>35</sup>	164,92/72,61.6 ± 9.7 y, 6.1 ± 4.0 y,NR	178,94/84,60.9 ± 9.7 y, 5.9 ± 3.8 y, NR	Pramipexole(4.5 mg/d) for 18 w	1. UPDRSII-IV; 2.on time (p1); 3.AE
<b>Olanow 2014</b> <sup>36</sup>	37,24/13,63.7 ± 9.5 y, 10 ± 4.6 y, NA	34,22/12,65.1 ± 6.8 y, 11.8 ± 5.6 y, NA	Intrajejunal infusion of levodopa/carbidopa intestinal gel for 12 w	1. UPDRSII-III (p1); 2.on/off time(p1) 3. AE

FA: first arm; SA: second arm; MA: mean age; DLT: Duration of levodopa treatment; MLD: mean levodopa dosage; Y: years; M: months; W: weeks; d: days; NR: no report; #: indicate the maximum dosage in the study; p1: p < 0.05; P2: P > 0.05; TS: transdermal system; UPDRS: Unified Parkinson's Disease Rating Scale; AE: adverse events.



Table 2 | The methodological quality of included studies based on the Cochrane handbook

Study	A	B	C	D	E	F	Total
<b>Toyokur 1985</b> <sup>17</sup>	+	–	+	–	?	+	3
<b>Olanow 1994</b> <sup>18</sup>	?	–	+	–	+	–	2
<b>Steiger 1996</b> <sup>19</sup>	?	+	+	–	?	–	3
<b>Hutton 1996</b> <sup>20</sup>	?	–	+	–	+	+	3
<b>Rascol 1996</b> <sup>21</sup>	–	–	+	–	?	?	1
<b>Lieberman 1997</b> <sup>22</sup>	?	–	+	–	+	+	3
<b>Guttman 1997</b> <sup>23</sup>	?	–	+	+	?	+	3
<b>Wermuth 1998</b> <sup>24</sup>	+	–	+	–	+	?	3
<b>Lieberman 1998</b> <sup>25</sup>	+	–	+	–	+	+	4
<b>Pinter 1999</b> <sup>26</sup>	+	–	+	+	?	+	4
<b>Stocchi 2002</b> <sup>27</sup>	?	–	–	+	+	+	3
<b>Nyholm 2005</b> <sup>28</sup>	+	+	+	–	+	+	5
<b>Moller 2005</b> <sup>29</sup>	+	–	+	–	?	+	3
<b>Peter 2007</b> <sup>30</sup>	+	+	+	–	+	+	5
<b>Poewe 2007</b> <sup>31</sup>	?	+	+	–	+	+	4
<b>R. Pahwa, 2007</b> <sup>32</sup>	+	?	+	–	+	+	4
<b>Hauser 2009</b> <sup>33</sup>	+	–	+	–	+	+	4
<b>Pablo 2011</b> <sup>34</sup>	+	–	–	?	+	–	2
<b>Schapira 2011</b> <sup>35</sup>	–	?	+	?	+	+	3
<b>Olanow 2014</b> <sup>36</sup>	+	+	+	+	+	+	6

A: Sequence generation; B: Allocation concealment; C: Blinding of participants, personnel and outcome assessors; D: Incomplete outcome data; E: Selective outcome reporting; F: Other sources of bias; +: Yes; –: No; ?: Unclear.

carbidopa intestinal gel infusion, continuous duodenal infusion, subcutaneous apomorphine or lisuride infusion, continuous transdermal delivery of rotigotine were very inadequate in this meta-analysis. Although the fact that an extensive search for such studies was performed, most of them were not RCTs. Therefore, it is necessary to carry out more RCTs to assess the efficacy of such CDS in the PD patients with motor complications. Thirdly, patients included in the trials were not always on behalf of patients in clinic. Patients with Mini-Mental State Examination score less than 24, atypical parkinsonian syndromes, any history of deep brain stimulation, psychiatric or clinically significant hypotension were excluded. Thus, the results cannot be generalized to the entire population of PD patients with motor complications. Finally, high heterogeneity occurred several times when comparing CDS with placebo treatment. Inevitably, studies brought together in a systematic review will differ. Any kind of variability among studies in a systematic review or meta-analysis may be termed heterogeneity<sup>42</sup>. Variability in the participants, interventions, study design and risk of bias all can result in heterogeneity. To solve this problem, in this meta-analysis, random-effects model may be used to incorporate heterogeneity among studies. However, random-effects model is not a substitute for a thorough investigation of heterogeneity. It is intended primarily for heterogeneity that cannot be explained<sup>43</sup>.

**Implications for Practice.** This meta-analysis of RCTs mainly focuses on the efficacy and safety of CDS therapy in PD patients with motor complications. According to our meta-analysis, patients receiving CDS therapy exhibit significant ameliorate in their PD symptoms as evidenced by improvements in their UPDRS scores, as well as off time reduction compared with placebo. In terms of the safety assessment of this meta-analysis, CDS therapy in generally showed significant higher rates of adverse events than placebo, especially at the expense of increased dyskinesia. Although acknowledging the limitations of this meta-analysis, our findings present a majority of high-quality trials and provide hopefully evidences that CDS therapy can additionally benefit relieve symptoms of PD patients with motor complications.

**Implications for research.** A number of implications for research arise from this paper. Firstly, improvement in the methodological

quality of RCTs is critical for later trials and more methodologically rigorous studies are needed in this field, and sample size calculation should be conducted before enrollment. Secondly, various kinds of different forms of CDS were administered in the 21 studies included. Thus, it is necessary to identify which form of the CDS displays the most effective anti-Parkinsonian action. Thirdly, a new theory points out standard oral administration of dopamine agonists does not result in constant plasma drug levels, therefore, more continuous drug delivery (CDD) may result in both prolonged reversal of motor deficits and reduced levels of dyskinesia. So, we need carry out more well-designed, randomized, double-blind, placebo-controlled trials and report in detail about continuous duodenal or intravenous L-dopa infusion, subcutaneous apomorphine or lisuride infusion, continuous transdermal delivery of rotigotine in future.

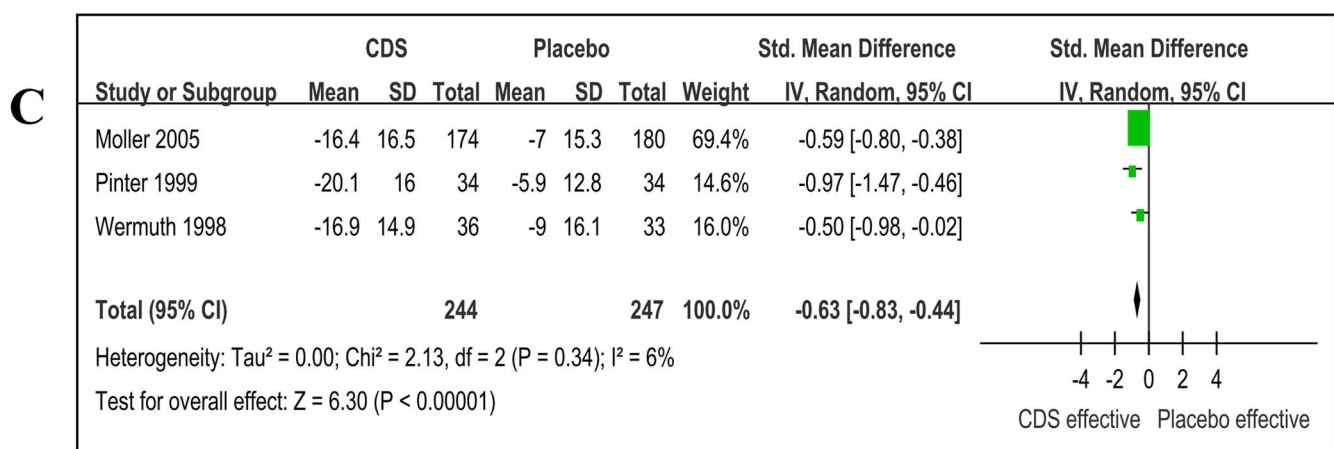
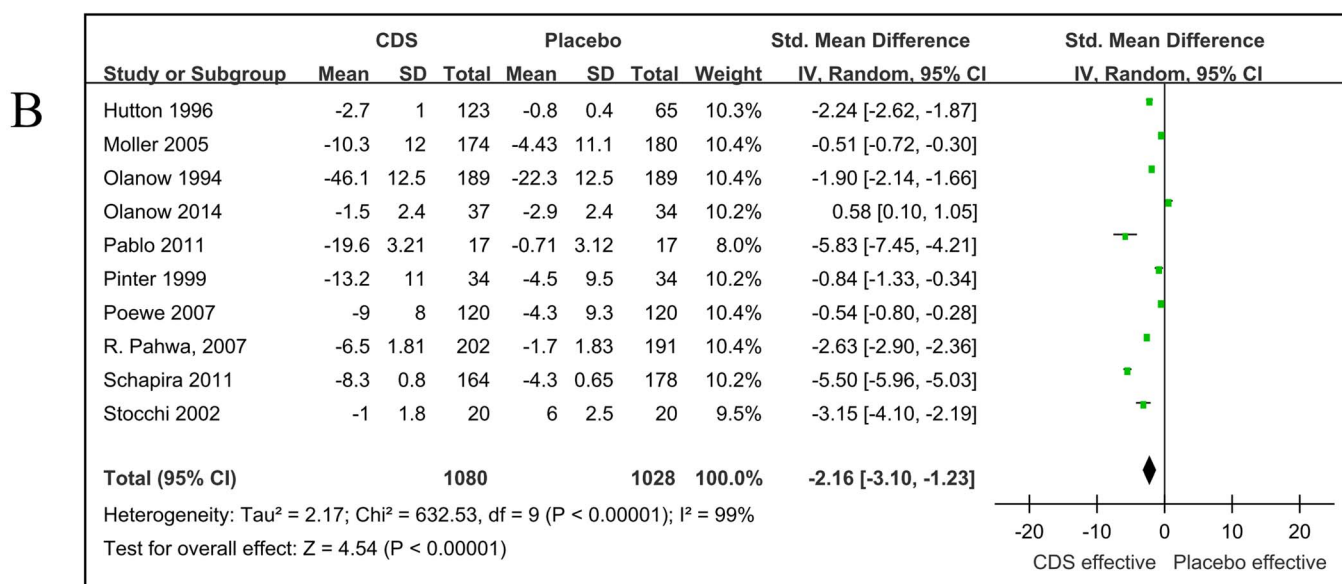
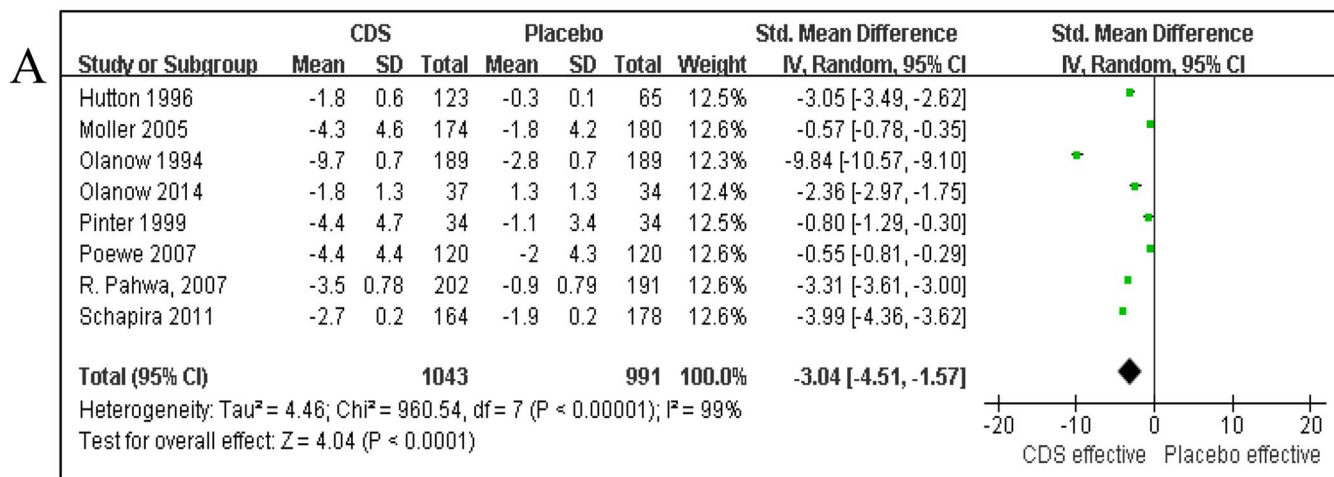
## Methods

**Inclusion and exclusion criteria.** Only Randomized Controlled Trials (RCTs) which evaluate CDS for PD patients with motor complications were included in this review. CDS is a therapeutic concept for the management of PD that proposes continuous, as opposed to intermittent or pulsatile, stimulation of striatal dopamine receptors. However, the form of the CDS is multitudinous. In this meta-analysis, we determine in advance the method to achieve CDS are as follow: (1) levodopa-carbidopa intestinal gel infusion; (2) long half-time dopamine agonists (e.g. ropinorole, bromocriptine and pramipexole); (3) subcutaneous apomorphine or lisuride infusion or continuous transdermal delivery of rotigotine. The former one kind belongs to L-dopa class, and the later two kinds were ascribed to dopamine agonist's class. Moreover, eligible studies had to meet all of the following criteria: (1) published in a peer-reviewed journal; (2) conducted to evaluate the CDS versus placebo, both on a background of L-dopa therapy, with all other aspects of treatment being the same in both arms; (3) had original data being independent from other studies; (4) had adequate data such as absolutely change on/off time or UPDRS score as the main outcome measures.

**Literature search.** We electronically searched six databases of Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, EMBASE database up to February 2014 for all English language publications. Reference lists from the resulting publications and reviews were used to identify further relevant publications. The following search strategy, using the grouped terms, was used for MEDLINE, and was modified to suit other databases.

Medline (Pubmed) search strategy.

1. Motor complications
2. Dyskinesia
3. Fluctuation
4. On/off time
5. Wearing-off.
6. or/1–5



**Figure 2** | (A) change from baseline to endpoint in UPDRS Part II of CDS vs Placebo in PD patients with motor complications; (B) change from baseline to endpoint in UPDRS Part III of CDS vs Placebo in PD patients with motor complications; (C) change from baseline to endpoint in UPDRS total score of CDS vs Placebo in PD patients with motor complications.

7. Parkinson's disease
8. Parkinson disease
9. PD
10. or/7-9
11. 6 and 10

**Data extraction.** For each study, information was carefully collected from all eligible publications, including first author, year of publication, number of cases and controls, sex ratio, mean age of cases and controls, duration of PD disease, mean L-dopa dosage, intervention of the trial groups, and main outcome measures. For studies including subjects of different arms, data were extracted separately for each arm

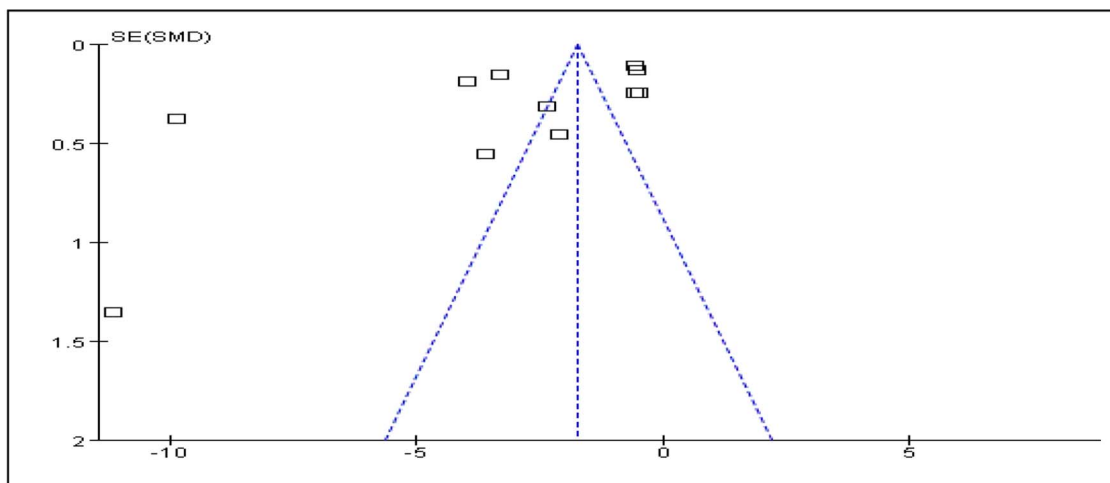
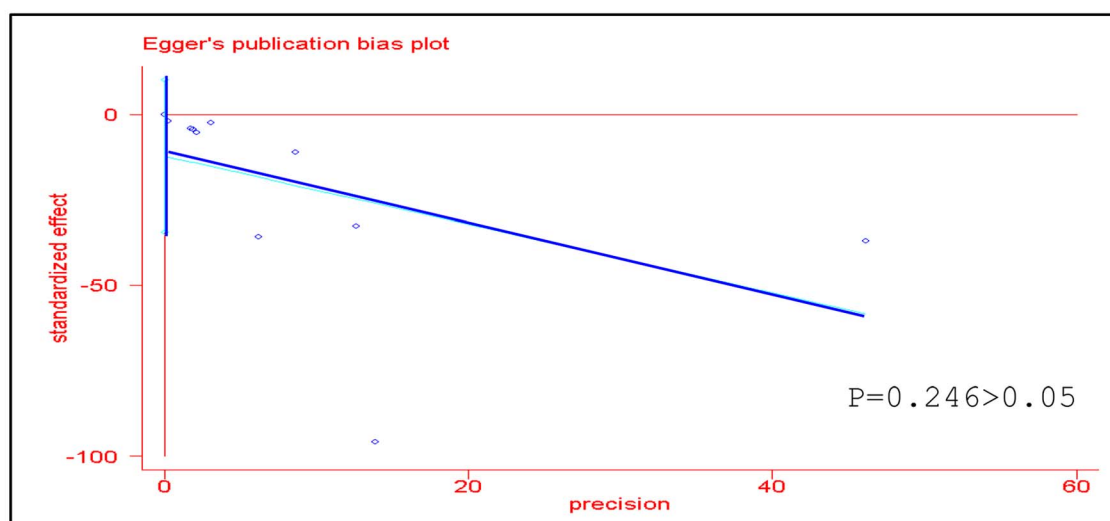
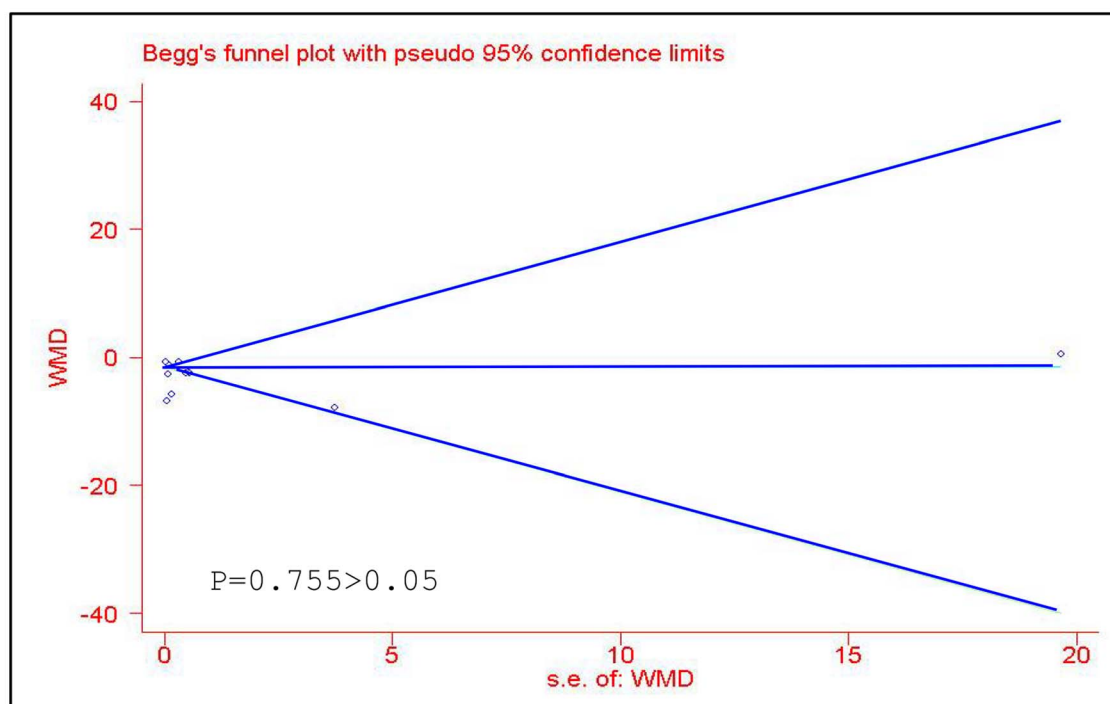
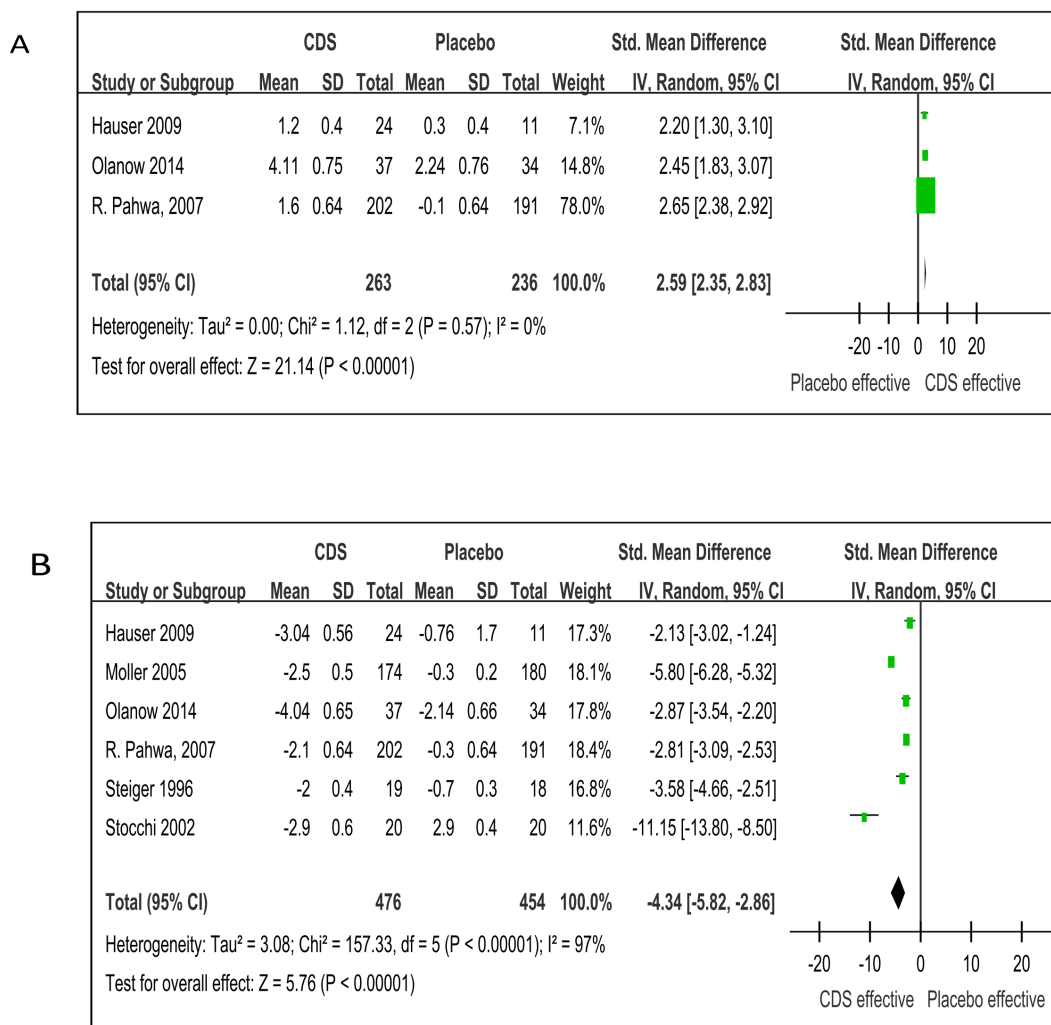
**A****B****C**

Figure 3 | Bias assessment plot for the effect of CDS on UPDRS score by funnel blot (A), Egger's test (B) and Begg's test (C).



**Figure 4** | (A) change from baseline to endpoint in on time of CDS vs Placebo in PD patients with motor complications; (B) change from baseline to endpoint in off time reduction of CDS vs Placebo in PD patients with motor complications.

whenever possible. If more than one paper with the same study was found, the one that contained the most detailed was reviewed. If the data for meta-analysis were missing or only expressed graphically, we tried to contact authors to inquire for further information or calculated by ourselves if available or excluded.

**Quality assessment of RCTs.** The methodological quality of RCTs was assessed independently using the Cochrane Handbook for Systematic Reviews of Interventions. Two investigators independently evaluated the methodological quality of the included articles. Disagreements were resolved through consensus or discussed with a third author.

**Statistical analysis.** We considered the main outcome measures as continuous data, and then were given an estimate of the combined overall effect sizes utilizing SMD with a random effects model. We used a random effects rather than a fixed effects model because of this takes into account heterogeneity between multi-studies. We looked for publication bias using funnel plotting, Egger's test and Begg's test. SMD with its 95% CI was used to assess the strength of efficacy of CDS in PD patients with motor complications. If any trials with two or more treatment arms were included, then we predetermine two methods to resolve the matter: (1) if the study was comparing two different drugs within the same drug class versus control, then the data for those drugs were combined to give one comparison of adjuvant therapy versus control; (2) if the study was comparing the same drug but at different dosages versus control, then the arm using generally recommended dose was chosen for inclusion in the analysis. Difference between n groups was assessed by partitioning heterogeneity and using the  $\chi^2$  distribution with  $n-1$  degrees of freedom (df), where  $n$  equals the number of groups. All analysis was performed with Revman version 5.1. Probability value  $p < 0.05$  were considered significant.

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## Author contributions

C.L.X. and W.W.W. conceived and participated in its design, searched databases, extracted and assessed studies and helped to draft the manuscript. J.G. and S.F.Z. carried out the statistical analysis and interpretation of data. Z.G.L. participated in the conceptualization and design of the review, performed the selection of studies, data extraction and analysis, and drafted the review. All authors read and approved the final manuscript.

## Additional information

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