Efficacy and Safety of Adjuvant Treatment with Entacapone in Advanced Parkinson's Disease with Motor Fluctuation: A Systematic Meta-Analysis

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Keywords

Entacapone · Parkinson's disease · Motor fluctuation · Efficacy and safety · Meta-analysis

Abstract

Aims: To assess the efficacy and safety of adjuvant treatment with entacapone in the treatment of later Parkinson's disease (PD) patients with motor fluctuation. **Methods:** We conducted a systematic review of relevant studies from 8 databases to June 23, 2016. **Results:** Fourteen studies were included in this review ($n = 2,804$). The results showed that compared with placebo, adjuvant therapy with entacapone significantly increased on time ($p < 0.01$) and reduced off time ($p < 0.01$), the required levodopa (LD) dose ($p < 0.01$) and improved Parkinson's Disease Rating Scale (UPDRS) scores (activities of daily living score: $p < 0.01$; motor score: $p < 0.01$; UPDRS I–III score: $p > 0.05$). However, the withdrawal (OR 1.44, 95% CI 1.10–1.89, $p < 0.01$) due to adverse events

and adverse events rates including nausea (OR 2.23, 95% CI 1.56–3.20, $p < 0.01$), urine discoloration (OR 14.99, 95% CI 7.63–29.44, $p < 0.01$), gastrointestinal disorder (OR 2.6, 95% CI 1.89–3.57, $p < 0.01$) and dyskinesia (OR 2.00, 95% CI 1.56–2.58, $p < 0.01$) increased in patients with entacapone compared with those given a placebo. **Conclusions:** This meta-analysis suggests that the entacapone used as adjuvant therapy to LD is effective in the management of later PD with fluctuation. However, patients on entacapone had a higher frequency of adverse events than those on placebo but no occurrence of severe adverse reactions.

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Introduction

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disease with neuropathological hallmarks of the loss of dopaminergic neurons in the Sub-

stantia Nigra pars compact and the reduction of dopamine in striatum. The clinical features of PD are akinesia, bradykinesia, rigidity and tremors, which are known to be directly related to dopaminergic striatal loss [1]. Levodopa (LD) is the most effective antiparkinsonian drug used in treatment regimens. LD could cross blood brain barrier, while dopamine could not [2]. Thus LD is used to increase brain dopamine concentrations in the treatment of PD since the 1960s [3]. However, long-term LD use is related to the development of motor complications such as loss of efficacy, dyskinesia, “wearing-off” phenomena, unpredictable “on-off” fluctuations and freezing episodes, especially in advanced PD [4–7]. Considering the limitations of LD monotherapy, the adjuvant therapy with adding other anti-Parkinson’s drugs has been used in advanced PD treatment. Dopamine agonists, including catechol-O-methyl transferase (COMT) inhibitors and monoamine oxidase type B inhibitors, are usually the first choice for adjuvant therapy in advanced PD. COMT is a major catabolic regulator of synaptic catecholamine neurotransmitters. It has been found that COMT inhibitors increase LD bioavailability and reduce the breakdown of LD by inhibiting the activity of COMT in brain [8]. Therefore, the addition of COMT inhibitors combined with LD reduced risks of motor complication.

Entacapone is a selective, reversible, peripheral inhibitor of the COMT, which mediates LD metabolized to 3-O-methyldopa (3-OMD) and prolongs LD half-life in vivo. Entacapone can be bounded to plasma proteins and transported by the circulatory system after being absorbed. It can be glucuronised in liver and eliminated by kidneys and biliary route [9]. Entacapone could increase the area under the plasma concentration-time curve (AUC) of LD [8]. The Cmax and Tmax of LD could be significantly delayed by entacapone [10, 11]. On the other hand, entacapone could decrease the AUC of 3-O-methyldopa by 55–60%, and increase the AUC of LD by 30–40% [12, 13].

Several prospective, double-blind, placebo-controlled trials have demonstrated that entacapone is effective when combined with LD therapy in PD patients experiencing wearing-off type motor fluctuations [14–16]. However, many of these studies are of a small size and the results are inconsistent; thus, we cannot fully evaluate the safety and efficacy implications of the therapy.

To compare the effectiveness and safety of adjuvant treatment with entacapone and LD in advanced PD, a systematic meta-analysis was performed by analyzing

the data from all published randomized, double blind-ing, placebo-controlled trials in this study. We focused on the effects of treatment on clinically important efficacy outcomes (changes in “on” and “off” time and LD dose as well as Unified Parkinson’s Disease Rating Scale [UPDRS] II, activities of daily living [ADL], III [motor] and I–III total) and safety outcomes (nausea, dyskinesia, gastrointestinal [GI] disorder, urine discoloration).

Material and Methods

Literature Search Strategy

A systematic search of the literature was conducted in PubMed, Web of science, Ebsco, Science direct, Embase, Cochrane Central Register of Controlled Trials, Chinese National Knowledge Infrastructure and Weipu databases. Combination of key words including “entacapone or comtan or COMT inhibitors or Catechins – O – methyl transferase inhibitors,” “fluctuation” AND “parkinson or PD.” All databases were researched from inception up to June 23, 2016, without any language restriction.

Inclusion and Exclusion Criteria

Studies were eligible if they meet the following criteria: (1) parallel, randomized, controlled trials that compared entacapone with placebo or other anti-PD drugs, such as pramipexole and rasagiline; (2) LD has been taken when treatment with adding entacapone in Parkinson’s patients; (3) the target population was individuals with fluctuating PD of later period; (4) Other basic treatment is the same in 2 groups of patients; and (5) The target patients compliance with the UK Parkinson’s Disease Society Brain Bank criteria without age and gender restriction. We excluded studies that on (1) parkinsonism-plus or secondary PD; (2) mild or moderate PD without fluctuation symptom; (3) open or non-blind test; and (4) the poor design lacking the basic patient information.

Quality Assessment and Data Extraction

The methodological quality of the identified studies was assessed using the validated Jadad Scale [17]. This rating scale assesses inherent controllers of bias by using the following quality assessment criteria. (1) Was the study described as randomized such as using the words randomly, random, and randomization? (2) Was the study described as double blind? (3) Was there a description of withdrawals and dropouts? One point was given for each satisfied criterion. Based on the Jadad Scale, studies with a total score of 5 points were considered to be of the highest quality, 0 points indicated lowest quality. The studies points <3 deemed to have lower methodological quality.

The data from identified studies were extracted independently by 2 investigators and included the following: the name of the first author, year of the publication, age, gender, number of the study subjects, duration of PD, duration of patients follow-up, change in LD dose, change in “on” and “off” time, effect on UPDRS score (including ADL, motor, and UPDRS I–III), adverse events (nausea, dyskinesia, GI disorder, urine discoloration) and withdrawals due to adverse events.

Fig. 1. Flowchart showing the process of study identification.

Statistical Analysis

The results of each identified trial were combined by using standard meta-analytic methods to evaluate the overall effect for adjuvant treatment versus control (entacapone plus LD vs. placebo-treated) patients. For the dichotomous data, the combined effect sizes were evaluated using OR value. For the continuous data, the combined effect sizes were evaluated using the mean difference (MD) and its standard error. The RR with 95% CIs was calculated for all effect sizes. The heterogeneity of identified studies was assessed using Cochran's Q test and Higgins's (I^2) test. Based on the results of heterogeneity test, the OR was calculated using a fixed-effects model ($p > 0.05$ or $I^2 < 50\%$) or random-effects model ($p < 0.05$ or $I^2 > 50\%$). All statistical analyses were conducted using STATA 12.0 software. Probability value $p < 0.05$ was considered significant.

Results

Characteristics and Quality of Studies

A total of 1,649 studies were identified after excluding duplicates. Of them, 278 studies were excluded based on

books, chapter and conference. By screening the titles and abstract, 1,086 studies were removed because they failed to meet the inclusion criteria. After reading the full text of the remaining 185 studies, 171 studies were removed based on study eligibility criteria, including (1) open-labeled design; (2) advanced PD without fluctuating symptoms; (3) not testing the effect of comparing entacapone plus LD with placebo in advanced PD patients; and (4) no available information. Finally, 14 studies were included in this meta-analysis (Fig. 1) [14, 18–30].

The characteristics of included studies are shown in Table 1. Fourteen randomized placebo-controlled trials, with a total of 2,804 patients, met the inclusion criteria and were included in this meta-analysis. The number of participants ranged from 20 to 481. The length of follow-up ranged 40 days to 24 weeks. The mean age of the participants in the trials was approximately 62 years, and most of them (%) had had PD for approximately 8 years.

According to quality assessment criteria, no studies of inferior quality were included in this review. All trials described the method of randomization and double blind used, and no inappropriate methods were observed. Four studies were of high-quality (5 points), 6 and 4 studies were 4 and 3 points respectively (Table 2).

The Efficacy of Entacapone for PD

Among the 14 studies, the motor complications, including the “on” and “off” phenomena were observed in 12 [14, 18–21, 24–30] and 9 studies [14, 18–20, 22, 25–27, 30], respectively. Overall, forest plots of the motor complications between placebo and adjuvant therapy are shown in Figure 2. Based on the results of the heterogeneity test, the “wearing-on” and “wearing-off” phenomena were analyzed with a random-effects model ($P_{\text{het}} < 0.005$). Compared with placebo, entacapone significantly increased patient on-time (MD 0.79, 95% CI 0.67–0.91, $p < 0.01$; Fig. 2a). Meanwhile, patients receiving entacapone had significantly reduced off-time (MD –0.98, 95% CI –1.33 to –0.63, $p < 0.01$; Fig. 2b).

UPDRS scores, including ADL, motor and UPDRS I–III was also assessed in 7 [14, 18, 19, 25, 26, 30], 6 [14, 18, 19, 25, 26, 30] and 5 studies [14, 18, 19, 24, 30], respectively. Based on the results of heterogeneity test, a fixed-effects model was analyzed ($P_{\text{het}} > 0.005$). Patients receiving entacapone had statistically significant reduction in the UPDRS ADL score (MD –1.22, 95% CI –1.71 to –0.73, $p < 0.01$) and UPDRS motor score (MD –2.38, 95% CI

Table 1. Characteristics of trials included in the meta-analysis

Authors, years	Total	Treat	Gender, male, %	Age, years, mean $\pm$ SD	Duration of PD, year	Treat-time	Planned outcome of trial
Brooks et al. [18], 2003	172	E P	69 40	65.9 $\pm$ 8.9 64.7 $\pm$ 8.5	9.6 $\pm$ 5.1 9.1 $\pm$ 5.3	6 weeks	On-/off-time, UPDRS score, LD dose
Ding et al. [19], 2005	40		N/A	N/A	N/A	12 weeks	On-/off-time, UPDRS score, LD dose
Fenelon et al. [20], 2003	162	E P	64 60	63.5 $\pm$ 9.96 65 $\pm$ 6.61	77 $\pm$ 26.3 days 74.8 $\pm$ 24.4 days	12 weeks	On-time
Ferreira et al. [21], 2008	35	N/A	14	65.3 $\pm$ 8.6	9.5 $\pm$ 5.2	18 weeks	UPDRS score, LD dose
Ferreira et al. [22], 2010	99	E P	27 32	65.3 $\pm$ 8.6 64.1 $\pm$ 10.1	8.2 $\pm$ 4.37 8.3 $\pm$ 3.98	8 weeks	On-/off-time, UPDRS score, LD dose
Mizuno et al. [24], 2007	183	E P	42 41	62.7 $\pm$ 9.9 62.7 $\pm$ 8.7	10.2 $\pm$ 5.6 10.1 $\pm$ 5.2	8 weeks	On-time, UPDRS score
Poewe et al. [25], 2002	301	E P	40 48	60.7 $\pm$ 9.6 61.1 $\pm$ 9.9	8.3 (4.5) 9.5 (4.9)	24 weeks	UPDRS score, LD dose
Parkinson Study Group [23], 1997	205	E P	67 62.80	63.9 $\pm$ 8 62.7 $\pm$ 9.7	10.8 $\pm$ 4.9 11.3 $\pm$ 6.4	24 weeks	On-time, UPDRS score
Rascol et al. [26], 2005	456	E P	58 72	63 $\pm$ 9.4 64.8 $\pm$ 8.8	9.2 $\pm$ 4.7 8.8 $\pm$ 4.8	18 weeks	Off-time, LD dose
Rascol et al. [27], 2012	481	E P	58 60	63.7 $\pm$ 9.88 63.6 $\pm$ 8.82	7.6 6.9	18 weeks	Off-time
Reichmann et al. [28], 2005	270	E P	94 57	67 $\pm$ 8 66 $\pm$ 9	7.5 $\pm$ 4.7 7.1 $\pm$ 4	13 weeks	UPDRS score, LD dose
Rinne et al. [14], 1998	171	E P	47 47	62.6 $\pm$ 7.6 62.8 $\pm$ 8.7	10.2 $\pm$ 4.8 11.3 $\pm$ 4.8	24 weeks	On-/off-time, UPDRS score, LD dose
Ruottinen et al. [29], 1996	20	N/A	9	63 $\pm$ 8	14 $\pm$ 5	40 days	On-time
Zhang et al. [30], 2003	209	E P	73.1 64.80	65.6 $\pm$ 9.4 67.1 $\pm$ 7.6	8.7 (5.0) 9.5 (5.0)	12 weeks	On-/off-time, UPDRS score, LD dose

N, number of participants; E, entacapone; P, placebo; UPDRS, united Parkinson's disease rating scale; N/A, not available; LD, levodopa.

–3.42 to –1.34, $p < 0.01$) compared to those receiving placebo (Fig. 3a, b), while, there was no statistically significance for UPDRS-III scores (MD –2.14, 95% CI –4.29 to 0.01, $p > 0.05$) between entacapone and placebo (Fig. 3c). In the 8 studies [14, 18–20, 25, 26, 28, 30] that reported change in LD dose (MD –37.82, 95% CI –64.80 to –10.83, $p < 0.01$), patients receiving entacapone had greater reduction compared to placebo and was statistically significant (Fig. 3d).

The Safety of Entacapone for PD

Two out of fourteen studies pointed out the maximum daily dose of entacapone [14, 18–21, 23, 25, 28]. The patients in most of the studies received 2 or 3–10

does of LD per day, and 200 mg entacapone or placebo were consumed along with each dose of LD. The maximum daily dose of entacapone was slightly less in the study of Ferreira et al. [21], which was 200 mg entacapone, 3–7 times per day. The doses of entacapone were acceptable (the maximum allowed doses is 10 times in Europe) [31].

Forest plots of the withdrawal and adverse events between placebo and adjuvant therapy are showed in Figure 4. The number of patient withdrawal due to adverse drug reactions were evaluated in 13 studies [14, 18, 20–30] with a fixed-effects model ($p > 0.05$ or $I^2 < 50\%$), patients receiving entacapone had a greater increase than placebo (OR 1.44, 95% CI 1.10–1.89; $I^2 =$

Table 2. Quality assessment of included trials using the Jadad Scale

Author, year	Was the study described as randomized such as using the words randomly, random, and randomization?	An additional point was given if methods of randomization was described and it was appropriate	A point was deducted if the method of randomization was inappropriate	Was the study described as double blind?	A point was given if method of blinding was described and it was appropriate	An additional point was deducted if method of blinding was inappropriate	Was there a description of withdrawals and dropouts?	Score
Brooks et al. [18], 2003	1	1	0	1	1	0	1	5
Ding et al. [19], 2005	1	1	0	1	1	0	1	5
Fnelon et al. [20], 2003	1	0	0	1	0	0	1	3
Ferreira et al. [21], 2008	1	0	0	1	1	0	1	4
Ferreira et al. [22], 2010	1	1	0	1	1	0	1	5
Mizuno et al. [24], 2007	1	0	0	1	1	0	1	4
Poewe et al. [25], 2002	1	1	0	1	0	0	1	4
Parkinson Study Group [23], 1997	1	0	0	1	1	0	1	4
Rascol et al. [26], 2005	1	0	0	1	0	0	1	3
Rascol et al. [27], 2012	1	0	0	1	0	0	1	3
Reichmann et al. [28], 2005	1	1	0	1	0	0	1	4
Rinne et al. [14], 1998	1	0	0	1	1	0	1	5
Ruottinen et al. [29], 1996	1	0	0	1	0	0	1	3
Zhang et al. [30], 2003	1	0	0	1	1	0	1	4

For the Jadad 5 criteria, a 3-scale level of certainty: studies with a total score of 5 points were considered to be highest quality, 0 points were lowest quality articles; points <3 deemed to have lower methodological quality.

0.0%, $p < 0.01$; Fig. 4a). Ten studies on nausea [14, 18, 21–25, 27, 28, 30], 10 studies on urine discoloration [14, 18–24, 28, 30], 11 studies on GI disorder [14, 18–20, 22–25, 27, 28, 30] and 10 studies on dyskinesia [14, 18–20, 23–25, 27, 28, 30] were also assessed. The ORs for nausea, urine discoloration, GI disorder and dyskinesia were 2.23 (95% CI 1.56–3.20, $p < 0.01$), 14.99 (95% CI 7.63–29.44, $p < 0.01$), 2.6 (95% CI 1.89–3.57, $p < 0.01$) and 2.00 (95% CI 1.56–2.58, $p < 0.01$), respectively (Fig. 4b–e). These results illustrated that patients receiving entacapone had a greater frequency of adverse events than placebo.

The Effect on the Life Quality of Entacapone for PD

Three out of fourteen studies assessed the quality of life after applying entacapone [18, 19, 28]. Brooks et al. [18] found that the quality of life improved in the enta-

capone group in non-fluctuating patients ($p < 0.01$ vs. placebo) but not in fluctuating patients ($p > 0.05$). Both self-evaluation and researcher evaluation were applied in the study of Ding et al. [19] The result showed that entacapone could significantly improve the quality of life. Reichmann et al. [28] used the European Quality of Life 5-dimension questionnaire to evaluate the quality, but no significant effect was observed. The results suggest that entacapone may partly improve the quality of life in patients; however, more evidence should be provided.

Publication Bias

As shown in Figure 5, publication bias was evaluated using Begg's test ($p > |z|$). The shape of funnel plots is symmetric in all adverse events, and the results of Begg's test demonstrated no significant publication bias ($p > 0.05$).

Fig. 2. Meta-analysis of the reduction of on-time (**a**) and off-time (**b**) (entacapone vs. placebo). MD, mean difference.

Discussion

Entacapone, frequently used in combination with LD, may increase the AUC of LD, prolonging the half-life elimination and increasing its bioavailability for treatment of PD [8, 32]. Though there were additional drug costs for entacapone, it could reduce other costs of patients. A study on the pharmacoeconomic of entacapone showed that the usage of the drug decreased the costs from 111,317 to 110,038 Netherlands Guilder [33]. Compared with other COMT inhibitors, such as tolcapone, entacapone is a very safe drug and it has been widely used in the treatment of PD, while tolcapone is used in a limited manner for Parkinson's patients and needs careful monitoring of hepatic functions due to hepatotoxicity [34].

In this meta-analysis, we systematically evaluated the efficacy and safety of the entacapone used as adjuvant therapy for later PD patients with motor fluctuation (on LD therapy). It provides the most reliable available summary of the current evidence from clinical trials of entacapone plus LD versus placebo in the treatment of later PD patients.

Based on the total of 2,804 subjects, our meta-analysis found that adjuvant therapy with entacapone could significantly improve the motor complications by increasing the "on" time, reducing the "off" time and the need in LD dose compared to placebo in those patients with later PD who were on LD therapy. Meanwhile, the UPDRS (ADL, motor and I-III) scores were also evaluated in this review, and a significant reduction was ob-

Fig. 3. Meta-analysis of the reduction of ADL (**a**), motor (**b**), UPDRS scores (**c**) and levodopa dose (**d**) (entacapone vs. placebo). ADL, activities of daily living score; UPDRS, Unified Parkinson's Disease Rating Scale; MD, mean difference.

served in UPDRS ADL and motor scores, but no statistical significance was observed in UPDRS I–III scores. We found the “on-off” time and UPDRS scores were recorded by the lasting time. Thus, we converted the outcomes to the same scale “hours”, and measured the

absolute difference between studies by the mean difference. The experimental changes were directly demonstrated by this method. The favorable efficacy suggested that adjuvant therapy with entacapone may be beneficial in the treatment of later PD patients with motor

Fig. 4. Meta-analysis of the side effect (entacapone vs. placebo). Withdrawal (**a**), nausea (**b**), urine discoloration (**c**), GI disorder (**d**) and dyskinesia (**e**). GI, gastrointestinal. (For figure 4 d, e see next page.)

d

e

fluctuation. However, the reduction in off-time and UPDRS scores showed statistical significance ($p < 0.01$), but they did not meet the newly suggested criteria for clinical relevance, where a reduction in off-time of 1 h, ADL score of 2 points and motor score of 5 points are considered to be the minimal clinically important changes in advanced and early PD [35, 36]. Therefore, the application of entacapone needs to be further optimized.

In our meta-analysis, the adverse events including nausea, urine discoloration, GI disorder and dyskinesia evidently increased in those groups with entacapone. It may be related to the increase of dopamine caused by entacapone in corpus striatum. In addition, there was a trend towards increased patient withdrawal due to adverse events (largely because of intolerable side effects or lack of efficacy.) in patients on entacapone but not associated with serious adverse experiences. These

findings indicated that the balance of efficacy versus side-effects favoured adjuvant therapy with entacapone.

In this meta-analysis, several potential limitations should be considered when interpreting the present results. First, all included trials in this review demonstrated randomization, but only a few trials detailed the randomized grouping methods. Second, the number of subjects included was small, and thus, our results might only reflect small-study effects. Third, the majority of trials followed-up patients for 24 weeks, only 3 trials for 24 weeks. Finally, only 5 studies provided the data of UPDRS I–III score; therefore, the results should be interpreted with caution. Studies with appropriate random allocation methods and large sample sizes are necessary to evaluate the efficacy and safety of adjuvant therapy with entacapone in later PD patients with motor fluctuation.

Fig. 5. Begg's Funnel plot of the side effect. Withdrawal (**a**), nausea (**b**), urine discoloration (**c**), GI disorder (**d**) and dyskinesia (**e**). GI, gastrointestinal.

Conclusions

In conclusion, our findings demonstrate that the entacapone used as adjuvant therapy to LD is effective in the management of later PD with fluctuation. But patients on entacapone may have a higher risk of the patient experiencing side effects. To clarify the long-term balance of benefits and risk of entacapone plus LD, further large sample size and well-designed RCTs are still necessary.

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