Meta-analysis of Placebo-controlled Clinical Trials of Safinamide and Entacapone as Add-on Therapy to Levodopa in the Treatment of Parkinson's Disease

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Abstract

Chronic levodopa (L-dopa) treatment of Parkinson's disease (PD) patients is sooner or later associated with the onset of motor complications, for example wearing off and dyskinesia. PD patients with motor complications usually require the addition of further PD drugs to reduce these L-dopa side effects and enhance its efficacy. Entacapone is an available catechol-*O*-methyltransferase (COMT) inhibitor, which was extensively investigated as add-on to L-dopa/dopadecarboxylase inhibitor (DDCI) application in PD patients. Safinamide, a water-soluble, orally active α-aminoamide derivative, which modulates dopaminergic and glutamatergic neurotransmission with a unique dual mechanism of action, has been studied in two placebo-controlled clinical trials as add-on therapy to L-dopa in fluctuating PD patients. To date, there are no head-to-head clinical trials comparing the efficacy of safinamide and entacapone in the clinic. The aim of this meta-analysis was to determine effect sizes of safinamide and entacapone as add-on treatment to L-dopa in fluctuating PD patients. A systematic search of the literature on entacapone trials up to the end of September 2014 was first conducted on the MEDLINE and EMBASE databases in order to identify appropriate studies. Definition criteria for inclusion were prospective, randomised, placebo-controlled and double-blinded trials on the efficacy and safety of entacapone or safinamide in fluctuating L-dopa-treated PD patients. Four studies for entacapone and two trials on safinamide were considered. Data from the safinamide trials were provided by Zambon and therefore 'safinamide' was not used as a search term. Safinamide and entacapone treatment was comparable in terms of the main efficacy variables (*off* time, percentage *on* time, Unified Parkinson's Disease Rating Scale). Significant advantages in favour of safinamide were shown in terms of the total incidence of adverse events (AEs) in comparison to placebo, the study discontinuation due to AEs and deaths and in the risk differences of the AEs versus placebo, particularly for nausea, vomiting, diarrhoea, dizziness, urine abnormality and shortness of breath. The odds ratio (OR) of 0.907 for any AE corresponds to an overall AE rate of 68.7 % for safinamide whereas the OR of 2.089 to an overall AE rate of 84.4 % for entacapone.

Keywords

Add-on therapy, entacapone, levodopa, L-dopa, Parkinson's disease, safinamide

Disclosure: Jörg Schnitker has received funding from Zambon SpA to perform the statistical meta-analysis and to write the report. Thomas Müller participated in advisory boards for the safinamide studies and served as a principal investigator.

Acknowledgements: Editorial assistance was provided by Catherine Amey, at Touch Medical Media, London, UK.

Received: 15 January 2015 **Accepted**: 6 February 2015 **Citation**: *European Neurological Review*, 2015;10(1):15–22 *DOI: 10.17925/ENR.2015.10.01.15*

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Support: The publication of this article was supported by Zambon SpA. The views and opinions expressed are those of the author and do not necessarily reflect those of Zambon SpA.

The signs and symptoms of Parkinson's disease (PD), a chronic neurodegenerative disorder predominantly characterised by the loss of dopaminergic neurons in the substantia nigra pars compacta, are most effectively treated by levodopa (L-dopa). However, nearly all PD patients experience a fluctuating response to L-dopa sooner or later within the first 5 years of therapy dependent on dosing of L-dopa.

End-of-dose wearing off and dykinesias are the most common motor complications associated with L-dopa treatment.[1–3] Once they appear, the management of motor complications is often challenging and patients require recurrent drug therapy adjustments to improve fluctuations of movement without exacerbating severe dyskinesia.[4]

Safinamide recently received a European Committee for Medicinal Products for Human Use (CHMP) positive opinion for the treatment of adult patients with idiopathic PD as add-on therapy to a stable dose of L-dopa, alone or in combination with other PD compounds, in mid-to-late-stage fluctuating patients. It is a unique molecule with novel mechanisms of action, both dopaminergic and non-dopaminergic ones, which include monoamine oxidase-B (MAO-B) inhibition, sodium channel blockade and calcium channel modulation, thus inhibiting the excessive glutamate release. Safinamide improves motor symptoms, motor complications and quality of life in combination with other PD drugs such as dopamine agonists and L-dopa, reduces *off* time and extends *on* time without troublesome dyskinesia.[5–7] Entacapone is a

potent and specific peripherally acting catechol-*O*-methyltransferase (COMT) with a nitro-catechol structure.[8] It is used as an adjunct to L-dopa/dopadecarboxylase inhibitor (DDCI) therapy and slows the peripheral degradation of L-dopa only (has no anti-parkinsonian activity on its own). There are no head-to-head clinical trials comparing safinamide and entacapone under clinical conditions as an add-on therapy to L-dopa.

The aim of the present analysis is a comparison of entacapone and safinamide as add-on treatments to L-dopa in fluctuating PD patients; therefore, a meta-analysis of all the pertinent double-blind, placebo-controlled studies was performed to determine effect sizes of safinamide and entacapone.

Methods

Search Strategy

The complete sets of data on placebo-controlled efficacy trials with safinamide as add-on to L-dopa were provided by Zambon, which is currently developing this still investigational compound. These comprise all completed, randomised, double-blind, placebo-controlled studies in PD patients with motor fluctuations, already treated with stable L-dopa dose and who may be receiving further anti-parkinsonian drugs (study 016, NCT01187966, labelled SAF1[7] and SETTLE, NCT00627640, labelled SAF2[9,10,11]). The duration of the trials was 24 weeks each.

A systematic search of the literature up to the end of September 2014 was performed on the MEDLINE and EMBASE databases using 'entacapone' and 'levodopa' or 'L-dopa' as search terms. Ongoing trials and other possible completed trials still unpublished as full papers (available through clinical trial registries, conference proceedings or other literature where it proved difficult to retrieve complete data sets for the analysis) were not identified as part of the search strategy. A 2010 Cochrane Database Systematic Review on add-on therapies to L-dopa treatment was used as a primary reference for the literature.[12]

Study Selection

Eligible studies for the search were defined as any prospective, randomised, placebo-controlled and double-blinded trials (24 weeks/6 months' duration) on the efficacy and safety of entacapone in PD patients already receiving L-dopa (usually commercial formulations of L-dopa in a fixed combination with a DDCI), i.e. L-dopa+carbidopa, L-dopa+benserazide, with motor fluctuations. All other aspects of planned treatment were to be the same in both arms. Therefore, the following types of studies were not considered:

- Studies in healthy subjects or subjects in early-stage PD, without motor fluctuations;
- Switch studies (investigating the introduction of entacapone as add-on to L-dopa or L-dopa+DDCI), or any studies with a fixed L-dopa+DDCI+entacapone combination compared with the separate drug formulations, without parallel entacapone placebo treatment groups;
- Crossover studies – since focus was given to studies of sufficient duration to be comparable to the studies investigating safinamide;
- Studies not investigating efficacy and safety of entacapone, or entacapone and other treatments (for example, studies regarding physiology parameters, magnetic resonance imaging or pharmacokinetic parameters); and
- Studies of COMT inhibitors (COMTIs)-genotype interaction, which selected patients based on COMT gene polymorphism.

Study Appraisal and Methods

If different doses and/or dose ranges were found in the selected studies, these were to be analysed both as separate studies and collectively. Among the analysed efficacy parameters were changes from baseline in daily L-dopa dose, total daily *off* time, total and percent *on* time and Unified Parkinson's Disease Rating Scale (UPDRS) scores (part I, II and III only). Safety was analysed mainly on binary criteria (incidence of treatment-emergent adverse events [AEs], AEs plus deaths, discontinuation from the trials and the incidence of some specific AEs). Only parameters that had been evaluated and documented for both treatments were to be included in the analyses.

The effects within studies are quantified by changes from baseline in quantitative parameters or incidences of events (non-completers, discontinuations, incidences of treatment-emergent AEs). Fixed-effect and random-effects meta-analyses are used to provide effect sizes within each treatment group and to compare both groups. Fixed-effects methods aim at estimating unknown but constant effect sizes based on the assumption that the (retrieved) studies estimate a common (fixed) effect. Random-effect methods consider the (retrieved) collection of studies as one possible random sample of a larger population, and aim at estimating the mean of a possible distribution of effect sizes.

The statistical analyses were carried out by means of Comprehensive Meta-Analysis Version 2 (CMA2) (Biostat, Englewood, NJ, US). Trial design, inclusion and exclusion criteria, blinding and randomisation of the selected trials were compared with regard to possible risk of bias. The following summary measures were used:

- Hedges' g, which is a measure of effect size[13] (as standardised mean difference);
- Odds ratios (ORs) (as a measure of association of binary data); and
- Risk differences (as a measure of difference between binary data).

The heterogeneity across studies was quantified by the I^2-index, i.e. the ratio in percent of the true heterogeneity (the between-study variance) to the total observed variance.

Results

Study Selection

The synthesis of results was based on four studies with entacapone, and the two safinamide studies. Initially, 30 publications (published from 1996 to 2012) concerning entacapone, describing a total of 13 distinct randomised, double-blinded and placebo-controlled clinical trials, were considered. For the period up to 2008 these results matched with the findings of Stowe et al.[12] Eventually, four entacapone studies were included for the meta-analysis (see *Table 1*). The four studies are Poewe et al. (ENT1),[14] the Parkinson Study Group (labelled ENT2),[15] Rinne et al. (ENT3)[16] and Brooks et al. (ENT4).[17] This last trial[17] recruited both fluctuating and non-fluctuating patients, but separate study results on the fluctuating patients were available; therefore, only those parts of the study results were included, whenever available (see *Table 1*). The main reason for exclusion of some studies was the short duration, which did not allow appropriate comparison with the safinamide studies. All included entacapone studies considered a placebo-controlled administration of 200 mg oral dose with each dose of L-dopa. Meta-analyses were performed with all four studies whenever possible (or with only ENT1,[14,15] ENT2[14] and ENT3,[16] whenever outcomes for the subgroup of fluctuating PD patients were not documented in the available publications).

Table 1: Overview Studies Included in the Meta-Analysis – Randomised, Double-blind, Placebo-controlled Studies Evaluating The Safety And Efficacy of Entacapone or Safinamide Treatment as Add-on Treatment to Levodopa

Study/Reference	Study Code	Study Design	Treatment (Number of Patients Enrolled)
Safinamide 016 study (NCT01187966)[7]	SAF1	Phase III, multicentre, randomised, double-blind, placebo-controlled, parallel-group study for 24 weeks	Safinamide 100 mg/day (n=224), 50 mg/day (n=223); placebo (n=222)
SETTLE (NCT00627640)[9,10,11]	SAF2	Phase III, multicentre, randomised, placebo-controlled, double-blind, study for 24 weeks	Safinamide 50–100 mg/day (n=274); placebo (n=275)
Poewe et al.[14]	ENT1	Randomised, multicentre, double-blind, placebo-controlled study. Two parallel groups: L-dopa/DDCI with entacapone or placebo (2:1) for 6 months	Double-blind phase: entacapone 200 mg (n=197); placebo (n=104)
Parkinson Study Group[15]	ENT2	Randomised, multicentre, double-blind, placebo-controlled Two parallel groups: L-dopa/DDCI with entacapone or placebo (1:1) for 6 months	Double-blind phase: entacapone 200 mg (n=103); placebo (n=102)
Rinne et al.[16]	ENT3	Randomised, multicentre, double-blind, placebo-controlled study. Two parallel groups: L-dopa/DDCI with entacapone or placebo (1:1) for 6 months	Double-blind phase: entacapone 200 mg (n=85); placebo (n=86)
Brooks et al.[17]	ENT4[a]	Randomised, multicentre, double-blind, placebo-controlled study. Two parallel groups: L-dopa/DDCI with entacapone or placebo (2:1) for 6 months 200 mg	Double-blind phase (fluctuating patients only): entacapone (n=115); placebo (n=57)

[a]In ENT4, patients with fluctuating and non-fluctuating Parkinson's disease were included. There were 128 non-fluctuating patients (entacapone, 88; placebo, 40). This meta-analysis considered the fluctuating disease only and ENT4 was only included in the analysis for the parameters where separate subgroup results were presented. DDCI = dopadecarboxylase inhibitor.

Table 2: Patient Numbers by Data Analyses

Treatment	Study Code	Patient Numbers		
		Active treatment	Placebo	Total
Safinamide				
High dose[a]	SAF1B, SAF2B	498	497	995
All doses	SAF1A, SAF1B, SAF2B	721	719[b]	1,440[b]
Combined doses	SAF1C, SAF2B	721	497	1,218
Entacapone	ENT1, ENT2, ENT3, fluctuating patients in ENT4[c]	500	349	849
Entacapone	ENT1, ENT2, ENT3[d]	385	292	677

[a]Only safinamide low-dose is not analysed separately (SAF1A: number of patients receiving active treatment: 223; number of patients receiving placebo: 222; total: 445). [b]Any dose considered as a separate study; the same placebo population in study SAF1 is considered twice for doses A and B. [c]Only fluctuating patients are considered. [d]Any analysis depends on the availability of the respective item; ENT4 was removed in some cases.

One of the safinamide trials (SAF1) had two dose arms (low dose and high dose, 50 mg/day and 100 mg/day, respectively), which were analysed as two separate studies (SAF1A, SAF1B, each compared with placebo) and additionally as a combined placebo-controlled dose group (SAF1C). The other safinamide trial (SAF2) had only one dose arm (50–100 mg/day), which was ascribed to high dose (hence labelled SAF2B) since after week 2 of the study period a large majority of the patients (224/274) had a dose of 100 mg/day for the rest of the study. Therefore, meta-analyses for safinamide trials are performed: (a) using all safinamide doses (SAF1A, SAF1B, SAF2B); (b) using combined safinamide doses (SAF1C, SAF2B); and (c) using the high safinamide dose (SAF1B, SAF2B) only (see *Table 2*).

The safinamide studies included 1,218 patients in total and the entacapone studies 849 patients. No relevant differences were detected in terms of trial design, inclusion and exclusion criteria, blinding and randomisation of the selected trials.

Efficacy Endpoints

There was a greater decrease from baseline in the daily oral L-dopa dose observed with entacapone treatment compared with treatment with safinamide all doses ($p<0.05$; *Figure 1* and *Tables 3* and *4*). This was also seen with the safinamide combined dose data, and with the random effects analyses. No significant differences between entacapone and safinamide treatment were observed in terms of total daily *off* time, total daily *on* time and percentage of *on* time (*Figure 1* and *Tables 3* and *4*). This was found with safinamide all doses, with safinamide-combined doses and with the fixed- and random-effect analyses. Similarly, no statistically significant differences appeared between safinamide and entacapone treatment with respect to changes from baseline in the UPDRS total score using all safinamide doses. The alternative analysis where the two active treatment arms (low and high dose) have been combined revealed similar results to the main analysis (see *Figure 1*).

Safety Endpoints

Some AEs regarded as candidates for the indirect comparison of entacapone and safinamide were not considered in this report because they were not reported in the entacapone studies (anxiety, confusion and agitation, depression, dry mouth, orthostatic hypotension and syncope) or because they were reported only in entacapone trials (ataxia and forgetfulness). The analysis of the number of discontinuations due to AEs and deaths was performed after exclusion of the study ENT4 by Brooks et al.,[17] because premature discontinuations in this study were not stratified by fluctuating and non-fluctuating patients.

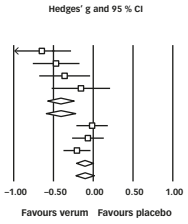
There were no differences on study discontinuations due to AEs and deaths between safinamide and entacapone ($p=0.2564$), even if the number of discontinuations due to AEs occurred more frequently with entacapone treatment (OR 1.777; $p=0.0464$) than with safinamide

Figure 1: Forest Plot Presentation of Meta-analyses Using All Safinamide Doses and Combined Safinamide Doses for the Following Efficacy Endpoints

A

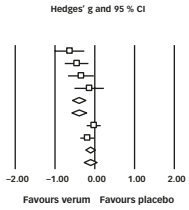
All safinamide doses

Model	Group by Prep	Study	Outcome	Statistics for each study: Hedges' g	Standard error	Lower limit	Upper limit	p Value	Sample size: Verum	Placebo
	ENT	ENT1	Daily levodopa dose	−0.644	0.189	−1.015	−0.274	0.0007	93	42
	ENT	ENT2	Daily levodopa dose	−0.466	0.150	−0.759	−0.173	0.0018	90	92
	ENT	ENT3	Daily levodopa dose	−0.358	0.163	−0.677	−0.039	0.0278	77	75
	ENT	ENT4*	Daily levodopa dose	−0.154	0.187	−0.520	0.213	0.4110	80	44
Fixed	ENT			−0.408	0.085	−0.574	−0.242	0.0000	340	253
Random	ENT			−0.408	0.094	−0.592	−0.223	0.0000	340	253
	SAF	SAF1A	Daily levodopa dose	−0.013	0.100	−0.209	0.183	0.8969	203	197
	SAF	SAF1B	Daily levodopa dose	−0.066	0.101	−0.263	0.132	0.5139	195	197
	SAF	SAF2B	Daily levodopa dose	−0.204	0.086	−0.371	−0.036	0.0173	273	275
Fixed	SAF			−0.106	0.055	−0.213	0.001	0.0518	671	669
Random	SAF			−0.104	0.059	−0.220	0.012	0.0776	671	669



Combined safinamide doses

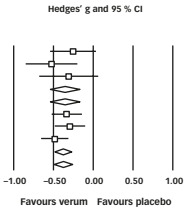
Model	Group by Prep	Study	Outcome	Statistics for each study: Hedges' g	Standard error	Lower limit	Upper limit	p Value	Sample size: Verum	Placebo
	ENT	ENT1	Daily levodopa dose	−0.644	0.189	−1.015	−0.274	0.0007	93	42
	ENT	ENT2	Daily levodopa dose	−0.466	0.150	−0.759	−0.173	0.0018	90	92
	ENT	ENT3	Daily levodopa dose	−0.358	0.163	−0.677	−0.039	0.0278	77	75
	ENT	ENT4*	Daily levodopa dose	−0.154	0.187	−0.520	0.213	0.4110	80	44
Fixed	ENT			−0.408	0.085	−0.574	−0.242	0.0000	340	253
Random	ENT			−0.408	0.094	−0.592	−0.223	0.0000	340	253
	SAF	SAF1C	Daily levodopa dose	−0.039	0.087	−0.210	0.131	0.6512	398	197
	SAF	SAF2B	Daily levodopa dose	−0.204	0.086	−0.371	−0.036	0.0173	273	275
Fixed	SAF			−0.123	0.061	−0.242	−0.003	0.0439	671	472
Random	SAF			−0.122	0.082	−0.283	0.039	0.1367	671	472



B

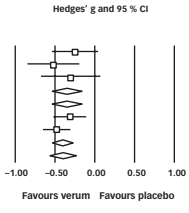
All safinamide doses

Model	Group by Prep	Study	Outcome	Statistics for each study: Hedges' g	Standard error	Lower limit	Upper limit	p Value	Sample size: Verum	Placebo
	ENT	ENT1	Total daily OFF time	−0.244	0.146	−0.530	0.042	0.0944	129	74
	ENT	ENT3	Total daily OFF time	−0.513	0.164	−0.835	−0.191	0.0018	77	75
	ENT	ENT4*	Total daily OFF time	−0.299	0.187	−0.666	0.069	0.1110	80	44
Fixed	ENT			−0.346	0.094	−0.531	−0.162	0.0002	286	193
Random	ENT			−0.346	0.094	−0.531	−0.162	0.0002	286	193
	SAF	SAF1A	Total daily OFF time	−0.325	0.097	−0.516	−0.135	0.0008	215	213
	SAF	SAF1B	Total daily OFF time	−0.284	0.097	−0.474	−0.094	0.0034	217	213
	SAF	SAF2B	Total daily OFF time	−0.473	0.086	−0.642	−0.303	0.0000	274	275
Fixed	SAF			−0.369	0.054	−0.475	−0.264	0.0000	706	701
Random	SAF			−0.368	0.059	−0.484	−0.252	0.0000	706	701



Combined safinamide doses

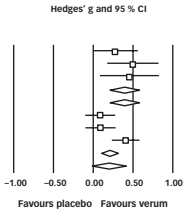
Model	Group by Prep	Study	Outcome	Statistics for each study: Hedges' g	Standard error	Lower limit	Upper limit	p Value	Sample size: Verum	Placebo
	ENT	ENT1	Total daily OFF time	−0.244	0.146	−0.530	0.042	0.0944	129	74
	ENT	ENT3	Total daily OFF time	−0.513	0.164	−0.835	−0.191	0.0018	77	75
	ENT	ENT4*	Total daily OFF time	−0.299	0.187	−0.666	0.069	0.1110	80	44
Fixed	ENT			−0.346	0.094	−0.531	−0.162	0.0002	286	193
Random	ENT			−0.346	0.094	−0.531	−0.162	0.0002	286	193
	SAF	SAF1C	Total daily OFF time	−0.305	0.099	−0.499	−0.111	0.0021	428	213
	SAF	SAF2B	Total daily OFF time	−0.473	0.086	−0.642	−0.303	0.0000	274	275
Fixed	SAF			−0.400	0.065	−0.528	−0.272	0.0000	702	488
Random	SAF			−0.396	0.084	−0.559	−0.232	0.0000	702	488



C

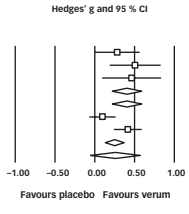
All safinamide doses

Model	Group by Prep	Study	Outcome	Statistics for each study: Hedges' g	Standard error	Lower limit	Upper limit	p Value	Sample size: Verum	Placebo
	ENT	ENT1	Total daily ON time	0.277	0.146	−0.009	0.563	0.0574	129	74
	ENT	ENT3	Total daily ON time	0.502	0.164	0.180	0.823	0.0022	77	75
	ENT	ENT4*	Total daily ON time	0.459	0.189	0.089	0.829	0.0151	80	44
Fixed	ENT			0.397	0.094	0.212	0.582	0.0000	286	193
Random	ENT			0.397	0.094	0.212	0.582	0.0000	286	193
	SAF	SAF1A	Total daily ON time	0.090	0.097	−0.099	0.280	0.3487	215	213
	SAF	SAF1B	Total daily ON time	0.094	0.096	−0.095	0.283	0.3279	217	213
	SAF	SAF2B	Total daily ON time	0.412	0.089	0.238	0.585	0.0000	264	256
Fixed	SAF			0.211	0.054	0.105	0.317	0.0001	696	682
Random	SAF			0.202	0.109	−0.013	0.416	0.0651	696	682



Combined safinamide doses

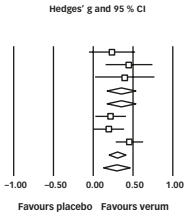
Model	Group by Prep	Study	Outcome	Statistics for each study: Hedges' g	Standard error	Lower limit	Upper limit	p Value	Sample size: Verum	Placebo
	ENT	ENT1	Total daily ON time	0.277	0.146	−0.009	0.563	0.0574	129	74
	ENT	ENT3	Total daily ON time	0.502	0.164	0.180	0.823	0.0022	77	75
	ENT	ENT4*	Total daily ON time	0.459	0.189	0.089	0.829	0.0151	80	44
Fixed	ENT			0.397	0.094	0.212	0.582	0.0000	286	193
Random	ENT			0.397	0.094	0.212	0.582	0.0000	286	193
	SAF	SAF1C	Total daily ON time	0.092	0.084	−0.072	0.256	0.2731	432	213
	SAF	SAF2B	Total daily ON time	0.412	0.089	0.238	0.585	0.0000	264	256
Fixed	SAF			0.243	0.061	0.124	0.362	0.0001	696	469
Random	SAF			0.250	0.160	−0.063	0.564	0.1176	696	469



D

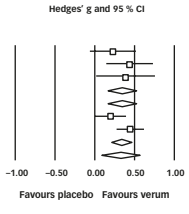
All safinamide doses

Model	Group by Prep	Study	Outcome	Statistics for each study: Hedges' g	Standard error	Lower limit	Upper limit	p Value	Sample size: Verum	Placebo
	ENT	ENT1	Percent ON time	0.232	0.146	−0.054	0.517	0.1119	129	74
	ENT	ENT2	Percent ON time	0.441	0.149	0.149	0.734	0.0031	90	92
	ENT	ENT4*	Percent ON time	0.391	0.188	0.022	0.760	0.0377	80	44
Fixed	ENT			0.347	0.091	0.168	0.526	0.0001	299	210
Random	ENT			0.347	0.091	0.168	0.526	0.0001	299	210
	SAF	SAF1A	Percent ON time	0.214	0.097	0.024	0.404	0.0271	215	213
	SAF	SAF1B	Percent ON time	0.193	0.097	0.004	0.382	0.0459	217	213
	SAF	SAF2B	Percent ON time	0.449	0.086	0.279	0.618	0.0000	274	275
Fixed	SAF			0.298	0.054	0.193	0.403	0.0000	706	701
Random	SAF			0.290	0.085	0.123	0.456	0.0006	706	701



Combined safinamide doses

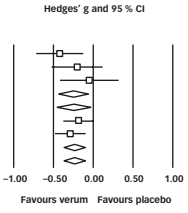
Model	Group by Prep	Study	Outcome	Statistics for each study: Hedges' g	Standard error	Lower limit	Upper limit	p Value	Sample size: Verum	Placebo
	ENT	ENT1	Percent ON time	0.232	0.146	−0.054	0.517	0.1119	129	74
	ENT	ENT2	Percent ON time	0.441	0.149	0.149	0.734	0.0031	90	92
	ENT	ENT4*	Percent ON time	0.391	0.188	0.022	0.760	0.0377	80	44
Fixed	ENT			0.347	0.091	0.168	0.526	0.0001	299	210
Random	ENT			0.347	0.091	0.168	0.526	0.0001	299	210
	SAF	SAF1C	Percent ON time	0.203	0.097	0.012	0.393	0.0371	432	213
	SAF	SAF2B	Percent ON time	0.449	0.086	0.279	0.618	0.0000	274	275
Fixed	SAF			0.340	0.065	0.214	0.467	0.0000	706	488
Random	SAF			0.330	0.123	0.089	0.571	0.0073	706	488



E

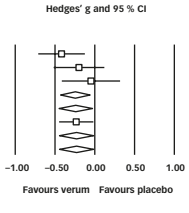
All safinamide doses

Model	Group by Prep	Study	Outcome	Statistics for each study: Hedges' g	Standard error	Lower limit	Upper limit	p Value	Sample size: Verum	Placebo
	ENT	ENT2	UPDRS total	−0.415	0.149	−0.707	−0.122	0.0054	90	92
	ENT	ENT3	UPDRS total	−0.196	0.162	−0.513	0.121	0.2259	77	75
	ENT	ENT4*	UPDRS total	−0.045	0.187	−0.410	0.321	0.8112	80	44
Fixed	ENT			−0.245	0.095	−0.430	−0.060	0.0096	247	211
Random	ENT			−0.239	0.107	−0.449	−0.030	0.0254	247	211
	SAF	SAF1A	UPDRS total	−0.178	0.096	−0.367	0.010	0.0640	214	217
	SAF	SAF1B	UPDRS total	−0.282	0.096	−0.471	−0.093	0.0034	217	217
Fixed	SAF			−0.230	0.068	−0.364	−0.097	0.0007	431	434
Random	SAF			−0.230	0.068	−0.364	−0.097	0.0007	431	434



Combined safinamide doses

Model	Group by Prep	Study	Outcome	Statistics for each study: Hedges' g	Standard error	Lower limit	Upper limit	p Value	Sample size: Verum	Placebo
	ENT	ENT2	UPDRS total	−0.415	0.149	−0.707	−0.122	0.0054	90	92
	ENT	ENT3	UPDRS total	−0.196	0.162	−0.513	0.121	0.2259	77	75
	ENT	ENT4*	UPDRS total	−0.045	0.187	−0.410	0.321	0.8112	80	44
Fixed	ENT			−0.245	0.095	−0.430	−0.060	0.0096	247	211
Random	ENT			−0.239	0.107	−0.449	−0.030	0.0254	247	211
	SAF	SAF1C	UPDRS total	−0.230	0.109	−0.444	−0.015	0.0358	431	217
Fixed	SAF			−0.230	0.109	−0.444	−0.015	0.0358	431	217
Random	SAF			−0.230	0.109	−0.444	−0.015	0.0358	431	217



*(A) Changes in the daily oral L-dopa dose; (B) changes from baseline in total daily off time; (C) changes from baseline in total daily on time; (D) changes from baseline in percentage on time; (E): changes from baseline in the total Unified Parkinson's Disease Rating Scales (UPDRS) score. Interventions: Safinamide low dose (SAF A; 50 mg/day); safinamide high dose (SAF B; 100 mg/day); entacapone (ENT; 200 mg with each dose of L-dopa). SAF1, Borgohain et al.;[7] SAF2, Schapira et al.;[11] ENT1, Poewe et al.;[14] ENT2, Parkinson Study Group;[15] ENT3, Rinne et al.;[16] ENT4, Brooks et al.[17] *In study ENT4, only fluctuating patients were considered.*

(OR 1.167; p=0.5037) (*Figure 2* and *Tables 3* and *4*). No changes in comparison with placebo were observed with safinamide treatment in terms of the number of non-completers, whereas this number was increased slightly with entacapone treatment.

A statistically significant difference in favour of safinamide was determined in the ORs versus placebo of total incidences of treatment-emergent AEs (p=0.0020) (see *Tables 3* and *4*). The funnel plot corresponding to the total incidences of treatment-emergent AEs identifies the trial by Poewe et al.[14] as an outlier among the trials with respect to the total AE incidences (see *Figure 3A*). No heterogeneities were detected within both groups of studies however. The funnel plot generated with the alternative analysis where the two safinamide dose groups were combined confirms the result (see *Figure 3B*).

The risk differences of the events/symptoms versus placebo are described in *Figures 4* and *5*. Significant differences in favour of safinamide were seen particularly in terms of nausea (p=0.002), vomiting (p=0.007), shortness

Table 3: Statistical Meta-analysis Estimates using All Safinamide Doses (Fixed Effect Model)

Parameter	Effect Measure	Entacapone				Safinamide				p Value for Entacapone versus Safinamide
		Value	I^2 (p Value)	95 % CI	p Value*	Value	I^2 (p Value)	95 % CI	p Value*	
Efficacy Parameters										
Changes in the daily L-dopa dose	Hedges' g (SE)	–0.408 (0.085)	18.1 % (0.3001)	[–0.574; –0.242]	<0.0001	–0.106 (0.055)	8.0 % (0.7303)	[–0.213; 0.001]	0.0518	**0.0027**
Changes from baseline in total daily *off* time	Hedges' g (SE)	–0.346 (0.094)	0.0 % (0.4516)	[–0.531; –0.162]	0.0002	–0.369 (0.054)	17.1 % (0.2995)	[–0.475; –0.264]	<0.0001	0.8330
Changes from baseline in total daily *on* time	Hedges' g (SE)	0.397 (0.094)	0.0 % (0.5523)	[0.212; 0.582]	<0.0001	0.211 (0.054)	75.5 % (0.0168)	[0.105; 0.317]	<0.0001	0.0877
Changes from baseline in per cent *on* time	Hedges' g (SE)	0.347 (0.091)	0.0 % (0.5828)	[0.168; 0.526]	0.0001	0.298 (0.054)	59.9 % (0.0824)	[0.193; 0.403]	<0.0001	0.6395
Changes from baseline in the total UPDRS score	Hedges' g (SE)	–0.245 (0.095)	21.4 % (0.2804)	[–0.430; –0.060]	0.0096	–0.230 (0.068)	0.0 % (0.4461)	[–0.364; –0.097]	0.0007	0.9003
Safety Parameters										
Study discontinuation due to AE or death	Odds ratio	1.777	0.0 % (0.3816)	[1.009; 3.129]	0.0464	1.167	0.0 % (0.7303)	[0.742; 1.838]	0.5037	0.2564
Total incidences of (treatment-emergent) AEs	Odds ratio	2.089	0.0 % (0.9434)	[1.293; 3.374]	0.0026	0.907	0.0 % (0.9592)	[0.727; 1.132]	0.3880	**0.0020**

**p Values refer to active treatment versus placebo unless otherwise indicated. Statistically significant p values for entacapone versus safinamide are shown in bold, red font. AE = adverse event; CI = confidence interval; SE = standard error; UPDRS = Unified Parkinson's Disease Rating Scale.*

Table 4: Statistical Meta-analysis Estimates using All Safinamide Doses (Random Effects Model)

Parameter	Effect Measure	Entacapone			Safinamide Entacapone			p Value for Entacapone versus Safinamide
		Value	95 % CI	p Value*	Value	95 % CI	P-value*	
Efficacy Parameters								
Changes in the daily L-dopa dose	Hedges' g (SE)	–0.408 (0.094)	[–0.592; –0.223]	<0.0001	–0.104 (0.059)	[–0.220; – 0.012]	0.0776	**0.0064**
Changes from baseline in total daily *off* time	Hedges' g (SE)	–0.346 (0.094)	[–0.531; –0.162]	0.0002	–0.368 (0.059)	[–0.484; –0.252]	<0.0001	0.8483
Changes from baseline in total daily *on* time	Hedges' g (SE)	0.397 (0.094)	[0.212; 0.582]	<0.0001	0.202 (0.109)	[–0.013; 0.416]	0.0651	0.1764
Changes from baseline in percent *on* time	Hedges' g (SE)	0.347 (0.091)	[0.168; 0.526]	0.0001	0.290 (0.085)	[0.123; 0.456]	0.0006	0.6451
Changes from baseline in the total UPDRS score	Hedges' g (SE)	–0.239 (0.107)	[–0.449; –0.030]	0.0254	–0.230 (0.068)	[–0.364; –0.097]	0.0007	0.9430
Safety Parameters								
Study discontinuation due to AE + deaths	Odds ratio	1.777	[1.009; 3.129]	0.0464	1.167	[0.742; 1.838]	0.5037	0.2564
Total incidences of (treatment-emergent) AEs	Odds ratio	2.089	[1.293; 3.374]	0.0026	0.907	[0.727; 1.132]	0.3880	**0.0020**

**p Values refer to active treatment versus placebo unless otherwise indicated. Statistically significant P-values for entacapone versus safinamide are shown in bold, red font. AE = adverse event; CI = confidence interval; L-dopa = levodopa; SE = standard error; UPDRS = Unified Parkinson's Disease Rating Scale.*

of breath (p=0.009), urine abnormality (p=0.006), dizziness (p=0.009) and diarrhoea (p=0.001). The raw overall AE rates are 68.7 % with safinamide treatment and 84.4 % with entacapone treatment. The OR for active treatment in comparison with placebo for the total incidence of AEs were entacapone: 2.089 (p=0.0026) and safinamide: 0.907 (p=0.3880) (see *Figure 6A*), resulting in an indirect OR of 0.434 of safinamide versus entacapone (95 % confidence interval [CI] 0.256–0.737). The ORs for active treatment using high safinamide doses versus placebo and combined safinamide doses versus placebo are shown in *Figures 6B* and *6C*, respectively.

Discussion

The number of trials included in this analysis is low. However, the study numbers are still valid for meta-analytical methods. In addition, the results of the present selection of entacapone studies are in line with those presented by Brooks et al.[18] in a pooled analysis aimed at evaluating the efficacy and safety of long-term L-dopa/DDCI and entacapone therapy. Safinamide and entacapone treatments appeared comparable in terms of the main efficacy variables (*off* time, percentage *on* time, UPDRS). These results are in line with those obtained previously in the LARGO trial,[19] comparing rasagiline to entacapone, where the efficacy of the two drugs was similar. Thus, safinamide can be considered as an efficacious drug for reducing motor fluctuations, with a magnitude similar to that of entacapone.

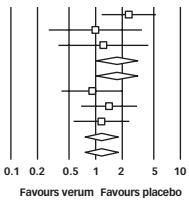
Advantages in favour of safinamide were detected in terms of tolerability, particularly in terms of nausea, vomiting, shortness of breath, urine abnormality, dizziness and diarrhoea. A previous meta-analysis performed by the Cochrane Collaboration,[12,20] assessing

Figure 2: Forest Plot Presentation of Meta-Analyses Using All Safinamide Doses for the Following Safety Endpoints

A

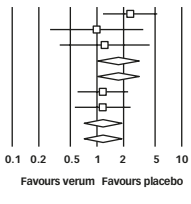
All safinamide doses

Model	Group by Prep	Study	Outcome	Odds ratio	Lower limit	Upper limit	p Value	Verum	Placebo
	ENT	ENT1	AE+DE	2.471	1.182	5.163	0.0162	41/197	10/104
	ENT	ENT2	AE+DE	0.990	0.278	3.528	0.9874	5/103	5/102
	ENT	ENT3	AE+DE	1.230	0.361	4.195	0.7404	6/85	5/86
Fixed	ENT			1.777	1.009	3.129	0.0464	52/385	20/292
Random	ENT			1.777	1.009	3.129	0.0464	52/385	20/292
	SAF	SAF1A	AE+DE	0.908	0.392	2.104	0.8219	11/223	12/222
	SAF	SAF1B	AE+DE	1.437	0.670	3.084	0.3518	17/224	12/222
	SAF	SAF2B	AE+DE	1.167	0.545	2.502	0.6910	15/274	13/275
Fixed	SAF			1.167	0.742	1.838	0.5037	43/721	37/719
Random	SAF			1.167	0.742	1.838	0.5037	43/721	37/719



Combined safinamide doses

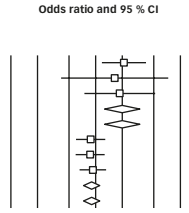
Model	Group by Prep	Study	Outcome	Odds ratio	Lower limit	Upper limit	p Value	Verum	Placebo
	ENT	ENT1	AE+DE	2.471	1.182	5.163	0.0162	41/197	10/104
	ENT	ENT2	AE+DE	0.990	0.278	3.528	0.9874	5/103	5/102
	ENT	ENT3	AE+DE	1.230	0.361	4.195	0.7404	6/85	5/86
Fixed	ENT			1.777	1.009	3.129	0.0464	52/385	20/292
Random	ENT			1.777	1.009	3.129	0.0464	52/385	20/292
	SAF	SAF1C	AE+DE	1.169	0.583	2.346	0.6595	28/447	12/222
	SAF	SAF2B	AE+DE	1.167	0.545	2.502	0.6910	15/274	13/275
Fixed	SAF			1.168	0.699	1.954	0.5529	43/721	25/497
Random	SAF			1.168	0.699	1.954	0.5529	43/721	25/497



B

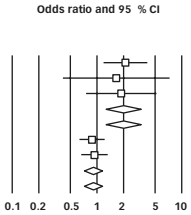
All safinamide doses

Model	Group by Prep	Study	Outcome	Odds ratio	Lower limit	Upper limit	p Value	Verum	Placebo
	ENT	ENT1	Any AE	2.208	1.215	4.013	0.0094	170/197	77/104
	ENT	ENT2	Any AE	1.718	0.400	7.386	0.4669	100/103	97/102
	ENT	ENT4*	Any AE	1.969	0.751	5.158	0.1680	105/115	48/57
Fixed	ENT			2.089	1.293	3.374	0.0026	375/415	222/263
Random	ENT			2.089	1.293	3.374	0.0026	375/415	222/263
	SAF	SAF1A	Any AE	0.891	0.599	1.324	0.5669	147/223	152/222
	SAF	SAF1B	Any AE	0.879	0.592	1.305	0.5231	147/224	152/222
	SAF	SAF2B	Any AE	0.946	0.660	1.356	0.7607	186/274	190/275
Fixed	SAF			0.907	0.727	1.132	0.3880	480/721	494/719
Random	SAF			0.907	0.727	1.132	0.3880	480/721	494/719



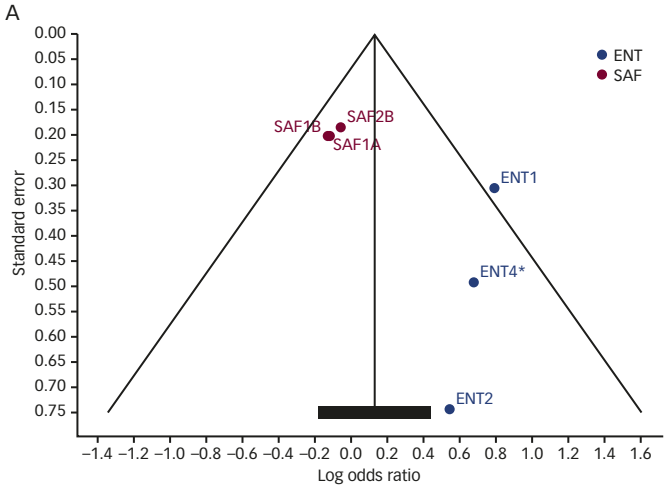
Combined safinamide doses

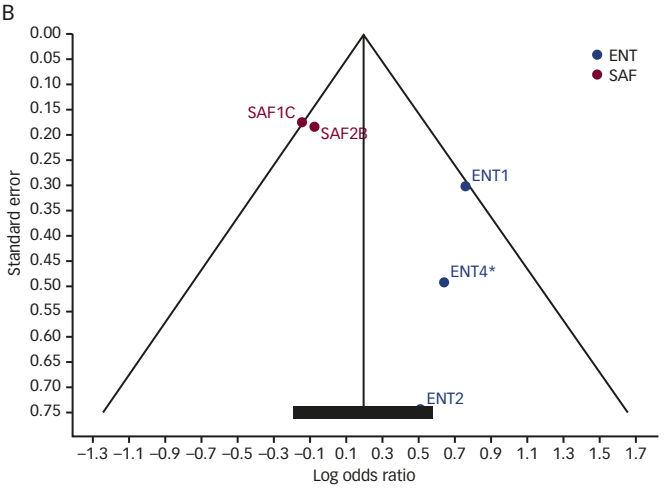
Model	Group by Prep	Study	Outcome	Odds ratio	Lower limit	Upper limit	p Value	Verum	Placebo
	ENT	ENT1	Any AE	2.208	1.215	4.013	0.0094	170/197	77/104
	ENT	ENT2	Any AE	1.718	0.400	7.386	0.4669	100/103	97/102
	ENT	ENT4*	Any AE	1.969	0.751	5.158	0.1680	105/115	48/57
Fixed	ENT			2.089	1.293	3.374	0.0026	375/415	222/263
Random	ENT			2.089	1.293	3.374	0.0026	375/415	222/263
	SAF	SAF1C	Any AE	0.885	0.627	1.248	0.4861	294/447	152/222
	SAF	SAF2B	Any AE	0.946	0.660	1.356	0.7607	186/274	190/275
Fixed	SAF			0.913	0.712	1.171	0.4752	480/721	342/497
Random	SAF			0.913	0.712	1.171	0.4752	480/721	342/497



*(A) Study discontinuation due to adverse events or deaths (excluding ENT4)[16] and (B) total incidences of treatment-emergent adverse events. Interventions: safinamide low dose (SAF A; 50 mg/day); safinamide high dose (SAF B; 100 mg/day); entacapone (ENT; 200 mg with each dose of L-dopa). SAF1, Borgohain et al.,[7] SAF2, Schapira et al.,[11] ENT1, Poewe et al.,[14] ENT2, Parkinson Study Group;[15] ENT3, Rinne et al.,[16] ENT4, Brooks et al.[17] *In study ENT4, only fluctuating patients were considered.*

Figure 3: Funnel Plot Associated with the Random Effects Meta-Analysis of Total Incidences of Treatment-emergent Adverse Events Using All Safinamide Doses (A) and Combined Safinamide Doses (B)





*SAF1, Borgohain et al.,[7] SAF2, Schapira et al.,[11] ENT1, Poewe et al.,[14] ENT2, Parkinson Study Group;[15] ENT3, Rinne et al.,[16] ENT4, Brooks et al.[17] *In study ENT4, only fluctuating patients are considered.*

the efficacy and safety of three drug classes commonly used as adjuvant therapy to L-dopa for PD patients with motor complications (COMT inhibitors, MAO-B inhibitors and dopamine agonists), showed that COMT inhibitors reduce *off* time and improve UPDRS at the expense of increased onset of dyskinesia and numerous other side effects. They concluded that: "… in terms of safety, dopamine agonists and COMT inhibitors have a similar incidence of side effects, although more than MAO-B inhibitors". In particular, the Cochrane review reported that the frequency of dyskinesia and patient withdrawal due to AEs were increased with COMT inhibitors while there was no difference between MAO-B inhibitors and placebo. These data have been confirmed by the present meta-analysis, where the number of discontinuations due to AEs, in particular dopaminergic reactions, occurred more frequently with entacapone treatment than with safinamide, despite a significant reduction in the oral L-dopa dosing with entacapone. Moreover, a retrospective pooled analysis performed by Brooks[18] on four entacapone comparable trials showed that the most commonly reported AEs were aggravation of PD, dyskinesia, nausea, dizziness and diarrhoea.

Conclusions

Motor fluctuations are among the most frequent and disabling complications of L-dopa treatment. Addition of COMT inhibitors improves motor complications, but increases the risk of side effects and

Figure 4: Risk Difference of Adverse Events Using Entacapone and All Safinamide Doses – Active Treatment versus Placebo

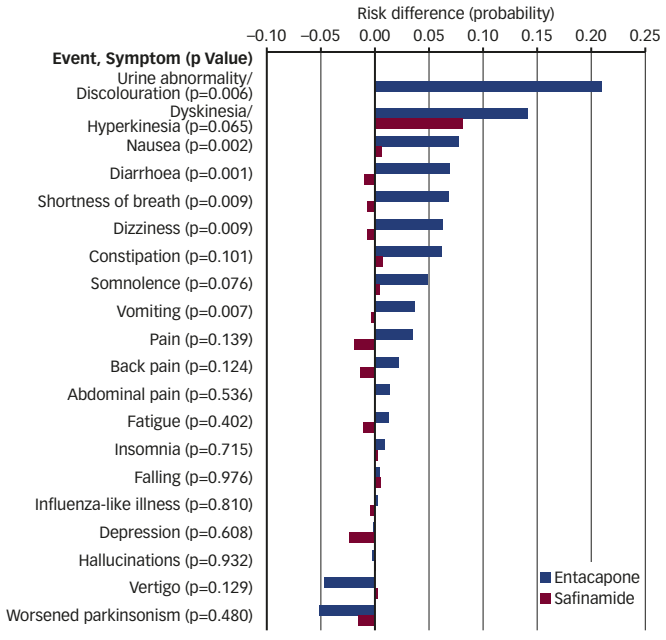


Figure 5: Risk Differences of Adverse Events Using Entacapone and High Safinamide Dose – Active Treatment versus Placebo

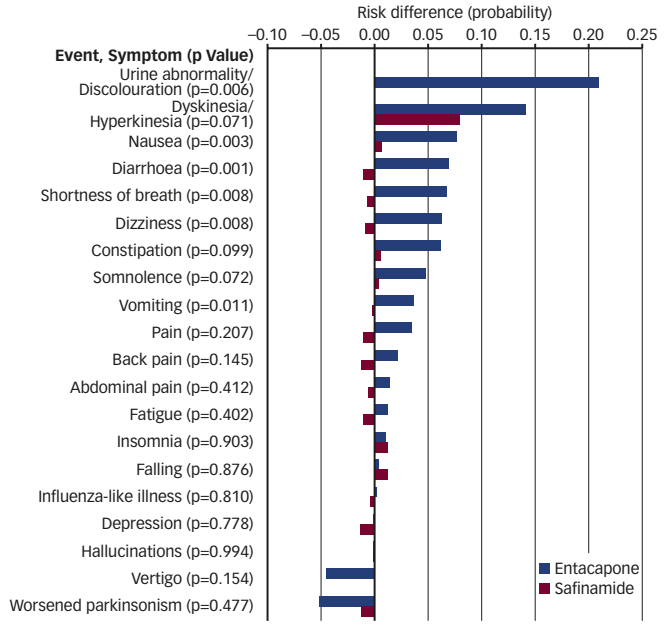
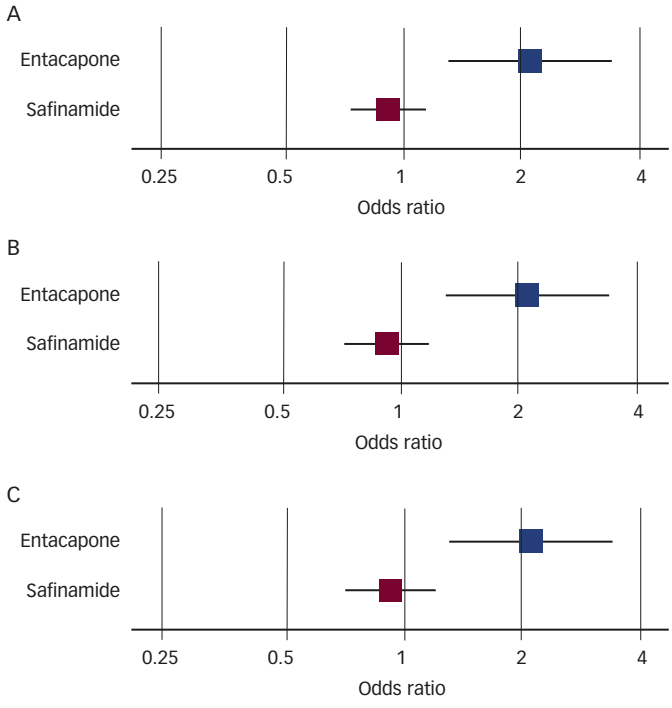


Figure 6: Odds ratio of Active Treatment versus Placebo (95 % Confidence Interval) of the Total Incidence of Adverse Events Using Entacapone and (A) All Safinamide Doses, (B) High Safinamide Dose and (C) Combined Safinamide Doses



the complexity in administration. There is a need for new easy-to-use, efficacious treatments. Safinamide is a safe and well-tolerated drug, due to its high selectivity and reversibility, and does not have amphetamine or methamphetamine metabolites (such as selegiline). This meta-analysis has shown that safinamide reduces disability and improves fluctuations without raising the frequency of troublesome dyskinesia with a magnitude of efficacy similar to entacapone. Moreover, safinamide was well tolerated with a safety profile not different from placebo, whereas comparison with placebo was significantly less favourable with entacapone. No dopaminergic AEs were recorded, despite a significantly lower reduction of L-dopa dose relative to entacapone, confirming that safinamide has no major drug–drug interactions and no need of diet restrictions. Furthermore, safinamide was given once a day without titration (whereas entacapone application rates vary from 3 to 10 daily in clinical practice), both relevant factors for patients usually receiving complicated oral drug regimens. In summary, these properties confirm that safinamide is straightforward to administer, is an effective and safe drug for the treatment of PD and is a favourable candidate as adjunct therapy to L-dopa and other anti-parkinsonian therapies. ■

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2. Rinne UK, Treatment of Parkinson's disease: problems with a progressing disease, *J Neural Transm*, 1981;51:161–74.
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