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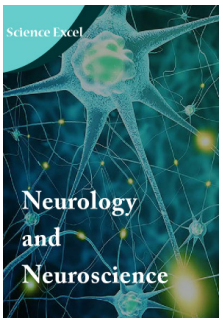

Incidence of Adverse Events in Individuals With Parkinson's Disease Treated With Monoamine Oxidase-B Inhibitor Safinamide as an Add-On to Levodopa Treatment: A Systematic Review and Meta-Analysis

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Keywords

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Abstract

Introduction: *Parkinson's Disease (PD) is a disabling neurodegenerative disease. Its long-term high-dose treatment with Levodopa increases the incidence of motor adverse events such as worsening of PD and dyskinesia. These motor adverse events can be managed by monoamine oxidase-B (MAO-B) inhibitors. Safinamide is used as an add-on to Levodopa because it is associated with fewer adverse events than other MAO-B inhibitors.* ***Methods:*** *A systematic literature search and meta-analysis were performed with randomized controlled trials that investigated the incidence of adverse events in individuals with PD treated with Safinamide as an add-on to Levodopa treatment. The systematic search was conducted in PubMed, Cochrane, and EBSCO databases. Methodological quality was assessed using the Cochrane Grading Recommendations Assessment, Development and Evaluation approach.* ***Results:*** *Five studies were included in our review. The incidence of adverse events and serious adverse events in the Safinamide groups was like that in the placebo group (RR = 0.97, RR = 1, RR = 1.06, RR = 1.02). The incidence of worsening of PD was non-significantly lower in the Safinamide groups compared to the placebo group (RR = 0.94, RR = 0.87). The incidence of dyskinesia was significantly higher in the Safinamide groups compared to the placebo group (RR = 1.58, RR = 1.91). The incidence of back pain was non-significantly lower in the Safinamide groups compared to the placebo group (RR = 0.60, RR = 0.75). The incidence of headache was non-significantly higher in the 50 mg/day Safinamide group compared to the placebo group (RR = 1.65), but in the 100 mg/day Safinamide group it was similar to that in the placebo group (RR = 0.97).* ***Conclusion:*** *Safinamide as an add-on to Levodopa could lower the incidence of worsening of PD and back pain, warranting further study. However, the effects of Safinamide on the overall incidence of adverse events, serious adverse events, dyskinesia, and headache are inconclusive due to study limitations.*

Introduction

Parkinson's Disease (PD) is a disabling neurodegenerative disease [1]. The major pathological change in PD is the loss of dopaminergic neurons and the neurotransmitter dopamine. To delay the disabling effects of PD, dopaminergic medication has been used to substitute dopamine, with Levodopa being the leading choice [2]. Because PD is a progressive neurodegenerative disease, gradual increases in Levodopa doses must be administered. However, long-term high-dose Levodopa treatment increases the incidence of motor adverse events such as worsening of PD (i.e. worsening of tremors, bradykinesia, and stiffness) [3] and dyskinesia [4]. These motor adverse events can be managed by dopamine agonists, monoamine oxidase-B (MAO-B) inhibitors, and catechol O-methyltransferase (COMT) inhibitors [2].

MAO-B inhibitors include Selegiline, Rasagiline, and Safinamide. Selegiline is a first-generation irreversible MAO-B inhibitor and is associated with higher rates of adverse events due to its amphetamine backbone chemical structure. When Selegiline undergoes first-pass metabolism in the liver, it is transformed into L-amphetamine and L-methamphetamine, which can cause cardiovascular (hypertension, tachycardia) and central nervous system (insomnia, nervousness) adverse events [5]. Rasagiline is a second-generation irreversible MAO-B inhibitor that does not have an amphetamine backbone and is associated

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with fewer adverse events than Selegiline [6]. In comparison to Selegiline or Rasagiline, Safinamide is an alpha-aminoamide derivative introduced into the market as a reversible MAO-B inhibitor. Safinamide has a higher MAO-B selectivity and leads to fewer adverse events than both Selegiline and Rasagiline [7].

Safinamide is a reversible MAO-B inhibitor with a dual mechanism of action. It reversibly inhibits MAO-B, blocking dopamine breakdown, and regulates the release of the neurotransmitter glutamate [8]. Preliminary evidence shows Safinamide has been safe and well-tolerated as an add-on to Levodopa treatment. Clinical trial investigations have found a decreased incidence of motor adverse events and non-motor adverse events in individuals treated with Safinamide as an add-on to Levodopa treatment compared to placebo [9].

Despite the preliminary evidence, a systematic review with meta-analysis has not been performed to investigate the incidence of motor adverse events and non-motor adverse events in individuals with PD treated with Safinamide as an add-on to Levodopa treatment compared to placebo. Our purpose was to conduct a systematic review with meta-analysis to investigate the incidence of motor adverse events and non-motor adverse events in individuals with PD treated with Safinamide as an add-on to Levodopa treatment compared to placebo.

Materials and methods

Source of Data and Search Strategy

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [10]. The review protocol was registered on PROSPERO: CRD42024550618 and vetted by a professional research librarian. An extensive literature search on the MAO-B inhibitor Safinamide as an add-on to Levodopa treatment was performed using PubMed, Cochrane, and EBSCO electronic databases and manual searches. They were searched from inception to June 16th, 2024. Searches were restricted to articles in the English language and randomized controlled trials (RCTs). Appendix 1 provides a detailed list of search terms utilized.

Outcome Measures

Adverse events were defined as untoward medical occurrences that occurred after exposure to Safinamide [11]. Serious adverse events were defined as adverse events that resulted in death, were life-threatening, required hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, or were a birth defect [11]. Adverse events and serious adverse events were further divided into motor adverse events (worsening of PD, dyskinesia) and non-motor adverse events (back pain, headache). Adverse events and serious adverse events were reported separately for the 50 mg/day Safinamide group and the 100 mg/day Safinamide group compared to placebo. All types of adverse events that occurred were reported and included in analyses, from providing informed consent (baseline) until the last patient visit.

Inclusion and Exclusion Criteria

Studies were included with the following criteria: female and male individuals aged 18 or over with a clinical diagnosis of PD consistent with the UK Brain Bank criteria [12] who have a Hoehn and Yahr (H&Y) Stage 1 to 4 who are experiencing motor fluctuations while receiving Levodopa treatment. The intervention studied is the MAO-B inhibitor Safinamide as an add-on to Levodopa treatment and the outcomes assessed are adverse events or serious adverse events, and further divided into motor adverse events (worsening of PD, dyskinesia) and non-motor adverse events (back pain, headache). The study design search was limited to RCTs published in English (Table 1). Studies were excluded with the following criteria: individuals with severe disabling peak-dose or biphasic dyskinesia or with unpredictable or widely swinging symptom fluctuations. Studies were also excluded if the outcomes assessed were not adverse events or serious adverse events, or if the study design was expert opinion, editorial, case report, abstracts without full results, and preprints.

Study Selection

Two reviewers (PA, NA) independently screened all titles and abstracts of the identified studies. Full texts were obtained for the studies deemed eligible from the initial screening. Two reviewers (PA, NA) independently reviewed full texts. Any discrepancies were discussed and resolved through discussion between reviewers (PA, NA). Studies that met the inclusion and exclusion criteria were included in the full review.

Data Extraction

Data were extracted into a standardized form that included lead author, publication date, country, study design, intervention type, sample size, age, and results for adverse events and serious adverse events, further divided into motor adverse events (worsening of PD, dyskinesia) and non-motor adverse events (back pain, headache), by one independent reviewer (PA). A second reviewer (NA) conducted a reliability check. No discrepancies in data extraction were identified between the reviewers. If there was missing data, the authors were contacted for additional information.

Risk of Bias

Methodological quality was examined using the Cochrane Risk of Bias 2 (RoB 2) tool [13]. The RoB 2 is structured into five domains of bias: (1) randomization process, (2) deviations from the intended interventions (effect of assignment and adhering to intervention), (3) missing outcome data, (4) measurement of the outcome, and (5) selection of the reported result. From the results in each domain, an overall risk of bias was determined. Overall risk of bias was judged as high risk of bias, some concerns, or low risk of bias. Two reviewers (PA, NA) independently conducted the risk of bias analysis. Any discrepancies were discussed and resolved through discussion between reviewers (PA, NA).

Data Analysis

We performed a random-effects meta-analysis using the restricted maximum likelihood (REML) method to calculate the log risk ratio and 95% confidence interval (CI) of adverse events for Safinamide as an add-on to Levodopa treatment compared to placebo. We then performed a random-effects inverse-variance meta-analysis using the DerSimonian-Laird estimate of tau2 to calculate the risk ratio and 95% CI of adverse events for Safinamide as an add-on to Levodopa treatment compared to placebo. This analysis was performed for adverse events and serious adverse events, which were further divided into motor adverse events (worsening of PD, dyskinesia) and non-motor adverse events (back pain, headache). We assessed heterogeneity using Q, p, and I2 values and the 95% prediction interval (PI). The I2 value of 0% - 40% was interpreted as small heterogeneity, 30% - 60% as moderate heterogeneity, 50% - 90% as substantial heterogeneity, and 75% - 100% as considerable

heterogeneity [14]. The 95% PI was estimated when the meta-analysis included more than two studies. Publication bias was assessed in meta-analyses with at least ten studies [15]. Publication bias was assessed by inspection of the standard error funnel plots, trim-and-fill analysis, Egger's regression test, and Begg and Mezumdar's rank correlation test. If a meta-analysis did not include at least ten studies, the standard error funnel plot was still generated for qualitative review. All statistical analyses were conducted using STATA 18 (StataCorp. Stata statistical software: release 18. College Station, TX: StataCorp LP. 2023).

Certainty of Evidence

Two reviewers (PA, NA) independently assessed the certainty of evidence using the GRADE approach for each meta-analysis (GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University and Evidence Prime, 2022. Available from gradepro.org) [16]. Each meta-analysis was classified as very low, low, moderate, or high-quality certainty of evidence.

Results

Study Selection

The electronic search of databases yielded 39 articles. Eleven articles were found to be duplicates, leaving a total of 28 articles. Fifteen articles were excluded after reviewing titles and abstracts. The remaining 13 articles were retrieved and assessed for eligibility. Eight articles were excluded because they did not meet the inclusion criteria. Five remaining articles were found eligible and included in the review [17-21] (Figure 1). All of the included articles were utilized to perform meta-analyses.

Characteristics of selected studies

As summarized in Table 2, 2462 individuals were assessed in studies across Europe [17-19], India [17,18], Asia-Pacific region [19], North America [19], Japan [20], and China [21]. The duration of the studies ranged between 16 to 78 weeks. Three studies included a 50 mg/day and a 100 mg/day Safinamide group [17,18,20]. Two studies administered 50 mg/day for two weeks, switching to 100 mg/day after two weeks if no tolerability issues occurred [19,21]. The studies reported adverse events over 16 weeks [21], 24 weeks [17,19,20], and 78 weeks [18]. All studies included placebo as the control.

There was an overlap of individuals between two of the studies: 544 participants from the Borghain et al., 2013 study [17] rolled over to the Borghain et al., 2014 study [18]. Individuals continued in the same treatment group to which they were randomized in the parent study. Adverse events in the Borghain et al., 2014 study [18] were reported as newly emergent and independent of the adverse events in the Borghain et al., 2013 study [17].

Characteristics of participants

The mean age of individuals ranged from 60.1 to 68.4 years in the Safinamide groups and from 59.4 to 68.6 in the placebo groups. The H&Y Stage of individuals was 1 to 4. The mean H&Y scores for the Safinamide groups were 2.5 to 3.17 in the 50 mg/day group [17,19,20], 3.25 in the 100 mg/day group [20], and 2.5-3.14 in the placebo group [17,19,20]. The Borghain et al., 2014 study [18] did not report separate baseline characteristics for the participants that rolled over from the Borghain et al., 2013 study [17]. The mean percentage of female individuals ranged from 27.2% to 58.1%.

Study Quality

The overall risk of bias was low for one included study [18], some concerns for three included studies [17,20,21], and high risk for one included study [19]. In two studies [17,20], the cause of some concern in the first domain was the lack of information regarding intervention allocation techniques. In two studies [20,21], the cause of some concern in the second domain was the lack of information regarding appropriate analysis to estimate the effect of assignment to intervention. For one study [19], the cause of high risk was the lack of information regarding the impact of the failure to analyze individuals in the group to which they were randomized.

Study Outcomes

All included studies reported outcomes from providing informed consent (baseline) until the last patient visit. All adverse events reported from baseline until the last patient visit were analyzed. In three studies [17,18,20], adverse events, serious adverse events, dyskinesia, back pain, and headache were reported for 50 mg/day Safinamide and placebo. In all studies, adverse events, serious adverse events, and dyskinesia were reported for 100 mg/day Safinamide and placebo. In two studies [17,18], worsening of PD was reported for 50 mg/day Safinamide and placebo. In three studies [17,18,21], worsening of PD was reported for 100 mg/day Safinamide and placebo. In four studies {17-20], back pain and headache were reported for 100 mg/day Safinamide and placebo. The adverse events were evaluated based on subjective symptoms, objective findings, laboratory tests, physiological tests, vital signs, and electrocardiograms.

Adverse Events

Three studies [17,18,20] investigated the incidence of adverse events between 50 mg/day Safinamide and placebo (n = 1083). There was a non-significant lower incidence of adverse events for 50 mg/day Safinamide compared to placebo (RR = 0.97; 95% CI 0.87, 1.08; p = 0.59). There was a small and statistically non-significant degree of heterogeneity identified in the meta-analysis (Q = 0.23, p = 0.89, I2 = 0.00%; 95% PI -0.74, 0.68) (Figure 3). Asymmetry was not observed in the funnel plot (Appendix 2).

All studies [17-21] investigated the incidence of adverse events between 100 mg/day Safinamide and placebo (n = 1928). There was no overall difference in the incidence of adverse events between 100 mg/day Safinamide and placebo (RR = 1; 95% CI 0.92, 1.09; p = 0.99). There was a small and statistically non-significant degree of heterogeneity identified in the meta-analysis (Q = 1.55, p = 0.82, I2 = 0.00%; 95% PI -0.13, 0.13) (Figure 4). Asymmetry was observed in the funnel plot (Appendix 3).

Serious Adverse Events

Three studies [17,18,20] investigated the incidence of serious adverse events between 50 mg/day Safinamide and placebo (n = 1083). There was a non-significant higher incidence of serious adverse events for 50 mg/day Safinamide compared to placebo (RR = 1.06; 95% CI 0.42, 2.67; p = 0.90). There was a substantial and statistically significant degree of heterogeneity identified in the meta-analysis (Q = 7.51, p = 0.02, I2 = 73.4%; 95% PI -10.29, 10.41) (Figure 5). Asymmetry was not observed in the funnel plot (Appendix 4).

All studies [17-21] investigated the incidence of serious adverse events between 100 mg/day Safinamide and placebo (n = 1928). There was a non-significant higher incidence of serious adverse events for 100 mg/day Safinamide compared to placebo

(RR = 1.02; 95% CI 0.73, 1.42; p = 0.92). There was a small and statistically non-significant degree of heterogeneity identified in the meta-analysis (Q = 2.47, p = 0.65, I2 = 0.00%; 95% PI -0.52, 0.56) (Figure 6). Asymmetry was observed in the funnel plot (Appendix 5).

Meta-analysis: motor adverse events

Worsening of PD

Two studies [17,18] investigated the incidence of worsening PD between 50 mg/day Safinamide and placebo (n = 809). There was a non-significant lower incidence of worsening PD for 50 mg/day Safinamide compared to placebo (RR = 0.94; 95% CI 0.58, 1.52; p = 0.79). There was a small and statistically non-significant degree of heterogeneity identified in the meta-analysis (Q = 1.34, p = 0.25, I2 = 25.2%) (Figure 7). Due to only two studies included in the meta-analysis, the 95% prediction interval was not estimated. Asymmetry was not observed in the funnel plot (Appendix 6).

Three studies [17,18,21] investigated the incidence of worsening PD between 100 mg/day Safinamide and placebo (n = 1106). There was a non-significant lower incidence of worsening PD for 100 mg/day Safinamide compared to placebo (RR = 0.87; 95% CI 0.32, 2.39; p = 0.78). There was a considerable and statistically significant degree of heterogeneity identified in the meta-analysis (Q = 11.11, p = 0.004, I2 = 82.0%; 95% PI -11.58, 11.31) (Figure 8). Asymmetry was not observed in the funnel plot (Appendix 7).

Dyskinesia

Three studies [17,18,20] investigated the incidence of dyskinesia between 50 mg/day Safinamide and placebo (n = 1083). There was a significant higher incidence of dyskinesia for 50 mg/day Safinamide compared to placebo (RR = 1.58; 95% CI 1.00, 2.49; p < 0.05). There was a small and statistically non-significant degree of heterogeneity identified in the meta-analysis (Q = 2.47, p = 0.29, I2 = 19.0%; 95% PI -1.94, 2.83) (Figure 9). Asymmetry was not observed in the funnel plot (Appendix 8).

All studies [17-21] investigated the incidence of dyskinesia between 100 mg/day Safinamide and placebo (n = 1928). There was a significant higher incidence of dyskinesia for 100 mg/day Safinamide compared to placebo (RR = 1.91; 95% CI 1.19, 3.06; p = 0.007). There was a substantial and statistically non-significant degree of heterogeneity identified in the meta-analysis (Q = 8.28, p = 0.08, I2 = 51.7%; 95% PI -0.75, 2.04) (Figure 10). Asymmetry was not observed in the funnel plot (Appendix 9).

Meta-analysis: non-motor adverse events

Back pain

Three studies [17,18,20] investigated the incidence of back pain between 50 mg/day Safinamide and placebo (n = 1083). There was a non-significant lower incidence of back pain for 50 mg/day Safinamide compared to placebo (RR = 0.60; 95% CI 0.32, 1.14; p = 0.12). There was a small and statistically non-significant degree of heterogeneity identified in the meta-analysis (Q = 1.41, p = 0.49, I2 = 0.00%; 95% PI -4.63, 3.61) (Figure 11). Asymmetry was not observed in the funnel plot (Appendix 10).

Four studies [17-20] investigated the incidence of back pain between 100 mg/day Safinamide and placebo (n = 1623). There was a non-significant lower incidence of back pain for 100 mg/day Safinamide compared to placebo (RR = 0.75; 95% CI 0.42, 1.35; p = 0.33). There was a small and statistically non-significant degree of heterogeneity identified in the meta-analysis (Q = 3.72, p = 0.29, I2 = 19.4%; 95% PI -1.37, 0.83) (Figure 12). Asymmetry was not observed in the funnel plot (Appendix 11).

Headache

Three studies [17,18,20] investigated the incidence of headache between 50 mg/day Safinamide and placebo (n = 1083). There was a non-significant higher incidence of headache for 50 mg/day Safinamide compared to placebo (RR = 1.65; 95% CI 0.85, 3.17; p = 0.14). There was a small and statistically non-significant degree of heterogeneity identified in the meta-analysis (Q = 1.61, p = 0.45, I2 = 0.00%; 95% PI -3.75, 4.75) (Figure 13). Asymmetry was not observed in the funnel plot (Appendix 12).

Four studies [17-20] investigated the incidence of headache between 100 mg/day Safinamide and placebo (n = 1623). There was a non-significant lower incidence of headache for 100 mg/day Safinamide compared to placebo (RR = 0.97; 95% CI 0.60, 1.56; p = 0.90). There was a small and statistically non-significant degree of heterogeneity identified in the meta-analysis (Q = 1.39, p = 0.71, I2 = 0.00%; 95% PI -1.07, 1.01) (Figure 14). Asymmetry was observed in the funnel plot (Appendix 13).

Overall Quality of Evidence

The overall quality was deemed very low to moderate for all meta-analyses (Appendix 14).

Discussion

To our knowledge, this is the first systematic review with meta-analysis to investigate the incidence of motor adverse events and non-motor adverse events in individuals with PD treated with Safinamide as an add-on to Levodopa treatment compared to placebo. Based on very low to moderate certainty of evidence, our study did not reveal significantly lower incidences in adverse events or serious adverse events, or motor adverse events (worsening of PD, dyskinesia) and non-motor adverse events (back pain, headache), in individuals with PD treated with Safinamide as an add-on to Levodopa treatment compared to placebo. However, our results were based on a low number of included studies and suggest there is a need for further investigation of Safinamide as an add-on to Levodopa treatment compared to placebo in the long-term and including a greater participant pool.

Although Levodopa is considered the most effective treatment for PD, long-term high-dose Levodopa treatment increases the incidence of worsening of PD and dyskinesia. Approximately 40% of individuals with PD develop motor fluctuations after four to six years of Levodopa treatment [22]. Many individuals require an add-on treatment to improve these motor fluctuations, which can increase the risk of adverse events. Studies have shown that MAO-B inhibitors can manage the motor fluctuations caused by Levodopa without increasing the risk of adverse events [2] [4]. Consistent with others, our results suggest that adding Safinamide as an adjunct prescription intervention to Levodopa does not increase the risk of adverse events or serious adverse events in individuals with PD.

Adverse Events and Serious Adverse Events

The incidence of adverse events and serious adverse events in individuals receiving 50 mg/day or 100 mg/day Safinamide was similar to the individuals receiving the placebo as an add-on to Levodopa. Consistent with our findings, in 2023 an investigation

studying the risks of adverse events among different add-on treatments to Levodopa was performed. The study showed that the incidence of adverse events in individuals receiving extended-release Pramipexole as an add-on to Levodopa treatment was similar to the individuals receiving the placebo. However, individuals receiving other add-on treatments such as Pramipexole, Ropinirole, extended-release Ropinirole, Opicapone, and Istradefylline had a lower incidence of adverse events than individuals receiving the placebo [23]. The study investigated the risks of adverse events among different add-on treatments but did not focus on one specific treatment. In 2013, a study showed that MAO-B inhibitors can manage motor fluctuations caused by Levodopa without increasing the risk of adverse events [2]. Whereas our study focused on the newest reversible MAO-B inhibitor Safinamide.

Motor Adverse Events

The most common motor adverse event occurring from PD medication is dyskinesia. The incidence of dyskinesia in individuals with PD receiving either 50 or 100 mg/day Safinamide as an add-on to Levodopa treatment was significantly higher than in individuals receiving placebo as an add-on to Levodopa treatment. Based on a limited number of studies, very low to low certainty of evidence, and small to substantial heterogeneity, the incidence of dyskinesia was higher (RR = 1.91) for the individuals receiving 100 mg/day Safinamide than for the individuals receiving 50 mg/day Safinamide (RR = 1.58) compared to placebo.

Although the incidence of dyskinesia was higher in individuals receiving Safinamide, most cases of dyskinesia were mild, and the individuals recovered or showed evidence of recovering from dyskinesia after reducing the dose of Levodopa. Research shows that Levodopa dose should be decreased when adjunctive therapies such as MAO-B inhibitors are used. Decreasing the dosage of Levodopa has been shown to reduce the incidence of dyskinesia and other motor adverse events caused by high dose Levodopa [24]. Therefore, it is important for clinicians to consider modifying Levodopa dose when prescribing add-on therapies to Levodopa treatment.

Non-Motor Adverse Events

The most commonly reported non-motor adverse events reported in our investigation were back pain and headache. Incidence of back pain in individuals with PD receiving either 50 or 100 mg/day Safinamide as an add-on to Levodopa treatment was non-significantly lower than in individuals receiving placebo as an add-on to Levodopa treatment. The results of our study suggest that the incidence of back pain is lower when receiving a lower dose (50 mg) of Safinamide than when receiving a higher dose (100 mg) of Safinamide. Our findings of a direct relationship between the incidence of back pain and Safinamide dose administration are consistent with others who found that individuals who were administered Safinamide consumed less pain medication than individuals receiving the placebo (24%) and reported a significant reduction in back pain [25]. The results of our study and the results of others reveal that Safinamide as an add-on to Levodopa can reduce the incidence of back pain in individuals with PD, and its dose dependence requires further long-term study in larger participant populations.

Beyond low back pain, Safinamide as an add-on to Levodopa can increase the incidence of headaches in individuals with PD, regardless of the dosage. Headaches caused by Safinamide could potentially impact patient care as patients may take additional anti-pain medication for their headache. To our knowledge, this is the first study that has identified a higher incidence of headaches in individuals with PD that take a lower dose (50 mg/day) compared to a higher dose (100 mg/day) of Safinamide. However, we were unable to determine if the headaches occurred from the ongoing Levodopa treatment or the add-on Safinamide treatment. There is no previous research on the dose dependence of add-on treatments to Levodopa on the incidence of headaches. Further study is required with Safinamide as an add-on to Levodopa treatment with participants receiving various doses of Safinamide compared to placebo as an add-on to the various doses of Levodopa in the long-term.

Limitations

This study had several limitations. First, due to the limited number of studies included in each meta-analysis, we did not investigate the long-term effects of Safinamide as an add-on to Levodopa treatment on adverse events. Second, our review only included published randomized controlled trials and did not include "gray literature." Third, due to the limited number of studies, we were unable to adequately assess the potential for publication bias.

Conclusion

Based on very low to moderate certainty of evidence, our study provides a foundation for future research to investigate the incidence of adverse events and serious adverse events, further divided into motor adverse events (worsening of PD, dyskinesia) and non-motor adverse events (back pain, headache), in individuals with PD treated with Safinamide as an add-on to Levodopa treatment compared to placebo. Our findings suggest that Safinamide as an add-on to Levodopa could lower the incidence of non-motor adverse events (back pain, headache). The effects of Safinamide on the overall incidence of adverse events, serious adverse events, and motor adverse events (dyskinesia) are inconclusive due to study limitations. Nevertheless, Safinamide has shown non-significantly lower incidences of some adverse events which should be investigated further in the long-term in a larger study population using various doses of Levodopa to distinguish between adverse events occurring from Levodopa treatment versus adverse events occurring from the add-on Safinamide treatment.

Declarations

Ethics Approval and Consent to Participate

This is not applicable to this manuscript because this is a systematic review and meta-analysis of previously published literature and there were no interactions with human patients.

Consent for Publication

Not applicable.

Availability of Data and Materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the study.

Competing Interests

The authors declare that they have no competing interests.

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There was no funding for this study.

Authors Contributions

Two researchers (PA, NA) worked independently to perform

two (independent) searches using three electronic databases: PubMed, Cochrane, and EBSCO. Both authors were involved in the writing and editing of the manuscript (PA, NA).

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Appendix 1

Search terms

The search terms for the PubMed database were: ("Parkinson's disease" OR "Parkinson" OR "Parkinson disease") AND ("Safinamide") AND ("adverse events" OR "serious adverse events" OR "safety concerns") AND ("Levodopa" OR "L-DOPA"). Filters: Randomized Controlled Trials (RCTs), Humans, English, Exclude preprints.

The search terms for the Cochrane database were: ("Parkinson's disease" OR "Parkinson" OR "Parkinson disease") AND ("Safinamide") AND ("adverse events" OR "serious adverse events" OR "safety concerns") AND ("Levodopa" OR "L-DOPA"). Filters: English.

The search terms for the EBSCO database were: ("Parkinson's disease" OR "Parkinson" OR "Parkinson disease") AND ("Safinamide") AND ("adverse events" OR "serious adverse events" OR "safety concerns") AND ("Levodopa" OR "L-DOPA"). Filters: Search mode “find any of my search terms”, English.

Table 1. PICOS criteria for inclusion and exclusion criteria of studies

Parameter	Inclusion criteria	Exclusion criteria
Population	Female and male individuals over the age of 18 with a clinical diagnosis of PD consistent with the UK Brain Bank criteria who have a Hoehn and Yahr Stage 1 to 4 who are experiencing motor fluctuations while receiving Levodopa treatment	Individuals with severe disabling peak-dose or biphasic dyskinesia or with unpredictable or widely swinging symptom fluctuations
Intervention	MAO-B inhibitor Safinamide as an add-on to Levodopa treatment	Other types of PD medication
Comparator	Placebo	No comparator
Outcome	Adverse events or serious adverse events	Adverse events or serious adverse events not included as safety endpoints
Study design	Randomized Controlled Trials published in English	Expert opinions, editorials, case reports, abstracts without full reports, and preprints. Published in any other language than English

Figure 1. *PRISMA flow diagram for searches*

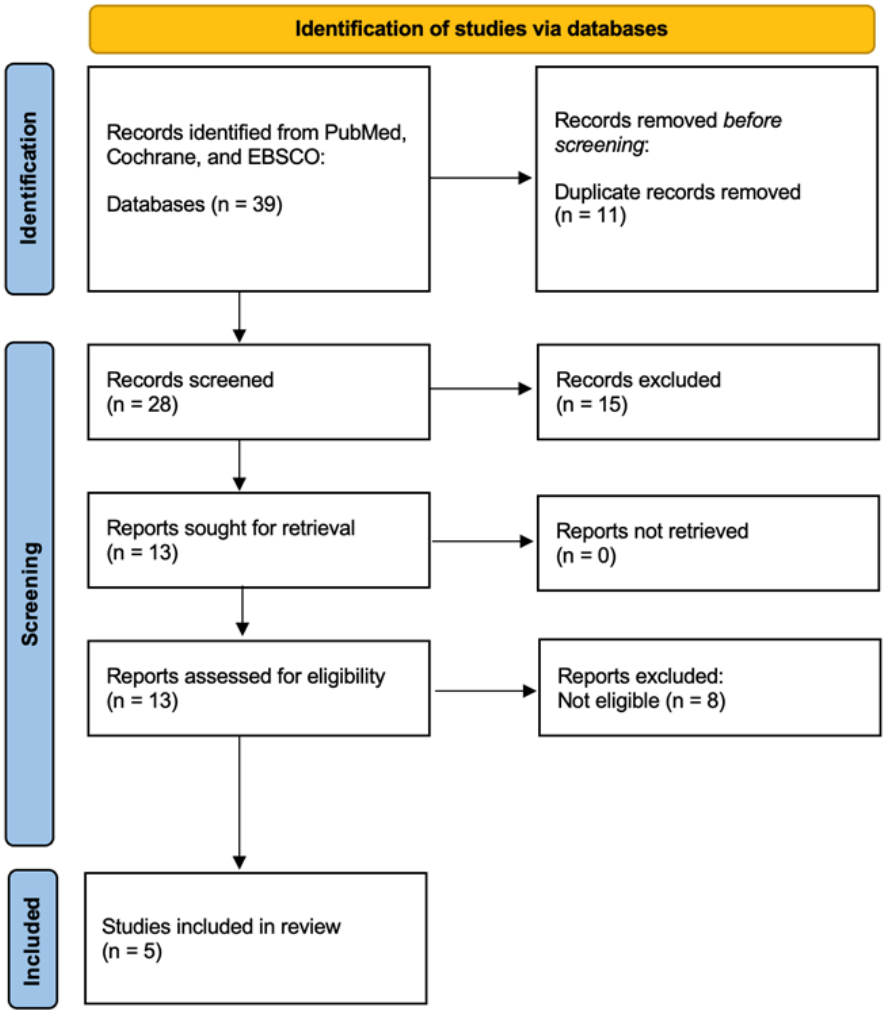


Table 2. *Summary of the studies on the MAO-B inhibitor Rasagiline retrieved from the literature*

Authors	Number of participants at baseline	Gender allocation	Mean age of participants in the Safinamide group	Group allocation	Intervention duration
Borgohain et al., 2013	669	71.7% male, 28.3% female	60.1 ± 9.7 in the 50 mg/day Safinamide group, 60.1 ± 9.2 in the 100 mg/day Safinamide group	223 participants received 50 mg/day Safinamide, 224 participants received 100 mg/day Safinamide, 222 participants received the placebo	24 weeks
Borgohain et al., 2014	544			189 participants received 50 mg/day Safinamide, 180 participants received 100 mg/day Safinamide, 175 participants received the placebo	78 weeks
Schapira et al., 2017	549	60.8% male, 39.2% female	61.7 ± 9.0	274 participants received Safinamide (50 mg/day for the first two weeks followed by 100 mg/day for the rest of the study if no tolerability issues occurred), 275 participants received the placebo	24 weeks
Hattori et al., 2020	406	43.8% male, 56.2% female	67.2 ± 9.0 in the 50 mg/day Safinamide group, 68.4 ± 7.7 in the 100 mg/day Safinamide group	131 participants received 50 mg/day Safinamide, 128 participants received 100 mg/day Safinamide, 136 participants received the placebo	24 weeks
Wei et al., 2022	305	58.0% male, 42.0% female	61.4 ± 9.3	151 participants received Safinamide (50 mg/day for the first two weeks followed by 100 mg/day for the rest of the study if no tolerability issues occurred), 154 participants received the placebo	16 weeks

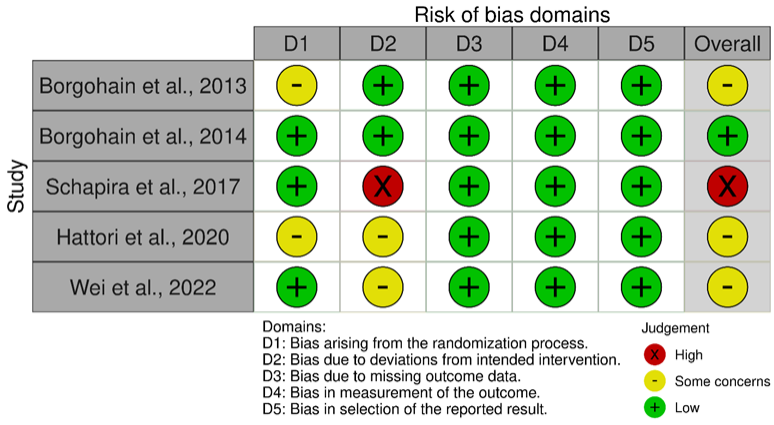


Figure 2. *Traffic-light plot of RoB 2*

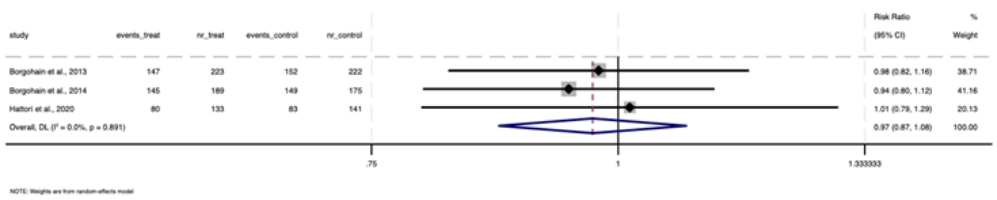
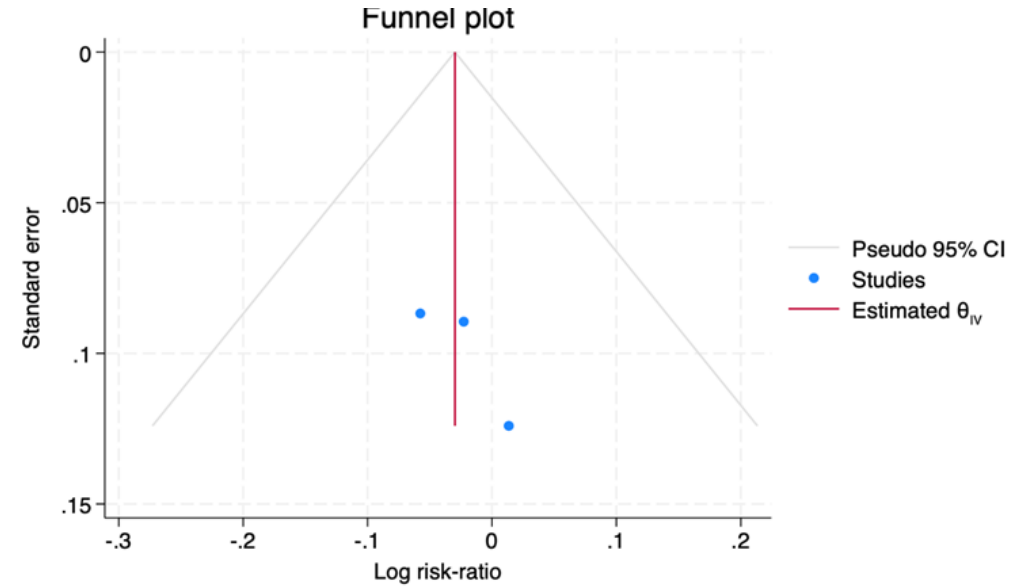


Figure 3. Forestplot adverse events 50 mg/day Safinamide compared to placebo

Appendix 2

Funnel plot adverse events 50 mg/day Safinamide compared to placebo



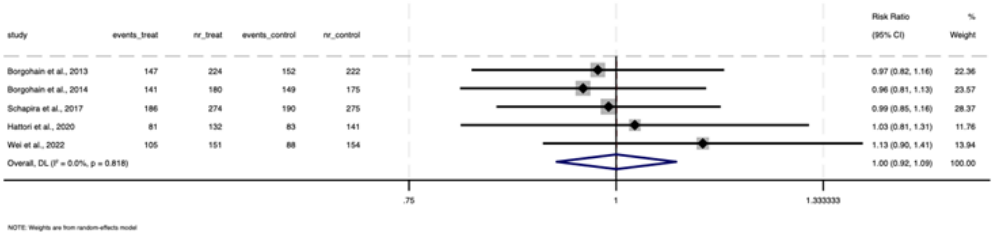
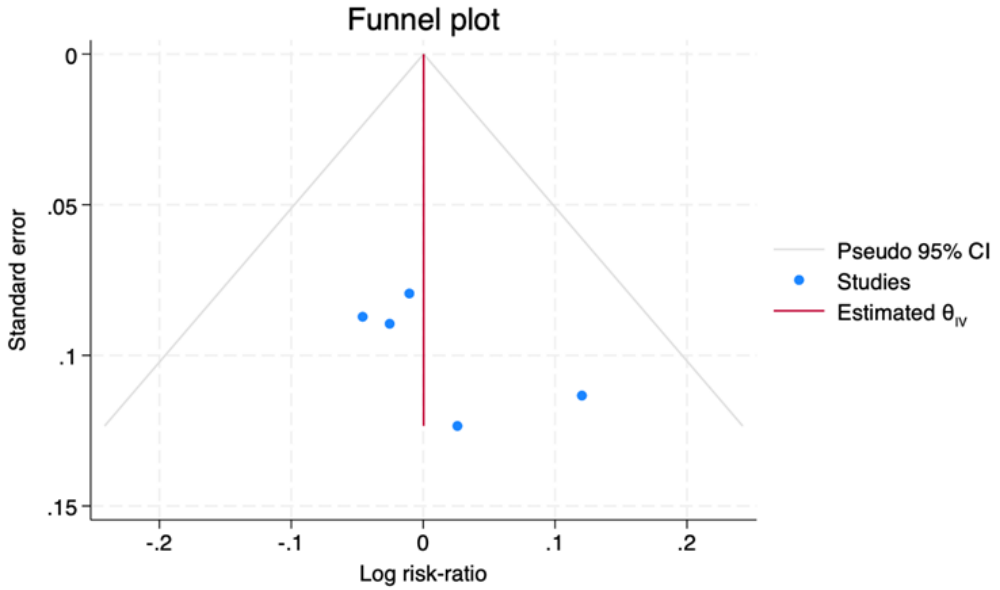


Figure 4. *Forestplot adverse events 100 mg/day Safinamide compared to placebo*

Appendix 3

Funnel plot adverse events 100 mg/day Safinamide compared to placebo



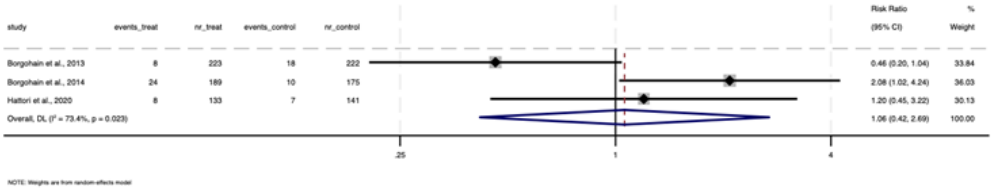
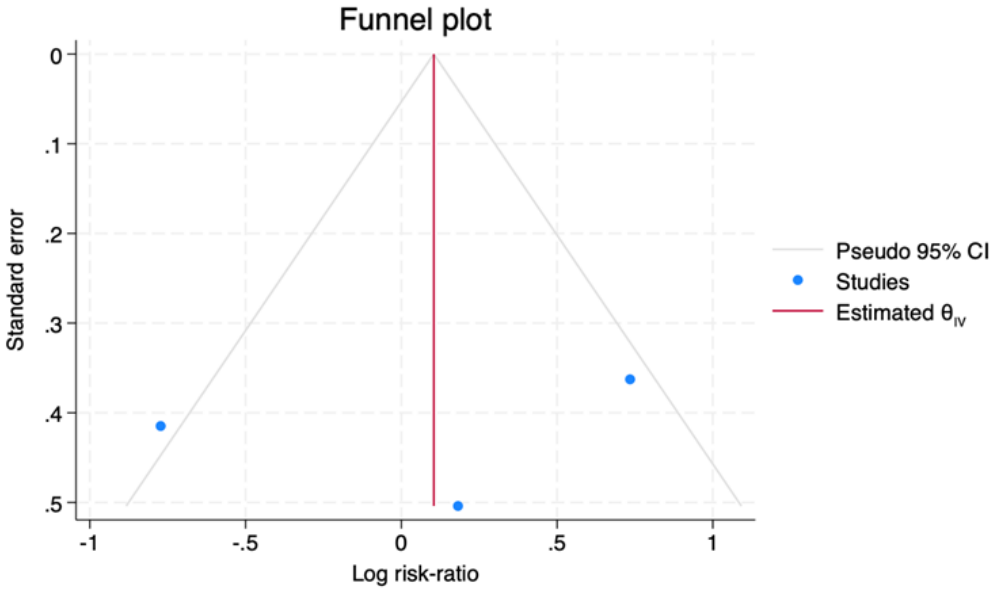


Figure 5. *Forestplot serious adverse events 50 mg/day Safinamide compared to placebo*

Appendix 4

Funnel plot serious adverse events 50 mg/day Safinamide compared to placebo



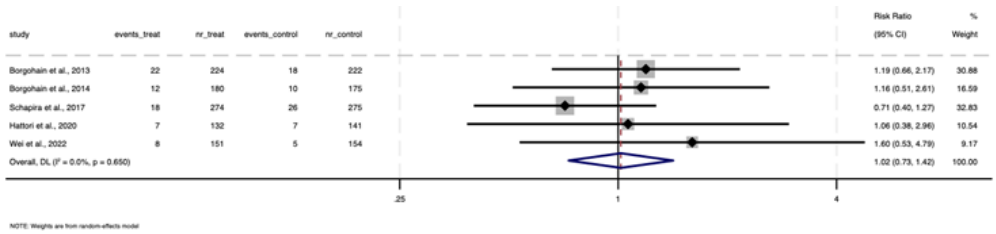
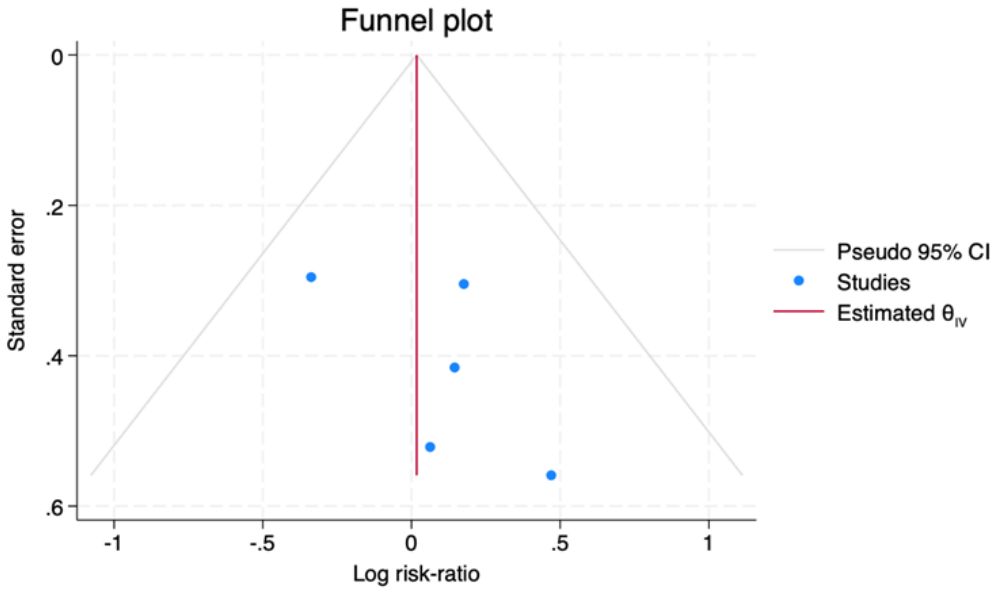


Figure 6. Forestplot serious adverse events 100 mg/day Safinamide compared to placebo

Appendix 5

Funnel plot serious adverse events 100 mg/day Safinamide compared to placebo



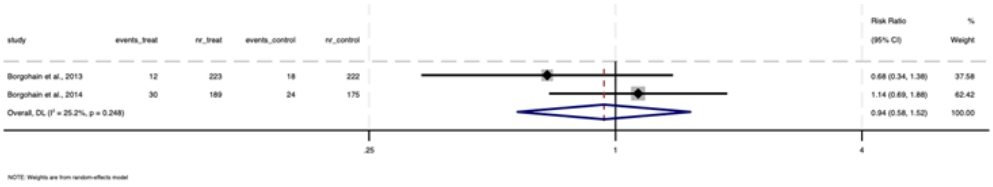
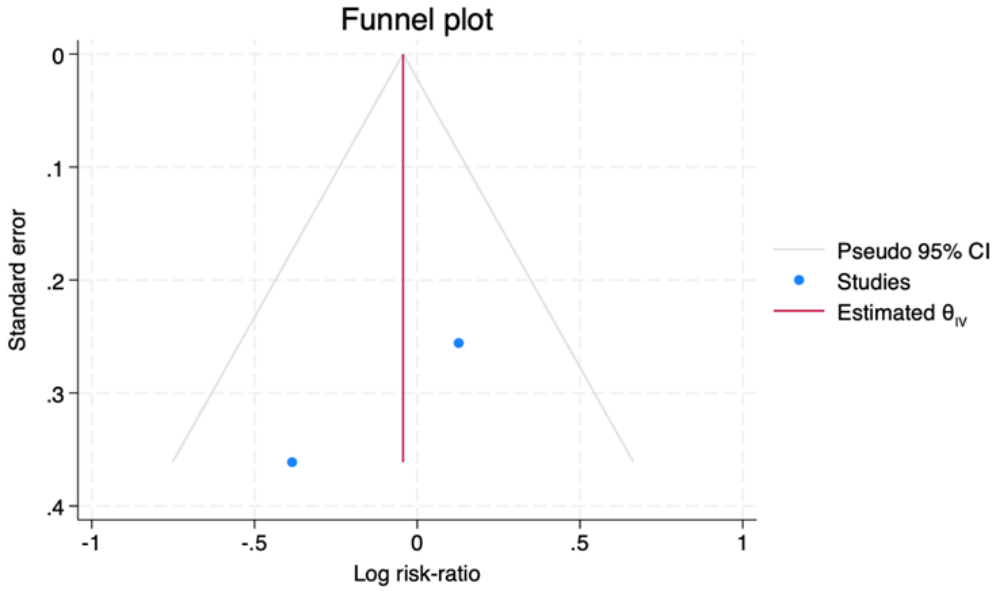


Figure 7. *Forestplot worsening of PD 50 mg/day Safinamide compared to placebo*

Appendix 6

Funnel plot worsening of PD 50 mg/day Safinamide compared to placebo



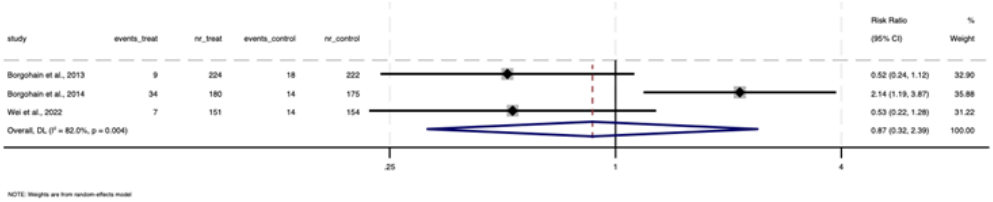
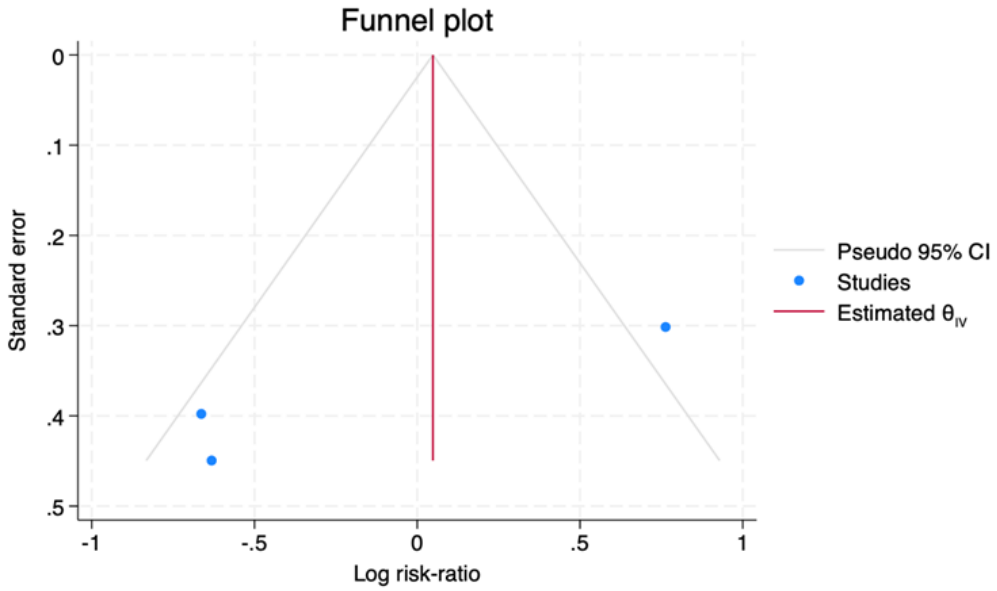


Figure 8. *Forestplot worsening of PD 100 mg/day Safinamide compared to placebo*

Appendix 7

Funnel plot worsening of PD 100 mg/day Safinamide compared to placebo



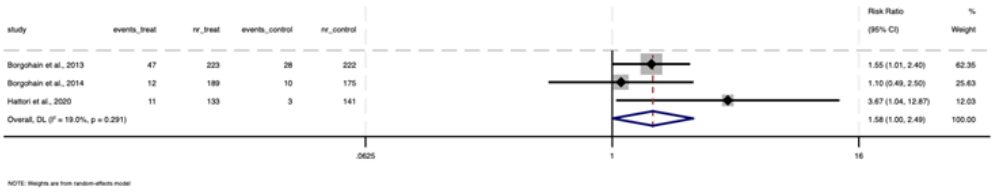
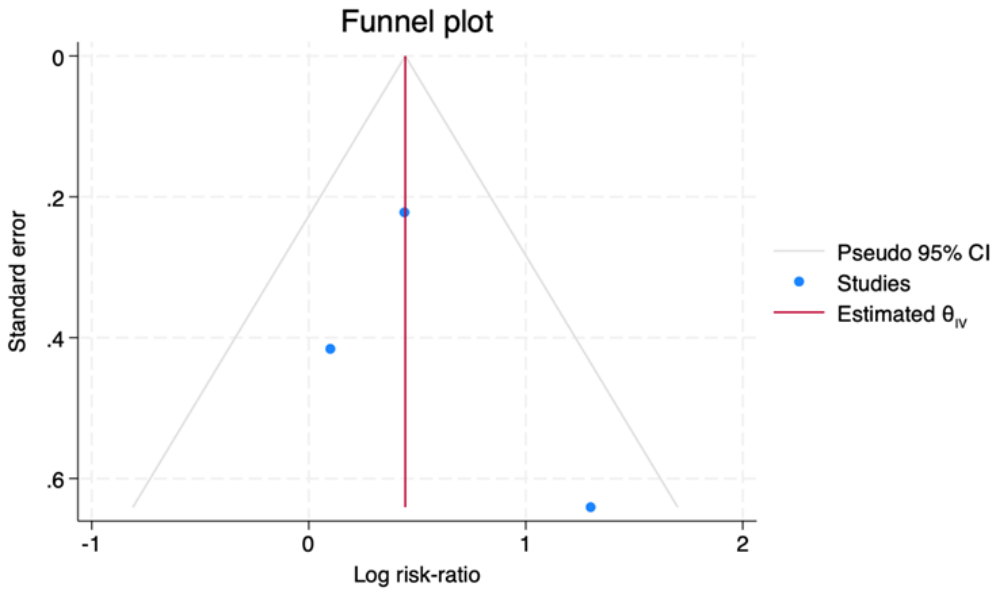


Figure 9. *Forestplot dyskinesia 50 mg/day Safinamide compared to placebo*

Appendix 8

Funnel plot dyskinesia 50 mg/day Safinamide compared to placebo



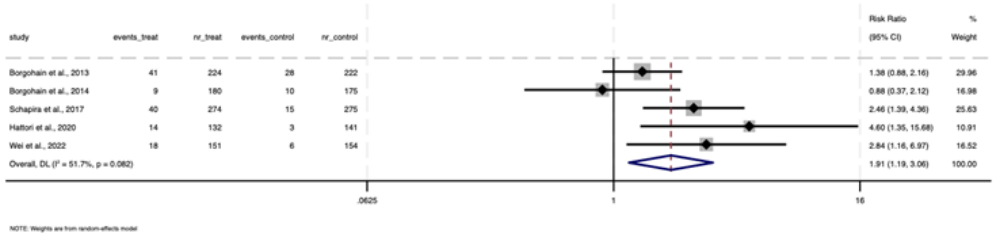


Figure 10. Forestplot dyskinesia 100 mg/day Safinamide compared to placebo

Appendix 9

Funnel plot dyskinesia 100 mg/day Safinamide compared to placebo

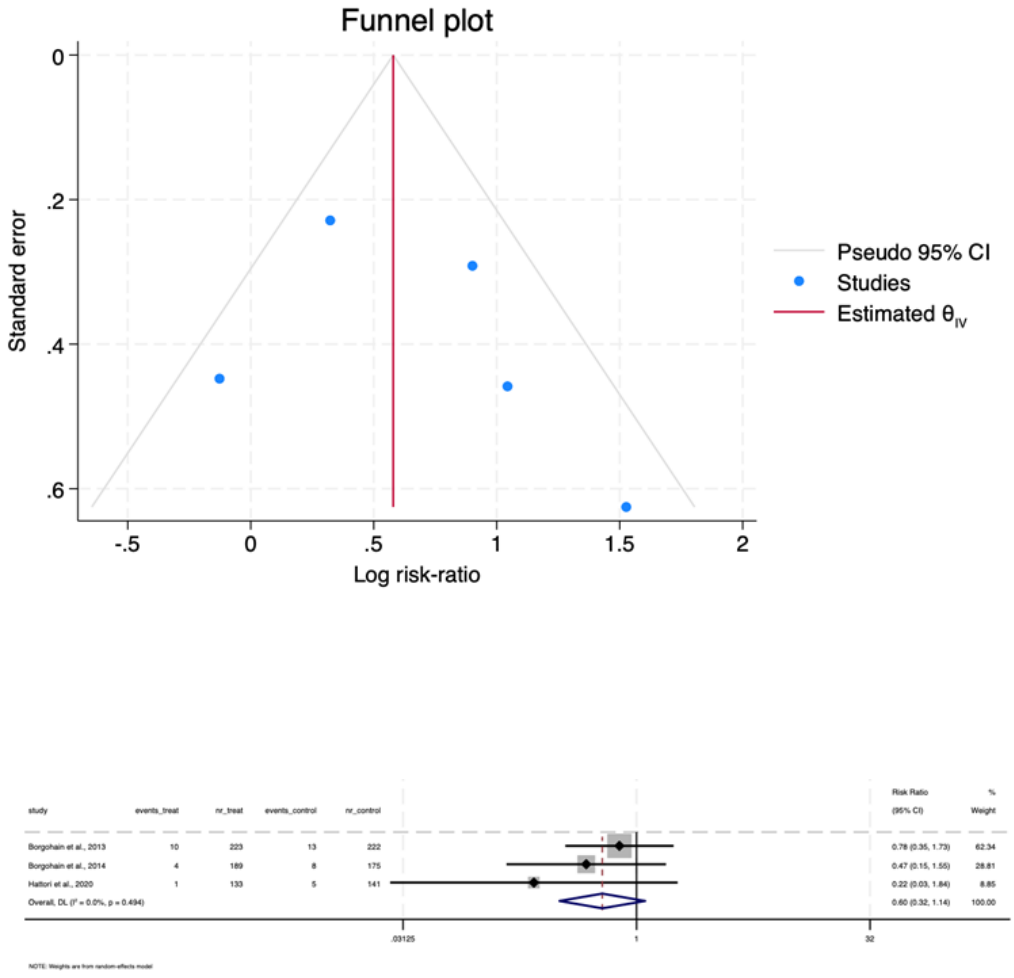
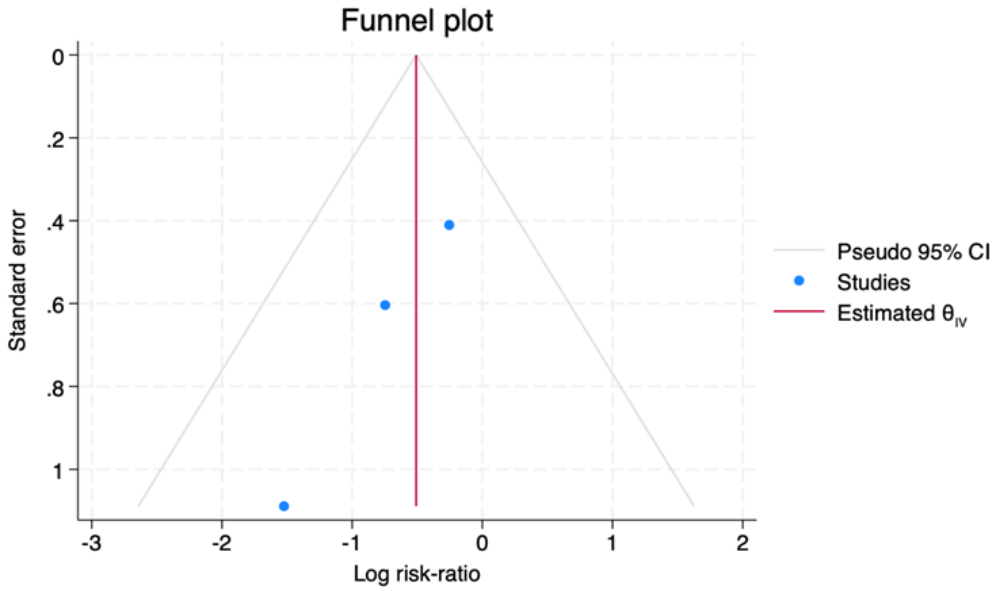


Figure 11. Forestplot back pain 50 mg/day Safinamide compared to placebo

Appendix 10

Funnel plot back pain 50 mg/day Safinamide compared to placebo



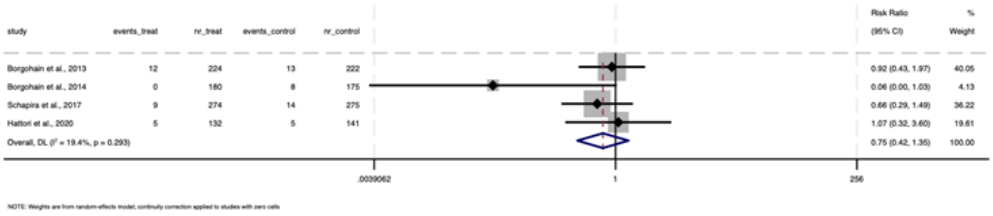
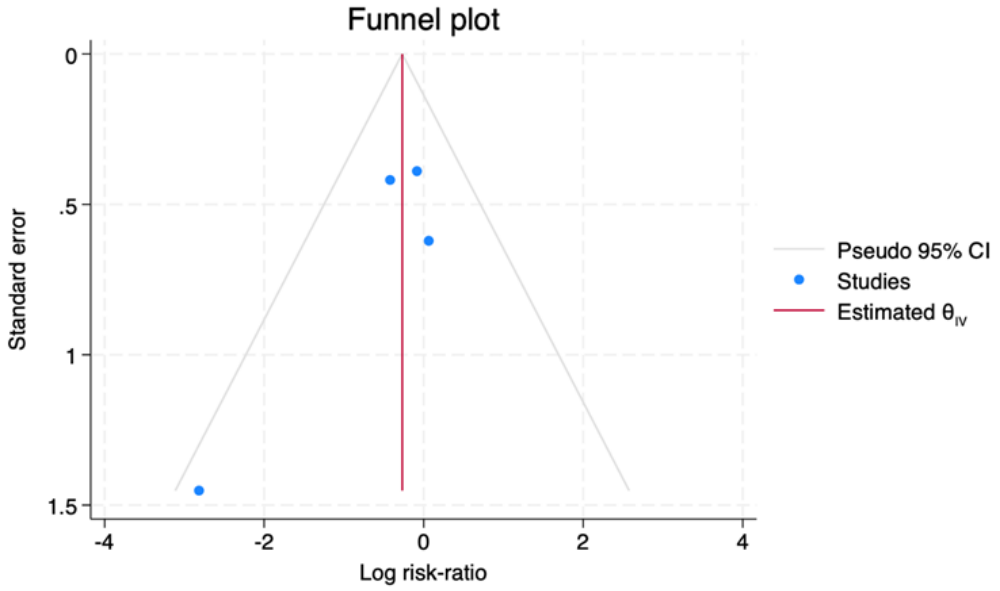


Figure 12. Forestplot back pain 100 mg/day Safinamide compared to placebo

Appendix 11

Funnel plot back pain 100 mg/day Safinamide compared to placebo



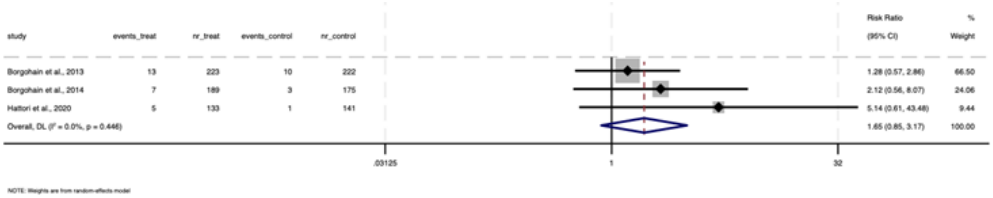
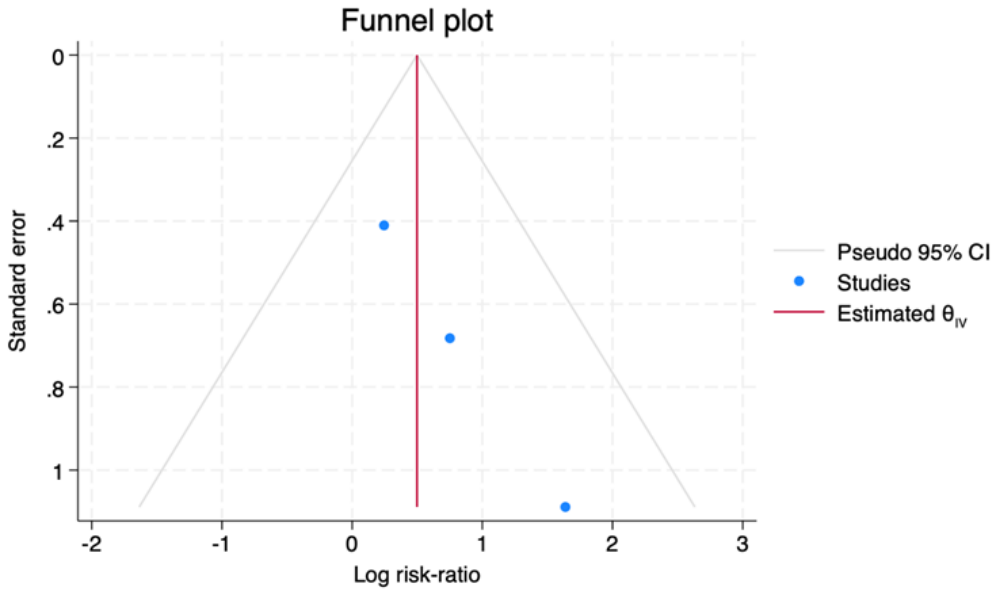


Figure 13. *Forestplot headache 50 mg/day Safinamide compared to placebo*

Appendix 12

Funnel plot headache 50 mg/day Safinamide compared to placebo



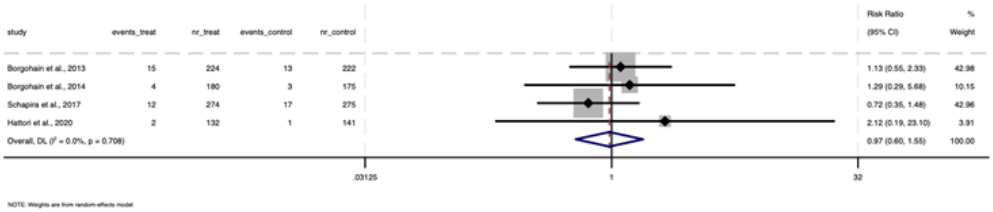
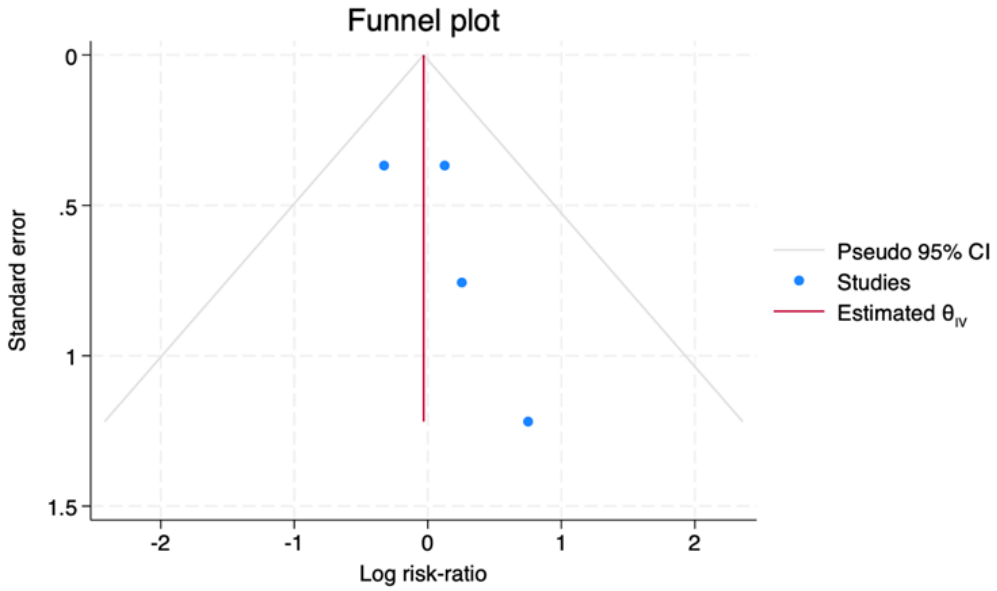


Figure 14. *Forestplot headache 100 mg/day Safinamide compared to placebo*

Appendix 13

Funnel plot headache 100 mg/day Safinamide compared to placebo



Appendix 14

GRADE Approach for Adverse Event Outcomes

Question: Safinamide as an add-on to Levodopa treatment compared to placebo for individuals with PD

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Safinamide	placebo	Relative (95% CI)	Absolute (95% CI)		
Adverse Events: 50 mg/day Safinamide (assessed with: RR)												
3	randomised trials	serious	not serious	serious	not serious	none	372/545 (68.3%)	384/538 (71.4%)	**RR 0.97** (0.87 to 1.08)	**21 fewer per 1,000** (from 93 fewer to 57 more)	⊕⊕◯◯ Low	
Adverse Events: 100 mg/day Safinamide (assessed with: RR)												
5	randomised trials	serious	not serious	serious	not serious	publication bias strongly suspected	660/961 (68.7%)	662/967 (68.5%)	**RR 1.00** (0.92 to 1.09)	**0 fewer per 1,000** (from 55 fewer to 62 more)	⊕◯◯◯ Very low	
Serious Adverse Events: 50 mg/day Safinamide (assessed with: RR)												
3	randomised trials	serious	serious	serious	not serious	none	40/545 (7.3%)	35/538 (6.5%)	**RR 1.06** (0.42 to 2.67)	**4 more per 1,000** (from 38 fewer to 109 more)	⊕◯◯◯ Very low	
Serious Adverse Events: 100 mg/day Safinamide (assessed with: RR)												
5	randomised trials	serious	not serious	serious	not serious	publication bias strongly suspected	67/961 (7.0%)	66/967 (6.8%)	**RR 1.02** (0.73 to 1.42)	**1 more per 1,000** (from 18 fewer to 29 more)	⊕◯◯◯ Very low	
Worsening of PD: 50 mg/day Safinamide (assessed with: RR)												
2	randomised trials	not serious	not serious	serious	not serious	none	42/412 (10.2%)	42/397 (10.6%)	**RR 0.94** (0.58 to 1.52)	**6 fewer per 1,000** (from 44 fewer to 55 more)	⊕⊕⊕◯ Moderate	
Worsening of PD: 100 mg/day Safinamide (assessed with: RR)												
3	randomised trials	serious	serious	serious	not serious	none	50/555 (9.0%)	46/551 (8.3%)	**RR 0.87** (0.32 to 2.39)	**11 fewer per 1,000** (from 57 fewer to 116 more)	⊕◯◯◯ Very low	
Dyskinesia 50 mg/day Safinamide (assessed with: RR)												
3	randomised trials	serious	not serious	serious	not serious	none	70/545 (12.8%)	41/538 (7.6%)	**RR 1.58** (1.00 to 2.49)	**44 more per 1,000** (from 0 fewer to 114 more)	⊕⊕◯◯ Low	
Dyskinesia 100 mg/day Safinamide (assessed with: RR)												
5	randomised trials	serious	serious	serious	not serious	none	122/961 (12.7%)	62/967 (6.4%)	**RR 1.91** (1.19 to 3.06)	**58 more per 1,000** (from 12 more to 132 more)	⊕◯◯◯ Very low	
Back Pain 50 mg/day Safinamide (assessed with: RR)												
3	randomised trials	serious	not serious	serious	not serious	none	15/545 (2.8%)	26/538 (4.8%)	**RR 0.60** (0.32 to 1.14)	**19 fewer per 1,000** (from 33 fewer to 7 more)	⊕⊕◯◯ Low	
Back Pain 100 mg/day Safinamide (assessed with: RR)												
4	randomised trials	serious	not serious	serious	not serious	none	26/810 (3.2%)	40/813 (4.9%)	**RR 0.75** (0.42 to 1.35)	**12 fewer per 1,000** (from 29 fewer to 17 more)	⊕⊕◯◯ Low	

Headache 50 mg/day Safinamide (assessed with: RR)

3	randomised trials	serious	not serious	serious	not serious	none	25/545 (4.6%)	14/538 (2.6%)	**RR 1.65** (0.85 to 3.17)	**17 more per 1,000** (from 4 fewer to 56 more)	⨁⨁◯◯ Low	

Headache 100 mg/day Safinamide (assessed with: RR)

4	randomised trials	serious	not serious	serious	not serious	publication bias strongly suspected	33/810 (4.1%)	34/813 (4.2%)	**RR 0.97** (0.60 to 1.56)	**1 fewer per 1,000** (from 17 fewer to 23 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio