STM JOURNALS

Research & Reviews: A Journal of
Pharmacology

https://journals.stmjournals.com/rrjop

ISSN: 2230-9861 (Online)
ISSN: 2349-1299 (Print)
Volume 14, Issue 3, 2024
September–December
DOI (Journal):
10.37591/RRJoP

Review RRJoP

Comparative Efficacy and Safety of Safinamide and Rasagiline in the Treatment of Parkinson's Disease: A Meta-Analysis and Systematic Review

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Abstract

Background: *Recent studies have suggested Rasagiline and Safinamide monotherapy as potential management options for Parkinson's disease. Parkinson's disease, a neurological disorder characterized by tremors and movement difficulties, necessitates treatments aimed at managing clinical symptoms. Levodopa remains the primary effective treatment for Parkinson's disease symptoms; however, its long-term use often leads to motor complications in many patients. Additional therapeutic drugs, such as dopamine agonists and monoamine oxidase B inhibitors, including Safinamide and Rasagiline, have proven beneficial in enhancing levodopa therapy to better control motor symptoms. Studies have indicated that Safinamide significantly reduces motor fluctuations without exacerbating troublesome dyskinesia due to its dual mechanism. These offer distinct advantages for Parkinson's disease patients with fluctuating symptoms compared to placebo or other medications. Transitioning from Rasagiline to Safinamide has been shown to improve the "ON-OFF" effect, where Parkinsonism symptoms worsen predictably as the effect of a levodopa dose fades. Safinamide might reduce the overall daily need for levodopa, enhance periods of improved symptoms ("ON" time), and potentially periods of worsened symptoms ('OFF' time), and potentially prove more effective than the other MAO-B inhibitors. This meta-analysis and systematic review aim to investigate the comparative efficacy and safety of Safinamide and Rasagiline among patients with motor complications as a viable and beneficial strategy to optimize antiparkinsonian medication.*

Objective: *The objective of this study is to systematically evaluate and compare the clinical efficacy and safety profiles of Safinamide and Rasagiline as adjunct therapies for Parkinson's disease among patients experiencing motor complications. Specifically, the study aims to investigate the effectiveness of Safinamide and Rasagiline in reducing motor fluctuations, improving overall motor symptoms, enhancing 'ON' time, reducing 'OFF' time, and potentially minimizing the need for levodopa dosage adjustments. Additionally, the study seeks to assess the safety profiles of both medications, including the incidence of adverse events and their impact on potential tolerability and quality of life. The evaluation will be conducted using standardized measures, such as the Unified Parkinson's Disease Rating Scale Part III and the clinical global impression of severity (CGIS) score levels, providing objective assessments of motor symptoms severity and overall disease severity, respectively. Ultimately, the research aims to provide valuable insights into the optimal*

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Received Date: September 26, 2024
Accepted Date: November 13, 2024
Published Date: December 31, 2024

Citation: Joy Das, Utpal Bhui, Soumyadip Nayak, Rahul Bishayee, Udita Dutta, Poulomi Mishra,Radheshyam Pal, Pratibha Bhowmick, Mithun Bhowmick. Comparative Efficacy and Safety of Safinamide and Rasagiline in the Treatment of Parkinson's Disease: A Meta-Analysis and Systematic Review. Research & Reviews: A Journal of Pharmacology. 2024; 14(3): 74–91p.

pharmacotherapeutics strategies for managing motor complications in Parkinson's disease, thereby contributing to the optimization of antiparkinsonian medication regimen. ***Methodology:*** *To identify relevant studies, we conducted a comprehensive computerized literature search covering Pubmed, Google Scholar, Embase, ScienceDirect, Scopus, and Embase up to 2023. We concentrated our efforts on randomized controlled trials that directly compared the efficacy and safety of Safinamide and Rasagiline against placebo groups. Our primary outcomes of interest include assessing alterations in UPDRS II, UPDRS III, and CGIS scores, alongside monitoring the incidence of adverse events. We employed mean difference (MD), standardized mean difference (SMD), and risk ratio (RR), and calculated 95% confidence intervals (CI) to quantify the effect sizes and their statistical significance. Additionally, to assess the degree of heterogeneity across studies, we utilized the* I^2 *test.* ***Results:*** *Our analysis revealed significant improvements in the Safinamide group compared to the placebo group across various measures. Firstly, the MD of changes in "UPDRS II" favored the Safinamide group, with a value of 0.71 (95% CI ranging from –1.04 to –0.37). Moreover, examining changes in "UPDRS III", we observed a similar trend. The overall MD of changes in UPDRS III favored the Safinamide group, with a value of –1.83 (95% CI ranging from –2.43 to –1.23). Similarly, when evaluating the changes in CGIS scores, the overall MD was –0.18 (95% CI = –0.24 to –0.12). On the other hand, a meta-analysis on Rasagiline concentrated on patients administered a daily dosage of 1 mg. Rasagiline exhibited significant improvements in "UPDRS II" and "UPDRS III" scores compared to the placebo group. However, notable heterogeneity among the studies was evident, with an* I^2 *value exceeding 70%. Importantly, neither Safinamide nor Rasagiline showed an increased relative risk (RR) for any serious adverse events, or adverse events leading to withdrawal when compared to placebo. Upon concluding this analysis, it's clear that Safinamide appears as a more favorable choice for patients with Parkinson's disease when compared to Rasagiline.* ***Conclusion:*** *In conclusion, MAO-B inhibitors have proven to be valuable therapeutic options for managing PD. Rasagiline, for instance, has demonstrated its efficacy in reducing "off" time and increasing "on" time without any troublesome dyskinesia in PD patients experiencing fluctuations in symptoms. Moreover, clinical trials have underscored Rasagiline tolerability and low incidence of cognitive and behavioral AEs, solidifying its position as a valuable treatment choice for PD. On the other hand, Safinamide emerges as a compelling long-term adjunctive therapy alongside levodopa in PD patients.*

Keywords: Parkinson's disease, movement disorder, safinamide, rasagiline, UPDRS, CGIS, MAO-B inhibitors, dopamine agonist, motor fluctuations

INTRODUCTION

Parkinson's disease (PD) stands as a complex and debilitating neurodegenerative disorder affecting millions of individuals worldwide (Capriotti and Terzakis, 2016) [1]. Characterized by a progressive loss of dopaminergic neurons in the substantia nigra pars compacta of the brain (Dehay and Fernagut, 2016) [2]. At the core of Parkinson's pathology lies the aberrant aggregation of a protein called alpha-synuclein (α-syn) (Mehra et al., 2019; Srinivasan et al., 2021) [3, 4]. Normally present in the brain, α-syn plays vital roles in synaptic function and neurotransmitter release (Volpicelli-Daley et al., 2011) [5]. However, in PD, α-syn undergoes pathological changes, leading to the formation of toxic protein aggregates known as Lewy bodies and Lewy neuritis (Lücking and Brice, 2000; Hansen and Li, 2012) [6, 7]. The α-syn aggregates are considered hallmarks of PD and are implicated in the degeneration of dopaminergic neurons, particularly those responsible for producing dopamine, a chemical crucial for smooth and coordinated muscle movements (Wan and Chung, 2012; Diering and Nishijima, Daniel; K. Simel, David L; Wisner, David H; Holmes, 2016) [8, 9]. As these cells degenerate, individuals with PD often experience a range of symptoms that significantly impact their daily lives (Bhatia and Gupta, 2003) [10]. The most well-known symptoms of PD are movement-related, such as tremors, stiffness, slowness of movement (bradykinesia), and difficulty with balance and coordination (Politis et al., 2010; Moustafa et al., 2016) [11, 12]. These symptoms can start subtly and gradually worsen

over time (Xia and Mao, 2012) [13]. However, PD isn't just about movement; it can also cause a variety of non-motor symptoms like cognitive changes, mood disturbances, sleep problems, and autonomic dysfunction (issues with blood pressure regulation, digestion, and bladder control) (Hou and Lai, 2007; Poewe, 2008; Reichmann et al., 2009) [14–16].

PD represents the second most common neurodegenerative disorder globally, trailing only Alzheimer's disease in prevalence (Carmichael and Lockhart, 2012; Elbaz et al., 2015) [17–18]. According to recent estimates, PD affects approximately 1–2% of individuals aged 65 and older, with prevalence rates rising sharply with advancing age (Ng, 2019) [19]. However, PD can also manifest in younger individuals, although less frequently, with an estimated 4–5% of cases occurring before the age of 50, categorized as early-onset PD (Schrag et al., 2003; Camerucci et al., 2021) [20–21]. The prevalence of PD exhibits considerable geographical variations, with higher rates observed in developed regions, such as North America and Europe compared to developing regions (Marras et al., 2018; Lim et al., 2019) [22–23]. The growing prevalence of PD underscores the urgent need for effective management strategies to alleviate symptom burden, delay disease progression, and improve patients' overall quality of life (QoL) (Fereshtehnejad, 2016; Tarolli et al., 2020; Hwang and Norris, 2021) [24–26].

For decades, the primary pharmacological strategy for managing PD symptoms has revolved around enhancing dopaminergic neurotransmission, primarily through the administration of Levodopa (L-dopa), a precursor of dopamine (Zhang and Chew-Seng Tan, 2016; Pacetti et al., 2020; Masood and Jimenez-Shahed, 2023) [27–29]. However, while L-dopa remains the gold standard therapy for PD, its long-term use is frequently accompanied by the development of motor complications, which can severely impact a patient's functional capacity and overall well-being (Bandopadhyay et al., 2022; Rus et al., 2022) [30–31]. In response to the limitations of L-dopa therapy, adjunctive medications, such as dopamine agonists (DA) and monoamine oxidase B (MAO-B) inhibitors have emerged as valuable therapeutic options for optimizing PD management (Oertel and Schulz, 2016; Alborghetti and Nicoletti, 2018; Tan et al., 2022) [32–34]. Among these adjunctive therapies, Safinamide and Rasagiline have gained particular attention for their potential to mitigate motor fluctuations and improve overall motor symptom control in PD patients (deSouza and Schapira, 2017; Lo Monaco et al., 2020) [35–36]. MAO-B inhibitors, such as Rasagiline and Safinamide, work by blocking the activity of the enzyme monoamine oxidase B (MAO-B), these medications help to increase dopamine levels, thereby improving motor symptoms and reducing fluctuations in movement experienced by individuals with PD (Robakis and Fahn, 2015; Dezsi and Vecsei, 2017) [37–38]. MAO-B inhibitors are often used as adjunctive therapy to L-dopa as above-mentioned or as monotherapy in the early stages of PD. Safinamide, a novel MAO-B inhibitor with additional mechanism of action, and Rasagiline, a selective MAO-B inhibitor, have both shown promise in clinical trials as adjunctive therapies L-dopa (Müller, 2020) [39]. Despite their clinical efficacy, there remains a lack of comprehensive comparative data regarding the relative efficacy and safety of Safinamide and Rasagiline in the management of PD motor complications (Mínguez-Mínguez et al., 2013; Perez-Lloret and Rascol, 2016) [40, 41]. While individual studies have provided valuable insights into the benefits of each medication, a systematic synthesis of the existing evidence is warranted to inform evidence-based treatment decisions and optimize therapeutic outcomes for PD patients (Zhuo et al., 2017a, 2017b) [42–43].

Considering this need, the present meta-analysis and systematic review aim to comprehensively evaluate the efficacy and safety profiles of Safinamide and Rasagiline as adjunct therapies for PD, both UPDRS and CGIS scores serve as important outcome measures. Statistical analysis of changes in UPDRS part III scores before and after treatment assessed improvements or worsening of motor symptoms, while changes in CGIS scores provide insights into overall changes in disease severity and treatment response. By analyzing these outcomes, we aim to provide valuable insights into the optimal treatment approach for PD patients experiencing motor complications, ultimately improving QoL.

METHODOLOGY

Search Strategy

This meta-analysis and systematic review aimed to compare the efficacy and safety of Safinamide and Rasagiline in the treatment of PD. The preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines were meticulously adhered to throughout the preparation of this manuscript (Prill et al., 2021) [44]. As this systematic review did not involve the collection of human or animal data, ethical approval was not deemed necessary. A comprehensive literature search was conducted across relevant databases, including PubMed, Google Scholar, Scopus, and Embase, using appropriate keywords and medical subject headings (MeSH) terms. The search was limited to studies published in English up to 2023. This approach facilitated a thorough examination of available studies relevant to the research question. The search strategy employed specific keywords, such as "Safinamide", "Rasagiline", "Parkinson's disease", "Parkinsonism", "UPDRS score", "CGIS score", "treatment outcome", "drug therapy", and "meta-analysis", combined with appropriate boolean operators ("OR" and "AND"). Reference list of included studies and relevant review articles were hand-searched for additional studies. Grey literature sources, such as conference proceedings and clinical trial registries were also searched using relevant terms. Duplicated records were identified and removed using reference management software. This comprehensive search strategy aimed to identify all relevant studies comparing Safinamide and Rasagiline in the treatment of PD to ensure the robustness and validity of the meta-analysis and systematic review.

Study Selection and Eligibility Criteria

The inclusion criteria for studies were developed using a PICO (problem/population, intervention, comparison, and outcome) framework. The exclusion criteria were aligned with the inclusion criteria to ensure consistency and strictness in the selection process. Inclusion criteria encompassed randomized controlled trials (RCT) comparing Safinamide and Rasagiline for PD treatments, and studies reporting efficacy outcomes, such as changes in UPDRS scores, CGIS scores, and adverse events (AEs) data. Studies were included irrespective of publication status, language, or blinding. Exclusion criteria comprised non-RCTs, animal studies, conference abstracts, and studies lacking primary outcome measures relevant to the meta-analysis, and studies with inadequate data were also excluded. Two independent reviewers screened the titles and abstracts of identified studies for eligibility. Full texts of potentially relevant articles were then assessed according to the inclusion and exclusion criteria. Any discrepancies were resolved through discussion or consultation with a third reviewer.

Data Extraction

Data extraction was performed independently by a single reviewer using a standardized form. Retrieval of relevant information like General information, Study design, UPDRS scores, CGIS scores, detailing interventions including dosage, frequency, duration of administration, and any discontinuation, along with demographic data, such as age, gender, distribution, and disease duration of participants. Additionally, the duration of each study from baseline assessment to final follow-up was noted, alongside comprehensive cataloging of adverse events associated with Safinamide and Rasagiline treatment, safety, and efficacy linked with Safinamide and Rasagiline treatment. Subsequently, a second reviewer performed a thorough double-check of the extracted data to ensure accuracy and completeness. Any conflicts or discrepancies that arose during this process were resolved through constructive discussion between two reviewers or by consulting a third reviewer when necessary.

Quality Assessment

Quality assessment of included studies in this meta-analysis was conducted using the Cochrane risk

of bias assessment tool, which evaluates various domains including i) selection bias; ii) performance bias; iii) detection bias; iv) attrition bias; v) reporting bias, and vi) other potential sources of bias that could impact study outcomes (Farrah et al., 2019) [45]. Each domain was independently rated by one reviewer and the main author as low, high, or unclear risk of bias. To summarize the risk of bias across included randomized controlled trials, Review Manager Software (RevMan 5.4) was utilized.

Data Synthesis & Analysis

Quantitative data synthesis and meta-analysis were conducted using the appropriate statistical method R software environment (Version 4.2.2). Effect sizes were calculated, and forest plots were generated to visualize the pooled estimates of efficacy and safety outcomes for Safinamide and Rasagiline. Regarding efficacy measures, the study focused on continuous data, with each efficacy measure presented as the mean difference (MD) between two treatment groups from baseline to endpoint, accompanied by its Standard Error (SE). The DerSimonian-Laird random-effect model was employed to pool both MD and SE values for Safinamide. For studies reporting data at multiple time points, the last endpoint was considered for analysis. On the other hand, for Rasagiline, standard mean difference (SMD) was calculated and a random effect, the Mantel-Haenszel Model (95% CI) was utilized to determine the effect sizes between studies. Statistical heterogeneity was assessed using I^2 statistics; significant I^2 values exceeding 75% indicated considerable heterogeneity, values below 40% were considered unimportant, while intermediate values denoted moderate heterogeneity. To assess adverse events, the proportion of risk ratio or relative risk (RR) was calculated by pooling events reported in the studies using the Forrest plot analysis. Publication bias was also evaluated using funnel plots and statistical tests, such as Egger's test, to assess the potential impact of unpublished studies on the overall findings.

Software

All analysis and calculations for this meta-analysis were conducted using Review Manager Software Version 5.4.1 (RevMan 5.4.1).

RESULTS & DISCUSSION

Results

Screening Results

In this meta-analysis and systematic review, our initial search covered Google Scholar, PubMed, mbase, ScienceDirect, and Scopus databases identifying a collective sum of 1270 potentially relevant papers. Furthermore, no additional records were identified through our exploration of supplementary sources. Moreover, we adhered to predefined inclusion and exclusion criteria to select studies that met the objective of our analysis. Following the elimination of duplicates, 685 unique articles remained for thorough examination. Subsequently, during the screening of records/studies, 537 articles were excluded for failing to meet the predefined criteria. A comprehensive assessment of full-text content of 119 papers followed, leading to the exclusion of 104 records for various reasons. Ultimately, our study incorporated a total of 15 studies that aligned with the predefined inclusion criteria, forming the basis of our analysis. The visual representation of the study selection process is provided in Figure 1.

In-Depth Analysis of Included Safinamide Studies

Given that all the data within the study are continuous, we represent each measure of efficacy as the mean difference (MD) between the two groups, ranging from the baseline to the endpoint. Additionally, we provided the standard error (SE) for each measure to ensure accuracy and reliability. Moreover, we utilized the risk ratio (RR) to combine the adverse events reported in the studies, comparing the occurrences within each group against the total number in both groups.

The follow-up durations varied across the studies, ranging from 12 weeks as seen in (F. et al., 2004) [46] and (Stocchi et al., 2012) [47] to 24 weeks in studies conducted by (Schapira et al., 2013, 2017; Borgohain et al., 2014b, 2014a) [35, 48–50]. Regarding Safinamide dosage, participants received

daily doses ranging from 40 mg in (F. et al., 2004) to 200 mg in studies by (Stocchi et al., 2012) and (Schapira et al., 2013) [35, 47, 48]. It's noteworthy that all included studies featured a homogenous population that remained on dopaminergic treatment throughout the entire study duration. Comprehensive overview and Baseline Characteristics of Study populations are displayed in Table 1.

Safinamide demonstrated a favorable outcome over placebo in terms of changes in "UPDRS II" from baseline to endpoint, with an overall MD of –0.71 (95% CI [–1.04 to –0.37] and P < 0.00001, as depicted in Figure 2(a). The pooled studies exhibited homogeneity (P = 0.28). Likewise, after conducting a thorough analysis, it was found that Safinamide exhibits significant advantages over placebo in terms of changes in "UPDRS III" from baseline to endpoint, with an overall MD of –1.83 (95% CI [–2.43 to –1.23] and P < 0.00001, as illustrated in Figure 2(b). Additionally, the pooled studies demonstrated homogeneity (P = 0.80). Similarly, when assessing the alteration "CGIS" from baseline to endpoint, Safinamide also displayed superiority over placebo, with an overall MD of –0.18 (95% CI [–0.24 to –0.12] and P < 0.00001, as depicted in Figure 2(c). Notably, the pooled studies showed homogeneity (P = 0.70).

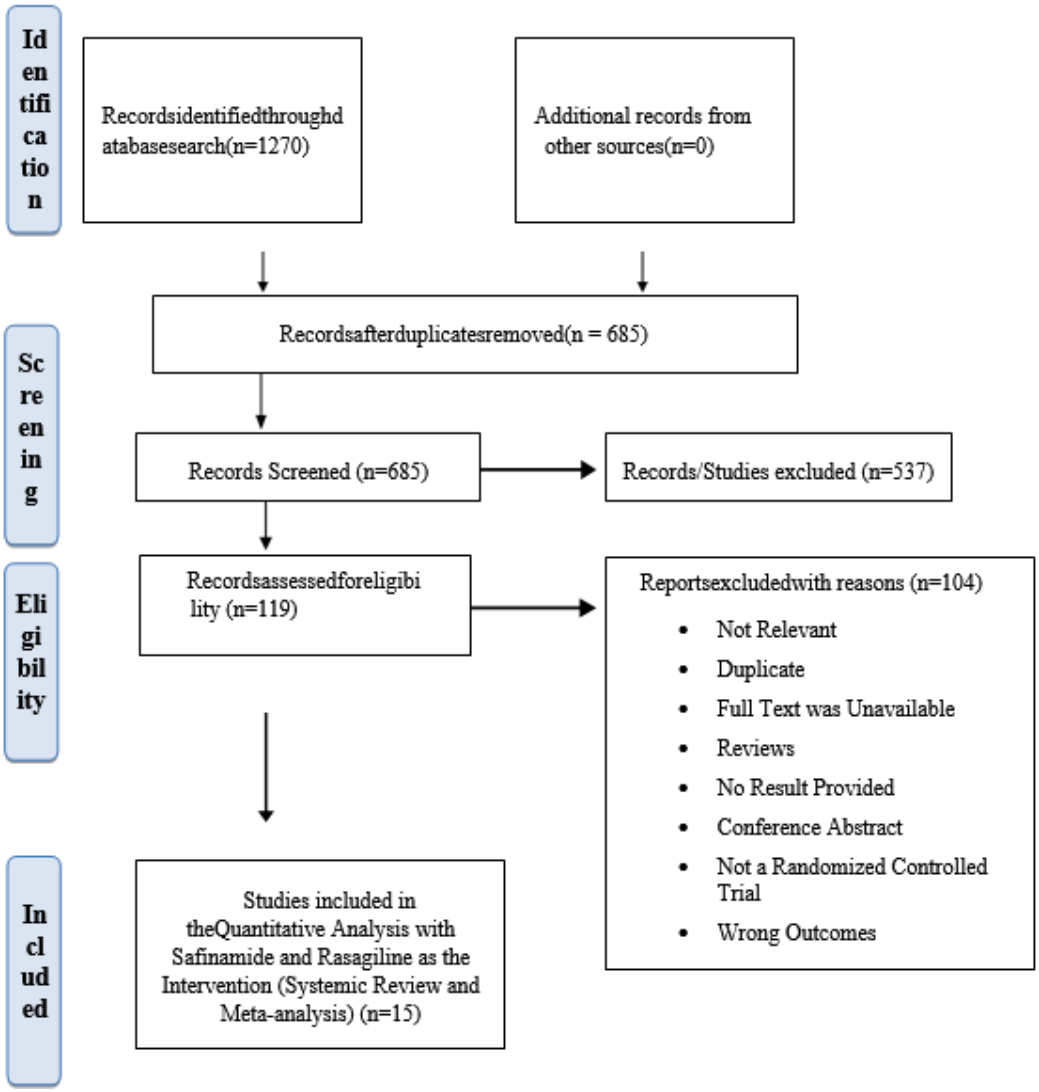


Figure 1. Flow diagram: Selection process and screening in the study according to PRISMA guidelines.

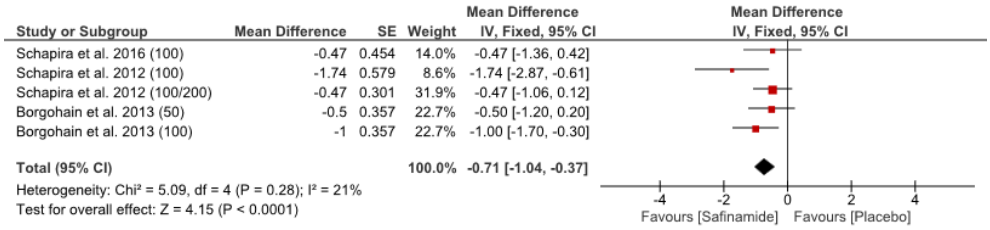
Adverse events were documented across the studies included in our analysis. Specifically, seven

studies reported instances of dyskinesia. Our pooled meta-analysis revealed a notable increase in dyskinesia among patients receiving a placebo compared to those treated with Safinamide (RR 1.50, 95% CI [1.25 to 1.80], as depicted in Figure 3(i). Notably, the pooled studies exhibited homogeneity (P = 0.10). Furthermore, seven studies documented cases of patients experiencing worsening of PD during the study period. However, our pooled meta-analysis did not show a significant preference for either treatment in this regard (RR 0.82, 95% CI [0.65 to 1.03], as illustrated in Figure 3(ii). It's worth mentioning that the pooled studies displayed homogeneity (0.54).

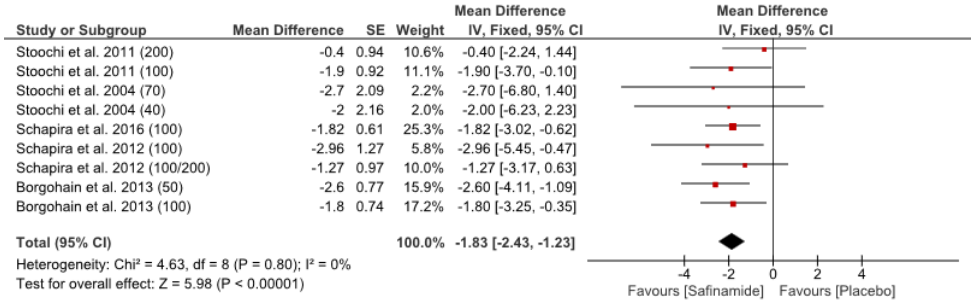
As depicted in Figure 4, funnel plots examining UPDRS II, UPDRS III, and CGIS indicate the absence of noteworthy publication bias among the included studies. This absence of significant publication bias ensures the reliability and validity of our findings, providing greater confidence in the strength of the meta-analysis results.

Table 1. Characteristics of Safinamide studies selected in the meta-analysis.

Study ID	Design	Final Endpoint	Group	N	Age	Male %	UPDRS III	CGI-S
(Stocchi et al., 2012) [47]	RCT	12 weeks	Safinamide 200 mg/day	89	58.5 (11.7)	61	19.3 (9.80)	3.1 (0.85)
			Safinamide 100 mg/day	90	56.5 (11.3)	66	22.0 (10.15)	3.1 (0.79)
			placebo	90	57.3 (10.8)	62	20.7 (9.63)	3.1 (0.76)
(Schapira et al., 2013) [48]	RCT	24 weeks	Safinamide 200 mg/day	69	56.5 (25.5)	62.3	20.1 (10.44)	NR
			Safinamide 100 mg/day	80	53 (23)	67.5	22.5 (9.28)	NR
			placebo	78	55.5 (19.5)	47	21.0 (9.73)	NR
(Borgohain et al., 2014a) [49]	RCT	24 weeks	Safinamide 100 mg/day	224	60.1 (9.19)	72.8	28.3 (13.30)	4.0 (0.72)
			Safinamide 50 mg/day	223	60.1 (9.65)	70.4	27.3 (12.66)	4.0 (0.70)
			placebo	222	59.4 (9.41)	72.1	28.7 (12.02)	4.0 (0.66)
(Schapira et al., 2017) [18]	RCT	24 weeks	Safinamide 100 mg/day	274	61.7 (9.0)	62.4	22.4 (11.8)	3 (1.1)
			placebo	163	62.1 (8.9)	59.3	23.4 (12.9)	3 (1.1)
(F. et al., 2004) [46]	RCT	12 weeks	Safinamide 90 mg /day	34	45.3 (18.9)	NR	16.9 (7.4)	NR
			Safinamide 40 mg/day	33	45 (19.1)	NR	17.6 (7.5)	NR
			placebo	34	45.3 (18.9)	NR	17.1 (8.6)	NR
(Borgohain et al., 2014b) [50]	RCT	24 weeks	Safinamide 50 mg/day	223	43 (19.3)	70.4	27.3 (12.66)	NR
			Safinamide 100 mg/day	224	45 (20.1)	72.8	28.3 (13.30)	NR
			placebo	222	42 (18.9)	72.1	28.7 (12.02)	NR



(a)



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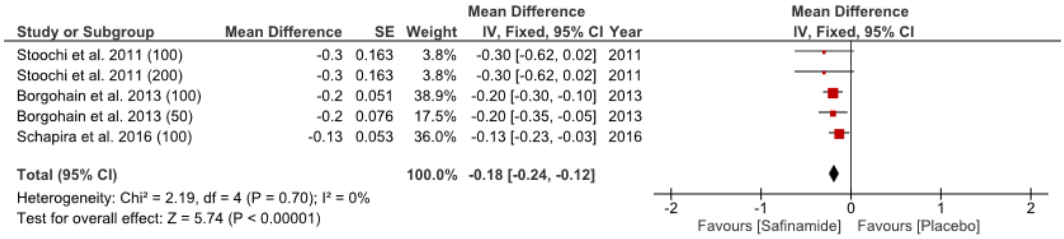
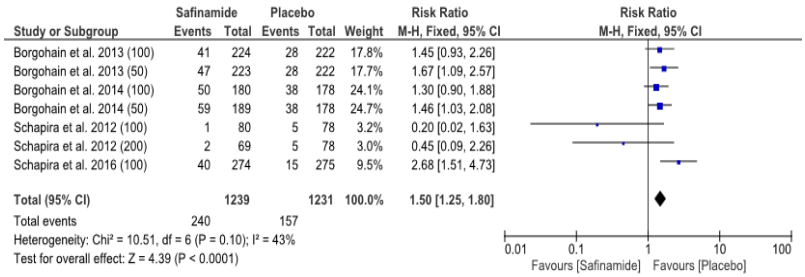
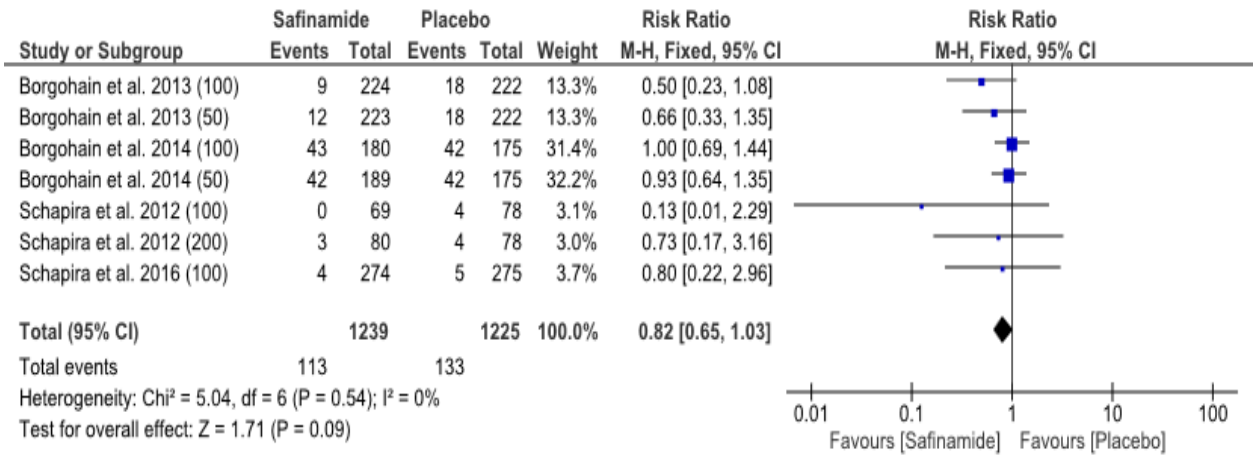


(c)

Figure 2. Graphical representation of Forest plot analysis (MD and 95% CI) for selected outcomes (a) UPDRS II (b) UPDRS III (c), and CGIS.



(i)



(ii)

Figure 3. Graphical representation illustrated Forest plot analysis of risk ratio (RR) for following AEs (i) Dyskinesia (ii) Worsening of PD.

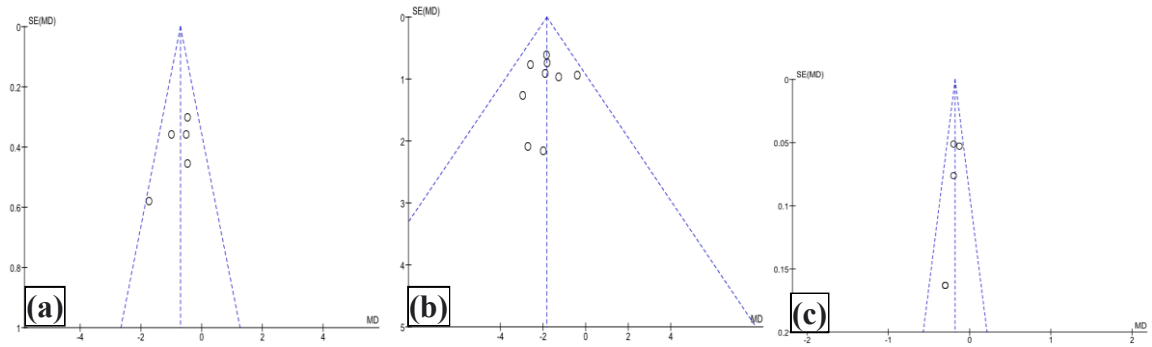


Figure 4. Visual representation depicting Funnel plot analysis of publication bias for – (a) UPDRS II (b) UPDRS III (c), and CGIS.

Descriptive Analysis of Rasagiline Studies

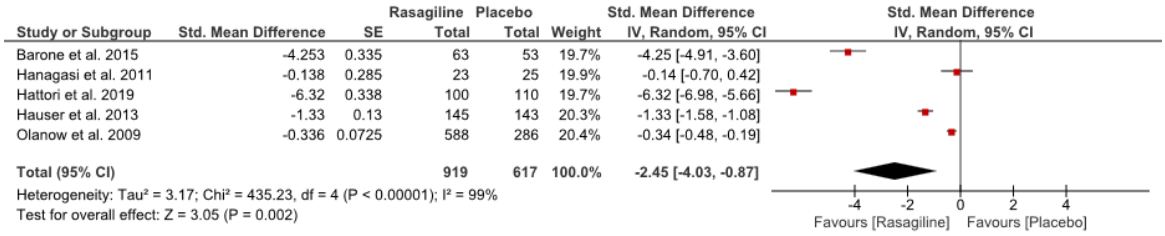
Results from seven out of nine contributed data regarding UPDRS II, and UPDRS III, as shown in Table 2. In the Rasagiline groups, the alteration in UPDRS II scores ranged between 0.78 to –2.17, whereas in the placebo groups, it varied from 2.32 to –1.64. Similarly, changes in UPDRS III scores in the Rasagiline groups ranged from 0.5 to –4.47, while in the placebo groups, it fluctuated between 2.38 to –2.20.

Moreover, five studies were examined in this meta-analysis to compare the effectiveness of Rasagiline (1 mg/day) with a placebo, as evaluated through UPDRS II and UPDRS III scores. Due to significant diversity in the study outcomes, a random-effect model was employed. Rasagiline demonstrated a notable enhancement in UPDRS II (SMD = –2.45, 95% CI = –4.03 to –0.87, P = 0.002) and UPDRS III compared to placebo (SMD = –2.58, 95% CI = –4.50 to –0.66, P = 0.008). However substantial heterogeneity was observed among the studies included in both analyses (UPDRS II: $Chi^2 = 435.23$, $P < 0.00001$, $I^2 = 99\%$) and (UPDRS III: $Chi^2 = 524.48$, $P < 0.00001$, $I^2 = 99\%$). In this analysis, for both UPDRS II and UPDRS III scores, publication bias was not observed (Egger's test p-value less than 0.05). The findings from the meta-analysis regarding UPDRS II and UPDRS III are depicted in Figure 5.

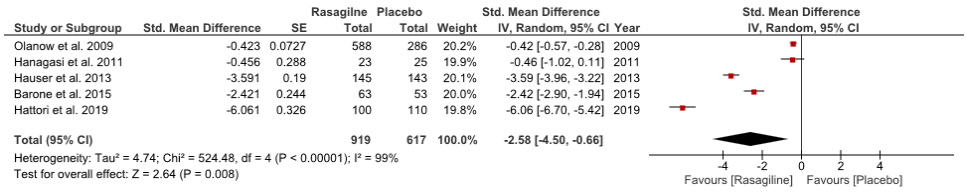
Table 2. Key characteristics of Rasagiline included studies (changes in UPDRS II and III scores).

Author, Year	Duration of Treatment	Interventions	Population (n)	UPDRS II	UPDRS III
(Hauser et al.,	18 Weeks	placebo	165	0.3 ± 0.3	–1.6 ± 0.5

2014) [51]		Rasagiline 1 mg	163	–0.1 ± 0.3 (P = 0.3)	–3.4 ± 0.5 (P = 0.007)
(Barone et al., 2015) [52]	12 Weeks	placebo Rasagiline 1 mg	65 58	0.06 ± 0.32 –1.37 ± 0.35 (P = 0.003)	0.42 ± 0.51 –0.88 ± 0.56 (P = 0.09)
(Hattori et al., 2019) [53]	26 Weeks	placebo Rasagiline 1mg	126 118	2.32 ± 0.34 0.13 ± 0.35 (P < 0.0001)	
(Olanow et al., 2009) [54] (Rascol et al., 2011) [55]	72 Weeks	placebo Rasagiline 1 mg Rasagiline 2 mg	595 288 293	1.64 (1.43–1.85) 0.78 (0.49–1.06) –0.86 ± 0.18 (P < 0.0001) 0.76 (0.47–1.04) –0.88 ± 0.18 (P < 0.0001)	2.38 (1.96–2.79) 0.50 (–0.07–1.07) –1.88 ± 0.35 (P < 0.0001) 0.20 (–0.37–0.76) –2.18 ± 0.35 (P < 0.0001)
(Hanagasi et al., 2011) [56]	12 Weeks	placebo Rasagiline 1 mg	25 23	–1.64 ± 3.59 –2.17 ± 3.95 (P = 0.539)	–2.20 ± 4.05 –4.35 ± 5.21 (P = 0.116)
(Palareti et al., 2016) [57]	8 Weeks	placebo Rasagiline 1mg	10 20	NR NR	NR –2.0 ± 6.2 (P = 0.205)
(Stern et al., 2004) [58]	10 Weeks	placebo Rasagiline 1 mg Rasagiline 2 mg Rasagiline 4 mg	13 15 14 14	NR NR NR NR	NR NR NR NR



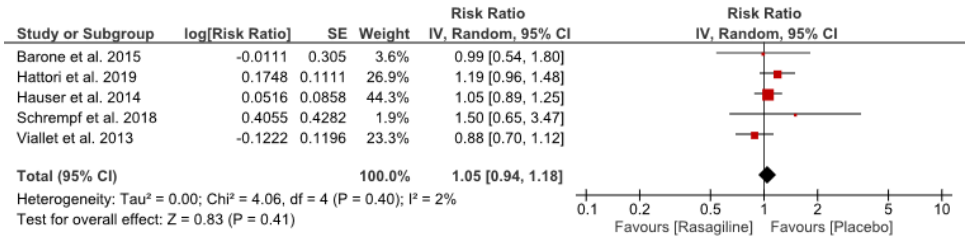
(A)



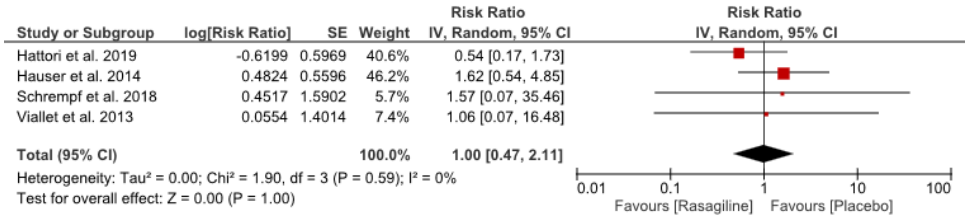
(B)

Figure 5. Visual representation depicting Forest plot analysis of SMD for (A) UPDRS II (B), and UPDRS III after Rasagiline administration.

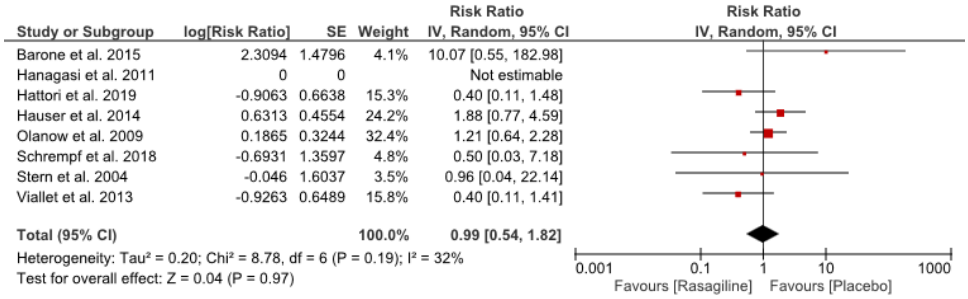
The meta-analysis examined the frequency of various AEs, serious AEs, and events leading to withdrawal (illustrated in Figure 6). Among the AEs associated with Rasagiline use reported across multiple studies, the most prevalent were headache (ranging from 3.4% to 26%), dizziness (ranging from 5.7% to 23%), nausea (ranging from 4.2% to 9.4%), back pain (ranging from 2.6% to 5.1%), and somnolence (ranging from 0.7% to 6.8%).



(a)



(b)



(c)

Figure 6. Graphical representation of Forest plot analysis depicting relative risk of experiencing any AEs (a) Serious AEs (b) AEs leading to withdrawal (c), and Rasagiline impact on AEs compared to placebo.

In our analysis, the likelihood of experiencing any AEs in patients treated with Rasagiline was like that in patients treated with either placebo (RR = 1.05; 95% CI = 0.94 to 1.18, P = 0.41). Because of the heterogeneity in this study, the reporting of total AEs after administering Rasagiline was minimal (Chi^2 = 4.06, P = 0.40, I^2 = 2%). Similarly, the chances of experiencing AEs in patients treated with Rasagiline were comparable to those in patients treated with placebo (RR = 1.00, 95% CI = 0.47 to 2.11, P = 1.00). And there was no heterogeneity among studies reporting serious AEs (Chi^2 = 1.90, P = 0.59, I^2 = 0%). Moreover, eight out of nine studies were analyzed in this meta-analysis focusing on AEs leading to withdrawal. The risk of experiencing AEs leading to withdrawal in patients treated with Rasagiline was found to be like that in patients treated with placebo (RR = 0.99, 95% CI = 0.54 to 1.82, P = 0.97). There was moderate heterogeneity among the studies reporting AEs resulting in withdrawal (Chi^2 = 8.78, P = 0.19, I^2 = 32%). Notably, no evidence of publication bias was observed in any of the analyses (Egger's test p-value less than 0.05).

Managing Therapeutic Transition: From Rasagiline to Safinamide

After analyzing the 15 studies included in our meta-analysis to assess the safety and efficacy of Safinamide and Rasagiline, we further examined additional studies to provide evidence regarding the transition from Rasagiline to Safinamide. Studies have indicated that transitioning from Rasagiline to Safinamide can effectively improve the wearing-off phenomenon, characterized by the predictable worsening of PD symptoms towards the end of a Levodopa (L-dopa) dose until the next dose is administered (Bianchini et al., 2021; Stocchi et al., 2021) [59–60]. In this context, initial findings indicate that transitioning from Rasagiline to high-dose Safinamide could offer advantages for PD

patients experiencing fluctuations in symptoms (Chang et al., 2017; Stocchi et al., 2021; Nomoto et al., 2022) [60–62]. Another observational study, involving 17 patients with PD, examined the transition to Safinamide. These patients had previously been treated with either L-dopa alongside Rasagiline or L-dopa alongside DA. Alternatively, they had experienced the return of symptoms despite prior management of fluctuations. In this study, the patients were transitioned to Safinamide at a dosage of 100 mg. Results showed that this transition brought about noticeable clinical improvements in 9 out of the 17 patients, which accounts for 52.9% of the participants. Specifically, it significantly decreased occurrences of wear-off without causing any AEs (Lee and Gilbert, 2016) [63]. In a prospective clinical practice study, the impact of Safinamide on motor fluctuations was investigated in a group of 47 PD patients. Among these, 10 patients had previously been receiving treatment with Rasagiline. Following a recommended 2-week washout period, these patients were transitioned to Safinamide. Among the patients who had been on Safinamide, mild to moderate worsening of Parkinsonism was noted in 2 out of 10 cases. However, over the subsequent three months of Safinamide treatment at 100 mg/day, there was a notable moderate improvement in wearing-off and Parkinsonism (as per CGI: 2). Conversely, in 3 out of 10 patients, discontinuation of Rasagiline was associated with a reduction in biphasic dyskinesia (a condition characterized by alternating periods of excessive and reduced involuntary movements) in 1 patient and generalized choreoathetosis (a neurological condition where the body experiences involuntary jerky movements along with writhing and twisting motions) in 2 patients, with these symptoms either stabilizing or showing further improvement upon initiation of Safinamide at 100 mg/day (Kulisevsky et al., 2022) [64]. To further validate these findings, a prospective observational study was conducted involving 90 patients diagnosed with PD who initiated treatment with Safinamide. Among them, 68.8% were prescribed a combination therapy including a DA, and 52.7% had previously been treated with Rasagiline. After a 6 months period, notable improvements were observed. Specifically, there was a statistically significant reduction in morning akinesia (loss or impairment of voluntary movements) among 33.3% of patients, while 34.4% experienced a decreased in wearing-off symptoms. Additionally, there was an improvement noted in UPDRS III scores. Based on these outcomes, the researchers conclude that Safinamide demonstrated safety and efficacy, significantly improving motor fluctuations, motor symptoms, and the subjective understanding of PD (Morales-Casado MI, López-Ariztegui N, García-Meléndez DD, 2022) [65]. Several other researchers retrospectively analyzed the first-time users of MAO-B Inhibitors (MAO-BIs) in combination with L-dopa to provide updated evidence on additional therapy for PD. Out of 4734 patients receiving MAO-BIs alongside L-dopa, 1059 were new users. In the group taking Rasagiline, 18% switched to another MAO-BIs, while for Selegiline and Safinamide users, the percentage was 11% and 4.3%, respectively. Over 70% of those discontinuing Rasagiline switched to Safinamide. Results indicated that switching from Selegiline to Rasagiline led to improvements in motor behaviors, motor complications, mood, and sleep among 30 PD patients (Ronconi et al., 2022) [66]. Moreover, in a multicenter retrospective cohort study, researchers used the CGIS to evaluate improvements in both motor and non-motor symptoms among patients treated with Safinamide. More than 75% of patients experienced enhancements in motor symptoms like bradykinesia, gait, resting tremor, and muscle rigidity, as well as improvements in non-motor symptoms, such as sleep, cognitive function, sensory disturbances, and attention. Notably, among those who had previously used Rasagiline, about 54% of the cohorts, significant clinical benefits were observed after switching to Safinamide (Martí-Andrés et al., 2019) [67]. Furthermore, before initiating Safinamide treatment, some neurologists suggest a period of discontinuation from MAO-BIs. Opinions vary on the duration of this washout period; while some prefer a shorter interval, others opt to start Safinamide immediately after stopping Rasagiline. A study evaluated the safety and tolerability of immediately transitioning, without the typical two-week washout period, from Rasagiline to Safinamide (at doses of 50 mg and 100 mg) in a group of 20 patients. Following the transition, there was no notable change in blood pressure, and no occurrences of serotonin syndrome or hypertension were reported, nor were any other AEs observed (Stocchi et al., 2021) [60]. The study findings confirmed that Safinamide was well-tolerated and safe for the patients involved [18]. In addition, compared to Rasagiline, Safinamide is considered safer because it more selectively inhibits

MAO-B. This makes it a preferable option, especially when dealing with conditions like serotonin syndrome as well as hypertension. Unlike Rasagiline, Safinamide is broken down by CYP1A2. Moreover, its levels in the bloodstream remain unaffected by commonly prescribed medications, such as insulin, amiodarone, fluoroquinolones, omeprazole or verapamil, which are broken down by the same enzyme (Csoti et al., 2019; Pagonabarraga et al., 2020) [68–69]. Furthermore, the Movement Disorder Society also categorizes Safinamide separately from Selegiline as well as Rasagiline due to its unique mechanism of action: functioning as both an MAO-BI and glutamate release inhibitor. Despite belonging to the same therapeutic class of MAO-BIs, Safinamide stands out for its ability to enhance dopamine levels in the stratum while reducing glutamate release in regions marked by hyperexcitabilityglutamatergic system (Liguori et al., 2018) [70]. Upon concluding this analysis, it becomes evident that Safinamide emerges as a more favourable option for patients with PD in comparison to Rasagiline. Safinamide shows promising result in effectively managing symptoms associated with PD, making it a valuable treatment option, particularly for those in the early stages of the disease as well as those experiencing mild symptoms.

DISCUSSION

In our discussion, we employed a comprehensive approach to analyse the data from the studies included in our meta-analysis. We utilized mean difference (MD) to present the efficacy measures, ensuring accuracy and reliability by providing the standard errors (SE) for each measure. Additionally, adverse events were assessed using the risk ratio (RR) to compare occurrences between treatment groups. The follow-up durations varied across studies, ranging from 12 to 24 weeks (F. et al., 2004; Stocchi et al., 2012; Schapira et al., 2013; Borgohain et al., 2014b, 2014) [46–48, 60] with corresponding Safinamide dosages ranging from to 40 mg to 200 mg daily (F. et al., 2004; Stocchi et al., 2012) [46–47]. Notably, the patient population remained homogenous, receiving consistent dopaminergic treatment throughout the study duration. Our findings indicate that Safinamide demonstrated favorable outcomes compared to placebo in terms of improvements in UPDRS II, UPDRS III, and CGIS scores from baseline to endpoint. Safinamide demonstrated significant advantages in terms of improvement from baseline to endpoint. The observed mean differences (MD) of –0.71, –1.83, and –0.18 for UPDRS II, UPDRS III, and CGIS, respectively, along with their corresponding confidence intervals, underscore the robustness of these findings. These improvements were statistically significant, with pooled studies showing homogeneity. Regarding adverse events, dyskinesia was notably increased in patients receiving a placebo compared to Safinamide, as evidenced by a risk ratio of 1.50 with a narrow CI. However, no significant preference was observed between treatments for worsening PD during the study period. For Safinamide, the absence of significant publication bias, as indicated by the funnel plots examining UPDRS II, UPDRS III, and CGIS scores, lends credibility to the reliability and validity of our findings.

Similarly, Rasagiline also exhibited significant improvements in UPDRS II and UPDRS III scores, indicative of its efficacy in alleviating both motor and non-motor symptoms associated with the condition (Olanow et al., 2009; Rascol et al., 2011; Hauser et al., 2014; Hattori et al., 2019) [51, 53–55]. For instance, UPDRS II scores ranged from 0.78 to –2.17 in the Rasagiline groups, compared to 2.32 to –1.64 in the placebo groups, indicating a clear advantage in symptom management with Rasagiline. The standardized mean differences (SMD) of –2.45 for UPDRS II and –2.58 for UPDRS III, along with their corresponding confidence intervals, underscore the robustness of these findings. However, the substantial heterogeneity observed among the included studies warrants careful interpretation of these results and highlights the need for further exploration into potential contributing factors. In terms of safety, the examination of adverse events associated with Rasagiline revealed a spectrum of reported AEs, including headache, dizziness, nausea, back pain, and somnolence. Interestingly, the likelihood of experiencing any AEs with Rasagiline was comparable to

that with placebo, suggesting a favorable safety profile for Rasagiline treatment. Similarly, the risk of AEs leading to withdrawal was found to be similar between Rasagiline and placebo groups, indicating good tolerability of Rasagiline treatment in the patient population studied. While some degree of heterogeneity existed among the studies reporting AEs and AEs leading to withdrawal, the absence of publication bias in any of the analyses enhances the credibility of these findings. However, it's important to acknowledge the limitations inherent in meta-analyses, such as variations in study methodologies and patient populations, which could influence the interpretation of results.

The studies we examined indicate that making the switch from Rasagiline to Safinamide could be a game-changer for PD patients experiencing fluctuations in their symptoms, particularly the wearing-off phenomenon (Bianchini et al., 2021; Stocchi et al., 2021) [59–60]. This phenomenon, where PD symptoms worsen as the medication wears off, can significantly impact daily life. Initial findings suggest that Safinamide, especially at higher doses, could offer advantages in managing these fluctuations(Chang et al., 2017; Stocchi et al., 2021 [47]; Nomoto et al., 2022). Observational studies provided encouraging results, showing that many PD patients experienced noticeable clinical improvements after transitioning to Safinamide. Importantly, these improvements came without any additional adverse effects, marking a positive step forward in PD management (Lee and Gilbert, 2016) [63]. Further investigation into the impact of Safinamide on motor fluctuations revealed promising outcomes. Despite some initial challenges noted during the transition period, patients saw significant improvements in their symptoms over time, suggesting that Safinamide could be a valuable addition to their treatment regimen (Kulisevsky et al., 2022) [64]. Other studies examined the real-world experiences of PD patients transitioning from Rasagiline to Safinamide. The findings reflected the positive trend, with many patients reporting improvements in various aspects of their condition, including motor behaviors, mood, and sleep (Ronconi et al., 2022) [66]. Safety was also a key consideration in our analysis. We found that transitioning directly from Rasagiline to Safinamide was generally well-tolerated, with no major adverse events reported (Borgohain et al., 2014; Schapira et al., 2017) [35, 71]. This underscores the potential for Safinamide to be a safe and effective option for PD patients seeking alternative treatment options (Borgohain et al., 2014b) [50]. What sets Safinamide apart is its unique pharmacological profile, which offers a more targeted approach to managing PD symptoms. Its ability to selectively inhibit MAO-B while also modulating glutamate release makes it an intriguing candidate for PD treatment (Liguori et al., 2018; Csoti et al., 2019; Pagonabarraga et al., 2020) [68–70].

Moreover, the safety profile of Safinamide, coupled with its unique pharmacological properties, makes it an attractive option for PD treatment (Sharaf et al., 2022) [72–73]. Its ability to selectively inhibit MAO-B while modulating glutamate release offers a targeted approach to symptom management, potentially minimizing adverse effects commonly associated with other treatment modalities(Casado MI, López-Ariztegui N, García-Meléndez DD, 2022) [65]. Overall, Safinamide emerges as a promising therapeutic option for PD patients, offering not only improvements in symptom control but also a favorable safety profile. While further research is necessary to validate these results, the current study suggests that Safinamide could potentially have beneficial effects on symptoms. This indicates a potential avenue for Safinamide to be considered as a treatment option for patients recently diagnosed with PD and experiencing mild symptoms.

CONCLUSIONS

In conclusion, MAO-B inhibitors have proven to be valuable therapeutic options for managing PD. Rasagiline, for instance, has demonstrated its efficacy in reducing “off” time and increasing “on” time without any troublesome dyskinesia in PD patients experiencing fluctuations in symptoms. Moreover, clinical trials have underscored Rasagiline tolerability and low incidence of cognitive and behavioral AEs, solidifying its position as a valuable treatment choice for PD. On the other hand, Safinamide emerges as a compelling long-term adjunctive therapy alongside levodopa in PD patients. Its unique dual action offers additional benefits beyond those provided by Rasagiline, particularly in addressing

both motor and non-motor symptoms associated with PD. Switching from other MAO inhibitors to Safinamide presents a promising therapeutic strategy, especially for patients experiencing motor complications like wearing-off phenomena. This transition has been shown to be safe and well-tolerated, offering an opportunity to optimize PD treatment and potentially enhance patients' QoL. While Safinamide shows promise in early PD management, including long-term and comparative research, is crucial to substantiate current findings and fully understand its role in PD treatment. Nonetheless, these advancements in therapeutic options signify significant progress in improving outcomes and QoL for individuals living with PD.

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