Effects of MAO-B inhibitors on non-motor symptoms and quality of life in Parkinson’s disease: A systematic review

Takashi Tsuboi, Yuki Satake, Keita Hiraga, and Masahisa Katsuno

Non-motor symptoms (NMS) are common among patients with Parkinson’s disease and reduce patients’ quality of life (QOL). However, there remain considerable unmet needs for NMS management. Three monoamine oxidase B inhibitors (MAO-BIs), selegiline, rasagiline, and safinamide, have become commercially available in many countries. Although an increasing number of studies have reported potential beneficial effects of MAO-BIs on QOL and NMS, there has been no consensus. Thus, the primary objective of this study was to provide an up-to-date systematic review of the QOL and NMS outcomes from the available clinical studies of MAO-BIs. We conducted a literature search using the PubMed, Scopus, and Cochrane Library databases in November 2021. We identified 60 publications relevant to this topic. Overall, rasagiline and safinamide had more published evidence on QOL and NMS changes compared with selegiline. This was likely impacted by selegiline being introduced many years prior to the field embarking on the study of NMS. The impact of MAO-BIs on QOL was inconsistent across studies, and this was unlikely to be clinically meaningful. MAO-BIs may potentially improve depression, sleep disturbances, and pain. In contrast, cognitive and olfactory dysfunctions are likely unresponsive to MAO-BIs. Given the paucity of evidence and controlled, long-term studies, the effects of MAO-BIs on fatigue, autonomic dysfunctions, apathy, and ICD remain unclear. The effects of MAO-BIs on static and fluctuating NMS have never been investigated systematically. More high-quality studies will be needed and should enable clinicians to provide personalized medicine based on a non-motor symptom profile.

npj Parkinson's Disease (2022) 8:75; https://doi.org/10.1038/s41531-022-00339-2

INTRODUCTION

Three monoamine oxidase B inhibitors (MAO-BIs) are now commercially available in many countries for the management of motor symptoms in patients with Parkinson’s disease (PD). Selegiline and rasagiline are irreversible MAO-BIs, while safinamide is a reversible MAO-BI. These MAO-BIs possess distinct pharmacological profiles (i.e., potency, MAO-B/MAO-A selectivity, and pharmacokinetics). In addition, safinamide modulates voltage-sensitive sodium and calcium channels activity and reduces glutamate release.

The results of large clinical trials have been reported since the 1990s for selegiline, since the 2000s for rasagiline, and since the 2010s for safinamide. Notably, selegiline was largely studied before the field embarked on defining non-motor symptoms (NMS) of PD and developing specific and applicable scales. Recognition of NMS has also evolved over recent years. Many double-blind, placebo-controlled, randomized controlled studies (RCTs) revealed the beneficial effects of MAO-BIs on motor symptoms and wearing-off compared with placebo. These findings are corroborated by meta-analyses. The superiority of one MAO-BI over others remains undetermined because there have been no high-quality direct comparative trials among the MAO-BIs.

NMS of PD include depression, anxiety, sleep disturbances, fatigue, pain, and cognitive and autonomic dysfunctions, and underpin the entire course from the prodromal to late stage. Past studies revealed that NMS were more relevant than motor symptoms in quality of life (QOL). A review on level 1 evidence for treatment of NMS by the Movement Disorders Society was published in 2019 and suggested that there remain considerable unmet needs for NMS management. Although an increasing number of MAO-BI studies have reported QOL or NMS outcomes, to the best of our knowledge, no reviews have systematically summarized those results. Thus, this systematic review aimed (1) to summarize QOL and NMS outcomes from clinical studies of MAO-BIs, (2) to guide clinicians to select MAO-BIs based on a patient’s symptom profile, and (3) to facilitate future investigations on these issues.

RESULTS

Literature search

The systematic literature search revealed 1850 records (Fig. 1). By performing duplicate removal, title/abstract screening, full-text assessments, and hand searches, we identified 60 clinical studies which met the eligibility criteria. Most studies enrolled either early PD patients or advanced PD patients experiencing wearing-off, whereas a minority of studies focused on specific populations: patients with sleep disturbances (three studies), depression (two studies), mild cognitive impairment (MCI) (two studies), freezing of gait (two studies), fatigue (one study), urinary symptoms (one study), high non-motor burden (one study), or RBD (one study). There are only five double-blind, placebo-controlled RCTs that investigated non-motor outcomes as the primary outcomes (rasagiline for MCI, freezing of gait, fatigue, and safinamide for depression), and rasagiline for sleep disturbances. The remaining studies are RCTs reporting QOL or non-motor results as the secondary outcomes or open-label studies. In the following paragraphs, QOL and NMS outcomes in the literature will be systematically summarized along with Tables 1–7.
Quality of life (Table 1)
The Parkinson’s Disease Questionnaire-39 (PDQ-39) was most commonly used to estimate the changes in QOL after MAO-BI administration27. Eight double-blind, placebo-controlled RCTs reported the effects of rasagiline on QOL based on PDQ-39: three RCTs for patients with early PD28–30, two for those with advanced PD31,32, one for those with moderate depression17, one for those with moderate to severe fatigue23, and one for those with sleep disturbances14. Of these studies, only two studies reported significant benefits of rasagiline on QOL at 12–26 weeks (one RCT on advanced PD patients and another RCT for those with moderate to severe fatigue23, and one for those with sleep disturbances14). Of these studies, only two studies reported significant benefits of rasagiline on QOL despite the non-significant results based on the PDQ-3930,32. Based on the PDQ-39 outcomes from the RCTs, effect sizes for safinamide 100 mg and 50 mg were small (0.22–0.23) and trivial (0.11–0.15), respectively. Based on the PD-QOL outcomes from the RCTs, significant improvement in the PDQUALIF scale was observed not in early PD patients but in advanced PD patients. In addition, open-label studies reported significant35 or non-significant36,37 benefits of rasagiline on the PDQ-39.

All the studies of safinamide enrolled advanced PD patients37–46 except for one study for those with high non-motor burden (defined as the NMS Scale (NMSS) ≥ 40)25. RCTs and open-label studies using safinamide 100 mg reported positive or negative QOL outcomes with safinamide25,37–40,42,43,45,46, whereas all the studies using safinamide 50 mg reported negative outcomes37,39,40,44. Based on the PDQ-39 outcomes from the RCTs, effect sizes for safinamide 100 mg and 50 mg were small (0.22–0.23) and trivial (0.11–0.15), respectively.

Collectively, a minority of the RCTs (rasagiline or safinamide vs. placebo) for advanced PD patients reported statistically significant QOL improvement. There have been no selegiline studies reporting QOL outcomes. The clinical impact of the QOL changes will be discussed later.

Depression and anxiety (Table 2)
The ACCORDO study, a multicenter, double-blind, placebo-controlled RCT, enrolled non-demented PD patients with moderately severe depressive symptoms (Beck Depression Inventory, BDI ≥ 15)17. Compared with placebo, rasagiline 1 mg led to a significantly larger reduction in the BDI scores at 4 weeks (effect size, 1.01) without a significant between-group difference at 12 weeks. Another multicenter, double-blind, placebo-controlled RCT enrolled 30 PD patients with moderate to severe fatigue23. In parallel with fatigue improvement, rasagiline 1 mg showed a significantly greater reduction of the BDI scores than placebo (5.5 vs. 0.5 points, P = 0.018). In contrast, significant improvement in anxiety was not observed based on the State-Trait Anxiety Inventory. 

Fig. 1 Flowchart of the literature search. A systematic literature search using the PubMed, Scopus, and Cochrane Library databases was conducted.
| Studies                          | Study design                        | Participants                               | Study quality | Age (median) | Disease duration | Instruments   | Outcome                                                                 | Effect size      |
|---------------------------------|-------------------------------------|--------------------------------------------|---------------|--------------|-----------------|--------------|-------------------------------------------------------------------------|-----------------|
| Parkinson study group (2005)     | Multicenter, double-blind, placebo-controlled RCT, 26 weeks | 472 patients, advanced PD with off time ≥ 2.5 h | 1             | 63.3 (9.5)  | 9.3 (5.3)       | PDQUALIF scale | No significant difference between rasagiline 1 mg and placebo, −1.48 (−3.86 to 0.90), p = 0.22 | IC               |
| Parkinson study group (2002)     | Multicenter, double-blind, placebo-controlled RCT, 26 weeks | 404 patients, early PD not requiring dopaminergic therapy | 1             | 60.8 (10.8) | 1.0 (1.2)       | PDQUALIF scale | No significant difference between rasagiline 0.5 mg and placebo, −2.18 (−4.49 to 0.14), p = 0.07 | IC               |
| Hattori et al. (2018)           | Multicenter, double-blind, placebo-controlled RCT, 26 weeks | 404 patients, advanced PD with off time ≥ 2.5 h | 1             | 66.1 (8.3)  | 9.0 (4.7)       | PDQUALIF scale | Significantly better in rasagiline 1 mg vs placebo, −2.91 (−5.19 to −0.64), P < 0.05 | IC               |
| Zang et al. (2018)              | Multicenter, double-blind, placebo-controlled RCT, 16 weeks | 324 patients, advanced PD with off time ≥ 1 h | 1             | 62.2 (9.4)  | 7.3 (4.6)       | PDQ-39        | Significantly better in rasagiline 2 mg vs placebo, −2.74 (−5.02 to −0.45), P < 0.05 | IC               |
| Hauser et al. (2014)            | Multicenter, double-blind, placebo-controlled RCT, 18 weeks | 321 patients, early PD not adequately controlled with dopamine agonists | 1             | 62.6 (9.7)  | 2.1 (2.1)       | PDQ-39        | No significant differences between groups; rasagiline and placebo; statistics not shown | IC               |
| Hattori et al. (2019)           | Multicenter, double-blind, placebo-controlled RCT, 26 weeks | 244 early PD patients not taking antiparkinsonian medication | 1             | 66.4 (8.9)  | 1.8 (1.6)       | PDQ-39        | No significant differences between rasagiline 1 mg and placebo; −1.8 (−3.96 to 0.38), p = 0.1122 | IC               |
| Hattori et al. (2019)           | Open-label extension of a multicenter, double-blind, placebo-controlled RCT, 52 weeks | 198 early PD patients not taking antiparkinsonian medication | 1             | 66.5 (9.1)  | 1.8 (1.7)       | PDQ-39        | No significant differences between rasagiline 1 mg and placebo; statistics not shown | IC               |
| Zhang et al. (2018)             | Multicenter, double-blind, placebo-controlled RCT, 26 weeks | 130 early PD patients not taking antiparkinsonian medication | 1             | 59.0 (8.9)  | 0.1 (median)    | PDQ-39        | No significant differences between groups; rasagiline 1 mg −0.77 ± 1.12 vs. placebo 1.97 ± 1.15, P = 0.425 | IC               |
| Barone et al. (2015)            | Multicenter, double-blind, placebo-controlled RCT, 12 weeks | 123 patients, PD with moderate depression (BDI ≥ 15) | 1             | 66.1 (8.5)  | 4.3 (12.5)      | PDQ-39        | No significant difference between groups; rasagiline 1 mg −2.49 ± 1.61 vs. placebo −4.31 ± 1.65, P = 0.002 | IC               |
| Lim et al. (2015)               | Multicenter, double-blind, placebo-controlled RCT, 12 weeks | 30 patients, PD with moderate to severe fatigue (FSS ≥ 4) | 1             | 68.7 (7.4)  | 3 (median)      | PDQ-39        | Significantly better in rasagiline 1 mg vs placebo (19 IC vs -6 points), P = 0.018 | IC               |
| Studies                        | Study design                                     | Participants                                                                 | Study quality | Age (SD) | Disease duration | Instruments | Outcome                                                                 | Effect size |
|-------------------------------|-------------------------------------------------|-------------------------------------------------------------------------------|---------------|-----------|------------------|-------------|--------------------------------------------------------------------------|-------------|
| Schrempf et al. (2018)        | Single-center, double-blind, placebo-controlled RCT, 8 weeks | 20 patients, PD with sleep disturbances (PSQI > 5)                           | 1             | 69.9 (6.9) | 4.0 (3.5)       | PDQ-39      | No significant change with rasagiline 1 mg; baseline 30.4 ± 19.3 and post 29.4 ± 22.9, p = 0.686 | 0.05        |
| Hattori et al. (2019)         | Multicenter, open-label, prospective, phase 3 study, 52 weeks | 222 PD patients taking levodopa with or without motor fluctuation            | 3             | 68.0 (8.4) | 7.1 (5.0)       | PDQ-39      | No significant change with rasagiline 1 mg; baseline to post −0.64 ± 9.41, P value not shown | 0.05        |
| Cibulcik et al. (2016)        | Single-center, open-label, prospective study, 3 months | 42 patients, PD with freezing of gait                                         | 3             | 69.5 (7.9) | 8.3 (4.3)       | PDQ-39      | Significant improvement with rasagiline 1 mg; baseline 31.4 ± 13.2 and post 28.7 ± 14.7, p < 0.0001 | 0.19        |
| Müller et al. (2013)          | Single-center, open-label, prospective study, 4 months | 30 patients, PD with sleep disturbances                                       | 3             | 66.6 (6.5) | NA               | PDQ-39      | Not significantly changed after switching selegiline 7.5 mg to rasagiline 1 mg; baseline 24.6 ± 2.8 to 22.6 ± 2.6, P value not shown | 0.13        |
| Borgohain et al. (2014)       | Multicenter, double-blind, placebo-controlled RCT, 24 weeks | 669 patients, advanced PD with off time > 1.5 h                              | 1             | 59.9 (9.4) | 8.1 (3.9)       | PDQ-39      | Significantly better in safinamide; safinamide 100 mg − 28.4 vs. placebo − 11.9, P = 0.0360 | 0.23        |
| Schapia et al. (2017)         | Multicenter, double-blind, placebo-controlled RCT, 24 weeks | 549 patients, advanced PD with off time > 1.5 h                              | 1             | 61.9 (9.0) | 8.9 (4.6)       | EQ-5D       | Significantly better in safinamide; safinamide 100 mg − 0.03 ± 0.19 vs. placebo − 0.03 ± 0.19, P < 0.0001 | 0.17        |
| Borgohain et al. (2014)       | Multicenter, double-blind, placebo-controlled RCT, 2 years | 544 patients, advanced PD with off time > 1.5 h                              | 1             | 59.9 (9.4) | 8.1 (3.9)       | PDQ-39      | Significantly better in safinamide 100 mg vs IC placebo; statistics not shown | 0.23        |
| Hattori et al. (2020)         | Multicenter, double-blind, placebo-controlled RCT, 24 weeks | 406 patients, advanced PD with wearing off                                   | 1             | 68.1 (8.6) | 8.2 (4.9)       | PDQ-39      | No significant improvement with safinamide 50 mg IC vs placebo; statistics not shown | 0.05        |
| Cattaneo et al. (2020)        | Post-hoc analysis of a multicenter, double-blind, placebo-controlled RCT, 2 years | 352 patients, advanced PD with off time > 1.5 h                              | 1             | NA        | NA               | PDQ-39      | No significant differences between groups; safinamide 50 mg − 1.70 ± 0.84 vs. placebo − 1.37 ± 0.86, P = 0.783 | 0.11        |
| Tsuboi et al. (2020)          | Multicenter, open-label, prospective study, 52 weeks | 203 patients, advanced PD with wearing off                                   | 3             | 67.2 (8.6) | 9.8 (5.3)       | PDQ-39      | No significant differences between groups; safinamide 100 mg − 3.38 ± 0.85 vs. placebo − 1.37 ± 0.86, P = 0.097 | 0.23        |
| Santos Garcia et al. (2021)   | Multicenter, open-label, prospective study, 6 months | 50 patients, PD with high non-motor burden (NMSS ≥ 40)                       | 3             | 68.5 (9.1) | 6.4 (5.1)       | PDQ-39      | No significant change with safinamide 50 or 100 mg; baseline to post −0.85 ± 0.90, P value not shown | 0.06        |
| Grigoriou et al. (2021)       | Multicenter, open-label, prospective study, 6 months | 27 patients, advanced PD with off time > 1.5 h                               | 3             | 65        | 6.8              | PDQ-8       | No significant change with safinamide 100 mg; baseline 30.1 ± 17.6 and post 21.2 ± 13.5, P < 0.0001 | 0.50        |
### Table 1 continued

| Study | Design | Participants | Disease duration | Outcome | Effect size |
|-------|--------|--------------|------------------|---------|-------------|
| De Nicole et al. | Single-center, open-label, prospective study, 6 months | 20 patients, advanced PD with 3 motor fluctuations | 63.8 ± 6.6 (10.2 | EQ-5D | 0.22 |
| Bianchi et al. | Single-center, open-label, retrospective study, 44 months | 20 patients, advanced PD with 4 motor fluctuations | 75.0 ± 6.3 (6.2) | PDQ-39 | 0.34 |
| Gamei et al. | Single-center, open-label, prospective study, 12 weeks | 13 patients, advanced PD with 3 motor fluctuation and pain (NRS ≥ 4) | 64.1 ± 6.7 (6.7) | PDQ-39 | 0.20 |

**Sleep disturbances (Table 3)**

Two large multicenter, double-blind, placebo-controlled RCTs for early PD patients reported non-significant effects of rasagiline 1 mg on sleep disturbances at 18–26 weeks based on the PDQUALIFE sleep subscore or Scales for Outcomes in PD (SCOPA) daytime sleepiness score. Similarly, one small multicenter, double-blind, placebo-controlled RCT for PD patients with moderate to severe fatigue demonstrated non-significant effects of rasagiline 1 mg on sleep disturbances based on the Parkinson’s Disease Sleep Scale (PDSS) at 12 weeks. One single-center, double-blind, placebo-controlled RCT enrolled 20 PD patients with sleep disturbances. Rasagiline 1 mg led to significantly better sleep maintenance as assessed by polysomnography (effect size, 0.71), with significantly decreased wake time after sleep onset, number of arousals, and percentage of light sleep. Although daytime sleepiness, as measured by the Epworth Sleepiness Scale (ESS), improved significantly with rasagiline (effect size, 0.19), there was no significant change in the PDSS-2. The authors found no correlations of polysomnographic sleep parameters or PDSS-2 score with changes in motor function. Open-label studies reported positive or non-significant effects of rasagiline on sleep disturbances.

Six open-label studies have reported the impact of safinamide on sleep disturbances. Most studies employed the PDSS-2 and ESS; however, the outcomes were inconsistent. An open-label cross-over study enrolled 30 PD patients with RBD. Interestingly, safinamide 50 mg alleviated RBD as assessed by polysomnography and questionnaires at 3 months. This study is the only one investigating the effects of MAO-BIs on RBD.

In a large multicenter, double-blind, placebo-controlled RCT for advanced PD patients, orally disintegrating selegiline 1.25–2.5 mg did not prolong asleep time based on patient diaries.
| Studies | Study design | Participants | Study quality | Age | Disease duration | Instruments | Outcome | Effect size |
|---------|--------------|---------------|---------------|-----|-----------------|-------------|---------|------------|
| Parkinson study group (2002)\(^{34}\) | Multicenter, double-blind, placebo-controlled RCT, 26 weeks | 404 patients, early PD not requiring dopaminergic therapy | 1 | 60.8 (10.8) | 1.0 (1.2) | BDI | No significant difference between rasagiline 1 mg and placebo, \(-0.35 (\pm 0.16), P > 0.05\) | IC |
| Hattori et al. (2018)\(^{35}\) | Multicenter, double-blind, placebo-controlled RCT, 26 weeks | 404 patients, advanced PD with off time ≥ 25 h | 1 | 66.1 (8.3) | 9.0 (4.7) | PDQ-39: emotional well-being | Significantly better in rasagiline 1 mg vs placebo, \(-0.35 (-0.72 to -0.03), p = 0.030\) | IC |
| Zhang et al. (2018)\(^{36}\) | Multicenter, double-blind, placebo-controlled RCT, 26 weeks | 324 patients, advanced PD with off time ≥ 1 h | 1 | 62.2 (9.4) | 7.3 (4.6) | PDQ-39: emotional well-being | No significant difference between rasagiline 1 mg and placebo, \(-0.21 (-0.72 to 0.30), P > 0.05\) | IC |
| Hattori et al. (2019)\(^{37}\) | Multicenter, double-blind, placebo-controlled RCT, 26 weeks | 244 early PD patients not taking antiparkinsonian medication | 1 | 66.4 (8.9) | 1.8 (1.6) | PDQ-39: emotional well-being | Significantly better in rasagiline 0.5 mg vs placebo, \(-0.21 (-0.72 to 0.30), p = 0.0414\) | IC |
| Zhang et al. (2018)\(^{38}\) | Multicenter, double-blind, placebo-controlled RCT, 26 weeks | 130 early PD patients not taking antiparkinsonian medication | 1 | 59.0 (8.9) | 0.1 (median) | PDQ-39: emotional well-being | No significant differences between groups; rasagiline 1 mg vs placebo, \(-0.72 (-0.77 to 0.30), P = 0.0150\) | IC |
| Barone et al. (2015)\(^{39}\) | Multicenter, double-blind, placebo-controlled RCT, 12 weeks | 123 patients, PD with moderate depression (BDI ≥ 15) | 1 | 66.1 (8.5) | 4.3 (12.5) | BDI | No significant differences between groups at 12 weeks; rasagiline 1 mg vs placebo, \(-0.72 (-0.77 to 0.30), P = 0.0150\) | IC |
| Stern et al. (2004)\(^{40}\) | Multicenter, double-blind, placebo-controlled RCT, 16 weeks | 56 early PD patients not taking antiparkinsonian medication | 1 | 61.5 (8.8) | 0.7 (1.5) | BDI | No significant difference between rasagiline and placebo, statistics not shown | IC |
| Hanagasi et al. (2011)\(^{41}\) | Multicenter, double-blind, placebo-controlled RCT, 12 weeks | 55 patients, mild to moderate PD (HY stage 1–3) with mild cognitive impairment | 1 | 66.4 (9.8) | 4.0 (2.4) | Geriatric depression scale | No significant differences between rasagiline 1 mg and placebo, \(-0.16 (\pm 0.37), P = 0.86\) | 0.12 |
| Lim et al. (2015)\(^{42}\) | Multicenter, double-blind, placebo-controlled RCT, 12 weeks | 30 patients, PD with moderate to severe fatigue (FSS ≥ 4) | 1 | 68.7 (7.4) | 3 (median) | State-trait anxiety inventory | No significant differences between rasagiline 1 mg and placebo (12.5 vs 5.5 points), \(P = 0.30\) | IC |
| Hattori et al. (2019)\(^{43}\) | Multicenter, open-label, prospective 3 study, 52 weeks | 222 PD patients taking levodopa with or without motor fluctuation | 3 | 68.0 (8.4) | 7.1 (5.0) | PDQ-39: emotional well-being | No significant change with rasagiline 1 mg; baseline to post 0.37 ± 1.83, \(P = 0.018\) | IC |
| Cibulčík et al. (2016)\(^{44}\) | Single-center, open-label, prospective study, 3 months | 42 patients, PD with freezing of gait | 3 | 69.5 (7.9) | 8.3 (4.3) | PDQ-39: emotional well-being | No significant change with rasagiline 1 mg; baseline to post 19.5 ± 14.5, \(p = 0.099\) | 0.16 |
Table 2 continued

| Studies                        | Study design                          | Participants                          | Study quality | Age     | Disease duration | Instruments        | Outcome                                      | Effect size |
|-------------------------------|---------------------------------------|---------------------------------------|---------------|---------|------------------|---------------------|----------------------------------------------|-------------|
| Müller et al. (2013)          | Single-center, open-label, prospective study, 4 months | 30 patients, PD with sleep disturbances | 3             | 66.6 (65) | NA               | HAMD                | Significantly improved after switching selegiline 7.5 mg to rasagiline 1 mg: baseline −8.1 ± 0.6 to −6.9 ± 0.7, P = 0.003 | 0.37        |
| Rahimi et al. (2016)          | Single-center, open-label, prospective study, 90 days | 14 patients, PD with freezing of gait | 3             | 68.9 (6.7) | 11.8 (5.0)       | Beck anxiety inventory | No significant change with rasagiline 1 mg: IC mean values for the whole cohort not shown, P = 0.80 | IC          |
| Borgohain et al. (2014)       | Multicenter, double-blind, placebo-controlled RCT, 24 weeks | 669 patients, advanced PD with off time > 1.5 h | 1             | 59.9 (9.4) | 8.1 (3.9)        | PDQ-39: emotional well-being | Significantly better in safinamide: safinamide 100 mg −5.1 vs. placebo −1.7, P = 0.0116 | 0.27        |
| Schapira et al. (2017)        | Multicenter, double-blind, placebo-controlled RCT, 24 weeks | 549 patients, advanced PD with off time > 1.5 h | 1             | 61.9 (9.0) | 8.9 (4.6)        | GRID-HAMD           | No significant differences between groups; safinamide 50 mg −24 vs. placebo −17, P = 0.12 | 0.12        |
| Borgohain et al. (2014)       | Multicenter, double-blind, placebo-controlled RCT, 2 years | 544 patients, advanced PD with off time > 1.5 h | 1             | 59.9 (9.4) | 8.1 (3.9)        | GRID-HAMD           | No significant differences between groups; safinamide 100 mg −0.8 vs. placebo 0.3, P = 0.0731 | 0.23        |
| Cattaneo et al. (2017)        | Post-hoc analysis of two multicenter, double-blind, placebo-controlled RCTs, 6 and 24 months | 446 patients, advanced PD with off time > 1.5 h | 1             | NA      | NA               | PDQ-39: emotional well-being | At 6 months, significantly better in safinamide 100 mg vs placebo: −3.77 (−6.49 to −1.05), P = 0.0067 | IC          |
| Stocchi et al. (2012)         | Multicenter, double-blind, placebo-controlled RCT, 24 weeks | 269 patients, early PD receiving a stable dose of a single dopamine agonist | 1             | 57.4 (11.3) | 2.5 (1.3)        | HAMD                | No significant difference between safinamide and placebo; statistical values not shown | IC          |
| Schapira et al. (2013)        | Multicenter, double-blind, placebo-controlled RCT, 18 months | 227 patients, early PD taking a single dopamine agonist | 1             | median 56.6 and 59.8 for 100 mg and 200 mg | NA | HAMD | No significant differences between groups; safinamide 100 or 200 mg −0.5 ± 3.42 vs. placebo −0.3 ± 2.54, P = 0.389 | IC          |
| Perla et al. (2021)           | Multicenter, open-label, retrospective study, 3 months | 82 patients, PD with depressive symptoms (HAMD-17 > 14) | 4             | 68.3 (11.4) | 8.7 (8.6)        | HAMD-17             | Significant improvement with safinamide 50 mg: baseline to post −4.7 ± 4.5, P < 0.0001 | 1.76        |
| Schapira et al. (2013)        | Multicenter, double-blind, placebo-controlled RCT, 24 weeks | 227 patients, early PD taking a single dopamine agonist | 1             | median 56.6 and 59.8 for 100 mg and 200 mg | NA | HAMD | No significant differences between groups; safinamide 100 or 200 mg −0.5 ± 3.42 vs. placebo −0.3 ± 2.54, P = 0.389 | IC          |
| Schapira et al. (2013)        | Multicenter, double-blind, placebo-controlled RCT, 18 months | 227 patients, early PD taking a single dopamine agonist | 1             | median 56.6 and 59.8 for 100 mg and 200 mg | NA | HAMD | No significant differences between groups; safinamide 100 or 200 mg −0.5 ± 3.42 vs. placebo −0.3 ± 2.54, P = 0.389 | IC          |
## Table 2 continued

| Studies                      | Study design                                      | Participants                                                                 | Study quality | Age     | Disease duration | Instruments | Outcome                                                                 | Effect size |
|------------------------------|---------------------------------------------------|------------------------------------------------------------------------------|---------------|---------|------------------|-------------|--------------------------------------------------------------------------|-------------|
| Santos García et al. (2021)  | Multicenter, open-label, prospective study, 6 months | 50 patients, PD with high non-motor burden (NMSS ≥ 40)                        | 3             | 68.5 (9.1) | 6.4 (5.1)        | BDI-II      | Significant improvement with safinamide 100 mg; baseline 15.9 ± 10.5 and post 10.2 ± 6.8, P < 0.0001 | 0.54        |
| Grigoriou et al. (2021)      | Multicenter, open-label, prospective study, 6 months | 27 patients, advanced PD with off time > 1.5 h                               | 3             | 65      | 6.8              | HADS: anxiety | No significant change with safinamide 100 mg; baseline 5.2 ± 3.7 and post 4.8 ± 2.9, p = 0.50 | 0.11        |
| De Micco et al. (2021)       | Single-center, open-label, prospective study, 6 months | 20 patients, advanced PD with off time > 1.5 h                               | 3             | 63.8 (10.2) | 6.0 (2.2)        | BDI         | No significant change with safinamide 50 mg; baseline 6.90 ± 5.05 and post 6.70 ± 5.93, P = 0.91 | 0.04        |
| Bianchi et al. (2019)        | Single-center, open-label, retrospective study, 4.4 months | 20 patients, advanced PD with motor fluctuations                              | 4             | 75.0 (6.3) | 14.5 (6.8)       | HADS        | No significant change with safinamide 100 mg; baseline 10.1 ± 7.1 and post 5.4 ± 5.3, P = 0.05 | 0.66        |
| Shoulson et al. (1992)       | Multicenter, double-blind, placebo-controlled RCT, 3 months | 800 patients, early PD not taking antiparkinsonian medication                  | 1             | 61.1 (9.5) | NA               | HAMD        | Significantly better in selegiline; selegiline 10 mg, baseline 2.8 ± 3.0 and post 2.5 ± 3.0, placebo or tocopherol, baseline 2.9 ± 2.9 and post 2.96 ± 3.81, P = 0.0028 | 0.10        |
| Pålhagen et al. (2006)       | Multicenter, double-blind, placebo-controlled RCT, 7 years | 140 patients, early de novo PD                                                | 1             | 63.4 (8.1) | 3.0 (2.1)        | HAMD        | Significantly better in selegiline 10 mg than IC placebo; mean values not shown, P = 0.016 | 0.67        |
| Allain et al. (1991)         | Multicenter, double-blind, placebo-controlled RCT, 3 months | 93 patients, early de novo PD                                                 | 1             | 64.9 (9.3) | NA               | HAMD        | Significantly better in selegiline 10 mg, baseline 6.0 ± 4.5 and post 3.0 ± 1.4, placebo, baseline 6.0 ± 5.0 and post 5.0 ± 4.4, P = 0.010 | 0.25        |
| Dalrymple-Alford et al. (1995) | Single-center, placebo-controlled RCT, 8 weeks | 21 patients, early PD not taking antiparkinsonian medication                  | 1             | 65.7 (9.2) | 1.7 (1.7)        | BDI         | No significant difference between groups; IC selegiline 10 mg, baseline 11.0 and post 7.0, placebo, baseline 10.0 and post 4.0, P value not shown | 0.28        |
| Hietanen et al. (1991)       | Single-center, double-blind, placebo-controlled RCT, 4 weeks | 20 patients, early PD not taking levodopa                                     | 1             | 56.9 (8.9) | 4.2 (2.2)        | BDI         | No significant difference between groups; selegiline 30 mg, baseline 5 ± 4 and post 5 ± 4, placebo, baseline 5 ± 3 and post 5 ± 3, P value not shown | 0.25        |

Age and disease duration are presented as mean (SD) if available.

BDI Beck Depression Inventory, FSS Fatigue Severity Scale, HADS Hospital Anxiety and Depression Scale, HAMD Hamilton Depression Rating Scale, HY stage Hoehn–Yahr stage, IC incalculable, NA not assessed, PD Parkinson’s Disease, PDQ Parkinson’s Disease Questionnaire, RCT Randomized Controlled Trial.
| Studies            | Study design                                      | Participants                              | Study quality | Age  | Disease duration | Instruments                  | Outcome                                                                 | Effect size |
|-------------------|--------------------------------------------------|-------------------------------------------|---------------|------|------------------|-----------------------------|-------------------------------------------------------------------------|-------------|
| Biglan et al. (2006) | Multicenter, double-blind, placebo-controlled RCT, 26 weeks | 404 patients, early PD not requiring dopaminergic therapy | 1             | 60.8 (10.8) | 1.0 (1.2) | PDQUALIF: sleep | No significant difference between rasagiline 1 mg and placebo, −0.07, P = 0.69 |             |
|                   |                                                  |                                           |               |      |                  | PDQUALIF: sleep | No significant difference between rasagiline 2 mg and placebo, 0.02, P = 0.92 |             |
| Hauser et al. (2014) | Multicenter, double-blind, placebo-controlled RCT, 18 weeks | 321 patients, early PD not adequately controlled with dopamine agonists | 1             | 62.6 (9.7) | 2.1 (2.1) | SCOPA daytime sleepiness | No significant differences between rasagiline 1 mg and placebo; statistics not shown |             |
| Lim et al. (2015)   | Multicenter, double-blind, placebo-controlled RCT, 12 weeks | 30 patients, PD with moderate to severe fatigue (FSS ≥ 4) | 1             | 68.7 (7.4) | 3 (median) | PDSS | No significant difference between rasagiline 1 mg and placebo (10.4 vs 3.25 points), P = 0.11 |             |
| Schrempf et al. (2018) | Single-center, double-blind, placebo-controlled RCT, 8 weeks | 20 patients, PD with sleep disturbances (PSQI > 5) | 1             | 69.9 (6.9) | 4.0 (3.5) | Polysomnography: sleep maintenance | Significant improvement with rasagiline 1 mg; baseline 62.1 ± 11.9 and post 70.6 ± 13.9, p = 0.024 | 0.71        |
|                   |                                                  |                                           |               |      |                  | Polysomnography: sleep efficiency | No significant change with rasagiline 1 mg; baseline 58.1 ± 14.0 and post 63.5 ± 15.4, p = 0.097 | 0.39        |
|                   |                                                  |                                           |               |      |                  | PDSS                   | No significant change with rasagiline 1 mg; baseline 19.6 ± 9.6 and post 20.1 ± 9.1, p = 0.798 | 0.04        |
|                   |                                                  |                                           |               |      |                  | ESS                     | Significant improvement with rasagiline 1 mg; baseline 9.0 ± 4.8 and post 8.1 ± 4.7, p = 0.011 | 0.19        |
|                   |                                                  |                                           |               |      |                  | PSQI                    | No significant change with rasagiline 1 mg; baseline 9.5 ± 2.6 and post 9.2 ± 2.5, p = 0.546 | 0.12        |
| Panisset et al. (2016) | Multicenter, open-label, prospective study, 2 months | 110 PD patients not taking MAO-BI | 3             | 67.0 (9.4) | 3 (0–28) median (range) | PDSS | Significant improvement with rasagiline 0.5 or 1 mg; baseline 96.2 ± 21.6 and post 105.5 ± 21.9, P = 0.003 | 0.42        |
|                   |                                                  |                                           |               |      |                  | ESS                     | No significant change with rasagiline 0.5 or 1 mg, baseline 10 ± 5.2 and post 9.4 ± 5.0, p = 0.4407 | 0.12        |
| Schettino et al. (2016) | Single-center, open-label, prospective study, 12 weeks | 38 patients, mild-to-moderate PD with sleep disturbances (PDSS ≥ 100) | 3             | 70.3 (10.6) | 4.7 (0.5) | Patient sleep diaries: sleep latency time (h) | Significantly better in rasagiline + levodopa; rasagiline + levodopa −1.68 ± 1.21 vs. levodopa alone −0.55 ± 0.69, P = 0.001 | IC          |
|                   |                                                  |                                           |               |      |                  | Patient sleep diaries: total sleep time (h) | Significantly better in rasagiline + levodopa; rasagiline + levodopa 1.26 ± 1.62 vs. levodopa alone 0.32 ± 0.70, P = 0.026 | IC          |
| Müller et al. (2013) | Single-center, open-label, prospective study, 4 months | 30 patients, PD with sleep disturbances | 3             | 66.6 (6.5) | NA | PDSS | Significantly improved after switching selegiline 7.5 mg to rasagiline 1 mg; baseline 111.3 ± 2.9 to 126.0 ± 2.0, P < 0.001 | 0.94        |
| Studies             | Study design                                      | Participants                                      | Study quality | Age        | Disease duration | Instruments | Outcome                                                                 | Effect size |
|---------------------|--------------------------------------------------|--------------------------------------------------|---------------|------------|------------------|-------------|--------------------------------------------------------------------------|-------------|
| Liguori et al. (2018) | Single-center, open-label, retrospective study, 4 months | 15 patients, advanced PD with wearing off        | 4             | 70.0 (7.7) | 6.2 (3.4)       | PDSS-2      | No significant change with rasagiline (dose not specified); baseline 19.5 ± 4.5 and post 17.8 ± 5.5, P value not shown | 0.39        |
|                     |                                                  |                                                  |               |            |                  | PSQI        | No significant change with rasagiline (dose not specified); baseline 7.3 ± 3.0 and post 6.5 ± 3.4, P value not shown      | 0.25        |
|                     |                                                  |                                                  |               |            |                  | ESS         | No significant change with rasagiline (dose not specified); baseline 9.0 ± 2.1 and post 8.8 ± 3.7, P value not shown         | 0.09        |
| Santos García et al. (2021) | Multicenter, open-label, prospective study, 6 months | 50 patients, PD with high non-motor burden (NMSS ≥ 40) | 3             | 68.5 (9.1) | 6.4 (5.1)       | ESS         | Significant improvement with safinamide 100 mg; baseline 9.2 ± 5.6 and post 6.9 ± 5.1, P = 0.012                     | 0.40        |
|                     |                                                  |                                                  |               |            |                  | PSQI        | Significant improvement with safinamide 100 mg; baseline 10.4 ± 4.0 and post 8.4 ± 4.4, P = 0.001                       | 0.51        |
| Liguori et al. (2018) | Single-center, open-label, retrospective study, 4 months | 46 patients, advanced PD with wearing off        | 4             | 70.0 (7.7) | 6.2 (3.4)       | PDSS-2      | Significant improvement with safinamide (dose not specified); baseline 20.1 ± 12.1 and post 16.9 ± 10.6, P < 0.05      | 0.26        |
|                     |                                                  |                                                  |               |            |                  | PSQI        | No significant change with safinamide (dose not specified); baseline 8.94 ± 4.38 and post 7.8 ± 3.6, P value not shown   | 0.27        |
|                     |                                                  |                                                  |               |            |                  | ESS         | Significant improvement with safinamide (dose not specified); baseline 9.8 ± 5.5 and post 8.0 ± 4.5, P < 0.05            | 0.32        |
| Plastino et al. (2021) | Single-center, open-label, single-blinded, cross-over study, 12 weeks | 30 patients, PD with RBD                          | 3             | 65 (7.9)   | 6.0 (3.1)       | PDSS-2      | Significant improvement with safinamide 50 mg; baseline 20.0 ± 7.7 and post 17.3 ± 4.7, P = 0.042                  | 0.35        |
|                     |                                                  |                                                  |               |            |                  | RBD questionnaire | Significant improvement with safinamide 50 mg; baseline 31.4 ± 12.4 and post 26.4 ± 12.4, P = 0.04               | 0.40        |
|                     |                                                  |                                                  |               |            |                  | ESS         | No significant changes with safinamide 50 mg; statistics not shown       | IC          |
|                     |                                                  |                                                  |               |            |                  | Polysomnography: total sleep time (min) | Significant improvement with safinamide 50 mg; baseline 400 ± 57 and post 427 ± 63, P = 0.041 | 0.47        |
| Grigoriou et al. (2021) | Multicenter, open-label, prospective study, 6 months | 27 patients, advanced PD with off time > 1.5 h    | 3             | 65         | 6.8              | PDSS-2      | No significant change with safinamide 100 mg; baseline 14.8 ± 7.4 and post 13.8 ± 8.2, p = 0.35                           | 0.14        |
| De Micco et al. (2021) | Single-center, open-label, prospective study, 6 months | 20 patients, advanced PD with off time > 1.5 h    | 3             | 63.8 (10.2) | 6.0 (2.2)       | ESS         | No significant change with safinamide 50 mg; baseline 5.50 ± 3.55 and post 4.20 ± 2.97, P = 0.42                      | 0.24        |

**Table 3 continued**
A single-center, open-label, retrospective study analyzed the effects of selegiline 10 mg on excessive daytime sleepiness at 3 months. The authors reported significant alleviation of excessive daytime sleepiness based on the ESS with a large effect size (1.21). This benefit was accompanied by improved self-perceived quality of sleep. In a single-center, open-label, prospective study, switching from selegiline 7.5 mg to rasagiline 1 mg led to an improvement in sleep disturbances based on the PDSS. However, the results should be cautiously interpreted because of the potential effect of patients’ expectations of treatment benefits.

In summary, no RCTs showed significant benefits of MAO-Bs based on the sleep-specific rating scales. However, one RCT using polysomnography and some open-label studies reported positive effects of MAO-Bs on sleep disturbances.

### Pain (Table 4)

All the rasagiline studies (6 large RCTs and 1 small open-label study) reported pain outcomes based on the PDQ-39 bodily discomfort subscore. The two large RCTs for advanced PD patients showed significant benefits of rasagiline 1 mg on pain at 16–26 weeks (effect size, incalculable). Alleviation of pain with rasagiline 0.5 mg was numerically smaller and did not reach statistical significance. Two large RCTs for early PD patients did not find significant benefits of rasagiline 1 mg on pain.

In a large double-blind, placebo-controlled RCT, advanced PD patients were randomized to selegiline 100 mg, 50 mg, or placebo for 24 weeks. Compared with placebo, only patients taking selegiline 100 mg experienced significant amelioration of pain based on the PDQ-39 bodily discomfort subscore. Similar results were observed in another large RCT for advanced PD patients, although the outcomes did not reach statistical significance.

Furthermore, small open-label studies and post hoc analyses of large RCTs for advanced PD patients support the efficacy of selegiline 100 mg on pain. Two open-label studies reported detailed outcomes based on the King’s PD pain scale, suggesting that selegiline 100 mg improves fluctuation-related pain. Collectively, selegiline 100 mg possibly ameliorates pain, especially fluctuation-related pain, with trivial to small effect size (0.16–0.41).

Collectively, rasagiline and selegiline might improve pain, especially in patients with more advanced disease stages. Note that no selegiline studies have reported pain outcomes.

### Autonomic dysfunctions (Table 6)

A large RCT for early PD patients found no significant benefits of rasagiline on urinary symptoms based on the PDQUALIF urinary function subscore at 26 weeks. In a small single-center, open-label, prospective study, urodynamic evaluations revealed a
Table 4. Pain outcomes of MAO-BI studies.

| Studies                  | Study design                                      | Participants                                                                 | Study quality | Age       | Disease duration | Instruments          | Outcome                                                                 | Effect size |
|--------------------------|--------------------------------------------------|-------------------------------------------------------------------------------|---------------|-----------|------------------|----------------------|------------------------------------------------------------------------|------------|
| Hattori et al. (2018)    | Multicenter, double-blind, placebo-controlled RCT, 26 weeks | 404 patients, advanced PD with off time ≥ 2.5 hours                          | 1             | 66.1 (8.3) | 9.0 (4.7)        | PDQ-39 bodily discomfort | Significantly better in rasagiline 1 mg vs placebo, −4.28 (−8.20 to −0.36), p = 0.0326 | IC 0.0326 |
| Zang et al. (2018)       | Multicenter, double-blind, placebo-controlled RCT, 16 weeks | 324 patients, advanced PD with off time ≥ 1 hour                             | 1             | 62.2 (9.4) | 7.3 (4.6)        | PDQ-39 bodily discomfort | No significant difference between rasagiline 0.5 mg and placebo, 1.00 (−4.85 to 2.85), p = 0.6099 | IC −0.6099 |
| Hattori et al. (2019)    | Multicenter, double-blind, placebo-controlled RCT, 26 weeks | 244 early PD patients not taking antiparkinsonian medication                  | 1             | 66.4 (8.9) | 1.8 (1.6)        | PDQ-39 bodily discomfort | No significant differences between rasagiline 1 mg and placebo, −0.47 (−4.28 to 3.35), P = 0.8093 | IC 0.8093 |
| Zhang et al. (2018)      | Multicenter, double-blind, placebo-controlled RCT, 26 weeks | 130 early PD patients not taking antiparkinsonian medication                 | 1             | 59.0 (8.9) | 0.1 (median)     | PDQ-39 bodily discomfort | No significant differences between IC groups; rasagiline 1 mg 2.14 ± 2.01 vs. placebo 1.28 ± 2.05, P = 0.749 | IC 0.749   |
| Barone et al. (2015)     | Multicenter, double-blind, placebo-controlled RCT, 12 weeks | 123 patients, PD with moderate depression (BDI ≥ 15)                         | 1             | 66.1 (8.5) | 4.3 (12.5)       | PDQ-39 bodily discomfort | No significant difference between IC groups, rasagiline 1 mg 2.01 ± 2.97 vs. placebo 2.72 ± 2.65, P value not shown | IC 0.09    |
| Hattori et al. (2019)    | Multicenter, open-label, prospective study, 52 weeks | 222 PD patients taking levodopa with or without motor fluctuation            | 3             | 68.0 (8.4) | 7.1 (5.0)        | PDQ-39 bodily discomfort | No significant change with rasagiline 1 mg; baseline to post −1.29 ± 19.45, P value not shown | IC 0.24    |
| Cibulcik et al. (2016)   | Single-center, open-label, prospective study, 3 months | 42 patients, PD with freezing of gait                                         | 3             | 69.5 (7.9) | 8.3 (4.3)        | PDQ-39 bodily discomfort | Significant improvement with rasagiline 1 mg; baseline 27.5 ± 17.3 and post 23.4 ± 18.9, p = 0.0396 | IC 0.0396 |
| Cattaneo et al. (2017)   | Post-hoc analysis of two multicenter, double-blind, placebo-controlled RCTs, 6 months | 995 patients, advanced PD with off time > 1.5 h                              | 1             | 60.9 (9.2) | 8.6 (4.2)        | PDQ-39 bodily discomfort | Significantly better in safinamide; safinamide 100 mg −5.28 ± 1.49 vs. placebo −1.59 ± 1.50, P = 0.0007 | IC 0.23    |
| Borgohain et al. (2014)  | Multicenter, double-blind, placebo-controlled RCT, 24 weeks | 669 patients, advanced PD with off time > 1.5 h                              | 1             | 59.9 (9.4) | 8.1 (3.9)        | PDQ-39 bodily discomfort | Significantly better in safinamide; safinamide 100 mg −3.5 vs. placebo 0.2, P = 0.0159 | IC 0.16    |
| Tsuboi et al. (2021)     | Multicenter, double-blind, placebo-controlled RCT, 24 weeks | 406 patients, advanced PD with wearing off                                   | 1             | 68.1 (8.6) | 8.2 (4.9)        | PDQ-39 bodily discomfort | No significant differences between groups; safinamide 50 mg −1.3 vs. placebo 0.2, P = 0.4937 | IC 0.06    |
| Cattaneo et al. (2018)   | Post-hoc analysis of a multicenter, double-blind, placebo-controlled RCT, 2 years | 355 patients, advanced PD with off time > 1.5 h                              | 1             | NA        | NA               | PDQ-39 bodily discomfort | No significant differences between groups; safinamide 100 mg −1.71 ± 1.44 vs. placebo −2.94 ± 1.41, P = 0.5407 | IC 0.07    |
| Santos García et al. (2021) | Multicenter, open-label, prospective study, 6 months | 50 patients, PD with high non-motor burden (NMSS ≥ 40)                       | 3             | 68.5 (9.1) | 6.4 (5.1)        | King's PD pain scale   | Significantly better in safinamide 100 mg vs placebo, −3.66 (−6.71 to −0.60), P = 0.0190 | IC 0.0190 |

Note: IC = International Classification; PDQ-39 = Parkinson’s Disease Questionnaire; NMSS = Non-motor Symptoms Scale; PD = Parkinson’s Disease; BDHI = Basal Ganglia Disease Heidelberg Inventory; PDQ-39 bodily discomfort = Parkinson’s Disease Questionnaire-39 for bodily discomfort; PDQ-39 bodily discomfort = Parkinson’s Disease Questionnaire-39 for bodily discomfort; significance levels for pain scale are not provided in the table.
| Studies                  | Study design                                      | Participants                                                                 | Study quality | Age | Disease duration | Instruments                        | Outcome                                                                 | Effect size |
|-------------------------|--------------------------------------------------|------------------------------------------------------------------------------|---------------|-----|------------------|--------------------------------------|-------------------------------------------------------------------------|-------------|
| Grigoriou et al. (2021) | Multicenter, open-label, prospective study, 6 months | 27 patients, advanced PD with off time > 1.5 h                              | 3             | 65  | 6.8              | Visual Analog Scale: pain            | No significant change with safinamide 100 mg; baseline 4.6 ± 3.2 and post 3.7 ± 2.7, \( P = 0.071 \) | 0.29        |
| De Micco et al. (2021)  | Single-center, open-label, prospective study, 6 months | 20 patients, advanced PD with off time > 1.5 h                              | 3             | 63.8 (10.2) | 6.0 (2.2)       | PDQ-39: bodily discomfort            | Significant improvement with safinamide 100 mg; baseline 44.6 ± 27.4 and post 33.3 ± 19.9, \( P = 0.018 \) | 0.41        |
| Geroin et al. (2020)    | Single-center, open-label, prospective study, 12 weeks | 13 patients, advanced PD with motor fluctuation and pain (NRS ≥ 4)          | 3             | 64.1 (6.7) | 5.8 (2.9)       | King's PD pain scale                 | Significant improvement with safinamide 100 mg; mean score, baseline 18.0 and post 12.4, \( P = 0.02 \) | IC          |

Age and disease duration are presented as mean (SD) if available.

BDI Beck Depression Inventory, IC incalculable, ICD Impulse Control Disorders, NA not assessed, NMSS Non-Motor Symptoms Scale, NRS Numeric Rating Scale, PD Parkinson’s Disease, PDQ Parkinson’s Disease Questionnaire, RCT Randomized Controlled Trial.
| Studies                  | Study design                                         | Participants                                                                 | Study quality | Age      | Disease duration | Instruments                                           | Outcome                                                                                           | Effect size |
|-------------------------|------------------------------------------------------|------------------------------------------------------------------------------|---------------|-----------|------------------|--------------------------------------------------------|--------------------------------------------------------------------------------------------------|-------------|
| Stocchi et al. (2014)   | Multicenter, double-blind, placebo-controlled RCT, 36 weeks | 1105 patients, early PD not requiring dopaminergic therapy                   | 1             | 62.2 (9.7)| 4.5 (4.6)       | Parkinson's fatigue scale                              | Significantly better in rasagline 1 mg vs placebo, −0.14 ± 0.05, P < 0.01                          | 0.03        |
|                         |                                                      |                                                                              |               |           |                  | Parkinson's fatigue scale                              | Significantly better in rasagline 2 mg vs placebo, −0.19 ± 0.05, P < 0.0001                    | 0.02        |
| Lim et al. (2015)       | Multicenter, double-blind, placebo-controlled RCT, 12 weeks | 30 patients, PD with moderate to severe fatigue (FSS ≥ 4)                    | 1             | 68.7 (7.4)| 3 (median)      | Modified fatigue impact Scale                          | Significantly better in rasagline 1 mg IC vs placebo (12 vs 8.5 points), P = 0.003              | 0.02        |
|                         |                                                      |                                                                              |               |           |                  | FSS                                                    | Significantly better in rasagline 1 mg IC vs placebo (13 vs 3 points), P = 0.027                | 0.03        |
|                         |                                                      |                                                                              |               |           |                  | Multidimensional fatigue inventory                      | Significantly better in rasagline 1 mg IC vs placebo (5 vs 1 points), P = 0.04                 | 0.04        |
|                         |                                                      |                                                                              |               |           |                  | Objective physical and mental fatigue testing          | No significant differences between IC rasagline 1 mg and placebo (0 vs 0.07 points), P = 0.26 | 0.26        |
| Santos García et al. (2021) | Multicenter, open-label, prospective study, 6 months | 50 patients, PD with high non-motor burden (NMSS ≥ 40)                        | 3             | 68.5 (9.1)| 6.4 (5.1)       | Visual analog fatigue scale: physical                  | No significant change with safinamide 100 mg: baseline 4.2 ± 2.8 and post 3.6 ± 2.6, P = 0.293 | 0.19        |
|                         |                                                      |                                                                              |               |           |                  | Visual analog fatigue scale: mental                    | No significant change with safinamide 100 mg: baseline 3.1 ± 2.7 and post 2.5 ± 2.8, P = 0.118 | 0.26        |
| De Micco et al. (2021)  | Single-center, open-label, prospective study, 6 months | 20 patients, advanced PD with off time > 1.5 h                               | 3             | 63.8 (10.2)| 6.0 (2.2)       | PD fatigue scale                                        | Significant improvement with safinamide 50 mg: baseline 2.85 ± 0.67 and post 2.20 ± 1.07, P = 0.02 | 0.97        |
| Bianchi et al. (2019)   | Single-center, open-label, retrospective study, 4.4 months | 20 patients, advanced PD with motor fluctuations                             | 4             | 75.0 (6.3)| 14.5 (6.8)      | Physical fatigue scales                                 | No significant change with safinamide 100 mg: baseline 39.4 ± 19.8 and post 39.4 ± 22.5, P = 1.00 | 0.00        |
|                         |                                                      |                                                                              |               |           |                  | Mental fatigue scales                                   | No significant change with safinamide 100 mg: baseline 20.0 ± 17.0 and post 20.0 ± 14.1, P = 1.00 | 0.00        |

Age and disease duration are presented as mean (SD) if available.

FSS Fatigue Severity Scale, IC incalculable, NMSS Non-Motor Symptoms Scale, PD Parkinson's Disease, RCT Randomized Controlled Trial.
| Studies                  | Study design                                      | Participants                              | Study quality | Age       | Disease duration | Instruments                        | Outcome                                                                 | Effect size |
|-------------------------|--------------------------------------------------|-------------------------------------------|---------------|-----------|-----------------|-------------------------------------|--------------------------------------------------------------------------|-------------|
| Biglan et al. (2006)    | Multicenter, double-blind, placebo-controlled RCT, 26 weeks | 404 patients, early PD not requiring dopaminergic therapy | 1             | 60.8 (10.8) | 1.0 (1.2)       | PDQUALIF: urinary function          | No significant difference between rasagiline 1 mg and placebo, 0.14, \( P = 0.39 \) | IC          |
|                         |                                                  |                                           |               |           |                 | PDQUALIF: urinary function          | No significant difference between rasagiline 2 mg and placebo, 0.00, \( P = 0.99 \) | IC          |
| Brusa et al. (2014)     | Single-center, open-label, prospective study, 2 months | 20 patients, early PD patients with HY stage \( \leq 2.5 \) | 3             | 67 (3.2)  | 5.0 (2.1)       | Urodynamics: first sensation (ml)   | Significant improvement with rasagiline 1 mg; baseline 118 ± 53 and post 158 ± 42, \( p < 0.001 \) | 0.75        |
|                         |                                                  |                                           |               |           |                 | Urodynamics: bladder capacity (ml)  | No significant change with rasagiline 1 mg; baseline 170 ± 86 and post 188 ± 73, NS | 0.21        |
|                         |                                                  |                                           |               |           |                 | Urodynamics: First sensation (ml)   | Significant improvement with rasagiline 1 mg; baseline 290 ± 98 and post 337 ± 115, \( p < 0.001 \) | 0.48        |
|                         |                                                  |                                           |               |           |                 | Urodynamics: residual urine (ml)    | Significant improvement with rasagiline 1 mg; baseline 47 ± 23 and post 25 ± 15, \( p < 0.001 \) | 0.96        |
|                         |                                                  |                                           |               |           |                 | International Prostate Symptoms Score questionnaire | Significant improvement with rasagiline 1 mg; baseline 12.3 ± 2.1 and post not shown, \( p < 0.0005 \) | IC          |
| Gómez-López et al. (2021) | Single-center, open-label, retrospective study, 3 months | 114 patients, PD with urinary symptoms | 4             | 72.6 (10.0) | 6.9 (6.1)       | SCOPA-AUT: urinary problems          | Significant improvement with safinamide 100 mg; baseline 9.1 ± 3.1 and post 6.6 ± 3.0, \( P < 0.0001 \) | 0.81        |
| Santos García et al. (2021) | Multicenter, open-label, prospective study, 6 months | 50 patients, PD with high non-motor burden (NMSS ≥ 40) | 3             | 68.5 (9.1) | 6.4 (5.1)       | NMSS: urinary symptoms              | Significant improvement with safinamide 100 mg; baseline 42.72 ± 30.41 and post 30.62 ± 23.94, \( p = 0.003 \) | 0.40        |
|                         |                                                  |                                           |               |           |                 | NMSS: cardiovascular                | No significant change with safinamide 100 mg; baseline 9.58 ± 2.46 and post 6.72 ± 11.94, \( p = 0.268 \) | 1.16        |
|                         |                                                  |                                           |               |           |                 | NMSS: gastrointestinal symptoms     | Significant improvement with safinamide 100 mg; baseline 19.61 ± 18.01 and post 13.13 ± 13.39, \( p = 0.01 \) | 0.36        |
|                         |                                                  |                                           |               |           |                 | NMSS: sexual dysfunction            | No significant change with safinamide 100 mg; baseline 28.25 ± 35.69 and post 25.28 ± 33.58, \( p = 0.784 \) | 0.08        |
| De Micco et al. (2021)  | Single-center, open-label, prospective study, 6 months | 20 patients, advanced PD with off time > 1.5 h | 3             | 63.8 (10.2) | 6.0 (2.2)       | SCOPA-AUT                           | Significant improvement with safinamide 50 mg; baseline 12.8 ± 5.69 and post 7.95 ± 4.40, \( P = 0.04 \) | 0.85        |

Age and disease duration are presented as mean (SD) if available.

HY stage Hoehn–Yahr stage, IC incalculable, NMSS Non-Motor Symptoms Scale, PD Parkinson’s Disease, RCT Randomized Controlled Trial, SCOPA SCales for Outcomes in Parkinson’s disease.
significant gain in volume variables after the 2-month administration of rasagiline 1 mg.63

In a small single-center, open-label, prospective study for advanced PD patients, safinamide 50 mg ameliorated overall autonomic symptoms based on the SCOPA-Autonomic at 6 months.64 The result for each domain was not reported. A large single-center, open-label, retrospective study showed that safinamide 100 mg reduced the SCOPA-Autonomic urinary problems subscore at 3 months.65 The benefits were driven mainly by alleviating incontinence, urgency, daily frequency, and nocturia. A multicenter, open-label, prospective study on PD patients with high non-motor burden reported the effects of safinamide 100 mg on autonomic symptoms using the NMSs subscore.66 Significant improvement was observed not in cardiovascular and sexual symptoms domains but in gastrointestinal and urinary symptoms domains. In summary, the effects of MAO-BIs on various autonomic symptoms remain unclear because of the scarcity of data.

Cognitive dysfunctions

A total of 29 studies tested the effects of MAO-BIs on cognitive functions using various assessment batteries (Supplementary Table 2). No studies for either early or advanced PD patients found significant benefits in global cognition based on the Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), or SCOPA-Cognition,20,22,28,38,44,45,52,64–66. Likewise, except for the following ones, most studies did not find beneficial effects of MAO-BIs using domain-specific cognition assessment batteries. Two multicenter, double-blind, placebo-controlled RCTs investigated the effects of rasagiline 1 mg on cognitive functions in PD patients with MCI.20,22 One RCT assessed the effects of rasagiline on global cognition and cognition-related instrumental activities of daily living based on the SCOPA-Cognition, MoCA, and Penn Daily Activities Questionnaire but failed to show significant benefits.22 The other RCT reported the effects of rasagiline on various cognitive domains: attention, executive functions, memory, visuospatial functions, and language.19 Although digit span backward and verbal fluency total scores showed significantly better outcomes in rasagiline compared with placebo, the additional analysis showed significant benefits of rasagiline only in the attentional domain. Two single-center open-label prospective studies from the same group investigated the effects of MAO-BIs in PD patients with wearing-off.67,68 The unique point of these studies was that cognitive assessments were performed 20 min before the second scheduled daily dose of levodopa. Consequently, executive functions improved with either rasagiline or safinamide.

Collectively, MAO-BIs are unlikely to improve global cognition but might have the potential to improve fluctuation-related cognitive dysfunctions.

Miscellaneous: apathy, olfactory dysfunctions, and ICD (Table 7)

In a small single-center, open-label, prospective study for advanced PD patients, significant improvement in apathy was observed 6 months after administrating safinamide 50 mg with a moderate effect size (0.58).69 Conversely, multicenter RCTs did not find significant benefits of rasagiline on apathy.17,21 Two double-blind, placebo-controlled RCTs tested the effects of rasagiline 1 mg on olfactory functions with non-significant benefits.28,69 A single-center, open-label, prospective study reported no significant impact of safinamide 50 mg on ICD based on the Questionnaire for ICD in PD rating scale (QUIP-RS).44

DISCUSSION

This systematic review summarized the QOL and NMS outcomes drawn from the available clinical studies of MAO-BIs. The impact of MAO-BIs on QOL was inconsistent across studies, and this was unlikely to be clinically meaningful. Overall, rasagiline and safinamide had more evidence supporting improvements in NMS when compared with selegiline. MAO-BIs potentially improve depression, sleep disturbances, and pain (particularly pain related to motor fluctuations). In contrast, MAO-BIs are unlikely to improve cognitive and olfactory dysfunctions. Given the paucity of evidence, the effects of MAO-BIs on fatigue, autonomic dysfunctions, apathy, and ICD remain unknown. As the recent review on NMS treatment by the Movement Disorders Society demonstrated, there still remain significant unmet needs in this field. Thus, the potential roles of MAO-BIs in the treatment of NMS will be discussed in the following paragraphs.

A subset of RCTs for advanced PD patients demonstrated statistically significant benefits of rasagiline or safinamide on QOL, with trivial to small effect sizes.53,57,59,41. The minimal clinically important difference (MCID) is the smallest difference in scores that are subjectively meaningful to patients. The MCID threshold for the PDQ-39 summary index was reported to be −4.72 (improvement) and +4.22 (worsening).70 No MAO-BI studies demonstrated improvement of the PDQ-39 summary index larger than this MCID threshold. Thus, the impact of MAO-BI on overall QOL may not be clinically meaningful.

Depression and anxiety are among the most common NMS in PD and are key determinants of QOL.71 Past studies showed beneficial effects of rasagiline 1 mg,59 safinamide 100 mg,53,41, and selegiline 10 mg1,2,4,52 for depressive symptoms, although the results were inconsistent across studies. Of note, most RCTs of MAO-BIs excluded patients with clinically-relevant depression or patients on concurrent antidepressants for safety reasons19,22,23. The positive findings presumably because sleep disturbances in PD cohorts did not observe serotonin syndrome despite the combined therapy.66,74,75. Although serotonin syndrome seems rare, the long-term safety of the combined therapy needs to be clarified because of the potentially fatal nature of the serotonin syndrome. Finally, three studies using either rasagiline or safinamide assessed anxiety, and all three had negative results19,22,23. The positive effects of MAO-BIs on anxiety, therefore, remain unproven.

Nocturnal sleep disturbances include difficulty initiating sleep, difficulty maintaining sleep, and early morning awakenings; another issue for PD patients is excessive daytime sleepiness.76 A small placebo-controlled RCT for PD patients with sleep disturbances demonstrated, using polysomnography, significantly better sleep maintenance with rasagiline 1 mg with statistically non-significant improvement in sleep efficacy by 9.3%.14 However, other studies of rasagiline, safinamide, or selegiline reported contrasting findings presumably because sleep disturbances in PD patients are multifactorial: e.g., nocturnal hypokinesia, nocturia, pain, muscle cramps, restless legs syndrome, RBD, or adverse...
| Studies                | Study design                                                                 | Participants                                                                 | Study quality | Age        | Disease duration | Instruments      | Outcome                                                                 | Effect size            |
|-----------------------|------------------------------------------------------------------------------|-------------------------------------------------------------------------------|---------------|------------|-----------------|------------------|-------------------------------------------------------------------------|------------------------|
| Barone et al. (2015)  | Multicenter, double-blind, placebo-controlled RCT, 12 weeks                 | 123 patients, PD with moderate depression (BDI ≥ 15)                         | 1             | 66.1 (8.5) | 4.3 (12.5)     | Apathy scale     | No significant difference between rasagiline 1 mg and placebo, statistics not shown | IC                     |
| Lim et al. (2015)     | Multicenter, double-blind, placebo-controlled RCT, 12 weeks                 | 30 patients, PD with moderate to severe fatigue (FSS ≥ 4)                     | 1             | 68.7 (7.4) | 3 (median)     | Marin Apathy inventory | No significant differences between rasagiline 1 mg and placebo (2 vs 0.5 points), P = 0.32 | IC                     |
| De Micco et al. (2021)| Single-center, open-label, prospective study, 6 months                      | 20 patients, advanced PD with off time > 1.5 h                               | 3             | 63.8 (10.2) | 6.0 (2.2)      | Apathy evaluation scale | Significant improvement with safinamide 50 mg; baseline 34.65 ± 7.41 and post 30.35 ± 7.80, P = 0.01 | 0.58                   |
| Hauser et al. (2014)  | Multicenter, double-blind, placebo-controlled RCT, 18 weeks                 | 321 patients, early PD not adequately controlled with dopamine agonists       | 1             | 62.6 (9.7) | 2.1 (2.1)      | Brief smell identification test | No significant differences between groups: IC rasagiline 1 mg −0.1 ± 2.2 vs. placebo −0.0 ± 1.9, P value not shown | IC                     |
| Haehner et al. (2013) | Single-center, double-blind, placebo-controlled RCT, 120 days               | 34 patients with PD                                                          | 1             | 59.1 (9.0)  | 2.9 (1.8)      | Sniffin’ Sticks test kit                              | No significant differences in threshold, IC discrimination, and identification were found between rasagiline 1 mg and placebo (all P > 0.05) | IC                     |
| De Micco et al. (2021)| Single-center, open-label, prospective study, 6 months                      | 20 patients, advanced PD with off time > 1.5 h                               | 3             | 63.8 (10.2) | 6.0 (2.2)      | Questionnaire for ICD in PD rating scale | 3-factorial ANOVA showed no significant main IC effects of drug (rasagiline vs placebo), session (baseline vs 120 days), or stimulant (all P > 0.05) | 0.20 (IC)               |

Age and disease duration are presented as mean (SD) if available. 

BDI Beck Depression Inventory, IC = incalculable, ICD = Impulse Control Disorders, PD = Parkinson’s Disease, RCT = Randomized Controlled Trial.
effects of medications. Therefore, treatment options should be tailored to the putative etiology of patients’ sleep disturbances. In the review on NMS treatment by the Movement Disorders Society, no treatment options were classified as “efficacious” for sleep disturbances, and rotigotine was the only parkinsonian medication that was classified as “likely efficacious.” A small placebo-controlled RCT assessed the impact of rotigotine on nocturnal sleep using polysomnography in advanced PD patients with sleep disturbances. Consequently, rotigotine administration led to significantly larger improvement in sleep efficacy as compared with placebo (8.0% vs. 0.5%, P < 0.001). In other studies, ropinirole and rotigotine have been shown to improve nocturnal sleep disturbances mainly by improving nocturnal motor symptoms. MAO-BIs potentially improve sleep disturbances through a similar mechanism; however, this remains speculative.

Multiple etiologies of pain in PD patients have been suggested: fluctuation-related, central, musculoskeletal, or neuropathic pain. However, in the review on NMS treatment by the Movement Disorders Society, no treatment options were labeled as “efficacious” or “likely efficacious” for pain. Rasagiline and safinamide have been beneficial for pain in advanced PD patients. Detailed investigations on pain, based on the King’s PD pain scale, have suggested that fluctuation-related pain responded best to safinamide 100 mg. Similarly, dopamine agonists such as ropinirole or apomorphine have been reported to improve fluctuation-related pain. Therefore, compared with patients with early PD, those with advanced PD might benefit more from long-acting dopaminergic agents (e.g., MAO-BIs or dopamine agonists) in pain relief.

Accumulating evidence suggests that MAO-BIs are unlikely to improve cognitive and olfactory dysfunctions. The limited available evidence did not allow us to determine the effects of MAO-BIs on fatigue, autonomic dysfunctions, apathy, and ICD. Note that selegiline suppressed cardiovascular autonomic responses and could result in orthostatic hypotension. Clinicians should be aware of this potential adverse effect, as it may increase the risk of falling. The pathophysiology of NMS remains uncertain but may involve both dopaminergic and non-dopaminergic dysfunctions. Further clinical and preclinical investigations will be required.

There are several possible mechanisms for MAO-BIs improving NMS. MAO-BIs may improve nocturnal sleep disturbances or pain by improving motor symptoms and motor fluctuations. Other NMS might improve through alleviation of non-motor fluctuations. Open-label studies have suggested that executive dysfunctions related to non-motor fluctuations improved with MAO-BIs. Future studies should investigate the effects of MAO-BIs specifically on NMS with or without fluctuations. The Non-Motor Fluctuation Assessment Questionnaire (NoMoFA) was recently validated and should be helpful to capture static and fluctuating NMS. In addition, the effects of MAO-BIs on MAO-A, which metabolizes catecholamines and serotonin, might account for part of the effects of MAO-BIs.

Another potential mechanism of action exclusively for safinamide is the modulation of overactive glutamatergic tone. Increasing evidence from preclinical and clinical studies supports the importance of glutamatergic transmission in motor and NMS of PD. Since safinamide 50 mg completely inhibits MAO-B activity, additional benefits with safinamide 100 mg might be due to non-dopaminergic mechanisms. Interestingly, post hoc analysis of a large placebo-controlled RCT reported that safinamide 100 mg might improve dyskinesia. This effect was analogous to the dyskinesia-suppressing effects of amantadine, an NMDA glutamate receptor antagonist. In addition, a large RCT demonstrated that safinamide 100 mg improved depressive symptoms and pain with greater effect sizes compared with safinamide given at 50 mg. The clinical relevance of dopaminergic and non-dopaminergic effects of safinamide needs further exploration.

In conclusion, MAO-BIs may potentially improve depression, sleep disturbances, and pain. In contrast, MAO-BI administration may not lead to clinically-meaningful improvement in QOL or cognitive and olfactory dysfunctions. The effects of MAO-BIs on other NMS remain unclear. If NMS is related to poor motor symptoms, or if NMS fluctuates along with blood levodopa concentration, the NMS may be more likely to improve with MAO-BIs. With the increasing number of treatment options available, it will be important to compare the efficacy of MAO-BIs with other options, such as dopamine agonists and COMT inhibitors. Especially, the effects of these agents on static and fluctuating NMS should be investigated in future studies. Non-dopaminergic effects of safinamide are also of great interest. Ideally, clinicians should be able to provide personalized medicine based on patients’ symptoms and genetic profiles. By drawing attention to the gaps in knowledge, we hope to encourage researchers to conduct high-quality research exploring the efficacy of MAO-BIs and other agents on NMS for persons living with PD.

METHODS

Search strategy

We conducted a systematic literature search from January 1990 to November 2021 using the PubMed, Scopus, and Cochrane Library databases according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. The search terms included Parkinson’s disease, Parkinson disease, selegiline, rasagiline, and safinamide. The search syntax is provided in Supplementary Material. Two investigators (TT and YS) independently screened all records for duplicates and then performed title/abstract screening and full-text assessments based on the eligibility criteria below. Disagreements were resolved through review of the primary study and expert discussion.

Eligibility criteria and calculation of effect sizes

The inclusion criteria for this systematic review were: (1) clinical studies on patients with Parkinson’s disease (n ≥ 10), (2) reporting the effects of selegiline, rasagiline, or safinamide on NMS or QOL using symptom-specific assessment batteries or objective measures, and (3) written in English. NMS included the following ones: depression, anxiety, sleep disturbances, fatigue, pain, autonomic dysfunctions, olfactory dysfunctions, cognitive dysfunctions, apathy, psychosis, impulse control disorders (ICD), and rapid eye movement sleep behavior disorders (RBD). Conference papers, review articles, and meta-analyses were excluded. “Real-world” studies were excluded because uncontrolled factors hindered the estimation of the impact of MAO-BIs.

We reviewed the reference lists of included publications to find additional publications.
By using mean values and standard deviations (SD) at baseline (meanT1 and SDT1) and mean values after intervention (meanT2), for the scales of interest, we calculated effect sizes according to the following formula: Effect size = (meanT2 − meanT1)/SDT1. When the publications lacked required values, effect sizes were shown as “incalculable.” Based on the values, effect sizes were considered trivial (< 0.2), small (0.20–0.49), moderate (0.50–0.79), or large (≥0.8) [106].

Quality assessments
We assessed the study quality of the included studies using a PD-specific assessment form designed by den Brok et al., which was based on the Newcastle–Ottawa quality assessment scale (Supplementary Table 1) [107].

DATA AVAILABILITY
All data relevant to the study are included in the article or uploaded as supplementary information.

Received: 5 January 2022; Accepted: 24 May 2022; Published online: 13 June 2022

REFERENCES
1. Alborgheetti, M. & Nicotelli, F. Different generations of type-B monoamine oxidase inhibitors in Parkinson's disease: From bench to bedside. Curr. Neuropharmacol. 17, 861–873 (2019).
2. Sciaccaluga, M. et al. Effects of safinamide on the glutamatergic striatal network in experimental Parkinson's disease. Neuropharmacology 170, 108024 (2020).
3. Morini, G. et al. Safenamide differentially modulates in vivo glutamate and GABA release in the rat hippocampus and basal ganglia. J. Pharmacol. Exp. Ther. 364, 198–206 (2018).
4. Langston, J. W. The Parkinson’s complex: Parkinsonism is just the tip of the iceberg. Ann. Neurol. 59, 591–596 (2006).
5. Seppi, K. et al. Update on treatments for nonmotor symptoms of Parkinson's disease—an evidence-based medicine review. Mov. Disord. 34, 180–198 (2019).
6. Táboas, V. et al. Effects of safinamide on the efficacy of rasagiline for the treatment of Parkinson's disease. Drug Des. Devel. Ther. 15, 2507–2517 (2021).
7. Giossi, R. et al. Overall efficacy and safety of safinamide in Parkinson's disease: A systematic review and a meta-analysis. Clin. Drug Invest. 41, 321–339 (2021).
8. Binde, C. D., Tetsu, J. F., Glasmeyer, J., Nativig, B. & Klemm, M. A multiple treatment comparison meta-analysis of monoamine oxidase type B inhibitors for Parkinson's disease. Br. J. Clin. Pharmacol. 84, 1917–1927 (2018).
9. Chang, Y., Wang, L. B., Liu, D., Lei, K. & Liu, S. Y. Efficacy of rasagiline for the treatment of Parkinson's disease: An updated meta-analysis. Ann. Med. 49, 421–434 (2017).
10. LeWitt, P. A. & Chaudhuri, K. R. Unmet needs in Parkinson's disease: Motor and non-motor. Parkinsonism Relat. Disord. 80, 57–512 (2020).
11. Skorvanek, M. et al. Relationship between the MDS-UPDRS and quality of life: A large multicenter study of 3206 patients. Parkinsonism Relat. Disord. 52, 83–89 (2021).
12. Prakash, K. M., Nadkarni, N. V., Lye, W. K., Yong, M. H. & Tan, E. K. The impact of non-motor symptoms on the quality of life of Parkinson’s disease patients: A longitudinal study. Eur. J. Neurol. 23, 854–860 (2016).
13. Schrempf, M. et al. Rasagiline improves polysomnographic sleep parameters in patients with Parkinson's disease: a double-blind, baseline-controlled trial. Eur. J. Neurol. 25, 672–679 (2018).
14. Müller, T., Hoffmann, J. A., Dimpfel, W. & Oehlwiele, C. Switch from selegiline to rasagiline is beneficial in patients with Parkinson’s disease. J. Neurotransm. 120, 761–765 (2013).
15. Gallazzi, M. et al. Selegiline reduces daytime sleepiness in patients with Parkinson's disease. Brain Behav. 11, e01880 (2021).
16. Barone, P. et al. A randomized clinical trial to evaluate the effects of rasagiline on depressive symptoms in non-demented Parkinson's disease patients. Eur. J. Neurol. 22, 1184–1191 (2015).
17. Peña, E. et al. Impact of SAmide on depressive symptoms in Parkinson's disease patients (SADness-PD study): A multicenter retrospective study. Brain Sci. 11, 232 (2021).
18. Hanagasi, H. A. et al. The effects of rasagiline on cognitive deficits in Parkinson's disease patients without dementia: A randomized, double-blind, placebo-controlled, multicenter study. Mov. Disord. 26, 1851–1858 (2011).
49. Dalymple-Alford, J. C., Jamieson, C. F. & Donaldson, I. M. Effects of selegiline (deprenyl) on cognition in early Parkinson’s disease. Clin. Neuropharmacol. 18, 348–359 (1995).
50. Hietanen, M. H. Selegiline and cognitive function in Parkinson’s disease. Acta Neurol. Scand. 84, 407–410 (1991).
51. Shouldice, I. An interim report of the effect of selegiline (L-deprenyl) on the progression of disability in early Parkinson’s disease. The Parkinson Study Group. Eur. Neurol. 32(Suppl 1), 46–53 (1992).
52. Pålhiagen, S. et al. Selegiline slows the progression of the symptoms of Parkinson disease. Neurology 66, 1200–1206 (2006).
53. Allan, H., Cogneau, J. & Neukirch, H. C. Selegiline in de novo parkinsonian patients: The French selegiline multicenter trial (FSMT). Acta Neurol. Scand. 136, 73–78 (1991).
54. Biglan, K. M. et al. Rasagiline improves quality of life in patients with early Parkinson’s disease. Mov. Disord. 21, 616–623 (2006).
55. Panisset, M. et al. Open-label study of sleep disturbances in patients with Parkinson’s disease treated with rasagiline. Can. J. Neurol. Sci. 43, 809–814 (2016).
56. Schettino, C. et al. Rasagline for sleep disorders in patients with Parkinson’s disease: A prospective observational study. Neuropsychiatr. Dis. Treat. 12, 2497–2502 (2016).
57. Liguori, C., Stefani, A., Ruf, J. & During, E. H. Sleep issues in Parkinson disease. Mov. Disord. Clin. Pract. 3, 178–187 (2016).
58. Waters, C. H. et al. Zydis selegiline reduces off time in Parkinson disease patients with motor fluctuations: results from the SAFINONMOTOR study. J. Parkinsons. Dis. 7, 348–356 (2017).
59. Tsuboi, Y. et al. Effects of safinamide adjunct therapy on pain in patients with Parkinson’s disease: Post hoc analysis of a Japanese phase 2/3 study. J. Neurol. Sci. 429, 118070 (2021).
60. Cattaneo, C., Kulisevsky, J., Tubazo, V. & Castellani, P. Long-term efficacy of safinamide on Parkinson’s disease chronic pain. Adv. Ther. 35, 515–522 (2018).
61. Santos García, D. et al. Pain improvement in Parkinson’s disease patients: The French selegiline multicenter trial (FSMT). Parkinsonism Relat. Disord. 20, 931–932 (2014).
62. Stocchi, F. et al. A randomized, double-blind, placebo-controlled trial of safinamide as add-on therapy in early Parkinson’s disease patients. Mov. Disord. 27, 106–112 (2012).
63. Schapira, A. H. et al. Long-term efficacy and safety of safinamide as add-on therapy in early Parkinson’s disease. Eur. J. Neurol. 21, 357–360 (2014).
64. Brusa, L. et al. Rasagiline effect on bladder disturbances in early mild Parkinson’s disease patients. Parkinsonism Relat. Disord. 20, 931–932 (2014).
65. Stocchi, F. et al. Randomized, double-blind, placebo-controlled trial of safinamide as add-on therapy in early Parkinson’s disease patients. Mov. Disord. 27, 106–112 (2012).
66. Zuzuárregui, J. R. P. & During, E. H. Sleep issues in Parkinson’s disease and their management. Neuropsychiatr. Neuropsych. 17, 1480–1494 (2020).
67. Pierantozzi, M. et al. Rotigotine may improve sleep architecture in Parkinson’s disease: A double-blind, randomized, placebo-controlled polysomnographic study. Sleep, Med. 21, 140–144 (2016).
68. Ray Chaudhuri, K. et al. Improvements in nocturnal symptoms with ropinirole prolonged release in patients with advanced Parkinson’s disease. Eur. J. Neurol. 19, 105–113 (2012).
69. Haehner, A. et al. Effects of rasagiline on olfactory function in patients with Parkinson disease: A double-blind, randomized, placebo-controlled trial using an axial inertial sensor. Parkinsonism Relat. Disord. 44, 124–128 (2017).
70. Buhmann, C., Kassubek, J. & Jost, W. H. Management of pain in Parkinson’s disease. J. Parkinsons. Dis. 10, 537–548 (2020).
71. Kassubek, J. et al. Rotigotine transdermal system and evaluation of pain in patients with Parkinson’s disease: A post hoc analysis of the RECOVERY study. BMC Neuro. 14, 42 (2014).
72. Factor, S. A., Brown, L. & Molho, E. S. Subcutaneous apomorphine injections as a treatment for intractable pain in Parkinson’s disease. Mov. Disord. 15, 167–169 (2000).
73. Haapaniemi, T. H. et al. Levodopa, bromocriptine, and selegiline modify cardiovascular responses in Parkinson’s disease. J. Neurol. 247, 868–874 (2000).
74. Turkka, J., Suominen, K., Tolonen, U., Sotaniemi, K. & Myllylä, V. V. Selegiline diminishes cardiovascular autonomic responses in Parkinson’s disease. Neurology 48, 662–667 (1997).
75. Strijer, R., Klein, C., Treves, T. A. & Rabey, J. M. The effects of acute loading with levodopa and levodopa with selegiline on blood pressure and plasma noradrenergic levels in chronic Parkinson’s disease patients. Acta Neurol. Scand. 111, 89–94 (2005).
76. Churchyard, A., Mathias, C. J. & Lees, A. J. Selegiline-induced postural hypotension in Parkinson’s disease: A longitudinal study on the effects of drug withdrawal. Mov. Disord. 14, 246–251 (1999).
77. Pursiainen, V., Korpelaenen, T. J., Haapaniemi, H. T., Sotaniemi, A. K. & Myllylä, V. V. Selegiline and blood pressure in patients with Parkinson’s disease. Acta Neurol. Scand. 115, 104–108 (2007).
78. Heitertachi, E., Lord, S. R., Meyerkort, P., McCloskey, I. & Fitzpatrick, R. Blood pressure changes on upright tilting predict falls in older people. Age Aging 31, 181–186 (2002).
79. Bhidayasiri, R. & Trenkwalder, C. Getting a good night sleep? The importance of recognizing and treating nocturnal hypokinesia in Parkinson’s disease. Parkinsonism Relat. Disord. 50, 10–18 (2018).
80. Martinez-Fernandez, R., Schmitt, E., Martinez-Martin, P. & Krack, P. The hidden sister of motor fluctuations in Parkinson’s disease: A review on nonmotor fluctuations. Mov. Disord. 31, 1080–1094 (2016).
81. Klein, G. et al. Non-motor fluctuations in Parkinson’s disease: Validation of the non-motor fluctuation assessment questionnaire. Mov. Disord. 36, 1392–1400 (2021).
82. Pagonabarraga, J., Tinaazzi, M., Caccia, C. & Jost, W. H. The role of glutamatergic neurotransmission in the motor and non-motor symptoms in Parkinson’s disease: Clinical cases and a review of the literature. J. Clin. Neurosci. 90, 178–183 (2021).
83. Cattaneo, C., Ferla, R., La Bonizzoni, E. & Sardina, M. Long-term effects of safinamide on dyskinesia in mid-to late-stage Parkinson’s disease: A post-hoc Analysis. J. Parkinsons. Dis. 5, 475–481 (2015).
84. Oey-Magne, F. et al. Withdrawing amantadine in dyskinetic patients with Parkinson disease: The AMANDYSK trial. Neurology 82, 300–307 (2014).
85. Martinez-Martin, P. et al. Health-related quality-of-life scales in Parkinson’s disease: Critique and recommendations. Mov. Disord. 26, 2371–2380 (2011).
86. Schrag, A. et al. Depression rating scales in Parkinson’s disease: Critique and recommendations. Mov. Disord. 22, 1077–1092 (2007).
87. Leentjens, A. F. et al. Anxiety rating scales in Parkinson’s disease: Critique and recommendations. Mov. Disord. 23, 2015–2025 (2008).
88. Högl, B. et al. Scales to assess sleep impairment in Parkinson’s disease: Critique and recommendations. Mov. Disord. 25, 2704–2716 (2010).
89. Perez-Lloret, S. et al. Rating scales for pain in Parkinson’s disease: Critique and recommendations. Mov. Disord. Clin. Pract. 3, 527–537 (2016).
90. Skovranek, M. et al. Global scales for cognitive screening in Parkinson’s disease: Critique and recommendations. Mov. Disord. 33, 208–218 (2018).
91. Soraya, G. V. et al. Polymorphisms of the dopamine metabolic and signaling pathways are associated with susceptibility to motor levodopa-induced complications (MLIC) in Parkinson’s disease: A systematic review and meta-analysis. Neurol Sci. https://doi.org/10.1007/s10072-021-05829-4 (2022).
92. Madzarac, Z. et al. The associations between COMT and MAO-B genetic variants with depressive symptoms in patients with schizophrenia. Curr. Issues Mol. Biol. 43, 618–636 (2021).
93. Yen, J. Y. et al. Roles of hostility and depression in the association between the MAOA gene polymorphism and internet gaming disorder. Int. J. Env. Res. Public Health 18, 6910 (2021).
94. Horvát, K. et al. Minimal clinically important difference on Parkinson’s disease sleep scale 2nd version. Parkinsons Dis. 2015, 970534 (2015).
106. Middel, B. & van Sonderen, E. Statistical significant change versus relevant or important change in (quasi) experimental design: Some conceptual and methodological problems in estimating magnitude of intervention-related change in health services research. *Int. J. Integr. Care* 2, e15 (2002).

107. den Brok, M. et al. Apathy in Parkinson’s disease: A systematic review and meta-analysis. *Mov. Disord.* 30, 759–769 (2015).

108. Cattaneo, C., Barone, P., Bonizzoni, E. & Sardina, M. Effects of safinamide on pain in fluctuating Parkinson’s disease patients: A post hoc analysis. *J. Parkinsons. Dis.* 7, 95–101 (2017).

ACKNOWLEDGEMENTS
This study was supported by AMED under Grant Number JP21km0908001 and Nagoya University Research Fund. We would like to acknowledge the Parkinson’s Foundation Center of Excellence at the University of Florida Norman Fixel Institute for Neurological Diseases.

AUTHOR CONTRIBUTIONS
T.T. conceived and designed the study. T.T. and Y.S. performed the systematic search and constructed the tables. T.T. wrote the first draft. Inclusions and exclusions of the identified studies from the current systematic review were discussed among T.T., Y.S., A.R.Z., and M.S.O. K.H., M.H., M.S., K.H., A.R.Z., M.S.O., and M.K. reviewed and revised the draft. All authors hold accountability for all aspects of the work.

COMPETING INTERESTS
The authors declare no competing interests.

ADDITIONAL INFORMATION
Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41531-022-00339-2.

Correspondence and requests for materials should be addressed to Masahisa Katsuno.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2022