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Comparative Safety of Istradefylline Among Parkinson Disease Adjunctive Therapies: A Systematic Review and Meta-Analysis of Randomized Controlled Studies

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Introduction: Adjunctive therapies to treat OFF episodes resulting from long-term levodopa treatment in Parkinson disease (PD) are hampered by safety and tolerability issues. Istradefylline offers an alternative mechanism (adenosine A_{2A} receptor antagonist) and therefore potentially improved tolerability.

Methods: A systematic review of PD adjuncts published in 2011 was updated to include randomized controlled trials published from January 1, 2010–April 15, 2019. Pairwise meta-analyses were updated, and Bucher indirect comparisons were used to generate estimates of relative safety, presented as odds ratio (OR) and 95% confidence interval (CI) for comparators versus istradefylline.

Results: Fifty-seven randomized controlled trials involving 11,517 patients were included in the meta-analysis. Relative to istradefylline, dopamine agonists and catechol-O-methyl transferase (COMT) inhibitors had statistically significant higher odds of dyskinesia and somnolence. Monoamine oxidase-B inhibitors had significantly higher odds of hypotension. Amantadine extended-release (ER) had statistically significant higher odds of hallucination, orthostatic hypotension, insomnia, and withdrawals due to adverse events. All interventions combined had significantly higher odds of dyskinesia versus istradefylline 20 mg and somnolence versus istradefylline 40 mg. Considering overall incidence of adverse events, COMT inhibitors and amantadine ER had statistically significant higher odds versus both istradefylline doses (COMT versus istradefylline 40 mg, OR: 1.33; 95% CI: 1.03, 1.75; versus istradefylline 20 mg, OR: 1.32; 95% CI: 1.01, 1.72; amantadine ER versus istradefylline 40 mg, OR: 3.45; 95% CI: 1.85, 6.25; versus istradefylline 20 mg, OR: 3.33; 95% CI: 1.82, 6.25).

Conclusion: Istradefylline was associated with a generally favorable safety profile relative to other adjunct medications in this study.

Key Words: Parkinson disease, comparative safety, adjunctive therapies, istradefylline

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Parkinson disease (PD) is a progressive neurodegenerative disorder characterized by a variety of motor and nonmotor symptoms stemming from loss of dopaminergic neurons.[1] The mainstay of treatment is dopaminergic therapy with levodopa/decarboxylase inhibitor (carbidopa/benserazide) to replace lost dopamine[2]; however, long-term treatment can lead to motor complications including "wearing-off" or OFF episodes and dyskinesia.[1] It is estimated that after five years, as many as 50% of patients with PD will experience OFF episodes, with an incidence of motor fluctuations of 100% at 10 years.[3] Several adjunctive therapies across multiple classes are approved to treat OFF episodes and motor complications, including dopamine agonists (DAs), catechol-*O*-methyltransferase (COMT) inhibitors, monoamine oxidase-B (MAO-B) inhibitors, and amantadine. However, the dopaminergic treatment-emergent adverse effects of these interventions limit their clinical utility as patients and clinicians attempt to achieve both effective symptom control as well as safety and tolerability.[1,2] Treatment with DAs can precipitate a wide spectrum of side effects, including hallucinations, dyskinesia, somnolence, orthostatic hypotension, headaches, and nausea.[4] Similar adverse events (AEs) are observed with MAO-B inhibitors; in particular, dyskinesia and orthostatic hypotension are more common when MAO-B inhibitors are used in combination with levodopa in advanced PD.[5] COMT inhibitors act to prevent peripheral degradation of levodopa and therefore are burdened with a similar dopaminergic side effect profile.[6] Amantadine is associated with a number of side effects; most notably, in clinical trials, 21% of participants treated with amantadine extended-release (ER) experienced visual and auditory hallucinations.[7]

Istradefylline is a first-in-class adenosine A_{2A} receptor antagonist approved in the United States and Japan as an adjunct to levodopa for the treatment of OFF episodes or "wearing-off" phenomenon in adult patients with PD.[8] Istradefylline acts through a novel, nondopaminergic pathway.[1,8]

Several placebo-controlled trials have evaluated the safety and tolerability of istradefylline in patients with PD[9–15]; however, there are no comparative data on the safety of istradefylline versus other adjunctive treatments. A systematic literature review (SLR) and meta-analysis published in 2011 compared the safety of several PD adjunctive treatments[16]; however, there is a need for an update to this SLR to include more recent studies and new treatments that have been launched since 2010, such as istradefylline, amantadine, safinamide, opicapone, and tozadenant. The objective of this study was to assess the comparative safety of istradefylline relative to other PD adjunctive therapies.

MATERIALS AND METHODS

SLR Update Search Strategy

A SLR update was conducted (in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] checklist) to identify randomized controlled trials

(RCTs) evaluating adjunctive therapies in patients with PD. The search strategy was based on the Stowe et al (2011) SLR and was amended to include additional terms for amantadine, safinamide, opicapone, tozadenant, and istradefylline.

The SLR was conducted on April 15, 2019 and searched the electronic databases of Medline, Medline Epub Ahead of Print (in-process and other nonindexed citations), and Medline Daily. Search terms are listed in Supplementary Table 1, http://links.lww.com/CNP/A66.

Study Selection

Citations were screened based on the title and abstract first, and then based on the full text, by two analysts independently, with any discrepancies resolved by consensus. Eligible studies for inclusion in the update were RCTs published since 2010, including patients with PD of any age who were receiving levodopa (any duration) and had developed motor complications. Interventions included COMT inhibitors, MAO-B inhibitors, DAs, istradefylline, and amantadine. For new interventions (amantadine, safinamide, opicapone, tozadenant, and istradefylline), RCTs published before 2010 were also included. Studies must have reported at least one of the following safety outcomes: hallucination, dyskinesia, hypotension, orthostatic hypotension, somnolence, insomnia, overall incidence of AEs, and/or withdrawals due to AEs.

Data Extraction

Relevant outcomes data were extracted into a Microsoft Excel based extraction table by an analyst and independently checked by a second analyst.

Meta-Analysis

Outcomes of interest for the meta-analysis were dichotomous outcomes that reported the proportion of patients experiencing an AE outcome. Where trials compared different doses of the same intervention, only the licensed dose or doses of the drug were included. Where more than one intervention was compared, these trials were included more than once in the pairwise meta-analysis. Pairwise meta-analyses were conducted using the inverse variance (Peto) method of Review Manager (Version 5.3) to calculate summary odds ratios (ORs) and 95% confidence intervals (CIs). All pairwise meta-analyses were conducted using the fixed effect model as per Stowe et al (2011).[16] The Review Manager file from the Stowe et al (2011) SLR and meta-analysis was obtained to include in the analysis.

Indirect comparisons were calculated in Microsoft Excel using the Bucher method,[17] in which randomization and the transitivity of treatment effects are preserved. All indirect comparisons were based on fixed effect pairwise meta-analysis estimates.

Heterogeneity

Data on the study design, eligibility criteria, and baseline characteristics from the included RCTs were extracted for heterogeneity assessment. Heterogeneity was assessed to understand the potential impact on conclusions from statistical modeling and identify any effect modifiers that may not have been considered.

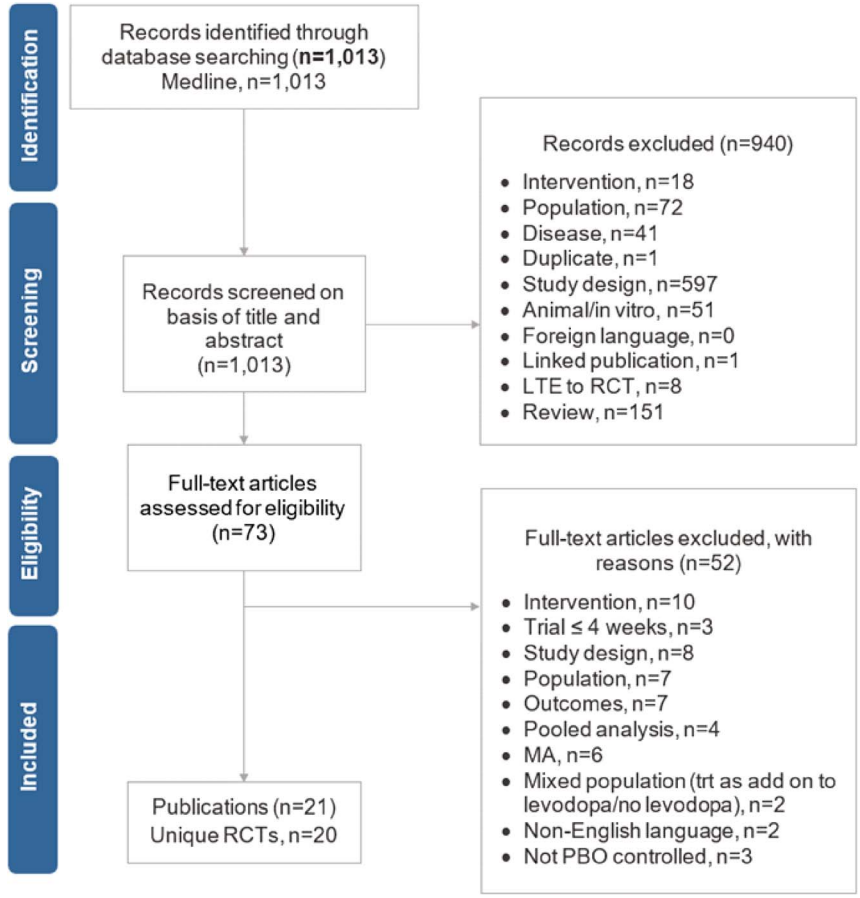

FIGURE 1. PRISMA flow diagram. Abbreviations: LTE, long-term extension; MA, meta-analysis; PBO, placebo; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial.

RESULTS

SLR Update

The search identified a total of 1,013 articles for title and abstract screening. Of these, 940 articles were excluded, and 73 were progressed to full publication review. Upon full publication review, a further 52 articles were excluded, and 21 articles were deemed eligible for inclusion.[15,18–37] The most common reasons for exclusion were intervention, study design, population, and outcomes; full details are presented in Figure 1. The 21 eligible articles reported on 20 unique RCTs and are summarized in Supplementary Tables 2–4, http://links.lww.com/CNP/A66.

The trials identified in the SLR update reported evidence for interventions already included in the Stowe et al (2011) meta-analysis (rasagiline [n = 3], rotigotine [n = 4], ropinirole [n = 3], pramipexole [n = 1]) in addition to safinamide (n = 2), opicapone (n = 2), amantadine ER (n = 3), and istradefylline (n = 3). The search strategy included all amantadine formulations (including delayed release/extended release [DR/ER], extended release [ER], and immediate release [IR]); however, only trials for amantadine ER were identified. Although three publications were identified relating to istradefylline, data from eight RCTs investigating istradefylline were extracted from Clinical Study Reports and used in the meta-analysis. A summary of the studies identified in the SLR update and the eight istradefylline trials is provided in Supplementary Tables 2–7, http://links.lww.com/CNP/A66.

Pairwise Meta-Analysis and Indirect Comparison

Of the 21 publications identified for inclusion in the SLR update, 18 publications reporting on 17 unique RCTs were extracted for inclusion in the meta-analysis.[18–26,29–37] Articles reporting on istradefylline (n = 3) were not considered further in the meta-analysis as data for eight RCTs investigating istradefylline were taken from the Clinical Study Reports. When combined with the studies from Stowe et al (2011), 57 RCTs involving 11,517 patients were included in the pairwise meta-analysis and indirect comparisons.

Forest plots for the pairwise meta-analyses are presented in Supplementary Figures 1–16, http://links.lww.com/CNP/A66. A summary of the indirect comparison results is shown in Table 1, and the results for each outcome are described in the following sections.

Dyskinesia

The indirect comparisons demonstrated that all comparators except for MAO-B inhibitors were associated with numerically

TABLE 1. Summary of Indirect Comparison Results for Other PD Adjunctive Versus 40 mg and 20 mg Istradefylline

	Comparator Versus Istradefylline, OR (95% CI)				
Istradefylline Dose	**DAs**	**COMT Inhibitors**	**MAO-B Inhibitors**	**Amantadine ER**	**All Interventions**
Dyskinesia					
40 mg	**1.30 (1.01, 1.69)**	1.23 (0.93, 1.61)	0.75 (0.53, 1.05)	NA*	1.18 (0.93, 1.49)
20 mg	**1.61 (1.16, 2.22)**	**1.52 (1.09, 2.13)**	0.93 (0.62, 1.39)	NA*	**1.45 (1.06, 2.00)**
Hallucination					
40 mg	1.61 (0.79, 3.23)	0.81 (0.38, 1.75)	1.08 (0.41, 2.78)	**3.57 (1.30, 10.00)**	1.39 (0.70, 2.78)
20 mg	2.13 (0.97, 4.76)	1.09 (0.46, 2.56)	1.43 (0.51, 4.00)	**4.76 (1.64, 14.29)**	1.85 (0.85, 4.00)
Hypotension					
40 mg	2.94 (0.87, 10.00)	2.63 (0.63, 11.11)	**8.33 (1.67, 50.00)**	NA†	3.03 (0.90, 10.0)
20 mg	1.75 (0.41, 7.69)	1.56 (0.31, 8.33)	5.00 (0.83, 33.33)	NA†	1.82 (0.43, 7.69)
Insomnia					
40 mg	0.91 (0.53, 1.56)	1.28 (0.71, 2.33)	1.14 (0.52, 2.50)	5.88 (0.77, 50.0)	1.06 (0.65, 1.75)
20 mg	1.27 (0.71, 2.27)	1.79 (0.96, 3.33)	1.59 (0.70, 3.57)	**8.33 (1.06, 50.00)**	1.49 (0.86, 2.56)
Orthostatic hypotension					
40 mg	2.13 (0.72, 6.25)	2.08 (0.55, 7.69)	4.17 (0.71, 25)	**12.50 (1.33, 100.00)**	2.22 (0.74, 6.67)
20 mg	0.61 (0.27, 1.41)	0.59 (0.19, 1.82)	1.19 (0.23, 6.25)	3.7 (0.43, 33.33)	0.63 (0.27, 1.45)
Somnolence					
40 mg	**2.50 (1.28, 5.00)**	**3.33 (1.49, 7.69)**	2.17 (0.85, 5.56)	NA‡	**2.63 (1.35, 5.00)**
20 mg	1.52 (0.83, 2.78)	2.04 (0.96, 4.35)	1.32 (0.54, 3.23)	NA‡	1.56 (0.88, 2.78)
Overall incidence of AEs					
40 mg	1.22 (0.96, 1.56)	**1.33 (1.03, 1.75)**	0.99 (0.76, 1.30)	**3.45 (1.85, 6.25)**	1.22 (0.98, 1.54)
20 mg	1.20 (0.93, 1.56)	**1.32 (1.01, 1.72)**	0.98 (0.74, 1.28)	**3.33 (1.82, 6.25)**	1.22 (0.96, 1.54)
Withdrawals due to AEs					
40 mg	0.70 (0.45, 1.09)	0.98 (0.62, 1.56)	0.82 (0.47, 1.43)	2.33 (0.98, 5.56)	0.84 (0.55, 1.28)
20 mg	0.85 (0.53, 1.37)	1.19 (0.74, 1.96)	1.00 (0.56, 1.79)	**2.86 (1.18, 6.67)**	1.02 (0.65, 1.61)

Dark gray shading indicates indirect comparison results statistically significantly favor istradefylline. White cells indicate the indirect comparison results are not statistically significant.

*Dyskinesia was not reported across trials investigating amantadine ER.

†Hypotension was not reported across trials investigating amantadine ER.

‡Somnolence was not reported across trials investigating amantadine ER.

AE, adverse event; CI, confidence interval; COMT, catechol-O-methyl transferase; DA, dopamine agonist; ER, extended release; MAO-B, monoamine oxidase type B; NA, not applicable; OR, odds ratio.

higher odds of dyskinesia compared with istradefylline (Table 1). This difference was statistically significant for DAs versus 40 mg and 20 mg istradefylline (versus 40 mg istradefylline, OR: 1.30; 95% CI: 1.01, 1.69; versus 20 mg istradefylline, OR: 1.61; 95% CI: 1.16, 2.22), COMT inhibitors versus 20 mg istradefylline (OR: 1.52; 95% CI: 1.09, 2.13), and for all interventions combined versus 20 mg istradefylline (OR: 1.45; 95% CI: 1.06, 2.00).

Hallucination

The indirect comparisons demonstrated that DAs, MAO-B inhibitors, and amantadine ER were associated with numerically higher odds of hallucination versus istradefylline (Table 1), but this was only statistically significant for amantadine ER (amantadine ER versus 40 mg istradefylline, OR: 3.57; 95% CI: 1.30, 10.00; amantadine ER versus 20 mg istradefylline, OR: 4.76; 95% CI: 1.64, 14.29).

Hypotension

The indirect comparisons demonstrated that DAs, COMT inhibitors, and MAO-B inhibitors were associated with numerically higher odds of hypotension compared with istradefylline (Table 1); however, this was only statistically significant for MAO-B inhibitors versus istradefylline 40 mg (OR: 8.33; 95% CI: 1.67, 50.00).

Insomnia

The indirect comparisons demonstrated that all comparators except for DAs were associated with numerically higher odds of insomnia compared with istradefylline (Table 1). However, results were only statistically significant for amantadine ER versus istradefylline 20 mg (OR: 8.33; 95% CI: 1.06, 50.00).

Orthostatic Hypotension

The indirect comparisons demonstrated that all comparators were associated with numerically higher odds of orthostatic hypotension compared with istradefylline 40 mg (Table 1), but this was only statistically significant for amantadine ER (OR: 12.50; 95% CI: 1.33, 100.00). When compared with 20 mg istradefylline, MAO-B inhibitors and amantadine ER were associated with higher odds of orthostatic hypotension, though these effects were not statistically significant.

Somnolence

The indirect comparisons demonstrated that when grouped, all interventions were associated with statistically significant higher odds of somnolence compared with istradefylline 40 mg (OR: 2.63; 95% CI: 1.35, 5.00). Individually, DAs and COMT inhibitors were also associated with statistically significant higher odds of somnolence versus istradefylline 40 mg (OR: 2.50; 95% CI: 1.28, 5.00 and OR: 3.33; 95% CI: 1.49, 7.69, for DAs and COMT inhibitors, respectively). MAO-B inhibitors were associated with numerically higher odds of somnolence versus istradefylline 40 mg (Table 1). All comparators were associated with numerically higher odds of somnolence versus istradefylline 20 mg; however, these effects were not statistically significant (Table 1).

Overall Incidence of AEs

The indirect comparisons demonstrated that all comparators except for MAO-B inhibitors were associated with numerically higher odds of overall incidence of AEs compared with istradefylline (Table 1). These results were statistically significant for COMT inhibitors (versus istradefylline 40 mg, OR: 1.33; 95% CI: 1.03, 1.75; versus istradefylline 20 mg, OR: 1.32; 95% CI: 1.01, 1.72) and amantadine ER (versus istradefylline 40 mg, OR: 3.45; 95% CI: 1.85, 6.25; versus istradefylline 20 mg, OR: 3.33; 95% CI: 1.82, 6.25) at both istradefylline doses.

Withdrawals Due to AEs

Amantadine ER was associated with higher odds of withdrawal due to AEs compared with istradefylline, though this was only statistically significant for the 20 mg dose (Table 1; OR: 2.86; 95% CI: 1.18, 6.67).

Heterogeneity

It was evident across the pairwise meta-analyses for both istradefylline and comparators that almost all of the analyses included trial level estimates with opposite treatment effects (ie, the direction of the treatment effect was not consistent across trials of the same class of interventions). Thus, heterogenous data sets were used to conduct the pairwise meta-analysis and indirect comparisons. The heterogeneity assessment identified differences in follow-up time, differences in concomitant treatments, differences in levodopa dose, and differences in disease duration. Although the trials were generally comparable for most baseline characteristics investigated, it is not clear whether any of the observed differences between trials were important and likely to contribute to differences in relative treatment effects.

DISCUSSION

Across the analyses, the majority of indirect comparisons of the safety outcomes evaluated favored istradefylline, and where results were statistically significant, all favored istradefylline. All comparators except for MAO-B inhibitors were associated with numerically higher odds of overall incidence of AEs compared with istradefylline.

The results of this study are in line with previous reports that although adjuvant therapy with DAs, COMT inhibitors, MAO-B inhibitors, or amantadine is effective at reducing OFF time in patients with PD, this is often at the expense of increased dyskinesia, hypotension, hallucinations, and somnolence.[16,38] Dyskinesia is a known complication of DAs, as highlighted in guidelines from the American Academy of Neurology (AAN),[2] and is suggested to be one of the most debilitating complications in patients with PD.[39] In this study, at both 40 mg and 20 mg, istradefylline demonstrated significantly lower odds of dyskinesia versus DAs.

DAs are also associated with a greater risk of excessive daytime somnolence and sleep attacks in patients with PD.[2] Daytime sleepiness has been identified as one of the most influential nonmotor symptoms related to health-related quality of life in patients with PD.[40] It has also been linked to more severe nonmotor symptoms and cognitive impairment.[40] Previous studies have found improvements in daytime sleepiness in patients with PD treated with istradefylline.[41,42] In addition, in an open-label study, istradefylline was found to have no negative impact on sleep over the 3-month study period.[41] In this indirect comparison study, istradefylline demonstrated significantly lower odds of somnolence compared with DAs, further highlighting the potential of istradefylline in managing somnolence in patients with PD.

Orthostatic hypotension is common in patients with PD, with reports estimating a prevalence of orthostatic hypotension in PD as high as 30%.[43] Some reports suggest a higher prevalence of orthostatic hypotension in patients treated with MAO-B inhibitors.[44] Orthostatic hypotension may be associated with lightheadedness, loss of consciousness, shortness of breath, unexplained falls, cognitive impairment, fatigue, and blurred vision.[44,45] This study suggests that istradefylline is associated with a lower risk of hypotension compared with MAO-B inhibitors.

Visual hallucinations are also common in PD, affecting as many as 75% of patients over the disease course, with a significant impact on quality of life.[46] Case reports highlight further exacerbation of hallucinations with dopaminergic treatments, including amantadine,[47] which was associated with hallucinations in over 20% of patients in clinical trials.[7] This meta-analysis determined that istradefylline, both 20 mg and 40 mg, is associated with lower odds of hallucinations compared with amantadine. To this end, a recent observational study found no significant difference in hallucinations between istradefylline-treated patients and those who did not receive istradefylline.[48]

The results of this study therefore demonstrate multiple potential benefits to treatment with istradefylline, with lower odds of many AEs commonly associated with other PD adjunctive therapies. Further to this, previous studies have highlighted the potential for adjunctive istradefylline treatment to reduce cumulative levodopa use in PD patients through slowing levodopa dose escalation.[49,50] Initiating istradefylline before other adjunctive therapies therefore has the potential to reduce the occurrence or severity of levodopa-induced complications as compared with other medications.[50] Historically, DAs, amantadine derivatives, and MAO-B inhibitors were used as monotherapy prior to initiation of levodopa. However, the AAN guidelines now favor starting levodopa/carbidopa monotherapy as the first-line approach, with the addition of adjunctive medications as OFF episodes and/or tolerability issues arise. This change in treatment practice may impact not only the selection of adjunct treatments but importantly, in what sequence they should be used. It is reasonable to consider the potential of istradefylline to extend the therapeutic window for patients over the natural course of disease due to its favorable safety profile. Given its profile, istradefylline may establish itself as a pillar of treatment in combination with carbidopa/levodopa without having to be withdrawn or reduced, as is the case for alternative therapies. Alongside the potential to reduce levodopa dose escalation, this supports an argument for use of istradefylline early in the course of treatment as the first adjunctive to levodopa/carbidopa treatment.

Importantly, there are several limitations to consider with this analysis. As highlighted, a degree of heterogeneity was identified among the studies included in this analysis, with varying trial lengths, levodopa dose, and duration and severity of PD in participants. Heterogeneity may limit the validity of the indirect comparisons between studies. Further to this, some outcomes were associated with low event numbers, resulting in estimates of relevant treatment effects with large levels of uncertainty.

There may also be challenges with the grouping of drugs by class in this analysis, due to potential differences in safety and tolerability profiles within a class. However, summarizing results in such a way facilitates comparison between interventions targeting the dopaminergic pathway versus other mechanisms.

Notably, the methodology to the pairwise analysis with indirect treatment comparisons included only placebo-controlled trials, and thereby excluded other data that could impact the estimate of the relative treatment effect.

Finally, this SLR update was conducted in April 2019, and therefore does not include all studies to date (2024). There have also been new drug approvals since this SLR was conducted. Work is underway to conduct a further update to this SLR and include the most recently launched PD adjunctive therapies, which is planned for publication separately. This work will include more rigorous methodology through network meta-analysis to address some of the limitations around heterogeneity and interpretability. Additional clinically meaningful outcomes such as impulse control disorders, falls, and nausea are also being explored in future work.

CONCLUSIONS

Istradefylline was associated with a generally favorable safety profile relative to other adjunct medications in this study. Istradefylline has a unique mechanism of action among PD adjunctive therapies, which may contribute to its notable safety profile. Based on this safety profile, istradefylline has the potential to meet the unmet needs of patients with PD, with lower odds of commonly experienced AEs.

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REFERENCES

1. Cummins L, Cates ME. Istradefylline: a novel agent in the treatment of "off" episodes associated with levodopa/carbidopa use in Parkinson disease. *Mental Health Clinician* 2022;12(1):32–36.
2. Pringsheim T, Day GS, Smith DB, et al. Dopaminergic therapy for motor symptoms in early Parkinson disease practice guideline summary: a report of the AAN guideline subcommittee. *Neurology* 2021;97(20):942–957.
3. Kim HJ, Mason S, Foltynie T, et al. Motor complications in Parkinson's disease: 13-year follow-up of the CamPaIGN cohort. *Movement Disord* 2020;35(1):185–190.
4. Borovac JA. Side effects of a dopamine agonist therapy for Parkinson's disease: a mini-review of clinical pharmacology. *Yale J Biol Med* 2016; 89(1):37–47.
5. Robottom BJ. Efficacy, safety, and patient preference of monoamine oxidase B inhibitors in the treatment of Parkinson's disease. *Patient Prefer Adherence* 2011;5:57–64.
6. Rivest J, Barclay CL, Suchowersky O. COMT inhibitors in Parkinson's disease. *Can J Neurolo Sci* 1999;26(Suppl 2):S34–S38.
7. Elmer LW, Juncos JL, Singer C, et al. Pooled analyses of phase III studies of ADS-5102 (amantadine) extended-release capsules for dyskinesia in Parkinson's disease. *CNS Drugs* 2018;32(4):387–398.
8. Chen JF, Cunha RA. The belated US FDA approval of the adenosine a(2A) receptor antagonist istradefylline for treatment of Parkinson's disease. *Purinergic Signal* 2020;16(2):167–174.
9. LeWitt PA, Guttman M, Tetrud JW, et al. Adenosine A2A receptor antagonist istradefylline (KW-6002) reduces "off" time in Parkinson's disease: a double-blind, randomized, multicenter clinical trial (6002-US-005). *Ann Neurol* 2008;63(3):295–302.
10. Hauser RA, Shulman LM, Trugman JM, et al. Study of istradefylline in patients with Parkinson's disease on levodopa with motor fluctuations. *Movement Disord* 2008;23(15):2177–2185.
11. Mizuno Y, Hasegawa K, Kondo T, et al. Clinical efficacy of istradefylline (KW-6002) in Parkinson's disease: a randomized, controlled study. *Movement Disord* 2010;25(10):1437–1443.
12. Mizuno Y, Kondo T. Adenosine A2A receptor antagonist istradefylline reduces daily OFF time in Parkinson's disease. *Movement Disord* 2013;28(8): 1138–1141.
13. Isaacson S, Eggert K, Kumar R, et al. Efficacy and safety of istradefylline in moderate to severe Parkinson's disease: a phase 3, multinational, randomized, double-blind, placebo-controlled trial (i-step study). *J Neurol Sci* 2017;381:351–352.
14. Stacy M, Silver D, Mendis T, et al. A 12-week, placebo-controlled study (6002-US-006) of istradefylline in Parkinson disease. *Neurology* 2008; 70(23):2233–2240.
15. Pourcher E, Fernandez HH, Stacy M, et al. Istradefylline for Parkinson's disease patients experiencing motor fluctuations: results of the KW-6002-US-018 study. *Parkinsonism Relat Disord* 2012;18(2):178–184.
16. Stowe R, Ives N, Clarke CE, et al. Meta-analysis of the comparative efficacy and safety of adjuvant treatment to levodopa in later Parkinson's disease. *Movement Disord* 2011;26(4):587–598.

17. Bucher HC, Guyatt GH, Griffith LE, et al. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol* 1997;50(6):683–691.
18. Zhang ZX, Liu CF, Tao EX, et al. Rotigotine transdermal patch in Chinese patients with advanced Parkinson's disease: a randomized, double-blind, placebo-controlled pivotal study. *Parkinsonism Relat Disord* 2017; 44:6–12.
19. Zhang Z, Wang J, Zhang X, et al. The efficacy and safety of ropinirole prolonged release tablets as adjunctive therapy in Chinese subjects with advanced Parkinson's disease: a multicenter, double-blind, randomized, placebo-controlled study. *Parkinsonism Relat Disord* 2013;19(11): 1022–1026.
20. Zhang Z, Shao M, Chen S, et al. Adjunct rasagiline to treat Parkinson's disease with motor fluctuations: a randomized, double-blind study in China. *Transl Neurodegener* 2018;7:14.
21. Zhang L, Zhang Z, Chen Y, et al. Efficacy and safety of rasagiline as an adjunct to levodopa treatment in Chinese patients with Parkinson's disease: a randomized, double-blind, parallel-controlled, multi-centre trial. *Int J Neuropsychopharmcol* 2013;16(7):1529–1537.
22. Zesiewicz TA, Chriscoe S, Jimenez T, et al. A randomized, fixed-dose, dose-response study of ropinirole prolonged release in advanced Parkinson's disease. *Neurodegener Dis Manag* 2017;7(1):61–72.
23. Trenkwalder C, Kies B, Rudzinska M, et al. Rotigotine effects on early morning motor function and sleep in Parkinson's disease: a double-blind, randomized, placebo-controlled study (RECOVER). *Mov Disord* 2011; 26(1):90–99.
24. Pahwa R, Tanner CM, Hauser RA, et al. ADS-5102 (amantadine) extended-release capsules for levodopa-induced dyskinesia in Parkinson disease (EASE LID study): a randomized clinical trial. *JAMA Neurol* 2017; 74(8):941–949.
25. Oertel W, Eggert K, Pahwa R, et al. Randomized, placebo-controlled trial of ADS-5102 (amantadine) extended-release capsules for levodopa-induced dyskinesia in Parkinson's disease (EASE LID 3). *Mov Disord* 2017;32(12): 1701–1709.
26. Nomoto M, Mizuno Y, Kondo T, et al. Transdermal rotigotine in advanced Parkinson's disease: a randomized, double-blind, placebo-controlled trial. *J Neurol* 2014;261(10):1887–1893.
27. Mizuno Y, Kondo T, Japanese Istradefylline Study G. Adenosine A2A receptor antagonist istradefylline reduces daily OFF time in Parkinson's disease. *Mov Disord* 2013;28(8):1138–1141.
28. Mizuno Y, Hasegawa K, Kondo T, et al, Japanese Istradefylline Study G. Clinical efficacy of istradefylline (KW-6002) in Parkinson's disease: a randomized, controlled study. *Mov Disord* 2010;25(10):1437–1443.
29. Lees AJ, Ferreira J, Rascol O, et al. Opicapone as adjunct to levodopa therapy in patients with Parkinson disease and motor fluctuations: a randomized clinical trial. *JAMA Neurol* 2017;74(2):197–206.
30. Hattori N, Takeda A, Takeda S, et al. Efficacy and safety of adjunctive rasagiline in Japanese Parkinson's disease patients with wearing-off phenomena: a phase 2/3, randomized, double-blind, placebo-controlled, multicenter study. *Parkinsonism Relat Disord* 2018;53:21–27.
31. Ferreira JJ, Lees A, Rocha JF, et al. Opicapone as an adjunct to levodopa in patients with Parkinson's disease and end-of-dose motor fluctuations: a randomised, double-blind, controlled trial. *Lancet Neurol* 2016;15(2):154–165.
32. Schapira AH, Barone P, Hauser RA, et al. Extended-release pramipexole in advanced Parkinson disease: a randomized controlled trial. *Neurology* 2011;77(8):767–774.
33. Pahwa R, Tanner CM, Hauser RA, et al. Amantadine extended release for levodopa-induced dyskinesia in Parkinson's disease (EASED study). *Mov Disord* 2015;30(6):788–795.
34. Mizuno Y, Nomoto M, Hasegawa K, et al. Rotigotine vs ropinirole in advanced stage Parkinson's disease: a double-blind study. *Parkinsonism Relat Disord* 2014;20(12):1388–1393.
35. Schapira AH, Fox SH, Hauser RA, et al. Assessment of safety and efficacy of safinamide as a levodopa adjunct in patients with Parkinson disease and motor fluctuations: a randomized clinical trial. *JAMA Neurol* 2017;74(2): 216–224.
36. Borgohain R, Szasz J, Stanzione P, et al. Two-year, randomized, controlled study of safinamide as add-on to levodopa in mid to late Parkinson's disease. *Mov Disord* 2014;29(10):1273–1280.
37. Borgohain R, Szasz J, Stanzione P, et al. Randomized trial of safinamide add-on to levodopa in Parkinson's disease with motor fluctuations. *Mov Disord* 2014;29(2):229–237.
38. Sako W, Kogo Y, Koebis M, et al. Comparative efficacy and safety of adjunctive drugs to levodopa for fluctuating Parkinson's disease—network meta-analysis. *NPJ Parkinson's Dis* 2023;9(1):143.
39. Bastide MF, Meissner WG, Picconi B, et al. Pathophysiology of L-dopa-induced motor and non-motor complications in Parkinson's disease. *Prog Neurobiol* 2015;132:96–168.
40. Heimrich KG, Schönenberg A, Santos-García D, Mir P, Coppadis Study G, Prell T. The impact of nonmotor symptoms on health-related quality of life in Parkinson's disease: a network analysis approach. *J Clin Med* 2023;12(7).
41. Suzuki K, Miyamoto M, Miyamoto T, et al. Istradefylline improves daytime sleepiness in patients with Parkinson's disease: an open-label, 3-month study. *J Neurol Sci* 2017;380:230–233.
42. Matsuura K, Kajikawa H, Tabei KI, et al. The effectiveness of istradefylline for the treatment of gait deficits and sleepiness in patients with Parkinson's disease. *Neurosci Lett* 2018;662:158–161.
43. Velseboer DC, de Haan RJ, Wieling W, et al. Prevalence of orthostatic hypotension in Parkinson's disease: a systematic review and meta-analysis. *Parkinsonism Relat Disord* 2011;17(10):724–729.
44. Tsuboi T, Satake Y, Hiraga K, et al. Effects of MAO-B inhibitors on non-motor symptoms and quality of life in Parkinson's disease: a systematic review. *NPJ Parkinson's Dis* 2022;8(1):75.
45. Fanciulli A, Leys F, Falup-Pecurariu C, et al. Management of orthostatic hypotension in Parkinson's disease. *J Parkinsons Dis* 2020;10(s1):S57–s64.
46. Weil RS, Reeves S, et al. *Adv Clin Neurosc Rehabil* 2020;19(4):Onns5189.
47. Postma JU, Van Tilburg W. Visual hallucinations and delirium during treatment with amantadine (Symmetrel). *J Am Geriatr Soc* 1975;23(5): 212–215.
48. Shimo Y, Maeda T, Chiu SW, et al. Influence of istradefylline on non-motor symptoms of Parkinson's disease: a subanalysis of a 1-year observational study in Japan (J-FIRST). *Parkinsonism Relat Disord* 2021;91:115–120.
49. Hatano T, Sengoku R, Nagayama H, et al. Impact of istradefylline on levodopa dose escalation in Parkinson's disease: ISTRA ADJUST PD study, a multicenter, open-label, randomized, parallel-group controlled study. *Neurol Ther* 2024;13(2):323–338.
50. Hattori N, Kabata D, Asada S, et al. Real-world evidence on levodopa dose escalation in patients with Parkinson's disease treated with istradefylline. *PLoS One* 2023;18(12):e0269969.