Efficacy and safety of adjunctive oral therapy in Parkinson's disease with motor complications: a systematic review and network meta-analysis

Vibuthi Sisodia [1,2] Lars Dubbeld,[1] Rob M A De Bie,[1,2] Gonçalo S Duarte [3,4] João Costa,[4,5] Joke M Dijk [1,2]

¹Neurology, Amsterdam UMC Location AMC, Amsterdam, The Netherlands
²Amsterdam Neuroscience, Neurodegeneration, Amsterdam, the Netherlands
³Clinical Pharmacology Department, Hospital da Luz, Lisboa, Portugal
⁴Laboratory of Clinical Pharmacology and Therapeutics, University of Lisbon Faculty of Medicine, Lisboa, Portugal
⁵Institute of Molecular Medicine, University of Lisbon Faculty of Medicine, Lisboa, Portugal

Correspondence to
Dr Joke M Dijk;
j.m.dijk@amsterdamumc.nl

ABSTRACT

Background The aim of this manuscript is to review the evidence and compare the efficacy and safety of catechol-O-methyltransferase inhibitors (COMT-Is), dopamine receptor agonists (DRAs) and monoamine-oxidase B inhibitors (MAOB-Is) as adjunctive treatment to levodopa in patients with Parkinson's disease (PD) experiencing motor complications.

Methods In this systematic review and network meta-analysis, literature searches were performed in MEDLINE and Embase to identify eligible randomised controlled trials (RCTs) with a minimal follow-up of at least 4 weeks published in English between 1980 and 2021. RCTs were included if either a COMT-I, DRA or MAOB-I was evaluated as an adjunctive therapy to levodopa in patients with PD experiencing motor complications and dyskinesia. The main outcomes included daily off-medication time, motor and non-motor examination scales, and adverse events including dyskinesia.

Results 74 RCTs reporting on 18 693 patients were included. All three studied drug classes decreased daily off-medication time compared with placebo (COMT-Is mean −0.8 hours (95% CI −1.0 to −0.6), DRAs −1.1 hours (95% CI −1.4 to −0.8), MAOB-Is −0.9 hours (95% CI −1.2 to −0.6)). Safety analysis showed an increased risk of dyskinesia for all three drug classes (COMT-Is OR 3.3 (95% CI 2.7 to 4.0), DRAs 3.0 (95% CI 2.5 to 3.5), MAOB-Is 1.6 (95% CI 1.2 to 2.2)). According to surface under the cumulative ranking curve scores, pramipexole IR was associated with the most favourable benefit–risk profile.

Conclusions COMT-Is, DRAs and MAOB-Is effectively reduce motor complications and increase incidence of dyskinesia. In the network meta-analysis, adjunctive use of DRAs appeared most effective.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ When Parkinson's disease (PD) progresses, motor complications frequently occur. To optimise dopaminergic therapy, catechol-O-methyltransferase inhibitors, dopamine receptor agonists (DRAs) or monoamine oxidase type B inhibitors are often prescribed in addition to levodopa. To date, guidelines do not state a preference for one of the three drug classes, leading to practice variation.

WHAT THIS STUDY ADDS

⇒ This systematic review offers a comprehensive overview of the existing evidence concerning adjunctive oral therapy in PD. It includes data from 74 randomised controlled trials, with the notable inclusion of nearly half that were not included in prior reviews. Furthermore, the network meta-analysis allowed for one-on-one comparisons between various adjunctive oral therapies through direct and indirect analyses. We also rated the quality of evidence and included outcomes related to quality of life and impulse control disorders.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ We provide a useful overview of the current evidence for physicians to help guide their clinical decisions and provide better personalised treatment strategies. The results of our analyses suggest a preference for DRAs, and especially pramipexole immediate-release, as an adjunctive oral therapy for reducing motor complications in advanced PD.

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disease causing motor and non-motor symptoms.[1] Dopaminergic therapy generally effectively reduces motor symptoms such as bradykinesia, rest tremor and muscular rigidity. Levodopa is the drug of first choice.[2] Due to disease progression, motor complications frequently occur. These include motor fluctuations (wearing-off phenomenon) and levodopa-induced dyskinesia. They can be improved with adjunctive oral therapy. According to international guidelines, catechol-O-methyltransferase inhibitors (COMT-Is), dopamine receptor agonists (DRAs) and monoamine oxidase type B inhibitors (MAOB-Is) are options to optimise dopaminergic treatment. However, no preference has been stated for one of the three therapies.[3–5]

In 2011, the evidence regarding efficacy and tolerability of COMT-Is, DRAs and MAOB-Is as adjunctive therapy to levodopa was described in a meta-analysis.[6] Since then, results of several randomised controlled trials (RCTs) on adjunctive drugs to levodopa have been reported, some including drugs that were not yet available in 2011. Moreover, to the best of our knowledge, a network meta-analysis (NMA) comparing the three adjunctive drugs has not been performed yet.

We set out to perform an up-to-date systematic review and NMA including RCTs comparing the efficacy of adjunctive oral therapies. We analysed the effects of COMT-Is, DRAs and MAOB-Is on daily off-medication time, motor symptoms and activities of daily living (ADL), but also on quality of life (QoL), and occurrence of specific adverse events (AEs) including impulse control disorders (ICDs). The effects of the three drug classes on the selected outcomes were compared.

METHODS

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[7] The study protocol has been registered in the PROSPERO database (CRD42022373935).

Search strategy and selection criteria

The search, screening of titles and abstracts, and article selection were conducted by two reviewers independently (VS and LD). Discrete, identical searches were performed for COMT-Is, DRAs and MAOB-Is on MEDLINE and Embase. The MESH and text words included "Levodopa", "Catechol-O-methyltransferase Inhibitors", "Dopamine Agonists", "Monoamine Oxidase Inhibitors", "Placebo" and "Parkinson's Disease". A full list of search terms is included in the online supplemental appendix e-1. Trials were included if they met the following criteria: RCTs evaluating either a COMT-I, DRA or MAOB-I as an adjunctive therapy to levodopa in patients with PD experiencing motor complications, either or not accompanied by dyskinesia. The focus of the current review was on oral adjunctive drugs aimed at reducing early motor complications in PD. Since patients in this stage of PD may also experience dyskinesia, possibly enhanced by adjunctive drugs, the impact of the investigated drugs on dyskinesia was also evaluated. The efficacy of drugs specifically aimed at the treatment of dyskinesia, such as amantadine, was outside the scope of this review.

Trials had to be published in the English language between January 1980 and March 2021 with a minimal follow-up duration of 4 weeks. Trials needed to report at least one of the following outcomes related to efficacy or tolerability: change in daily off-medication time reported using patient diaries, change in Unified Parkinson's Disease Rating Scale motor examination (UPDRS-ME),[8] change in dyskinesia (Dyskinesia Rating Scale (DRS)) score,[9] change in UPDRS-ADL,[8] change in total score of Parkinson's Disease Questionnaire (PDQ) version with 8 or 39 items,[10 11] change in daily levodopa dose, occurrence of dyskinesia, occurrence of hallucinations, occurrence of nausea, occurrence of ICD or trial withdrawal due to AE or lack of efficacy. Trials evaluating multiple adjunctive drugs or across a range of dosages were included if they met the inclusion criteria.

After retrieving all articles, two reviewers (VS and LD) independently screened for eligible studies by reading the titles and abstracts. These were then selected for full-text review. Moreover, a supplementary handsearch of bibliographies of selected articles was conducted. Any discrepancies between the two reviewers (VS and LD) were discussed and resolved through consultation with a third reviewer (JMD).

Validity assessment

The methodological quality of the included trials was assessed using the Jadad Quality Assessment Scale.[12] The methodological quality of a trial was considered sufficient if the score was three points or higher. Two reviewers (VS and LD) conducted this assessment independently from each other. Any discrepancies between the two reviewers (VS and LD) were discussed and resolved through consultation with a third reviewer (JMD).

Data extraction

Data extraction was performed by two reviewers (VS and LD). Information was extracted from each included trial on: (1) characteristics of trial participants (including mean age, sex ratio, sample size of each treatment arm, mean symptom duration, mean baseline UPDRS-ME score and mean UPDRS-ADL score); (2) type of intervention (including type, dose and duration of the oral adjunctive therapy) and (3) outcome measure(s) (change in daily off-medication time, UPDRS-ME score, DRS score, UPDRS-ADL score, PDQ-8 and PDQ-39 total scores, daily levodopa dose, and occurrence of either dyskinesia, hallucinations, ICD, nausea or trial withdrawal).

Statistical analyses

First, we performed a meta-analysis comparing adjunctive oral therapies with placebo for all outcomes using RevMan V.5.3 (The Cochrane Collaboration, Copenhagen).[13] The weighted mean difference (WMD) with a 95% CI was used to describe differences in continuous data, whereas the OR with a 95% CI was used for dichotomous data. A $p<0.05$ was considered significant unless otherwise specified (e.g., a $p<0.10$ was considered significant for Egger's weighted regression statistic). The WMD of the baseline characteristics between the intervention and placebo arm was calculated using the sample size (N) and mean (M).[14] The SD of the WMD is computed by taking the square root of the weighted sum of squared deviations from the overall WMD, divided by the sum of weights assigned to each study.[14] For AEs, the number needed to expose to harm (NNEH) was calculated using the OR and the event rate in the unexposed group.[15]
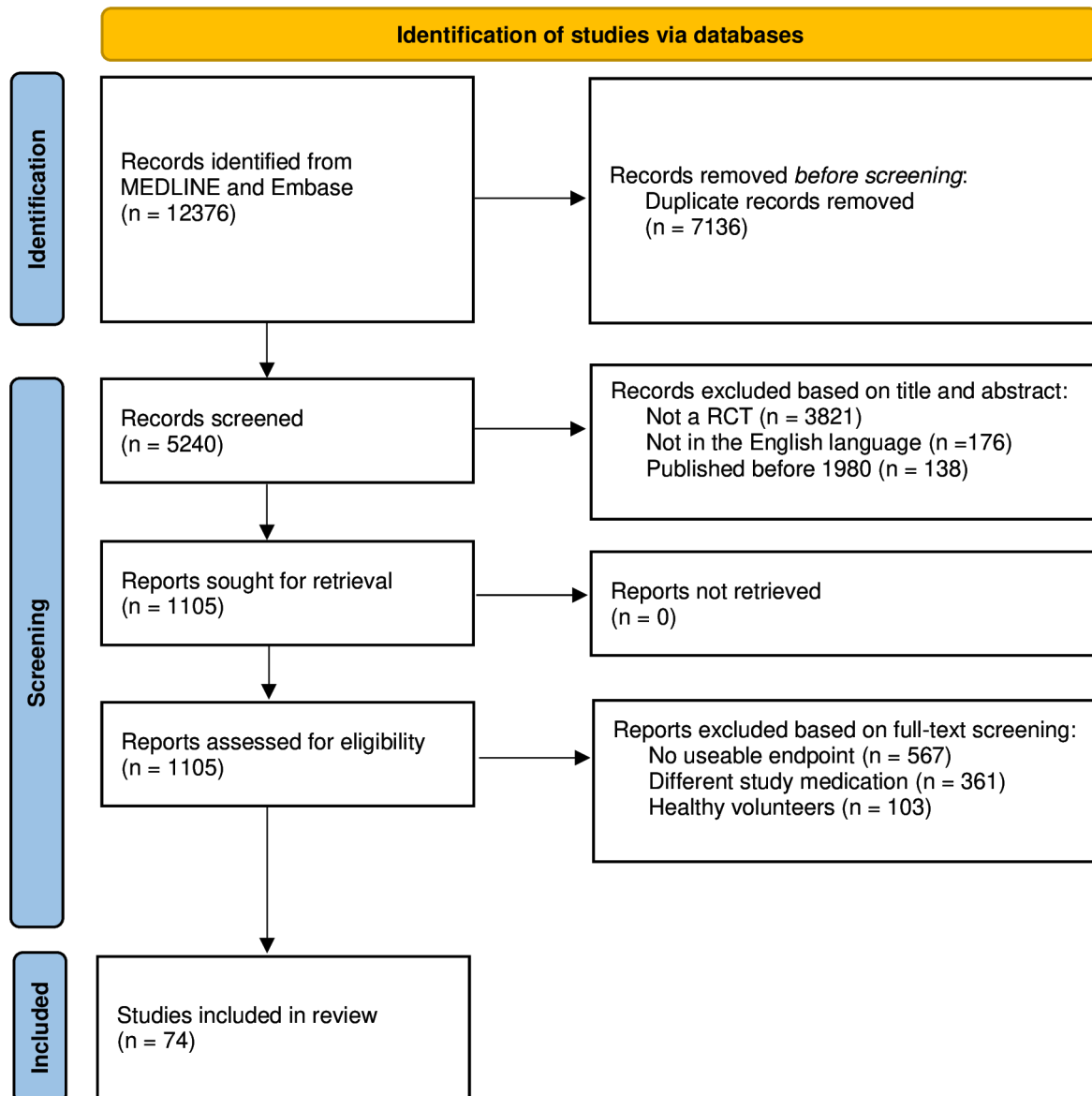
Figure 1 PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses RCT, randomised controlled trial.

For both continuous and dichotomous data, the DerSimonian and Laird random-effects model was used.[16] For each outcome measure, no trial participant was analysed more than once. In trials using multiple active treatment arms, the number of participants in the placebo group was divided by the number of active treatment arms for analysis purposes. Here, the means and SD in the placebo group were left unchanged for continuous outcomes, whereas the number of events for dichotomous outcomes was divided by the number of active treatment arms.[14] Additionally, the meta-analysis included subgroup analyses. These were performed for the individual drugs within each class as well as analyses excluding treatment arms in which dosages lower than recommended were used, to evaluate whether the use of suboptimal dosages altered the results. The used recommended dosages were based on Dutch guidelines and can be found in the online supplemental appendix table A-1 (e-1).[5 17 18]

In addition, we assessed how many studies reported the relation between the timing of levodopa administration and the assessment of motor symptoms with the UPDRS in the off-medication and the on-medication state. Next, NMA with a Bayesian hierarchical random effects model was performed by using R (V.4.0.5) for off-medication time, UPDRS-ME, UPDRS-ADL, dyskinesia, hallucinations and withdrawal due to AEs. Pairwise meta-analyses using a Sidik-Jonkman random effects model were used to compute the pooled estimates of WMD and OR with 95% CI of each combination of comparisons across therapies to assess the consistency of the effect size and were shown in league tables. The treatments subsequently were ranked by means of the surface under the cumulative ranking curve (SUCRA) for separate outcomes. A higher SUCRA score corresponds to a higher ranking and implies that, compared with the other interventions, the specific intervention is likely to be more efficacious. For

Table 1 Demographics and baseline characteristics

	Randomised to placebo (n=6043)	Randomised to adjunctive therapy (n=12650)	Randomised to COMT-Is (n=3212)	Randomised to DRAs (n=6849)	Randomised to MAOB-Is (n=2589)
Men, n (%)	3516 (58.2)	7248 (57.3)	1873 (58.3)	3962 (57.8)	1631 (63.0)
Age, mean±SD, years	63.8±1.5	63.6±2.0	63.7±2.1	63.6±2.8	63.8±2.6
Mean symptom duration, mean±SD, years	8.0±1.6	7.9±1.7	9.1±1.5	7.3±2.4	8.4±1.6
Baseline UPDRS-ME scores, mean±SD	26.4±4.0	26.1±4.1	25.5±7.8	27.5±4.3	23.0±3.5
Baseline UPDRS ADL scores, mean±SD	13.8±3.2	13.5±3.2	16.0±5.9	13.2±5.0	11.8±3.9
Baseline daily off-medication time, mean±SD, hours	6.0±0.8	6.0±0.7	6.4±0.5	5.6±1.5	6.2±0.5
Daily levodopa dose, mean±SD, mg	651.7±154.5	618.7±147.4	673.1±126.3	582.2±177.3	687.5±273.8

ADL, activities of daily living; COMT-Is, catechol-O-methyltransferase inhibitors; DRAs, dopamine receptor agonists; MAOB-Is, monoamine-oxidase B inhibitors; ME, motor examination; UPDRS, Unified Parkinson's Disease Rating Scale; WMD, weighted mean difference.

the analysed motor complications (off-medication time, UPDRS-ME and UPDRS-ADL), a higher SUCRA score is associated with better improvement, while it is associated with a lower risk of the analysed AEs (dyskinesia, hallucinations and withdrawal due to AEs).[19] To analyse the benefit–risk profile of each intervention in the NMA,

Table 2 Meta-analysis efficacy outcomes of adjunctive therapies

	Change in outcome of classes of drugs compared with placebo			Change in outcome of most effective drug of each class compared with placebo		
	COMT-Is	DRAs	MAOB-Is	COMT-Is Tolcapone	DRAs Pramipexole IR	MAOB-Is Rasagiline
	WMD* (95% CI)	WMD* (95% CI)	WMD* (95% CI)	WMD* (95% CI)	WMD* (95% CI)	WMD* (95% CI)
Reduction in daily off-medication time (hours)	−0.8 (−1.0 to −0.6) n=3100	−1.1 (−1.4 to −0.8) n=4465	−0.9 (−1.2 to −0.6) n=2086	−2.0 (−2.5 to −1.4) n=215	−2.2 (−2.7 to −1.6) n=604	−0.8 (−1.1 to −0.5) n=994
UPDRS-ME score (points)	−1.8 (−2.7 to −0.9) n=2451	−5.3 (−6.3 to −4.3) n=5115	−2.9 (−4.3 to −1.4) n=1254	−2.4 (−3.7 to −1.1) n=726	−6.3 (−7.7 to −4.9) n=1429	−1.6 (−3.1 to −0.1) n=310
DRS (points)	N/A	N/A	0.0 (−0.3, 0.3) n=1218	N/A	N/A	N/A
UPDRS-ADL score (points)	−0.2 (−0.6 to 0.1) n=1778	−2.1 (−2.4 to −1.8) n=5441	−0.6 (−1.0 to −0.3) n=1254	−0.0 (−0.5 to 0.4) n=549	−2.4 (−2.6 to −2.0) n=1429	−1.0 (−1.8 to −0.2) n=310
PDQ-39 (points)	−0.2 (−0.9 to 0.5) n=1641	−3.8 (−5.6 to −2.0) n=983	−1.8 (−2.9 to −0.7) n=1254	N/A	−4.5 (−7.1 to −1.8) n=498	−1.8 (−4.0 to 0.4) n=310
Reduction in daily levodopa dose (mg)	−94 (−123 to −64) n=1909)	−69 (−107 to −31) n=1821	−7 (−17 to 3) n=244	−134 (−164 to −105) n=887	−114 (−217 to −10) n=498	−7 (−17 to 3) n=244

*WMD at the end of follow-up period compared with baseline.
ADL, activities of daily living; CI, confidence interval; COMT-Is, catechol-O-methyltransferase inhibitors; DRAs, dopamine receptor agonists; DRS, dyskinesie rating scale; IR, immediate release; MAOB-Is, monoamine-oxidase B inhibitors; ME, motor examination; N/A, not available; PDQ-39, Parkinson's disease questionnaire; UPDRS, Unified Parkinson's Disease Rating Scale; WMD, weighted mean difference.

Table 3 Meta-analysis safety outcomes of adjunctive therapies

	OR and no needed to expose to harm of classes of drugs compared with placebo			OR and no needed to expose to harm of most effective drug of each class compared with placebo		
	COMT-Is	**DRAs**	**MAOB-Is**	**COMT-Is Tolcapone**	**DRAs Pramipexole IR**	**MAOB-Is Rasagiline**
	OR (95% CI); NNEH **n**	**OR (95% CI); NNEH** **n**	**OR (95% CI); NNEH** **n**	**OR (95% CI); NNEH** **n**	**OR (95% CI); NNEH** **n**	**OR (95% CI); NNEH** **n**
Dyskinesia	3.3 (2.7 to 4.0); 5 n=3564	3.0 (2.5 to 3.5); 7 n=8119	1.6 (1.2 to 2.2); 24 n=4105	4.4 (3.2 to 6.2); 3 n=909	2.7 (2.0 to 3.5); 5 n=1948	1.5 (1.1 to 2.3); 33 n=1779
Hallucinations	1.4 (0.9 to 2.4); 51 n=1941	3.2 (2.4 to 4.1); 19 n=7401	2.3 (1.2 to 4.5); 78 n=2533	2.1 (1.1 to 4.3); 16 n=571	3.5 (2.2 to 5.3); 12 n=1818	4.2 (1.1 to 16.0); 130 n=1063
Nausea	2.0 (1.5 to 2.6); 15 n=3237	1.8 (1.5 to 2.1); 15 n=7745	1.3 (0.9 to 2.0); 98 n=2582	2.3 (1.6 to 3.4); 7 n=909	1.3 (1.0 to 1.7); 28 n=1935	1.3 (0.6 to 2.9); 172 n=1312
Impulse control disorder	N/A	1.8 (0.7 to 4.9); 168 n=1891	N/A	N/A	1.0 (0.1 to 11.4); 4501 n=264	N/A
Trial withdrawal	1.2 (0.9 to 1.6); N/A n=3751	0.8 (0.7 to 1.0); N/A n=7936	1.1 (0.8 to 1.6); N/A n=3742	1.4 (0.8 to 2.4) N/A n=749	0.6 (0.4 to 0.8); N/A n=1657	1.3 (0.7 to 2.6); N/A n=1313

COMT-Is, catechol-O-methyltransferase inhibitors; DRAs, dopamine receptor agonists; IR, immediate-release; MAOB-Is, monoamine-oxidase B inhibitors; N/A, not available; NNEH, number needed to expose to harm; OR, odds ratio.

two scatter plots were made using the SUCRA values: (1) occurrence of dyskinesia versus daily off-medication time and (2) occurrence of withdrawal due to AEs versus daily off-medication time.

If studies reported Movement Disorder Society UPDRS instead of UPDRS, the conversion formula from Goetz et al was employed to convert MDS-UPDRS to UPDRS using the Hoehn and Yahr stage.[20] If no information was provided on the Hoehn and Yahr stage, the simplified method proposed by Hentz et al was used.[6 21] We employed the UPDRS to assess motor symptoms given its global prominence in PD research. This ensured consistency, facilitating direct comparisons with prior studies and enhancing result interpretation.

The quality of evidence was graded using the GradePRO software and a summary of findings table was created.[22] To determine heterogeneity among the identified studies, the I^2 statistic was assessed. Heterogeneity was considered high when I^2 was larger than 50%. Publication bias was evaluated by means of funnel plots if at least 10 studies were available for the specified drug class and outcome.[14] The Egger's weighted regression statistic was only used if funnel plots seemed asymmetrical to quantify the asymmetry (p<0.10).[14] This was calculated with Meta-Essentials (Erasmus Research Institute of Management,

Rotterdam).[23] RevMan calculator was used to calculate the SD if not reported.

RESULTS

A total of 12 376 articles were retrieved in the 4 separate literature searches, of which 5240 unique publications. After screening the titles, abstracts and full texts of articles and assessing the methodological quality, 74 RCTs compliant with the inclusion criteria were identified and included in this systematic review (see figure 1).

In total 18 693 patients with PD experiencing motor complications participated in the RCTs included in this systematic review, with 3212 patients randomised to a COMT-I, 6849 patients to a DRA and 2589 to a MAOB-I. At the time of trial inclusion, the patients had a mean age of 64 years and mean symptom duration of 7.9 years and used an average of 619 mg levodopa daily. Mean follow-up duration was 16.8 weeks (range 4–52 weeks). For details regarding trial characteristics and characteristics of patients randomised to COMT-I, DRA and MAOB-I, please refer to table 1 and online supplemental appendix table A-2, A-3.

The efficacy and safety outcomes of the meta-analysis for all evaluated adjunctive therapies along with the

Table 4 Ranking of adjunctive therapy based on SUCRA

Rank	Off-medication time TREAT (SUCRA)	UPDRS-ME TREAT (SUCRA)	UPDRS-ADL TREAT (SUCRA)	Dyskinesia TREAT (SUCRA)	Hallucinations TREAT (SUCRA)	Withdrawal due to adverse events TREAT (SUCRA)
1	TOL (94%)	PPX-IR (98%)	PPX-IR (94%)	PLB (92%)	CBG (91%)	PPX-IR (90%)
2	PPX-IR (93%)	ROT (88%)	ROT (94%)	ZNS (90%)	PLB (90%)	ROT (74%)
3	ROT (69%)	ROP (81%)	CBG (85%)	SEL (87%)	ENT (87%)	PPX-ER (70%)
4	SAF (68%)	PPX-ER (74%)	ROP (77%)	RAS (75%)	SAF (73%)	SEL (65%)
5	ROP (65%)	BCR (58%)	ENT (64%)	PIR (66%)	RAS (63%)	PLB (64%)
6	OPC (49%)	PIR (58%)	SUM (64%)	ENT (58%)	TOL (62%)	SAF (63%)
7	CBG (42%)	TOL (54%)	BCR (52%)	PPX (57%)	BCR (57%)	ROP (61%)
8	RAS (34%)	SAF (47%)	PPX-ER (50%)	SAF (55%)	PPX (48%)	CBG (59%)
9	SUM (33%)	PRG (43%)	RAS (46%)	PPX-ER (51%)	ROT (46%)	TOL (59%)
10	ENT (26%)	ENT (35%)	PIR (42%)	BCR (46%)	OPC (44%)	RAS (56%)

For the motor outcomes OFF-medication time, UPDRS-ME and UPDRS-ADL, higher SUCRA scores correspond to a higher ranking (better effect) for reducing motor complications compared with other interventions. For the adverse events dyskinesia, hallucinations and withdrawal due to adverse events, higher SUCRA scores correspond to a lower ranking (lower risk) for adverse events compared with other interventions.

ADL, activities of daily living; BCR, bromocriptine; CBG, cabergoline; ENT, entacapone; ER, extended-release; IR, immediate-release; ME, motor examination; OPC, opicapone; PIR, piribedil; PLB, placebo; PPX, pramipexole; PRG, pergolide; RAS, rasagiline; ROP, ropinirole; ROT, rotigotine; SAF, safinamide; SEL, selegiline; SUCRA, surface under the cumulative ranking curve; SUM, sumanirole; TOL, tolcapone; TREAT, treatment; UPDRS, Unified Parkinson's Disease Rating Scale; ZNS, zonisamide.

drug of each drug class that appeared most effective in reducing off-medication time are shown in table 2 (efficacy) and table 3 (safety). The ranking of adjunctive therapy based on the SUCRA according to the NMA is shown in table 4. Quality of evidence among the identified studies, including heterogeneity, can be viewed in table 5. The league tables can be found in online supplemental appendix table table A4–A9. The WMD from baseline to last follow-up in off-medication time, UPDRS-ME, UPDRS-ADL, DRS, QoL and PDQ-39 of patients randomised to placebo can be viewed in online supplemental appendix table A-10.

Most trials reported QoL by means of the PDQ-39; two trials, both evaluating rotigotine, used the PDQ-8 to report on the QoL.[24 25] Hence, only trials assessing QoL with the PDQ-39 were included in the current meta-analysis.

All studied adjunctive therapies provided a significant reduction in off-medication time compared with placebo (table 2). DRAs produced a reduction in daily off-medication time with a WMD of −1.1 hours (95% CI −1.4 to −0.8) compared with placebo, whereas both COMT-Is and MAOB-Is were associated with a WMD of −0.8 hours (95% CI −1.0 to −0.6) and −0.9 hours (95% CI −1.2 to −0.6), respectively. Intraclass comparison showed that of the DRAs, pramipexole immediate-release (IR) provided the largest reduction in daily off-medication time with −2.2 hours (95% CI −2.7 to −1.6). The NMA showed that for reduction in daily off-medication time, the best-ranked treatment and second best-ranked based on the SUCRA were tolcapone and pramipexole IR, respectively (table 4).

COMT-Is, DRAs and MAOB-Is also all significantly improved the UPDRS-ME score compared with placebo (table 2). The reduction was largest for DRAs, with a WMD of −5.3 points (95% CI −6.3 to −4.3). COMT-Is and MAOB-Is reduced the UPDRS-ME score with a WMD of −1.8 (95% CI −2.7 to −0.9) and −2.9 (95% CI −4.3 to −1.4) points, respectively. Of all the individual drugs, the largest reduction was seen among patients allocated to pramipexole IR (WMD −6.3, 95% CI −7.7 to −4.9). In the NMA, this was also the best-ranked treatment based on the SUCRA, followed by rotigotine (table 4).

Compared with placebo, both DRAs and MAOB-Is significantly improved the UPDRS-ADL score with a WMD of −2.1 points (95% CI −2.4 to −1.8) and −0.6 points (95% CI −1.0 to −0.3), respectively (table 2). No significant reduction was found among patients allocated to COMT-Is (WMD −0.2, 95% CI −0.6 to 0.1). Of the DRAs, rotigotine appeared to be associated with the largest reduction in the UPDRS-ADL score (WMD −2.6, 95% CI −3.1 to −2.1). According to the SUCRA it was the second best-ranked treatment, with pramipexole IR the best-ranked treatment (table 4), although the between-comparison difference in the NMA was negligible (WMD 0.01; 95% CI −0.53 to 0.58; online supplemental table A6).

For more details and the results of the outcomes change in dyskinesia, change in QoL and change in daily levodopa dose, please see tables 2 and 4.

All drug classes were significantly associated with dyskinesias when compared with placebo: COMT-Is OR 3.3 (95% CI 2.7 to 4.0), NNEH 5; DRAs OR 3.0 (95% CI 2.5

Table 5 Quality of evidence*

Adjunctive oral therapy with levodopa compared with placebo with levodopa for Parkinson's disease with dyskinesia and motor complications

Patient or population: Parkinson's disease with dyskinesia and motor complications intervention: adjunctive oral therapy with levodopa comparison: placebo with levodopa

Outcomes	COMT-Is	DRAs	MAOB-Is
Change in daily off-medication time (in hours)	⊕⊕⊕◯ MODERATE†‡	⊕⊕⊕◯ MODERATE†§¶	⊕⊕⊕◯ MODERATE†‡
UPDRS-ME score from 0 to 128 (worst)	⊕⊕⊕◯ MODERATE†‡	⊕⊕⊕⊕ HIGH†§	⊕⊕⊕⊕ HIGH‡
UPDRS-ADL score from 0 to 52 (worst)	⊕⊕⊕◯ MODERATE†‡	⊕⊕⊕◯ MODERATE†¶	⊕⊕⊕◯ MODERATE**‡
PDQ-39 from 0 to 100 (worst)	⊕⊕⊕◯ MODERATE**‡	⊕⊕⊕⊕ HIGH‡	⊕⊕⊕⊕ HIGH‡
Dyskinesia	⊕⊕⊕⊕ HIGH††	⊕⊕⊕⊕ HIGH††	⊕⊕⊕⊕ HIGH¶
Hallucination	⊕⊕⊕⊕ HIGH‡	⊕⊕⊕⊕ HIGH††	⊕⊕⊕⊕ HIGH‡
Nausea	⊕⊕⊕⊕ HIGH	⊕⊕⊕◯ MODERATE¶	⊕⊕⊕◯ MODERATE**‡
Impulse control disorder	–	⊕⊕⊕◯ MODERATE**‡	–

GRADE Working Group grades of evidence. High certainty: We are very confident that the true effect lies close to that of the estimate of the effect moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
*Quality of evidence table modified from the GRADE evidence profile.
†Quality of evidence table modified from the GRADE evidence profile.
‡Not enough studies to use the funnel plot.
§Upgrading of the quality of evidence as the effect is larger than the minimally clinically important change.[30 31]
¶Funnel plots appeared asymmetrical, but Egger's weighted regression statistic was not significant.
**Downgrading of the quality of evidence due to imprecision (the CIs were wide and crossed the line of no effect).
††Upgrading of the quality of evidence as the risk ratio is larger than 2.0.
ADL, activities of daily living; COMT-Is, catechol-O-methyltransferase inhibitors; DRAs, dopamine receptor agonists; GRADE, Grading of Recommendations, Assessment, Development, and Evaluations; MAOB-Is, monoamine-oxidase B inhibitors; ME, motor examination; PDQ-39, Parkinson's Disease Questionnaire-39; UPDRS, Unified Parkinson's Disease Rating Scale.

to 3.5), NNEH 7; and MAOB-Is OR 1.6 (95% CI 1.2 to 2.2), NNEH 24 (table 3). The best-ranked treatment associated with a lower risk of dyskinesia based on the SUCRA was zonisamide followed by selegiline (table 4).

DRAs and MAOB-Is were significantly associated with increased occurrence of hallucinations: DRAs OR 3.2 (95% CI 2.4 to 4.1), NNEH 19; MAOB-Is OR 2.3 (95% CI 1.2 to 4.5), NNEH 78. COMT-Is were not statistically significantly associated with hallucinations (OR 1.4 (95% CI 0.9 to 2.4), NNEH 51). The best-ranked treatment associated with a lower risk of hallucinations based on the SUCRA was cabergoline followed by entacapone (table 4).

None of the drug classes were significantly associated with trial withdrawal from the study due to AEs. The best-ranked and second best-ranked treatment (associated with a lower risk of withdrawal from the study due to AEs) based on the SUCRA were pramipexole IR and rotigotine, respectively (table 4). For details and the risk of nausea and ICD, please see tables 3 and 4.

Scatterplots of the SUCRA values of 'occurrence of dyskinesia versus daily off-medication time' and 'occurrence of trial withdrawal due to AEs versus daily off-medication'

can be found in figures 2 and 3, respectively. Overall, pramipexole IR seemed to be associated with the most favourable benefit–risk ratio.

Publication bias might be present for the studies included in our analyses regarding DRAs and the risk of hallucinations as the funnel plot appeared asymmetrical and Egger's weighted regression statistic was significant (p=0.09). For all other outcomes, publication bias was either unlikely (symmetrical funnel plots or non-significant Egger's weighted regression statistic scores) or could not be determined as there were less than ten studies.

Eleven RCTs evaluating COMT-Is and MAOB-Is used at least one dosage that was lower than the recommended dosage.[26–36] These RCTs did not substantially influence the results of the meta-analyses as additional analyses excluding suboptimal dosages produced similar results. Among the 26 studies examining motor function with UPDRS, only 5 studies provided detailed information on the timing of levodopa administration in relation to the assessment.[37–41] These studies addressed a practically defined off and administration of a levodopa test-dose 2 hours before the assessment, respectively. In contrast,
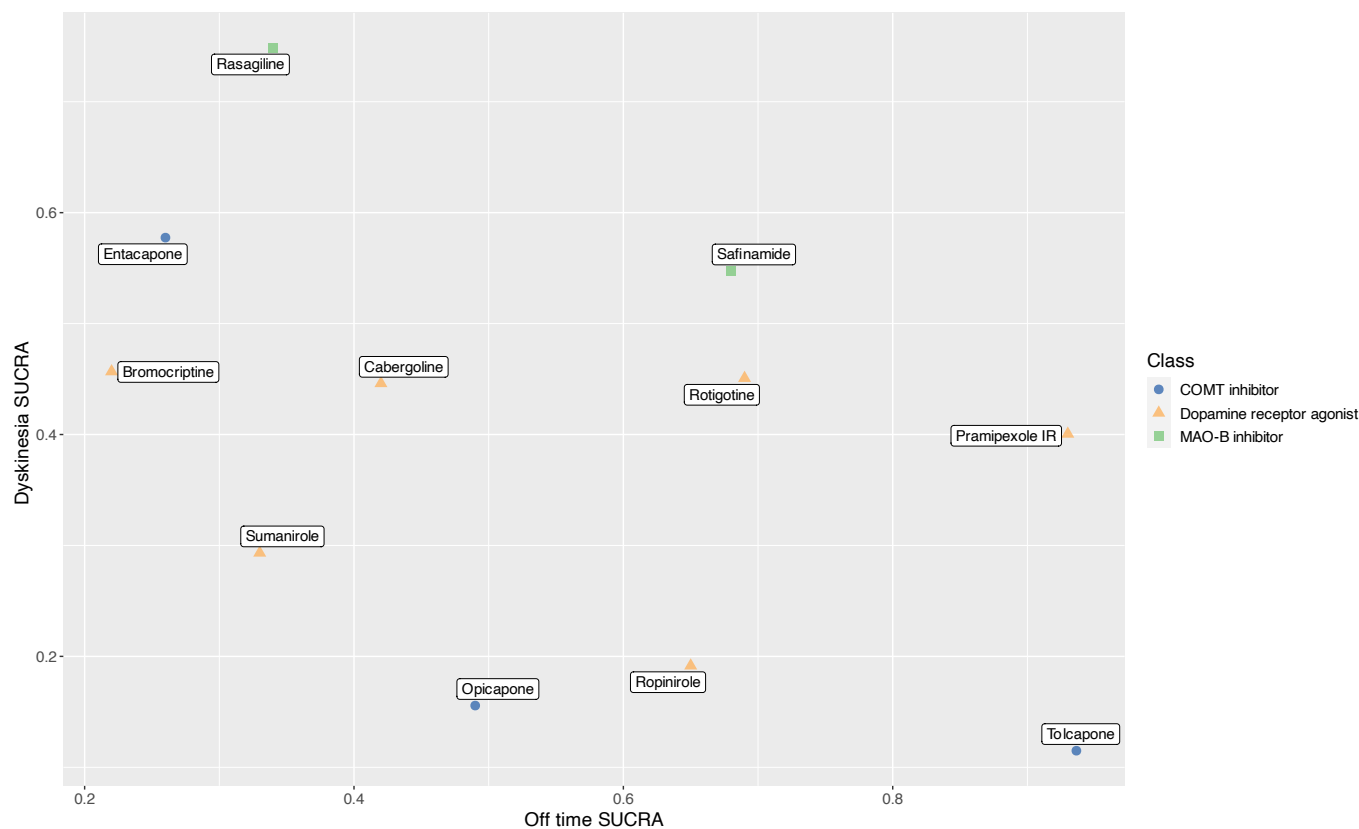
Figure 2 Scatterplots of the SUCRA values of 'occurrence of dyskinesia versus daily off-medication time'. Higher SUCRA scores correspond to a lower ranking (lower risk) for dyskinesia and higher ranking (better effect) for reducing daily off-medication, compared with other interventions. COMT, catechol-O-methyltransferase; MAO-B, monoamine-oxidase B inhibitors; SUCRA, surface under the cumulative ranking curve.

the remaining studies evaluated motor symptoms using the UPDRS without specifying the timing of levodopa administration.

The quality of evidence was assessed using GRADEpro (table 5). For COMTI-Is, the overall quality of evidence was moderate and for both DRAs and MAOB-Is the quality of evidence was high.

DISCUSSION

With this systematic review, including 74 publications, we aimed to provide an up-to-date appraisal of the evidence regarding adjunctive oral therapy for motor complications in patients with PD treated with levodopa. The systematic review and (network) meta-analysis demonstrated that the three studied adjunctive drug classes, COMT-Is, DRAs and MAOB-Is, all improve daily off-medication time, severity of motor symptoms, daily functioning, and QoL. The impact of these adjunctive therapies on dyskinesia is uncertain, as only three trials reported here.

The use of DRAs, especially pramipexole IR, appeared to be associated with the largest reductions in daily off-medication time, UPDRS-ME score, UPDRS-ADL score and PDQ-39 total score when compared with placebo. This was also observed in the NMA, as pramipexole IR was the overall best ranked treatment based on the SUCRA

and seemed to have the best benefit–risk profile in the scatter plots.

For DRAs and MAOB-Is, the improvement in the duration of daily off-medication time compared with placebo was larger than the defined minimally clinically important change (MCIC) of −1.0 hours per day with a reduction of 1.1 hours and 0.9 hours, respectively, with the 95% CI containing the MCIC.[42] This was not the case for COMT-Is, with a reduction of 0.8 hours. Likewise, the UPDRS-ME score reduction was clinically relevant for patients allocated to DRAs (−5.3 points) and MAOB-Is (−2.9 points) as the MCIC is 2.5 points.[43] COMT-Is (−1.8 points) did not meet the range of MCIC for UPDRS-ME.

Adjunctive oral therapy is associated with an increased risk of developing AEs, such as nausea, dyskinesia, ICD and hallucinations. It was not possible to determine which adjunctive oral therapy had the strongest association with the occurrence of ICD, as only studies evaluating DRAs reported this AE.

The results of this meta-analysis were largely in line with the 2011 meta-analysis of Stowe et al.[6] In both meta-analyses, DRAs seemed to be the most effective adjunctive oral therapy. However, there were small discrepancies. For instance, in the meta-analysis by Stowe et al,[6] a larger WMD reduction in daily off-medication time was shown
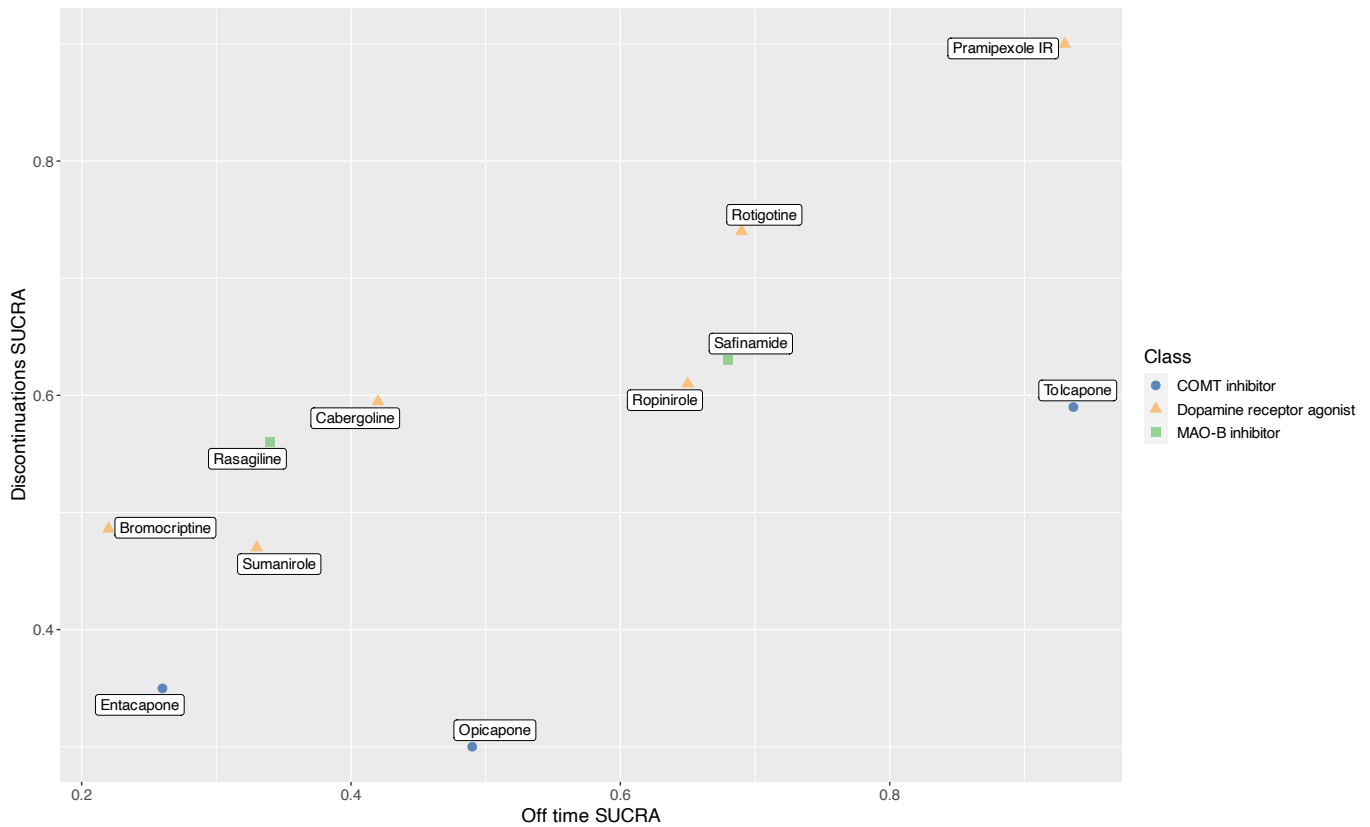
Figure 3 Scatterplots of the SUCRA values of 'occurrence of trial withdrawal due to adverse events versus daily off-medication'. Higher SUCRA scores correspond to a lower ranking (lower risk) of trial withdrawal due to adverse events and higher ranking (better effect) for reducing daily off-medication, compared with other interventions. COMT, catechol-O-methyltransferase; MAO-B, monoamine-oxidase B inhibitors; SUCRA, surface under the cumulative ranking curve.

for DRAs: of −1.6 hours vs −1.1 hours in the current meta-analysis. This discrepancy could be attributed to the inclusion of dose-ranging studies in the current review, such as Zesiewicz et al[44] and Nicholas et al.[45] Besides, 34 RCTs that were not included in the meta-analysis by Stowe et al[6] were included in the current meta-analysis, of which 21 were published after 2011. Stowe et al[6] included 14 publications published prior to 2012 that we did not include because they did not meet our inclusion criteria (e.g., publications had none of the selected outcomes or included Parkinson patients without motor complications).

There are some points that need to be considered for the interpretation of the results. First, the treatment duration was relatively short in most RCTs: in 43 publications, the treatment duration was less than 24 weeks. This may have influenced outcomes. Second, patients were allowed to use medications other than levodopa to treat PD symptoms in 47 RCTs. It was obligatory, however, that these drugs were used at a stable dose before entering the trial, but unknown interactions may have influenced the results. Third, even though patients with PD may experience certain motor symptoms, such as dyskinesia, before initiating adjunctive therapy, in this review the occurrence of side effects was compared between the use of adjunctive therapy and placebo. This suggests that the occurrence of side effects, including dyskinesia,

is treatment emergent. Fourth, treatment-specific AE, such as liver toxicity due to tolcapone, was not included in the analyses.[3–5 46] Fifth, few included RCTs were 'dose-finding studies' that used a variety of dosages with some dosages now considered suboptimal. The impact of the use of suboptimal dosages on the results was analysed and besides a somewhat later magnitude of some effects, this did not substantially alter the findings or interpretation. Sixth, patients with PD participating in RCTs may be a selection of patients with relatively less comorbidity such as cognitive and psychiatric symptoms due to exclusion criteria of the RCTs and as they probably are less inclined to participate. This needs to be taken into account when translating the study results to clinical practice. Seventh, among the 26 studies examining motor function with UPDRS, only 5 studies reported the relation between the timing of levodopa administration and the assessment of motor symptoms with the UPDRS.[3 37–41] Eighth, we employed the WMD in the current systematic review. Using the standardised mean difference could have facilitated the inclusion of a broader range of studies, particularly those assessing motor symptoms and QoL with scales beyond our inclusion criteria. However, we opted for the WMD to align with established methodological standards of previous studies and to maintain precision.[6] Finally, the systematic review consisted of 74 RCTs, yet only 13

funnel plots could be made to assess possible publication bias due to the small number of RCTs included for each outcome per adjunctive drug class. Likewise, no additional subgroup analyses could have been performed to investigate potential sources of heterogeneity because of insufficient data.

Despite the limitations, the review consists of 74 RCTs with data of over 18 500 patients. In addition to being the first NMA comparing oral adjunctive therapies in PD, it is also the first meta-analysis to include outcomes related to QoL, NNEH and ICD and that rates the quality of evidence.

Current clinical practice regarding the use of adjunctive oral therapies varies, because a head-to-head trial including all three adjunctive oral therapies is lacking. To guide clinical decision-making, indirect and direct comparisons as performed in this meta-analysis, currently are the best available evidence. DRAs appear to be more efficacious than COMT-Is and MAOB-Is for many clinically relevant outcomes, despite being associated with slightly more AEs. The results of the current systematic review suggest that DRAs should be considered as the primary treatment choice for adjunctive oral therapy in PD with motor complications. Still, to decisively determine an optimal treatment strategy, an extensive RCT comparing the most potent drugs of each class according to this review, taking side effects into account, is necessary. This strategy probably would lead to faster improvement of motor symptoms. Moreover, immediate start with the optimal treatment strategy could ultimately lead to a larger improvement of motor symptoms in an individual patient as this might prevent settling for less improvement during a period of trying various adjunctive therapies.[47] In addition, more research is needed to determine the impact of adjunctive oral therapy on QoL in PD along with the incidence of ICD.

Based on the results of this systematic review and NMA, it can be concluded that all adjunctive oral treatment options are effective in the management of advanced PD with dyskinesia and motor complications. DRAs, particularly pramipexole IR, seem to provide the largest efficacy on multiple relevant outcomes. In order to confirm this observation more head-to-head trials are needed.

ORCID iDs
Vibuthi Sisodia http://orcid.org/0000-0003-2671-9454
Gonçalo S Duarte http://orcid.org/0000-0001-7802-1897
Joke M Dijk http://orcid.org/0000-0001-8972-1530

REFERENCES

1. Tysnes OB, Storstein A. Epidemiology of Parkinson's disease. *J Neural Transm (Vienna)* 2017;124:901–5.
2. de Bie RMA, Clarke CE, Espay AJ, *et al*. Initiation of pharmacological therapy in Parkinson's disease: when, why, and how. *The Lancet Neurology* 2020;19:452–61.
3. Pahwa R, Factor SA, Lyons KE, *et al*. Practice Parameter: treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2006;66:983–95.
4. Bloem B, Keus S, De Beer H, *et al*. Multidisciplinaire Richtlijn Ziekte Van Parkinson; 2010. Available: https://www.parkinsonnet.nl/app/uploads/2019/11/multidisciplin_rl_parkinson_final_version.pdf
5. Fox SH, Katzenschlager R, Lim S-Y, *et al*. International Parkinson and movement disorder society evidence-based medicine review: update on treatments for the motor symptoms of Parkinson's disease. *Mov Disord* 2018;33:1248–66.
6. 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. *Mov Disord* 2011;26:587–98.
7. Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* 2010;8:336–41.
8. Goetz CG. The Unified Parkinson's Disease Rating Scale (UPDRS): status and recommendations. *Mov Disord* 2003;18:738–50.
9. Goetz CG, Stebbins GT, Shale HM, *et al*. Utility of an objective dyskinesia rating scale for Parkinson's disease: Inter- and intrarater reliability assessment. *Movement Disorders* 1994;9:390–4. 10.1002/mds.870090403 Available: https://movementdisorders.onlinelibrary.wiley.com/toc/15318257/9/4
10. Peto V, Jenkinson C, Fitzpatrick R. PDQ-39: a review of the development, validation and application of a Parkinson's disease quality of life questionnaire and its associated measures. *J Neurol* 1998;245:S10–4.
11. Jenkinson C, Fitzpatrick R, Peto V, *et al*. The Parkinson's Disease Questionnaire (PDQ-39): development and validation of a Parkinson's disease summary index score. *Age Ageing* 1997;26:353–7.
12. Jadad AR, Moore RA, Carroll D, *et al*. Assessing the quality of reports of randomized clinical trials: Is blinding necessary. *In English), Control Clin Trials* 1996;17:1–12.
13. Review manager (Revman) [computer software] version 5.3. Cochrane Collaboration: Copenhagen, Denmark; 2014.
14. Higgens J, Green S, ed. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0[updated March 2011]. *The Cochrane Collaboration* 2011.
15. Bender R, Blettner M. Calculating the "number needed to be exposed" with adjustment for confounding variables in epidemiological studies. *In English), J Clin Epidemiol* 2002;55:525–30.
16. DerSimonian R. Meta-analysis in the design and monitoring of clinical trials. *Stat Med* 1996;15:1237–48.
17. Zorginstituut Nederland. Farmacotherapeutisch Kompas. Available: https://www.farmacotherapeutischkompas.nl/bladeren/indicatieteksten/ziekte_van_parkinson," ed [Accessed 19 May 2023].

18 Lang AE, Lees A. Management of Parkinson's disease: An evidence-based review (in English). *Mov Disord* 2002;17.

19 Rouse B, Chaimani A, Li TJ. Network meta-analysis: an introduction for clinicians (in English). *Intern Emerg Med* 2017;12:103–11.

20 Goetz CG, Stebbins GT, Tilley BC. Calibration of unified Parkinson's disease rating scale scores to Movement Disorder Society-unified Parkinson's disease rating scale scores (in English). *Movement Disord* 2012;27:1239–42.

21 Hentz JG, Mehta SH, Shill HA, *et al*. Simplified conversion method for unified Parkinson's disease rating scale motor examinations (in English). *Mov Disord* 2015;30:1967–70.

22 GRADEpro. Gradepro GDT: Gradepro guideline development tool [software]. Mcmaster University, (developed by evidence prime, Inc.). 2015. Available: https://www.gradepro.org/

23 Suurmond R, van Rhee H, Hak T. Introduction, comparison, and validation of meta-essentials: a free and simple tool for meta-analysis. *Res Synth Methods* 2017;8:537–53.

24 Rascol O, Zesiewicz T, Chaudhuri KR, *et al*. A randomized controlled exploratory pilot study to evaluate the effect of rotigotine transdermal patch on parkinson's disease-associated chronic pain. *J Clin Pharmacol* 2016;56:852–61.

25 Zhang Z-X, Liu C-F, Tao E-X, *et al*. Rotigotine transdermal patch in Chinese patients with advanced Parkinson's disease: a randomized, double-blind, placebo-controlled pivotal study (in English). *Parkinsonism Relat Disord* 2017;44:6–12.

26 Ferreira JJ, Lees A, Rocha J-F, *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 (in English). *Lancet Neurol* 2016;15:154–65.

27 Ferreira JJ, Rocha J-F, Falcão A, *et al*. Effect of opicapone on levodopa pharmacokinetics, catechol-O-methyltransferase activity and motor fluctuations in patients with Parkinson's disease (in English). *Eur J Neurol* 2015;22:815–25,

28 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 (in English). *Parkinsonism Relat Disord* 2018;53:21–7.

29 Kurth MC, Adler CH, Hilaire MS, *et al*. Tolcapone improves motor function and reduces levodopa requirement in patients with Parkinson's disease experiencing motor fluctuations: A multicenter, double-blind, randomized, placebo-controlled trial. Tolcapone Fluctuator Study Group I. *Neurology* 1997;48:81–7.

30 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;74:197–206.

31 Mizuno Y, Kanazawa I, Kuno S, *et al*. Placebo-controlled, double-blind dose-finding study of entacapone in fluctuating parkinsonian patients (in English). *Mov Disord* 2007;22:75–80.

32 Murata M, Hasegawa K, Kanazawa I, *et al*. Zonisamide improves wearing-off in Parkinson's disease: a randomized, double-blind study (in English). *Mov Disord* 2015;30:1343–50.

33 Myllylä VV, Jackson M, Larsen JP, *et al*. Efficacy and safety of tolcapone in levodopa-treated Parkinson's disease patients with "wearing-off" phenomenon: a multicentre, double-blind, randomized, placebo-controlled trial (in English). *Euro J Neurology* 1997;4:333–41.

34 Ondo WG, Sethi KD, Kricorian G. Selegiline orally disintegrating tablets in patients with Parkinson disease and "wearing off" symptoms (in English). *Clin Neuropharmacol* 2007;30:295–300.

35 Schwid SR. A randomized placebo-controlled trial of rasagiline in levodopa-treated patients with parkinson disease and motor fluctuations. *Arch Neurol* 2005;62:241–8.

36 Waters CH, Sethi KD, Hauser RA, *et al*. Zydis selegiline reduces off time in Parkinson's disease patients with motor fluctuations: a 3-month, randomized, placebo-controlled study. *Mov Disord* 2004;19:426–32.

37 Mizuno Y, Yanagisawa N, Kuno S, *et al*. Randomized, double-blind study of pramipexole with placebo and bromocriptine in advanced Parkinson's disease. *Mov Disord* 2003;18:1149–56.

38 Möller JC, Oertel WH, Köster J, *et al*. Long-term efficacy and safety of pramipexole in advanced Parkinson's disease: results from a European multicenter trial. *Mov Disord* 2005;20:602–10.

39 Pahwa R, Stacy MA, Factor SA, *et al*. Ropinirole 24-hour prolonged release: randomized, controlled study in advanced Parkinson disease. *Neurology* 2007;68:1108–15.

40 Pogarell O, Gasser T, van Hilten JJ, *et al*. Pramipexole in patients with Parkinson's disease and marked drug resistant tremor: a randomised, double blind, placebo controlled multicentre study. *In English), J Neurol Neurosur Ps* 2002;72:713–20.

41 Rascol O, Brooks D, Melamed E, *et al*. Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and motor fluctuations (LARGO, Lasting effect in Adjunct therapy with Rasagiline Given Once daily, study): a randomised, double-blind, parallel-group trial. *The Lancet* 2005;365:947–54.

42 Hauser RA, Auinger P, Grp PS. Determination of minimal clinically important change in early and advanced Parkinson's disease. *Mov Disord* 2011;26:813–8.

43 Shulman LM, Gruber-Baldini AL, Anderson KE, *et al*. The clinically important difference on the unified Parkinson's disease rating scale. *Arch Neurol* 2010;67:64–70.

44 Zesiewicz TA, Chriscoe S, Jimenez T, *et al*. A fixed-dose, dose-response study of ropinirole prolonged release in early stage Parkinson's disease. *Neurodegener Dis Manag* 2017;7:49–59.

45 Nicholas AP, Borgohain R, Chaná P, *et al*. A randomized study of rotigotine dose response on "off" time in advanced Parkinson's disease. *J Parkinsons Dis* 2014;4:361–73.

46 Borges N. Tolcapone-related liver dysfunction: implications for use in Parkinson's disease therapy. *Drug Saf* 2003;26:743–7.

47 Verschuur CVM, Suwijn SR, Boel JA, *et al*. Randomized delayed-start trial of levodopa in Parkinson's Disease. *N Engl J Med* 2019;380:315–24.