Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson´ s disease patients with motor complications (Review)

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[Intervention Review]

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Rebecca Stowe[1], Natalie Ives[1], Carl E Clarke[2], Katherine Deane[3], van Hilten[4], Keith Wheatley[5], Richard Gray[6], Kelly Handley[1], Alex Furmston[1]

[1]Birmingham Clinical Trials Unit, University of Birmingham, Birmingham, UK. [2]School of Clinical and Experimental Medicine, College of Medicine and DentalSciences, Birmingham, UK. [3]Edith Cavell Building, University of East Anglia, Norwich, UK. [4]Department of Neurology, Leiden University of Medical Center, Leiden, Netherlands. [5]Cancer Research UK Clinical Trials Unit, School of Cancer Sciences, University of Birmingham, Birmingham, UK. [6]Clinical Trials Unit, The University of Birmingham, Birmingham, UK

Contact address: Rebecca Stowe, Birmingham Clinical Trials Unit, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK. r.l.harrison@bham.ac.uk.

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ABSTRACT

Background

One of the complications of long-term treatment of Parkinson's disease (PD) with levodopa is the development of motor complications. Generally, when motor complications develop, clinicians add in an additional drug (to the levodopa regimen) from one of three other classes of anti-Parkinsonian treatments (dopamine agonists, catechol-O-methyl transferase inhibitors (COMTIs) or monoamine oxidase type B inhibitors (MAOBIs)). However, despite trials having shown that these drugs are beneficial compared to placebo, it remains unclear as to the best way to treat patients experiencing motor complications and whether one class of drug is more effective than another.

Objectives

This meta-analysis aims to assess more reliably the benefits and risks of the three classes of drugs (dopamine agonists, COMTIs and MAOBIs) currently used as adjuvant treatment to levodopa in PD patients suffering from motor complications. The three drug classes were compared with the aim of determining whether one class of drug provides better symptomatic control than another.

Search methods

We searched CENTRAL (*The Cochrane Library*), MEDLINE, EMBASE, PubMed, LILACS and Web of Science, plus major journals in the field, abstract books, conference proceedings and reference lists of retrieved publications.

Selection criteria

Randomised trials comparing an orally administered dopamine agonist, COMTI or MAOBI versus placebo, both on a background of levodopa therapy, in PD patients experiencing motor complications.

Data collection and analysis

Two authors independently extracted data on off-time, levodopa dose, motor complications, side-effects, treatment concordance, clinician-rated disability, mortality, quality of life and health economic data.

Main results

Forty-four eligible trials, involving 8436 participants were identified. Compared to placebo, adjuvant therapy significantly reduced off-time (-1.05 hours/day, 95% confidence interval (CI) -1.19 to -0.90; P<0.00001), the required levodopa dose (-55.65 mg/day, CI -62.67 to -48.62; P<0.00001) and improved UPDRS scores (UPDRS ADL score: -1.31 points, CI -1.62 to -0.99; P<0.00001; UPDRS motor score: -2.84 points, CI -3.36 to -2.32; P<0.00001; UPDRS total score: -3.26 points, CI -4.52 to -2.00; P<0.00001). However, dyskinesia (odds ratio (OR) 2.50, CI 2.21 to 2.84; P<0.00001) and side-effects including constipation (OR 3.19, CI 2.17 to 4.68; P<0.00001), dizziness (OR 1.57, CI 1.30 to 1.90; P<0.00001), dry mouth (OR 2.33, CI 1.22 to 4.47; P=0.01), hallucinations (OR 2.16, CI 1.70 to 2.74; P<0.00001), hypotension (OR 1.47, CI 1.18 to 1.83; P=0.0007), insomnia (OR 1.38, CI 1.09 to 1.74; P= 0.007), nausea (OR 1.78, CI 1.53 to 2.07; P<0.00001), somnolence (OR 1.87, CI 1.40 to 2.51; P<0.0001) and vomiting (OR 2.56, CI 1.67 to 3.93; P<0.0001) were all increased with adjuvant therapy.

Indirect comparisons of the three drug classes suggested that dopamine agonists were more efficacious in reducing off-time (dopamine agonist: -1.54 hours/day; COMTI: -0.83 hours/day; MAOBI: -0.93 hours/day; test for heterogeneity between drug classes P=0.0003) and levodopa dose (dopamine agonist: -116 mg/day; COMTI: -52 mg/day; MAOBI: -29 mg/day; test for heterogeneity between drug classes P<0.00001). UPDRS scores also improved more with dopamine agonists than with COMTI or MAOBI (UPDRS total scores - dopamine agonist: -10.01 points versus COMTI: -1.46 points versus MAOBI: -2.20 points; test for heterogeneity between drug classes P<0.00001), although more dyskinesia were seen with dopamine agonists (OR 2.70) and COMTI (OR 2.50) than with MAOBI (OR 0.94) (test for heterogeneity between drug classes P=0.009). Although the increase in the overall incidence of side-effects was generally more marked with dopamine agonists (OR 1.52) and COMTI (OR 2.0) than with MAOBI (OR 1.32), heterogeneity between drug classes was only of borderline significance (P=0.07).

Authors' conclusions

Compared to placebo, adjuvant therapy reduces off-time, levodopa dose, and improves UPDRS scores in PD patients who develop motor complications on levodopa therapy. However, this is at the expense of increased dyskinesia and numerous other side-effects. Indirect comparisons suggest that dopamine agonist therapy may be more effective than COMTI and MAOBI therapy, which have comparable efficacy. However, as indirect comparisons should be interpreted with caution, direct head-to-head randomised trials assessing the impact of these different drug classes on overall patient-rated quality of life are needed.

PLAIN LANGUAGE SUMMARY

Drugs for motor complications in people with Parkinson´ s disease who are already taking levodopa

One of the complications of long-term treatment of Parkinson's disease (PD) with levodopa is the development of motor complications e.g. dyskinesia; a jerky, dance-like movement of the body. Generally clinicians add on drugs (to the levodopa regimen) from one of the other three classes of anti-Parkinsonian treatments available (e.g. dopamine agonists, catechol-O-methyl transferase inhibitors (COMTIs) or monoamine oxidase type B inhibitors (MAOBIs)). However, despite trials having shown that these drugs are beneficial compared to placebo, it remains unclear as to the best way to treat patients experiencing motor complications and, in particular, whether one class of drug may be more effective than another.

This review assesses data from randomised trials of the three classes of drugs commonly used as add-on (adjuvant) treatment to levodopa therapy in people with PD who have motor complications. Forty-four randomised trials, involving 8436 participants were identified as suitable for this review. The review confirms reports from individual trials that, compared to placebo, add-on therapy (on a background of levodopa) significantly reduces patient off-time, reduces the required levodopa dose and improves overall disability scores (measured on the Unified Parkinson's Disease Rating Scale - UPDRS). However, dyskinesia and other side-effects such as constipation, hallucinations and vomiting are increased with adjuvant therapy.

Indirect comparisons of the three drug classes (dopamine agonists, COMTIs and MAOBIs) suggest that dopamine agonists may provide more effective symptomatic control than COMTI and MAOBI therapy. COMTI and MAOBI have comparable efficacy. There was no significant evidence of differences in efficacy between individual drugs within the drug classes, other than tolcapone appearing

more effective than entacapone. However these observations are based on indirect comparisons between trials, so could be due to other factors, e.g. differences in the types of people included in the trials, and so should to be interpreted with caution.

This review highlights the need for large randomised studies that directly compare the different drug classes with patient-rated overall quality of life and health economic measures as the primary outcomes.

BACKGROUND

Parkinson's disease (PD) is a progressive disorder affecting over six million people worldwide, making it the most common neurodegenerative disease after Alzheimer's disease (Schapira 1999). With a growing elderly population and a reduction in other causes of mortality, the prevalence of PD is likely to increase (Quinn 1997). In the absence of curative therapy, treatment is directed towards alleviating the characteristic symptoms of PD such as bradykinesia, tremor, rigidity and postural instability (Clarke 2002). Levodopa combined with a peripheral dopa-decarboxylase inhibitor provides effective symptomatic control. However, it is now well established that most patients who are treated with levodopa in the early stages of PD, particularly at higher doses, develop motor complications such as abnormal involuntary movements (dyskinesia) and motor fluctuations (early wearing-off after each dose of medication and unpredictable switching between the mobile 'on' phase and the relatively immobile 'off' phase). Once motor complications have developed on levodopa therapy, clinicians add on other classes of anti-Parkinsonian drugs such as dopamine agonists, catechol-O-methyl transferase inhibitors (COMTIs) or monoamine oxidase type B inhibitors (MAOBIs). This is referred to as 'add-on', 'adjuvant' or 'adjunct' therapy in later PD. Previous randomised controlled trials have shown that these drugs can reduce a patient's off-time, reduce the required levodopa dose and improve motor function. However, there is uncertainty whether one add-on drug class is more effective than another, and a meta-analysis of the randomised evidence would be useful to clinicians and patients to help inform the best order in which to use these drugs.

OBJECTIVES

This 'umbrella' meta-analysis aims to compare the effectiveness and safety of the three main classes of add-on drugs that are used in the management of patients with later PD. We have undertaken a meta-analysis of data from all published randomised trials comparing any orally administered dopamine agonist, COMTI or MAOBI with placebo in patients with PD who are already established on levodopa and suffering from motor complications to quantify more reliably the evidence-base and to determine whether one class of drug provides better symptomatic control than another.

Thus, this review both complements previous individual reviews by updating and clarifying the existing evidence-base, and provides important information on possible class effects of add-on therapy in later PD.

METHODS

Criteria for considering studies for this review

Types of studies

Eligible studies were any randomised trials (including the first phase of crossover trials) in later PD comparing an orally administered dopamine agonist, COMTI or MAOBI versus placebo, both on a background of levodopa therapy, with all other aspects of planned treatment being the same in both arms.

Types of participants

Studies with PD patients (diagnosed by the enrolling investigators) receiving levodopa and who had developed motor complications. All durations of levodopa therapy were included. There were no age restrictions.

Types of interventions

Any orally administered dopamine agonist, COMTI or MAOBI (on a background of levodopa) versus placebo (also on a background of levodopa), with all other aspects of planned treatment being the same in both arms.

When this literature search was performed only three trials of transdermal skin patch agonists (rotigotine and piribedil) were identified (DA (Pi): Toulouse; DA (Ro): CLEOPATRA; DA (Ro): PREFER) (*See* Characteristics of excluded studies). These trials were excluded at this stage as (1) transdermal administered agents

may have different properties to oral preparations and (2) transdermal patches were not widely used at that time. In 2008, manufacturing problems with the rotigotine patch led to supply problems, meaning that initiation was not possible in most countries for a while and is still not possible in some. However, trials of transdermal patch agents will be included in the next update of this review.

Types of outcome measures

Outcome measures were time spent in the 'off' state, levodopa dose, changes in clinician-rated disability scales, e.g. Unified Parkinson's Disease Rating Scale (UPDRS), the incidence of dyskinesia and dystonia, frequency of adverse events, mortality, treatment compliance and withdrawals, quality of life and health economic data.

Search methods for identification of studies

See: Cochrane Movements Disorders Group methods used in reviews.

We undertook a systematic search of the literature up to the end of 2008 for publications or abstracts describing relevant trials. This included searching electronic databases such as the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*), MEDLINE, EMBASE, PubMed, LILACS and Web of Science. Ongoing and recently completed trials were identified by searching the Meta Register of Controlled Clinical Trials (mRCT). This electronic search was supplemented by handsearching of general (Lancet, BMJ, JAMA) and major journals (Movement Disorders, Neurology) in the field and abstract books and conference proceedings from the main society meetings (International Congress of Parkinson's Disease and Movement Disorders, World Congress on Parkinson's Disease and Related Disorders) to identify trials not yet indexed on the main databases and new trials presented as abstracts at meetings. Further information was sought from scanning reference lists of retrieved papers, in particular review papers and searching for grey literature (e.g. dissertations, government reports). Authors of trials were contacted for further information as required. Additional assistance including information on unpublished data was requested from pharmaceutical manufacturers. Randomised controlled trials were identified using the highly sensitive search strategy as recommended by The Cochrane Collaboration (Dickersin 1994), combined with added terms for Parkinson's disease (Parkinson's disease, parkinson*) and all adjuvant agents (dopamine agonist*, bromocriptine*, ropinirole*, cabergoline*, lisuride*, pergolide*, piribedil*, MAOB*, selegiline*, rasagiline*, COMT*, tolcapone*, entacapone*) (using free text or MESH terms, or both, where appropriate).

Data collection and analysis

Study Selection

From the search results, two review authors independently screened the abstracts of potentially relevant studies, with the full paper being obtained if the abstract did not provide sufficient information to determine eligibility for inclusion in the review. Disagreement was resolved by referral to a third review author.

Data Extraction

Two review authors independently assessed the eligible papers or abstracts for trial details and outcome data. This was validated by a third review author with any discrepancies resolved by consensus. Trial details were recorded on a standard trial description form and included: trial name, trial group, principal investigators and authors, randomised comparison, treatment schedule (including dose, duration, route), other therapy, eligibility criteria, method of randomisation, allocation concealment, blinding, accrual period, number of participants randomised, number of drop outs, duration of follow-up, analysis methods, outcomes planned, outcomes reported, use of intention-to-treat analysis and publication date(s). Outcome data extracted included data on off-time, levodopa dose, clinician-rated disability scales, e.g. UPDRS, dyskinesia, dystonia, adverse events, mortality, treatment compliance and withdrawals, quality of life and health economic data.

Data Analysis

Results of each trial were combined using standard meta-analytic methods to estimate an overall effect for adjuvant treatment versus control (placebo-treated) participants. For event data (e.g. mortality), estimates of the treatment effects were obtained for most trials from the number of events reported in each arm and combined using the methods of Mantel and Haenszel (Mantel 1959; Peto 1977). This involved comparing the number of events observed (O) with the number of events that would have been expected (E) if the probability of that event was unrelated to treatment. For each trial the 'observed minus expected' (O-E) difference and its variance was calculated for the treatment arm, then used to calculate odds ratios together with 95% confidence intervals (EBCTCG 1990). If an odds ratio, hazard ratio, relative risk or odds reduction, plus a confidence interval or a P value, were stated in the publication then this information was used to obtain a more accurate estimate of the treatment effect (Parmar 1998). Summing the statistics for each trial provides the overall statistics, which were then used to calculate reductions in the odds of each event, for example dyskinesia or death.

For continuous variables (e.g. levodopa dose), we calculated the mean differences (Fleiss 1993). For each trial the difference between the outcome measure means for each treatment group was calculated, along with its variance. These values were combined to give the overall mean difference and its standard error, with 95% confidence interval for this pooled estimate of the mean difference. If any trials with three or more treatment arms were identified, then the following assumptions were made for the analysis:

1. If the trial was comparing two different drugs within the same

drug class versus control , then the data for those drugs were combined to give one comparison of adjuvant therapy versus control. 2. If the trial was comparing the same drug but at different doses versus control, then the arm using the licensed or generally recommended dose was chosen for inclusion in the analysis.

This meant that trials were not included multiple times in the analysis, and the control arms from each trial were counted only once in the analysis.

The primary outcome measure was mean off-time reduction, with secondary outcome measures of levodopa dose reduction, changes in clinician-rated disability scales, e.g. UPDRS, the incidence of dyskinesia and dystonia, frequency of adverse events, mortality, treatment compliance and withdrawals, quality of life and health economic data.

The three adjuvant drug classes compared in this meta-analysis have different mechanisms of action: dopamine agonists directly stimulate post-synaptic dopamine receptors; COMTIs inhibit the metabolism of levodopa mainly in the periphery, but in the case of tolcapone, in the brain; and MAOBIs inhibit the metabolism of intracerebral dopamine. Given these different mechanisms of action, the adjuvant trials included in this meta-analysis were divided according to drug class:

Dopamine agonist versus placebo (both on a background of levodopa therapy)

COMTI versus placebo (both on a background of levodopa therapy)

MAOBI versus placebo (both on a background of levodopa therapy).

To assess for differences across the three add-on drug classes (interclass comparisons), indirect comparisons using tests for heterogeneity were used to investigate whether the treatment effect differed across the different drug classes (EBCTCG 1990; Deeks 2001). These tests may suggest the possible superiority of one drug class over another, and may provide clinicians and patients with more reliable information upon which to base decisions about add-on drug therapy. We also used tests for heterogeneity to indirectly investigate for differences between the drugs used within each of the add-on drug classes (intraclass comparisons). As with all subgroup comparisons, these analyses should be interpreted with caution and should be considered hypothesis generating (Assmann 2000; Clarke 2001).

No other subgroup analyses were planned or performed.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Seventy-eight randomised trials of adjuvant therapy using either a dopamine agonist, MAOBI or COMTI (on a background of levodopa) in PD patients experiencing motor complications were identified. Thirty-four studies were excluded (*See* Characteristics of excluded studies) - eighteen trials of dopamine agonist, seven of COMTI and nine of MAOBI. The reasons for excluding these trials were crossover study with data not presented for the first treatment period (n=16), patients with later PD but it was not clear if they were all suffering from motor complications (n=8), partial or skin patch agonist (n=5), not clear if properly randomised (n=2), single-dose study (n=2) and drug administered using intravenous infusion (also no outcome data reported) (n=1). There was also one trial comparing pramipexole versus rotigotine versus placebo (CLEOPATRA). For this trial, the comparison of the transdermal patch rotigotine versus placebo was excluded from this analysis (but will be included in the next update of the review) (DA (Ro): CLEOPATRA). The literature search also identified eight publications that were related to five studies (COMTI (T): TFSG 3; DA (C): USA 1; DA (Pe): N America; DA (Pr): US/Canada; MAOBI (S): USA) already included in the meta-analysis, with these additional publications reporting the results on a subset of participants from the main trial. To avoid duplication of results, data from these additional publications were not included in the analysis. Therefore, there were forty-four trials eligible for inclusion in the review.

The number of participants randomised into the forty-four trials included in this meta-analysis ranged from 23 to 687 participants, with 8436 randomised participants in total (giving an average trial size of less than 200 participants) (*See* Characteristics of included studies). The average length of follow-up was 20 weeks (range: 4 weeks to 2 years), and the majority of studies (36/44, 82%) were of six months or less in duration of follow-up. The mean age of the participants in the trials was approximately 63 years, 60% were male and they had had PD for approximately 9 years.

There was one three-arm trial comparing two dopamine agonists (bromocriptine and pramipexole) with placebo, for this trial the data from the two agonist arms were combined to give one comparison of dopamine agonist versus placebo (DA (Pr/B): Interntl). In the COMTI trials, there were seven trials with three or more arms. These were generally trials comparing different doses of COMTI treatment versus placebo. In these cases, where possible, the arm using the licensed or generally recommended dose of the drug (entacapone 200mg with each levodopa dose and tolcapone 100mg t.i.d) was chosen for inclusion in the data analysis. Thus for the COMTI (E): Japan trial comparing entacapone 100mg or 200mg versus placebo, the 200mg arm (with each levodopa dose) was included in the analysis; for the COMTI (T): Europe, COMTI (T): TFSG 3 and COMTI (T): US/Canada trials comparing tolcapone 100mg t.i.d. or 200mg t.i.d. versus placebo, the 100mg t.i.d arms were included in the analysis; for the COMTI (T): TFSG 1 and COMTI (T): TIPS I trials comparing tolcapone 50mg t.i.d., 200mg t.i.d. or 400mg t.i.d. versus placebo, the 200mg t.i.d. arms

were included in the analysis; and for the COMTI (T): TIPS II trial comparing tolcapone 200mg t.i.d. or 400mg t.i.d. versus placebo, the 200mg t.i.d. arm was included in the analysis. In the MAOBI trials, there was one three-arm trial comparing 0.5mg or 1mg rasagiline versus placebo (MAOBI (R): PRESTO), and one four-arm trial comparing 0.5mg, 1mg or 2mg rasagiline versus placebo (MAOBI (R): Isra/Hun), with the 1mg arm (the licensed dose for rasagiline) from both trials being included in the analysis. There were also two trials that included both fluctuating and non-fluctuating patients, where the results were split by type of patient, so only the fluctuating patients were included in the analysis (COMTI (E): UK/Irish; MAOBI (R): Isra/Hun). Thus, of the 8436 participants randomised into the forty-four trials, 7590 (90%) participants were included in the analysis.

There was one three-arm trial that contributed data to two add-on drug class comparisons (COMTI (E): LARGO). This was a trial of the COMTI entacapone versus the MAOBI rasagiline versus placebo, which contributed to both the COMTI versus placebo and MAOBI versus placebo add-on drug class comparisons. There were therefore, forty-four trials contributing to forty-five comparisons within the three add-on drug classes - twenty comparisons of dopamine agonist versus placebo, eighteen comparisons of COMTI versus placebo and seven comparisons of MAOBI versus placebo. In the dopamine agonist trials, pramipexole was being assessed in seven trials, bromocriptine in five, cabergoline in four, ropinirole in four and pergolide in one (note: DA (Pr/B): Interntl had two agonist arms - bromocriptine and pramipexole). There were eleven trials assessing the COMTI entacapone and seven assessing the COMTI tolcapone, and for the MAOBI trials, there were three trials of rasagiline and four of selegiline (two of deprenyl (selegiline) and two of zydis selegiline (sublingual - Zelapar using the Zydis fast-dissolving technology)).

Risk of bias in included studies

None of the available trial quality scoring systems are widely accepted, so these were not used in this review. The Characteristics of included studies and Risk of bias in included studies tables shows some aspects of the methodological quality of the included trials. Twenty-six trials (of the 44 eligible trials included in this meta-analysis) described the method of randomisation used (for example, random number generator, computer generated), but only five trials gave information that allowed the assessment of whether an adequate concealment of allocation procedure (by virtue of a central randomisation service) was used. All trials were double-blind, placebo-controlled and all trials reported follow-up data, although it was often unclear whether all randomised participants were included in the analyses, despite analyses being described as intention-to-treat.

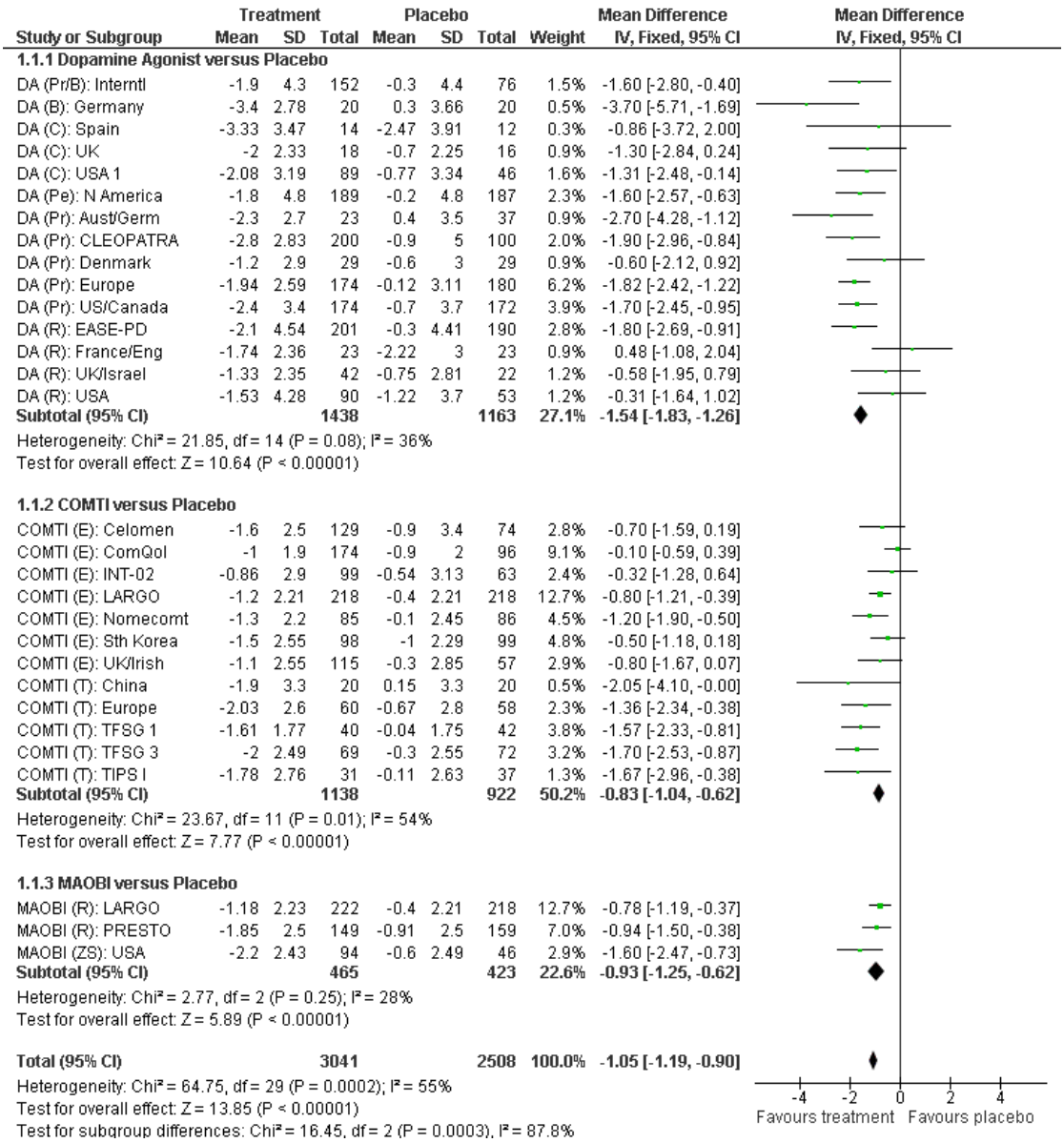
Effects of interventions

Off-Time Reduction (Analysis 1.1 to Analysis 1.4)

Comparison of Adjuvant Therapy versus Placebo (Analysis 1.1; Figure 1)

Data on off-time reduction were available from twenty-nine (of the 44) trials for thirty comparisons, with fifteen (out of 20) trials of dopamine agonists, twelve (out of 18) trials of COMTI and three (out of 7) trials of MAOBI. There were 5331 participants included in the analysis which represented 70% of the 7590 participants included in the meta-analysis. Compared to placebo, adjuvant therapy (on a background of levodopa) significantly reduced off-time by approximately one hour a day (mean reduction -1.05 hours/day, 95% confidence interval (CI) -1.19 to -0.90; P<0.00001; Analysis 1.1; Figure 1). There was however significant heterogeneity between trials (P=0.0002) and between the three add-on drug classes (test for heterogeneity between drug classes, P=0.0003).

Figure 1. Off-Time Reduction (Adjuvant Therapy versus Placebo).



Interclass Comparison of Adjuvant Therapy (Analysis 1.1; Figure 1 ***)***

Although (compared to placebo) all three adjuvant therapy drug classes significantly reduced patients' off-time, there was significant heterogeneity between the three add-on drug classes (test for heterogeneity between drug classes, P=0.0003), suggesting that there may be differences in off-time reduction across the different drug classes. Indirect comparisons of the three drug classes suggested that dopamine agonists (-1.54 hours/day, CI -1.83 to -1.26; P<0.00001; Analysis 1.1; Figure 1) reduced off-time more than COMTI (-0.83 hours/day, CI -1.04 to -0.62; P<0.00001) and MAOBI (-0.93 hours/day, CI -1.25 to -0.62; P<0.00001).

Intraclass Comparison of Drugs used as Adjuvant Therapy (Analysis 1.2 to Analysis 1.4 ***)***

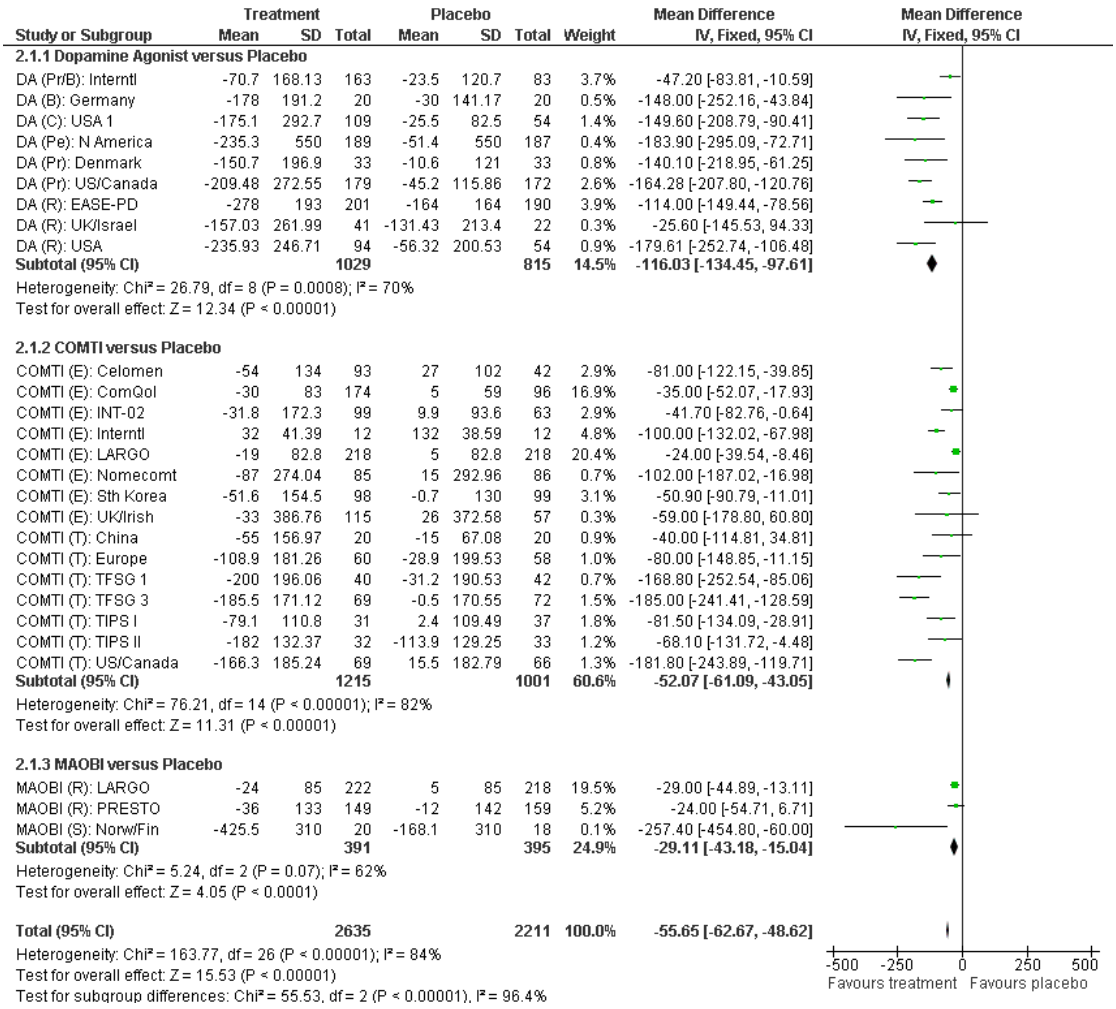
A comparison of the different drugs used as adjuvant therapy found that although dopamine agonists produced the greatest overall reduction in off-time (-1.54 hours/day), there was no evidence of a difference across the different dopamine agonists for which data were available (test for heterogeneity between drugs, P=0.15). The greatest reductions in off-time were observed with pramipexole (-1.81 hours/day, CI -2.19 to -1.43; P<0.00001; Analysis 1.2) followed by bromocriptine (-1.78 hours/day, CI -2.91 to -0.65; P=0.002); pergolide (-1.60 hours/day, CI -2.57 to -0.63; P=0.001); cabergoline (-1.29 hours/day, CI -1.89 to -0.69; P<0.0001) and ropinirole (-0.93 hours/day, CI -1.53 to -0.33; P= 0.002). Similarly, there was no difference in off-time reduction between the MAOBIs rasagiline (-0.84 hours/day, CI -1.17 to -0.50; P<0.00001; Analysis 1.4) and sublingual selegiline (-1.60 hours/day, CI -2.47 to -0.73; P=0.0003) (test for heterogeneity between drugs, P=0.11). In contrast, for the two COMTIs (entacapone and tolcapone) there was evidence of a difference between the two drugs (test for heterogeneity between drugs, P=0.0001), with participants randomised to tolcapone getting an extra hour of on-time (-1.60 hours/day, CI -2.04 to -1.15; P<0.00001; Analysis 1.3) compared to those randomised to entacapone (-0.61 hours/day, CI -0.85 to -0.37; P<0.00001).

Levodopa Dose Reduction (Analysis 2.1 to Analysis 2.4**)**

Comparison of Adjuvant Therapy versus Placebo (Analysis 2.1; Figure 2 ***)***

Data on levodopa dose were available from twenty-eight (of the 44) trials. Two of these trials stated that the levodopa dose should remain constant throughout the trial (DA (C): UK; DA (Pr): Aust/Germ). Since these trials were not trying to reduce the levodopa dose, they were excluded from this analysis. This left twenty-six trials for twenty-seven comparisons, with nine (out of 20) trials of dopamine agonist, fifteen (out of 18) trials of COMTI and three (out of 7) trials of MAOBI. All these trials allowed changes in levodopa dose, though some requested that the dose be kept stable in the period prior to an assessment point. One trial stated that the levodopa dose should be kept stable for the first six weeks of the trial, and then the dose could be reduced (DA (R): UK/Israel), and two other trials stated that changes in levodopa dose were allowed only in the first 6 weeks of the trial (MAOBI (R): LARGO; MAOBI (R): PRESTO). An analysis excluding these trials made little difference to the results, so these three trials were included. There were 4628 participants included in the analysis, which accounted for 61% of the 7590 randomised participants included in this meta-analysis. The required mean daily dose of levodopa was reduced with adjuvant therapy (compared to placebo) by 55.65 mg/day (CI -62.67 to -48.62; P<0.00001; Analysis 2.1; Figure 2).

Figure 2. Levodopa Dose Reduction (mg/day) (Adjuvant Therapy versus Placebo).



Interclass Comparison of Adjuvant Therapy (Analysis 2.1; Figure 2 ***)***

As with off-time reduction, although all three adjuvant therapy drug classes significantly reduced the required daily dose of levodopa, there were again differences across the different add-on drug classes (test for heterogeneity between drug classes, P<0.00001), with greater reductions in levodopa dose with dopamine agonists (-116.03 mg/day, CI -134.45 to -97.61; P<0.00001; Analysis 2.1; Figure 2) compared with both COMTI (-52.07 mg/day, CI -61.09 to -43.05; P<0.00001) and MAOBI (-29.11 mg/day, CI -43.18 to -15.04; P<0.0001).

Intraclass Comparison of Drugs used as Adjuvant Therapy (Analysis 2.2 to Analysis 2.4 ***)***

The greatest reductions in required levodopa dose were observed with dopamine agonists (-116.03 mg/day), but there was little evidence of a difference between the various dopamine agonists used (test for heterogeneity between drugs, P=0.03). The largest reduction in levodopa dose was seen with pergolide (-183.90 mg/day, CI -259.09 to -72.71; P=0.001; Analysis 2.2), though this was based on data from just one trial (DA (Pe): N America). Cabergoline reduced the required levodopa dose by 149.60 mg/day (CI -208.79 to -90.41; P<0.00001), ropinirole by 119.81 mg/day (CI -150.63 to -89.00; P<0.00001), pramipexole by 114.82 mg/day (CI -143.01 to -86.64; P<0.00001) and bromocriptine by 52.17 mg/day (CI -95.16 to -9.18; P=0.02). There was evidence of heterogeneity between the trials of pramipexole (test for heterogeneity between trials, P=0.003; Analysis 2.2) for which there was no obvious explanation. A comparison of the two MAOBIs also found little evidence to suggest that there was a difference between

rasagiline and selegiline (test for heterogeneity between drugs, P= 0.02; Analysis 2.4). A greater reduction in levodopa dose was observed with selegiline (-257.4 mg/day, CI -454.80 to -60.00; P= 0.01; Analysis 2.4) than with rasagiline (-27.94 mg/day, -42.05 to -13.84; P=0.0001), but the selegiline data was based on data from just one trial (MAOBI (S): Norw/Fin), and the two trials of rasagiline only allowed the levodopa dose to be adjusted in the first 6 weeks of the trial (MAOBI (R): LARGO; MAOBI (R): PRESTO). In contrast, differences were again observed between tolcapone and entacapone, with greater reductions in levodopa dose seen with tolcapone (-116.47 mg/day, CI -140.62 to -92.32; P<0.00001; Analysis 2.3) compared with entacapone (-41.62 mg/day, CI -51.35 to -31.89; P<0.00001) (test for heterogeneity between drugs, P<0.00001). However, for both COMTIs there was significant heterogeneity between trials (test for heterogeneity between trials, entacapone P=0.001, tolcapone P=0.002), which was not explained by drug dose (all trials used 200mg of entacapone) or treatment schedule (in all the COMTI studies changes in levodopa dose were allowed, though in some studies the dose had to be kept stable in the run-up to an assessment point) (*See* Characteristics of included studies).

Clinician-Rated Disability Scales (Analysis 3.1 to Analysis 3.11)

Comparison of Adjuvant Therapy versus Placebo *(* Analysis 3.1 to Analysis 3.3; Figure 3, Figure 4 and Figure 5 *)*

Data on the clinician-rated UPDRS activities of daily living (ADL), motor and total (parts I-III or parts I-IV) scores were available from twenty-three (of the 44) trials for twenty-four comparisons, with eight (out of 20) trials of dopamine agonist, fourteen (out of 18) trials of COMTI and two (out of 7) trials of MAOBI. For the UPDRS ADL score, sixteen trials had data available (six trials of dopamine agonist and ten trials of COMTI) with 2655 participants included in the analysis (2655/7590; 35% of randomised participants). Nineteen trials (for twenty comparisons) provided data on the UPDRS motor score (seven trials of dopamine agonist, twelve trials of COMTI and one trial of MAOBI) with 3682 participants included (3682/7590; 49% of all randomised participants). Finally, UPDRS total score data were available from ten trials (three trials of dopamine agonist reporting total parts I-IV, six trials of COMTI reporting total parts I-III and one trial of MAOBI reporting total parts I-IV) and included 1513 participants (1513/7590; 20% of all randomised participants).

Figure 3. UPDRS Activities of Daily Living Score (Adjuvant Therapy versus Placebo).

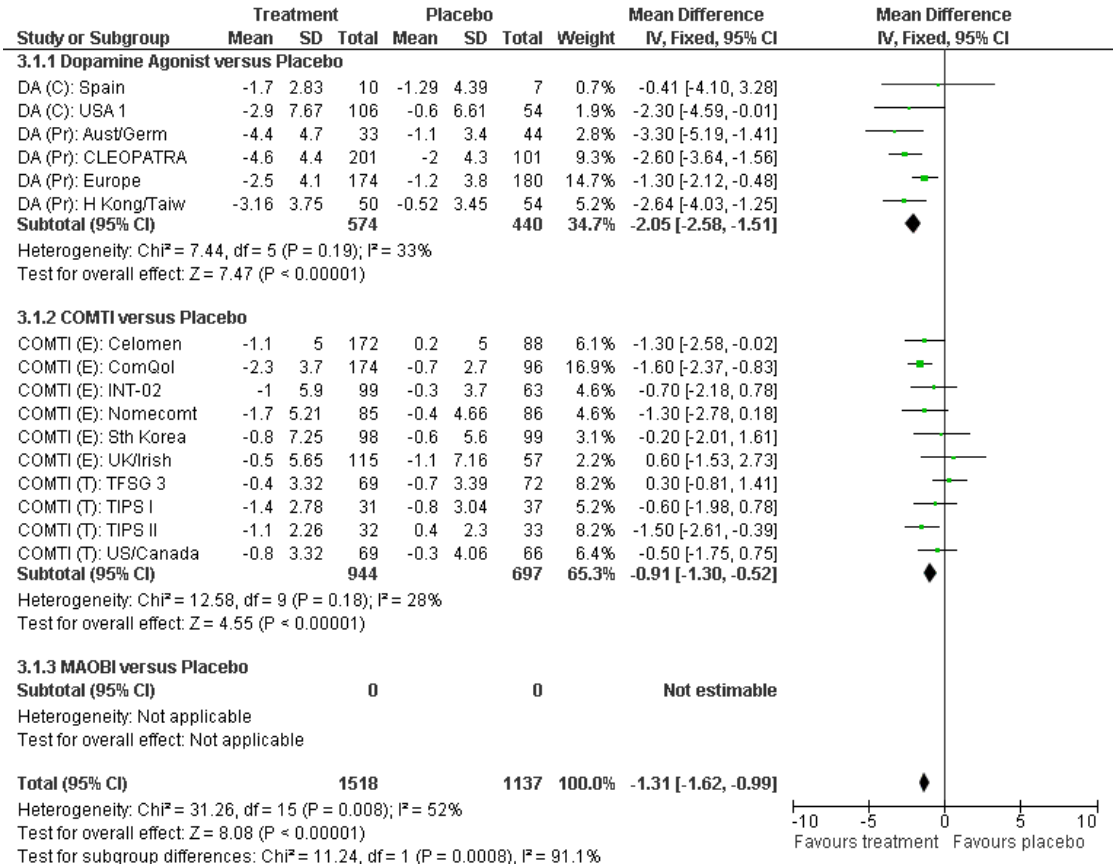


Figure 4. UPDRS Motor Score (Adjuvant Therapy versus Placebo).

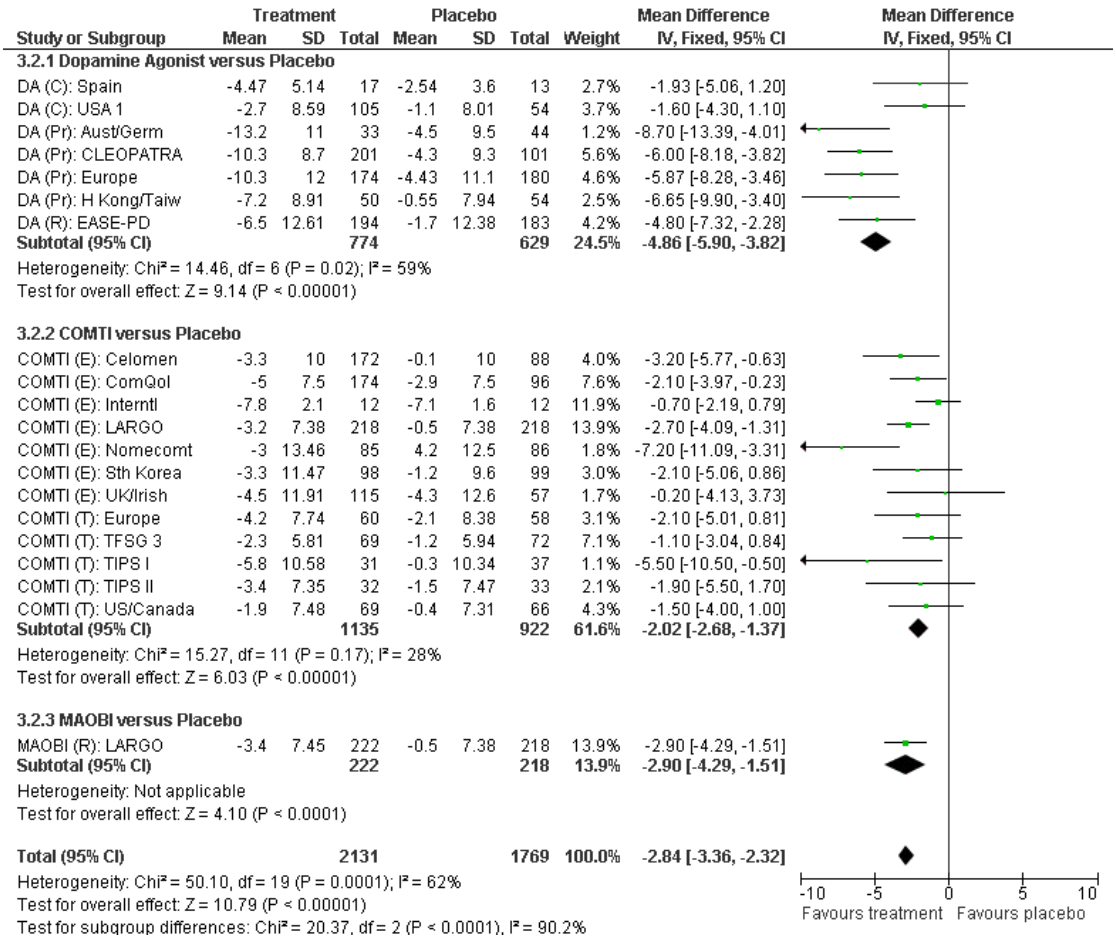
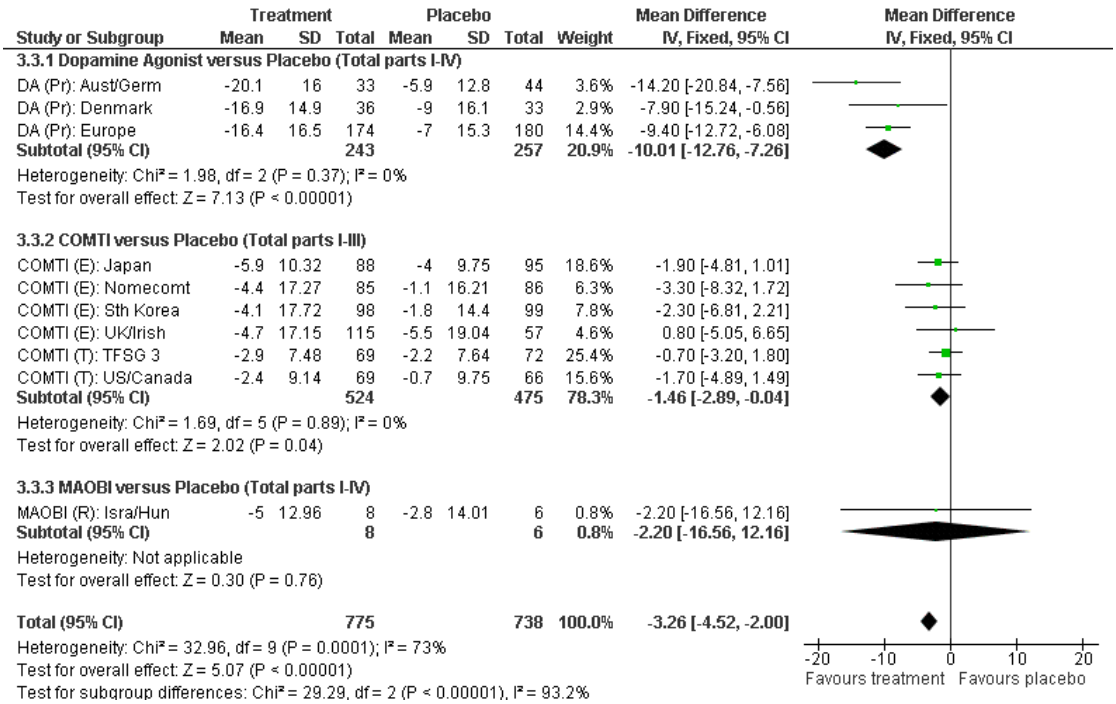


Figure 5. UPDRS Total Score (Adjuvant Therapy versus Placebo).



Compared to placebo, adjuvant therapy improved symptom control as measured by the UPDRS, with a 1.31 point (CI -1.62 to -0.99; P<0.00001; Analysis 3.1; Figure 3) improvement in the UPDRS ADL score, a 2.84 point (CI -3.36 to -2.32; P<0.00001; Analysis 3.2; Figure 4) improvement in the UPDRS motor score and a 3.26 point (CI -4.52 to -2.00; P<0.00001; Analysis 3.3; Figure 5) improvement in the UPDRS total score. For all three UPDRS scores there was significant heterogeneity between trials (P<=0.008) and between the three drug classes (P<=0.0008).

Interclass Comparison of Adjuvant Therapy (Analysis 3.1 to Analysis 3.3; Figure 3, Figure 4 and Figure 5 ***)***

Indirect comparisons of the three adjuvant drug classes suggest that improvements in all the UPDRS scores were greater with dopamine agonists compared with COMTI and MAOBI (though there were only two trials of MAOBI that reported UPDRS data (MAOBI (R): Isra/Hun; MAOBI (R): LARGO). For the UPDRS ADL score, there was a two point improvement with dopamine agonist (-2.05 points, CI -2.58 to -1.51; P<0.00001; Analysis 3.1; Figure 3) compared to nearly a one point improvement with COMTI (-0.91 points, CI -1.30 to -0.52; P<0.00001) (test for heterogeneity between drug classes, P=0.0008). Similarly, for the UPDRS motor score, a larger improvement was seen with dopamine agonists, with a five point improvement (-4.86 points, CI -5.90 to -3.82; P<0.00001; Analysis 3.2; Figure 4) compared with a two point improvement with COMTI (-2.02 points, CI -2.68 to -1.37; P<0.00001) and a three point improvement with MAOBI (-2.90 points, CI -4.29 to -1.51; P<0.0001) (test for heterogeneity between drug classes, P<0.0001). For the UPDRS total score, dopamine agonists improved the score by ten points (-10.01 points, CI -12.76 to -7.26; P<0.00001; Analysis 3.3; Figure 5) compared to improvements of one and half points with COMTI (-1.46 points, CI -2.89 to -0.04; P=0.04) and two points with MAOBI (-2.20 points, CI -16.56 to 12.16; p=0.76) (test for heterogeneity between drug classes, P<0.00001).

Intraclass Comparison of Drugs used as Adjuvant Therapy (Analysis 3.4 to Analysis 3.11 ***)***

Comparisons of the different drugs used as adjuvant therapy was limited to trials of dopamine agonist and COMTI (as there were only two trials of MAOBI, both of rasagiline). Indirect comparisons of dopamine agonists was limited to the agonists cabergoline, pramipexole and ropinirole for the UPDRS ADL and motor scores - UPDRS total data were only available for pramipexole. The agonist pramipexole appeared to produce larger improvements for both the UPDRS ADL (-2.07 points, CI -2.63 to -1.51; P<0.00001; Analysis 3.4) and UPDRS motor (-6.31 points, CI -7.69 to -4.93; P<0.00001; Analysis 3.6) scores compared to ropinirole (UPDRS motor: -4.80 points, CI -7.32 to -2.28; P= 0.0002) and cabergoline (UPDRS ADL: -1.78 points, CI -3.72 to 0.17; P=0.07; UPDRS motor: -1.74 points, CI -3.78 to 0.30; P=

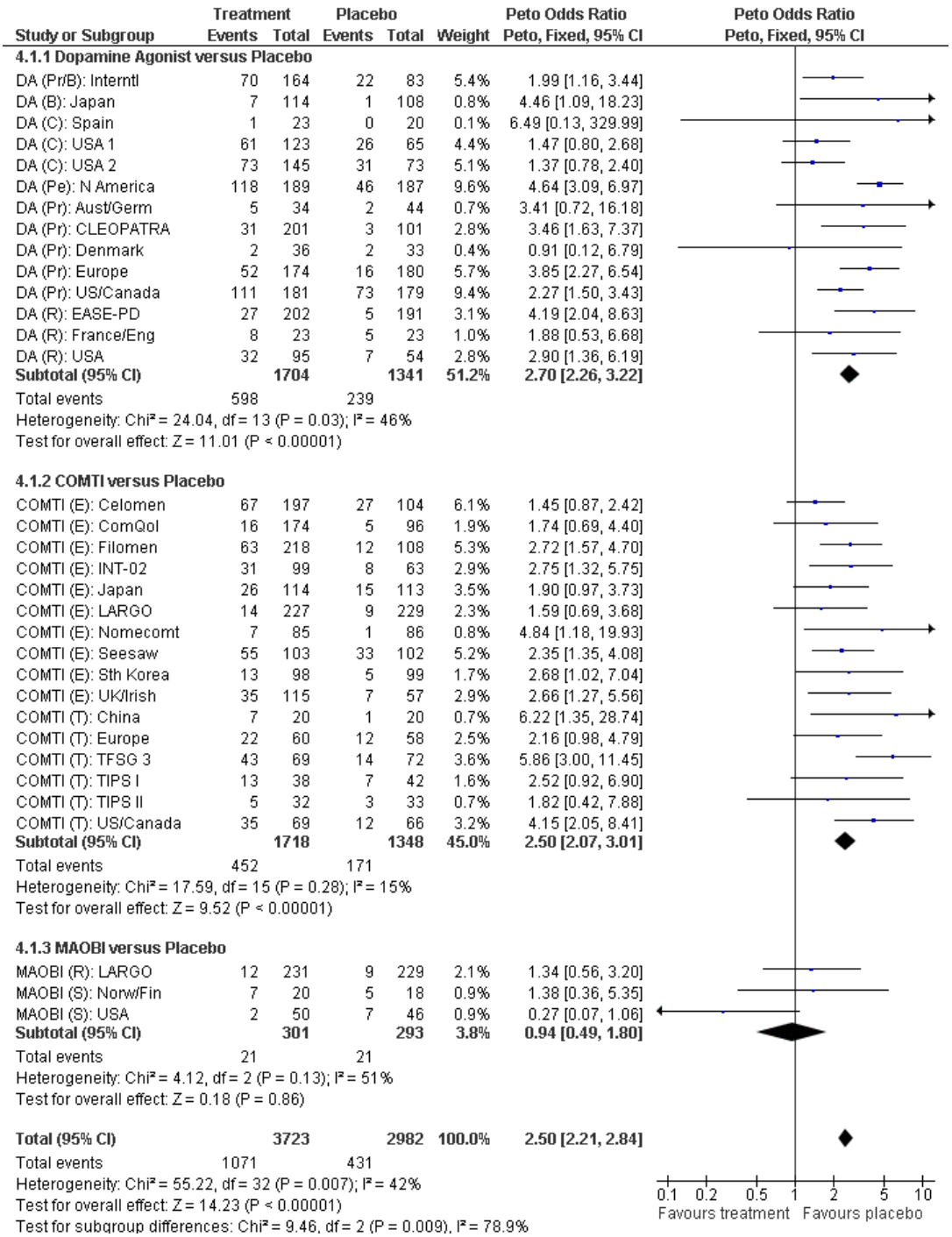
0.09). Though these differences between agonist drugs was only significant for the UPDRS motor score (test for heterogeneity between drugs, P=0.001). For COMTI (the drug class for which the most data were available for analysis), there were no significant differences between entacapone and tolcapone for any of the three UPDRS scores - UPDRS ADL (entacapone -1.16 points, CI -1.68 to -0.64; P<0.0001 versus tolcapone -0.58 points, CI -1.18 to 0.02; P=0.06; test for heterogeneity between drugs, P= 0.15; Analysis 3.5); UPDRS motor (entacapone -2.14 points, CI -2.92 to -1.36; P<0.00001 versus tolcapone -1.73 points, CI -2.96 to -0.51; P=0.006; test for heterogeneity between drugs, P= 0.59; Analysis 3.7); and UPDRS total (entacapone -1.88 points, CI -3.94 to 0.18; P=0.07 versus tolcapone -1.08 points, CI -3.05 to 0.89; P=0.28; test for heterogeneity between drugs, P=0.58; Analysis 3.10).

Dyskinesia and Dystonia (Analysis 4.1 to Analysis 4.5)

Comparison of Adjuvant Therapy versus Placebo *(* Analysis 4.1 to Analysis 4.2; Figure 6 *)*

Dyskinesia and dystonia were reported within the papers as adverse events without further definition. Data on dyskinesia were available from thirty-two (of the 44) trials for thirty-three comparisons, with fourteen (of the 20) trials of dopamine agonist, sixteen (of the 18) trials of COMTI and three (of the 7) trials of MAOBI. Dystonia was also reported in just five of these thirty-two trials (two trials of dopamine agonist and three trials of COMTI). The analysis of the incidence of dyskinesia included 6476 participants, which represented 85% of the 7590 randomised participants included in this meta-analysis. Compared to placebo, the incidence of dyskinesia (odds ratio (OR) 2.50, CI 2.21 to 2.84; P<0.00001; Analysis 4.1; Figure 6), but not dystonia (OR 0.77, CI 0.48 to 1.23; P=0.28; Analysis 4.2), was increased with adjuvant therapy.

Figure 6. Dyskinesia (Adjuvant Therapy versus Placebo).



Interclass Comparison of Adjuvant Therapy (Analysis 4.1 to Analysis 4.2; Figure 6 ***)***

Indirect comparisons of the three add-on drug classes suggest that there may be differences across the classes in the incidence of dyskinesia (test for heterogeneity between drug classes, P=0.009), but not dystonia (P=0.69). For dyskinesia, there was no difference between MAOBI and placebo (OR 0.94, CI 0.49 to 1.80; P= 0.86), but for both dopamine agonist (OR 2.70, CI 2.26 to 3.22; P<0.00001) and COMTI (OR 2.50, CI 2.07 to 3.01; P<0.00001), the incidence of dyskinesia was significantly increased with adjuvant therapy (Analysis 4.1; Figure 6).

Intraclass Comparison of Drugs used as Adjuvant Therapy (Analysis 4.3 to Analysis 4.5 ***)***

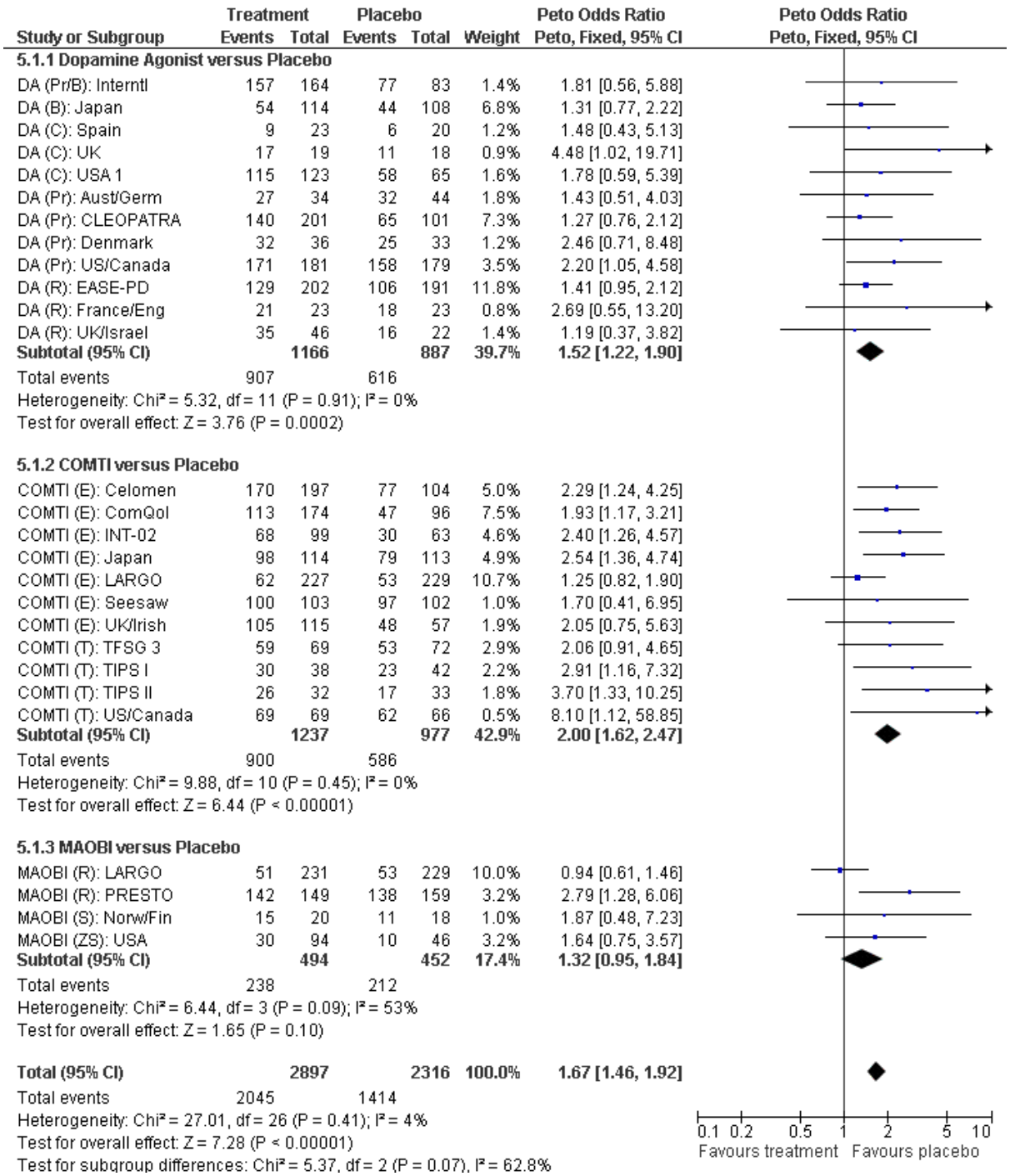
Data on the incidence of dystonia was limited (5 trials reporting just 85 cases of dystonia in 721 participants), so comparisons of the individual drugs were performed only for dyskinesia for which more data were available (1493 cases of dyskinesia in 6476 participants). Comparisons of the different dopamine agonist and COMTI drugs used suggested that there were some differences between the drugs and the risk of dyskinesia (test for heterogeneity between dopamine agonists, P=0.002; COMTI, P=0.01; MAOBI, P=0.24). For dopamine agonists, the incidence of dyskinesia was greatest with pergolide (OR 4.64, CI 3.09 to 6.97; P<0.00001; Analysis 4.3), though this was based on data from just one trial (DA (Pe): N America), followed by ropinirole (OR 3.21, CI 1.98 to 5.21; P<0.00001), pramipexole (OR 2.63, CI 2.01 to 3.42; P<0.00001), bromocriptine (OR 2.52, CI 1.42 to 4.48; P=0.002) and cabergoline (OR 1.44, CI 0.96 to 2.16; P=0.08). Dyskinesia was also increased with COMTI, with again a significant difference between the two drugs used, entacapone (OR 2.16, CI 1.73 to 2.70; P<0.00001; Analysis 4.4) and tolcapone (OR 3.66, CI 2.55 to 5.25; P<0.00001) (test for heterogeneity between drugs, P=0.01).

Adverse Events (Analysis 5.1 to Analysis 5.40)

Comparison of Adjuvant Therapy versus Placebo (Analysis 5.1, Analysis 5.5 to Analysis 5.40; Figure 7 ***)***

The incidence of any side-effect was increased with adjuvant therapy (OR 1.67, CI 1.46 to 1.92; P<0.00001; Analysis 5.1; Figure 7), with some evidence of a difference between the drug classes (test for heterogeneity between drug classes, P=0.07), but not between the individual trials (test for heterogeneity between trials, P= 0.41). Analysis of individual side-effects showed that constipation (OR 3.19, CI 2.17 to 4.68; P<0.00001; Analysis 5.5), dizziness (OR 1.57, CI 1.30 to 1.90; P<0.00001; Analysis 5.6), dry mouth (OR 2.33, CI 1.22 to 4.47; P=0.01; Analysis 5.7), hallucinations (OR 2.16, CI 1.70 to 2.74; P<0.00001; Analysis 5.8), hypotension (OR 1.47, CI 1.18 to 1.83; P=0.0007; Analysis 5.9), insomnia (OR 1.38, CI 1.09 to 1.74; P=0.007; Analysis 5.10), nausea (OR 1.78, CI 1.53 to 2.07; P<0.00001; Analysis 5.11), somnolence (OR 1.87, CI 1.40 to 2.51; P<0.0001; Analysis 5.12) and vomiting (OR 2.56, CI 1.67 to 3.93; P<0.0001; Analysis 5.13) were all increased with adjuvant therapy. Urine discolouration (OR 6.42, CI 4.63 to 8.90; P<0.00001; Analysis 5.40) was also increased with adjuvant therapy, but this side-effect was only reported in trials of COMTI.

Figure 7. Overall Incidence of Side-Effects (Adjuvant Therapy versus Placebo).



Interclass Comparison of Adjuvant Therapy (Analysis 5.1, Analysis 5.5 to Analysis 5.40; Figure 7)

There was little evidence of a difference across the drug classes with regards to the incidence of side-effects (test for heterogeneity between drug classes, P=0.07), with slightly more side-effects seen with both dopamine agonist (OR 1.52, CI 1.22 to 1.90; P= 0.0002) and COMTI (OR 2.00, CI 1.62 to 2.47; P<0.00001) than with MAOBI (OR 1.32, CI 0.95 to 1.84, P=0.1) (Analysis 5.1; Figure 7). The only individual side-effect for which there was evidence of a difference between the drug classes was for diarrhoea (test for heterogeneity between drug classes, P=0.006; Analysis 5.23). Diarrhoea was significantly more frequent with COMTI (OR 2.34, CI 1.67 to 3.28; P<0.00001), but not with dopamine agonist (OR 0.84, CI 0.27 to 2.63; P=0.77) or MAOBI (OR 0.39, CI 0.12 to 1.29; P=0.12).

Intraclass Comparison of Drugs used as Adjuvant Therapy (Analysis 5.2 to Analysis 5.4 ***)***

Although side-effects were increased with all types of adjuvant therapy, there was no evidence of any differences between the different drugs used. More side-effects were seen with the dopamine agonists cabergoline (OR 2.08, CI 1.01 to 4.29; P=0.05; Analysis 5.2) and pramipexole (OR 1.67, CI 1.16 to 2.39; P=0.005) than with ropinirole (OR 1.44, CI 0.99 to 2.09; P=0.05) or bromocriptine (OR 1.25, CI 0.77 to 2.03; P=0.36), but these differences between the drugs were not statistically significant (test for heterogeneity between drugs, P=0.64). This was similar for COMTI (entacapone OR 1.85, CI 1.47 to 2.33; P<0.00001 versus tolcapone OR 2.89, CI 1.74 to 4.79; P<0.0001; test for heterogeneity between drugs, P=0.12; Analysis 5.3) and MAOBI (rasagiline OR 1.22, CI 0.84 to 1.79; P=0.3 versus selegiline OR 1.87, CI 0.48 to 7.23; P=0.36 versus sublingual selegiline OR 1.64, CI 0.75 to 3.57; P=0.21; test for heterogeneity between drugs, P=0.7; Analysis 5.4).

Mortality (Analysis 6.1 to Analysis 6.4)

Comparison of Adjuvant Therapy versus Placebo (Analysis 6.1 ***)***

Most trials investigated only short-term efficacy, so data on mortality were available from just twelve of the 44 trials (with six of these trials reporting that there were no deaths during the trial): eight (out of 20) trials of dopamine agonist, two (out of 18) trials of COMTI and two (out of 7) trials of MAOBI. The analysis of mortality included 1845 participants, which represented 24% of the 7590 randomised participants included in this meta-analysis. The number of deaths reported in the twelve trials was small (n= 16), with the risk of mortality lower with adjuvant therapy (OR 0.32, CI 0.12 to 0.89; P=0.03; Analysis 6.1).

Interclass Comparison of Adjuvant Therapy (Analysis 6.1 ***)***

Mortality was reduced with all three add-on drug classes, and there was no evidence of a difference between the classes (dopamine agonist OR 0.35, CI 0.09 to 1.41; P=0.14; COMTI OR 0.33, CI 0.07 to 1.62, P=0.17; and MAOBI OR 0.14, CI 0.00 to 6.82; P= 0.32; test for heterogeneity between drug classes, P=0.9; Analysis 6.1).

Intraclass Comparison of Drugs used as Adjuvant Therapy (Analysis 6.2 to Analysis 6.4 ***)***

There was also no evidence that mortality differed depending on the adjuvant therapy drug being used, though this analysis is based on very small numbers (test for heterogeneity between agonists, P= 0.82 - the only drug class with data available for >2 drugs; Analysis 6.2).

Patient Withdrawal (Analysis 7.1 to Analysis 7.12)

Comparison of Adjuvant Therapy versus Placebo (Analysis 7.1 to Analysis 7.3; Figure 8, Figure 9 and Figure 10 ***)***

Data on patient withdrawal from treatment or from the trial were available from most trials (32/44 trials), and the analyses included 6176 participants (81% of the 7590 randomised participants). Overall patient withdrawal from the trials was less frequent with adjuvant therapy (OR 0.71, CI 0.62 to 0.81; P<0.00001; Analysis 7.1; Figure 8), though there was evidence of heterogeneity between trials (P<0.00001) and between the three drug classes (P<0.0001). Investigation into the reasons for patient withdrawal suggested that adjuvant therapy reduced the likelihood of a participant withdrawing due to lack of efficacy (OR 0.19, CI 0.13 to 0.28; P<0.00001; Analysis 7.3; Figure 10), but increased the risk of withdrawal due to adverse events (OR 1.20, CI 1.00 to 1.43; P=0.05; Analysis 7.2; Figure 9).

Figure 8. Overall Patient Withdrawal (Adjuvant Therapy versus Placebo).

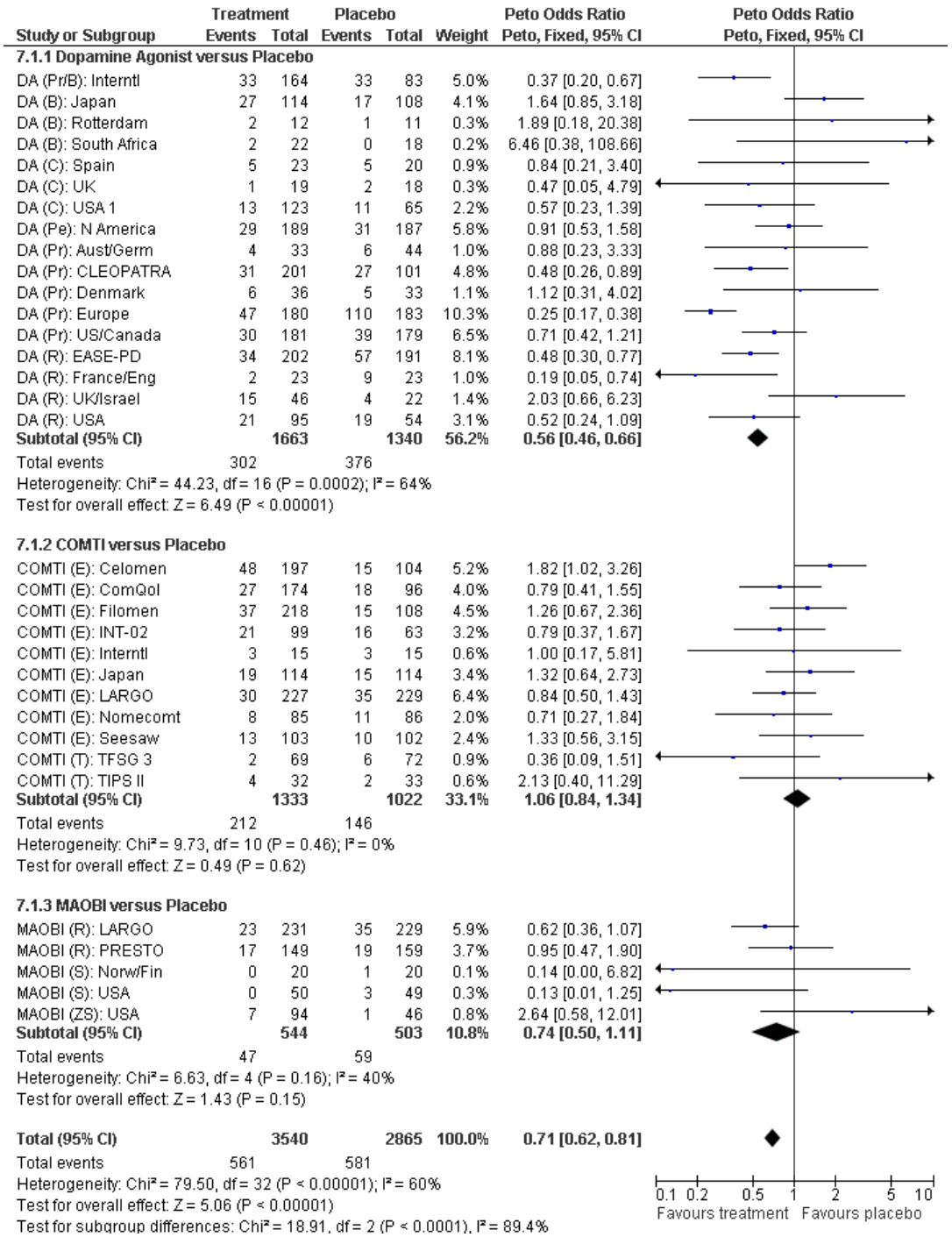


Figure 9. Patient Withdrawal due to Adverse Events (Adjuvant Therapy versus Placebo).

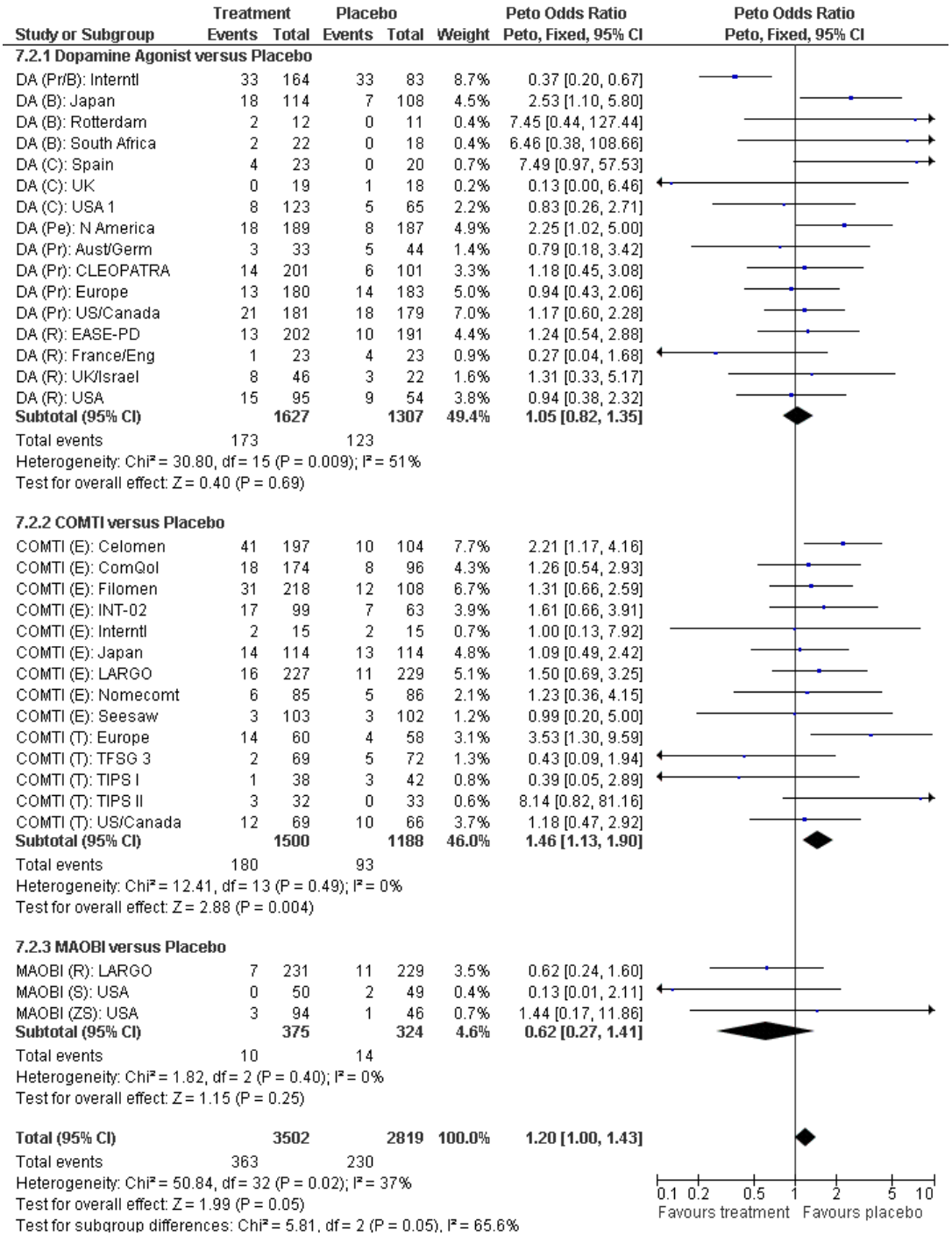
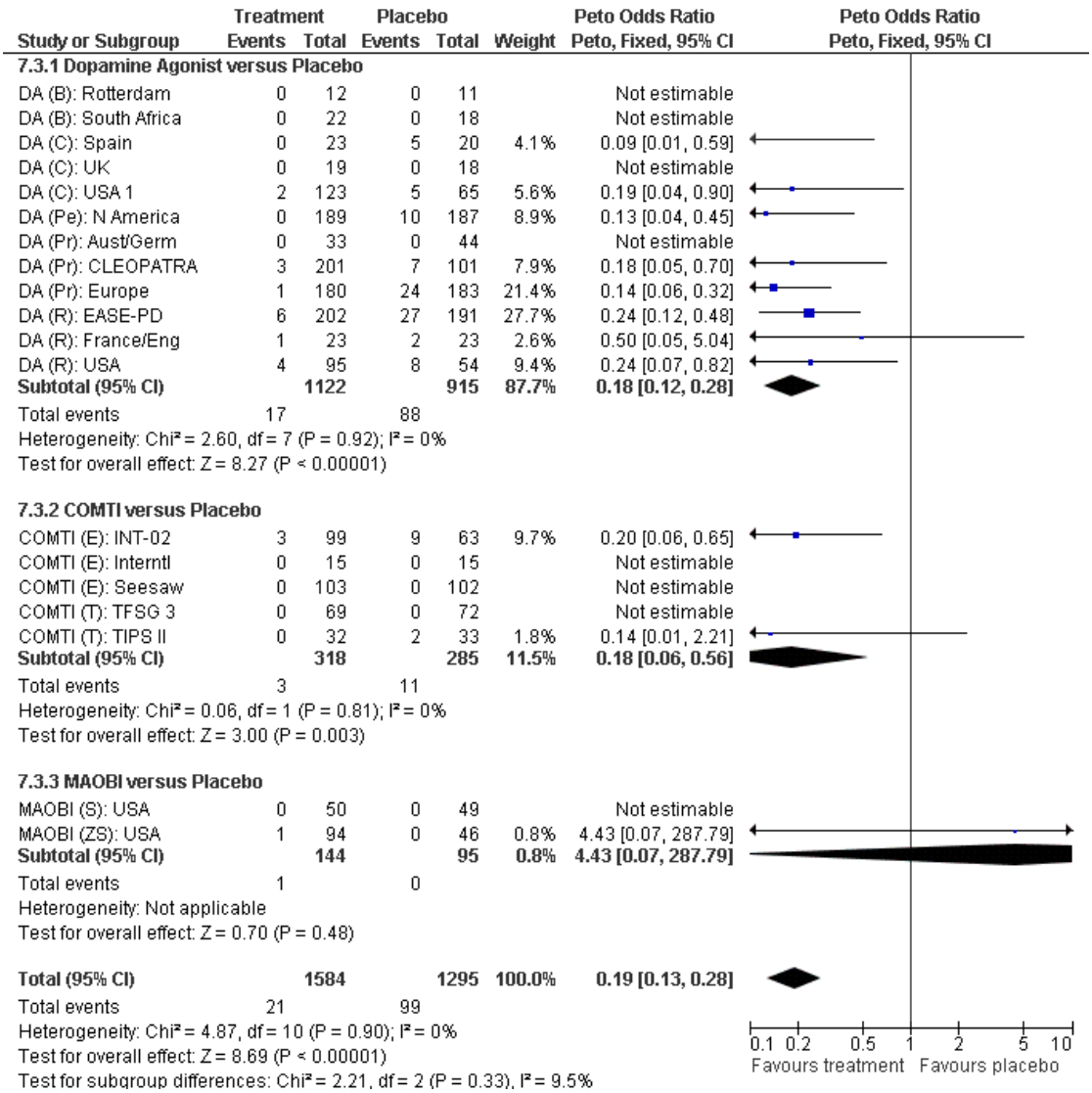


Figure 10. Patient Withdrawal due to Lack of Efficacy (Adjuvant Therapy versus Placebo).



Interclass Comparison of Adjuvant Therapy (Analysis 7.1 to Analysis 7.3; Figure 8, Figure 9 and Figure 10 ***)***

Although overall patient withdrawal was decreased with adjuvant therapy, there was significant heterogeneity between the three drug classes, suggesting that there may be differences between the types of adjuvant therapy used (test for heterogeneity between drug classes, P<0.0001). Patient withdrawal was less likely with either a dopamine agonist (OR 0.56, CI 0.46 to 0.66; P<0.00001; Analysis 7.1; Figure 8) or MAOBI (OR 0.74, CI 0.50 to 1.11; P=0.15), though for MAOBI this was not statistically significant. In contrast, patient withdrawal was slightly increased with COMTI (OR 1.06, CI 0.84 to 1.34; P=0.62), though the confidence interval is compatible with a 16% reduction or a 34% increase in the risk of patient withdrawal. For both patient drop-out due to adverse events and patient drop-out due to lack of efficacy, there was no evidence of a difference between the different drug classes (test for heterogeneity between drug classes, P>=0.05). Patient withdrawal due to adverse events were significantly increased with COMTI (OR 1.46, CI 1.13 to 1.90; P=0.004; Analysis 7.2; Figure 9), but not with dopamine agonist (OR 1.05, CI 0.82 to 1.35; P=0.69) or MAOBI (OR 0.62, CI 0.27 to 1.41; P=0.25) (test for heterogeneity between drug classes, P=0.05). However, the reverse was

observed for patient withdrawal due to a lack of efficacy, which were significantly reduced with dopamine agonist (OR 0.18, CI 0.12 to 0.28; P<0.00001; Analysis 7.3; Figure 10) and COMTI (OR 0.18, CI 0.06 to 0.56; P=0.003). The MAOBI data included only one patient withdrawal for lack of efficacy in two trials, and did not differ significantly from the other drug classes (test for heterogeneity between drug classes, P=0.33).

Intraclass Comparison of Drugs used as Adjuvant Therapy (Analysis 7.4 to Analysis 7.12 ***)***

Indirect comparisons of the drugs within each drug class found no strong evidence to suggest there were differences in overall patient withdrawal (P>=0.02; Analysis 7.4 to Analysis 7.6), patient withdrawal due to adverse events (P>0.2; Analysis 7.7 to Analysis 7.9) or patient withdrawal due to lack of efficacy (P>0.6; Analysis 7.10 to Analysis 7.12). For dopamine agonists, the smallest number of patient withdrawals was observed with pramipexole (OR 0.43, CI 0.33 to 0.55; P<0.00001; Analysis 7.4) and ropinirole (OR 0.53, CI 0.37 to 0.76; P=0.0006), but there was only weak evidence of a difference between the agonists (test for heterogeneity between drugs, P=0.02). Comparisons of the two COMTIs, showed that overall patient withdrawal was increased with entacapone (OR 1.08, CI 0.85 to 1.36; P=0.54; Analysis 7.5), but decreased with tolcapone (OR 0.77, CI 0.26 to 2.26; P=0.63), but this difference between the two drugs was not significant (test for heterogeneity between drugs, P=0.55). Similarly, for MAOBI, where patient withdrawal was reduced with both rasagiline (OR 0.73, CI 0.47 to 1.12; P=0.15) and selegiline (OR 0.13, CI 0.02 to 0.93; P= 0.04), but increased with sublingual selegiline (OR 2.64, CI 0.58 to 12.01), the differences across the three MAOBI drugs was not significant (test for heterogeneity between drugs, P=0.06).

Patient withdrawal due to adverse events were increased for the dopamine agonists cabergoline (OR 1.24, CI 0.46 to 3.33; P= 0.67; Analysis 7.7) and pergolide (OR 2.25, CI 1.02 to 5.00; P=0.05), similar for ropinirole (OR 1.00, CI 0.58 to 1.70; P= 0.99) and decreased for bromocriptine (OR 0.93, CI 0.56 to 1.53; P=0.77) and pramipexole (OR 0.79, CI 0.55 to 1.14; P=0.21), but there was no evidence of a difference between the agonists (test for heterogeneity between drugs, P=0.22). Increases in patient withdrawal due to adverse events were seen for both entacapone (OR 1.45, CI 1.09 to 1.94; P=0.01; Analysis 7.8) and tolcapone (OR 1.50, CI 0.85 to 2.65; P=0.16), with no difference between the two COMTIs (test for heterogeneity between drugs, P=0.92). Similarly, for MAOBI, where although patient withdrawal due to adverse events were lower with rasagiline (OR 0.62, CI 0.24 to 1.60; P=0.33; Analysis 7.9) and selegiline (OR 0.13, CI 0.01 to 2.11; P=0.15), but higher with sublingual selegiline (OR 1.44, CI 0.17 to 11.86; P=0.74), there was no evidence that this differed across the drugs (test for heterogeneity, P=0.40).

Patient withdrawal due to lack of efficacy was decreased for all dopamine agonists (Analysis 7.10) and COMTIs (Analysis 7.11), and there was no evidence that this patient withdrawal rate differed across the different drugs (test for heterogeneity between drugs, dopamine agonists P=0.61, COMTI P=0.81).

Quality of Life

Only three studies included a patient-rated quality of life assessment (COMTI (E): ComQol; COMTI (E): INT-02; DA (R): EASE-PD). Two trials reported data on the eight domains of the PDQ-39 - one trial of ropinirole (DA (R): EASE-PD) and one trial of entacapone (COMTI (E): ComQol). The other trial (also of entacapone) reported data using the mental and physical scores of the SF-36 (COMTI (E): INT-02). No significant differences in patient quality of life were observed between treatments in the two trials of entacapone (COMTI (E): ComQol; COMTI (E): INT-02). However, in the trial of ropinirole, there were significant differences (in favour of ropinirole) in the mobility (difference: -6.8 points, CI -10.07 to -3.53; p<0.0001), activities of daily living (difference: -6.5 points, CI -9.71 to -3.25; p<0.0001), emotional well-being (difference: -3.7 points, CI -6.68 to -0.82; p= 0.01), stigma (difference: -4.5 points, CI -8.06 to -0.87; p=0.02) and communication (difference: -3.7 points, CI -6.88 to -0.61; p=0.02) domains of the PDQ-39 (DA (R): EASE-PD).

Health Economics

No studies reported data on health economic outcomes.

DISCUSSION

Summary of main results

This is the first reported 'umbrella' meta-analysis to compare the three drug classes used as adjuvant therapy for patients with later PD who have developed motor complications (on levodopa therapy). It also reports the comparison of the different drugs used within the adjuvant therapy drugs classes, and thus provides a comprehensive assessment of adjuvant therapy. Previous Cochrane reviews have investigated individual drugs within the three classes of adjuvant therapy separately, making it difficult to compare the different add-on therapy regimens or the different drugs used as adjuvant therapy (Clarke 1999a; Clarke 1999b; Clarke 2000; Clarke 2001a; Clarke 2001b; Deane 2004; van Hilten 1998). This meta-analysis includes all oral drugs (excluding patches and pumps) commonly used as adjuvant therapy (on a background of levodopa) for the treatment of later PD, and includes a more comprehensive range of outcomes than previous reviews, and thus provides the most reliable summary available of the current published evidence.

Adjuvant Therapy versus Placebo

This review confirms reports from individual studies that adjuvant therapy with a dopamine agonist, COMTI or MAOBI can reduce patients' off-time, reduce the required levodopa dose and improve UPDRS scores in those patients with PD who have developed motor complications on levodopa therapy. However, this is at the expense of increased dyskinesia and numerous other side-effects including constipation, dizziness, hallucinations, hypotension, in-

somnia, nausea, somnolence and vomiting. It is unclear from the publications how severe or prolonged these side-effects were (most studies were of short duration), although there was a trend towards increased patient withdrawal due to adverse events in patients on adjuvant therapy. However, patient withdrawal from treatment or trial for any reason was less in those on adjuvant therapy indicating that the balance of efficacy versus side-effects favoured adjuvant therapy.

Interclass Comparisons of Adjuvant Therapy

Whilst it is clear that add-on therapy is beneficial in the treatment of later PD, it is less clear which class of add-on drug therapy, if any, is more efficacious. Clinicians and patients are obviously interested in whether one add-on drug class may be more effective than another, as such information may help to establish an order in which to use these drugs. Since the different drug classes target different pharmacodynamic mechanisms, the trials included in this meta-analysis were divided according to drug class (dopamine agonist, COMTI or MAOBI), and these classes were compared to investigate whether the treatment effect differed across the different adjuvant therapy drug classes. These indirect comparisons should however be interpreted cautiously, as differences in the trial populations studied, protocol specified dose modification schedules and the outcome measures assessed can introduce spurious differences between drug classes. In this meta-analysis, there was only one trial that included a randomisation between drugs from different classes (MAOBI and COMTI), but the study was not powered to compare the two active drugs (rasagiline and entacapone) (COMTI (E): LARGO). Thus, indirect comparisons such as those reported here are useful for generating hypotheses, but these hypotheses need to be tested in large randomised head-to-head trials. To date, there are only three small randomised trials in adjuvant PD therapy with direct class to class (COMTI versus DA) comparisons (CAMP Study Group 2007; Tolcapone/Pergolide Study Group 2001; Tolcapone Study Group 1999).

As expected there was considerable heterogeneity between the different adjuvant therapy drugs, whether examined by individual trial or when considering each class as a whole. In terms of the efficacy outcome measures (off-time, levodopa dose and UPDRS scores), the heterogeneity observed between the trials was probably due to real differences in efficacy between the three add-on drug classes, as there were significantly greater reductions in both off-time and levodopa dose, and greater improvements in UPDRS scores with dopamine agonists than with COMTI and MAOBI. For all cause withdrawal, the heterogeneity between trials was again probably due to differences between the adjuvant therapy drug classes, with the risk of patient withdrawal being significantly reduced with dopamine agonist therapy (compared with placebo), but not with MAOBI or COMTI. These benefits for dopamine agonists must however, be balanced against an increased risk of dyskinesia and other side-effects. There was a greater incidence of dyskinesia with dopamine agonists and COMTIs, but no increase with MAOBIs (when compared with placebo). The risk of side-effects was increased for all three add-on drug classes, with little evidence that the risk of side-effects differed between the three adjuvant therapy drug classes.

These indirect comparisons of placebo-controlled trials using tests of heterogeneity to compare the three adjuvant therapy drug classes indicates that dopamine agonist therapy may be more effective than COMTI and MAOBI therapy. In terms of safety, dopamine agonists and COMTIs have a similar prevalence of side-effects, though more than MAOBIs. Thus, this meta-analysis suggests that the greater efficacy and reduced likelihood of patient withdrawal with dopamine agonist therapy possibly outweighs the disadvantage of increased side-effects.

Intraclass Comparisons within the Adjuvant Therapy Drug Classes

In this review, we also compared the efficacy and safety of the individual drugs used within the different add-on drug classes. There were generally insufficient data to draw any reliable conclusions about the relative merits of for example, selegiline versus rasagiline, and between the different dopamine agonists. Only for the two COMTIs entacapone and tolcapone was there evidence of a possible difference in the efficacy of these drugs. Significant heterogeneity was found between entacapone and tolcapone for off-time reduction and levodopa dose reduction, which seems most likely to be explained by greater efficacy of tolcapone compared with entacapone. However, tolcapone has been associated with several cases of fatal hepatic toxicity. Consequently, in Europe it is licensed for use only after entacapone has been tried and failed, and with mandatory long-term liver function tests. This makes tolcapone therapy impractical for some patients.

Quality of the evidence

The majority of the trials included in this review were designed by the pharmaceutical industry. Most had narrow inclusion criteria, with patients being relatively young (early 60s) and predominantly white compared to typical clinical populations. It is not possible to examine differences in efficacy or side-effects by age in a published data meta-analysis. Therefore, it is possible, that the findings of this meta-analysis may be less applicable to, for example, older patients with PD, who form the majority of PD patients. It is certainly conceivable that older patients may not tolerate adjuvant therapy as well as the generally younger patients involved in these trials. Toxicity by age may well be better studied in a carefully conducted, and adequately large, individual trial rather than in meta-analyses. Another shortcoming of this meta-analysis is that the majority of the trials included in this review were of six months or less in duration. Only eight trials followed-up patients for longer than six months, the longest being just two years, meaning that there are inadequate data on the comparative efficacy and tolerability of these drugs beyond six months. In such a long-term disease as PD, it would obviously be valuable to know whether the drug effects persist for a much longer period. Further, only three studies

included a patient-rated quality of life assessment (PDQ-39 in two, SF-36 in one) (COMTI (E): ComQol; COMTI (E): INT-02; DA (R): EASE-PD) and no studies reported data on health economic outcomes. In the current cost-conscious health climate, such information on both clinical and cost-effectiveness is clearly important.

In summary, adjuvant therapy using dopamine agonists, COMTI or MAOBI therapy on a background of levodopa is clearly effective in the management of later PD. This review suggests that dopamine agonists may be more effective than COMTI and MAOBI therapy. However, these comparisons are based on inference from indirect comparisons rather than direct head-to-head comparisons - surprisingly few of which have been undertaken - so uncertainty remains as to which class of drug is really the most clinically and cost-effective in the treatment of PD patients experiencing motor complications. To clarify the long-term balance of benefits and risks of adjuvant therapy, further large well-designed randomised controlled trials directly comparing the differential impact of these drugs on patient-rated quality of life and cost-effectiveness are needed.

AUTHORS' CONCLUSIONS

Implications for practice

Adjuvant treatment (on a background of levodopa) with either a dopamine agonist, COMTI or MAOBI is effective in the management of patients with later Parkinson's disease with motor complications. Indirect comparisons suggest that dopamine agonists may be more effective than COMTI and MAOBI therapy, which have similar efficacy, and that the overall incidence of side-effects may be comparable between all three drug classes. Intraclass comparisons generally showed no differences between individual drugs within the drug classes, other than tolcapone appearing more effective than entacapone.

Clinicians need to choose between different adjuvant agents for individual patients. Dopamine agonists appear more effective, but may have a greater risk of the patient experiencing side-effects, particularly in the elderly. The choice of a less effective drug class, such as a COMTI or MAOBI, may reasonably be considered more appropriate in view of the lower risk of side-effects (at least with MAOBI).

Implications for research

The interclass and intraclass comparisons presented here are based on indirect comparisons between results of different trials. A more reliable comparison would be obtained in large randomised controlled clinical trials with direct head-to-head comparisons of these drug classes. One such trial is ongoing in the UK (PD MED: http://www.pdmed.bham.ac.uk/), but others are needed.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

COMTI (E): Celomen

Methods	Parallel group, double-blind trial (24 weeks)
Participants	Idiopathic PD patients with motor complications. Number Randomised: 301 (260 fluctuating; 41 non-fluctuating) Mean age: 61 years Number of males: 129 (43%) Mean duration of PD: 8.9 years
Interventions	COMTI Entacapone (n=197) vs. Placebo (n=104) (In fluctuating patients - Entacapone (n=172) vs. Placebo (n=88))
Outcomes	Clinician-rated disability Off-time Levodopa dose Side-effects
Notes	Treatment Schedule: Entacapone (200mg) was given with each daily LD dose (ranging from 2 to 10 doses daily). Additional Treatment: Changes in levodopa dose allowed. LD dose was to be kept stable between weeks 16 and 24 as far as possible

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomised (computer generated)
Allocation concealment?	Yes	Only the sponsor-employed person who generated the plan was aware of a given individual's assignment during the study
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

COMTI (E): ComQol

Methods	Parallel group, double-blind (13 weeks)
Participants	Idiopathic PD patients with motor fluctuations. Number Randomised: 270 Mean age: 67 years Number of males: 151 (56%) Mean duration of PD: 7.3 years

COMTI (E): ComQol (*Continued*)

Interventions	COMTI Entacapone (n=174) vs. Placebo (n=96)
Outcomes	Clinician-rated disability Patient-rated disability Motor fluctuations On/Off time Levodopa dose Side-effects
Notes	Treatment Schedule: Entacapone (200mg) was given with each LD dose. Additional Treatment: Changes in LD dose allowed during trial, however it had to remain unchanged 4 weeks prior to week 0, week 5 and week 13

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Randomised (method used not given)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

COMTI (E): Filomen

Methods	Parallel group, double-blind (12 months)
Participants	Idiopathic PD patients needing enhancement and/or smoothing of levodopa effects. Fluctuating and non-fluctuating patients. Number Randomised: 326 (275 analysed) Mean age: 62 years Number of males: 216 (66%) Mean duration of PD: 6.1 years
Interventions	COMTI Entacapone (n=218) vs. Placebo (n=108)
Outcomes	Clinician-rated disability Levodopa dose Side-effects
Notes	Treatment Schedule: Entacapone (200mg) taken with each LD dose. Additional Treatment: Changes in LD dose were allowed.

Risk of bias

Item	**Authors' judgement**	**Description**

COMTI (E): Filomen (*Continued*)

Adequate sequence generation?	Unclear	Randomised (method used not given)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

COMTI (E): INT-02

Methods	Parallel group, double-blind (12 weeks)
Participants	Idiopathic PD patients with motor fluctuations. Number Randomised: 162 Mean age: 64 years Number of males: 101 (62%) Mean duration of PD: Not available
Interventions	COMTI Entacapone (n=99) vs. Placebo (n=63)
Outcomes	Clinician-rated disability Patient-rated disability On/Off time Levodopa dose Side-effects
Notes	Treatment Schedule: Entacapone (200mg) taken with each LD dose. Additional Treatment: Changes in LD dose were allowed.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Randomised (method used not given)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

COMTI (E): Interntl

Methods	Parallel group, double-blind (2 years)
Participants	Idiopathic PD patients with motor complications. Number Randomised: 30 Mean age: 55 years Number of males: 16 (53%)

COMTI (E): Interntl (*Continued*)

	Mean duration of PD: 4.8 years
Interventions	COMTI Entacapone (n=15) vs. Placebo (n=15)
Outcomes	Clinician-rated disability Motor complications Off-time Levodopa dose
Notes	Treatment Schedule: Entacapone (200mg) taken with each LD dose. Additional Treatment: Changes in LD dose were allowed. LD dose frequency remained constant

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomised (computer generated random code)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

COMTI (E): Japan

Methods	Parallel group, double-blind (8 weeks)
Participants	Idiopathic PD patients with motor fluctuations. Number Randomised: 341 (282 in per protocol dataset) Mean age: 63 years Number of males: 127 (45%) Mean duration of PD: 10.2 years
Interventions	COMTI Entacapone 100mg (n=113) vs. COMTI Entacapone 200mg (n=114) vs. Placebo (n=114)
Outcomes	Clinician-rated disability On/Off time Levodopa dose Side-effects
Notes	Treatment Schedule: Entacapone 100mg (1 x 100mg tablet) or 200mg (2 x 100mg tablets) taken with each LD dose. Additional Treatment: Decreases in LD dose were allowed during trial

Risk of bias

COMTI (E): Japan (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Randomised (method used not given)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

COMTI (E): LARGO

Methods	Parallel group, double-blind (18 weeks)
Participants	Idiopathic PD patients with motor fluctuations. Number Randomised: 687 (456 randomised for entacapone vs. placebo comparison) Mean age: 64 years Number of males: 271 (59%) Mean duration of PD: 9 years
Interventions	COMTI Entacapone (n=227) vs. MAOBI Rasagiline (n=231) vs. Placebo (n=229)
Outcomes	Clinician-rated disability Motor complications On/Off time Side-effects
Notes	Treatment Schedule: Entacapone (200mg) taken with each LD dose. Additional Treatment: Changes in LD dose were allowed during first 6 weeks. LD dose remained constant for final 12 weeks

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomised (computer generated random numbers)
Allocation concealment?	Unclear	Randomisation scheme prepared by sponsors' statistics and data management department, but not clear if randomisation scheme held centrally
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

COMTI (E): Nomecomt

Methods	Parallel group, double-blind (24 weeks)
Participants	Idiopathic PD patients with motor fluctuations. Number Randomised: 171 Mean age: 63 years Number of males: 94 (55%) Mean duration of PD: 10.8 years
Interventions	COMTI Entacapone (n=85) vs. Placebo (n=86)
Outcomes	Clinician-rated disability On/Off time Levodopa dose Side-effects
Notes	Treatment Schedule: Entacapone (200mg) taken with each LD dose. Additional Treatment: Changes in LD dose were allowed. LD dose remained constant as far as possible at weeks 8, 16 and 24

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Randomised (method used not given)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

COMTI (E): Seesaw

Methods	Parallel group, double-blind (28 weeks)
Participants	Idiopathic PD patients with motor fluctuations. Number Randomised: 205 Mean age: 63 years Number of males: 133 (65%) Mean duration of PD: 11.1 years
Interventions	COMTI Entacapone (n=103) vs. Placebo (n=102)
Outcomes	Clinician-rated disability On-time Levodopa dose Side-effects

COMTI (E): Seesaw (*Continued*)

Notes	Treatment Schedule: Those randomised to receive entacapone were further randomised to either 24 or 26 weeks of active therapy followed respectively by either 4 or 2 weeks of placebo. Entacapone (200mg) taken with each LD dose (up to maximum of 10 doses per day) Additional Treatment: Changes in LD dose were allowed for first 8 weeks. LD dose was to remain constant for final 16 weeks. Controlled release carbidopa/LD not allowed

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomised (computer generated randomisation)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

COMTI (E): Sth Korea

Methods	Parallel group, double-blind (8 weeks)
Participants	Idiopathic PD patients with end of dose deterioration. Number Randomised: 197 Mean age: 57 years Number of males: 79 (40%) Mean duration of PD: 7.9 years
Interventions	COMTI Entacapone (n=98) vs. Placebo (n=99)
Outcomes	Clinician-rated disability On/Off time Levodopa dose
Notes	Treatment Schedule: Entacapone schedule not stated. Additional Treatment: LD schedule not stated.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Randomised (method used not given)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

COMTI (E): UK/Irish

Methods	Parallel group, double-blind (6 months)
Participants	Idiopathic PD patients. Fluctuating and non-fluctuating patients. Number Randomised: 300 (172 with fluctuations) Based on patients with fluctuations: Mean age: 65 years Number of males: 109 (63%) Mean duration of PD: 9.4 years
Interventions	COMTI Entacapone (n=203) vs. Placebo (n=97) (In fluctuating patients - Entacapone (n=115) vs. Placebo (n=57))
Outcomes	Clinician-rated disability On/Off time Levodopa dose Side-effects
Notes	Treatment Schedule: Entacapone (200mg) taken with each LD dose (up to maximum of 10 doses per day). Additional Treatment: Changes in LD dose were allowed.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomised (computerised)
Allocation concealment?	Yes	Carried out by department of biostatistics of Orion Pharma
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

COMTI (T): China

Methods	Parallel group, double-blind (6 weeks)
Participants	Idiopathic PD patients with motor fluctuations. Number Randomised: 40 Mean age: 67 years Number of males: 33 (82.5%) Mean duration of PD: 10.1 years
Interventions	COMTI Tolcapone (n=20) vs. Placebo (n=20)
Outcomes	Clinician-rated disability Motor complications Off-time

COMTI (T): China (*Continued*)

	Levodopa dose
Notes	Treatment Schedule: Tolcapone 100mg taken t.i.d. After 3 weeks, tolcapone dose could be increased to 200mg t.i.d. Additional Treatment: Decreases in LD dose were allowed.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Randomised (method used not given)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, controlled

COMTI (T): Europe

Methods	Parallel group, double-blind (12 weeks)
Participants	Idiopathic PD patients with motor fluctuations. Number Randomised: 177 Mean age: 63 years Number of males: 99 (56%) Mean duration of PD: 10 years
Interventions	COMTI Tolcapone 100mg (n=60) vs. COMTI Tolcapone 200mg (n=59) vs. Placebo (n=58)
Outcomes	Clinician-rated disability On/Off time Levodopa dose Side-effects
Notes	Treatment Schedule: Tolcapone dosages of 100mg or 200mg taken t.i.d. First dose taken with first daily dose of LD. The remaining two doses were taken at 6 hourly intervals thereafter. Additional Treatment: Decreases in LD dose were allowed, however changes were not allowed during the 2 weeks prior to 3 month assessment

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomised (computer generated random numbers)
Allocation concealment?	Unclear	No information provided

COMTI (T): Europe (*Continued*)

Blinding? All outcomes	Yes	Double-blind, placebo-controlled

COMTI (T): TFSG 1

Methods	Parallel group, double-blind (6 weeks)
Participants	Idiopathic PD patients with predictable end-of-dose 'off' periods. Number Randomised: 161 (151 analysed) Mean age: 65 years Number of males: 105 (65%) Mean duration of PD: 9.1 years
Interventions	COMTI Tolcapone 50mg (n=41) vs. COMTI Tolcapone 200mg (n=40) vs. COMTI Tolcapone 400mg (n=38) vs. Placebo (n=42)
Outcomes	Clinician-rated disability On/Off time Levodopa dose Side-effects
Notes	Treatment Schedule: Tolcapone dosages of 50mg, 200mg or 400mg taken t.i.d. First dose taken with first daily dose of LD. The remaining two doses were taken at 6 hourly intervals thereafter. Additional Treatment: Decreases in LD dose were allowed, however changes were not allowed after day 28

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomised (computer generated random number tables)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

COMTI (T): TFSG 3

Methods	Parallel group, double-blind (6 weeks)
Participants	Idiopathic PD patients with predictable end-of-dose 'off' time. Number Randomised: 215 Mean age: 63 years Number of males: 149 (69%) Mean duration of PD: 10.6 years

COMTI (T): TFSG 3 (*Continued*)

Interventions	COMTI Tolcapone 100mg (n=69) vs. COMTI Tolcapone 200mg (n=74) vs. Placebo (n=72)
Outcomes	Clinician-rated disability Motor complications On/Off time Levodopa dose Side-effects
Notes	Treatment Schedule: Tolcapone dosages of 100mg or 200mg taken t.i.d. First dose taken with first daily dose of LD. The remaining two doses were taken at 6 hourly intervals thereafter. Additional Treatment: Decreases in LD dose were allowed.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Randomised (blocking)
Allocation concealment?	Yes	No open key to blinding code available to investigators, study monitors or the sponsor's employees
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

COMTI (T): TIPS I

Methods	Parallel group, double-blind (6 weeks)
Participants	Idiopathic PD patients with predictable motor fluctuations. Number Randomised: 154 Mean age: 63 years Number of males: 95 (62%) Mean duration of PD: 10.6 years
Interventions	COMTI Tolcapone 50mg (n=37) vs. COMTI Tolcapone 200mg (n=38) vs. COMTI Tolcapone 400mg (n=37) vs. Placebo (n=42)
Outcomes	Clinician-rated disability Motor complications On/Off time Levodopa dose Side-effects
Notes	Treatment Schedule: Tolcapone dosages of 50mg, 200mg or 400mg taken t.i.d. First dose taken with first daily dose of LD. The remaining two doses were taken at 6 hourly intervals thereafter. Additional Treatment: LD dose kept constant on day 1 and then decreases in dose were allowed. Changes were not allowed in week 6

COMTI (T): TIPS I (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomised (computer generated random number tables)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

COMTI (T): TIPS II

Methods	Parallel group, then crossover, double-blind (9 weeks - 6 weeks parallel group, then 3 weeks crossover)
Participants	Patients with moderately advanced idiopathic PD whose wearing-off of levodopa effects had been successfully controlled by relatively frequent dosage. Number Randomised: 97 Mean age: 67 years Number of males: 62 (64%) Mean duration of PD: Not available
Interventions	COMTI Tolcapone 200mg (n=32) vs. COMTI Tolcapone 400mg (n=32) vs. Placebo (n=33)
Outcomes	Clinician-rated disability Levodopa dose Side-effects
Notes	Treatment Schedule: Tolcapone dosages of 200mg or 400mg taken t.i.d. First dose taken with first daily dose of LD. The remaining two doses were taken at 6 hourly intervals thereafter. At end of week 6, patients in tolcapone groups crossed over to receive other tolcapone dose for an additional 3 weeks. Placebo patients remained on placebo for 9 weeks. Additional Treatment: On first day of treatment, LD dosage reduced by about 35%. After initial reduction, doses retitrated as required. Changes were not allowed in weeks 6 or 9

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomised (computer generated random number tables)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

COMTI (T): US/Canada

Methods	Parallel group, double-blind (12 months)
Participants	Idiopathic PD patients with predictable motor fluctuations. Number Randomised: 202 Mean age: 64 years Number of males: 139 (69%) Mean duration of PD: 10.8 years
Interventions	COMTI Tolcapone 100mg (n=69) vs. COMTI Tolcapone 200mg (n=67) vs. Placebo (n=66)
Outcomes	Clinician-rated disability Motor complications Off-time Levodopa dose Side-effects
Notes	Treatment Schedule: Tolcapone dosages of 100mg or 200mg taken t.i.d. Additional Treatment: After the first day of treatment, LD dose reductions allowed during first 3 months. After month 3, LD dose could be increased

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomised (computer generated random number tables)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

DA (B): Germany

Methods	Parallel group, double-blind (4 weeks)
Participants	Idiopathic PD patients not optimally controlled with levodopa. Number Randomised: 40 Mean age: 65 years Number of males: 23 (57.5%) Mean duration of PD: 9.1 years
Interventions	DA Bromocriptine (n=20) vs. Placebo (n=20)
Outcomes	On/Off Time Levodopa dose

DA (B): Germany (*Continued*)

Notes	Treatment Schedule: Bromocriptine started at dose 2.5mg/day, then increased up to a maximum dose of 30 to 40mg/day. Additional Treatment: Decreases in LD dose allowed.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Randomised (method used not given)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

DA (B): Japan

Methods	Parallel group, double-blind (8 weeks)
Participants	Idiopathic PD patients not optimally controlled with levodopa. Number Randomised: 222 Mean age: 63 years Number of males: 109 (49%) Mean duration of PD: approximately 6.6 years
Interventions	DA Bromocriptine (n=114) vs. Placebo (n=108)
Outcomes	Motor complications On/Off Time Side-effects
Notes	Treatment Schedule: Bromocriptine started at dose 1.25mg/day, then increased up to a maximum dose of 22.5mg/day. Additional Treatment: LD dose remained constant throughout the study

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomised (computer generated)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

DA (B): Rotterdam

Methods	Parallel group, double-blind (5 months)
Participants	Idiopathic PD patients not optimally controlled with levodopa. Number Randomised: 23 Mean age: 59 years Number of males: 10 (43%) Mean duration of PD: 8.7 years
Interventions	DA Bromocriptine (n=12) vs. Placebo (n=11)
Outcomes	Clinician-rated disability
Notes	Treatment Schedule: Bromocriptine started at dose 2.5mg/day, then gradual titration by 2.5mg every 3rd day over the first 10 weeks. The dose was increased, if tolerated, up to a maximum of 100mg/day. Additional Treatment: LD dose regimen not stated.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomised (computer generated)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

DA (B): South Africa

Methods	Parallel group, double-blind (5 weeks)
Participants	Idiopathic PD patients with Hoehn and Yahr stage 2 to 4. Number Randomised: 44 (40 analysed) Mean age: 65 years Number of males: 21 (52.5%) Mean duration of PD: 13.4 years
Interventions	DA Bromocriptine (n=22) vs. Placebo (n=18)
Outcomes	Levodopa dose Side-effects
Notes	Treatment Schedule: Bromocriptine had a 5-week titration phase with starting dose of 2.5mg/day, titrated in increments of 2.5 to 5mg, up to a maximum dose of 20mg/day. Additional Treatment: Changes in LD dose not allowed.

Risk of bias

DA (B): South Africa (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomised (computer generated random number)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

DA (C): Spain

Methods	Parallel group, double-blind (14 weeks)
Participants	Idiopathic PD patients with motor fluctuations. Number Randomised: 43 Mean age: 61 years (range: 36 - 83 years) Number of males: 25 (58%) Mean duration of PD: 10.2 years (range: 0.5 - 21 years)
Interventions	DA Cabergoline (n=23) vs. Placebo (n=20)
Outcomes	Clinician-rated disability Off-time Side-effects
Notes	Treatment Schedule: Cabergoline started at dose 0.75mg/day. For 6 cabergoline and 9 placebo: titrated over 6 weeks up to a maximum dose of 2mg/day. For 12 cabergoline and 5 placebo: titrated over 10 weeks up to a maximum of 3mg/day. Additional Treatment: Changes in LD dose allowed.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomised (computer generated)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

DA (C): UK

Methods	Parallel group, double-blind (6 months)
Participants	Idiopathic PD patients with motor fluctuations. Number Randomised: 37 Mean age: 62 years (range: 44 - 75 years) Number of males: Not available Mean duration of PD: 12.8 years (range: 3 - 33 years)
Interventions	DA Cabergoline (n=19) vs. Placebo (n=18)
Outcomes	Clinician-rated disability Motor complications Off-time Levodopa dose Side-effects
Notes	Treatment Schedule: 12 week titration phase followed by a 3 month stable dose phase. Cabergoline started at dose 0.5mg/day. Doses gradually increased after a maximum of 1 week by 0.5mg, then fortnightly by 0.5mg increments up to 3mg, then 1mg fortnightly increments up to a dose of 5mg/day. A maximum dose of 10mg/day was allowed. Additional Treatment: LD dose kept constant throughout trial as far as possible

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Randomised (method used not given)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

DA (C): USA 1

Methods	Parallel group, double-blind (24 weeks)
Participants	Idiopathic PD patients with motor fluctuations. Number Randomised: 188 Mean age: 63 years (range: 37 - 85 years) Number of males: 125 (66%) Mean duration of PD: 10.6 years (range: 2 - 30 years)
Interventions	DA Cabergoline (n=123) vs. Placebo (n=65)
Outcomes	Clinician-rated disability On/Off time Levodopa dose

DA (C): USA 1 (*Continued*)

	Side-effects
Notes	Treatment Schedule: Cabergoline started at dose 0.5mg/day. Dose gradually increased by 0.5mg, not more than once a week, up to a maximum dose of 5mg/day. Additional Treatment: Decreases in LD dose were allowed during study

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Randomised (sequence of drug codes generated prospectively for each site)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

DA (C): USA 2

Methods	Parallel group, double-blind (24 weeks)
Participants	Idiopathic PD patients on levodopa. Number randomised: 218 Mean age: Not available Number of males: Not available Mean duration of PD: Not available
Interventions	DA Cabergoline (n=145) vs. Placebo (n=73)
Outcomes	Clinician-rated disability Off-time Levodopa dose Side-effects
Notes	Treatment Schedule: Cabergoline started at dose 0.5mg/day, then increased weekly by doses of 0.5mg, up to a maximum daily dose of 6mg/day. Additional Treatment: LD dose not stated.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Randomised (method used not given)
Allocation concealment?	Unclear	No information provided

DA (C): USA 2 (*Continued*)

Blinding? All outcomes	Yes	Double-blind, placebo-controlled

DA (Pe): N America

Methods	Parallel group, double-blind (6 months)
Participants	Idiopathic PD patients with motor fluctuations in Hoehn & Yahr stage 2 to 4. Number Randomised: 376 Mean age: 63 years Number of males: 239 (64%) Mean duration of PD: 10.9 years
Interventions	DA Pergolide (n=189) vs. Placebo (n=187)
Outcomes	Clinician-rated disability Motor complications Off-time Levodopa dose Side-effects
Notes	Treatment schedule: Pergolide started at dose 0.05mg/day, then titrated over 2 weeks up to 0.75mg/day. Dose then increased or decreased until optimal dose (up to a maximum dose of 5mg/day). Additional Treatment: Changes in LD dose allowed, but could not exceed baseline dose

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomised (computer generated)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

DA (Pr): Aust/Germ

Methods	Parallel group, double-blind (11 weeks)
Participants	Idiopathic PD patients with motor fluctuations. Number Randomised: 78 Mean age: 60 years Number of males: 51 (65%) Mean duration of PD: 8.2 years
Interventions	DA Pramipexole (n=34) vs. Placebo (n=44)

DA (Pr): Aust/Germ (*Continued*)

Outcomes	Clinician-rated disability Off-time Levodopa dose Side-effects
Notes	Treatment Schedule: Pramipexole had 7-week titration phase with dose started at 0.2mg/day and titrated up to 5mg/day. Then 4-week maintenance phase and 1-week dose reduction phase. Additional Treatment: MAOBI and amantadine allowed, but as with LD, dosages had to remain unchanged during the trial

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomised (computer generated)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

DA (Pr): CLEOPATRA

Methods	Parallel group, double-blind (6 months)
Participants	Idiopathic PD patients with motor fluctuations in Hoehn & Yahr stage 2 to 4. Number Randomised: 302 Mean age: 64 years Number of males: 183 (61%) Mean duration of PD: 8.5 years
Interventions	DA Pramipexole (n=201) vs. Placebo (n=101)
Outcomes	Clinician-rated disability Motor complications On/Off time Side-effects
Notes	Treatment Schedule: Pramipexole had 7-week titration phase with dose started at 0.375mg/day. Dose then doubled in first week, followed by weekly increments of 0.75mg/day up to a maximum dose of 4.5mg/day. Then 16-week maintenance phase. Additional Treatment: Decreases in LD dose allowed during study

Risk of bias

Item	Authors' judgement	Description

DA (Pr): CLEOPATRA (*Continued*)

Adequate sequence generation?	Yes	Randomised (computer generated)
Allocation concealment?	Yes	Central interactive voice response system
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

DA (Pr): Denmark

Methods	Parallel group, double-blind (12 weeks)
Participants	Idiopathic PD patients with motor fluctuations. Number Randomised: 69 Mean age: 63 years (range: 39 - 77 years) Number of males: 40 (58%) Mean duration of PD: 10 years (range: 3 - 27 years)
Interventions	DA Pramipexole (n=36) vs. Placebo (n=33)
Outcomes	Clinician-rated disability Motor complications Off-time Levodopa dose Side-effects
Notes	Treatment Schedule: Pramipexole had 7-week titration phase up to maximum dose of 5mg/day. Then 4-week maintenence phase, then 1-week dose reduction. Additional Treatment: Changes in LD dose allowed.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomised (computer generated)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

DA (Pr): Europe

Methods	Parallel group, double-blind (32 weeks)
Participants	Idiopathic PD patients with motor fluctuations. Number Randomised: 363 (354 analysed) Mean age: 64 years Number of males: 230 (65%) Mean duration of PD: 7.8 years
Interventions	DA Pramipexole (n=180) vs. Placebo (n=183)
Outcomes	Clinician-rated disability Off-time Levodopa dose Side-effects
Notes	Treatment Schedule: Pramipexole had 7-week titration phase of t.i.d. with LD in seven dosages (0.375 to 4.5mg/day). Then maintenance phase of up to 24 weeks. Additional Treatment: LD dose increases/decreases allowed, but total daily dose could not exceed baseline dose

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Randomised (method used not given)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

DA (Pr): H Kong/Taiw

Methods	Parallel group, double-blind (15 weeks)
Participants	Idiopathic PD patients with Hoehn & Yahr stage 1 to 4. Number Randomised: 150 Mean age: 60 years Number of males: 104 (69%) Mean duration of PD: 4.4 years
Interventions	DA Pramipexole (n=73) vs. Placebo (n=77)
Outcomes	Clinician-rated disability Off-time Side-effects

DA (Pr): H Kong/Taiw (*Continued*)

Notes	Treatment Schedule: Dose escalation phase in weeks 1-7: pramipexole started at dose 0.375mg/day, then increased in sequence of 0.75, 1.5, 2.25, 3 and 3.7mg/day up to a maximum of 4.5mg/day by week 7. Weeks 8-15: maintenence phase. Pramipexole taken t.i.d. Additional Treatment: LD dose could be adjusted.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Randomised (method used not given)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

DA (Pr): US/Canada

Methods	Parallel group, double-blind (32 weeks)
Participants	Idiopathic PD patients with motor fluctuations. Number Randomised: 360 Mean age: 63 years Number of males: 235 (65%) Mean duration of PD: 9.2 years
Interventions	DA Pramipexole (n=181) vs. Placebo (n=179)
Outcomes	Clinician-rated disability On/Off time Levodopa dose Side-effects
Notes	Treatment Schedule: Pramipexole started at dose 0.375mg/day. Titration <=7 weeks up to 4.5mg/day. Then maintenence phase <=24 weeks. Dose reduction for 1 week. Additional Treatment: LD dose increases and decreases allowed, but not to exceed baseline dose

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomised (computer generated)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

DA (Pr/B): Interntl

Methods	Parallel group, double-blind (9 months)
Participants	Idiopathic PD patients with motor fluctuations. Number Randomised: 247 Mean age: 63 years (range: 38 - 90 years) Number of males: 156 (63%) Median duration of PD: 7 years (range: 0.67 - 36 years)
Interventions	DA Pramipexole (n=79) vs. DA Bromocriptine (n=84) vs. Placebo (n=83)
Outcomes	Clinician-rated disability Off-time Side-effects
Notes	Treatment Schedule: Pramipexole/Bromocriptine ascending dose titration in fortnightly increments up to maximum tolerated dose (pramipexole - up to 4.5mg/day and bromocriptine - up to 30mg/day). 24-week maintenance dose period. Additional Treatment: Changes in LD dose allowed, but could not exceed baseline dose

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomised (computer generated)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

DA (R): EASE-PD

Methods	Parallel group, double-blind (24 weeks)
Participants	Idiopathic PD patients with motor fluctuations. Number randomised: 393 Mean age: 66 years Number of males: 246 (63%) Mean duration of PD: 8.6 years
Interventions	DA Ropinirole (24-hour) (n=202) vs. Placebo (n=191)
Outcomes	Clinician-rated disability Depression Sleep Scales Patient-rated quality of life On/Off Time Levodopa dose

DA (R): EASE-PD (*Continued*)

	Side-effects
Notes	Treatment Schedule: Ropinirole 24-hour. 14 day placebo run-in period, 24-week evaluation with 7-day dose titration phase with 8 dose titration levels (2mg/day to 24mg/day). Dose titrated to minimum of 6mg/day. Additional Treatment: If patients were taking >6 tablets of LD, LD could be reduced once ropinirole (or placebo) reached 8mg/day. If subsequent loss of symptom control, ropinirole dose could be adjusted

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomised (computer generated)
Allocation concealment?	Yes	Central telephone randomisation
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

DA (R): France/Eng

Methods	Parallel group, double-blind (12 weeks)
Participants	Idiopathic PD patients not optimally controlled with levodopa. Number Randomised: 46 Mean age: 63 years Number of males: 28 (61%) Mean duration of PD: 8 years
Interventions	DA Ropinirole (n=23) vs. Placebo (n=23)
Outcomes	Clinician-rated disability Motor complications Off-time Side-effects
Notes	Treatment Schedule: Ropinirole started at dose 1mg/day, then increased by 0.5mg increments up to a maximum dose of 8mg/day. Ropinirole taken b.i.d. Additional Treatment: LD dose remained constant throughout trial

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomised (computer generated random numbers)
Allocation concealment?	Unclear	No information provided

DA (R): France/Eng (*Continued*)

Blinding? All outcomes	Yes	Double-blind, placebo-controlled

DA (R): UK/Israel

Methods	Parallel group, double-blind (12 weeks)
Participants	Idiopathic PD patients not optimally controlled with LD (with DCI). Number randomised: 68 Mean age: 63 years (range: 36 - 78 years) Number of males: 41 (60%) Mean duration of PD: Not available
Interventions	DA Ropinirole (n=46) vs. Placebo (n=22)
Outcomes	Clinician-rated disability Off-time Levodopa dose Side-effects
Notes	Treatment Schedule: Ropinirole started at dose 1mg/day, then increased by doses of up to 1mg at each visit up to a maximum dose of 10mg/day. Ropinirole taken b.i.d. Additional Treatment: LD dose kept stable until week 6, then dose could be reduced

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomised (computer generated random numbers)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

DA (R): USA

Methods	Parallel group, double-blind (6 months)
Participants	Idiopathic PD patients with predictable motor fluctuations. Number Randomised: 149 Mean age: Not available Number of males: Not available Mean duration of PD: 9 years
Interventions	DA Ropinirole (n=95) vs. Placebo (n=54)

DA (R): USA (*Continued*)

Outcomes	Clinician-rated disability Motor complications Off-time Levodopa dose Side-effects
Notes	Treatment Schedule: Ropinirole started at dose 0.75mg/day, then increased gradually in 0.75mg/day increments until dose of 3mg/day reached over approximately 2 weeks. Thereafter, daily dose could be increased by 1.5mg each week up to a total dose of 9mg/day and by 3mg/day each week up to a maximum dose of 24mg/day. Minimum dose of 7.5mg/day. Additional Treatment: When patients titrated to 7.5mg/day of ropinirole/placebo, LD dose was decreased

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomised (computer generated randomisation)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

MAOBI (R): Isra/Hun

Methods	Parallel group, double-blind (12 weeks)
Participants	PD patients who had been treated with levodopa for at least 6 months, with disease severity ranging from Hoehn & Yahr stages 1 to 4, and who were insufficiently controlled by treatment. Fluctuating and non-fluctuating patients Number Randomised: 70 (32 with fluctuations) Mean age: 57 years (range: 42 - 65 years) Number of males: 39 (56%) Mean duration of PD: 6.1 years (range: 0.5 - 17.9 years)
Interventions	MAOBI Rasagiline 0.5mg (n=21) vs. MAOBI Rasagiline 1mg (n=18) vs. MAOBI Rasagiline 2mg (n=18) vs. Placebo (n=13) (In fluctuating patients - MAOBI Rasagiline 0.5mg (n=8) vs. MAOBI Rasagiline 1mg (n=8) vs. MAOBI Rasagiline 2mg (n=10) vs. Placebo (n=6))
Outcomes	Clinician-rated disability Levodopa dose Pharmacokinetics Pharmacodynamics
Notes	Treatment Schedule: Rasagiline (0.5mg, 1mg or 2mg) taken once daily. Additional Treatment: LD schedule not stated.

MAOBI (R): Isra/Hun (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Randomised (method used not given)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

MAOBI (R): LARGO

Methods	Parallel group, double-blind (18 weeks)
Participants	Idiopathic PD patients with motor fluctuations. Number Randomised: 687 (460 randomised for rasagiline vs. placebo comparison) Mean age: 64 years Number of males: 286 (62%) Mean duration of PD: 8.8 years
Interventions	MAOBI Rasagiline (n=231) vs. COMTI Entacapone (n=227) vs. Placebo (n=229)
Outcomes	Clinician-rated disability Motor complications On/Off time Side-effects
Notes	Treatment Schedule: Rasagiline (1mg) taken once daily. Additional Treatment: Changes in LD dose were allowed during first 6 weeks. LD dose remained constant for final 12 weeks

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomised (computer generated random numbers)
Allocation concealment?	Unclear	Randomisation scheme prepared by sponsors' statistics and data management department, but not clear if randomisation scheme held centrally
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

MAOBI (R): PRESTO

Methods	Parallel group, double-blind (26 weeks)
Participants	Idiopathic PD patients with motor fluctuations. Number Randomised: 472 Mean age: 64 years Number of males: 305 (65%) Mean duration of PD: 9.4 years
Interventions	MAOBI Rasagiline 0.5mg (n=164) vs. MAOBI Rasagiline 1mg (n=149) vs. Placebo (n=159)
Outcomes	Clinician-rated disability Motor complications On/Off time Levodopa dose Side-effects
Notes	Treatment Schedule: Rasagiline (0.5mg or 1mg) taken once daily. Additional Treatment: Changes in LD dose were allowed during first 6 weeks. LD dose remained constant for final 20 weeks

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomised (computer generated blocking)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

MAOBI (S): Norw/Fin

Methods	Parallel group, double-blind (8 weeks)
Participants	Idiopathic PD patients under continuous stabilised treatment with levodopa. Number Randomised: 40 (38 analysed) Mean age: 66 years Number of males: 20 (53%) Mean duration of PD: 10.3 years
Interventions	MAOBI Selegiline (n=20) vs. Placebo (n=20)
Outcomes	Clinician-rated disability Motor complications Off-time Levodopa dose Side-effects

MAOBI (S): Norw/Fin (*Continued*)

Notes	Treatment Schedule: 2 periods each lasting 4 weeks. During first 4 weeks, selegiline dose of 5mg. During second 4 weeks, selegiline dose of 10mg Additional Treatment: After second week, LD dose was reduced as much as possible

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Randomised (method used not given)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

MAOBI (S): USA

Methods	Parallel group, double-blind (8 weeks)
Participants	Idiopathic PD patients with motor complications. Number Randomised: 99 (96 analysed) Mean age: 62 years Number of males: Not available Mean duration of PD: 9.2 years
Interventions	MAOBI Selegiline (n=50) vs. Placebo (n=46)
Outcomes	Clinician-rated disability Motor complications Levodopa dose Side-effects
Notes	Treatment Schedule: Selegiline 5mg b.i.d. Additional Treatment: Decreases in LD dose allowed during study

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomised (computer generated)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

MAOBI (ZS): USA

Methods	Parallel group, double-blind (3 months)
Participants	Idiopathic PD patients with predictable motor complications. Number Randomised: 140 Mean age: 65 years (range: 38 - 85 years) Number of males: 89 (64%) Mean duration of PD: 6.9 years
Interventions	MAOBI Zydis Selegiline (n=94) vs. Placebo (n=46)
Outcomes	On/Off time Side-effects
Notes	Treatment Schedule: Zydis Selegiline started at dose 1.25mg once daily. At week 6, dose increased to 2.5mg/day and this dose was maintained for the rest of the study. Additional Treatment: LD doses not stated.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Randomised (method used not given)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

MAOBI (ZS): USA/UK

Methods	Parallel group, placebo-controlled (12 weeks)
Participants	Idiopathic PD patients taking stable doses of levodopa and with minimum of 3 hours 'off' time per day. Number Randomised: 163 Mean age: Not available Number of males: Not available Mean duration of PD: Not available
Interventions	MAOBI Zydis Selegiline (n=82) vs. Placebo (n=81) Selegiline/Placebo: Not stated (have assumed 82/81)
Outcomes	Clinician-rated disability Off-time
Notes	Treatment Schedule: Zydis Selegiline started at dose 1.25mg (one tablet) q.d. At week 7, dose increased to 2.5mg (2 tablets) q.d. and received this dose for further 6 weeks. Additional Treatment: LD doses not stated.

MAOBI (ZS): USA/UK (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Randomised (method used not given)
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Yes	Double-blind, placebo-controlled

COMTI = catechol-O-methyl transferase inhibitors; DA = dopamine agonist; MAOBI = monoamine oxidase type B inhibitors; PD = Parkinson's disease; LD = levodopa; DCI = decarboxylase inhibitor; q.d. = once a day; b.i.d. = twice a day; t.i.d. = three times a day.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
COMTI (E): Fin/USA	Crossover trial - data not split by treatment period
COMTI (E): Finland 1	Crossover trial - data not split by treatment period
COMTI (E): Finland 2	Crossover trial - data not split by treatment period. Mainly cardiovascular outcomes. Mixture of fluctuating and non-fluctuating patients - results not split by type of patient
COMTI (E): Italy	Crossover trial - data not split by treatment period. Mainly pharmacokinetic outcomes
COMTI (E): UK/Fin 1	Single-dose study
COMTI (E): UK/Fin 2	Single-dose study
COMTI (E/Ne): Portugal	Crossover trial - data not split by treatment period. Outcomes not relevant
COMTI (T): Switz/USA	Substudy involving 59 patients from the TFSG 3 study (Adler et al.). Study was assessing the pharmacokinetic and clinical effect of tolcapone withdrawal
DA (ABT): France/US	ABT-431 - partial dopamine agonist
DA (B): Copenhagen	Later PD, but not clear if patients had motor complications
DA (B): Denver	Not properly randomised
DA (B): Hammersmith	Crossover trial - data not split by treatment period

(*Continued*)

DA (B): USA	Crossover trial - data not split by treatment period
DA (Br): Japan	Trial of adjuvant treatment, but not clear if patients were suffering from motor complications
DA (Br): New York	Trial of adjuvant treatment, but not clear if patients were suffering from motor complications, and patients on optimal anti-parkinsonian treatment (so patients not necessarily on levodopa). Crossover trial - data not split by treatment period
DA (C): Arizona	Patients included in the multicentre USA 1 trial (Hutton et al.)
DA (Ci): New York	Ciladopa - partial dopamine agonist
DA (Pe): China	Trial of patients with advanced PD, but not clear if patients were suffering from motor complications
DA (Pe): Los Angeles	Formed part of large multicentre study (N America) which has now been published in full (Olanow et al.)
DA (Pe): N Carolina	Formed part of large multicentre study (N America) which has now been published in full (Olanow et al.)
DA (Pe): New Jersey	Formed part of large multicentre study (N America) which has now been published in full (Olanow et al.)
DA (Pe): Texas	Formed part of large multicentre study (N America) which has now been published in full (Olanow et al.)
DA (Pi): Europe	Trial of patients with PD insufficiently controlled by LD - not clear if patients had motor complications
DA (Pi): France	Single intravenous infusion of piribedil. No outcome data for meta-analysis
DA (Pi): Spain/Venez	Trial of patients with PD insufficiently controlled by LD - not clear if patients had motor complications. Text of paper in Spanish
DA (Pi): Toulouse	Piribedil skin patch
DA (Pr): US/Pu Rico	Trial of PD patients on LD, but not clear if patients were suffering from motor complications. Study aim was to assess the efficacy of pramipexole in PD patients of African, Asian and Hispanic heritage
DA (Pr): USA	Formed part of large multicentre study (US/Canada) which has now been published in full (Lieberman et al.)
DA (Pr/B): Japan	Trial of patients with advanced PD, but not clear if all patients were suffering from motor complications
DA (Ro): CLEOPATRA	Transdermal patch rotigotine versus placebo comparison of trial excluded from analysis (3 arm trial of pramipexole versus rotigotine versus placebo)
DA (Ro): Denmark	Crossover trial - data not split by treatment period

(*Continued)*

DA (Ro): PREFER	Transdermal patch rotigotine
DA (Te): Germany/Italy	Terguride - partial dopamine agonist
MAOBI (S): Aus/Fin	Crossover trial - data not split by treatment period
MAOBI (S): Australia	Crossover trial - data not split by treatment period
MAOBI (S): Denmark	Not properly randomised. Crossover trial - data not split by treatment period
MAOBI (S): Finland	Crossover trial - data not split by treatment period
MAOBI (S): France	Crossover trial - data not split by treatment period
MAOBI (S): Kansas/LA	Crossover trial - data not split by treatment period
MAOBI (S): London 1	Crossover trial - data not split by treatment period
MAOBI (S): London 2	Crossover trial - data not split by treatment period
MAOBI (S): New York	Part of Selegiline USA trial (Lieberman et al.), reporting the results of the patients recruited at the New York centre only
MAOBI (S): UK/Israel	Crossover trial - data not split by treatment period

COMTI = catechol-O-methyl transferase inhibitors; DA = dopamine agonist; MAOBI = monoamine oxidase type B inhibitors; PD = Parkinson's disease; LD = levodopa

Characteristics of ongoing studies *[ordered by study ID]*

PD MED (later disease)

Trial name or title	PD MED
Methods	Randomised controlled trial
Participants	PD patients who have developed motor complications that are uncontrolled by their current therapy (either LD alone or LD with the addition of a dopamine agonist or MAOBI)
Interventions	Dopamine Agonist vs. MAOBI vs. COMTI (on background of LD)
Outcomes	Patient-rated quality of life (using PDQ-39) Cost-effectiveness/Health Economics Cognitive function Toxicity and side-effects

PD MED (later disease) (*Continued*)

	Well being of patient carers
Starting date	November 2000
Contact information	PD-Trial@contacts.bham.ac.uk
Notes	

LD = levodopa; MAOBI = monoamine oxidase type B inhibitors; COMTI = catechol-O-methyl transferase inhibitors

DATA AND ANALYSES

Comparison 1. Off-Time

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Off-Time Reduction (Adjuvant Therapy versus Placebo)	30	5549	Mean Difference (IV, Fixed, 95% CI)	-1.05 [-1.19, -0.90]
1.1 Dopamine Agonist versus Placebo	15	2601	Mean Difference (IV, Fixed, 95% CI)	-1.54 [-1.83, -1.26]
1.2 COMTI versus Placebo	12	2060	Mean Difference (IV, Fixed, 95% CI)	-0.83 [-1.04, -0.62]
1.3 MAOBI versus Placebo	3	888	Mean Difference (IV, Fixed, 95% CI)	-0.93 [-1.25, -0.62]
2 Off-Time Reduction (Dopamine Agonist versus Placebo)	15	2677	Mean Difference (IV, Fixed, 95% CI)	-1.52 [-1.78, -1.25]
2.1 Bromocriptine	2	197	Mean Difference (IV, Fixed, 95% CI)	-1.78 [-2.91, -0.65]
2.2 Cabergoline	3	195	Mean Difference (IV, Fixed, 95% CI)	-1.29 [-1.89, -0.69]
2.3 Pergolide	1	376	Mean Difference (IV, Fixed, 95% CI)	-1.6 [-2.57, -0.63]
2.4 Pramipexole	6	1265	Mean Difference (IV, Fixed, 95% CI)	-1.81 [-2.19, -1.43]
2.5 Ropinirole	4	644	Mean Difference (IV, Fixed, 95% CI)	-0.93 [-1.53, -0.33]
3 Off-Time Reduction (COMTI versus Placebo)	12	2060	Mean Difference (IV, Fixed, 95% CI)	-0.83 [-1.04, -0.62]
3.1 Entacapone	7	1611	Mean Difference (IV, Fixed, 95% CI)	-0.61 [-0.85, -0.37]
3.2 Tolcapone	5	449	Mean Difference (IV, Fixed, 95% CI)	-1.60 [-2.04, -1.15]
4 Off-Time Reduction (MAOBI versus Placebo)	3	888	Mean Difference (IV, Fixed, 95% CI)	-0.93 [-1.25, -0.62]
4.1 Rasagiline	2	748	Mean Difference (IV, Fixed, 95% CI)	-0.84 [-1.17, -0.50]
4.2 Sublingual Selegiline	1	140	Mean Difference (IV, Fixed, 95% CI)	-1.60 [-2.47, -0.73]

Comparison 2. Levodopa Dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Levodopa Dose Reduction (mg/day) (Adjuvant Therapy versus Placebo)	27	4846	Mean Difference (IV, Fixed, 95% CI)	-55.65 [-62.67, -48.62]
1.1 Dopamine Agonist versus Placebo	9	1844	Mean Difference (IV, Fixed, 95% CI)	-116.03 [-134.45, -97.61]
1.2 COMTI versus Placebo	15	2216	Mean Difference (IV, Fixed, 95% CI)	-52.07 [-61.09, -43.05]
1.3 MAOBI versus Placebo	3	786	Mean Difference (IV, Fixed, 95% CI)	-29.11 [-43.18, -15.04]
2 Levodopa Dose Reduction (mg/day) (Dopamine Agonist versus Placebo)	9	1927	Mean Difference (IV, Fixed, 95% CI)	-110.75 [-128.37, -93.12]

2.1 Bromocriptine	2	207	Mean Difference (IV, Fixed, 95% CI)	-52.17 [-95.16, -9.18]
2.2 Cabergoline	1	163	Mean Difference (IV, Fixed, 95% CI)	-149.6 [-208.79, -90.41]
2.3 Pergolide	1	376	Mean Difference (IV, Fixed, 95% CI)	-183.9 [-295.09, -72.71]
2.4 Pramipexole	3	579	Mean Difference (IV, Fixed, 95% CI)	-114.82 [-143.01, -86.64]
2.5 Ropinirole	3	602	Mean Difference (IV, Fixed, 95% CI)	-119.81 [-150.63, -87.00]
3 Levodopa Dose Reduction (mg/day) (COMTI versus Placebo)	15	2216	Mean Difference (IV, Fixed, 95% CI)	-52.07 [-61.09, -43.05]
3.1 Entacapone	8	1567	Mean Difference (IV, Fixed, 95% CI)	-41.62 [-51.35, -31.89]
3.2 Tolcapone	7	649	Mean Difference (IV, Fixed, 95% CI)	-116.47 [-140.62, -92.32]
4 Levodopa Dose Reduction (mg/day) (MAOBI versus Placebo)	3	786	Mean Difference (IV, Fixed, 95% CI)	-29.11 [-43.18, -15.04]
4.1 Rasagiline	2	748	Mean Difference (IV, Fixed, 95% CI)	-27.94 [-42.05, -13.84]
4.2 Selegiline	1	38	Mean Difference (IV, Fixed, 95% CI)	-257.4 [-454.80, -58.00]

Comparison 3. Clinician Rated Disability Scales

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 UPDRS Activities of Daily Living (Adjuvant Therapy versus Placebo)	16	2655	Mean Difference (IV, Fixed, 95% CI)	-1.31 [-1.62, -0.99]
1.1 Dopamine Agonist versus Placebo	6	1014	Mean Difference (IV, Fixed, 95% CI)	-2.05 [-2.58, -1.51]
1.2 COMTI versus Placebo	10	1641	Mean Difference (IV, Fixed, 95% CI)	-0.91 [-1.30, -0.52]
1.3 MAOBI versus Placebo	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
2 UPDRS Motor (Adjuvant Therapy versus Placebo)	20	3900	Mean Difference (IV, Fixed, 95% CI)	-2.84 [-3.36, -2.32]
2.1 Dopamine Agonist versus Placebo	7	1403	Mean Difference (IV, Fixed, 95% CI)	-4.86 [-5.90, -3.82]
2.2 COMTI versus Placebo	12	2057	Mean Difference (IV, Fixed, 95% CI)	-2.02 [-2.68, -1.37]
2.3 MAOBI versus Placebo	1	440	Mean Difference (IV, Fixed, 95% CI)	-2.9 [-4.29, -1.51]
3 UPDRS Total (Adjuvant Therapy versus Placebo)	10	1513	Mean Difference (IV, Fixed, 95% CI)	-3.26 [-4.52, 0.00]
3.1 Dopamine Agonist versus Placebo (Total parts I-IV)	3	500	Mean Difference (IV, Fixed, 95% CI)	-10.01 [-12.76, -7.26]
3.2 COMTI versus Placebo (Total parts I-III)	6	999	Mean Difference (IV, Fixed, 95% CI)	-1.46 [-2.89, -0.04]

3.3 MAOBI versus Placebo (Total parts I-IV)	1	14	Mean Difference (IV, Fixed, 95% CI)	-2.2 [-16.56, 12.16]
4 UPDRS Activities of Daily Living (Dopamine Agonist versus Placebo)	6	1014	Mean Difference (IV, Fixed, 95% CI)	-2.05 [-2.58, -1.51]
4.1 Cabergoline	2	177	Mean Difference (IV, Fixed, 95% CI)	-1.78 [-3.72, 0.17]
4.2 Pramipexole	4	837	Mean Difference (IV, Fixed, 95% CI)	-2.07 [-2.63, -1.51]
5 UPDRS Activities of Daily Living (COMTI versus Placebo)	10	1641	Mean Difference (IV, Fixed, 95% CI)	-0.91 [-1.30, -0.52]
5.1 Entacapone	6	1232	Mean Difference (IV, Fixed, 95% CI)	-1.16 [-1.68, -0.64]
5.2 Tolcapone	4	409	Mean Difference (IV, Fixed, 95% CI)	-0.58 [-1.18, 0.02]
6 UPDRS Motor (Dopamine Agonist versus Placebo)	7	1403	Mean Difference (IV, Fixed, 95% CI)	-4.86 [-5.90, -3.82]
6.1 Cabergoline	2	189	Mean Difference (IV, Fixed, 95% CI)	-1.74 [-3.78, 0.30]
6.2 Pramipexole	4	837	Mean Difference (IV, Fixed, 95% CI)	-6.31 [-7.69, -4.93]
6.3 Ropinirole	1	377	Mean Difference (IV, Fixed, 95% CI)	-4.8 [-7.32, -2.28]
7 UPDRS Motor (COMTI versus Placebo)	12	2057	Mean Difference (IV, Fixed, 95% CI)	-2.02 [-2.68, -1.37]
7.1 Entacapone	7	1530	Mean Difference (IV, Fixed, 95% CI)	-2.14 [-2.92, -1.36]
7.2 Tolcapone	5	527	Mean Difference (IV, Fixed, 95% CI)	-1.73 [-2.96, -0.51]
8 UPDRS Motor (MAOBI versus Placebo)	1	440	Mean Difference (IV, Fixed, 95% CI)	-2.9 [-4.29, -1.51]
8.1 Rasagiline	1	440	Mean Difference (IV, Fixed, 95% CI)	-2.9 [-4.29, -1.51]
9 UPDRS Total (parts I-IV) (Dopamine Agonist versus Placebo)	3	500	Mean Difference (IV, Fixed, 95% CI)	-10.01 [-12.76, -7.26]
9.1 Pramipexole	3	500	Mean Difference (IV, Fixed, 95% CI)	-10.01 [-12.76, -7.26]
10 UPDRS Total (parts I-III) (COMTI versus Placebo)	6	999	Mean Difference (IV, Fixed, 95% CI)	-1.46 [-2.89, -0.04]
10.1 Entacapone	4	723	Mean Difference (IV, Fixed, 95% CI)	-1.88 [-3.94, 0.18]
10.2 Tolcapone	2	276	Mean Difference (IV, Fixed, 95% CI)	-1.08 [-3.05, 0.89]
11 UPDRS Total (parts I-IV) (MAOBI versus Placebo)	1	14	Mean Difference (IV, Fixed, 95% CI)	-2.2 [-16.56, 12.16]
11.1 Rasagiline	1	14	Mean Difference (IV, Fixed, 95% CI)	-2.2 [-16.56, 12.16]

Comparison 4. Dyskinesia & Dystonia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Dyskinesia (Adjuvant Therapy versus Placebo)	33	6705	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.50 [2.21, 2.84]
1.1 Dopamine Agonist versus Placebo	14	3045	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.70 [2.26, 3.22]
1.2 COMTI versus Placebo	16	3066	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.50 [2.07, 3.01]
1.3 MAOBI versus Placebo	3	594	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.94 [0.49, 1.80]

2 Dystonia (Adjuvant Therapy versus Placebo)	5	721	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.77 [0.48, 1.23]
2.1 Dopamine Agonist versus Placebo	2	435	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.84 [0.45, 1.59]
2.2 COMTI versus Placebo	3	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.70 [0.35, 1.39]
2.3 MAOBI versus Placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
3 Dyskinesia (Dopamine Agonist versus Placebo)	14	3128	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.67 [2.25, 3.17]
3.1 Bromocriptine	2	389	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.52 [1.42, 4.48]
3.2 Cabergoline	3	449	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.44 [0.96, 2.16]
3.3 Pergolide	1	376	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.64 [3.09, 6.97]
3.4 Pramipexole	6	1326	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.63 [2.01, 3.42]
3.5 Ropinirole	3	588	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.21 [1.98, 5.21]
4 Dyskinesia (COMTI versus Placebo)	16	3066	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.50 [2.07, 3.01]
4.1 Entacapone	10	2487	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.16 [1.73, 2.70]
4.2 Tolcapone	6	579	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.66 [2.55, 5.25]
5 Dyskinesia (MAOBI versus Placebo)	3	594	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.94 [0.49, 1.80]
5.1 Rasagiline	1	460	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.34 [0.56, 3.20]
5.2 Selegiline	2	134	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.62 [0.24, 1.62]

Comparison 5. Adverse Events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall Incidence of Side-Effects (Adjuvant Therapy versus Placebo)	27	5213	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.67 [1.46, 1.92]
1.1 Dopamine Agonist versus Placebo	12	2053	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.52 [1.22, 1.90]
1.2 COMTI versus Placebo	11	2214	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.00 [1.62, 2.47]
1.3 MAOBI versus Placebo	4	946	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.32 [0.95, 1.84]
2 Overall Incidence of Side-Effects (Dopamine Agonist versus Placebo)	12	2136	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.53 [1.23, 1.90]
2.1 Bromocriptine	2	389	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.25 [0.77, 2.03]
2.2 Cabergoline	3	268	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.08 [1.01, 4.29]
2.3 Pramipexole	5	972	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.67 [1.16, 2.39]
2.4 Ropinirole	3	507	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.44 [0.99, 2.09]
3 Overall Incidence of Side-Effects (COMTI versus Placebo)	11	2214	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.00 [1.62, 2.47]
3.1 Entacapone	7	1793	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.85 [1.47, 2.33]
3.2 Tolcapone	4	421	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.89 [1.74, 4.79]
4 Overall Incidence of Side-Effects (MAOBI versus Placebo)	4	946	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.32 [0.95, 1.84]
4.1 Rasagiline	2	768	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.84, 1.79]
4.2 Selegiline	1	38	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.87 [0.48, 7.23]

4.3 Sublingual Selegiline	1	140	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.64 [0.75, 3.57]
5 Constipation	12	2781	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.19 [2.17, 4.68]
5.1 Dopamine Agonist versus Placebo	2	410	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.51 [0.87, 7.22]
5.2 COMTI versus Placebo	9	1911	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.22 [2.12, 4.89]
5.3 MAOBI versus Placebo	1	460	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.39 [0.76, 71.39]
6 Dizziness	23	4669	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.57 [1.30, 1.90]
6.1 Dopamine Agonist versus Placebo	14	2706	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.44 [1.15, 1.80]
6.2 COMTI versus Placebo	7	1407	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.95 [1.30, 2.94]
6.3 MAOBI versus Placebo	2	556	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.26 [0.86, 5.96]
7 Dry Mouth	7	1945	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.33 [1.22, 4.47]
7.1 Dopamine Agonist versus Placebo	2	410	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.28 [0.31, 5.31]
7.2 COMTI versus Placebo	3	979	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.07 [1.25, 7.56]
7.3 MAOBI versus Placebo	2	556	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.17 [0.62, 7.61]
8 Hallucinations	24	5241	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.16 [1.70, 2.74]
8.1 Dopamine Agonist versus Placebo	11	2600	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.65 [1.97, 3.56]
8.2 COMTI versus Placebo	11	2085	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.43 [0.93, 2.19]
8.3 MAOBI versus Placebo	2	556	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.91 [0.61, 5.99]
9 Hypotension (including postural hypotension)	20	4184	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.47 [1.18, 1.83]
9.1 Dopamine Agonist versus Placebo	14	2706	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.46 [1.15, 1.84]
9.2 COMTI versus Placebo	4	980	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.32 [0.60, 2.93]
9.3 MAOBI versus Placebo	2	498	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.67 [0.65, 10.87]
10 Insomnia	17	3281	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.38 [1.09, 1.74]
10.1 Dopamine Agonist versus Placebo	9	1726	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.28 [0.96, 1.70]
10.2 COMTI versus Placebo	8	1555	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.59 [1.07, 2.36]
10.3 MAOBI versus Placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
11 Nausea	31	6343	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.78 [1.53, 2.07]
11.1 Dopamine Agonist versus Placebo	15	3082	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.63 [1.34, 1.99]
11.2 COMTI versus Placebo	13	2667	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.07 [1.62, 2.65]
11.3 MAOBI versus Placebo	3	594	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.51 [0.74, 3.06]
12 Somnolence	16	3599	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.87 [1.40, 2.51]
12.1 Dopamine Agonist versus Placebo	10	1998	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.82 [1.27, 2.61]
12.2 COMTI versus Placebo	5	1141	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.03 [1.21, 3.43]
12.3 MAOBI versus Placebo	1	460	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.48 [0.26, 8.63]
13 Vomiting	16	3014	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.56 [1.67, 3.93]
13.1 Dopamine Agonist versus Placebo	5	746	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.48 [0.73, 2.99]
13.2 COMTI versus Placebo	7	1366	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.68 [1.91, 7.09]
13.3 MAOBI versus Placebo	4	902	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.25 [1.27, 8.29]
14 Abdominal Pain	12	1949	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.33 [0.89, 2.00]
14.1 Dopamine Agonist versus Placebo	5	568	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.44, 2.15]
14.2 COMTI versus Placebo	6	1285	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.46 [0.89, 2.39]
14.3 MAOBI versus Placebo	1	96	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.85 [0.36, 9.61]

15 Abnormal Dreams	5	1278	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.68 [0.75, 3.77]
15.1 Dopamine Agonist versus Placebo	2	266	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.33 [0.49, 3.58]
15.2 COMTI versus Placebo	1	456	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.97 [0.20, 19.04]
15.3 MAOBI versus Placebo	2	556	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.22 [0.55, 18.73]
16 Aggravated PD	11	2229	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.67 [0.53, 0.85]
16.1 Dopamine Agonist versus Placebo	5	897	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.58 [0.41, 0.81]
16.2 COMTI versus Placebo	6	1332	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.78 [0.56, 1.09]
16.3 MAOBI versus Placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
17 Agitation	4	445	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.38 [0.45, 4.22]
17.1 Dopamine Agonist versus Placebo	2	300	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.51 [0.65, 9.77]
17.2 COMTI versus Placebo	2	145	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.39 [0.05, 2.79]
17.3 MAOBI versus Placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
18 Anorexia	7	1284	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.93 [1.25, 2.97]
18.1 Dopamine Agonist versus Placebo	4	700	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.48 [0.79, 2.78]
18.2 COMTI versus Placebo	2	276	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.00 [1.02, 3.92]
18.3 MAOBI versus Placebo	1	308	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.29 [1.41, 19.89]
19 Anxiety	4	1326	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.55 [0.27, 1.13]
19.1 Dopamine Agonist versus Placebo	2	410	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.08 [0.24, 4.89]
19.2 COMTI versus Placebo	1	456	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.30 [0.08, 1.04]
19.3 MAOBI versus Placebo	1	460	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.62 [0.21, 1.86]
20 Ataxia	4	620	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.17 [1.15, 4.11]
20.1 Dopamine Agonist versus Placebo	3	415	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.78 [0.87, 3.65]
20.2 COMTI versus Placebo	1	205	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.68 [1.14, 19.17]
20.3 MAOBI versus Placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
21 Confusion	12	2021	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.50 [0.92, 2.45]
21.1 Dopamine Agonist versus Placebo	5	561	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.89 [0.92, 3.87]
21.2 COMTI versus Placebo	5	904	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.12 [0.53, 2.35]
21.3 MAOBI versus Placebo	2	556	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.88 [0.37, 9.40]
22 Depression	8	1710	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.64, 1.56]
22.1 Dopamine Agonist versus Placebo	3	504	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.91 [0.46, 1.80]
22.2 COMTI versus Placebo	3	708	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.09 [0.50, 2.41]
22.3 MAOBI versus Placebo	2	498	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.05 [0.45, 2.47]
23 Diarrhoea	14	3001	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.92 [1.41, 2.62]
23.1 Dopamine Agonist versus Placebo	3	300	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.84 [0.27, 2.63]
23.2 COMTI versus Placebo	10	2241	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.34 [1.67, 3.28]
23.3 MAOBI versus Placebo	1	460	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.39 [0.12, 1.29]
24 Dyspepsia	5	866	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.05 [1.05, 4.01]
24.1 Dopamine Agonist versus Placebo	5	866	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.05 [1.05, 4.01]
24.2 COMTI versus Placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
24.3 MAOBI versus Placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
25 Dyspnoea	4	725	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.64 [1.02, 6.81]

25.1 Dopamine Agonist versus Placebo	3	607	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.18 [1.20, 8.44]
25.2 COMTI versus Placebo	1	118	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.00, 6.59]
25.3 MAOBI versus Placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
26 Excessive Dreaming	4	404	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.90 [1.00, 3.60]
26.1 Dopamine Agonist versus Placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
26.2 COMTI versus Placebo	4	404	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.90 [1.00, 3.60]
26.3 MAOBI versus Placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
27 Fainting	3	1104	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.51 [0.12, 2.08]
27.1 Dopamine Agonist versus Placebo	1	188	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.50 [0.03, 9.36]
27.2 COMTI versus Placebo	1	456	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.01, 2.18]
27.3 MAOBI versus Placebo	1	460	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.14, 7.08]
28 Falls	4	739	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.49 [0.87, 2.55]
28.1 Dopamine Agonist versus Placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
28.2 COMTI versus Placebo	4	739	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.49 [0.87, 2.55]
28.3 MAOBI versus Placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
29 Fatigue	5	1065	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.53 [0.87, 2.68]
29.1 Dopamine Agonist versus Placebo	2	266	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.99 [0.71, 5.56]
29.2 COMTI versus Placebo	3	799	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.37 [0.70, 2.67]
29.3 MAOBI versus Placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
30 Gastritis	3	393	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.17 [0.93, 5.05]
30.1 Dopamine Agonist versus Placebo	2	231	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.51 [0.32, 94.72]
30.2 COMTI versus Placebo	1	162	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.98 [0.81, 4.80]
30.3 MAOBI versus Placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
31 Headache	11	1606	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.30 [0.87, 1.96]
31.1 Dopamine Agonist versus Placebo	8	1195	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.36 [0.86, 2.14]
31.2 COMTI versus Placebo	2	315	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.36, 2.70]
31.3 MAOBI versus Placebo	1	96	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.82 [0.18, 17.93]
32 Hyperkinesia	3	1087	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.14 [1.03, 9.57]
32.1 Dopamine Agonist versus Placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
32.2 COMTI versus Placebo	2	627	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.91 [0.91, 9.32]
32.3 MAOBI versus Placebo	1	460	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.33 [0.15, 369.19]
33 Hypertension	3	300	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.05 [0.59, 15.77]
33.1 Dopamine Agonist versus Placebo	3	300	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.05 [0.59, 15.77]
33.2 COMTI versus Placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
33.3 MAOBI versus Placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
34 Muscle Cramps	4	451	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.58 [0.78, 3.17]
34.1 Dopamine Agonist versus Placebo	1	188	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.06 [0.10, 11.56]
34.2 COMTI versus Placebo	3	263	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.64 [0.79, 3.40]
34.3 MAOBI versus Placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
35 Oedema	3	1104	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.96 [0.80, 4.79]
35.1 Dopamine Agonist versus Placebo	1	188	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.77 [0.74, 30.72]

35.2 COMTI versus Placebo	1	456	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.35 [0.30, 5.99]
35.3 MAOBI versus Placebo	1	460	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.65 [0.41, 6.66]
36 Pain	5	1002	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.38 [0.86, 2.22]
36.1 Dopamine Agonist versus Placebo	3	504	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.29 [0.70, 2.37]
36.2 COMTI versus Placebo	2	498	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.53 [0.73, 3.25]
36.3 MAOBI versus Placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
37 Sleep Disorders	3	1104	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.67 [0.78, 3.58]
37.1 Dopamine Agonist versus Placebo	1	188	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.61 [0.07, 284.12]
37.2 COMTI versus Placebo	1	456	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.82 [0.63, 5.26]
37.3 MAOBI versus Placebo	1	460	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.39 [0.44, 4.38]
38 Sweating	4	476	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.43, 2.53]
38.1 Dopamine Agonist versus Placebo	3	335	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.91 [0.32, 2.52]
38.2 COMTI versus Placebo	1	141	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.58 [0.27, 9.34]
38.3 MAOBI versus Placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
39 Tremor	4	569	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.83 [0.43, 1.62]
39.1 Dopamine Agonist versus Placebo	3	504	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.86 [0.42, 1.77]
39.2 COMTI versus Placebo	1	65	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.67 [0.11, 4.12]
39.3 MAOBI versus Placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
40 Urine Discoloration	10	2006	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.42 [4.63, 8.90]
40.1 Dopamine Agonist versus Placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
40.2 COMTI versus Placebo	10	2006	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.42 [4.63, 8.90]
40.3 MAOBI versus Placebo	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable

Comparison 6. Mortality

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality (Adjuvant Therapy versus Placebo)	12	1845	Peto Odds Ratio (95% CI)	0.32 [0.12, 0.89]
1.1 Dopamine Agonist versus Placebo	8	1177	Peto Odds Ratio (95% CI)	0.35 [0.09, 1.41]
1.2 COMTI versus Placebo	2	488	Peto Odds Ratio (95% CI)	0.33 [0.07, 1.62]
1.3 MAOBI versus Placebo	2	180	Peto Odds Ratio (95% CI)	0.14 [0.00, 6.82]
2 Mortality (Dopamine Agonist versus Placebo)	8	1177	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.35 [0.09, 1.41]
2.1 Cabergoline	1	43	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.12 [0.00, 5.93]
2.2 Pergolide	1	376	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.51 [0.05, 4.90]
2.3 Pramipexole	3	251	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.4 Ropinirole	3	507	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.35 [0.05, 2.50]
3 Mortality (COMTI versus Placebo)	2	488	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.33 [0.07, 1.62]
3.1 Entacapone	2	488	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.33 [0.07, 1.62]

4 Mortality (MAOBI versus Placebo)	2	180	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.00, 6.82]
4.1 Selegiline	1	40	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.00, 6.82]
4.2 Sublingual Selegiline	1	140	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable

Comparison 7. Patient Withdrawal

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall Patient Withdrawal (Adjuvant Therapy versus Placebo)	33	6405	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.71 [0.62, 0.81]
1.1 Dopamine Agonist versus Placebo	17	3003	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.56 [0.46, 0.66]
1.2 COMTI versus Placebo	11	2355	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.06 [0.84, 1.34]
1.3 MAOBI versus Placebo	5	1047	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.74 [0.50, 1.11]
2 Patient Withdrawal due to Adverse Events (Adjuvant Therapy versus Placebo)	33	6321	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.20 [1.00, 1.43]
2.1 Dopamine Agonist versus Placebo	16	2934	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.05 [0.82, 1.35]
2.2 COMTI versus Placebo	14	2688	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.46 [1.13, 1.90]
2.3 MAOBI versus Placebo	3	699	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.62 [0.27, 1.41]
3 Patient Withdrawal due to Lack of Efficacy (Adjuvant Therapy versus Placebo)	19	2879	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.19 [0.13, 0.28]
3.1 Dopamine Agonist versus Placebo	12	2037	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.18 [0.12, 0.28]
3.2 COMTI versus Placebo	5	603	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.18 [0.06, 0.56]
3.3 MAOBI versus Placebo	2	239	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.43 [0.07, 287.79]
4 Overall Patient Withdrawal (Dopamine Agonist versus Placebo)	17	3086	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.55 [0.46, 0.65]
4.1 Bromocriptine	4	452	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.56, 1.38]
4.2 Cabergoline	3	268	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.62 [0.30, 1.27]
4.3 Pergolide	1	376	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.91 [0.53, 1.58]
4.4 Pramipexole	6	1334	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.43 [0.33, 0.55]
4.5 Ropinirole	4	656	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.53 [0.37, 0.76]
5 Overall Patient Withdrawal (COMTI versus Placebo)	11	2355	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.06 [0.84, 1.34]
5.1 Entacapone	9	2149	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.08 [0.85, 1.36]
5.2 Tolcapone	2	206	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.77 [0.26, 2.26]
6 Overall Patient Withdrawal (MAOBI versus Placebo)	5	1047	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.74 [0.50, 1.11]
6.1 Rasagiline	2	768	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.73 [0.47, 1.12]
6.2 Selegiline	2	139	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.02, 0.93]
6.3 Sublingual Selegiline	1	140	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.64 [0.58, 12.01]

7 Overall Patient Withdrawal due to Adverse Events (Dopamine Agonist versus Placebo)	16	3017	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.76, 1.23]
7.1 Bromocriptine	4	452	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.93 [0.56, 1.53]
7.2 Cabergoline	3	268	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.24 [0.46, 3.33]
7.3 Pergolide	1	376	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.25 [1.02, 5.00]
7.4 Pramipexole	5	1265	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.79 [0.55, 1.14]
7.5 Ropinirole	4	656	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.58, 1.70]
8 Overall Patient Withdrawal due to Adverse Events (COMTI versus Placebo)	14	2688	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.46 [1.13, 1.90]
8.1 Entacapone	9	2149	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.45 [1.09, 1.94]
8.2 Tolcapone	5	539	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.50 [0.85, 2.65]
9 Overall Patient Withdrawal due to Adverse Events (MAOBI versus Placebo)	3	699	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.62 [0.27, 1.41]
9.1 Rasagiline	1	460	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.62 [0.24, 1.60]
9.2 Selegiline	1	99	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.01, 2.11]
9.3 Sublingual Selegiline	1	140	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.44 [0.17, 11.86]
10 Overall Patient Withdrawal due to Lack of Efficacy (Dopamine Agonist versus Placebo)	12	2037	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.18 [0.12, 0.28]
10.1 Bromocriptine	2	63	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
10.2 Cabergoline	3	268	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.04, 0.46]
10.3 Pergolide	1	376	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.04, 0.45]
10.4 Pramipexole	3	742	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.15 [0.08, 0.30]
10.5 Ropinirole	3	588	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.25 [0.14, 0.45]
11 Overall Patient Withdrawal due to Lack of Efficacy (COMTI versus Placebo)	5	603	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.18 [0.06, 0.56]
11.1 Entacapone	3	397	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.20 [0.06, 0.65]
11.2 Tolcapone	2	206	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.01, 2.21]
12 Overall Patient Withdrawal due to Lack of Efficacy (MAOBI versus Placebo)	2	239	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.43 [0.07, 287.79]
12.1 Selegiline	1	99	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
12.2 Sublingual Selegiline	1	140	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.43 [0.07, 287.79]

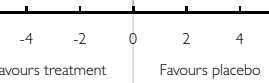
Analysis 1.1. Comparison 1 Off-Time, Outcome 1 Off-Time Reduction (Adjuvant Therapy versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 1 Off-Time

Outcome: 1 Off-Time Reduction (Adjuvant Therapy versus Placebo)

Study or subgroup	Treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Dopamine Agonist versus Placebo							
DA (Pr/B): Interntl	152	-1.9 (4.3)	76	-0.3 (4.4)		1.5 %	-1.60 [-2.80, -0.40]
DA (B): Germany	20	-3.4 (2.78)	20	0.3 (3.66)		0.5 %	-3.70 [-5.71, -1.69]
DA (C): Spain	14	-3.33 (3.47)	12	-2.47 (3.91)		0.3 %	-0.86 [-3.72, 2.00]
DA (C): UK	18	-2 (2.33)	16	-0.7 (2.25)		0.9 %	-1.30 [-2.84, 0.24]
DA (C): USA 1	89	-2.08 (3.19)	46	-0.77 (3.34)		1.6 %	-1.31 [-2.48, -0.14]
DA (Pe): N America	189	-1.8 (4.8)	187	-0.2 (4.8)		2.3 %	-1.60 [-2.57, -0.63]
DA (Pr): Aust/Germ	23	-2.3 (2.7)	37	0.4 (3.5)		0.9 %	-2.70 [-4.28, -1.12]
DA (Pr): CLEOPATRA	200	-2.8 (2.83)	100	-0.9 (5)		2.0 %	-1.90 [-2.96, -0.84]
DA (Pr): Denmark	29	-1.2 (2.9)	29	-0.6 (3)		0.9 %	-0.60 [-2.12, 0.92]
DA (Pr): Europe	174	-1.94 (2.59)	180	-0.12 (3.11)		6.2 %	-1.82 [-2.42, -1.22]
DA (Pr): US/Canada	174	-2.4 (3.4)	172	-0.7 (3.7)		3.9 %	-1.70 [-2.45, -0.95]
DA (R): EASE-PD	201	-2.1 (4.54)	190	-0.3 (4.41)		2.8 %	-1.80 [-2.69, -0.91]
DA (R): France/Eng	23	-1.74 (2.36)	23	-2.22 (3)		0.9 %	0.48 [-1.08, 2.04]
DA (R): UK/Israel	42	-1.33 (2.35)	22	-0.75 (2.81)		1.2 %	-0.58 [-1.95, 0.79]
DA (R): USA	90	-1.53 (4.28)	53	-1.22 (3.7)		1.2 %	-0.31 [-1.64, 1.02]
Subtotal (95% CI)	**1438**		**1163**			**27.1 %**	**-1.54 [-1.83, -1.26]**
Heterogeneity: Chi^2 = 21.85, df = 14 (P = 0.08); I^2 =36%							
Test for overall effect: Z = 10.64 (P < 0.00001)							
2 COMTI versus Placebo							
COMTI (E): Celomen	129	-1.6 (2.5)	74	-0.9 (3.4)		2.8 %	-0.70 [-1.59, 0.19]
COMTI (E): ComQol	174	-1 (1.9)	96	-0.9 (2)		9.1 %	-0.10 [-0.59, 0.39]
COMTI (E): INT-02	99	-0.86 (2.9)	63	-0.54 (3.13)		2.4 %	-0.32 [-1.28, 0.64]
COMTI (E): LARGO	218	-1.2 (2.21)	218	-0.4 (2.21)		12.7 %	-0.80 [-1.21, -0.39]
COMTI (E): Nomecomt	85	-1.3 (2.2)	86	-0.1 (2.45)		4.5 %	-1.20 [-1.90, -0.50]
COMTI (E): Sth Korea	98	-1.5 (2.55)	99	-1 (2.29)		4.8 %	-0.50 [-1.18, 0.18]



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Study or subgroup	Treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
COMTI (E): UK/Irish	115	-1.1 (2.55)	57	-0.3 (2.85)		2.9 %	-0.80 [-1.67, 0.07]
COMTI (T): China	20	-1.9 (3.3)	20	0.15 (3.3)		0.5 %	-2.05 [-4.10, 0.00]
COMTI (T): Europe	60	-2.03 (2.6)	58	-0.67 (2.8)		2.3 %	-1.36 [-2.34, -0.38]
COMTI (T): TFSG 1	40	-1.61 (1.77)	42	-0.04 (1.75)		3.8 %	-1.57 [-2.33, -0.81]
COMTI (T): TFSG 3	69	-2 (2.49)	72	-0.3 (2.55)		3.2 %	-1.70 [-2.53, -0.87]
COMTI (T): TIPS 1	31	-1.78 (2.76)	37	-0.11 (2.63)		1.3 %	-1.67 [-2.96, -0.38]
Subtotal (95% CI)	**1138**		**922**			**50.2 %**	**-0.83 [-1.04, -0.62]**
Heterogeneity: Chi^2 = 23.67, df = 11 (P = 0.01); I^2 =54%							
Test for overall effect: Z = 7.77 (P < 0.00001)							
3 MAOBI versus Placebo							
MAOBI (R): LARGO	222	-1.18 (2.23)	218	-0.4 (2.21)		12.7 %	-0.78 [-1.19, -0.37]
MAOBI (R): PRESTO	149	-1.85 (2.5)	159	-0.91 (2.5)		7.0 %	-0.94 [-1.50, -0.38]
MAOBI (ZS): USA	94	-2.2 (2.43)	46	-0.6 (2.49)		2.9 %	-1.60 [-2.47, -0.73]
Subtotal (95% CI)	**465**		**423**			**22.6 %**	**-0.93 [-1.25, -0.62]**
Heterogeneity: Chi^2 = 2.77, df = 2 (P = 0.25); I^2 =28%							
Test for overall effect: Z = 5.89 (P < 0.00001)							
Total (95% CI)	**3041**		**2508**			**100.0 %**	**-1.05 [-1.19, -0.90]**
Heterogeneity: Chi^2 = 64.75, df = 29 (P = 0.00015); I^2 =55%							
Test for overall effect: Z = 13.85 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 16.45, df = 2 (P = 0.00), I^2 =88%							

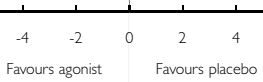
Analysis 1.2. Comparison 1 Off-Time, Outcome 2 Off-Time Reduction (Dopamine Agonist versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 1 Off-Time

Outcome: 2 Off-Time Reduction (Dopamine Agonist versus Placebo)

Study or subgroup	Dopamine Agonist N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Bromocriptine							
DA (B): Germany	20	-3.4 (2.78)	20	0.3 (3.66)		1.7 %	-3.70 [-5.71, -1.69]
DA (Pr/B): Interntl	81	-1.2 (4.3)	76	-0.3 (4.4)		3.8 %	-0.90 [-2.26, 0.46]
Subtotal (95% CI)	**101**		**96**			**5.5 %**	**-1.78 [-2.91, -0.65]**
Heterogeneity: Chi² = 5.09, df = 1 (P = 0.02); I² =80%							
Test for overall effect: Z = 3.09 (P = 0.0020)							
2 Cabergoline							
DA (C): Spain	14	-3.33 (3.47)	12	-2.47 (3.91)		0.9 %	-0.86 [-3.72, 2.00]
DA (C): UK	18	-2 (2.33)	16	-0.7 (2.25)		3.0 %	-1.30 [-2.84, 0.24]
DA (C): USA 1	89	-2.08 (3.19)	46	-0.77 (0.34)		15.6 %	-1.31 [-1.98, -0.64]
Subtotal (95% CI)	**121**		**74**			**19.5 %**	**-1.29 [-1.89, -0.69]**
Heterogeneity: Chi² = 0.09, df = 2 (P = 0.96); I² =0.0%							
Test for overall effect: Z = 4.20 (P = 0.000026)							
3 Pergolide							
DA (Pe): N America	189	-1.8 (4.8)	187	-0.2 (4.8)		7.5 %	-1.60 [-2.57, -0.63]
Subtotal (95% CI)	**189**		**187**			**7.5 %**	**-1.60 [-2.57, -0.63]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.23 (P = 0.0012)							
4 Pramipexole							
DA (Pr): Aust/Germ	23	-2.3 (2.7)	37	0.4 (3.5)		2.8 %	-2.70 [-4.28, -1.12]
DA (Pr): CLEOPATRA	200	-2.8 (2.83)	100	-0.9 (5)		6.3 %	-1.90 [-2.96, -0.84]
DA (Pr): Denmark	29	-1.2 (2.9)	29	-0.6 (3)		3.0 %	-0.60 [-2.12, 0.92]
DA (Pr): Europe	174	-1.94 (2.59)	180	-0.12 (3.11)		19.8 %	-1.82 [-2.42, -1.22]
DA (Pr): US/Canada	174	-2.4 (3.4)	172	-0.7 (3.7)		12.5 %	-1.70 [-2.45, -0.95]
DA (Pr/B): Interntl	71	-2.6 (4.3)	76	-0.3 (4.4)		3.5 %	-2.30 [-3.71, -0.89]
Subtotal (95% CI)	**671**		**594**			**48.1 %**	**-1.81 [-2.19, -1.43]**
Heterogeneity: Chi² = 4.24, df = 5 (P = 0.52); I² =0.0%							
Test for overall effect: Z = 9.27 (P < 0.00001)							
5 Ropinirole							
DA (R): EASE-PD	201	-2.1 (4.54)	190	-0.3 (4.41)		8.9 %	-1.80 [-2.69, -0.91]



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Study or subgroup	Dopamine Agonist N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
DA (R): France/Eng	23	-1.74 (2.36)	23	-2.22 (3)		2.9 %	0.48 [-1.08, 2.04]
DA (R): UK/Israel	42	-1.33 (2.35)	22	-0.75 (2.81)		3.7 %	-0.58 [-1.95, 0.79]
DA (R): USA	90	-1.53 (4.28)	53	-1.22 (3.7)		4.0 %	-0.31 [-1.64, 1.02]
Subtotal (95% CI)	**356**		**288**			**19.5 %**	**-0.93 [-1.53, -0.33]**
Heterogeneity: Chi^2 = 7.91, df = 3 (P = 0.05); I^2 =62%							
Test for overall effect: Z = 3.03 (P = 0.0025)							
Total (95% CI)	**1438**		**1239**			**100.0 %**	**-1.52 [-1.78, -1.25]**
Heterogeneity: Chi^2 = 24.08, df = 15 (P = 0.06); I^2 =38%							
Test for overall effect: Z = 11.23 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 6.75, df = 4 (P = 0.15), I^2 =41%							

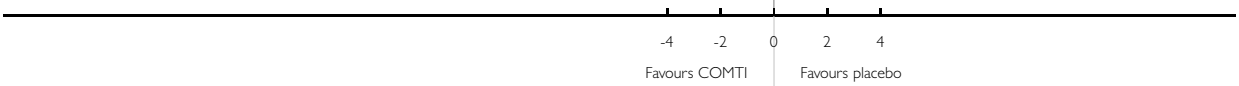
Analysis 1.3. Comparison 1 Off-Time, Outcome 3 Off-Time Reduction (COMTI versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 1 Off-Time

Outcome: 3 Off-Time Reduction (COMTI versus Placebo)

Study or subgroup	COMTI N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Entacapone							
COMTI (E): Celomen	129	-1.6 (2.5)	74	-0.9 (3.4)		5.5 %	-0.70 [-1.59, 0.19]
COMTI (E): ComQol	174	-1 (1.9)	96	-0.9 (2)		18.2 %	-0.10 [-0.59, 0.39]
COMTI (E): INT-02	99	-0.86 (2.9)	63	-0.54 (3.13)		4.7 %	-0.32 [-1.28, 0.64]
COMTI (E): LARGO	218	-1.2 (2.21)	218	-0.4 (2.21)		25.3 %	-0.80 [-1.21, -0.39]
COMTI (E): Nomecomt	85	-1.3 (2.2)	86	-0.1 (2.45)		9.0 %	-1.20 [-1.90, -0.50]
COMTI (E): Sth Korea	98	-1.5 (2.55)	99	-1 (2.29)		9.5 %	-0.50 [-1.18, 0.18]
COMTI (E): UK/Irish	115	-1.1 (2.55)	57	-0.3 (2.85)		5.7 %	-0.80 [-1.67, 0.07]
Subtotal (95% CI)	**918**		**693**			**78.0 %**	**-0.61 [-0.85, -0.37]**
Heterogeneity: Chi^2 = 8.39, df = 6 (P = 0.21); I^2 =29%							
Test for overall effect: Z = 5.05 (P < 0.00001)							
2 Tolcapone							
COMTI (T): China	20	-1.9 (3.3)	20	0.15 (3.3)		1.0 %	-2.05 [-4.10, 0.00]
COMTI (T): Europe	60	-2.03 (2.6)	58	-0.67 (2.8)		4.6 %	-1.36 [-2.34, -0.38]
COMTI (T): TFSG 1	40	-1.61 (1.77)	42	-0.04 (1.75)		7.5 %	-1.57 [-2.33, -0.81]
COMTI (T): TFSG 3	69	-2 (2.49)	72	-0.3 (2.55)		6.3 %	-1.70 [-2.53, -0.87]
COMTI (T): TIPS 1	31	-1.78 (2.76)	37	-0.11 (2.63)		2.6 %	-1.67 [-2.96, -0.38]
Subtotal (95% CI)	**220**		**229**			**22.0 %**	**-1.60 [-2.04, -1.15]**
Heterogeneity: Chi^2 = 0.49, df = 4 (P = 0.97); I^2 =0.0%							
Test for overall effect: Z = 7.04 (P < 0.00001)							
Total (95% CI)	**1138**		**922**			**100.0 %**	**-0.83 [-1.04, -0.62]**
Heterogeneity: Chi^2 = 23.67, df = 11 (P = 0.01); I^2 =54%							
Test for overall effect: Z = 7.77 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 14.79, df = 1 (P = 0.00), I^2 =93%							



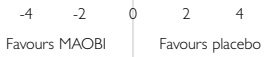
Analysis 1.4. Comparison 1 Off-Time, Outcome 4 Off-Time Reduction (MAOBI versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 1 Off-Time

Outcome: 4 Off-Time Reduction (MAOBI versus Placebo)

Study or subgroup	MAOBI N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Rasagiline							
MAOBI (R): LARGO	222	-1.18 (2.23)	218	-0.4 (2.21)		56.2 %	-0.78 [-1.19, -0.37]
MAOBI (R): PRESTO	149	-1.85 (2.5)	159	-0.91 (2.5)		31.0 %	-0.94 [-1.50, -0.38]
Subtotal (95% CI)	**371**		**377**			**87.2 %**	**-0.84 [-1.17, -0.50]**
Heterogeneity: Chi^2 = 0.20, df = 1 (P = 0.65); I^2 =0.0%							
Test for overall effect: Z = 4.92 (P < 0.00001)							
2 Sublingual Selegiline							
MAOBI (ZS): USA	94	-2.2 (2.43)	46	-0.6 (2.49)		12.8 %	-1.60 [-2.47, -0.73]
Subtotal (95% CI)	**94**		**46**			**12.8 %**	**-1.60 [-2.47, -0.73]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.60 (P = 0.00032)							
Total (95% CI)	**465**		**423**			**100.0 %**	**-0.93 [-1.25, -0.62]**
Heterogeneity: Chi^2 = 2.77, df = 2 (P = 0.25); I^2 =28%							
Test for overall effect: Z = 5.89 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 2.57, df = 1 (P = 0.11), I^2 =61%							



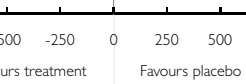
Analysis 2.1. Comparison 2 Levodopa Dose, Outcome 1 Levodopa Dose Reduction (mg/day) (Adjuvant Therapy versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 2 Levodopa Dose

Outcome: 1 Levodopa Dose Reduction (mg/day) (Adjuvant Therapy versus Placebo)

Study or subgroup	Treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Dopamine Agonist versus Placebo							
DA (Pr/B): Interntl	163	-70.7 (168.13)	83	-23.5 (120.7)		3.7 %	-47.20 [-83.81, -10.59]
DA (B): Germany	20	-178 (191.2)	20	-30 (141.17)		0.5 %	-148.00 [-252.16, -43.84]
DA (C): USA 1	109	-175.1 (292.7)	54	-25.5 (82.5)		1.4 %	-149.60 [-208.79, -90.41]
DA (Pe): N America	189	-235.3 (550)	187	-51.4 (550)		0.4 %	-183.90 [-295.09, -72.71]
DA (Pr): Denmark	33	-150.7 (196.9)	33	-10.6 (121)		0.8 %	-140.10 [-218.95, -61.25]
DA (Pr): US/Canada	179	-209.48 (272.55)	172	-45.2 (115.86)		2.6 %	-164.28 [-207.80, -120.76]
DA (R): EASE-PD	201	-278 (193)	190	-164 (164)		3.9 %	-114.00 [-149.44, -78.56]
DA (R): UK/Israel	41	-157.03 (261.99)	22	-131.43 (213.4)		0.3 %	-25.60 [-145.53, 94.33]
DA (R): USA	94	-235.93 (246.71)	54	-56.32 (200.53)		0.9 %	-179.61 [-252.74, -106.48]
Subtotal (95% CI)	**1029**		**815**			**14.5 %**	**-116.03 [-134.45, -97.61]**
Heterogeneity: Chi^2 = 26.79, df = 8 (P = 0.00077); I^2 =70%							
Test for overall effect: Z = 12.34 (P < 0.00001)							
2 COMTI versus Placebo							
COMTI (E): Celomen	93	-54 (134)	42	27 (102)		2.9 %	-81.00 [-122.15, -39.85]
COMTI (E): ComQol	174	-30 (83)	96	5 (59)		16.9 %	-35.00 [-52.07, -17.93]
COMTI (E): INT-02	99	-31.8 (172.3)	63	9.9 (93.6)		2.9 %	-41.70 [-82.76, -0.64]
COMTI (E): Interntl	12	32 (41.39)	12	132 (38.59)		4.8 %	-100.00 [-132.02, -67.98]
COMTI (E): LARGO	218	-19 (82.8)	218	5 (82.8)		20.4 %	-24.00 [-39.54, -8.46]
COMTI (E): Nomecomt	85	-87 (274.04)	86	15 (292.96)		0.7 %	-102.00 [-187.02, -16.98]
COMTI (E): Sth Korea	98	-51.6 (154.5)	99	-0.7 (130)		3.1 %	-50.90 [-90.79, -11.01]
COMTI (E): UK/Irish	115	-33 (386.76)	57	26 (372.58)		0.3 %	-59.00 [-178.80, 60.80]
COMTI (T): China	20	-55 (156.97)	20	-15 (67.08)		0.9 %	-40.00 [-114.81, 34.81]
COMTI (T): Europe	60	-108.9 (181.26)	58	-28.9 (199.53)		1.0 %	-80.00 [-148.85, -11.15]
COMTI (T): TFSG 1	40	-200 (196.06)	42	-31.2 (190.53)		0.7 %	-168.80 [-252.54, -85.06]



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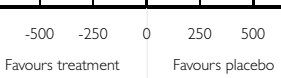
Study or subgroup	Treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
COMTI (T): TFSG 3	69	-185.5 (171.12)	72	-0.5 (170.55)		1.5 %	-185.00 [-241.41, -128.59]
COMTI (T): TIPS I	31	-79.1 (110.8)	37	2.4 (109.49)		1.8 %	-81.50 [-134.09, -28.91]
COMTI (T): TIPS II	32	-182 (132.37)	33	-113.9 (129.25)		1.2 %	-68.10 [-131.72, -4.48]
COMTI (T): US/Canada	69	-166.3 (185.24)	66	15.5 (182.79)		1.3 %	-181.80 [-243.89, -119.71]
Subtotal (95% CI)	**1215**		**1001**			**60.6 %**	**-52.07 [-61.09, -43.05]**
Heterogeneity: Chi^2 = 76.21, df = 14 (P<0.00001); I^2 =82%							
Test for overall effect: Z = 11.31 (P < 0.00001)							
3 MAOBI versus Placebo							
MAOBI (R): LARGO	222	-24 (85)	218	5 (85)		19.5 %	-29.00 [-44.89, -13.11]
MAOBI (R): PRESTO	149	-36 (133)	159	-12 (142)		5.2 %	-24.00 [-54.71, 6.71]
MAOBI (S): Norw/Fin	20	-425.5 (310)	18	-168.1 (310)		0.1 %	-257.40 [-454.80, -60.00]
Subtotal (95% CI)	**391**		**395**			**24.9 %**	**-29.11 [-43.18, -15.04]**
Heterogeneity: Chi^2 = 5.24, df = 2 (P = 0.07); I^2 =62%							
Test for overall effect: Z = 4.05 (P = 0.000050)							
Total (95% CI)	**2635**		**2211**			**100.0 %**	**-55.65 [-62.67, -48.62]**
Heterogeneity: Chi^2 = 163.77, df = 26 (P<0.00001); I^2 =84%							
Test for overall effect: Z = 15.53 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 55.53, df = 2 (P = 0.00), I^2 =96%							



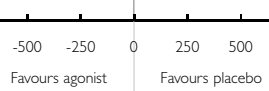
Analysis 2.2. Comparison 2 Levodopa Dose, Outcome 2 Levodopa Dose Reduction (mg/day) (Dopamine Agonist versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 2 Levodopa Dose

Outcome: 2 Levodopa Dose Reduction (mg/day) (Dopamine Agonist versus Placebo)

Study or subgroup	Dopamine Agonist N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Bromocriptine							
DA (B): Germany	20	-178 (191.2)	20	-30 (141.17)		2.9 %	-148.00 [-252.16, -43.84]
DA (Pr/B): Interntl	84	-56 (184.3)	83	-23.5 (120.7)		13.9 %	-32.50 [-79.70, 14.70]
Subtotal (95% CI)	**104**		**103**			**16.8 %**	**-52.17 [-95.16, -9.18]**
Heterogeneity: Chi² = 3.92, df = 1 (P = 0.05); I² =74%							
Test for overall effect: Z = 2.38 (P = 0.017)							
2 Cabergoline							
DA (C): USA 1	109	-175.1 (292.7)	54	-25.5 (82.5)		8.9 %	-149.60 [-208.79, -90.41]
Subtotal (95% CI)	**109**		**54**			**8.9 %**	**-149.60 [-208.79, -90.41]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.95 (P < 0.00001)							
3 Pergolide							
DA (Pe): N America	189	-235.3 (550)	187	-51.4 (550)		2.5 %	-183.90 [-295.09, -72.71]
Subtotal (95% CI)	**189**		**187**			**2.5 %**	**-183.90 [-295.09, -72.71]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.24 (P = 0.0012)							
4 Pramipexole							
DA (Pr): Denmark	33	-150.7 (196.9)	33	-10.6 (121)		5.0 %	-140.10 [-218.95, -61.25]
DA (Pr): US/Canada	179	-209.48 (272.55)	172	-45.2 (115.86)		16.4 %	-164.28 [-207.80, -120.76]
DA (Pr/B): Interntl	79	-85.4 (149)	83	-23.5 (120.7)		17.7 %	-61.90 [-103.78, -20.02]
Subtotal (95% CI)	**291**		**288**			**39.1 %**	**-114.82 [-143.01, -86.64]**
Heterogeneity: Chi² = 11.49, df = 2 (P = 0.003); I² =83%							
Test for overall effect: Z = 7.99 (P < 0.00001)							
5 Ropinirole							
DA (R): EASE-PD	201	-278 (193)	190	-164 (164)		24.7 %	-114.00 [-149.44, -78.56]
DA (R): UK/Israel	41	-157.03 (261.99)	22	-131.43 (213.4)		2.2 %	-25.60 [-145.53, 94.33]
DA (R): USA	94	-235.93 (246.71)	54	-56.32 (200.53)		5.8 %	-179.61 [-252.74, -106.48]
Subtotal (95% CI)	**336**		**266**			**32.7 %**	**-119.81 [-150.63, -89.00]**
Heterogeneity: Chi² = 5.04, df = 2 (P = 0.08); I² =60%							
Test for overall effect: Z = 7.62 (P < 0.00001)							



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Study or subgroup	Dopamine Agonist N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Total (95% CI)	**1029**		**898**		♦	**100.0 %**	**-110.75 [-128.37, -93.12]**

Heterogeneity: Chi² = 31.31, df = 9 (P = 0.00026); I² =71%

Test for overall effect: Z = 12.32 (P < 0.00001)

Test for subgroup differences: Chi² = 10.86, df = 4 (P = 0.03), I² =63%

-500 -250 0 250 500

Favours agonist Favours placebo

Analysis 2.3. Comparison 2 Levodopa Dose, Outcome 3 Levodopa Dose Reduction (mg/day) (COMTI versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 2 Levodopa Dose

Outcome: 3 Levodopa Dose Reduction (mg/day) (COMTI versus Placebo)

Study or subgroup	COMTI N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Entacapone							
COMTI (E): Celomen	93	-54 (134)	42	27 (102)		4.8 %	-81.00 [-122.15, -39.85]
COMTI (E): ComQol	174	-30 (83)	96	5 (59)		27.9 %	-35.00 [-52.07, -17.93]
COMTI (E): INT-02	99	-31.8 (172.3)	63	9.9 (93.6)		4.8 %	-41.70 [-82.76, -0.64]
COMTI (E): Interntl	12	32 (41.39)	12	132 (38.59)		7.9 %	-100.00 [-132.02, -67.98]
COMTI (E): LARGO	218	-19 (82.8)	218	5 (82.8)		33.7 %	-24.00 [-39.54, -8.46]
COMTI (E): Nomecomt	85	-87 (274.04)	86	15 (292.96)		1.1 %	-102.00 [-187.02, -16.98]
COMTI (E): Sth Korea	98	-51.6 (154.5)	99	-0.7 (130)		5.1 %	-50.90 [-90.79, -11.01]
COMTI (E): UK/Irish	115	-33 (386.76)	57	26 (372.58)		0.6 %	-59.00 [-178.80, 60.80]
Subtotal (95% CI)	**894**		**673**		♦	**86.0 %**	**-41.62 [-51.35, -31.89]**

Heterogeneity: Chi² = 24.03, df = 7 (P = 0.001); I² =71%

Test for overall effect: Z = 8.39 (P < 0.00001)

-500 -250 0 250 500

Favours COMTI Favours placebo

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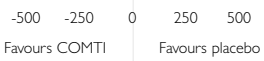
Study or subgroup	COMTI N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
2 Tolcapone							
COMTI (T): China	20	-55 (156.97)	20	-15 (67.08)		1.5 %	-40.00 [-114.81, 34.81]
COMTI (T): Europe	60	-108.9 (181.26)	58	-28.9 (199.53)		1.7 %	-80.00 [-148.85, -11.15]
COMTI (T): TFSG 1	40	-200 (196.06)	42	-31.2 (190.53)		1.2 %	-168.80 [-252.54, -85.06]
COMTI (T): TFSG 3	69	-185.5 (171.12)	72	-0.5 (170.55)		2.6 %	-185.00 [-241.41, -128.59]
COMTI (T): TIPS 1	31	-79.1 (110.8)	37	2.4 (109.49)		2.9 %	-81.50 [-134.09, -28.91]
COMTI (T): TIPS II	32	-182 (132.37)	33	-113.9 (129.25)		2.0 %	-68.10 [-131.72, -4.48]
COMTI (T): US/Canada	69	-166.3 (185.24)	66	15.5 (182.79)		2.1 %	-181.80 [-243.89, -119.71]
Subtotal (95% CI)	**321**		**328**			**14.0 %**	**-116.47 [-140.62, -92.32]**
Heterogeneity: Chi^2 = 20.43, df = 6 (P = 0.002); I^2 =71%							
Test for overall effect: Z = 9.45 (P < 0.00001)							
Total (95% CI)	**1215**		**1001**			**100.0 %**	**-52.07 [-61.09, -43.05]**
Heterogeneity: Chi^2 = 76.21, df = 14 (P<0.00001); I^2 =82%							
Test for overall effect: Z = 11.31 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 31.75, df = 1 (P = 0.00), I^2 =97%							

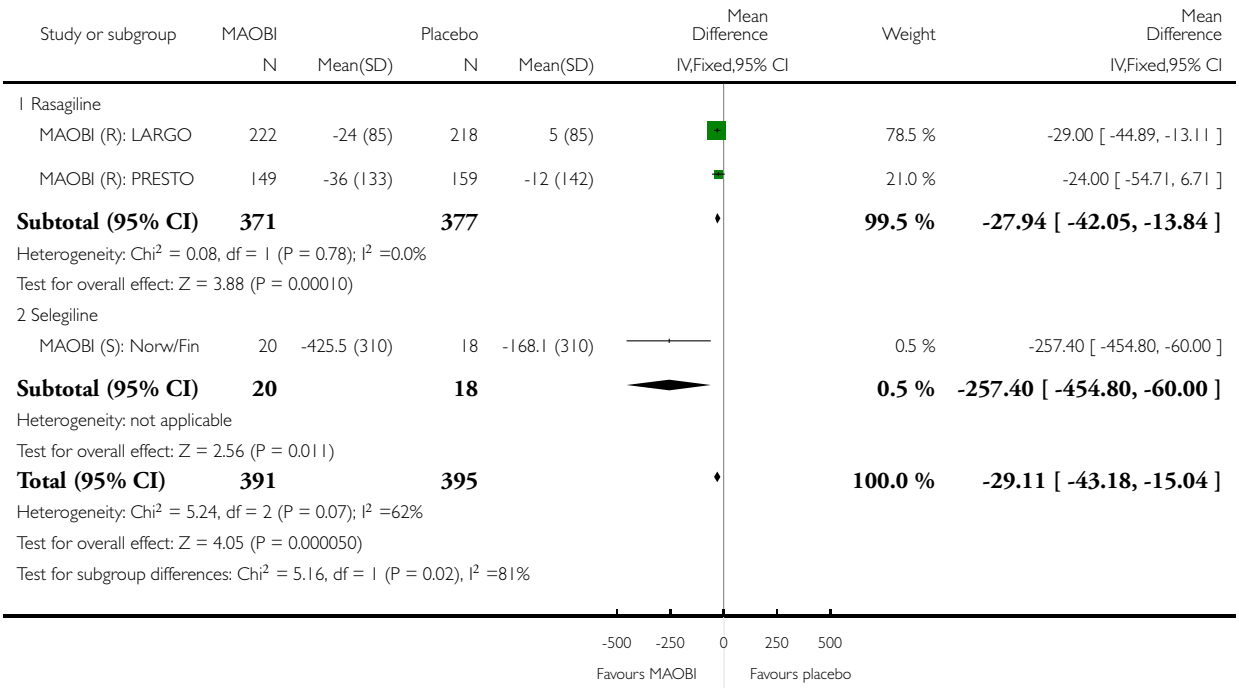


Analysis 2.4. Comparison 2 Levodopa Dose, Outcome 4 Levodopa Dose Reduction (mg/day) (MAOBI versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 2 Levodopa Dose

Outcome: 4 Levodopa Dose Reduction (mg/day) (MAOBI versus Placebo)



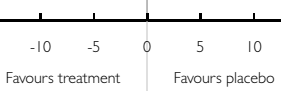
Analysis 3.1. Comparison 3 Clinician Rated Disability Scales, Outcome 1 UPDRS Activities of Daily Living (Adjuvant Therapy versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 3 Clinician Rated Disability Scales

Outcome: 1 UPDRS Activities of Daily Living (Adjuvant Therapy versus Placebo)

Study or subgroup	Treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Dopamine Agonist versus Placebo							
DA (C): Spain	10	-1.7 (2.83)	7	-1.29 (4.39)		0.7 %	-0.41 [-4.10, 3.28]
DA (C): USA 1	106	-2.9 (7.67)	54	-0.6 (6.61)		1.9 %	-2.30 [-4.59, -0.01]
DA (Pr): Aust/Germ	33	-4.4 (4.7)	44	-1.1 (3.4)		2.8 %	-3.30 [-5.19, -1.41]
DA (Pr): CLEOPATRA	201	-4.6 (4.4)	101	-2 (4.3)		9.3 %	-2.60 [-3.64, -1.56]
DA (Pr): Europe	174	-2.5 (4.1)	180	-1.2 (3.8)		14.7 %	-1.30 [-2.12, -0.48]
DA (Pr): H Kong/Taiw	50	-3.16 (3.75)	54	-0.52 (3.45)		5.2 %	-2.64 [-4.03, -1.25]
Subtotal (95% CI)	**574**		**440**			**34.7 %**	**-2.05 [-2.58, -1.51]**
Heterogeneity: Chi² = 7.44, df = 5 (P = 0.19); I² =33%							
Test for overall effect: Z = 7.47 (P < 0.00001)							
2 COMTI versus Placebo							
COMTI (E): Celomen	172	-1.1 (5)	88	0.2 (5)		6.1 %	-1.30 [-2.58, -0.02]
COMTI (E): ComQol	174	-2.3 (3.7)	96	-0.7 (2.7)		16.9 %	-1.60 [-2.37, -0.83]
COMTI (E): INT-02	99	-1 (5.9)	63	-0.3 (3.7)		4.6 %	-0.70 [-2.18, 0.78]
COMTI (E): Nomecomt	85	-1.7 (5.21)	86	-0.4 (4.66)		4.6 %	-1.30 [-2.78, 0.18]
COMTI (E): Sth Korea	98	-0.8 (7.25)	99	-0.6 (5.6)		3.1 %	-0.20 [-2.01, 1.61]
COMTI (E): UK/Irish	115	-0.5 (5.65)	57	-1.1 (7.16)		2.2 %	0.60 [-1.53, 2.73]
COMTI (T): TFSG 3	69	-0.4 (3.32)	72	-0.7 (3.39)		8.2 %	0.30 [-0.81, 1.41]
COMTI (T): TIPS 1	31	-1.4 (2.78)	37	-0.8 (3.04)		5.2 %	-0.60 [-1.98, 0.78]
COMTI (T): TIPS II	32	-1.1 (2.26)	33	0.4 (2.3)		8.2 %	-1.50 [-2.61, -0.39]
COMTI (T): US/Canada	69	-0.8 (3.32)	66	-0.3 (4.06)		6.4 %	-0.50 [-1.75, 0.75]
Subtotal (95% CI)	**944**		**697**			**65.3 %**	**-0.91 [-1.30, -0.52]**
Heterogeneity: Chi² = 12.58, df = 9 (P = 0.18); I² =28%							
Test for overall effect: Z = 4.55 (P < 0.00001)							
3 MAOBI versus Placebo							
Subtotal (95% CI)	**0**		**0**			**0.0 %**	**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							



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Study or subgroup	Treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Test for overall effect: not applicable							
Total (95% CI)	**1518**		**1137**		♦	**100.0 %**	**-1.31 [-1.62, -0.99]**
Heterogeneity: Chi² = 31.26, df = 15 (P = 0.01); I² =52%							
Test for overall effect: Z = 8.08 (P < 0.00001)							
Test for subgroup differences: Chi² = 11.24, df = 1 (P = 0.00), I² =91%							

-10 -5 0 5 10

Favours treatment Favours placebo

Analysis 3.2. Comparison 3 Clinician Rated Disability Scales, Outcome 2 UPDRS Motor (Adjuvant Therapy versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 3 Clinician Rated Disability Scales

Outcome: 2 UPDRS Motor (Adjuvant Therapy versus Placebo)

Study or subgroup	Treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Dopamine Agonist versus Placebo							
DA (C): Spain	17	-4.47 (5.14)	13	-2.54 (3.6)		2.7 %	-1.93 [-5.06, 1.20]
DA (C): USA 1	105	-2.7 (8.59)	54	-1.1 (8.01)		3.7 %	-1.60 [-4.30, 1.10]
DA (Pr): Aust/Germ	33	-13.2 (11)	44	-4.5 (9.5)		1.2 %	-8.70 [-13.39, -4.01]
DA (Pr): CLEOPATRA	201	-10.3 (8.7)	101	-4.3 (9.3)		5.6 %	-6.00 [-8.18, -3.82]
DA (Pr): Europe	174	-10.3 (12)	180	-4.43 (11.1)		4.6 %	-5.87 [-8.28, -3.46]
DA (Pr): H Kong/Taiw	50	-7.2 (8.91)	54	-0.55 (7.94)		2.5 %	-6.65 [-9.90, -3.40]
DA (R): EASE-PD	194	-6.5 (12.61)	183	-1.7 (12.38)		4.2 %	-4.80 [-7.32, -2.28]
Subtotal (95% CI)	**774**		**629**		◆	**24.5 %**	**-4.86 [-5.90, -3.82]**
Heterogeneity: Chi² = 14.46, df = 6 (P = 0.02); I² =59%							
Test for overall effect: Z = 9.14 (P < 0.00001)							
2 COMTI versus Placebo							

-10 -5 0 5 10

Favours treatment Favours placebo

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Study or subgroup	Treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
COMTI (E): Celomen	172	-3.3 (10)	88	-0.1 (10)		4.0 %	-3.20 [-5.77, -0.63]
COMTI (E): ComQol	174	-5 (7.5)	96	-2.9 (7.5)		7.6 %	-2.10 [-3.97, -0.23]
COMTI (E): Interntl	12	-7.8 (2.1)	12	-7.1 (1.6)		11.9 %	-0.70 [-2.19, 0.79]
COMTI (E): LARGO	218	-3.2 (7.38)	218	-0.5 (7.38)		13.9 %	-2.70 [-4.09, -1.31]
COMTI (E): Nomecomt	85	-3 (13.46)	86	4.2 (12.5)		1.8 %	-7.20 [-11.09, -3.31]
COMTI (E): Sth Korea	98	-3.3 (11.47)	99	-1.2 (9.6)		3.0 %	-2.10 [-5.06, 0.86]
COMTI (E): UK/Irish	115	-4.5 (11.91)	57	-4.3 (12.6)		1.7 %	-0.20 [-4.13, 3.73]
COMTI (T): Europe	60	-4.2 (7.74)	58	-2.1 (8.38)		3.1 %	-2.10 [-5.01, 0.81]
COMTI (T): TFSG 3	69	-2.3 (5.81)	72	-1.2 (5.94)		7.1 %	-1.10 [-3.04, 0.84]
COMTI (T): TIPS I	31	-5.8 (10.58)	37	-0.3 (10.34)		1.1 %	-5.50 [-10.50, -0.50]
COMTI (T): TIPS II	32	-3.4 (7.35)	33	-1.5 (7.47)		2.1 %	-1.90 [-5.50, 1.70]
COMTI (T): US/Canada	69	-1.9 (7.48)	66	-0.4 (7.31)		4.3 %	-1.50 [-4.00, 1.00]
Subtotal (95% CI)	**1135**		**922**			**61.6 %**	**-2.02 [-2.68, -1.37]**
Heterogeneity: Chi^2 = 15.27, df = 11 (P = 0.17); I^2 =28%							
Test for overall effect: Z = 6.03 (P < 0.00001)							
3 MAOBI versus Placebo							
MAOBI (R): LARGO	222	-3.4 (7.45)	218	-0.5 (7.38)		13.9 %	-2.90 [-4.29, -1.51]
Subtotal (95% CI)	**222**		**218**			**13.9 %**	**-2.90 [-4.29, -1.51]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.10 (P = 0.000041)							
Total (95% CI)	**2131**		**1769**			**100.0 %**	**-2.84 [-3.36, -2.32]**
Heterogeneity: Chi^2 = 50.10, df = 19 (P = 0.00013); I^2 =62%							
Test for overall effect: Z = 10.79 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 20.37, df = 2 (P = 0.00), I^2 =90%							

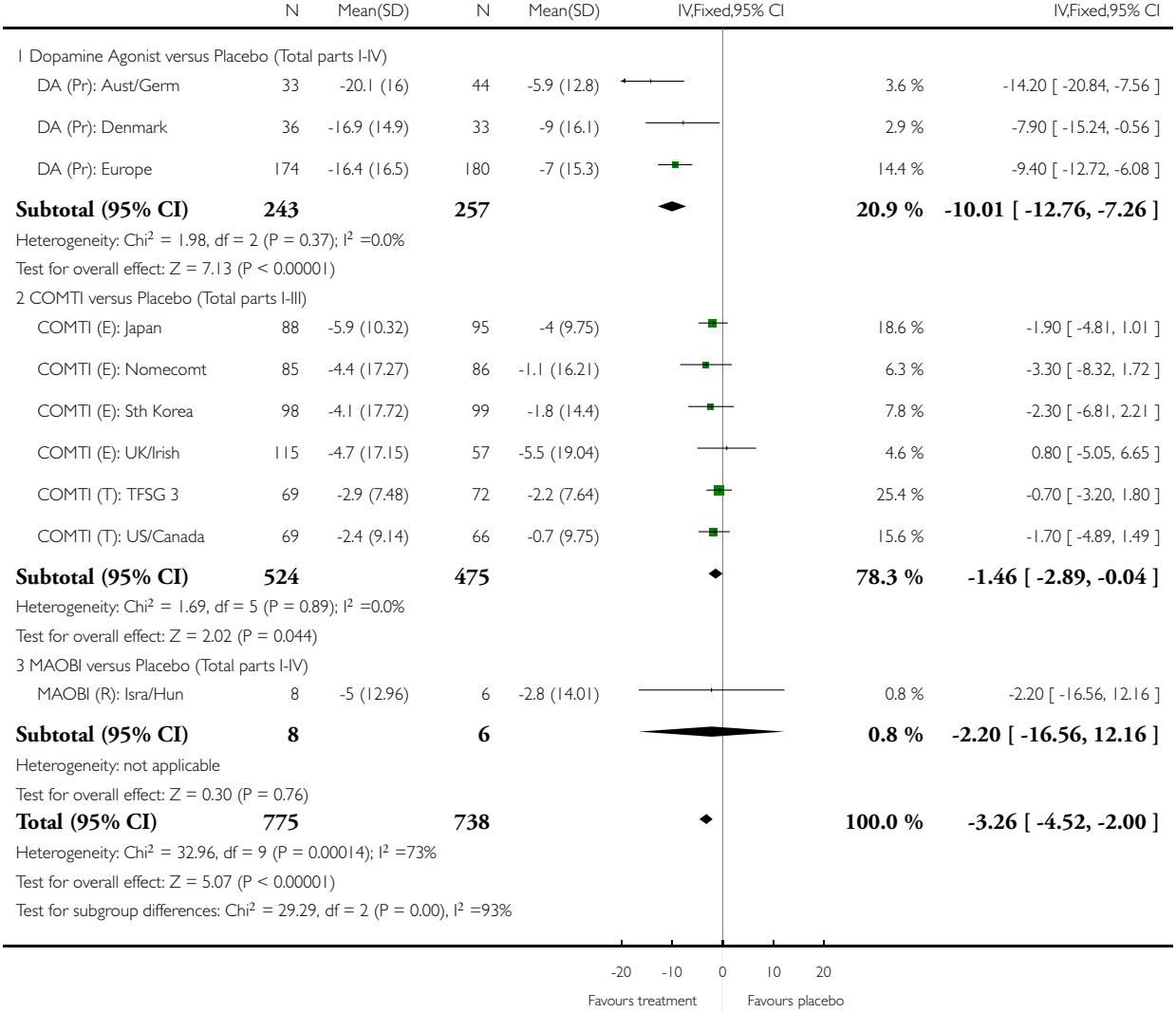
Analysis 3.3. Comparison 3 Clinician Rated Disability Scales, Outcome 3 UPDRS Total (Adjuvant Therapy versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 3 Clinician Rated Disability Scales

Outcome: 3 UPDRS Total (Adjuvant Therapy versus Placebo)

Study or subgroup	Treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Dopamine Agonist versus Placebo (Total parts I-IV)							
DA (Pr): Aust/Germ	33	-20.1 (16)	44	-5.9 (12.8)		3.6 %	-14.20 [-20.84, -7.56]
DA (Pr): Denmark	36	-16.9 (14.9)	33	-9 (16.1)		2.9 %	-7.90 [-15.24, -0.56]
DA (Pr): Europe	174	-16.4 (16.5)	180	-7 (15.3)		14.4 %	-9.40 [-12.72, -6.08]
Subtotal (95% CI)	**243**		**257**			**20.9 %**	**-10.01 [-12.76, -7.26]**
Heterogeneity: Chi^2 = 1.98, df = 2 (P = 0.37); I^2 =0.0%							
Test for overall effect: Z = 7.13 (P < 0.00001)							
2 COMTI versus Placebo (Total parts I-III)							
COMTI (E): Japan	88	-5.9 (10.32)	95	-4 (9.75)		18.6 %	-1.90 [-4.81, 1.01]
COMTI (E): Nomecomt	85	-4.4 (17.27)	86	-1.1 (16.21)		6.3 %	-3.30 [-8.32, 1.72]
COMTI (E): Sth Korea	98	-4.1 (17.72)	99	-1.8 (14.4)		7.8 %	-2.30 [-6.81, 2.21]
COMTI (E): UK/Irish	115	-4.7 (17.15)	57	-5.5 (19.04)		4.6 %	0.80 [-5.05, 6.65]
COMTI (T): TFSG 3	69	-2.9 (7.48)	72	-2.2 (7.64)		25.4 %	-0.70 [-3.20, 1.80]
COMTI (T): US/Canada	69	-2.4 (9.14)	66	-0.7 (9.75)		15.6 %	-1.70 [-4.89, 1.49]
Subtotal (95% CI)	**524**		**475**			**78.3 %**	**-1.46 [-2.89, -0.04]**
Heterogeneity: Chi^2 = 1.69, df = 5 (P = 0.89); I^2 =0.0%							
Test for overall effect: Z = 2.02 (P = 0.044)							
3 MAOBI versus Placebo (Total parts I-IV)							
MAOBI (R): Isra/Hun	8	-5 (12.96)	6	-2.8 (14.01)		0.8 %	-2.20 [-16.56, 12.16]
Subtotal (95% CI)	**8**		**6**			**0.8 %**	**-2.20 [-16.56, 12.16]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.30 (P = 0.76)							
Total (95% CI)	**775**		**738**			**100.0 %**	**-3.26 [-4.52, -2.00]**
Heterogeneity: Chi^2 = 32.96, df = 9 (P = 0.00014); I^2 =73%							
Test for overall effect: Z = 5.07 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 29.29, df = 2 (P = 0.00), I^2 =93%							



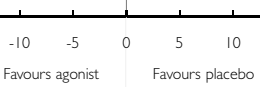
Analysis 3.4. Comparison 3 Clinician Rated Disability Scales, Outcome 4 UPDRS Activities of Daily Living (Dopamine Agonist versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 3 Clinician Rated Disability Scales

Outcome: 4 UPDRS Activities of Daily Living (Dopamine Agonist versus Placebo)

Study or subgroup	Dopamine Agonist N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Cabergoline							
DA (C): Spain	10	-1.7 (2.83)	7	-1.29 (4.39)		2.1 %	-0.41 [-4.10, 3.28]
DA (C): USA 1	106	-2.9 (7.67)	54	-0.6 (6.61)		5.5 %	-2.30 [-4.59, -0.01]
Subtotal (95% CI)	**116**		**61**			**7.6 %**	**-1.78 [-3.72, 0.17]**
Heterogeneity: Chi^2 = 0.73, df = 1 (P = 0.39); I^2 =0.0%							
Test for overall effect: Z = 1.79 (P = 0.074)							
2 Pramipexole							
DA (Pr): Aust/Germ	33	-4.4 (4.7)	44	-1.1 (3.4)		8.1 %	-3.30 [-5.19, -1.41]
DA (Pr): CLEOPATRA	201	-4.6 (4.4)	101	-2 (4.3)		26.9 %	-2.60 [-3.64, -1.56]
DA (Pr): Europe	174	-2.5 (4.1)	180	-1.2 (3.8)		42.5 %	-1.30 [-2.12, -0.48]
DA (Pr): H Kong/Taiw	50	-3.16 (3.75)	54	-0.52 (3.45)		15.0 %	-2.64 [-4.03, -1.25]
Subtotal (95% CI)	**458**		**379**			**92.4 %**	**-2.07 [-2.63, -1.51]**
Heterogeneity: Chi^2 = 6.63, df = 3 (P = 0.08); I^2 =55%							
Test for overall effect: Z = 7.26 (P < 0.00001)							
Total (95% CI)	**574**		**440**			**100.0 %**	**-2.05 [-2.58, -1.51]**
Heterogeneity: Chi^2 = 7.44, df = 5 (P = 0.19); I^2 =33%							
Test for overall effect: Z = 7.47 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 0.08, df = 1 (P = 0.78), I^2 =0.0%							



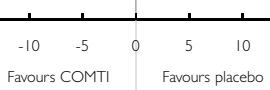
Analysis 3.5. Comparison 3 Clinician Rated Disability Scales, Outcome 5 UPDRS Activities of Daily Living (COMTI versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 3 Clinician Rated Disability Scales

Outcome: 5 UPDRS Activities of Daily Living (COMTI versus Placebo)

Study or subgroup	COMTI N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Entacapone							
COMTI (E): Celomen	172	-1.1 (5)	88	0.2 (5)		9.3 %	-1.30 [-2.58, -0.02]
COMTI (E): ComQol	174	-2.3 (3.7)	96	-0.7 (2.7)		25.8 %	-1.60 [-2.37, -0.83]
COMTI (E): INT-02	99	-1 (5.9)	63	-0.3 (3.7)		7.0 %	-0.70 [-2.18, 0.78]
COMTI (E): Nomecomt	85	-1.7 (5.21)	86	-0.4 (4.66)		7.0 %	-1.30 [-2.78, 0.18]
COMTI (E): Sth Korea	98	-0.8 (7.25)	99	-0.6 (5.6)		4.7 %	-0.20 [-2.01, 1.61]
COMTI (E): UK/Irish	115	-0.5 (5.65)	57	-1.1 (7.16)		3.4 %	0.60 [-1.53, 2.73]
Subtotal (95% CI)	**743**		**489**			**57.2 %**	**-1.16 [-1.68, -0.64]**
Heterogeneity: Chi^2 = 5.42, df = 5 (P = 0.37); I^2 =8%							
Test for overall effect: Z = 4.39 (P = 0.000011)							
2 Tolcapone							
COMTI (T): TFSG 3	69	-0.4 (3.32)	72	-0.7 (3.39)		12.5 %	0.30 [-0.81, 1.41]
COMTI (T): TIPS I	31	-1.4 (2.78)	37	-0.8 (3.04)		8.0 %	-0.60 [-1.98, 0.78]
COMTI (T): TIPS II	32	-1.1 (2.26)	33	0.4 (2.3)		12.5 %	-1.50 [-2.61, -0.39]
COMTI (T): US/Canada	69	-0.8 (3.32)	66	-0.3 (4.06)		9.8 %	-0.50 [-1.75, 0.75]
Subtotal (95% CI)	**201**		**208**			**42.8 %**	**-0.58 [-1.18, 0.02]**
Heterogeneity: Chi^2 = 5.09, df = 3 (P = 0.17); I^2 =41%							
Test for overall effect: Z = 1.89 (P = 0.059)							
Total (95% CI)	**944**		**697**			**100.0 %**	**-0.91 [-1.30, -0.52]**
Heterogeneity: Chi^2 = 12.58, df = 9 (P = 0.18); I^2 =28%							
Test for overall effect: Z = 4.55 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 2.08, df = 1 (P = 0.15), I^2 =52%							



Analysis 3.6. Comparison 3 Clinician Rated Disability Scales, Outcome 6 UPDRS Motor (Dopamine Agonist versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 3 Clinician Rated Disability Scales

Outcome: 6 UPDRS Motor (Dopamine Agonist versus Placebo)

Study or subgroup	Dopamine Agonist N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Cabergoline							
DA (C): Spain	17	-4.47 (5.14)	13	-2.54 (3.6)		11.1 %	-1.93 [-5.06, 1.20]
DA (C): USA 1	105	-2.7 (8.59)	54	-1.1 (8.01)		15.0 %	-1.60 [-4.30, 1.10]
Subtotal (95% CI)	**122**		**67**			**26.1 %**	**-1.74 [-3.78, 0.30]**
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.88); I² =0.0%							
Test for overall effect: Z = 1.67 (P = 0.095)							
2 Pramipexole							
DA (Pr): Aust/Germ	33	-13.2 (11)	44	-4.5 (9.5)		4.9 %	-8.70 [-13.39, -4.01]
DA (Pr): CLEOPATRA	201	-10.3 (8.7)	101	-4.3 (9.3)		22.9 %	-6.00 [-8.18, -3.82]
DA (Pr): Europe	174	-10.3 (12)	180	-4.43 (11.1)		18.7 %	-5.87 [-8.28, -3.46]
DA (Pr): H Kong/Taiw	50	-7.2 (8.91)	54	-0.55 (7.94)		10.3 %	-6.65 [-9.90, -3.40]
Subtotal (95% CI)	**458**		**379**			**56.9 %**	**-6.31 [-7.69, -4.93]**
Heterogeneity: Chi² = 1.25, df = 3 (P = 0.74); I² =0.0%							
Test for overall effect: Z = 8.95 (P < 0.00001)							
3 Ropinirole							
DA (R): EASE-PD	194	-6.5 (12.61)	183	-1.7 (12.38)		17.1 %	-4.80 [-7.32, -2.28]
Subtotal (95% CI)	**194**		**183**			**17.1 %**	**-4.80 [-7.32, -2.28]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.73 (P = 0.00019)							
Total (95% CI)	**774**		**629**			**100.0 %**	**-4.86 [-5.90, -3.82]**
Heterogeneity: Chi² = 14.46, df = 6 (P = 0.02); I² =59%							
Test for overall effect: Z = 9.14 (P < 0.00001)							
Test for subgroup differences: Chi² = 13.19, df = 2 (P = 0.00), I² =85%							

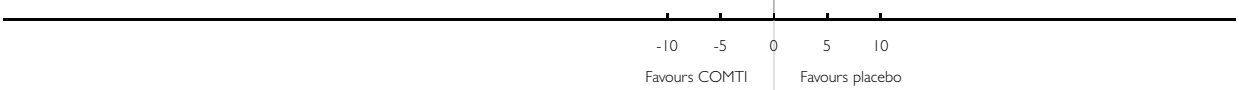
Analysis 3.7. Comparison 3 Clinician Rated Disability Scales, Outcome 7 UPDRS Motor (COMTI versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 3 Clinician Rated Disability Scales

Outcome: 7 UPDRS Motor (COMTI versus Placebo)

Study or subgroup	COMTI N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Entacapone							
COMTI (E): Celomen	172	-3.3 (10)	88	-0.1 (10)		6.6 %	-3.20 [-5.77, -0.63]
COMTI (E): ComQol	174	-5 (7.5)	96	-2.9 (7.5)		12.4 %	-2.10 [-3.97, -0.23]
COMTI (E): Interntl	12	-7.8 (2.1)	12	-7.1 (1.6)		19.4 %	-0.70 [-2.19, 0.79]
COMTI (E): LARGO	218	-3.2 (7.38)	218	-0.5 (7.38)		22.5 %	-2.70 [-4.09, -1.31]
COMTI (E): Nomecomt	85	-3 (13.46)	86	4.2 (12.5)		2.8 %	-7.20 [-11.09, -3.31]
COMTI (E): Sth Korea	98	-3.3 (11.47)	99	-1.2 (9.6)		4.9 %	-2.10 [-5.06, 0.86]
COMTI (E): UK/Irish	115	-4.5 (11.91)	57	-4.3 (12.6)		2.8 %	-0.20 [-4.13, 3.73]
Subtotal (95% CI)	**874**		**656**			**71.4 %**	**-2.14 [-2.92, -1.36]**
Heterogeneity: Chi^2 = 12.28, df = 6 (P = 0.06); I^2 =51%							
Test for overall effect: Z = 5.39 (P < 0.00001)							
2 Tolcapone							
COMTI (T): Europe	60	-4.2 (7.74)	58	-2.1 (8.38)		5.1 %	-2.10 [-5.01, 0.81]
COMTI (T): TFSG 3	69	-2.3 (5.81)	72	-1.2 (5.94)		11.5 %	-1.10 [-3.04, 0.84]
COMTI (T): TIPS I	31	-5.8 (10.58)	37	-0.3 (10.34)		1.7 %	-5.50 [-10.50, -0.50]
COMTI (T): TIPS II	32	-3.4 (7.35)	33	-1.5 (7.47)		3.3 %	-1.90 [-5.50, 1.70]
COMTI (T): US/Canada	69	-1.9 (7.48)	66	-0.4 (7.31)		6.9 %	-1.50 [-4.00, 1.00]
Subtotal (95% CI)	**261**		**266**			**28.6 %**	**-1.73 [-2.96, -0.51]**
Heterogeneity: Chi^2 = 2.69, df = 4 (P = 0.61); I^2 =0.0%							
Test for overall effect: Z = 2.77 (P = 0.0057)							
Total (95% CI)	**1135**		**922**			**100.0 %**	**-2.02 [-2.68, -1.37]**
Heterogeneity: Chi^2 = 15.27, df = 11 (P = 0.17); I^2 =28%							
Test for overall effect: Z = 6.03 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 0.30, df = 1 (P = 0.59), I^2 =0.0%							



Analysis 3.8. Comparison 3 Clinician Rated Disability Scales, Outcome 8 UPDRS Motor (MAOBI versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 3 Clinician Rated Disability Scales

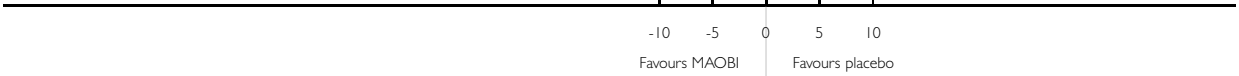
Outcome: 8 UPDRS Motor (MAOBI versus Placebo)

Study or subgroup	MAOBI N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Rasagiline							
MAOBI (R): LARGO	222	-3.4 (7.45)	218	-0.5 (7.38)		100.0 %	-2.90 [-4.29, -1.51]
Total (95% CI)	**222**		**218**			**100.0 %**	**-2.90 [-4.29, -1.51]**

Heterogeneity: not applicable

Test for overall effect: Z = 4.10 (P = 0.000041)

Test for subgroup differences: Not applicable



Analysis 3.9. Comparison 3 Clinician Rated Disability Scales, Outcome 9 UPDRS Total (parts I-IV) (Dopamine Agonist versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 3 Clinician Rated Disability Scales

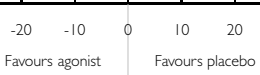
Outcome: 9 UPDRS Total (parts I-IV) (Dopamine Agonist versus Placebo)

Study or subgroup	Dopamine Agonist N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Pramipexole							
DA (Pr): Aust/Germ	33	-20.1 (16)	44	-5.9 (12.8)		17.2 %	-14.20 [-20.84, -7.56]
DA (Pr): Denmark	36	-16.9 (14.9)	33	-9 (16.1)		14.1 %	-7.90 [-15.24, -0.56]
DA (Pr): Europe	174	-16.4 (16.5)	180	-7 (15.3)		68.8 %	-9.40 [-12.72, -6.08]
Total (95% CI)	**243**		**257**			**100.0 %**	**-10.01 [-12.76, -7.26]**

Heterogeneity: Chi^2 = 1.98, df = 2 (P = 0.37); I^2 =0.0%

Test for overall effect: Z = 7.13 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 3.10. Comparison 3 Clinician Rated Disability Scales, Outcome 10 UPDRS Total (parts I-III) (COMTI versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 3 Clinician Rated Disability Scales

Outcome: 10 UPDRS Total (parts I-III) (COMTI versus Placebo)

Study or subgroup	COMTI N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Entacapone							
COMTI (E): Japan	88	-5.9 (10.32)	95	-4 (9.75)		23.8 %	-1.90 [-4.81, 1.01]
COMTI (E): Nomecomt	85	-4.4 (17.27)	86	-1.1 (16.21)		8.0 %	-3.30 [-8.32, 1.72]
COMTI (E): Sth Korea	98	-4.1 (17.72)	99	-1.8 (14.4)		9.9 %	-2.30 [-6.81, 2.21]
COMTI (E): UK/Irish	115	-4.7 (17.15)	57	-5.5 (19.04)		5.9 %	0.80 [-5.05, 6.65]
Subtotal (95% CI)	**386**		**337**			**47.7 %**	**-1.88 [-3.94, 0.18]**
Heterogeneity: Chi^2 = 1.15, df = 3 (P = 0.77); I^2 =0.0%							
Test for overall effect: Z = 1.79 (P = 0.073)							
2 Tolcapone							
COMTI (T): TFSG 3	69	-2.9 (7.48)	72	-2.2 (7.64)		32.5 %	-0.70 [-3.20, 1.80]
COMTI (T): US/Canada	69	-2.4 (9.14)	66	-0.7 (9.75)		19.9 %	-1.70 [-4.89, 1.49]
Subtotal (95% CI)	**138**		**138**			**52.3 %**	**-1.08 [-3.05, 0.89]**
Heterogeneity: Chi^2 = 0.23, df = 1 (P = 0.63); I^2 =0.0%							
Test for overall effect: Z = 1.08 (P = 0.28)							
Total (95% CI)	**524**		**475**			**100.0 %**	**-1.46 [-2.89, -0.04]**
Heterogeneity: Chi^2 = 1.69, df = 5 (P = 0.89); I^2 =0.0%							
Test for overall effect: Z = 2.02 (P = 0.044)							
Test for subgroup differences: Chi^2 = 0.31, df = 1 (P = 0.58), I^2 =0.0%							

Analysis 3.11. Comparison 3 Clinician Rated Disability Scales, Outcome 11 UPDRS Total (parts I-IV) (MAOBI versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 3 Clinician Rated Disability Scales

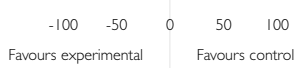
Outcome: 11 UPDRS Total (parts I-IV) (MAOBI versus Placebo)

Study or subgroup	MAOBI N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Rasagiline							
MAOBI (R): Isra/Hun	8	-5 (12.96)	6	-2.8 (14.01)		100.0 %	-2.20 [-16.56, 12.16]
Total (95% CI)	**8**		**6**			**100.0 %**	**-2.20 [-16.56, 12.16]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.30 (P = 0.76)

Test for subgroup differences: Not applicable



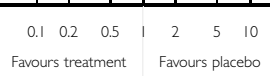
Analysis 4.1. Comparison 4 Dyskinesia & Dystonia, Outcome 1 Dyskinesia (Adjuvant Therapy versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 4 Dyskinesia % Dystonia

Outcome: 1 Dyskinesia (Adjuvant Therapy versus Placebo)

Study or subgroup	Treatment n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Dopamine Agonist versus Placebo					
DA (Pr/B): Interntl	70/164	22/83		5.4 %	1.99 [1.16, 3.44]
DA (B): Japan	7/114	1/108		0.8 %	4.46 [1.09, 18.23]
DA (C): Spain	1/23	0/20		0.1 %	6.49 [0.13, 329.99]
DA (C): USA 1	61/123	26/65		4.4 %	1.47 [0.80, 2.68]
DA (C): USA 2	73/145	31/73		5.1 %	1.37 [0.78, 2.40]
DA (Pe): N America	118/189	46/187		9.6 %	4.64 [3.09, 6.97]
DA (Pr): Aust/Germ	5/34	2/44		0.7 %	3.41 [0.72, 16.18]
DA (Pr): CLEOPATRA	31/201	3/101		2.8 %	3.46 [1.63, 7.37]
DA (Pr): Denmark	2/36	2/33		0.4 %	0.91 [0.12, 6.79]
DA (Pr): Europe	52/174	16/180		5.7 %	3.85 [2.27, 6.54]
DA (Pr): US/Canada	111/181	73/179		9.4 %	2.27 [1.50, 3.43]
DA (R): EASE-PD	27/202	5/191		3.1 %	4.19 [2.04, 8.63]
DA (R): France/Eng	8/23	5/23		1.0 %	1.88 [0.53, 6.68]
DA (R): USA	32/95	7/54		2.8 %	2.90 [1.36, 6.19]
Subtotal (95% CI)	**1704**	**1341**		**51.2 %**	**2.70 [2.26, 3.22]**
Total events: 598 (Treatment), 239 (Placebo)					
Heterogeneity: Chi^2 = 24.04, df = 13 (P = 0.03); I^2 =46%					
Test for overall effect: Z = 11.01 (P < 0.00001)					
2 COMT1 versus Placebo					
COMT1 (E): Celomen	67/197	27/104		6.1 %	1.45 [0.87, 2.42]
COMT1 (E): ComQol	16/174	5/96		1.9 %	1.74 [0.69, 4.40]
COMT1 (E): Filomen	63/218	12/108		5.3 %	2.72 [1.57, 4.70]
COMT1 (E): INT-02	31/99	8/63		2.9 %	2.75 [1.32, 5.75]
COMT1 (E): Japan	26/114	15/113		3.5 %	1.90 [0.97, 3.73]
COMT1 (E): LARGO	14/227	9/229		2.3 %	1.59 [0.69, 3.68]



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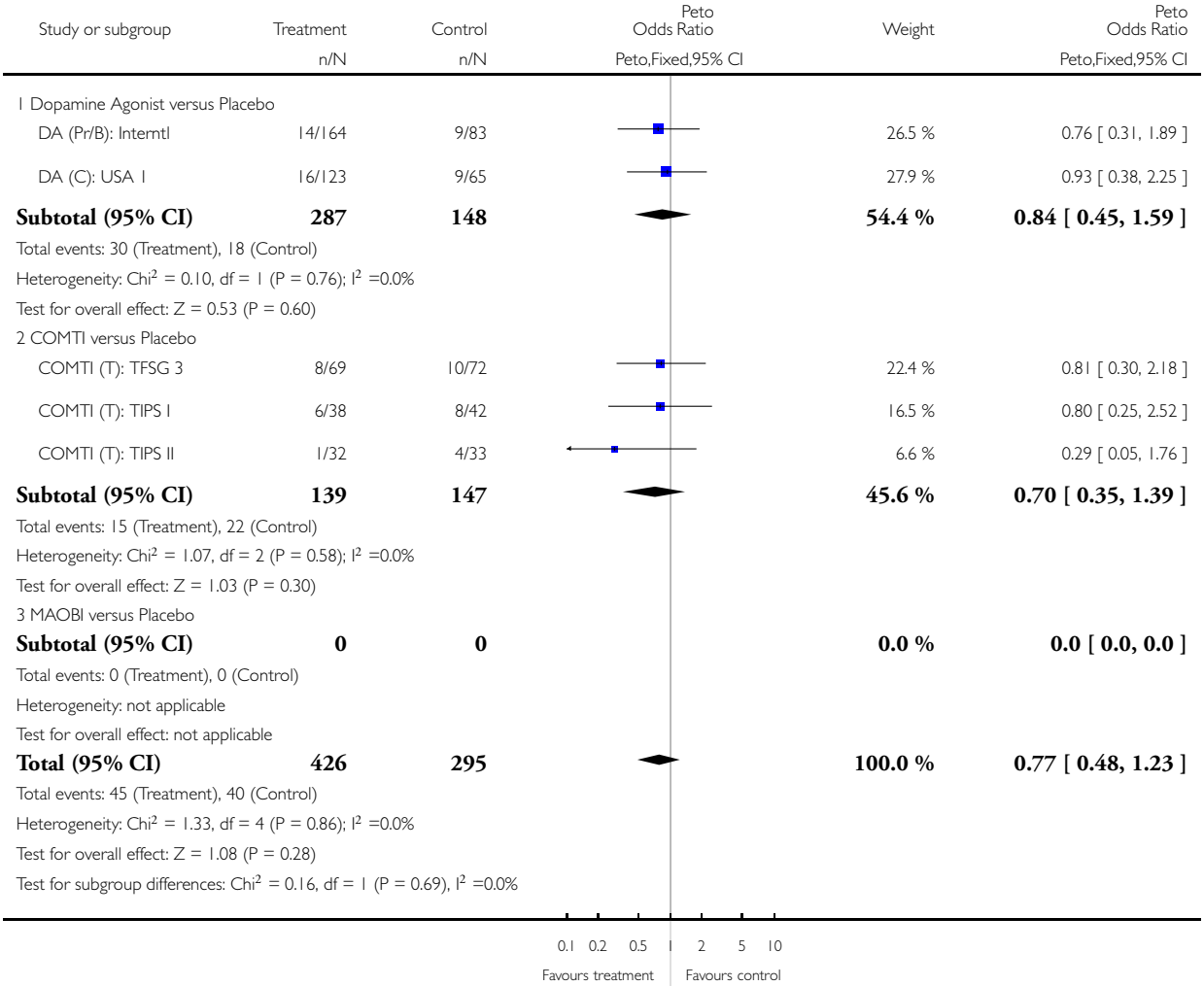
Study or subgroup	Treatment n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
COMTI (E): Nomecomt	7/85	1/86		0.8 %	4.84 [1.18, 19.93]
COMTI (E): Seesaw	55/103	33/102		5.2 %	2.35 [1.35, 4.08]
COMTI (E): Sth Korea	13/98	5/99		1.7 %	2.68 [1.02, 7.04]
COMTI (E): UK/Irish	35/115	7/57		2.9 %	2.66 [1.27, 5.56]
COMTI (T): China	7/20	1/20		0.7 %	6.22 [1.35, 28.74]
COMTI (T): Europe	22/60	12/58		2.5 %	2.16 [0.98, 4.79]
COMTI (T): TFSG 3	43/69	14/72		3.6 %	5.86 [3.00, 11.45]
COMTI (T): TIPS 1	13/38	7/42		1.6 %	2.52 [0.92, 6.90]
COMTI (T): TIPS II	5/32	3/33		0.7 %	1.82 [0.42, 7.88]
COMTI (T): US/Canada	35/69	12/66		3.2 %	4.15 [2.05, 8.41]
Subtotal (95% CI)	**1718**	**1348**		**45.0 %**	**2.50 [2.07, 3.01]**
Total events: 452 (Treatment), 171 (Placebo)					
Heterogeneity: Chi^2 = 17.59, df = 15 (P = 0.28); I^2 =15%					
Test for overall effect: Z = 9.52 (P < 0.00001)					
3 MAOBI versus Placebo					
MAOBI (R): LARGO	12/231	9/229		2.1 %	1.34 [0.56, 3.20]
MAOBI (S): Norw/Fin	7/20	5/18		0.9 %	1.38 [0.36, 5.35]
MAOBI (S): USA	2/50	7/46		0.9 %	0.27 [0.07, 1.06]
Subtotal (95% CI)	**301**	**293**		**3.8 %**	**0.94 [0.49, 1.80]**
Total events: 21 (Treatment), 21 (Placebo)					
Heterogeneity: Chi^2 = 4.12, df = 2 (P = 0.13); I^2 =51%					
Test for overall effect: Z = 0.18 (P = 0.86)					
Total (95% CI)	**3723**	**2982**		**100.0 %**	**2.50 [2.21, 2.84]**
Total events: 1071 (Treatment), 431 (Placebo)					
Heterogeneity: Chi^2 = 55.22, df = 32 (P = 0.01); I^2 =42%					
Test for overall effect: Z = 14.23 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 9.46, df = 2 (P = 0.01), I^2 =79%					

Analysis 4.2. Comparison 4 Dyskinesia & Dystonia, Outcome 2 Dystonia (Adjuvant Therapy versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 4 Dyskinesia % Dystonia

Outcome: 2 Dystonia (Adjuvant Therapy versus Placebo)



Analysis 4.3. Comparison 4 Dyskinesia & Dystonia, Outcome 3 Dyskinesia (Dopamine Agonist versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 4 Dyskinesia % Dystonia

Outcome: 3 Dyskinesia (Dopamine Agonist versus Placebo)

Study or subgroup	Dopamine Agonist n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Bromocriptine					
DA (Pr/B): Interntl	38/84	22/83		7.5 %	2.25 [1.20, 4.22]
DA (B): Japan	7/114	1/108		1.5 %	4.46 [1.09, 18.23]
Subtotal (95% CI)	**198**	**191**		**9.0 %**	**2.52 [1.42, 4.48]**
Total events: 45 (Dopamine Agonist), 23 (Placebo)					
Heterogeneity: Chi² = 0.76, df = 1 (P = 0.38); I² =0.0%					
Test for overall effect: Z = 3.14 (P = 0.0017)					
2 Cabergoline					
DA (C): Spain	1/23	0/20		0.2 %	6.49 [0.13, 329.99]
DA (C): USA 1	61/123	26/65		8.2 %	1.47 [0.80, 2.68]
DA (C): USA 2	73/145	31/73		9.4 %	1.37 [0.78, 2.40]
Subtotal (95% CI)	**291**	**158**		**17.9 %**	**1.44 [0.96, 2.16]**
Total events: 135 (Dopamine Agonist), 57 (Placebo)					
Heterogeneity: Chi² = 0.60, df = 2 (P = 0.74); I² =0.0%					
Test for overall effect: Z = 1.74 (P = 0.081)					
3 Pergolide					
DA (Pe): N America	118/189	46/187		18.0 %	4.64 [3.09, 6.97]
Subtotal (95% CI)	**189**	**187**		**18.0 %**	**4.64 [3.09, 6.97]**
Total events: 118 (Dopamine Agonist), 46 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 7.39 (P < 0.00001)					
4 Pramipexole					
DA (Pr): Aust/Germ	5/34	2/44		1.2 %	3.41 [0.72, 16.18]
DA (Pr): CLEOPATRA	31/201	3/101		5.2 %	3.46 [1.63, 7.37]
DA (Pr): Denmark	2/36	2/33		0.7 %	0.91 [0.12, 6.79]
DA (Pr): Europe	52/174	16/180		10.7 %	3.85 [2.27, 6.54]
DA (Pr/B): Interntl	32/80	22/83		7.0 %	1.83 [0.96, 3.51]
DA (Pr): US/Canada	111/181	73/179		17.5 %	2.27 [1.50, 3.43]
Subtotal (95% CI)	**706**	**620**		**42.4 %**	**2.63 [2.01, 3.42]**

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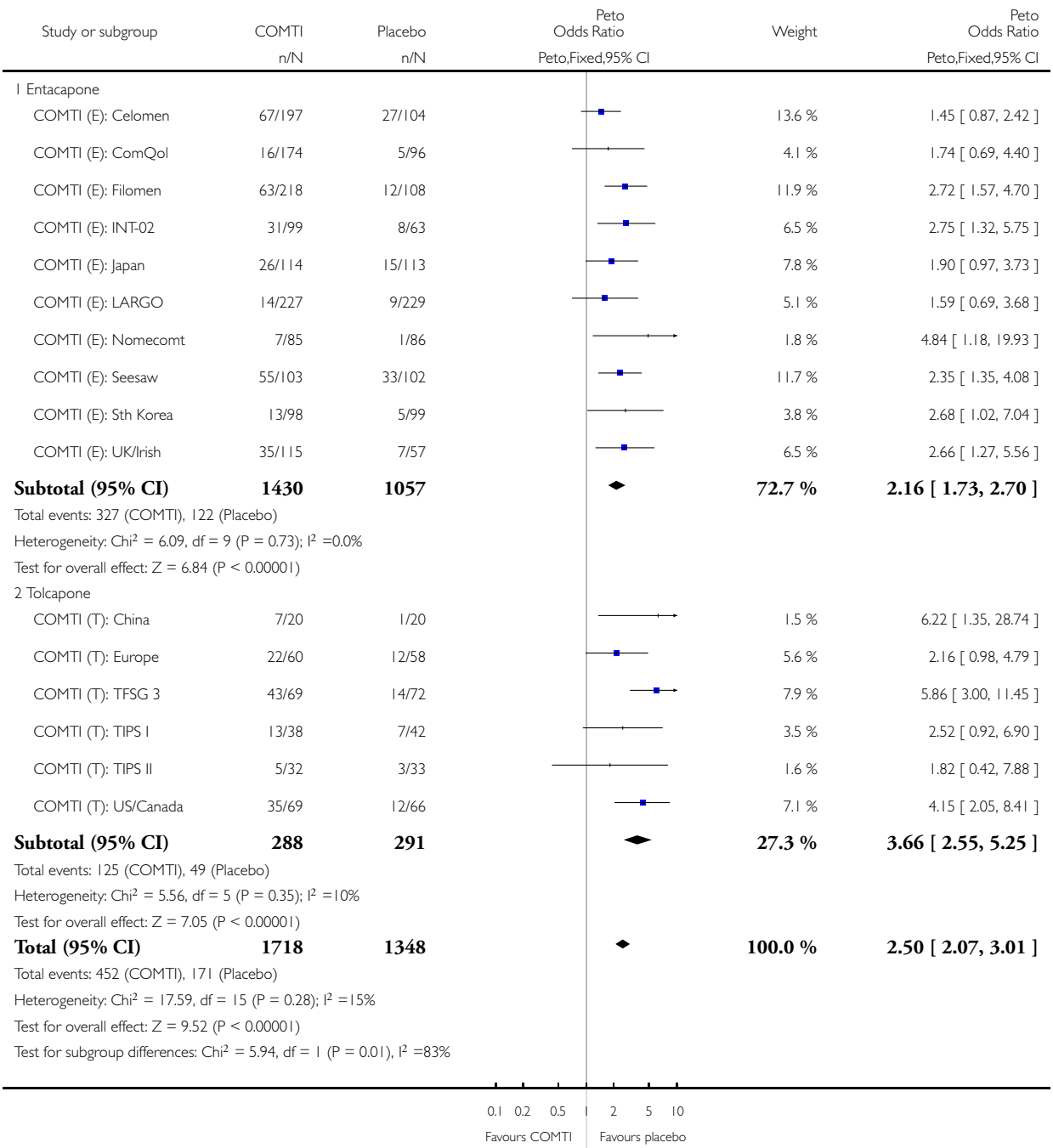
Study or subgroup	Dopamine Agonist n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Total events: 233 (Dopamine Agonist), 118 (Placebo)					
Heterogeneity: Chi^2 = 5.37, df = 5 (P = 0.37); I^2 =7%					
Test for overall effect: Z = 7.14 (P < 0.00001)					
5 Ropinirole					
DA (R): EASE-PD	27/202	5/191		5.7 %	4.19 [2.04, 8.63]
DA (R): France/Eng	8/23	5/23		1.8 %	1.88 [0.53, 6.68]
DA (R): USA	32/95	7/54		5.2 %	2.90 [1.36, 6.19]
Subtotal (95% CI)	**320**	**268**		**12.8 %**	**3.21 [1.98, 5.21]**
Total events: 67 (Dopamine Agonist), 17 (Placebo)					
Heterogeneity: Chi^2 = 1.28, df = 2 (P = 0.53); I^2 =0.0%					
Test for overall effect: Z = 4.73 (P < 0.00001)					
Total (95% CI)	**1704**	**1424**		**100.0 %**	**2.67 [2.25, 3.17]**
Total events: 598 (Dopamine Agonist), 261 (Placebo)					
Heterogeneity: Chi^2 = 24.52, df = 14 (P = 0.04); I^2 =43%					
Test for overall effect: Z = 11.15 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 16.51, df = 4 (P = 0.00), I^2 =76%					

Analysis 4.4. Comparison 4 Dyskinesia & Dystonia, Outcome 4 Dyskinesia (COMTI versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 4 Dyskinesia % Dystonia

Outcome: 4 Dyskinesia (COMTI versus Placebo)

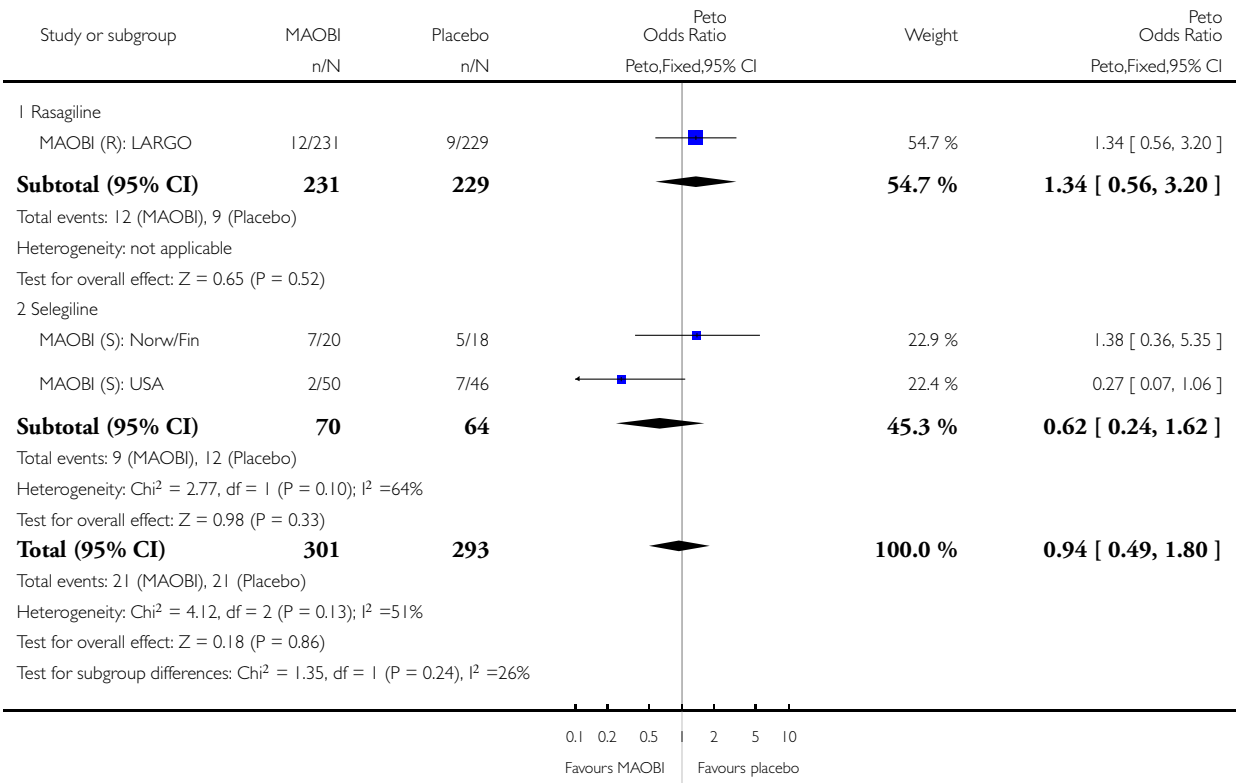


Analysis 4.5. Comparison 4 Dyskinesia & Dystonia, Outcome 5 Dyskinesia (MAOBI versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 4 Dyskinesia % Dystonia

Outcome: 5 Dyskinesia (MAOBI versus Placebo)



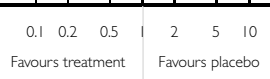
Analysis 5.1. Comparison 5 Adverse Events, Outcome 1 Overall Incidence of Side-Effects (Adjuvant Therapy versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 1 Overall Incidence of Side-Effects (Adjuvant Therapy versus Placebo)

Study or subgroup	Treatment n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Dopamine Agonist versus Placebo					
DA (Pr/B): Interntl	157/164	77/83		1.4 %	1.81 [0.56, 5.88]
DA (B): Japan	54/114	44/108		6.8 %	1.31 [0.77, 2.22]
DA (C): Spain	9/23	6/20		1.2 %	1.48 [0.43, 5.13]
DA (C): UK	17/19	11/18		0.9 %	4.48 [1.02, 19.71]
DA (C): USA 1	115/123	58/65		1.6 %	1.78 [0.59, 5.39]
DA (Pr): Aust/Germ	27/34	32/44		1.8 %	1.43 [0.51, 4.03]
DA (Pr): CLEOPATRA	140/201	65/101		7.3 %	1.27 [0.76, 2.12]
DA (Pr): Denmark	32/36	25/33		1.2 %	2.46 [0.71, 8.48]
DA (Pr): US/Canada	171/181	158/179		3.5 %	2.20 [1.05, 4.58]
DA (R): EASE-PD	129/202	106/191		11.8 %	1.41 [0.95, 2.12]
DA (R): France/Eng	21/23	18/23		0.8 %	2.69 [0.55, 13.20]
DA (R): UK/Israel	35/46	16/22		1.4 %	1.19 [0.37, 3.82]
Subtotal (95% CI)	**1166**	**887**		**39.7 %**	**1.52 [1.22, 1.90]**
Total events: 907 (Treatment), 616 (Placebo)					
Heterogeneity: Chi² = 5.32, df = 11 (P = 0.91); I² =0.0%					
Test for overall effect: Z = 3.76 (P = 0.00017)					
2 COMTI versus Placebo					
COMTI (E): Celomen	170/197	77/104		5.0 %	2.29 [1.24, 4.25]
COMTI (E): ComQol	113/174	47/96		7.5 %	1.93 [1.17, 3.21]
COMTI (E): INT-02	68/99	30/63		4.6 %	2.40 [1.26, 4.57]
COMTI (E): Japan	98/114	79/113		4.9 %	2.54 [1.36, 4.74]
COMTI (E): LARGO	62/227	53/229		10.7 %	1.25 [0.82, 1.90]
COMTI (E): Seesaw	100/103	97/102		1.0 %	1.70 [0.41, 6.95]
COMTI (E): UK/Irish	105/115	48/57		1.9 %	2.05 [0.75, 5.63]
COMTI (T): TFSG 3	59/69	53/72		2.9 %	2.06 [0.91, 4.65]



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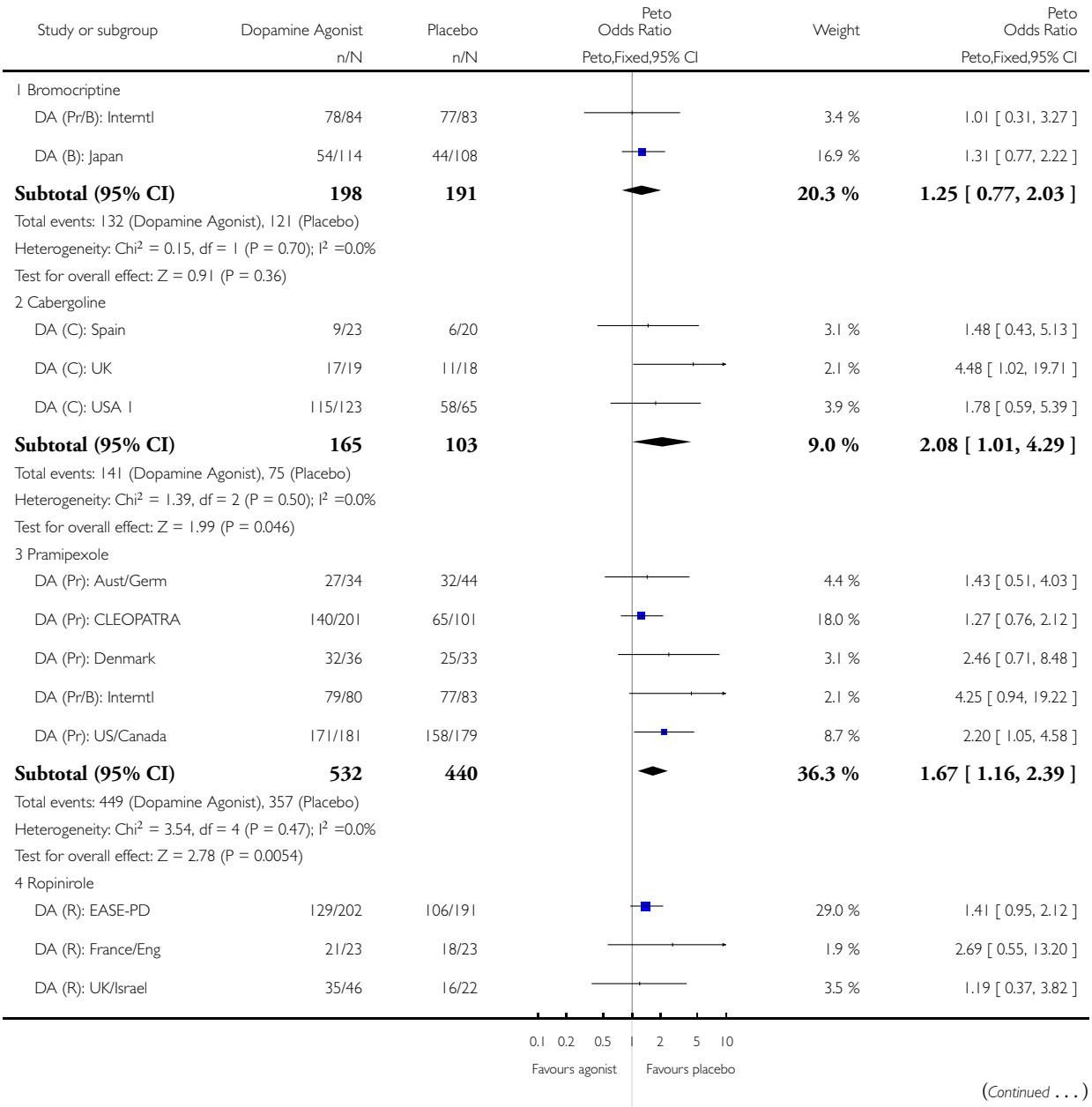
Study or subgroup	Treatment n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
COMTI (T): TIPS I	30/38	23/42		2.2 %	2.91 [1.16, 7.32]
COMTI (T): TIPS II	26/32	17/33		1.8 %	3.70 [1.33, 10.25]
COMTI (T): US/Canada	69/69	62/66		0.5 %	8.10 [1.12, 58.85]
Subtotal (95% CI)	**1237**	**977**		**42.9 %**	**2.00 [1.62, 2.47]**
Total events: 900 (Treatment), 586 (Placebo)					
Heterogeneity: Chi^2 = 9.88, df = 10 (P = 0.45); I^2 =0.0%					
Test for overall effect: Z = 6.44 (P < 0.00001)					
3 MAOBI versus Placebo					
MAOBI (R): LARGO	51/231	53/229		10.0 %	0.94 [0.61, 1.46]
MAOBI (R): PRESTO	142/149	138/159		3.2 %	2.79 [1.28, 6.06]
MAOBI (S): Norw/Fin	15/20	11/18		1.0 %	1.87 [0.48, 7.23]
MAOBI (ZS): USA	30/94	10/46		3.2 %	1.64 [0.75, 3.57]
Subtotal (95% CI)	**494**	**452**		**17.4 %**	**1.32 [0.95, 1.84]**
Total events: 238 (Treatment), 212 (Placebo)					
Heterogeneity: Chi^2 = 6.44, df = 3 (P = 0.09); I^2 =53%					
Test for overall effect: Z = 1.65 (P = 0.098)					
Total (95% CI)	**2897**	**2316**		**100.0 %**	**1.67 [1.46, 1.92]**
Total events: 2045 (Treatment), 1414 (Placebo)					
Heterogeneity: Chi^2 = 27.01, df = 26 (P = 0.41); I^2 =4%					
Test for overall effect: Z = 7.28 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 5.37, df = 2 (P = 0.07), I^2 =63%					

Analysis 5.2. Comparison 5 Adverse Events, Outcome 2 Overall Incidence of Side-Effects (Dopamine Agonist versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 2 Overall Incidence of Side-Effects (Dopamine Agonist versus Placebo)



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Study or subgroup	Dopamine Agonist n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Subtotal (95% CI)	**271**	**236**		**34.4 %**	**1.44 [0.99, 2.09]**
Total events: 185 (Dopamine Agonist), 140 (Placebo)					
Heterogeneity: Chi^2 = 0.70, df = 2 (P = 0.71); I^2 =0.0%					
Test for overall effect: Z = 1.93 (P = 0.054)					
Total (95% CI)	**1166**	**970**		**100.0 %**	**1.53 [1.23, 1.90]**
Total events: 907 (Dopamine Agonist), 693 (Placebo)					
Heterogeneity: Chi^2 = 7.47, df = 12 (P = 0.83); I^2 =0.0%					
Test for overall effect: Z = 3.82 (P = 0.00014)					
Test for subgroup differences: Chi^2 = 1.69, df = 3 (P = 0.64), I^2 =0.0%					

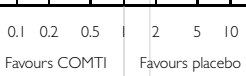
Analysis 5.3. Comparison 5 Adverse Events, Outcome 3 Overall Incidence of Side-Effects (COMTI versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 3 Overall Incidence of Side-Effects (COMTI versus Placebo)

Study or subgroup	COMTI n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Entacapone					
COMTI (E): Celomen	170/197	77/104		11.6 %	2.29 [1.24, 4.25]
COMTI (E): ComQol	113/174	47/96		17.4 %	1.93 [1.17, 3.21]
COMTI (E): INT-02	68/99	30/63		10.7 %	2.40 [1.26, 4.57]
COMTI (E): Japan	98/114	79/113		11.3 %	2.54 [1.36, 4.74]
COMTI (E): LARGO	62/227	53/229		25.0 %	1.25 [0.82, 1.90]
COMTI (E): Seesaw	100/103	97/102		2.2 %	1.70 [0.41, 6.95]
COMTI (E): UK/Irish	105/115	48/57		4.4 %	2.05 [0.75, 5.63]



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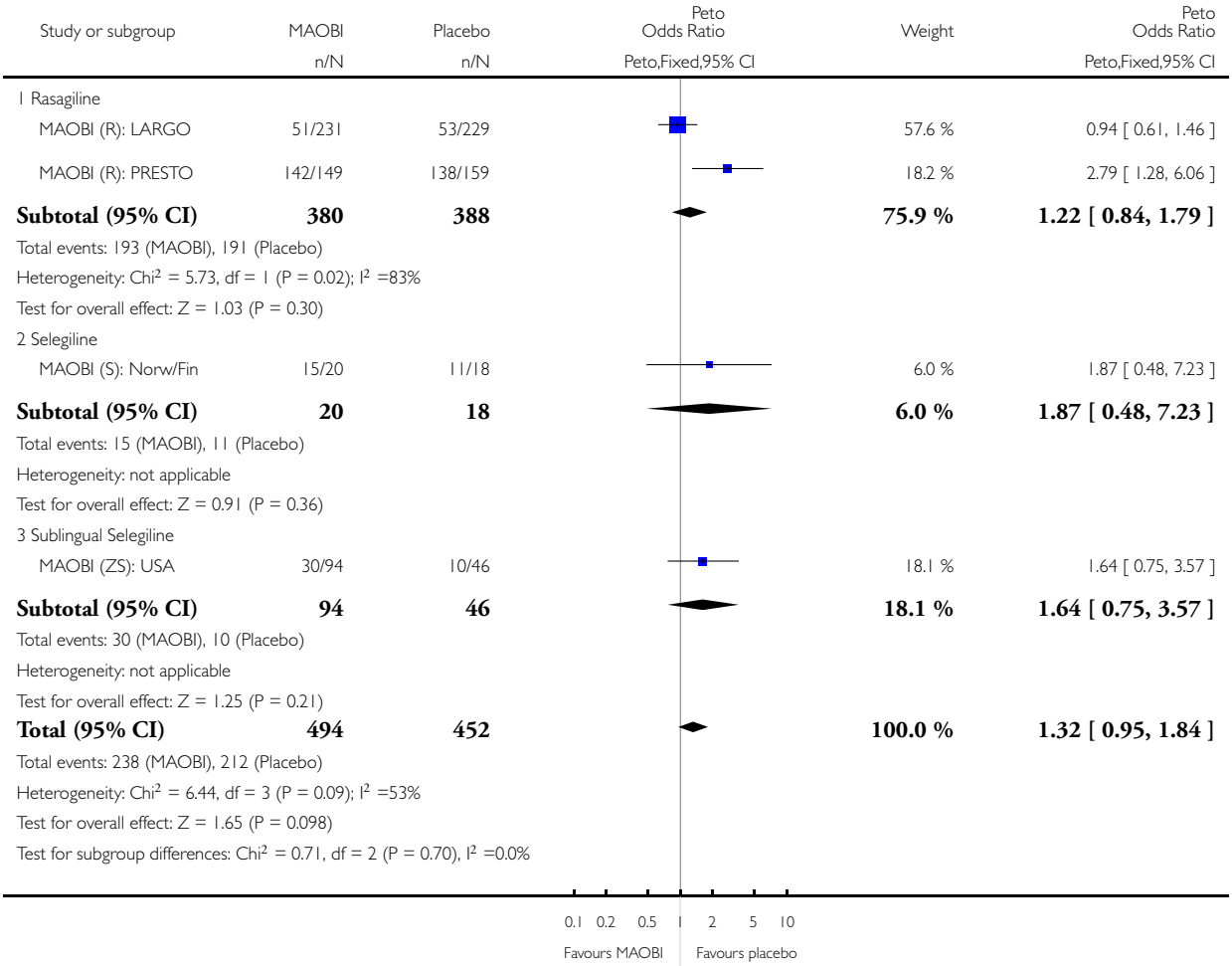
Study or subgroup	COMTI n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Subtotal (95% CI)	**1029**	**764**		**82.6 %**	**1.85 [1.47, 2.33]**
Total events: 716 (COMTI), 431 (Placebo)					
Heterogeneity: Chi^2 = 5.51, df = 6 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 5.20 (P < 0.00001)					
2 Tolcapone					
COMTI (T): TFSG 3	59/69	53/72		6.7 %	2.06 [0.91, 4.65]
COMTI (T): TIPS I	30/38	23/42		5.2 %	2.91 [1.16, 7.32]
COMTI (T): TIPS II	26/32	17/33		4.3 %	3.70 [1.33, 10.25]
COMTI (T): US/Canada	69/69	62/66		1.1 %	8.10 [1.12, 58.85]
Subtotal (95% CI)	**208**	**213**		**17.4 %**	**2.89 [1.74, 4.79]**
Total events: 184 (COMTI), 155 (Placebo)					
Heterogeneity: Chi^2 = 1.93, df = 3 (P = 0.59); I^2 =0.0%					
Test for overall effect: Z = 4.11 (P = 0.000040)					
Total (95% CI)	**1237**	**977**		**100.0 %**	**2.00 [1.62, 2.47]**
Total events: 900 (COMTI), 586 (Placebo)					
Heterogeneity: Chi^2 = 9.88, df = 10 (P = 0.45); I^2 =0.0%					
Test for overall effect: Z = 6.44 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 2.45, df = 1 (P = 0.12), I^2 =59%					

Analysis 5.4. Comparison 5 Adverse Events, Outcome 4 Overall Incidence of Side-Effects (MAOBI versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 4 Overall Incidence of Side-Effects (MAOBI versus Placebo)

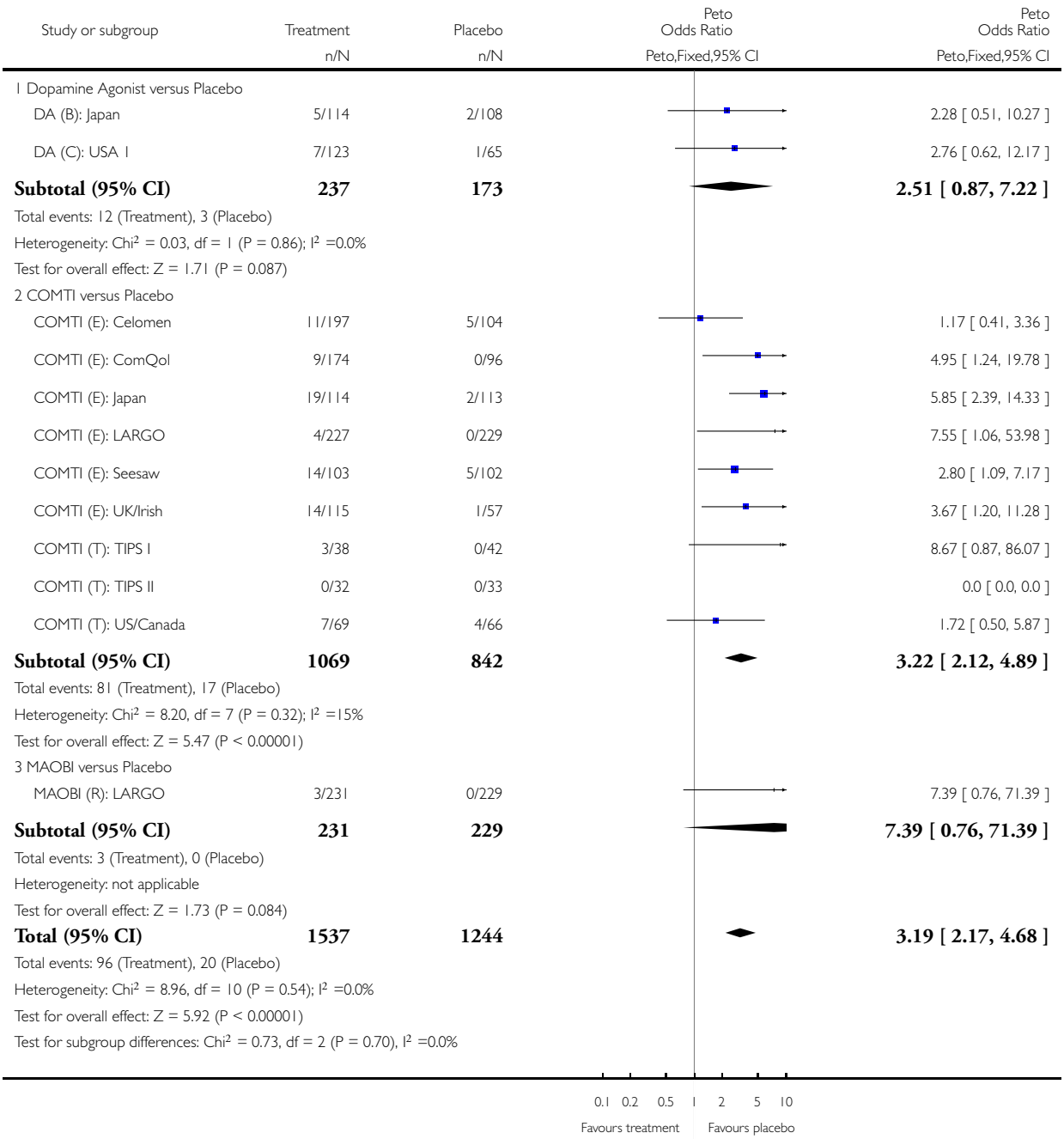


Analysis 5.5. Comparison 5 Adverse Events, Outcome 5 Constipation.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 5 Constipation

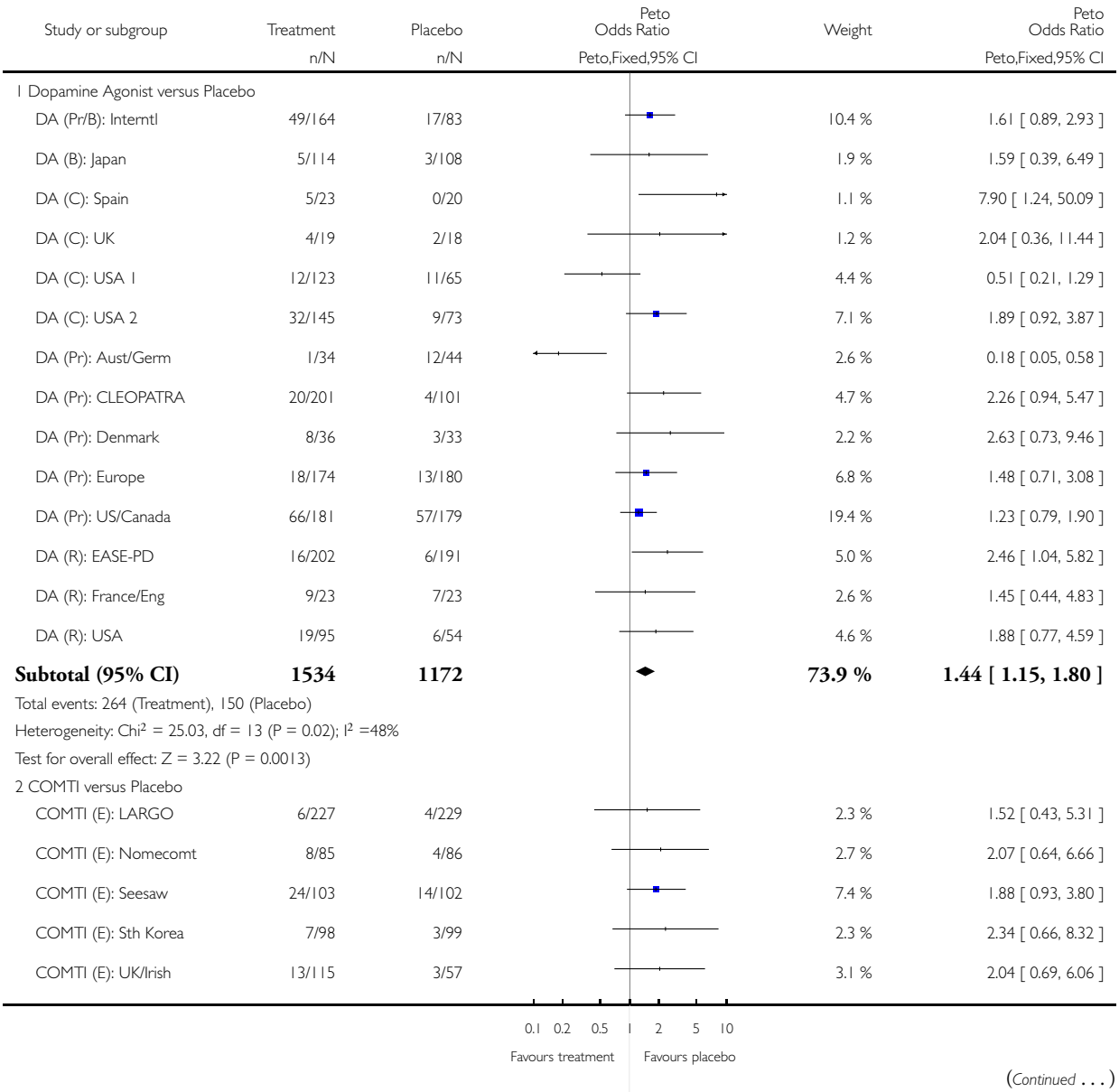


Analysis 5.6. Comparison 5 Adverse Events, Outcome 6 Dizziness.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 6 Dizziness



Study or subgroup	Treatment n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Dopamine Agonist versus Placebo					
DA (Pr/B): Interntl	49/164	17/83		10.4 %	1.61 [0.89, 2.93]
DA (B): Japan	5/114	3/108		1.9 %	1.59 [0.39, 6.49]
DA (C): Spain	5/23	0/20		1.1 %	7.90 [1.24, 50.09]
DA (C): UK	4/19	2/18		1.2 %	2.04 [0.36, 11.44]
DA (C): USA 1	12/123	11/65		4.4 %	0.51 [0.21, 1.29]
DA (C): USA 2	32/145	9/73		7.1 %	1.89 [0.92, 3.87]
DA (Pr): Aust/Germ	1/34	12/44		2.6 %	0.18 [0.05, 0.58]
DA (Pr): CLEOPATRA	20/201	4/101		4.7 %	2.26 [0.94, 5.47]
DA (Pr): Denmark	8/36	3/33		2.2 %	2.63 [0.73, 9.46]
DA (Pr): Europe	18/174	13/180		6.8 %	1.48 [0.71, 3.08]
DA (Pr): US/Canada	66/181	57/179		19.4 %	1.23 [0.79, 1.90]
DA (R): EASE-PD	16/202	6/191		5.0 %	2.46 [1.04, 5.82]
DA (R): France/Eng	9/23	7/23		2.6 %	1.45 [0.44, 4.83]
DA (R): USA	19/95	6/54		4.6 %	1.88 [0.77, 4.59]
Subtotal (95% CI)	**1534**	**1172**		**73.9 %**	**1.44 [1.15, 1.80]**
Total events: 264 (Treatment), 150 (Placebo)					
Heterogeneity: Chi² = 25.03, df = 13 (P = 0.02); I² =48%					
Test for overall effect: Z = 3.22 (P = 0.0013)					
2 COMTI versus Placebo					
COMTI (E): LARGO	6/227	4/229		2.3 %	1.52 [0.43, 5.31]
COMTI (E): Nomecomt	8/85	4/86		2.7 %	2.07 [0.64, 6.66]
COMTI (E): Seesaw	24/103	14/102		7.4 %	1.88 [0.93, 3.80]
COMTI (E): Sth Korea	7/98	3/99		2.3 %	2.34 [0.66, 8.32]
COMTI (E): UK/Irish	13/115	3/57		3.1 %	2.04 [0.69, 6.06]

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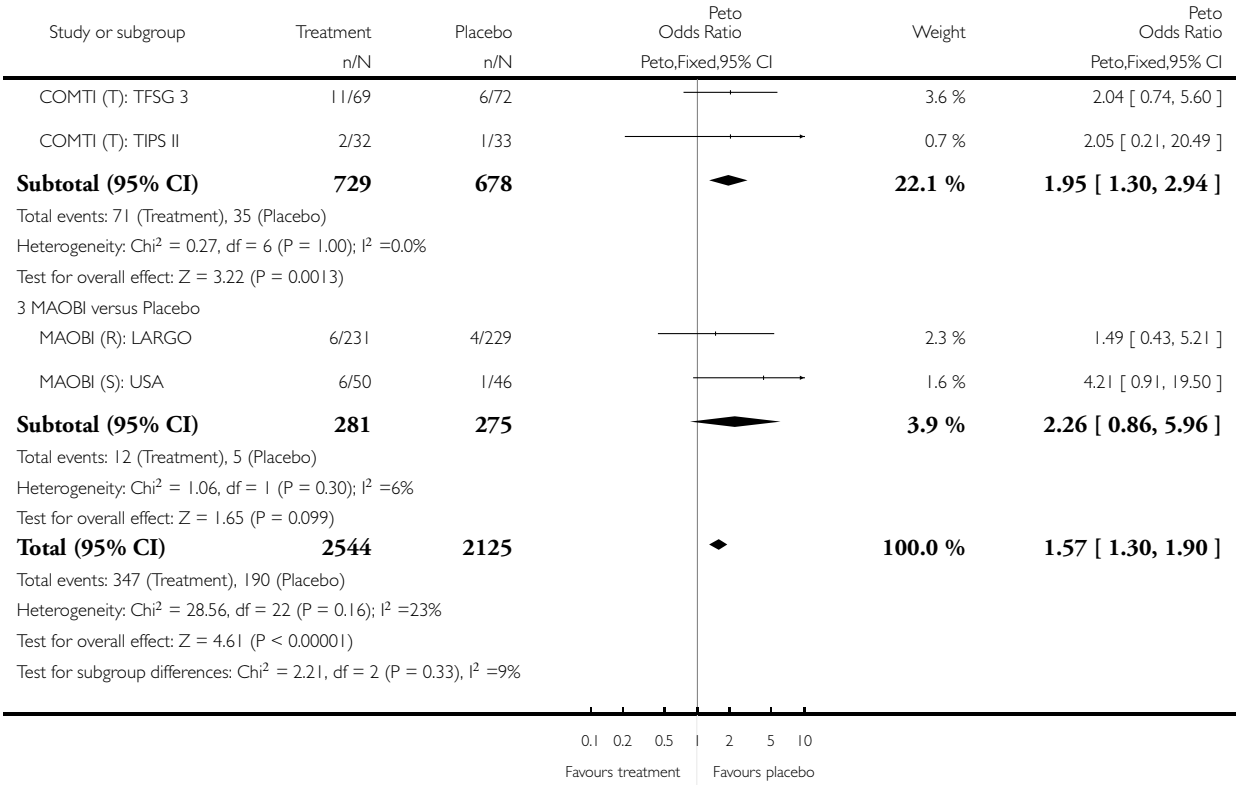
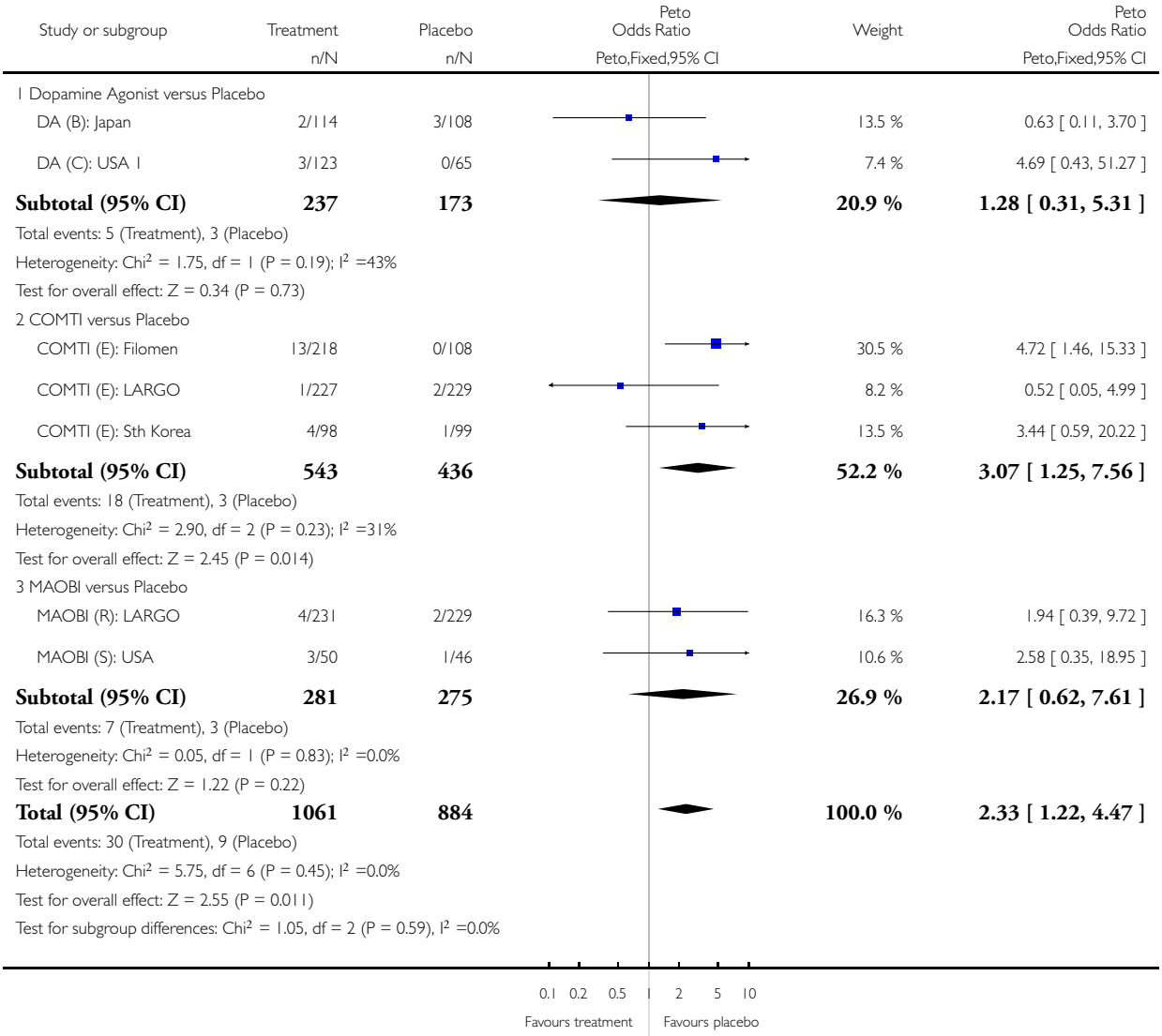


Analysis 5.7. Comparison 5 Adverse Events, Outcome 7 Dry Mouth.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 7 Dry Mouth

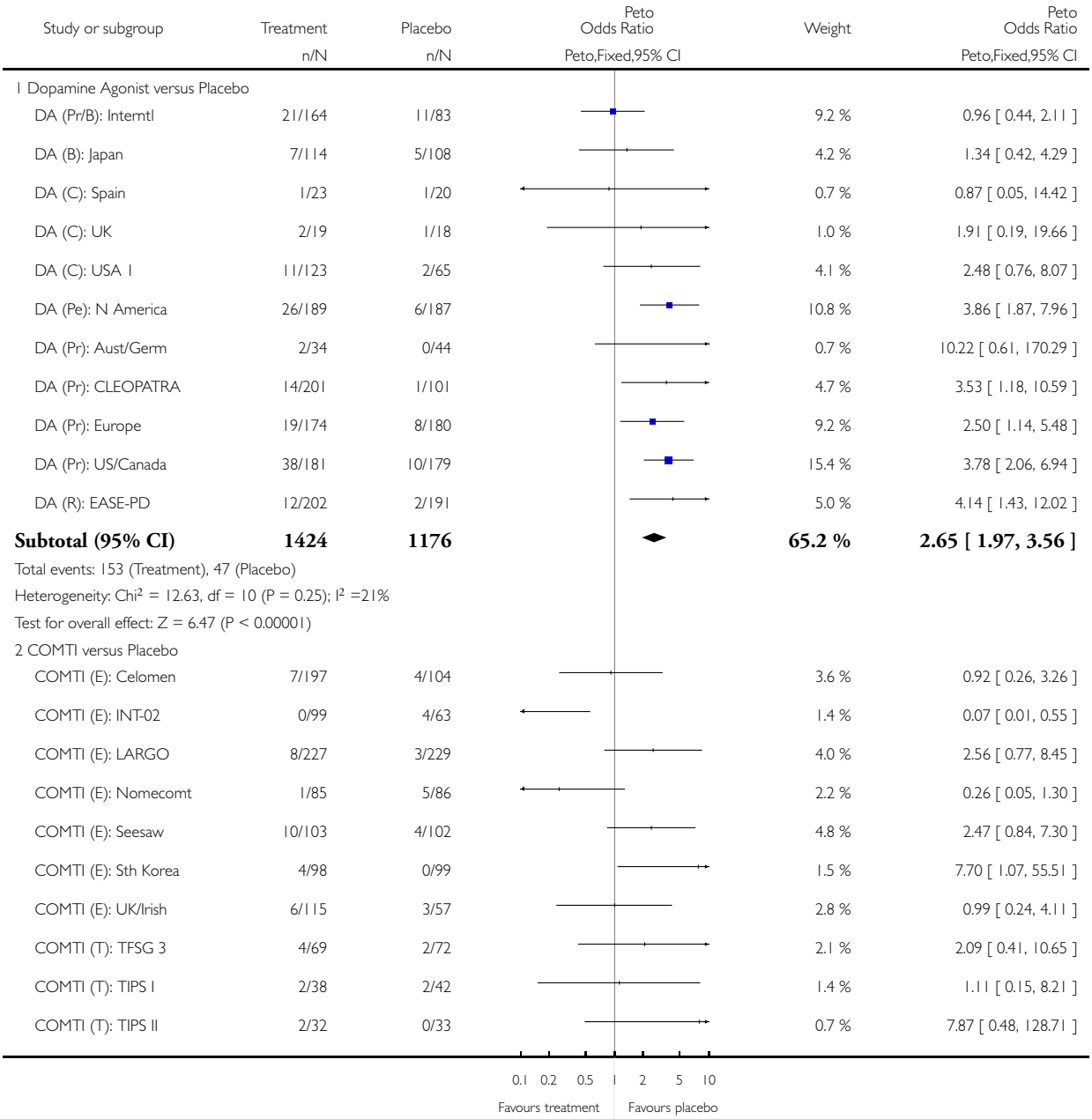


Analysis 5.8. Comparison 5 Adverse Events, Outcome 8 Hallucinations.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 8 Hallucinations



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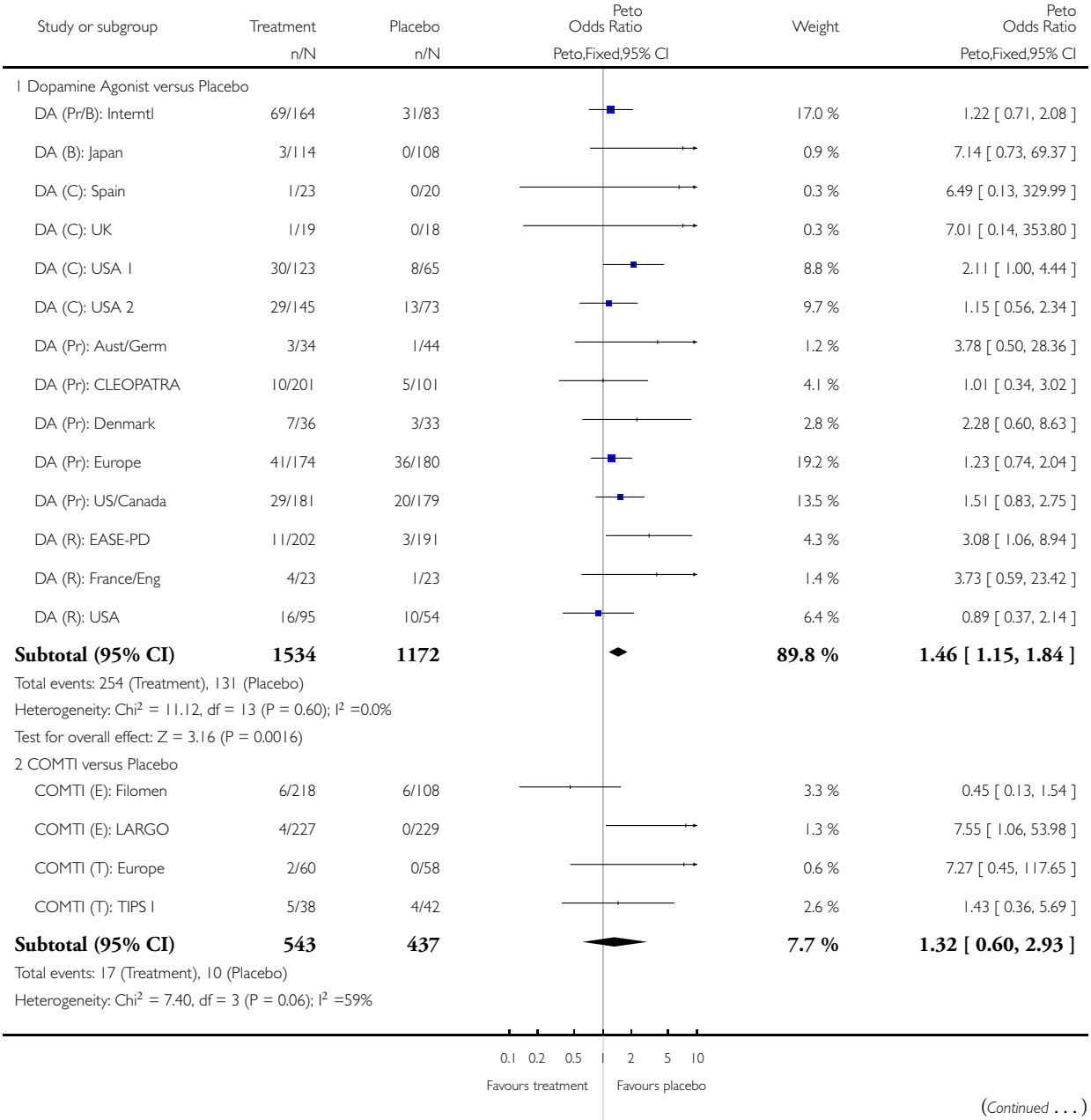
Study or subgroup	Treatment n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
COMTI (T): US/Canada	12/69	7/66		6.1 %	1.75 [0.66, 4.59]
Subtotal (95% CI)	**1132**	**953**		**30.5 %**	**1.43 [0.93, 2.19]**
Total events: 56 (Treatment), 34 (Placebo)					
Heterogeneity: Chi^2 = 19.84, df = 10 (P = 0.03); I^2 =50%					
Test for overall effect: Z = 1.61 (P = 0.11)					
3 MAOBI versus Placebo					
MAOBI (R): LARGO	5/231	3/229		2.9 %	1.65 [0.41, 6.66]
MAOBI (S): USA	3/50	1/46		1.4 %	2.58 [0.35, 18.95]
Subtotal (95% CI)	**281**	**275**		**4.3 %**	**1.91 [0.61, 5.99]**
Total events: 8 (Treatment), 4 (Placebo)					
Heterogeneity: Chi^2 = 0.13, df = 1 (P = 0.72); I^2 =0.0%					
Test for overall effect: Z = 1.11 (P = 0.27)					
Total (95% CI)	**2837**	**2404**		**100.0 %**	**2.16 [1.70, 2.74]**
Total events: 217 (Treatment), 85 (Placebo)					
Heterogeneity: Chi^2 = 38.04, df = 23 (P = 0.03); I^2 =40%					
Test for overall effect: Z = 6.34 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 5.43, df = 2 (P = 0.07), I^2 =63%					

Analysis 5.9. Comparison 5 Adverse Events, Outcome 9 Hypotension (including postural hypotension).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 9 Hypotension (including postural hypotension)



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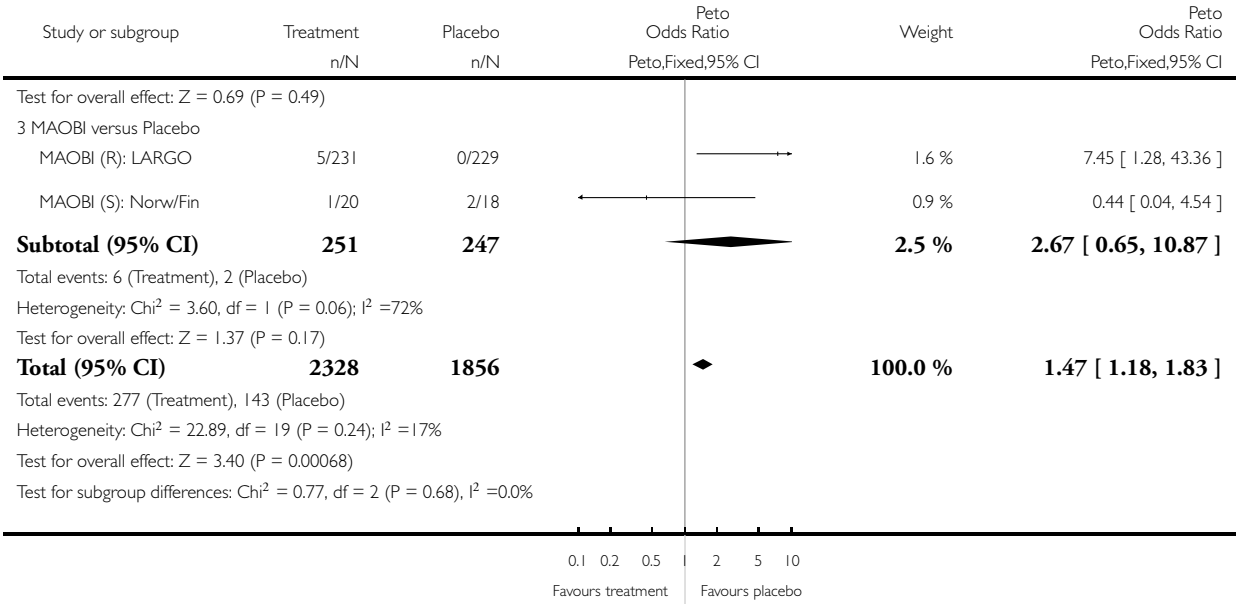
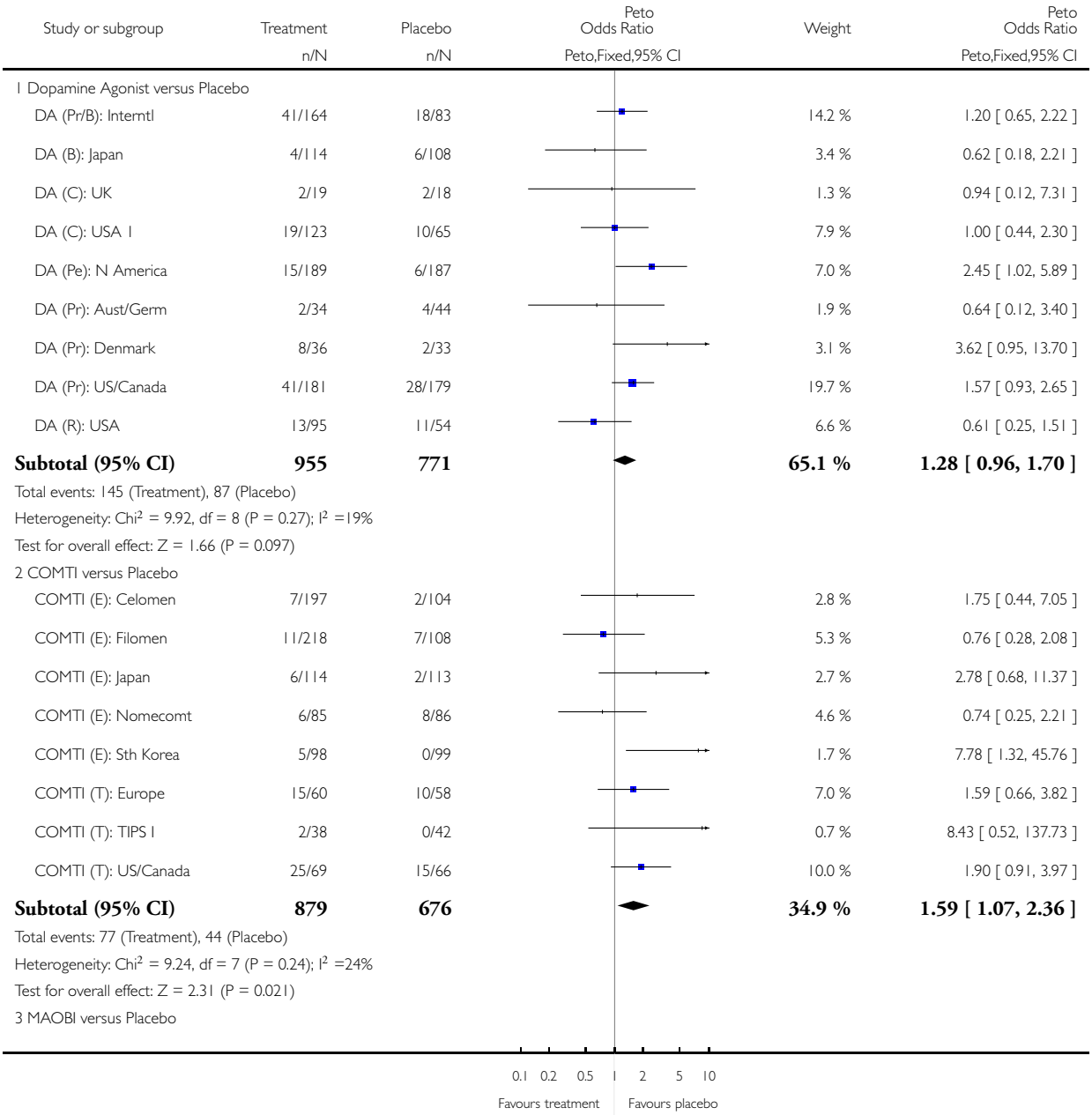


Analysis 5.10. Comparison 5 Adverse Events, Outcome 10 Insomnia.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 10 Insomnia



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Study or subgroup	Treatment n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**1834**	**1447**		**100.0 %**	**1.38 [1.09, 1.74]**
Total events: 222 (Treatment), 131 (Placebo)					
Heterogeneity: Chi^2 = 19.94, df = 16 (P = 0.22); I^2 =20%					
Test for overall effect: Z = 2.71 (P = 0.0068)					
Test for subgroup differences: Chi^2 = 0.79, df = 1 (P = 0.38), I^2 =0.0%					

Analysis 5.11. Comparison 5 Adverse Events, Outcome 11 Nausea.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 11 Nausea

Study or subgroup	Treatment n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Dopamine Agonist versus Placebo					
DA (Pr/B): Interntl	60/164	21/83		7.1 %	1.67 [0.95, 2.92]
DA (B): Japan	20/114	12/108		4.0 %	1.68 [0.80, 3.55]
DA (C): Spain	4/23	0/20		0.5 %	7.49 [0.97, 57.53]
DA (C): UK	4/19	3/18		0.9 %	1.32 [0.26, 6.70]
DA (C): USA 1	29/123	10/65		4.1 %	1.64 [0.78, 3.44]
DA (C): USA 2	30/145	11/73		4.4 %	1.44 [0.70, 2.96]
DA (Pe): N America	46/189	24/187		8.4 %	2.13 [1.27, 3.58]
DA (Pr): Aust/Germ	3/34	3/44		0.8 %	1.32 [0.25, 7.01]

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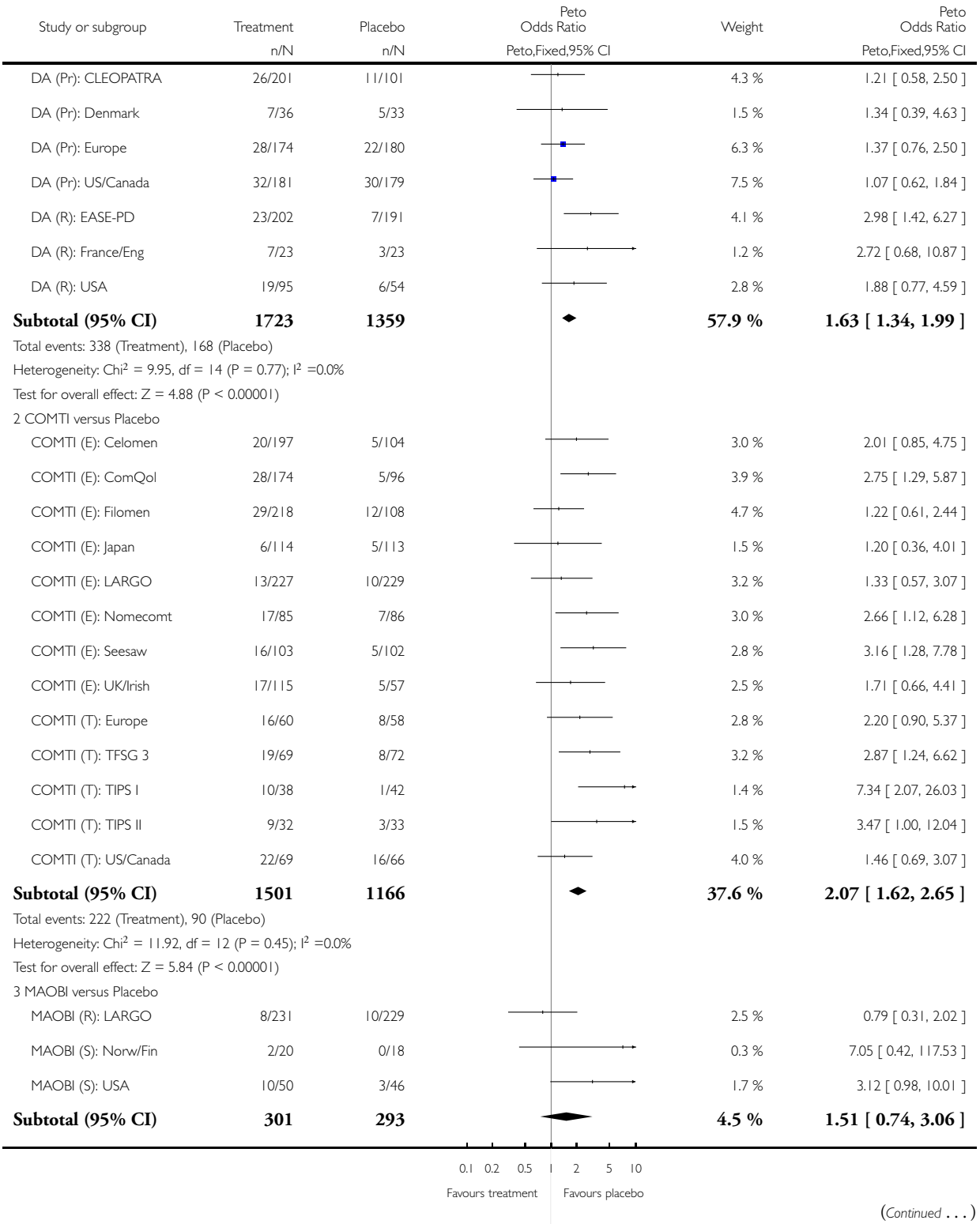

Study or subgroup	Treatment n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
DA (Pr): CLEOPATRA	26/201	11/101		4.3 %	1.21 [0.58, 2.50]
DA (Pr): Denmark	7/36	5/33		1.5 %	1.34 [0.39, 4.63]
DA (Pr): Europe	28/174	22/180		6.3 %	1.37 [0.76, 2.50]
DA (Pr): US/Canada	32/181	30/179		7.5 %	1.07 [0.62, 1.84]
DA (R): EASE-PD	23/202	7/191		4.1 %	2.98 [1.42, 6.27]
DA (R): France/Eng	7/23	3/23		1.2 %	2.72 [0.68, 10.87]
DA (R): USA	19/95	6/54		2.8 %	1.88 [0.77, 4.59]
Subtotal (95% CI)	**1723**	**1359**		**57.9 %**	**1.63 [1.34, 1.99]**
Total events: 338 (Treatment), 168 (Placebo)					
Heterogeneity: Chi² = 9.95, df = 14 (P = 0.77); I² =0.0%					
Test for overall effect: Z = 4.88 (P < 0.00001)					
2 COMTI versus Placebo					
COMTI (E): Celomen	20/197	5/104		3.0 %	2.01 [0.85, 4.75]
COMTI (E): ComQol	28/174	5/96		3.9 %	2.75 [1.29, 5.87]
COMTI (E): Filomen	29/218	12/108		4.7 %	1.22 [0.61, 2.44]
COMTI (E): Japan	6/114	5/113		1.5 %	1.20 [0.36, 4.01]
COMTI (E): LARGO	13/227	10/229		3.2 %	1.33 [0.57, 3.07]
COMTI (E): Nomecomt	17/85	7/86		3.0 %	2.66 [1.12, 6.28]
COMTI (E): Seesaw	16/103	5/102		2.8 %	3.16 [1.28, 7.78]
COMTI (E): UK/Irish	17/115	5/57		2.5 %	1.71 [0.66, 4.41]
COMTI (T): Europe	16/60	8/58		2.8 %	2.20 [0.90, 5.37]
COMTI (T): TFSG 3	19/69	8/72		3.2 %	2.87 [1.24, 6.62]
COMTI (T): TIPS I	10/38	1/42		1.4 %	7.34 [2.07, 26.03]
COMTI (T): TIPS II	9/32	3/33		1.5 %	3.47 [1.00, 12.04]
COMTI (T): US/Canada	22/69	16/66		4.0 %	1.46 [0.69, 3.07]
Subtotal (95% CI)	**1501**	**1166**		**37.6 %**	**2.07 [1.62, 2.65]**
Total events: 222 (Treatment), 90 (Placebo)					
Heterogeneity: Chi² = 11.92, df = 12 (P = 0.45); I² =0.0%					
Test for overall effect: Z = 5.84 (P < 0.00001)					
3 MAOBI versus Placebo					
MAOBI (R): LARGO	8/231	10/229		2.5 %	0.79 [0.31, 2.02]
MAOBI (S): Norw/Fin	2/20	0/18		0.3 %	7.05 [0.42, 117.53]
MAOBI (S): USA	10/50	3/46		1.7 %	3.12 [0.98, 10.01]
Subtotal (95% CI)	**301**	**293**		**4.5 %**	**1.51 [0.74, 3.06]**

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Study or subgroup	Treatment n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Total events: 20 (Treatment), 13 (Placebo)					
Heterogeneity: Chi^2 = 4.49, df = 2 (P = 0.11); I^2 =55%					
Test for overall effect: Z = 1.13 (P = 0.26)					
Total (95% CI)	**3525**	**2818**	◆	**100.0 %**	**1.78 [1.53, 2.07]**
Total events: 580 (Treatment), 271 (Placebo)					
Heterogeneity: Chi^2 = 28.80, df = 30 (P = 0.53); I^2 =0.0%					
Test for overall effect: Z = 7.54 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 2.44, df = 2 (P = 0.30), I^2 =18%					

0.1 0.2 0.5 1 2 5 10

Favours treatment Favours placebo

Analysis 5.12. Comparison 5 Adverse Events, Outcome 12 Somnolence.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 12 Somnolence

Study or subgroup	Treatment n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Dopamine Agonist versus Placebo					
DA (C): Spain	1/23	0/20		0.6 %	6.49 [0.13, 329.99]
DA (C): USA 1	8/123	3/65		5.2 %	1.41 [0.39, 5.04]
DA (Pe): N America	18/189	6/187		12.5 %	2.87 [1.26, 6.55]
DA (Pr): Aust/Germ	2/34	4/44		3.1 %	0.64 [0.12, 3.40]
DA (Pr): CLEOPATRA	24/201	8/101		14.2 %	1.53 [0.70, 3.31]
DA (Pr): Denmark	2/36	0/33		1.1 %	7.00 [0.43, 114.47]
DA (Pr): Europe	3/174	4/180		3.8 %	0.77 [0.17, 3.45]
DA (R): EASE-PD	14/202	7/191		11.1 %	1.90 [0.79, 4.58]
DA (R): France/Eng	6/23	2/23		3.8 %	3.27 [0.72, 14.77]

0.1 0.2 0.5 1 2 5 10

Favours treatment Favours placebo

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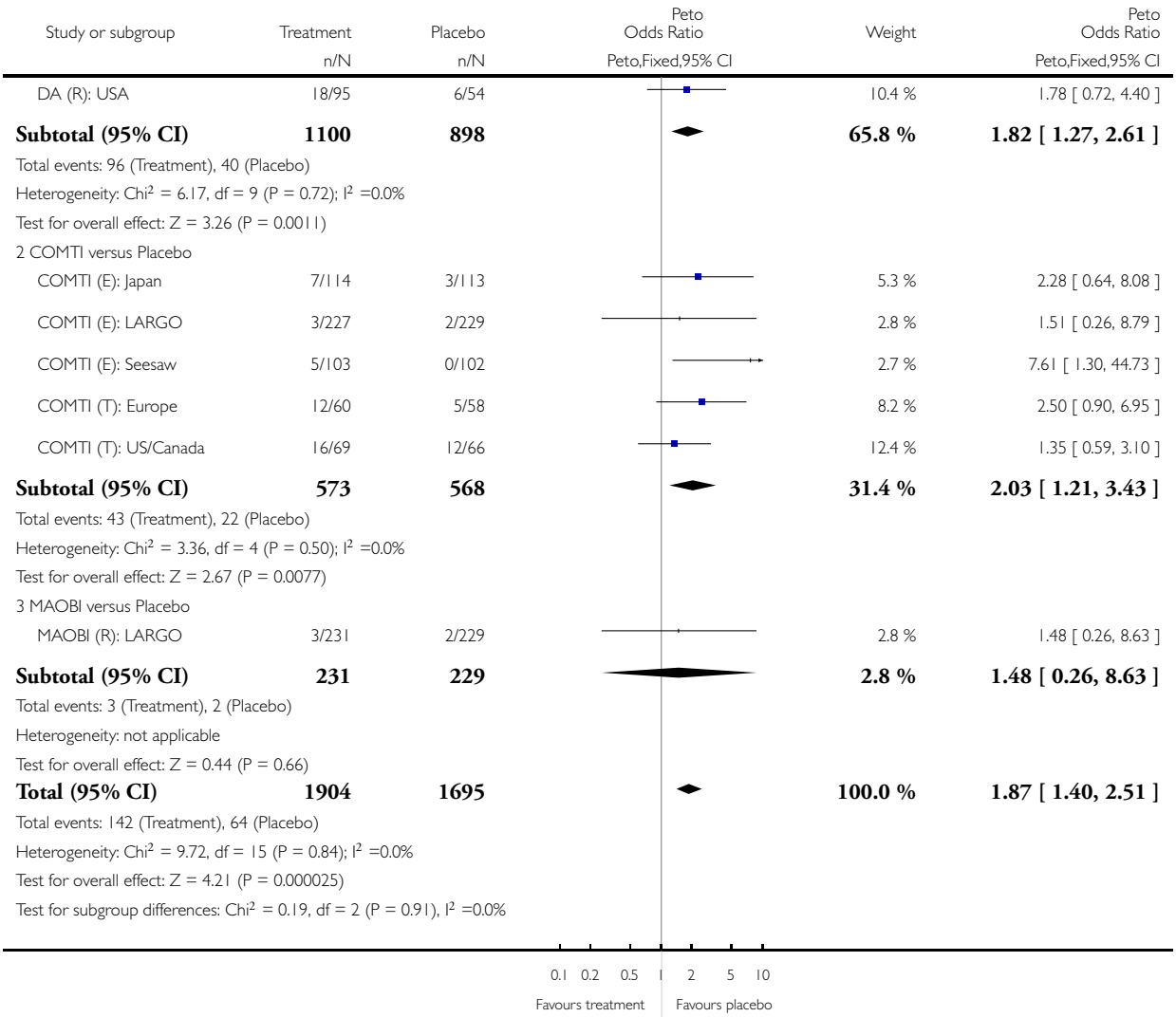
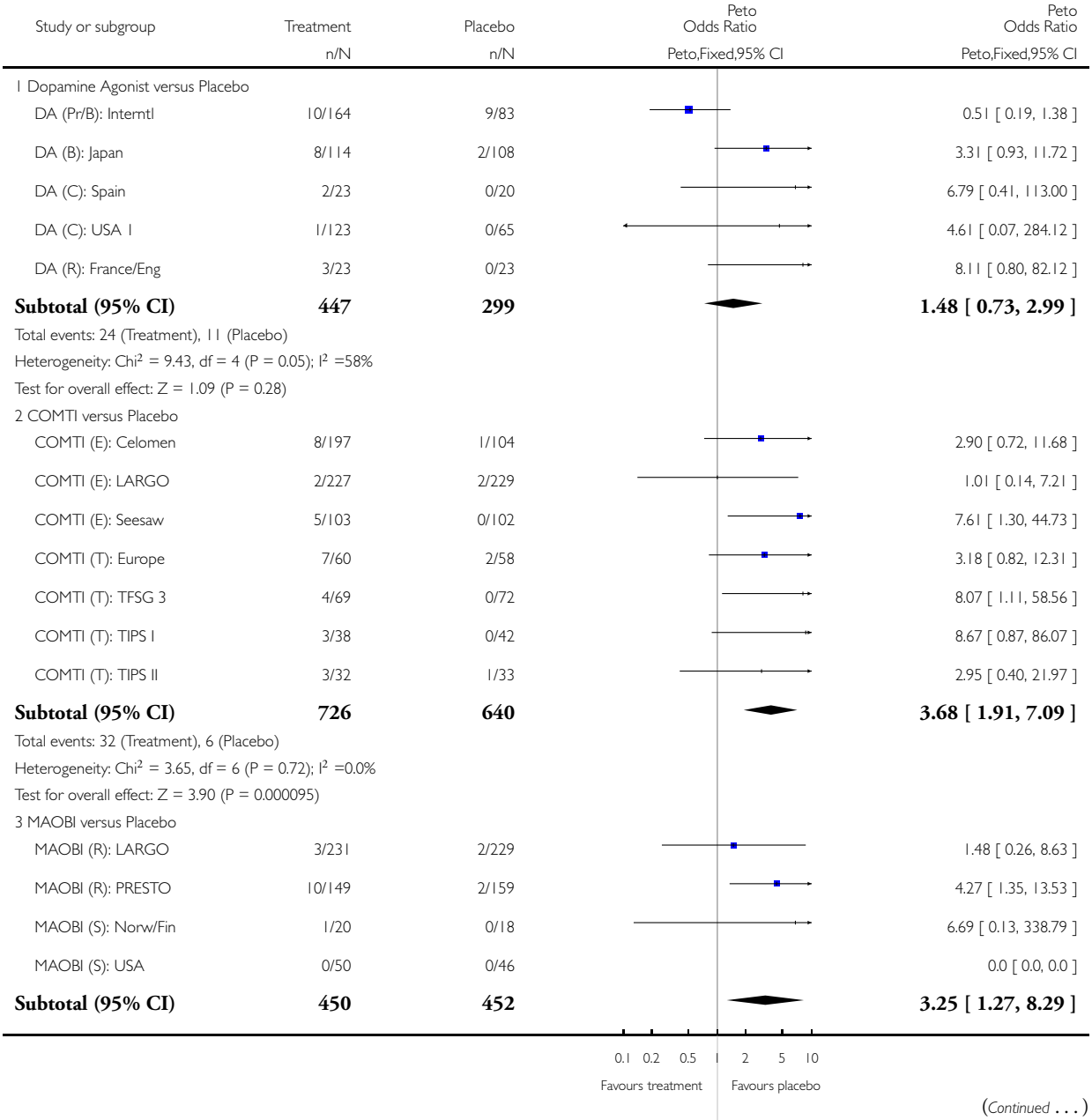


Analysis 5.13. Comparison 5 Adverse Events, Outcome 13 Vomiting.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 13 Vomiting



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Study or subgroup	Treatment n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Total events: 14 (Treatment), 4 (Placebo)				
Heterogeneity: Chi^2 = 1.11, df = 2 (P = 0.58); I^2 =0.0%				
Test for overall effect: Z = 2.47 (P = 0.014)				
Total (95% CI)	**1623**	**1391**		**2.56 [1.67, 3.93]**
Total events: 70 (Treatment), 21 (Placebo)				
Heterogeneity: Chi^2 = 17.97, df = 14 (P = 0.21); I^2 =22%				
Test for overall effect: Z = 4.33 (P = 0.000015)				
Test for subgroup differences: Chi^2 = 3.78, df = 2 (P = 0.15), I^2 =47%				

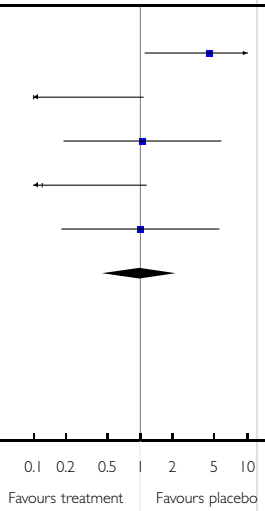
Analysis 5.14. Comparison 5 Adverse Events, Outcome 14 Abdominal Pain.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 14 Abdominal Pain

Study or subgroup	Treatment n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Dopamine Agonist versus Placebo					
DA (B): Japan	7/114	1/108		8.3 %	4.46 [1.09, 18.23]
DA (C): Spain	0/23	3/20		3.1 %	0.10 [0.01, 1.07]
DA (C): USA 1	4/123	2/65		5.7 %	1.06 [0.19, 5.82]
DA (Pr): Denmark	0/36	3/33		3.1 %	0.12 [0.01, 1.16]
DA (R): France/Eng	3/23	3/23		5.7 %	1.00 [0.18, 5.46]
Subtotal (95% CI)	**319**	**249**		**25.9 %**	**0.97 [0.44, 2.15]**
Total events: 14 (Treatment), 12 (Placebo)					
Heterogeneity: Chi^2 = 11.31, df = 4 (P = 0.02); I^2 =65%					
Test for overall effect: Z = 0.08 (P = 0.93)					
2 COMTI versus Placebo					



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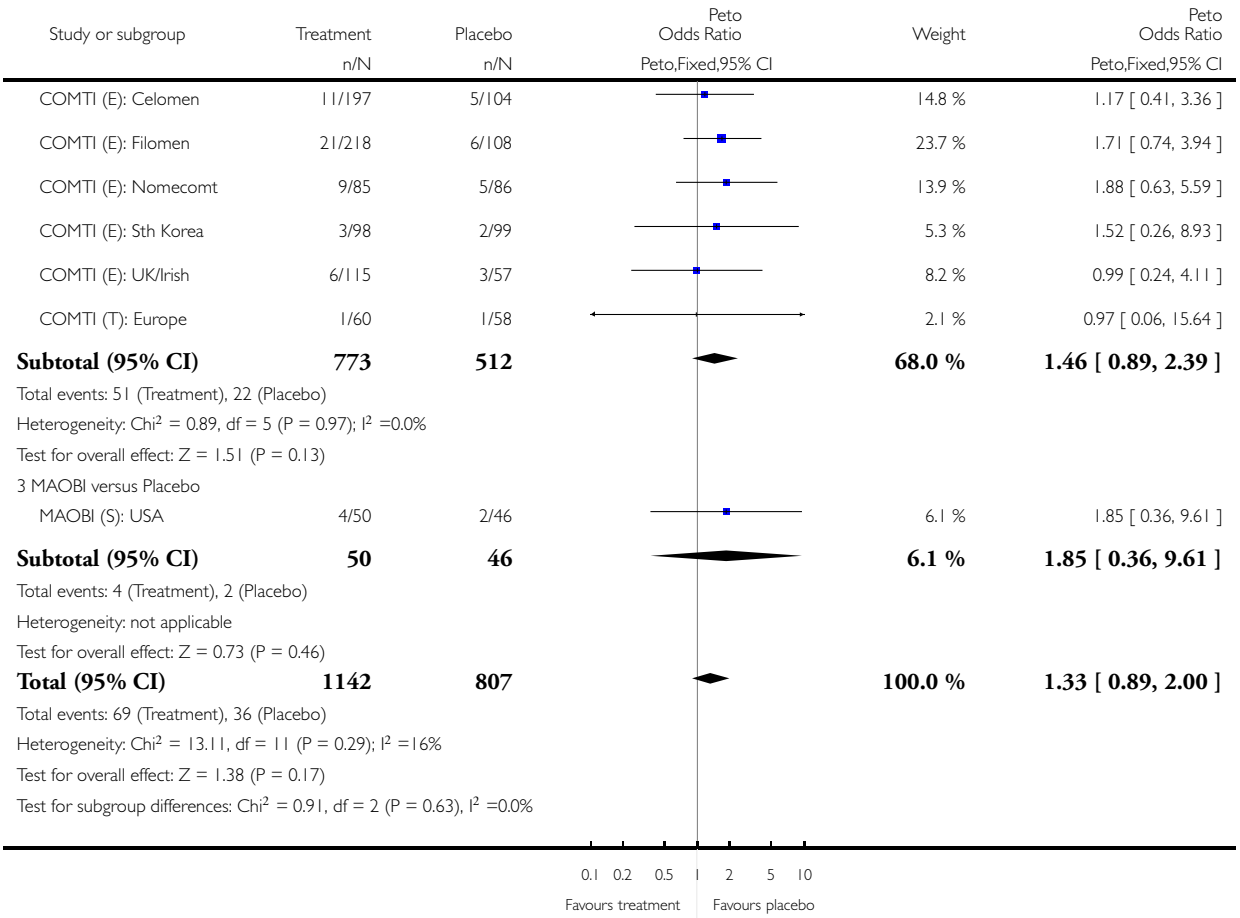
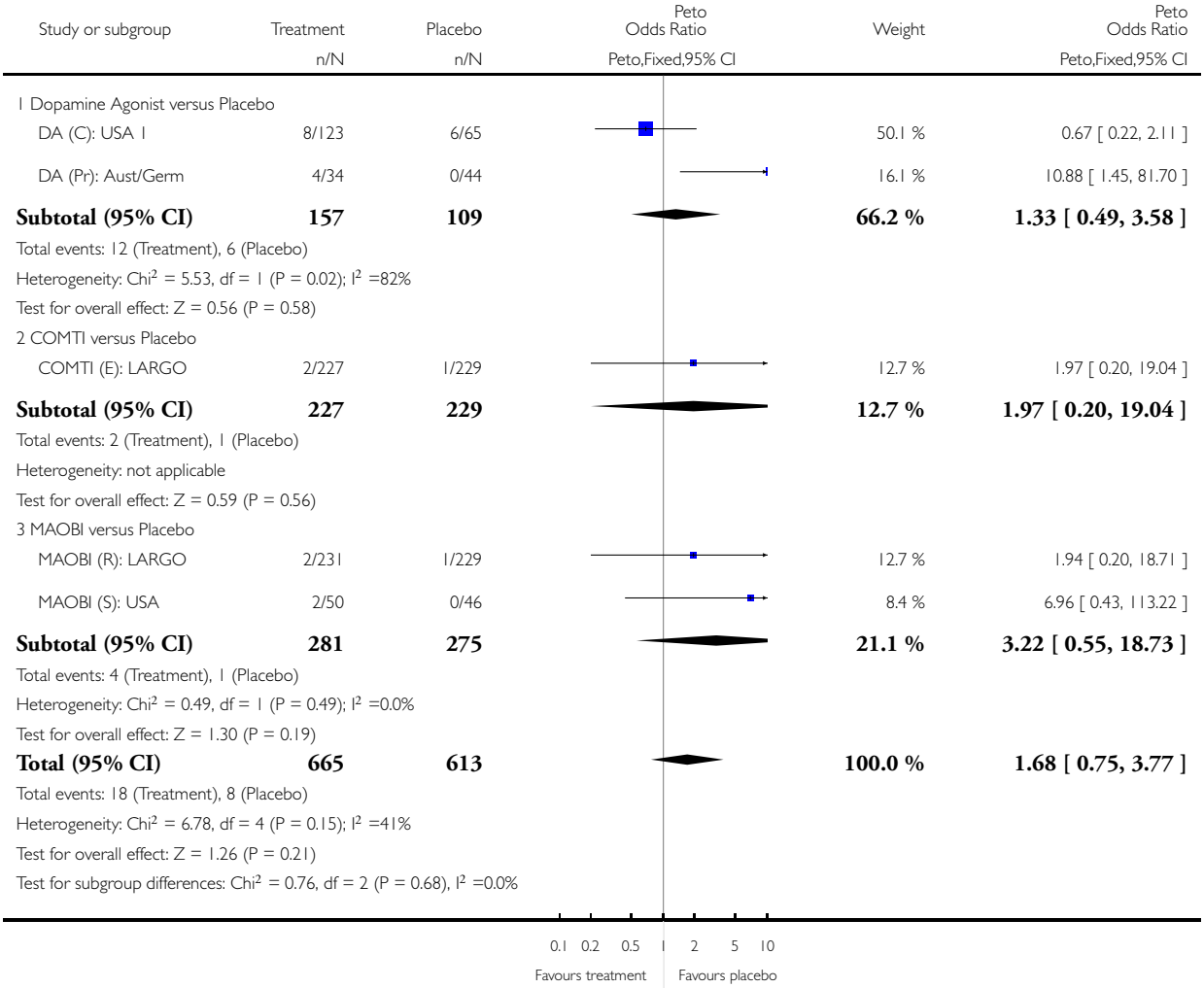


Analysis 5.15. Comparison 5 Adverse Events, Outcome 15 Abnormal Dreams.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 15 Abnormal Dreams

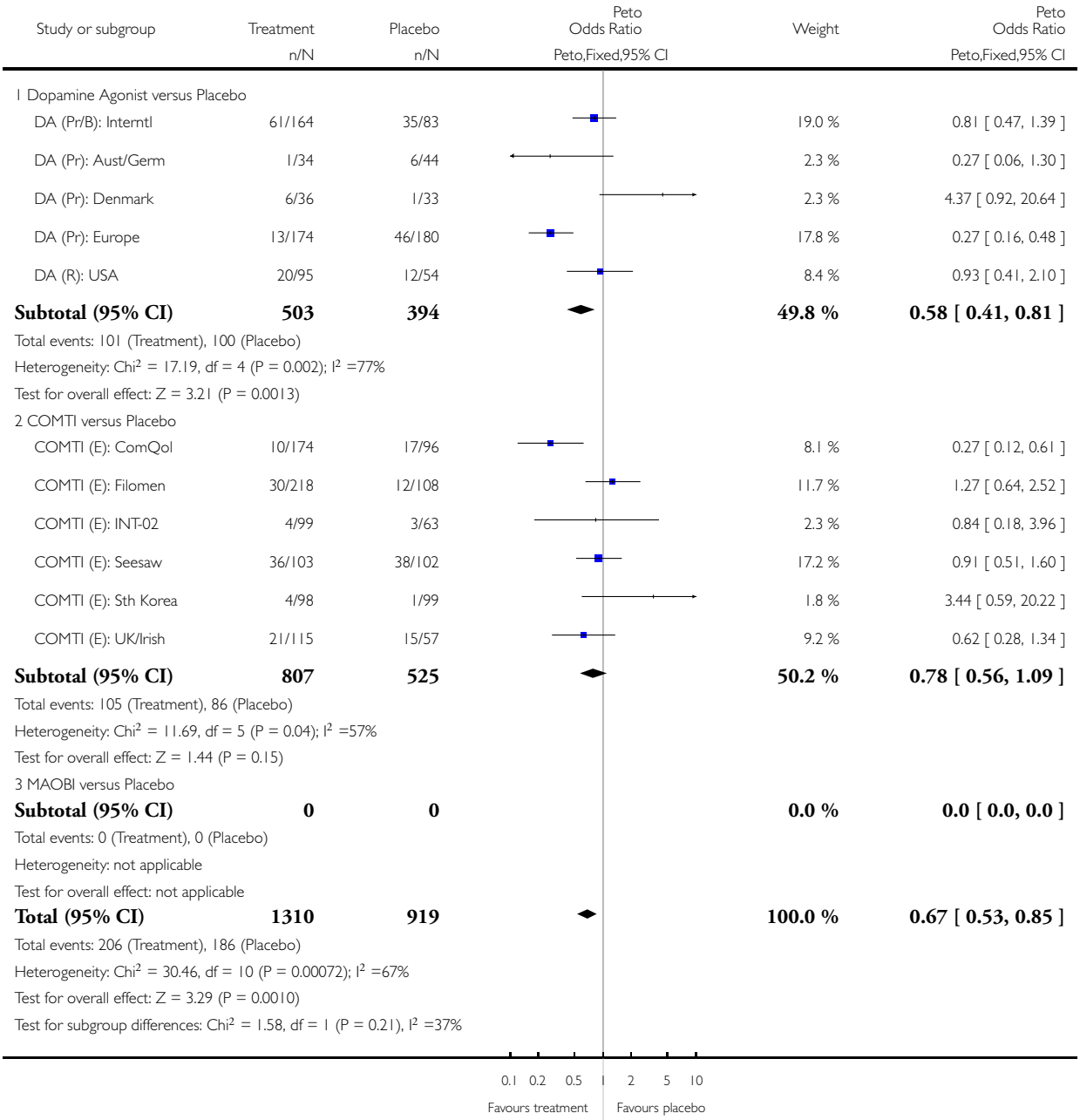


Analysis 5.16. Comparison 5 Adverse Events, Outcome 16 Aggravated PD.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 16 Aggravated PD

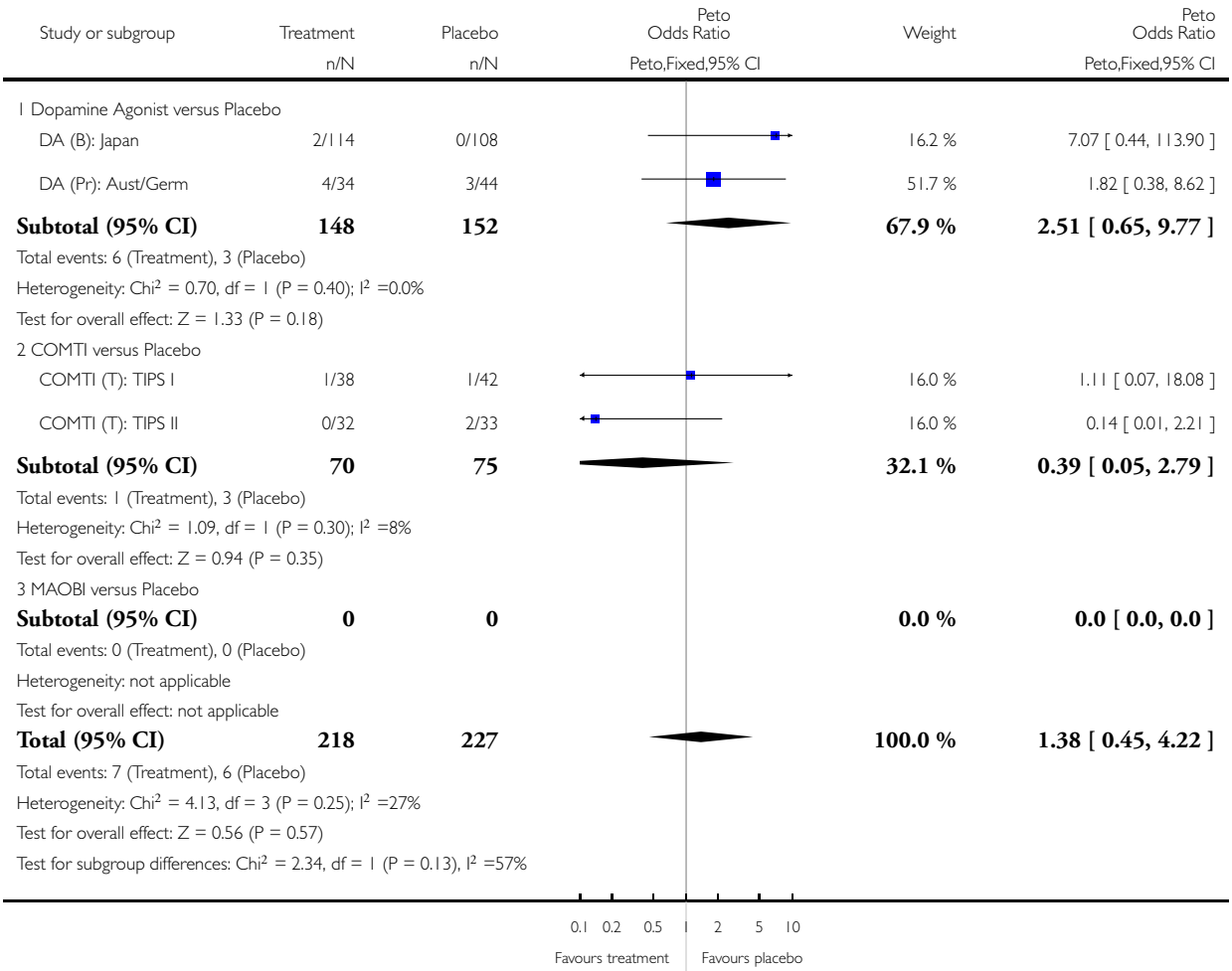


Analysis 5.17. Comparison 5 Adverse Events, Outcome 17 Agitation.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 17 Agitation

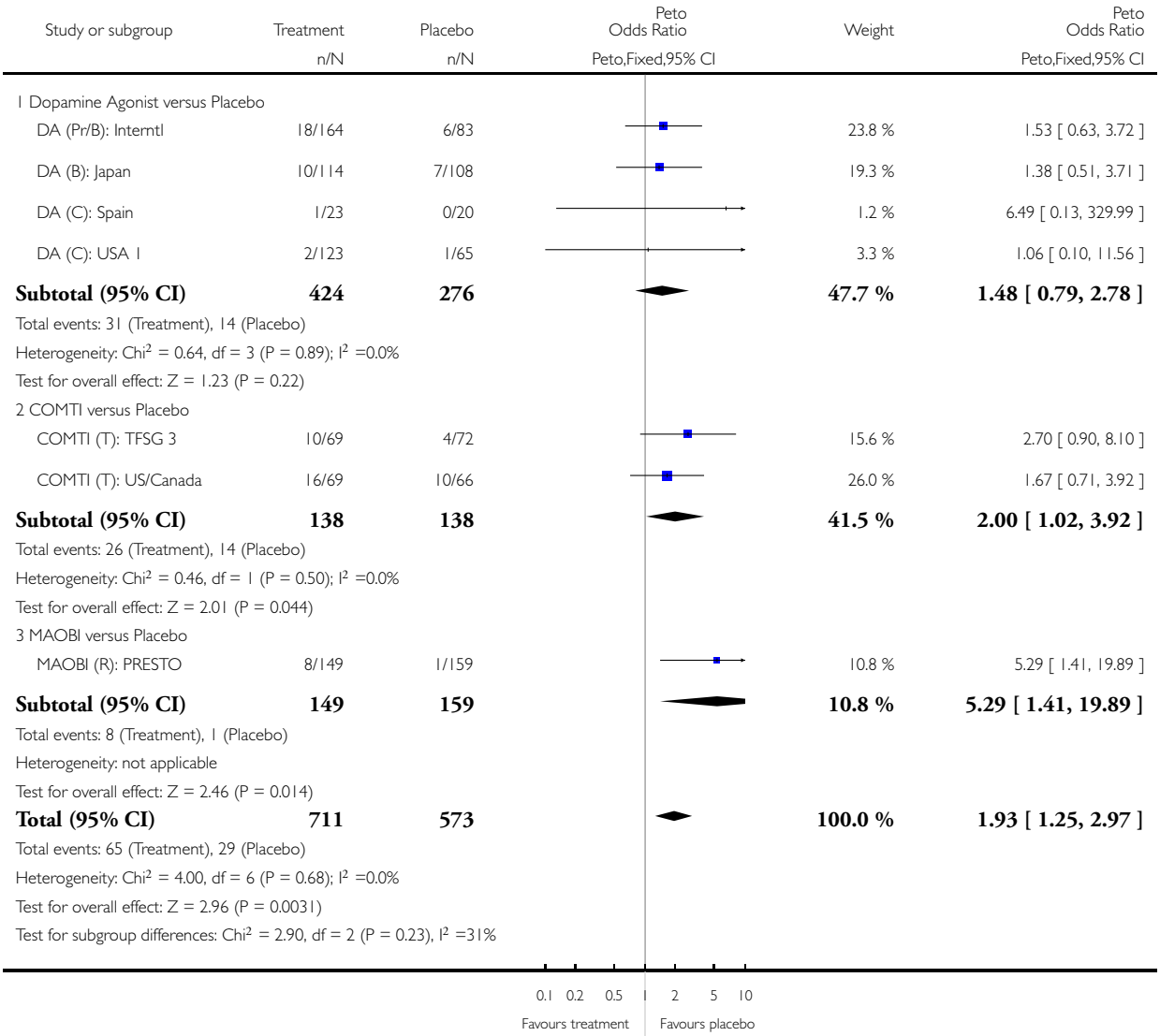


Analysis 5.18. Comparison 5 Adverse Events, Outcome 18 Anorexia.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 18 Anorexia

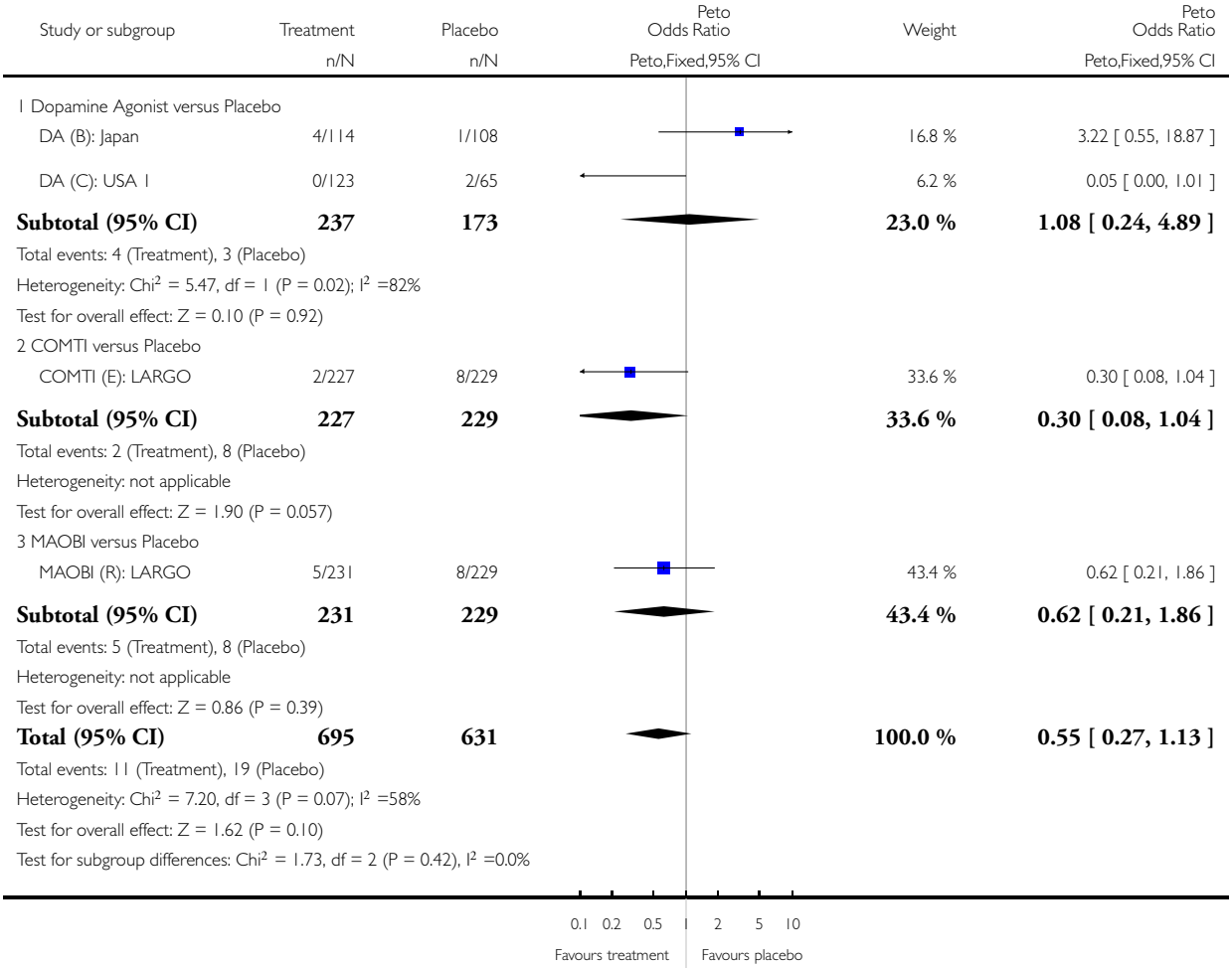


Analysis 5.19. Comparison 5 Adverse Events, Outcome 19 Anxiety.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 19 Anxiety

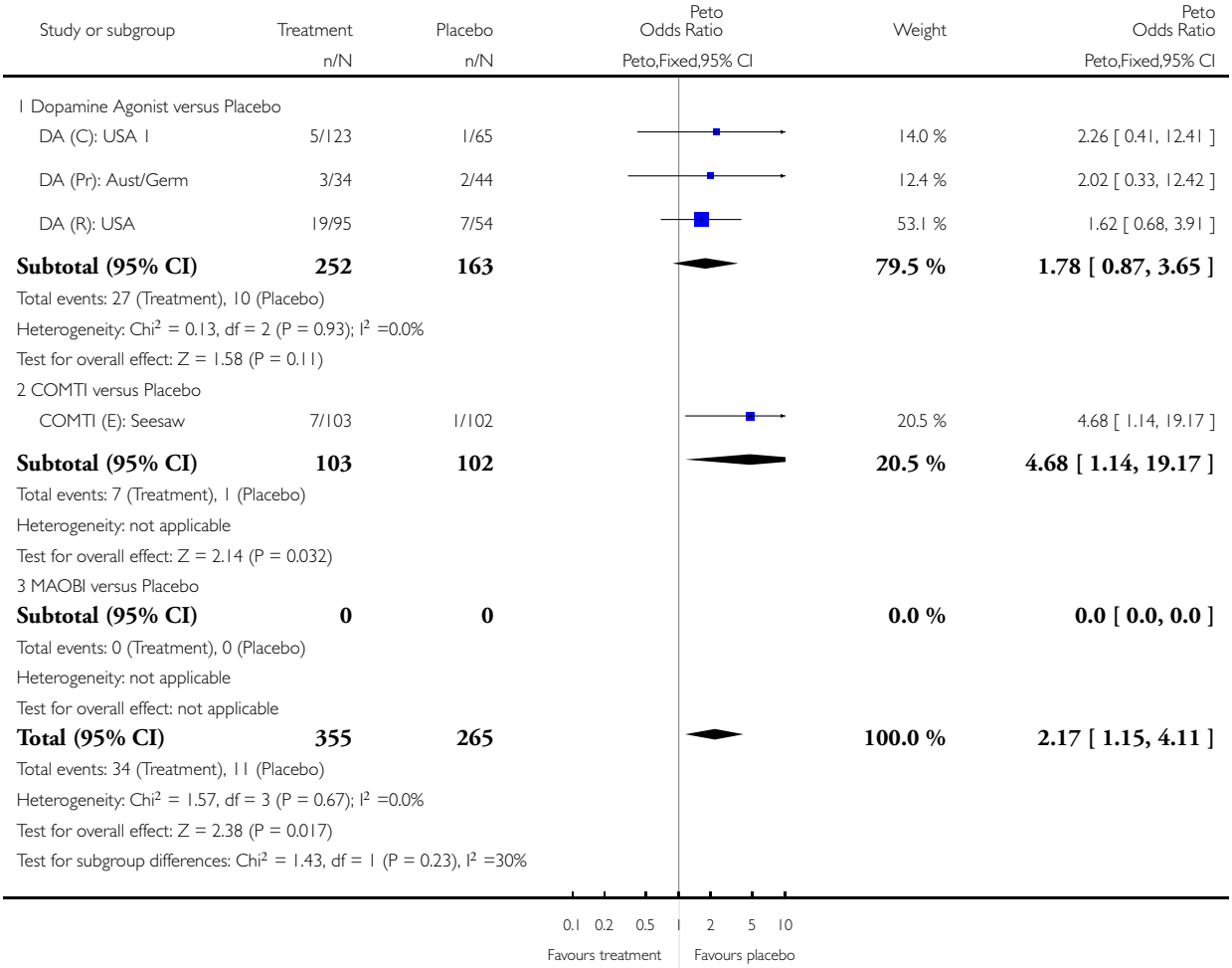


Analysis 5.20. Comparison 5 Adverse Events, Outcome 20 Ataxia.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 20 Ataxia

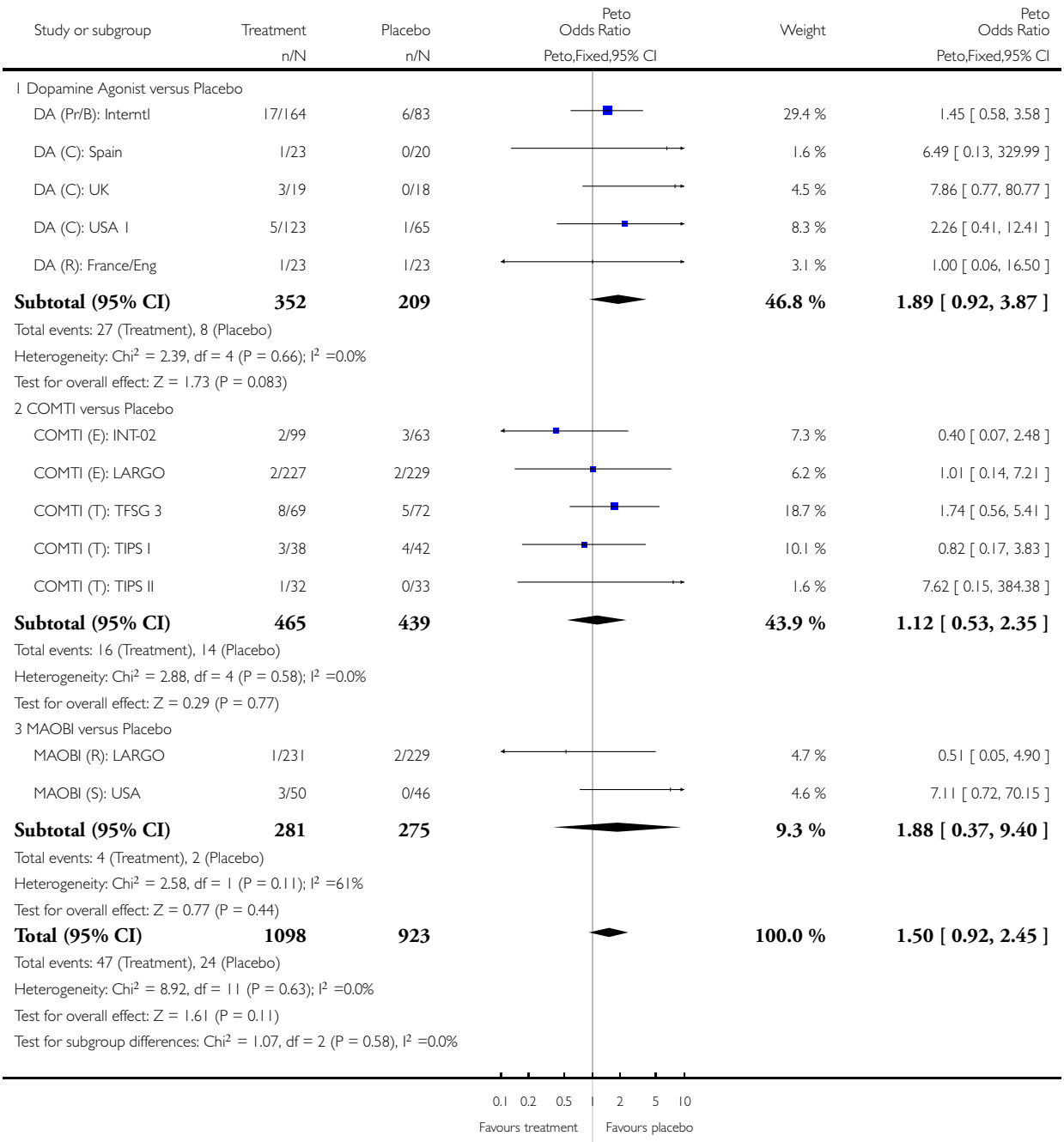


Analysis 5.21. Comparison 5 Adverse Events, Outcome 21 Confusion.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 21 Confusion

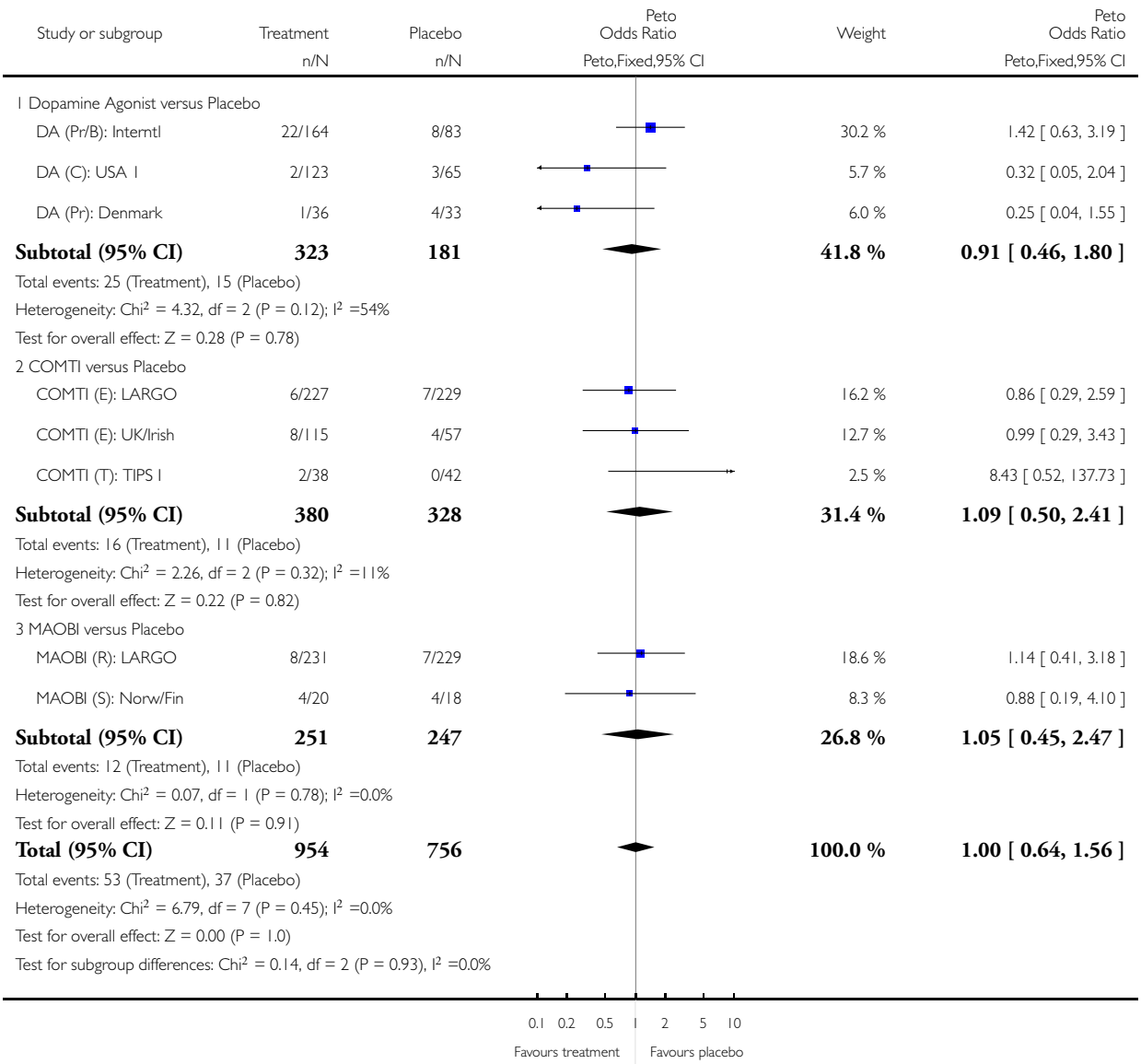


Analysis 5.22. Comparison 5 Adverse Events, Outcome 22 Depression.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 22 Depression

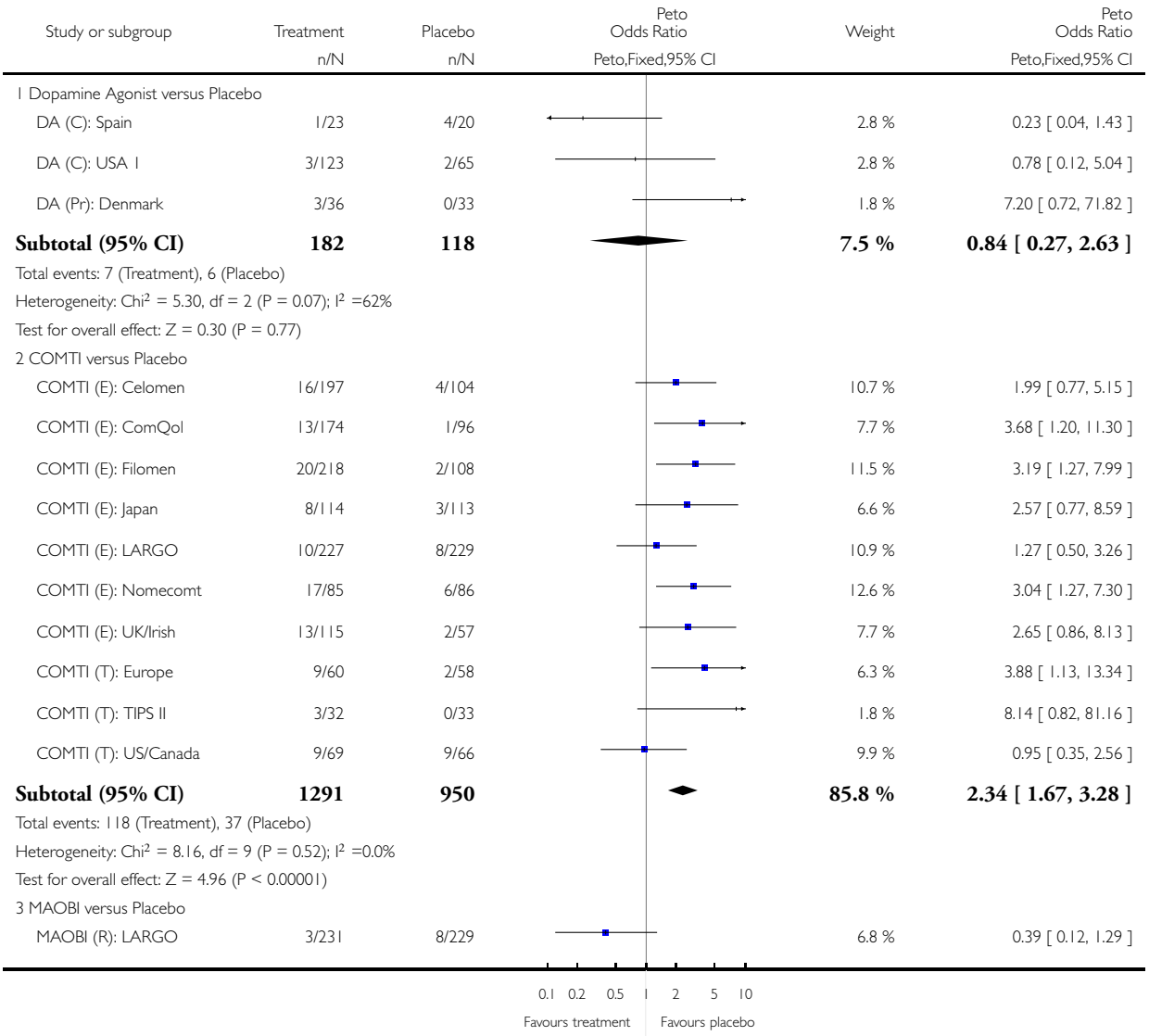


Analysis 5.23. Comparison 5 Adverse Events, Outcome 23 Diarrhoea.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 23 Diarrhoea



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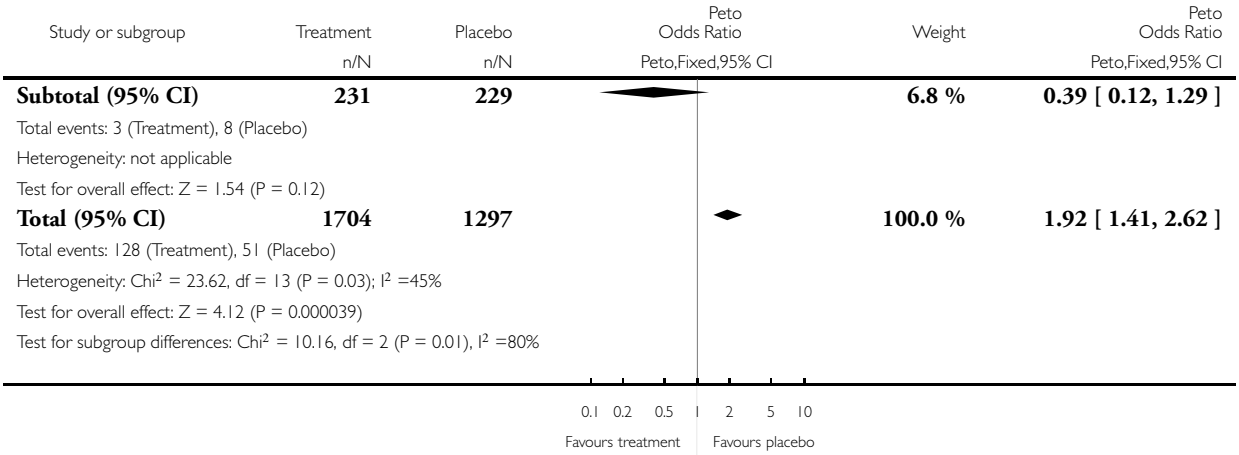
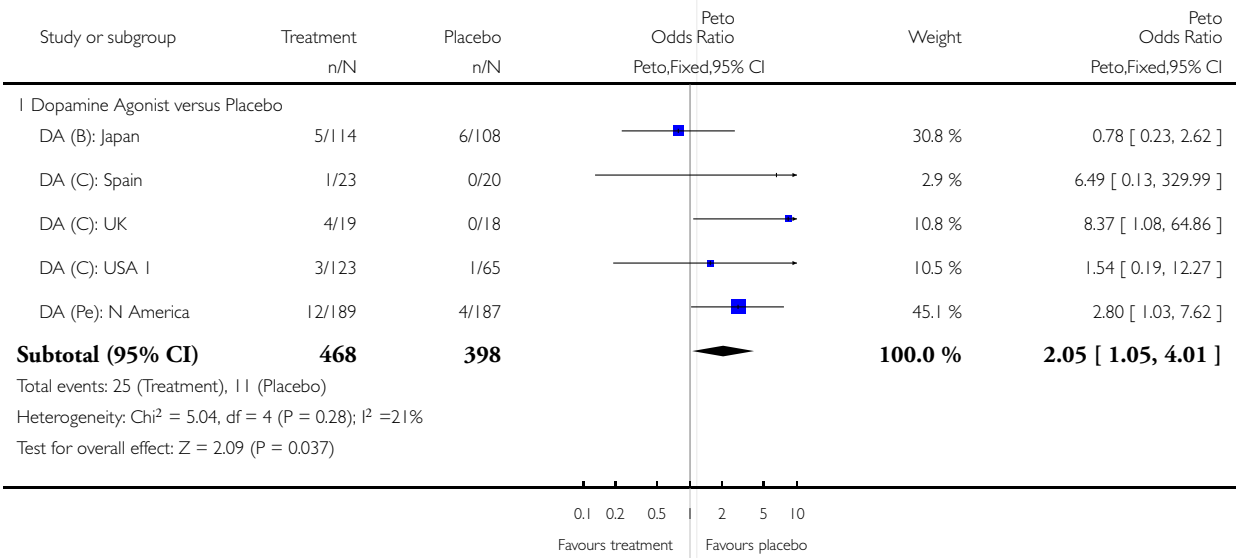


Analysis 5.24. Comparison 5 Adverse Events, Outcome 24 Dyspepsia.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 24 Dyspepsia



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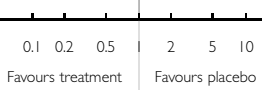
Study or subgroup	Treatment n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
2 COMTI versus Placebo					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 MAOBI versus Placebo					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**468**	**398**		**100.0 %**	**2.05 [1.05, 4.01]**
Total events: 25 (Treatment), 11 (Placebo)					
Heterogeneity: Chi^2 = 5.04, df = 4 (P = 0.28); I^2 =21%					
Test for overall effect: Z = 2.09 (P = 0.037)					
Test for subgroup differences: Not applicable					

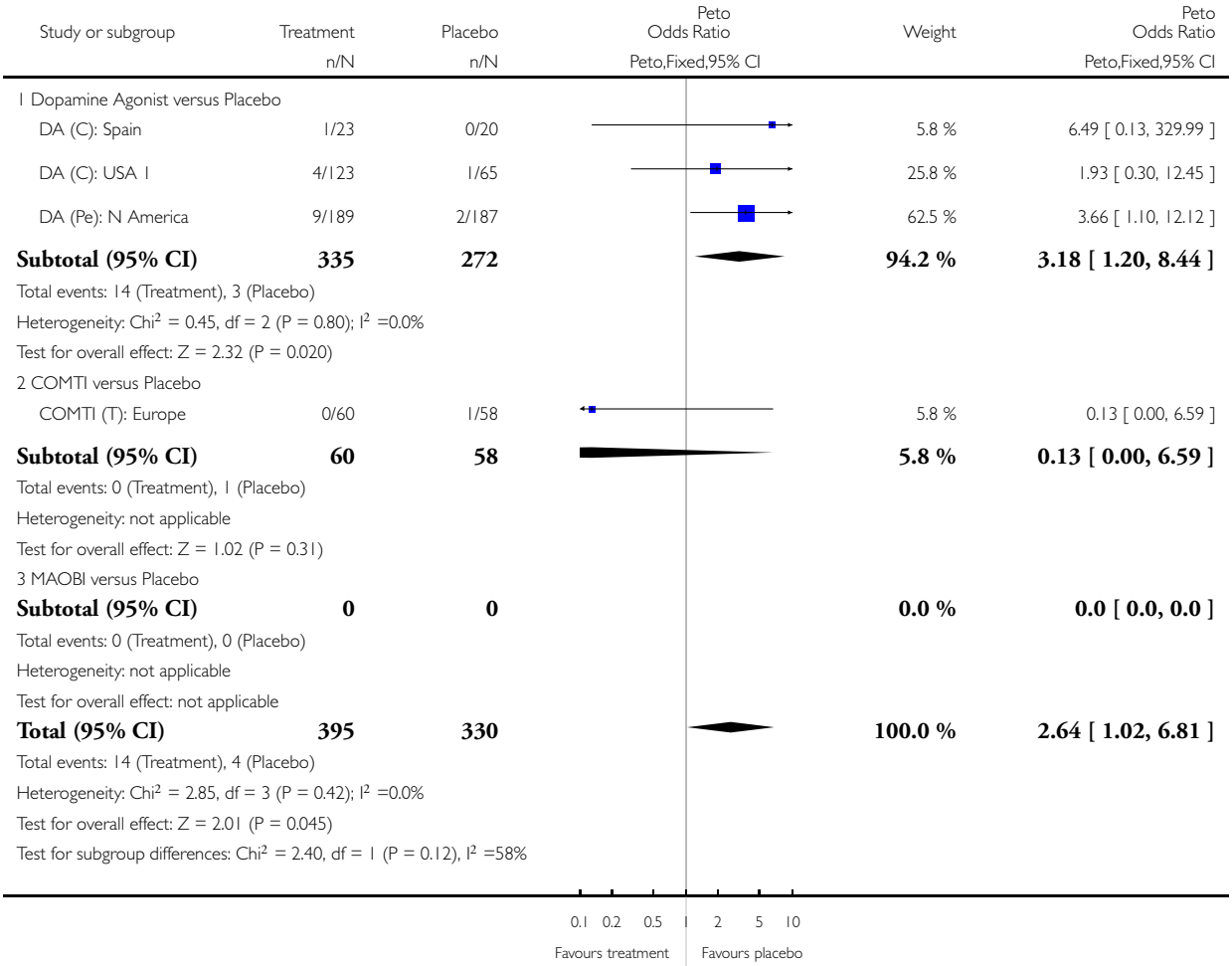


Analysis 5.25. Comparison 5 Adverse Events, Outcome 25 Dyspnoea.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 25 Dyspnoea

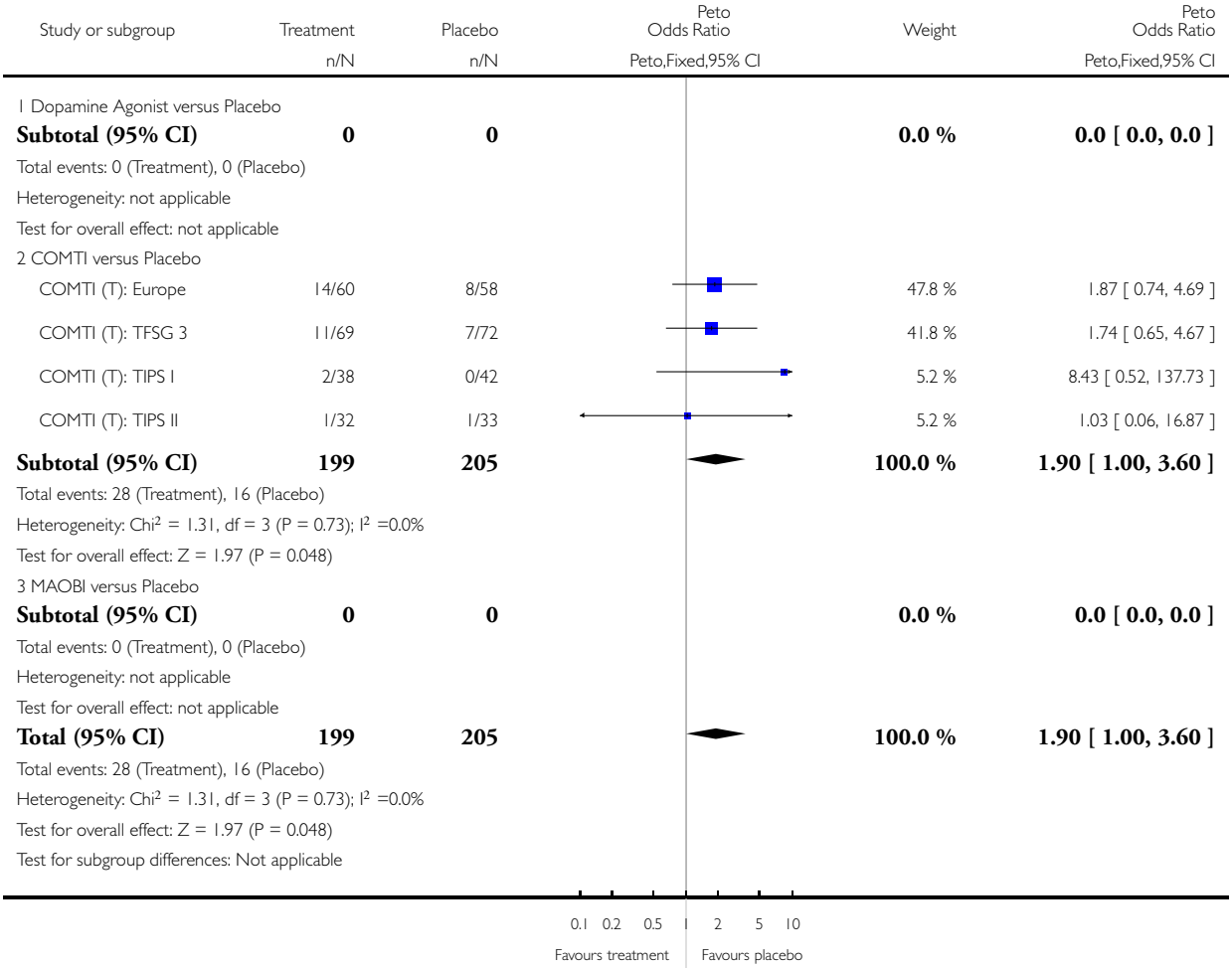


Analysis 5.26. Comparison 5 Adverse Events, Outcome 26 Excessive Dreaming.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 26 Excessive Dreaming

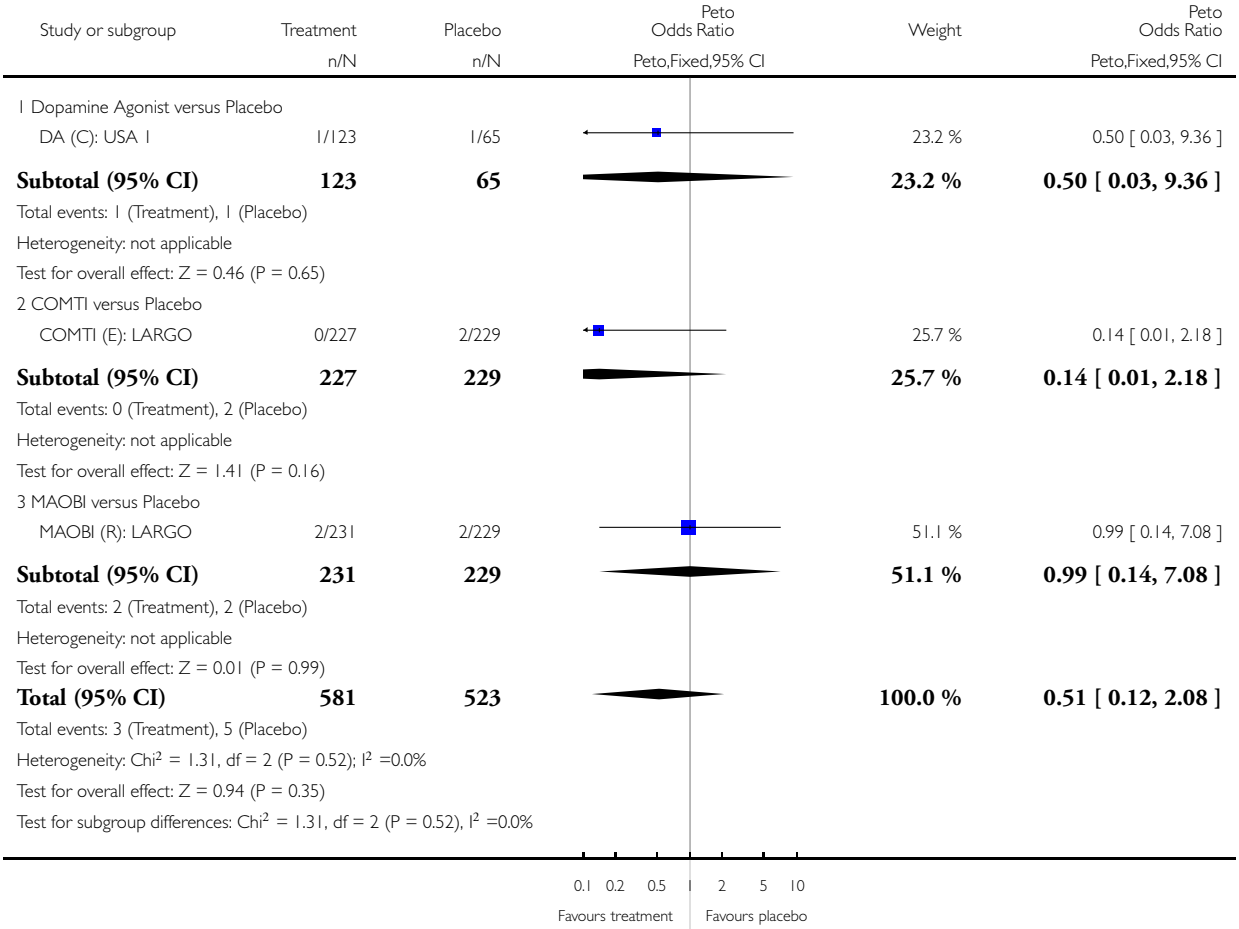


Analysis 5.27. Comparison 5 Adverse Events, Outcome 27 Fainting.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 27 Fainting

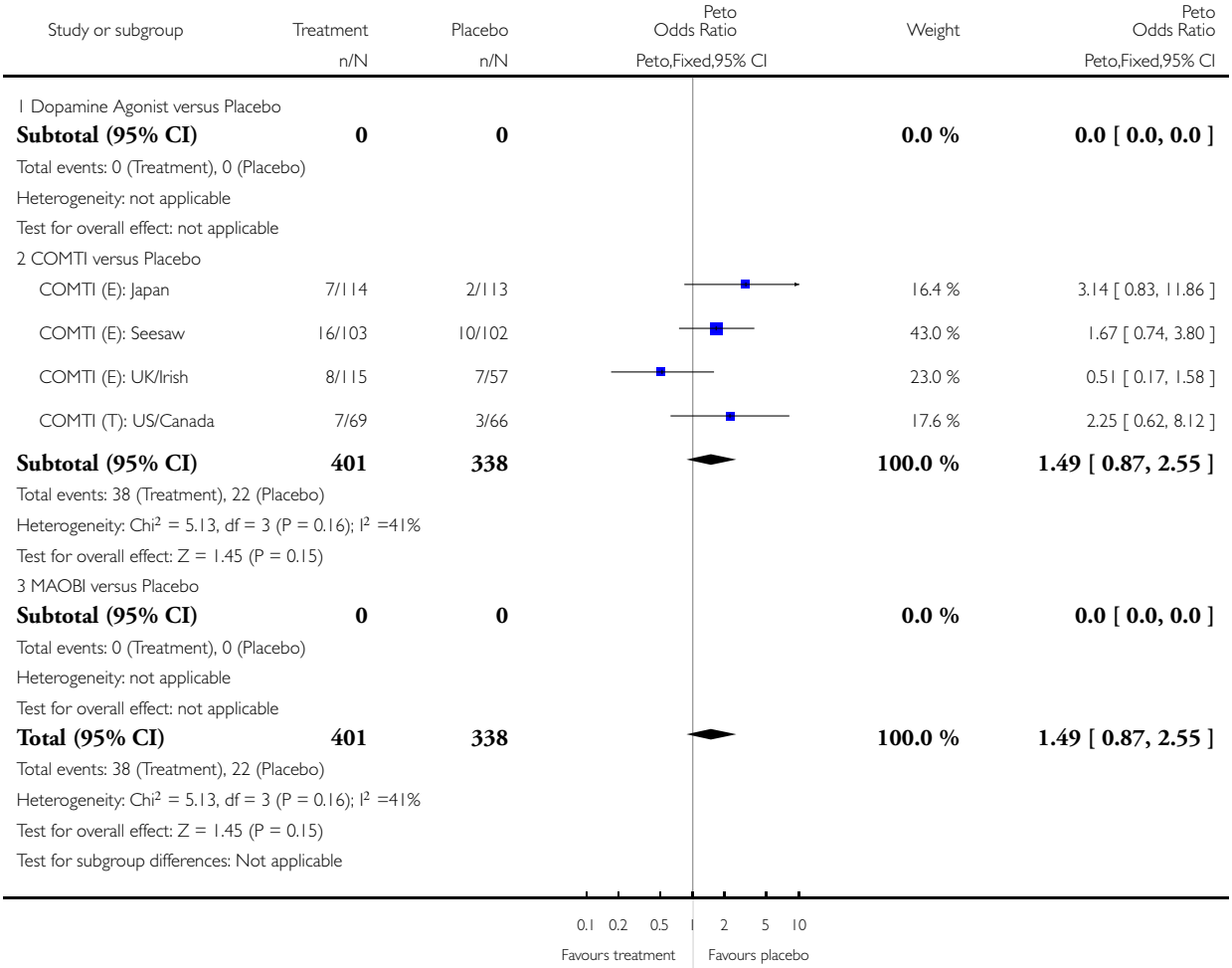


Analysis 5.28. Comparison 5 Adverse Events, Outcome 28 Falls.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 28 Falls

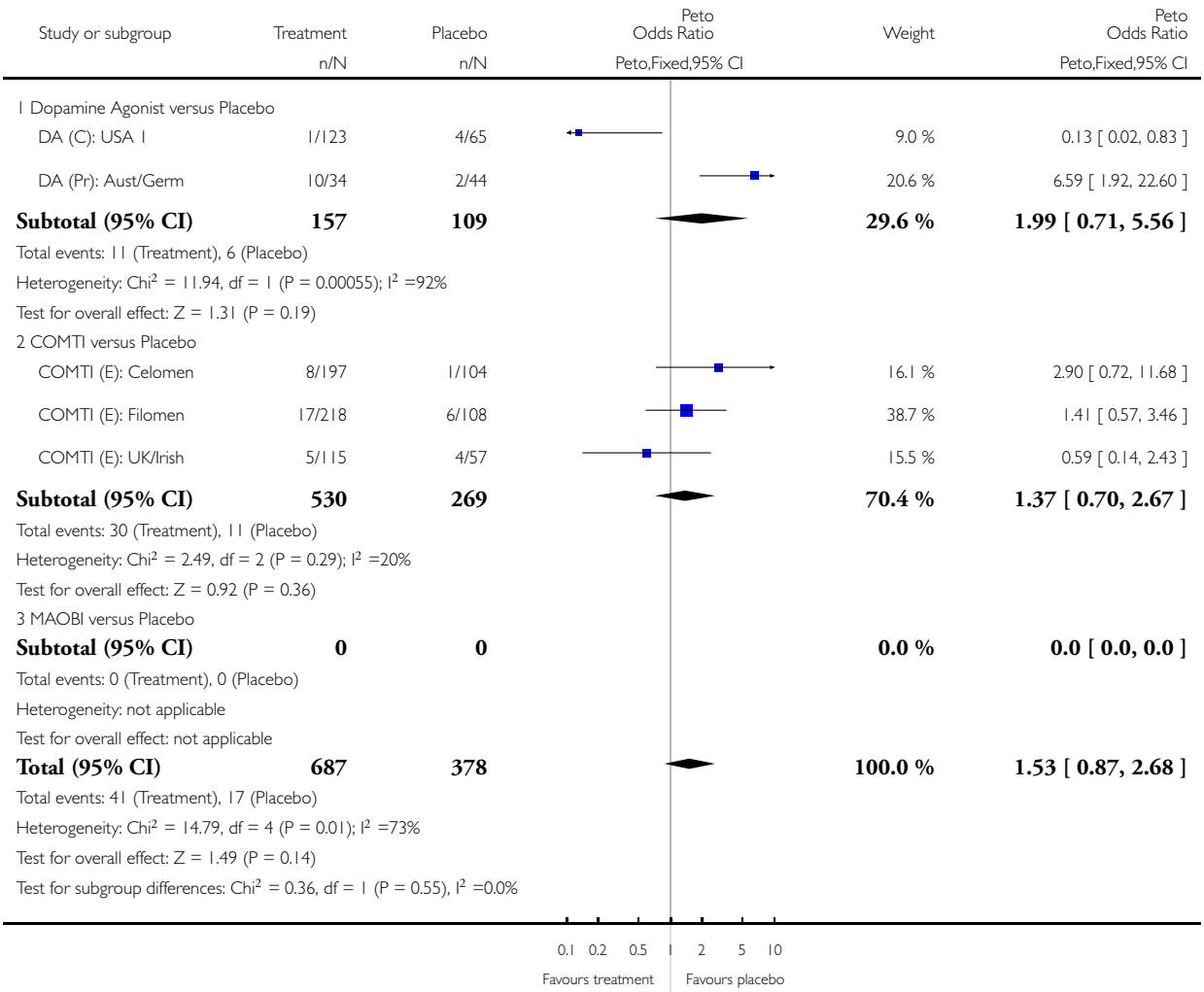


Analysis 5.29. Comparison 5 Adverse Events, Outcome 29 Fatigue.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 29 Fatigue

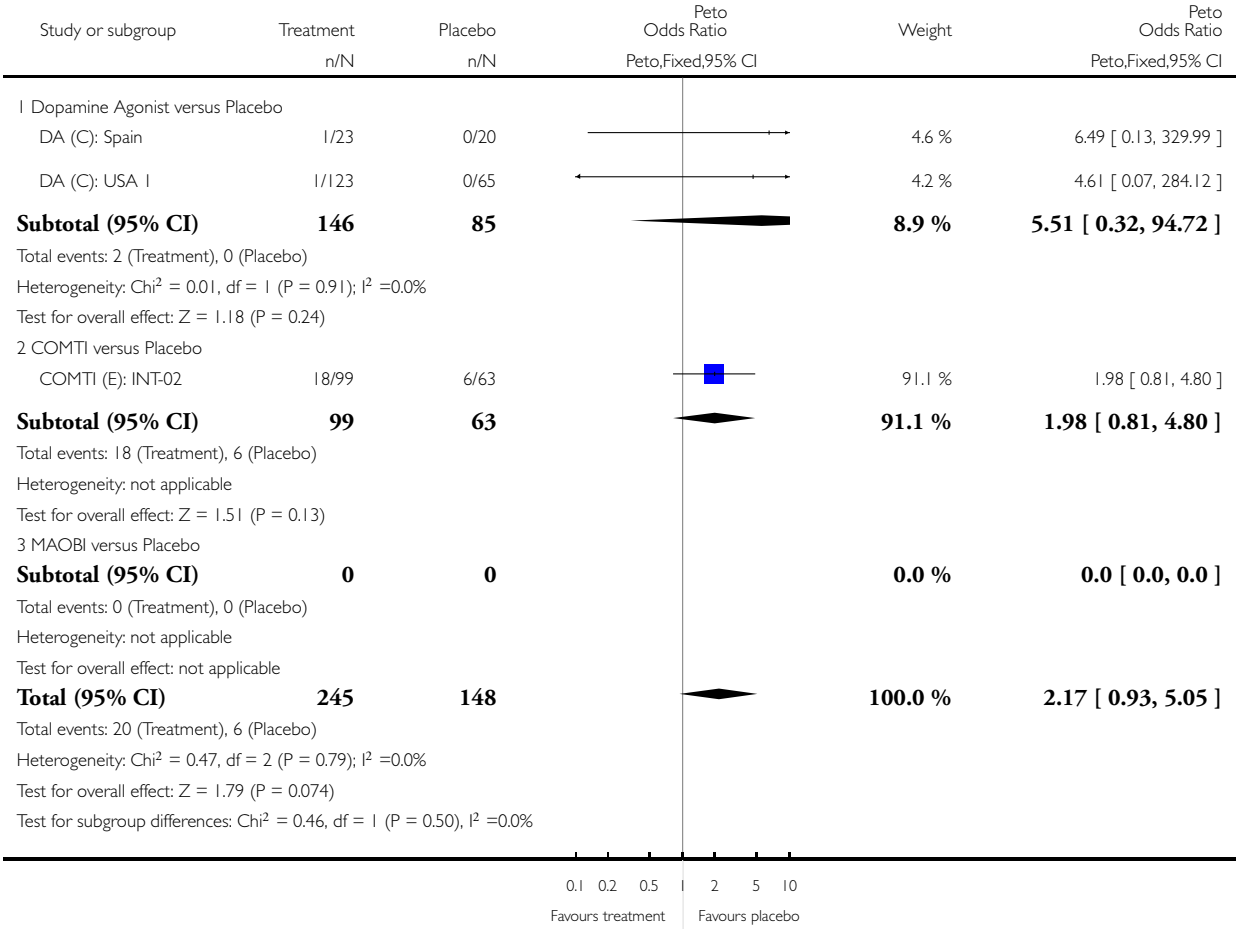


Analysis 5.30. Comparison 5 Adverse Events, Outcome 30 Gastritis.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 30 Gastritis

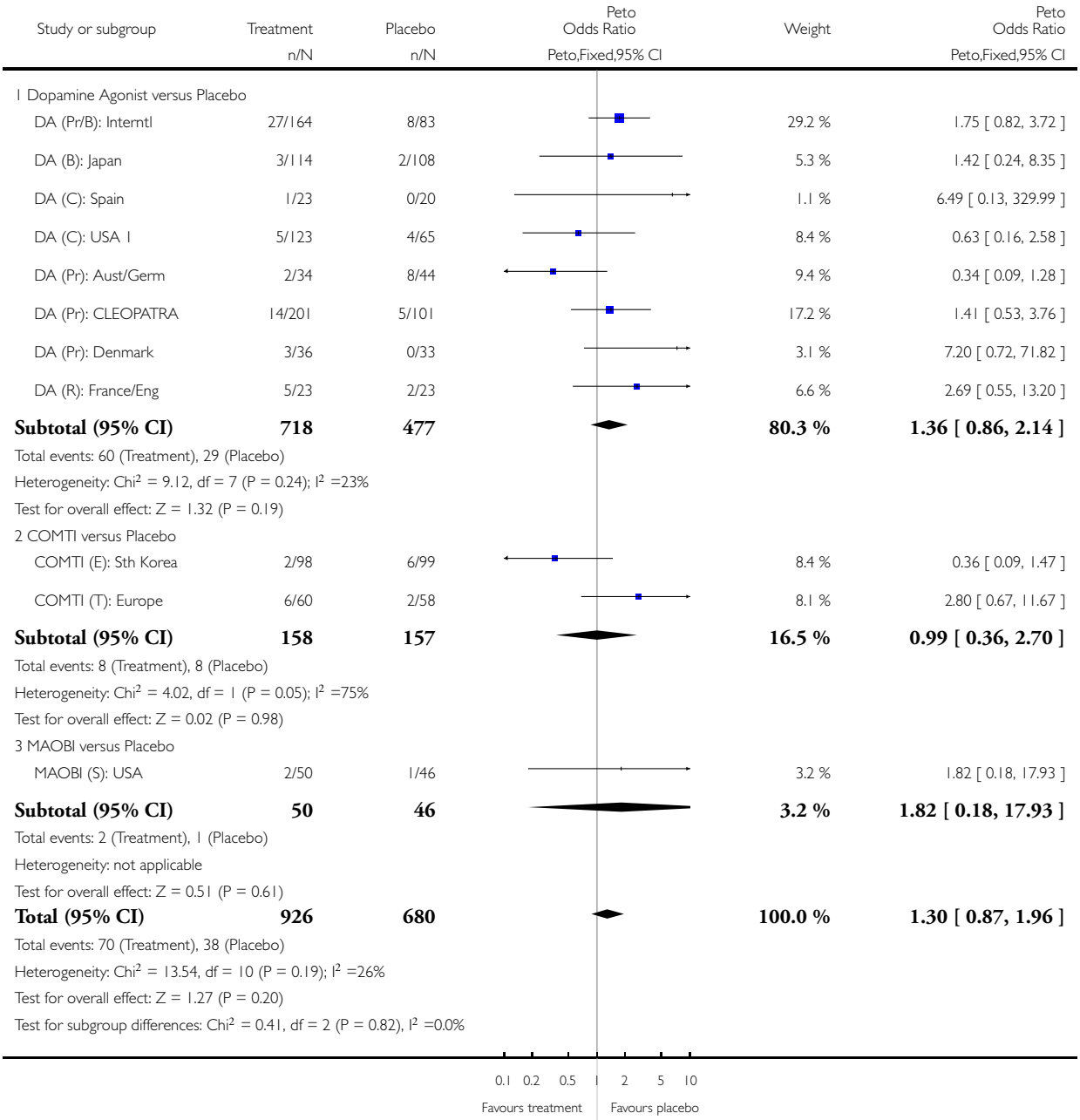


Analysis 5.31. Comparison 5 Adverse Events, Outcome 31 Headache.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 31 Headache



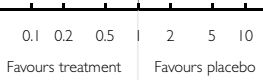
Analysis 5.32. Comparison 5 Adverse Events, Outcome 32 Hyperkinesia.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 32 Hyperkinesia

Study or subgroup	Treatment n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Dopamine Agonist versus Placebo					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 COMTI versus Placebo					
COMTI (E): LARGO	1/227	0/229		8.1 %	7.45 [0.15, 375.69]
COMTI (E): Nomecomt	8/85	3/86		83.8 %	2.66 [0.79, 8.99]
Subtotal (95% CI)	**312**	**315**		**91.9 %**	**2.91 [0.91, 9.32]**
Total events: 9 (Treatment), 3 (Placebo)					
Heterogeneity: Chi^2 = 0.24, df = 1 (P = 0.62); I^2 =0.0%					
Test for overall effect: Z = 1.80 (P = 0.072)					
3 MAOBI versus Placebo					
MAOBI (R): LARGO	1/231	0/229		8.1 %	7.33 [0.15, 369.19]
Subtotal (95% CI)	**231**	**229**		**8.1 %**	**7.33 [0.15, 369.19]**
Total events: 1 (Treatment), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.00 (P = 0.32)					
Total (95% CI)	**543**	**544**		**100.0 %**	**3.14 [1.03, 9.57]**
Total events: 10 (Treatment), 3 (Placebo)					
Heterogeneity: Chi^2 = 0.44, df = 2 (P = 0.80); I^2 =0.0%					
Test for overall effect: Z = 2.01 (P = 0.044)					
Test for subgroup differences: Chi^2 = 0.20, df = 1 (P = 0.66), I^2 =0.0%					

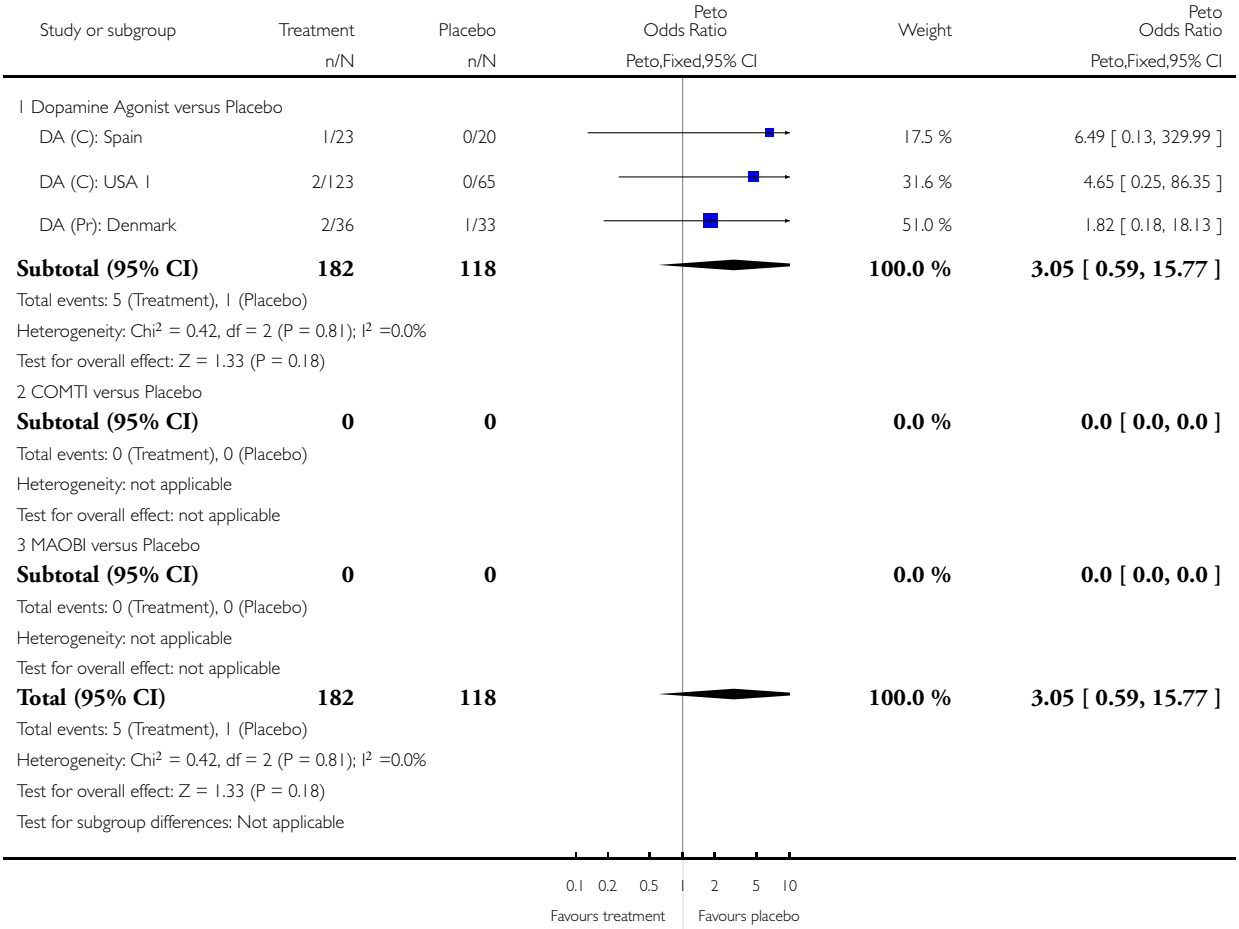


Analysis 5.33. Comparison 5 Adverse Events, Outcome 33 Hypertension.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 33 Hypertension

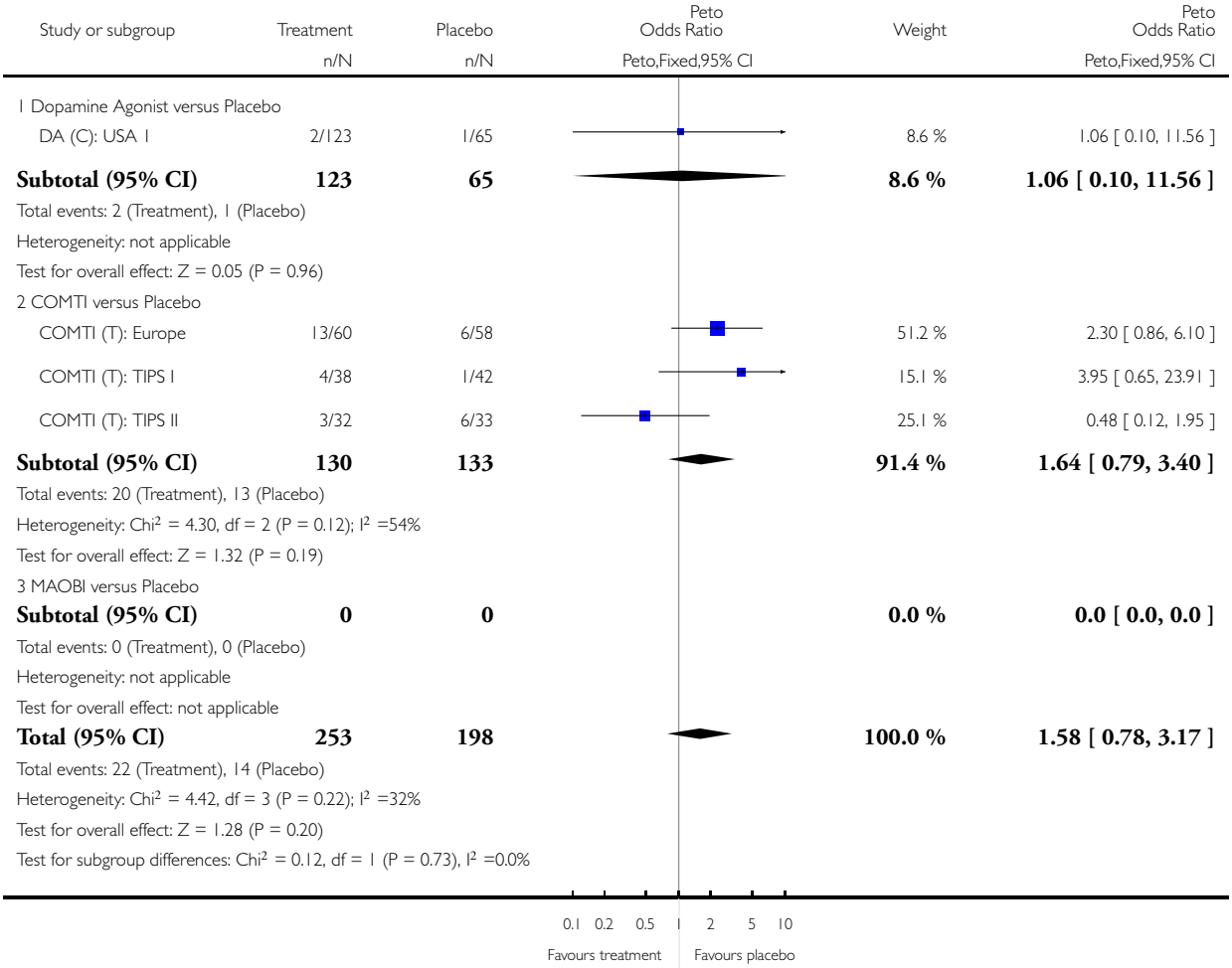


Analysis 5.34. Comparison 5 Adverse Events, Outcome 34 Muscle Cramps.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 34 Muscle Cramps

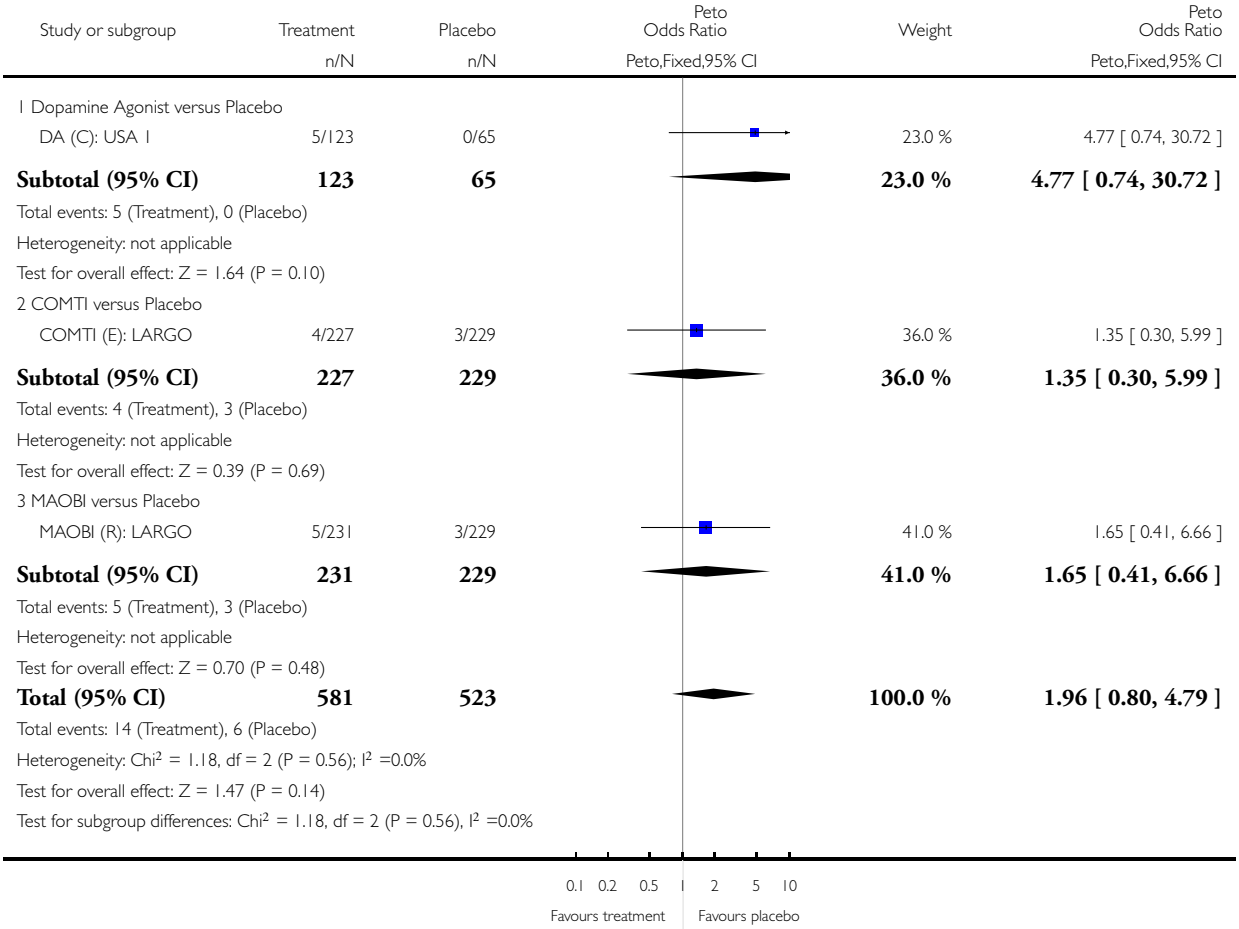


Analysis 5.35. Comparison 5 Adverse Events, Outcome 35 Oedema.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 35 Oedema

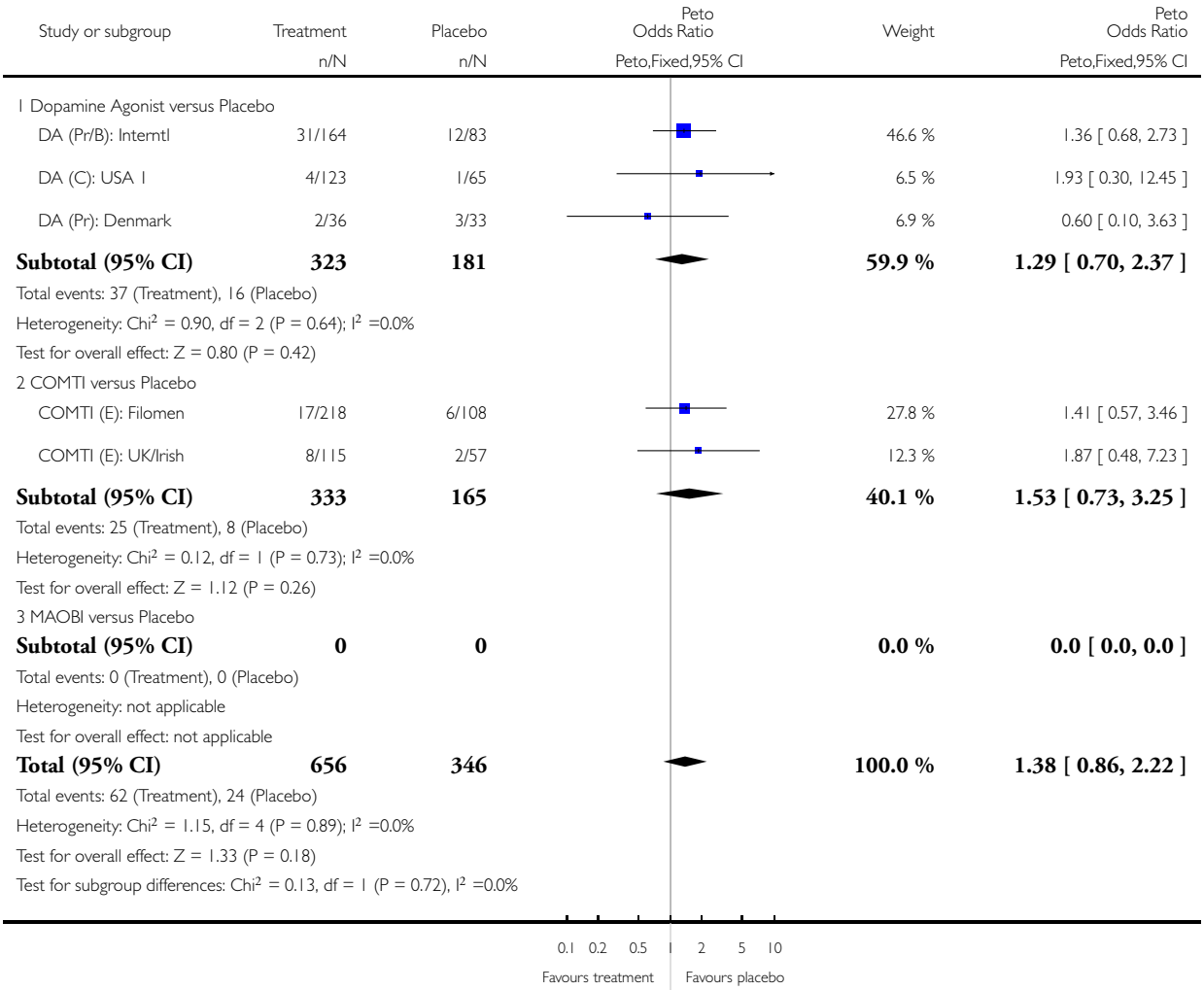


Analysis 5.36. Comparison 5 Adverse Events, Outcome 36 Pain.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 36 Pain

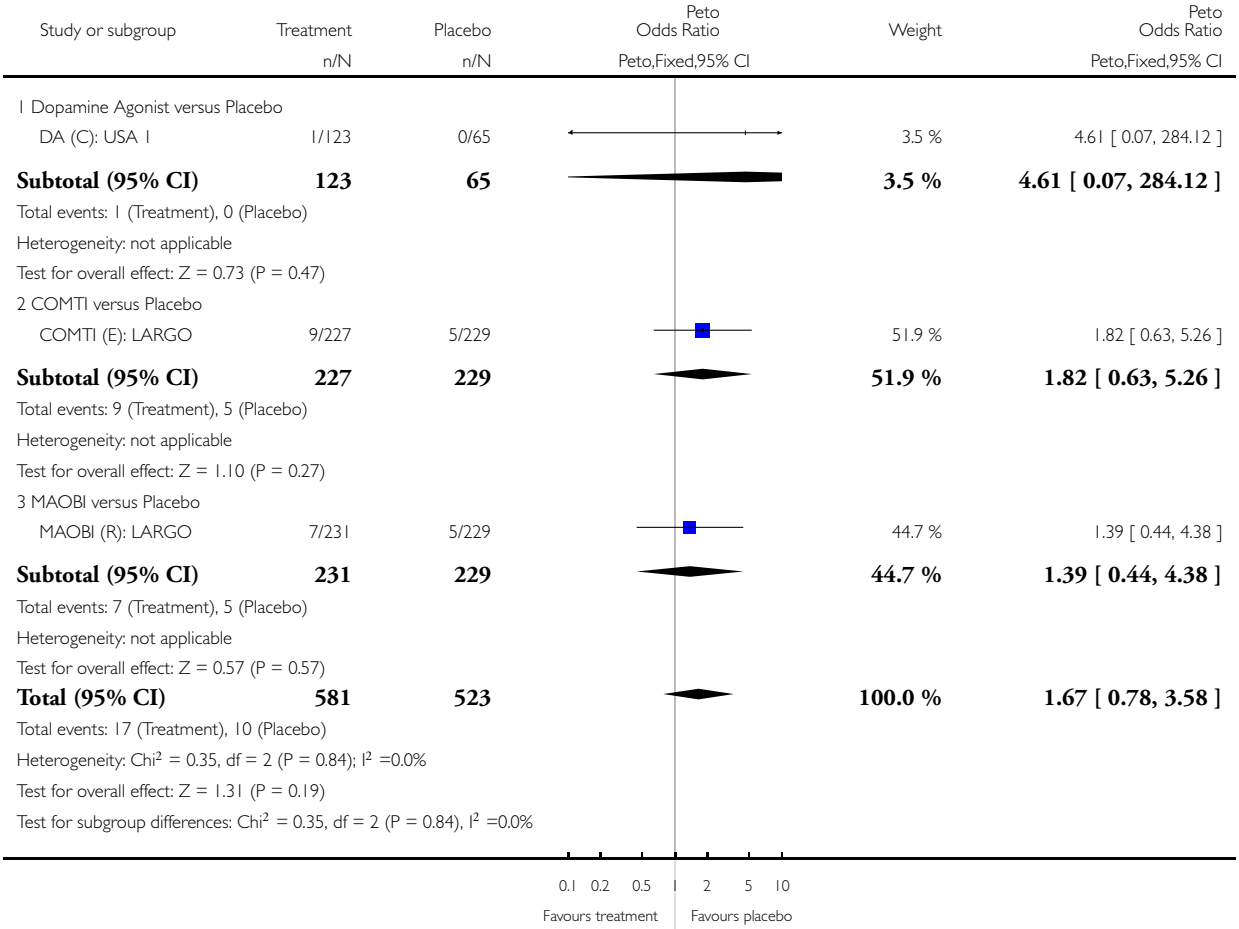


Analysis 5.37. Comparison 5 Adverse Events, Outcome 37 Sleep Disorders.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 37 Sleep Disorders

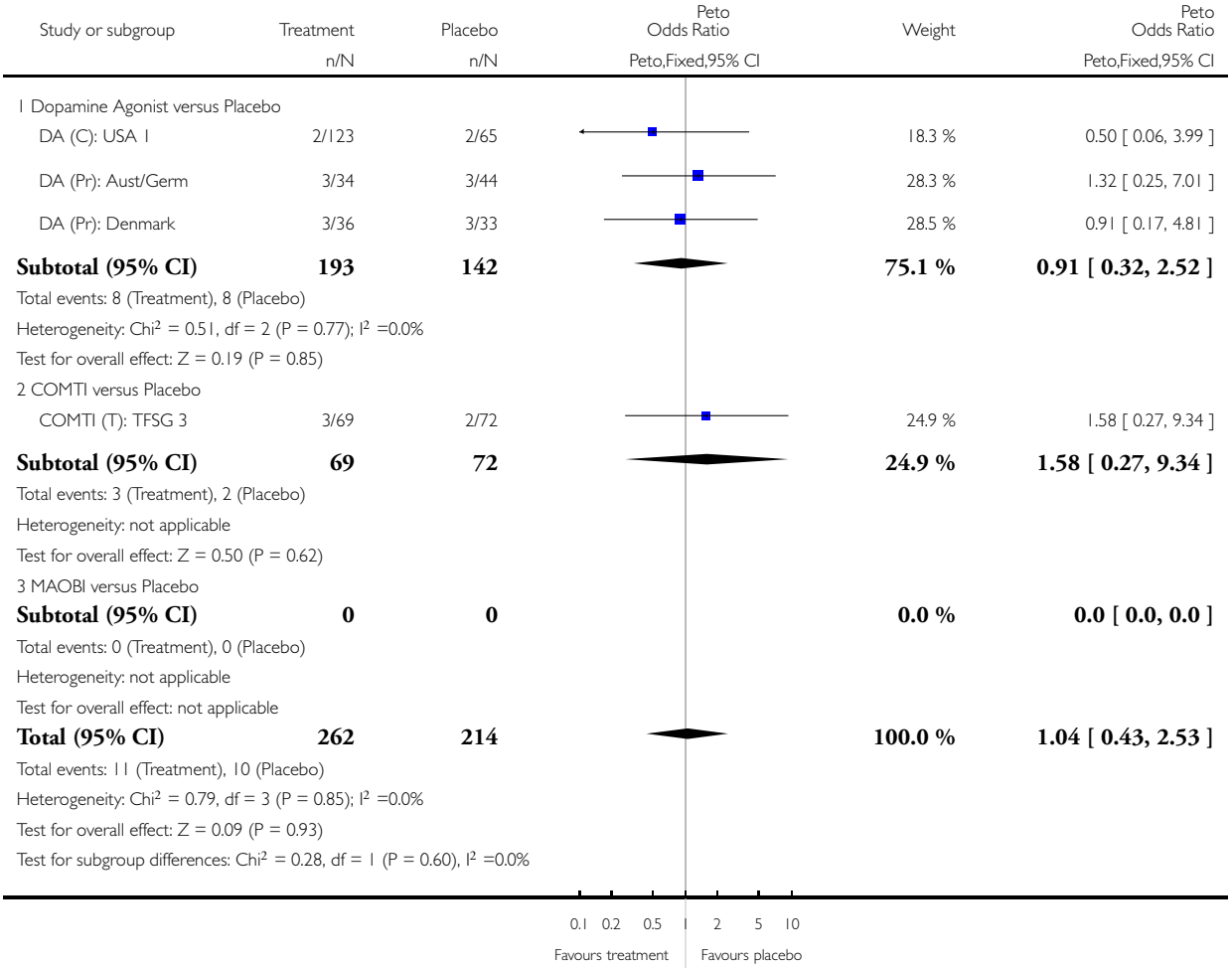


Analysis 5.38. Comparison 5 Adverse Events, Outcome 38 Sweating.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 38 Sweating

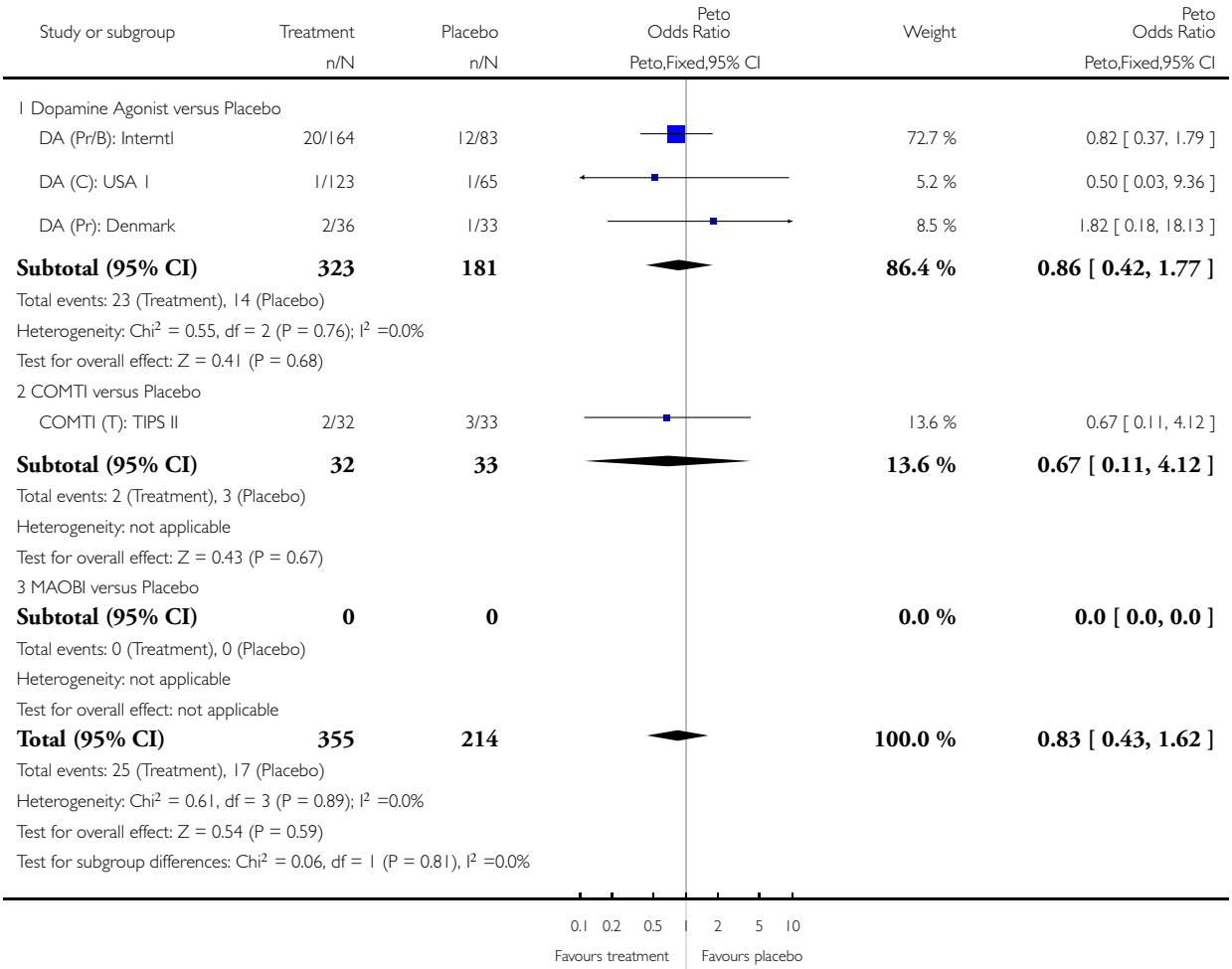


Analysis 5.39. Comparison 5 Adverse Events, Outcome 39 Tremor.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 39 Tremor

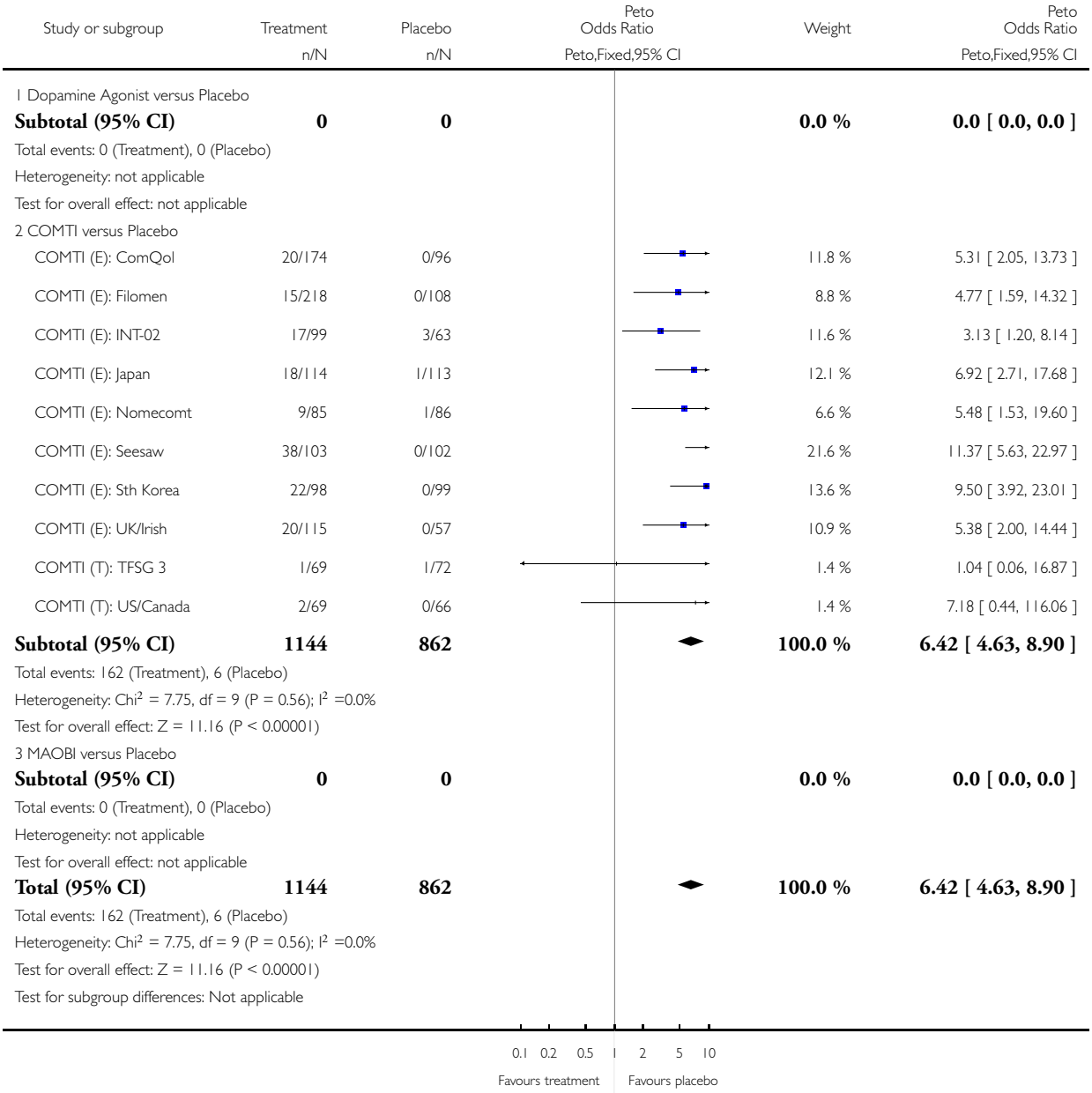


Analysis 5.40. Comparison 5 Adverse Events, Outcome 40 Urine Discoloration.

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 5 Adverse Events

Outcome: 40 Urine Discoloration



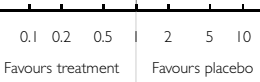
Analysis 6.1. Comparison 6 Mortality, Outcome 1 Mortality (Adjuvant Therapy versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 6 Mortality

Outcome: 1 Mortality (Adjuvant Therapy versus Placebo)

Study or subgroup	Treatment n/N	Placebo n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
1 Dopamine Agonist versus Placebo				
DA (C): Spain	0/23	1/20		0.12 [0.00, 6.05]
DA (Pe): N America	1/189	2/187		0.51 [0.05, 4.87]
DA (Pr): Aust/Germ	0/34	0/44		0.0 [0.0, 0.0]
DA (Pr): Denmark	0/36	0/33		0.0 [0.0, 0.0]
DA (Pr): H Kong/Taiw	0/50	0/54		0.0 [0.0, 0.0]
DA (R): EASE-PD	1/202	2/191		0.49 [0.05, 4.68]
DA (R): France/Eng	0/23	1/23		0.14 [0.00, 6.82]
DA (R): UK/Israel	0/46	0/22		0.0 [0.0, 0.0]
Subtotal (95% CI)	**603**	**574**		**0.35 [0.09, 1.41]**
Heterogeneity: Chi² = 0.70, df = 3 (P = 0.87); I² =0.0%				
Test for overall effect: Z = 1.47 (P = 0.14)				
2 COMTI versus Placebo				
COMTI (E): Filomen	3/218	4/108		0.33 [0.07, 1.62]
COMTI (E): INT-02	0/99	0/63		0.0 [0.0, 0.0]
Subtotal (95% CI)	**317**	**171**		**0.33 [0.07, 1.62]**
Heterogeneity: Chi² = 0.0, df = 0 (P = 1.00); I² =0.0%				
Test for overall effect: Z = 1.36 (P = 0.17)				
3 MAOBI versus Placebo				
MAOBI (S): Norw/Fin	0/20	1/20		0.14 [0.00, 6.82]
MAOBI (ZS): USA	0/94	0/46		0.0 [0.0, 0.0]
Subtotal (95% CI)	**114**	**66**		**0.14 [0.00, 6.82]**
Heterogeneity: Chi² = 0.0, df = 0 (P = 1.00); I² =0.0%				
Test for overall effect: Z = 1.00 (P = 0.32)				
Total (95% CI)				**0.32 [0.12, 0.89]**
Heterogeneity: Chi² = 0.90, df = 5 (P = 0.97); I² =0.0%				
Test for overall effect: Z = 2.19 (P = 0.028)				
Test for subgroup differences: Chi² = 0.21, df = 2 (P = 0.90), I² =0.0%				

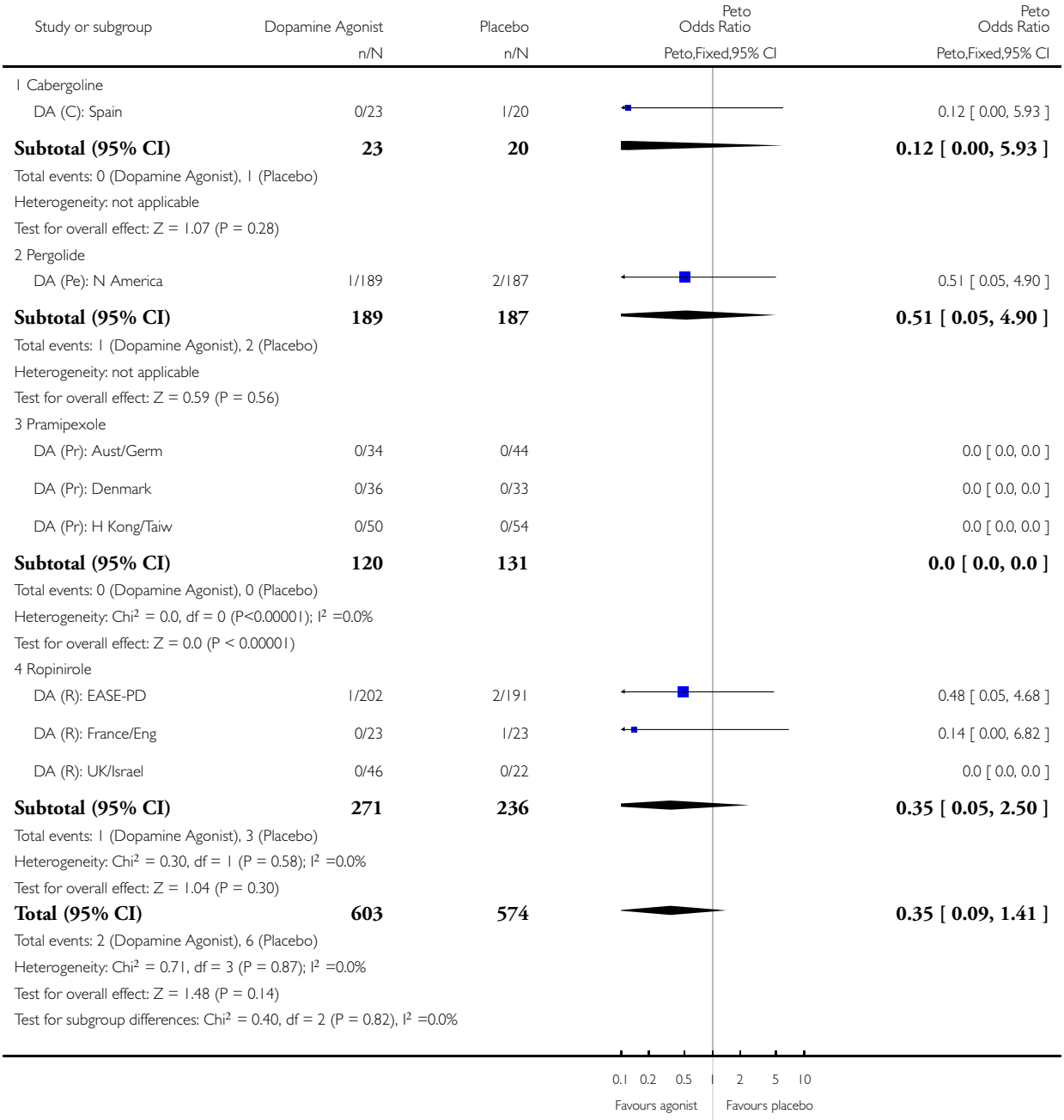


Analysis 6.2. Comparison 6 Mortality, Outcome 2 Mortality (Dopamine Agonist versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 6 Mortality

Outcome: 2 Mortality (Dopamine Agonist versus Placebo)



Analysis 6.3. Comparison 6 Mortality, Outcome 3 Mortality (COMTI versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 6 Mortality

Outcome: 3 Mortality (COMTI versus Placebo)

Study or subgroup	COMTI n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Entacapone				
COMTI (E): Filomen	3/218	4/108		0.33 [0.07, 1.62]
COMTI (E): INT-02	0/99	0/63		0.0 [0.0, 0.0]
Total (95% CI)	**317**	**171**		**0.33 [0.07, 1.62]**
Total events: 3 (COMTI), 4 (Placebo)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 1.36 (P = 0.17)				
Test for subgroup differences: Not applicable				

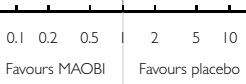
Analysis 6.4. Comparison 6 Mortality, Outcome 4 Mortality (MAOBI versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 6 Mortality

Outcome: 4 Mortality (MAOBI versus Placebo)

Study or subgroup	MAOBI n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Selegiline				
MAOBI (S): Norw/Fin	0/20	1/20		0.14 [0.00, 6.82]
Subtotal (95% CI)	**20**	**20**		**0.14 [0.00, 6.82]**
Total events: 0 (MAOBI), 1 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.00 (P = 0.32)				
2 Sublingual Selegiline				
MAOBI (ZS): USA	0/94	0/46		0.0 [0.0, 0.0]
Subtotal (95% CI)	**94**	**46**		**0.0 [0.0, 0.0]**
Total events: 0 (MAOBI), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Total (95% CI)	**114**	**66**		**0.14 [0.00, 6.82]**
Total events: 0 (MAOBI), 1 (Placebo)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 1.00 (P = 0.32)				
Test for subgroup differences: Not applicable				

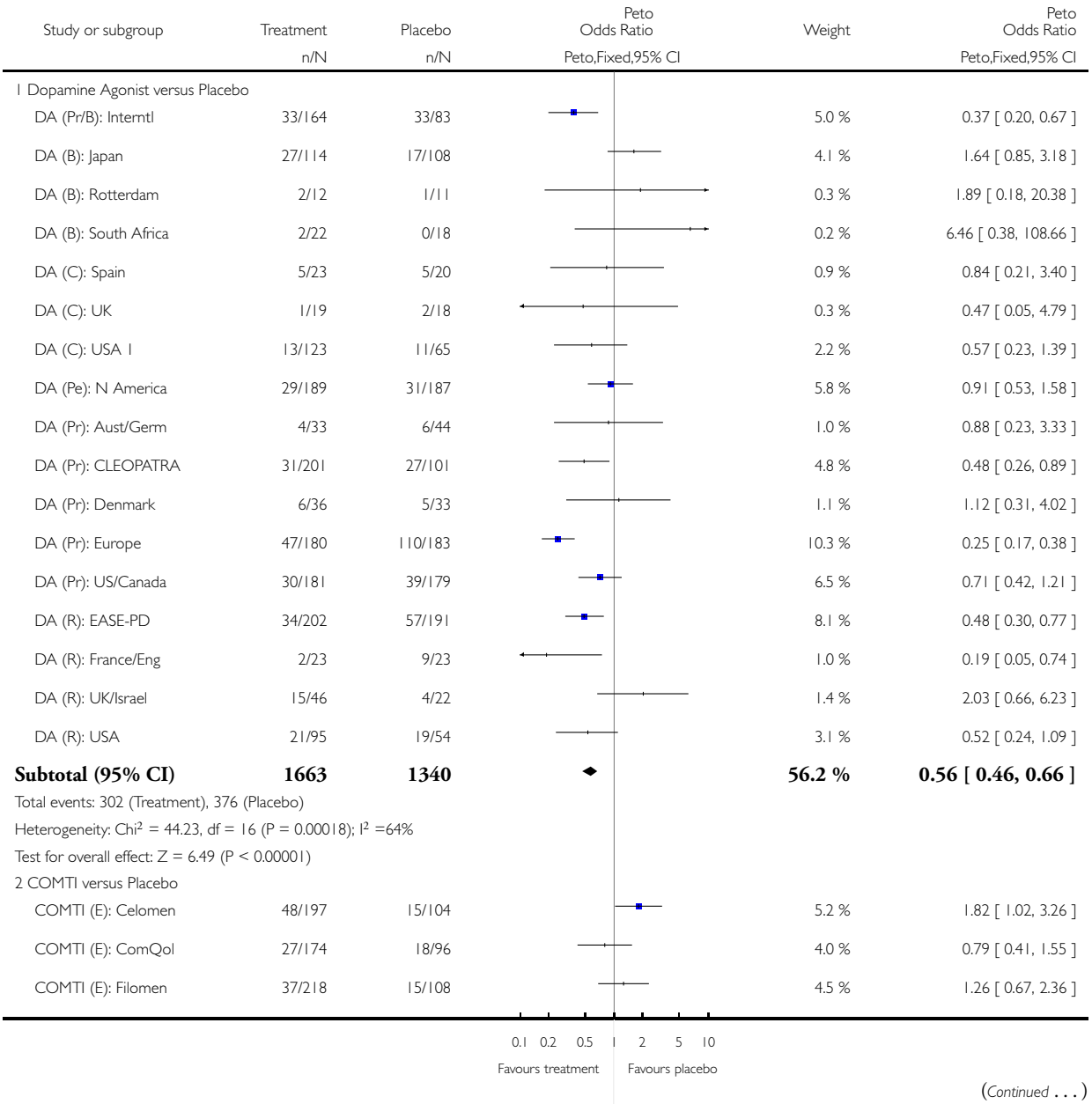


Analysis 7.1. Comparison 7 Patient Withdrawal, Outcome 1 Overall Patient Withdrawal (Adjuvant Therapy versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 7 Patient Withdrawal

Outcome: 1 Overall Patient Withdrawal (Adjuvant Therapy versus Placebo)



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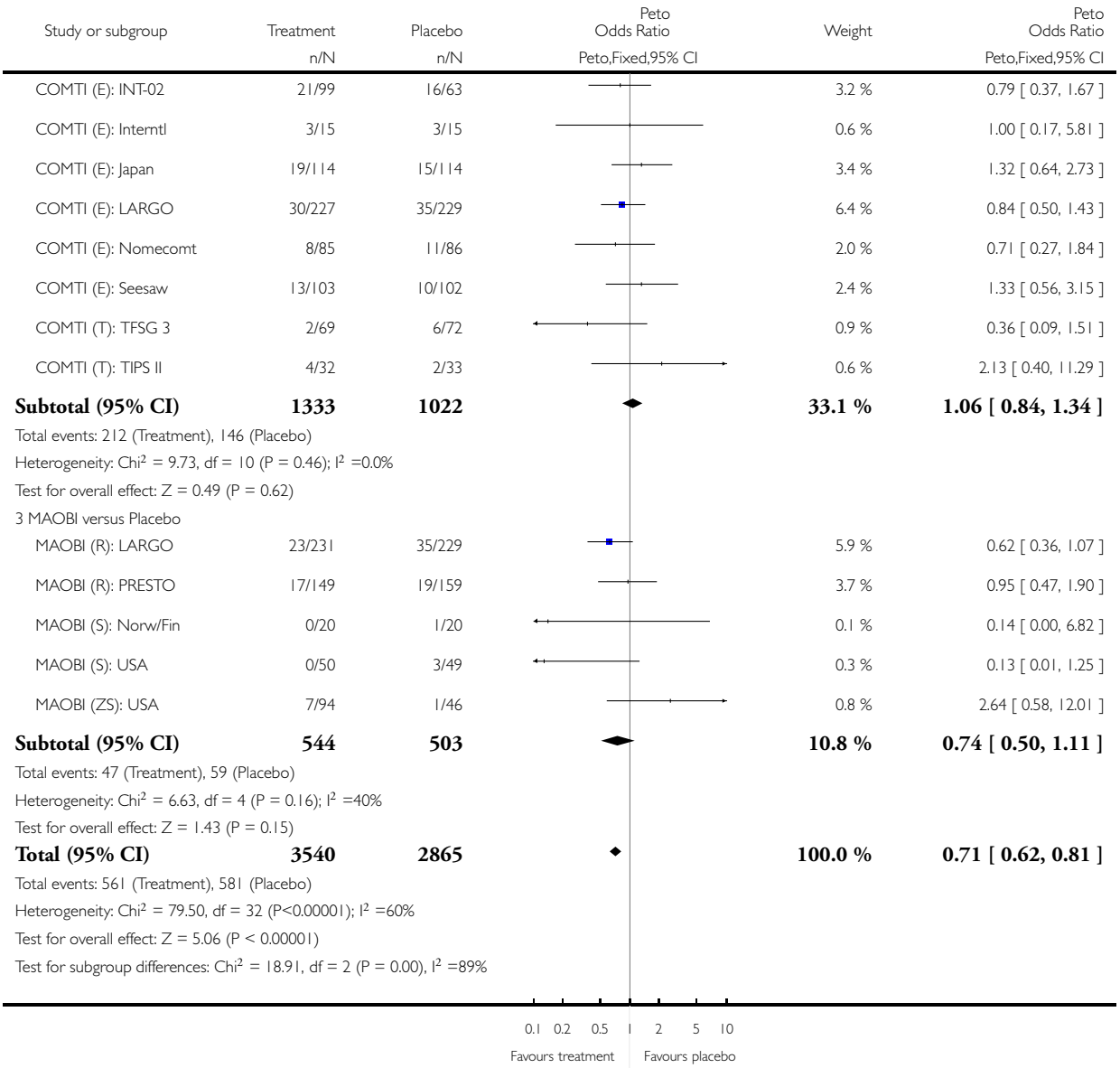


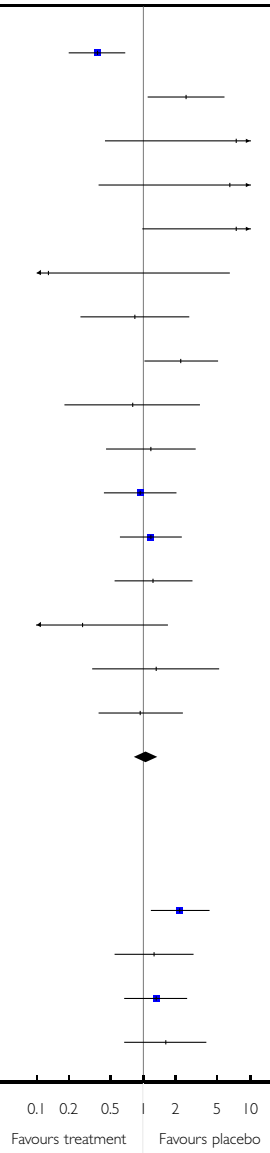
Analysis 7.2. Comparison 7 Patient Withdrawal, Outcome 2 Patient Withdrawal due to Adverse Events (Adjuvant Therapy versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 7 Patient Withdrawal

Outcome: 2 Patient Withdrawal due to Adverse Events (Adjuvant Therapy versus Placebo)

Study or subgroup	Treatment n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Dopamine Agonist versus Placebo					
DA (Pr/B): Interntl	33/164	33/83		8.7 %	0.37 [0.20, 0.67]
DA (B): Japan	18/114	7/108		4.5 %	2.53 [1.10, 5.80]
DA (B): Rotterdam	2/12	0/11		0.4 %	7.45 [0.44, 127.44]
DA (B): South Africa	2/22	0/18		0.4 %	6.46 [0.38, 108.66]
DA (C): Spain	4/23	0/20		0.7 %	7.49 [0.97, 57.53]
DA (C): UK	0/19	1/18		0.2 %	0.13 [0.00, 6.46]
DA (C): USA 1	8/123	5/65		2.2 %	0.83 [0.26, 2.71]
DA (Pe): N America	18/189	8/187		4.9 %	2.25 [1.02, 5.00]
DA (Pr): Aust/Germ	3/33	5/44		1.4 %	0.79 [0.18, 3.42]
DA (Pr): CLEOPATRA	14/201	6/101		3.3 %	1.18 [0.45, 3.08]
DA (Pr): Europe	13/180	14/183		5.0 %	0.94 [0.43, 2.06]
DA (Pr): US/Canada	21/181	18/179		7.0 %	1.17 [0.60, 2.28]
DA (R): EASE-PD	13/202	10/191		4.4 %	1.24 [0.54, 2.88]
DA (R): France/Eng	1/23	4/23		0.9 %	0.27 [0.04, 1.68]
DA (R): UK/Israel	8/46	3/22		1.6 %	1.31 [0.33, 5.17]
DA (R): USA	15/95	9/54		3.8 %	0.94 [0.38, 2.32]
Subtotal (95% CI)	**1627**	**1307**		**49.4 %**	**1.05 [0.82, 1.35]**
Total events: 173 (Treatment), 123 (Placebo)					
Heterogeneity: Chi^2 = 30.80, df = 15 (P = 0.01); I^2 =51%					
Test for overall effect: Z = 0.40 (P = 0.69)					
2 COMTI versus Placebo					
COMTI (E): Celomen	41/197	10/104		7.7 %	2.21 [1.17, 4.16]
COMTI (E): ComQol	18/174	8/96		4.3 %	1.26 [0.54, 2.93]
COMTI (E): Filomen	31/218	12/108		6.7 %	1.31 [0.66, 2.59]
COMTI (E): INT-02	17/99	7/63		3.9 %	1.61 [0.66, 3.91]



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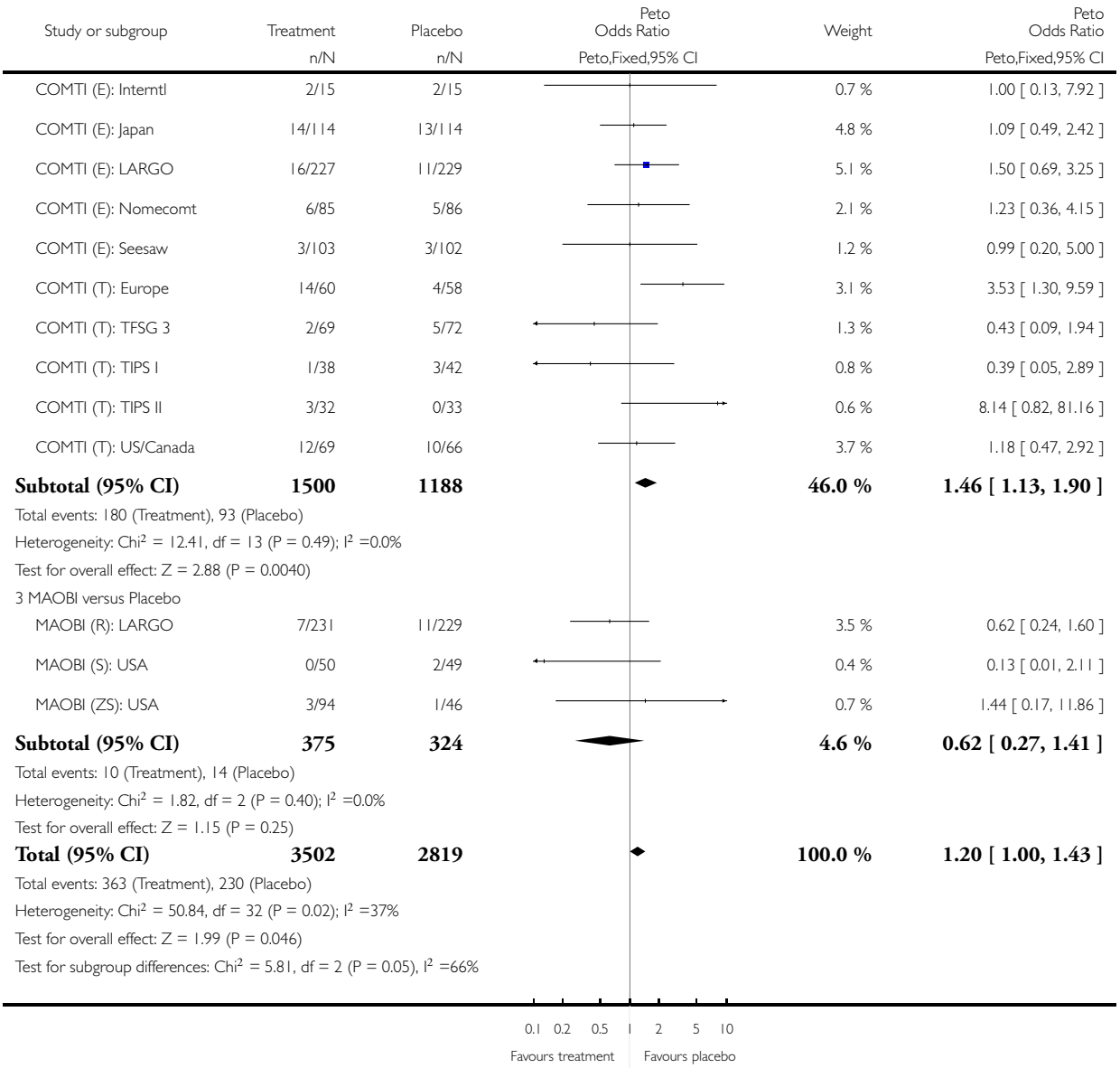
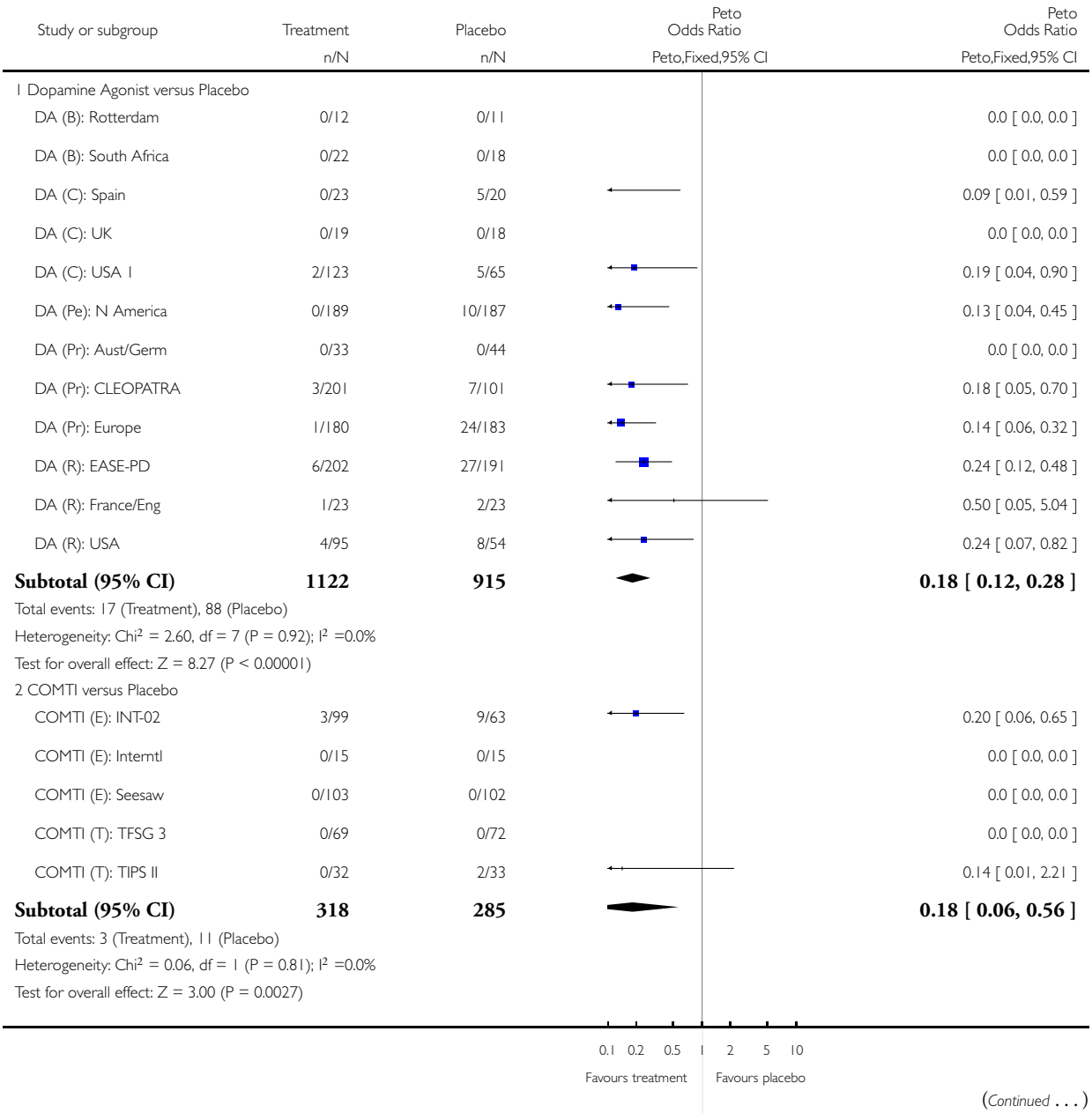


Analysis 7.3. Comparison 7 Patient Withdrawal, Outcome 3 Patient Withdrawal due to Lack of Efficacy (Adjuvant Therapy versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 7 Patient Withdrawal

Outcome: 3 Patient Withdrawal due to Lack of Efficacy (Adjuvant Therapy versus Placebo)



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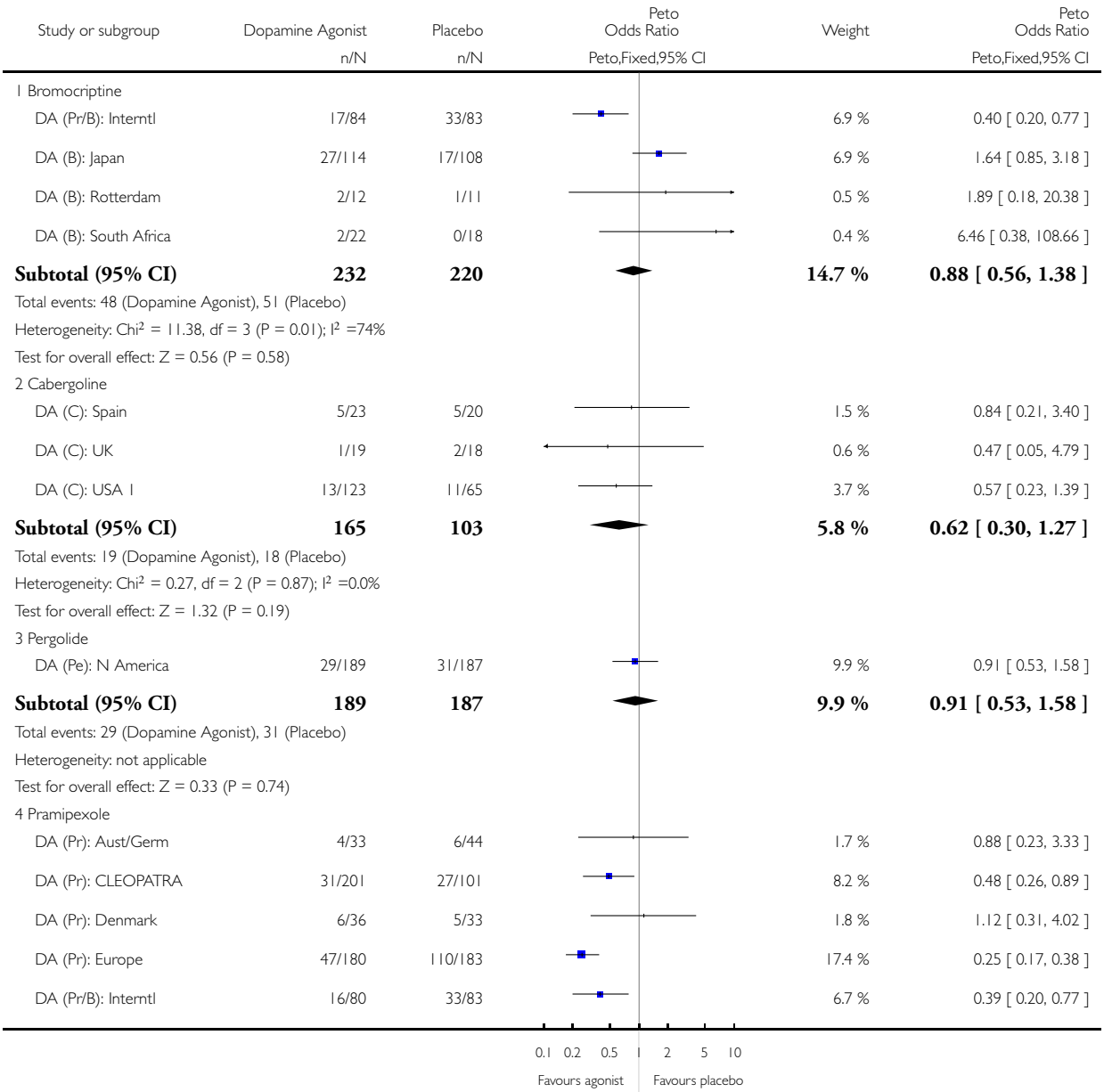
Study or subgroup	Treatment n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
3 MAOBI versus Placebo				
MAOBI (S): USA	0/50	0/49		0.0 [0.0, 0.0]
MAOBI (ZS): USA	1/94	0/46		4.43 [0.07, 287.79]
Subtotal (95% CI)	**144**	**95**		**4.43 [0.07, 287.79]**
Total events: 1 (Treatment), 0 (Placebo)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 0.70 (P = 0.48)				
Total (95% CI)	**1584**	**1295**		**0.19 [0.13, 0.28]**
Total events: 21 (Treatment), 99 (Placebo)				
Heterogeneity: Chi^2 = 4.87, df = 10 (P = 0.90); I^2 =0.0%				
Test for overall effect: Z = 8.69 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 2.21, df = 2 (P = 0.33), I^2 =10%				

Analysis 7.4. Comparison 7 Patient Withdrawal, Outcome 4 Overall Patient Withdrawal (Dopamine Agonist versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 7 Patient Withdrawal

Outcome: 4 Overall Patient Withdrawal (Dopamine Agonist versus Placebo)



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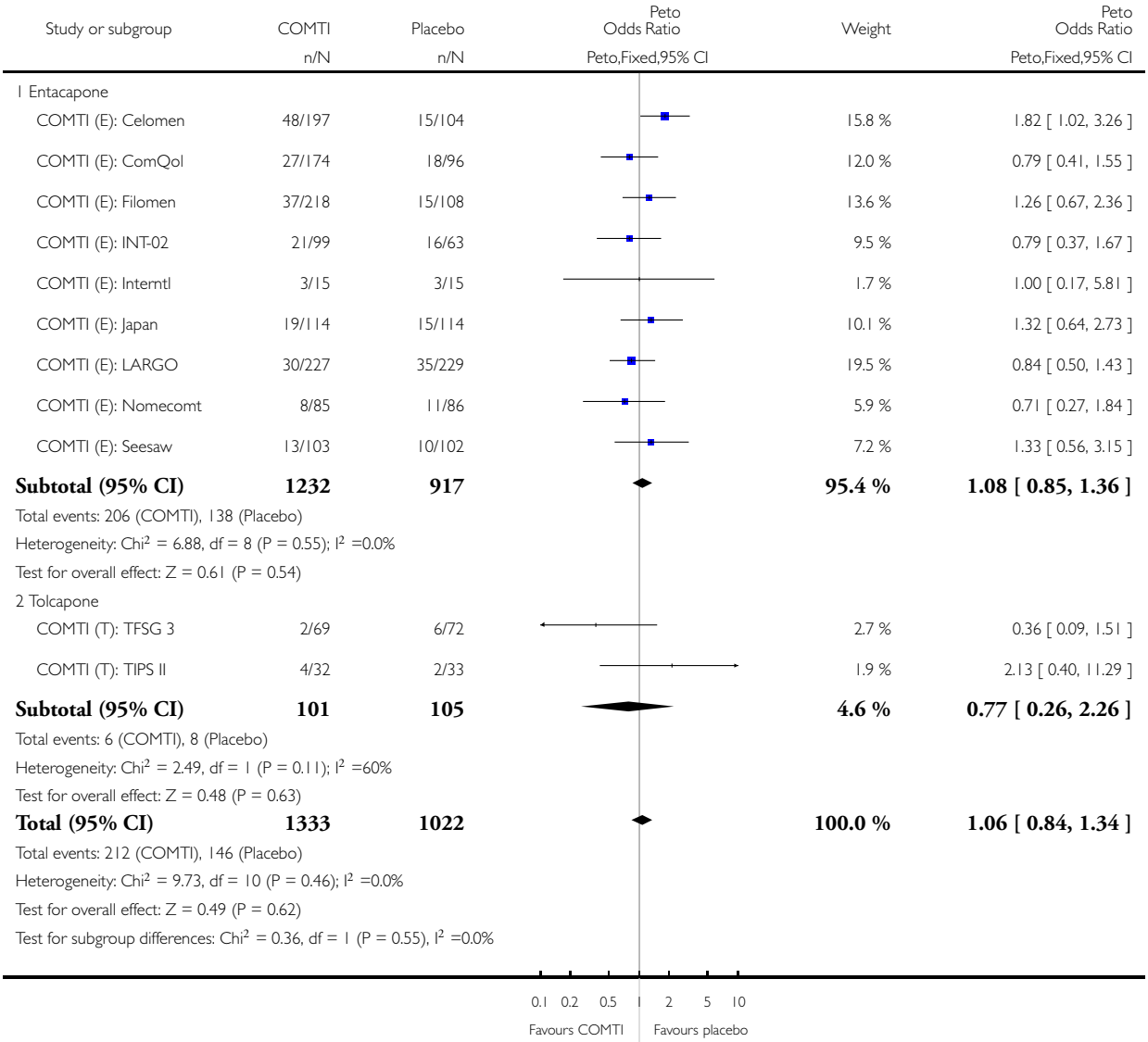
Study or subgroup	Dopamine Agonist n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
DA (Pr): US/Canada	30/181	39/179		10.9 %	0.71 [0.42, 1.21]
Subtotal (95% CI)	**711**	**623**		**46.7 %**	**0.43 [0.33, 0.55]**
Total events: 134 (Dopamine Agonist), 220 (Placebo)					
Heterogeneity: Chi^2 = 13.50, df = 5 (P = 0.02); I^2 =63%					
Test for overall effect: Z = 6.62 (P < 0.00001)					
5 Ropinirole					
DA (R): EASE-PD	34/202	57/191		13.7 %	0.48 [0.30, 0.77]
DA (R): France/Eng	2/23	9/23		1.7 %	0.19 [0.05, 0.74]
DA (R): UK/Israel	15/46	4/22		2.4 %	2.03 [0.66, 6.23]
DA (R): USA	21/95	19/54		5.3 %	0.52 [0.24, 1.09]
Subtotal (95% CI)	**366**	**290**		**23.0 %**	**0.53 [0.37, 0.76]**
Total events: 72 (Dopamine Agonist), 89 (Placebo)					
Heterogeneity: Chi^2 = 7.77, df = 3 (P = 0.05); I^2 =61%					
Test for overall effect: Z = 3.43 (P = 0.00060)					
Total (95% CI)	**1663**	**1423**		**100.0 %**	**0.55 [0.46, 0.65]**
Total events: 302 (Dopamine Agonist), 409 (Placebo)					
Heterogeneity: Chi^2 = 44.41, df = 17 (P = 0.00030); I^2 =62%					
Test for overall effect: Z = 6.80 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 11.49, df = 4 (P = 0.02), I^2 =65%					

Analysis 7.5. Comparison 7 Patient Withdrawal, Outcome 5 Overall Patient Withdrawal (COMTI versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 7 Patient Withdrawal

Outcome: 5 Overall Patient Withdrawal (COMTI versus Placebo)

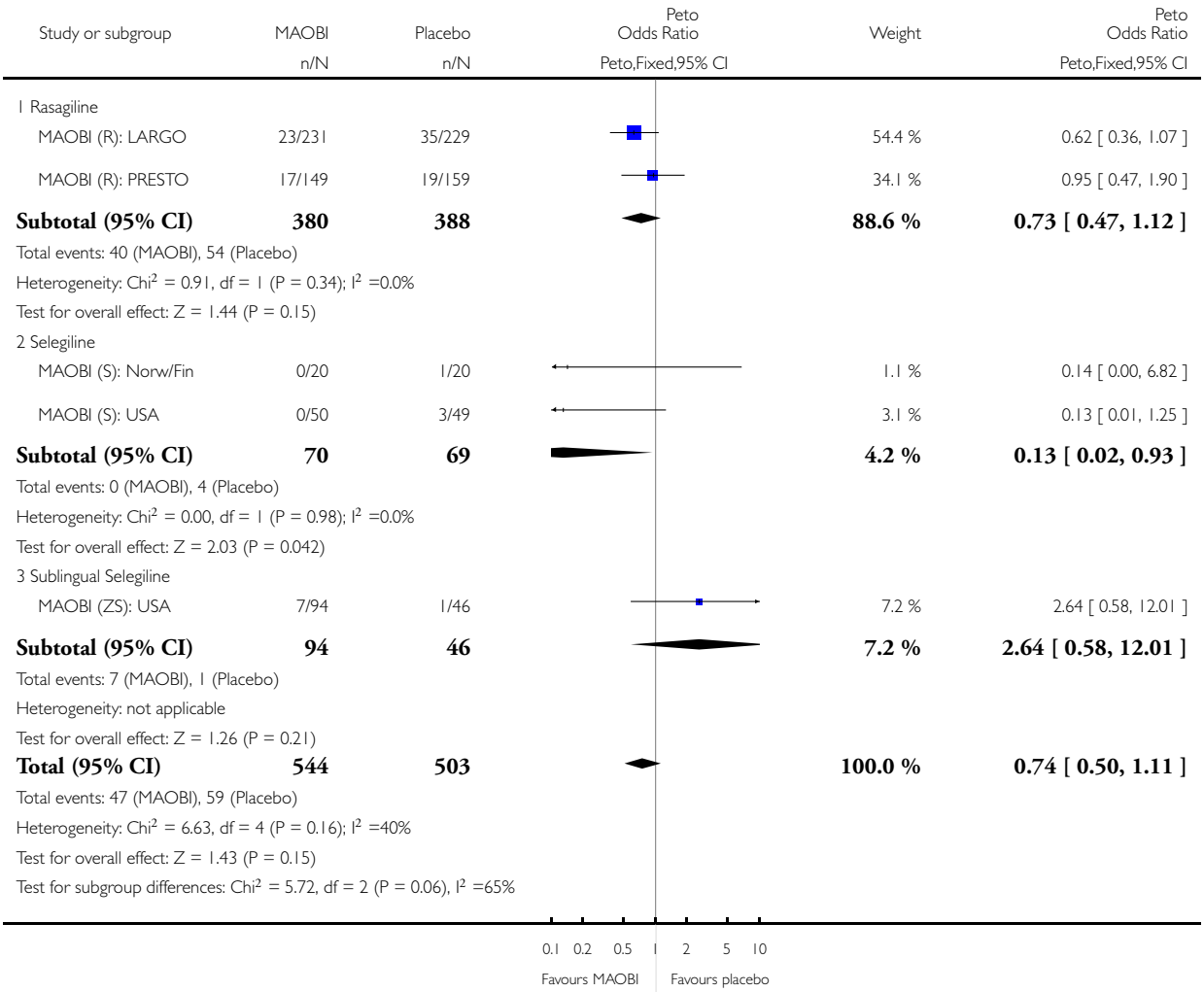


Analysis 7.6. Comparison 7 Patient Withdrawal, Outcome 6 Overall Patient Withdrawal (MAOBI versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 7 Patient Withdrawal

Outcome: 6 Overall Patient Withdrawal (MAOBI versus Placebo)

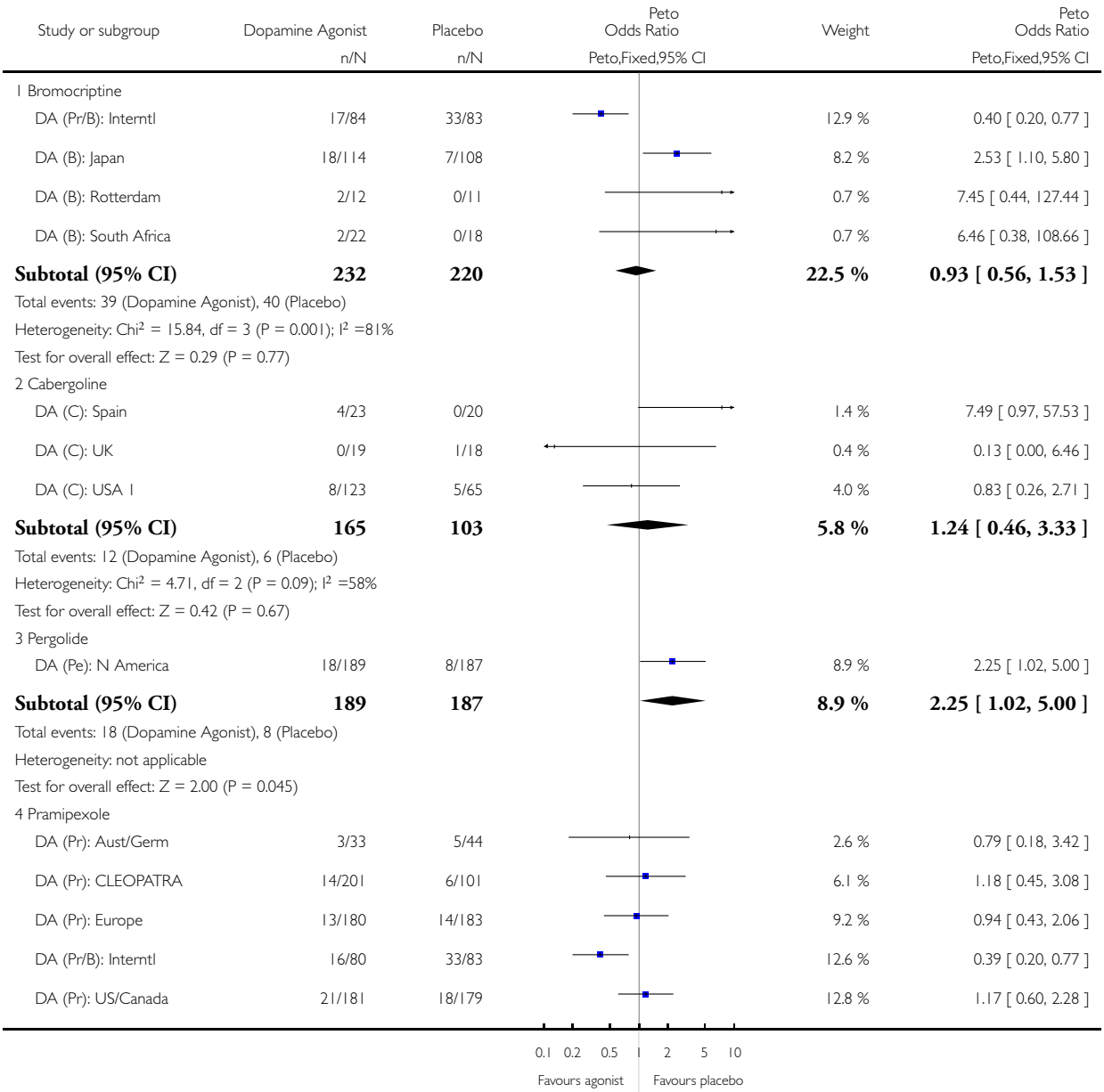


Analysis 7.7. Comparison 7 Patient Withdrawal, Outcome 7 Overall Patient Withdrawal due to Adverse Events (Dopamine Agonist versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 7 Patient Withdrawal

Outcome: 7 Overall Patient Withdrawal due to Adverse Events (Dopamine Agonist versus Placebo)



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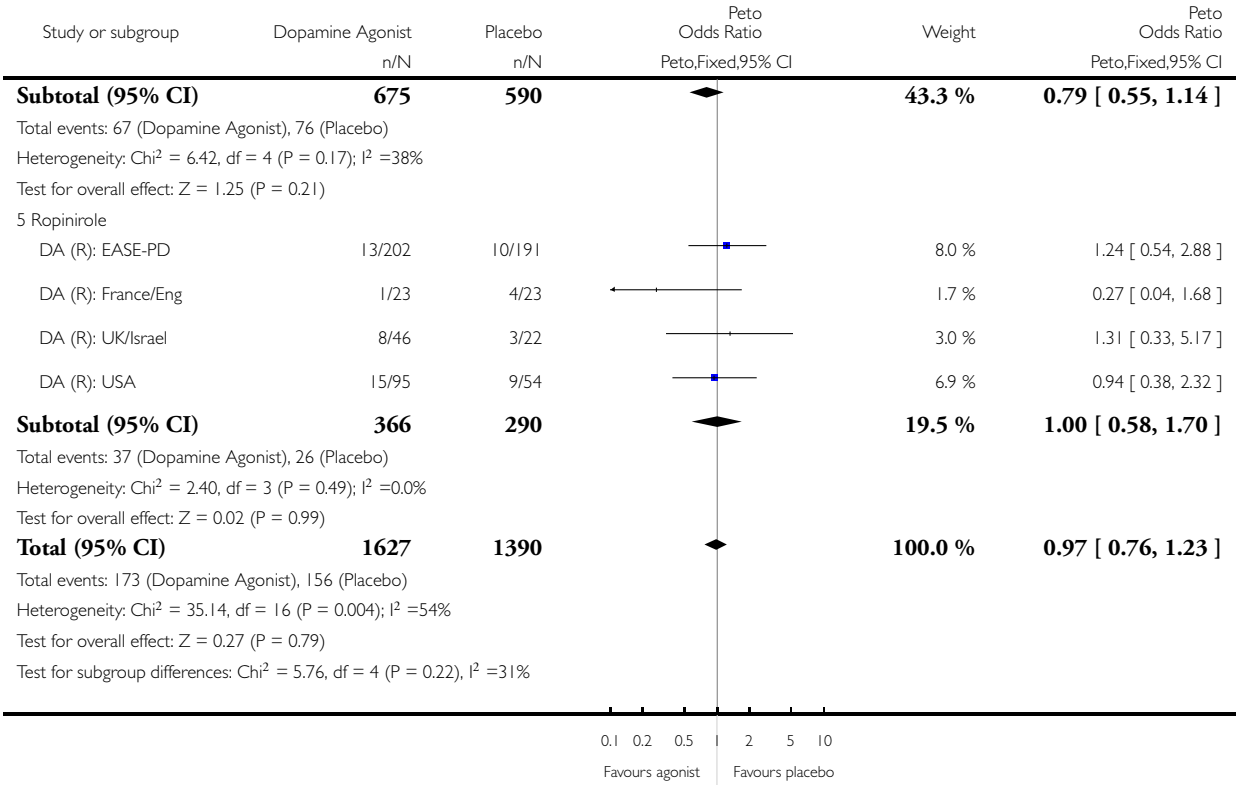
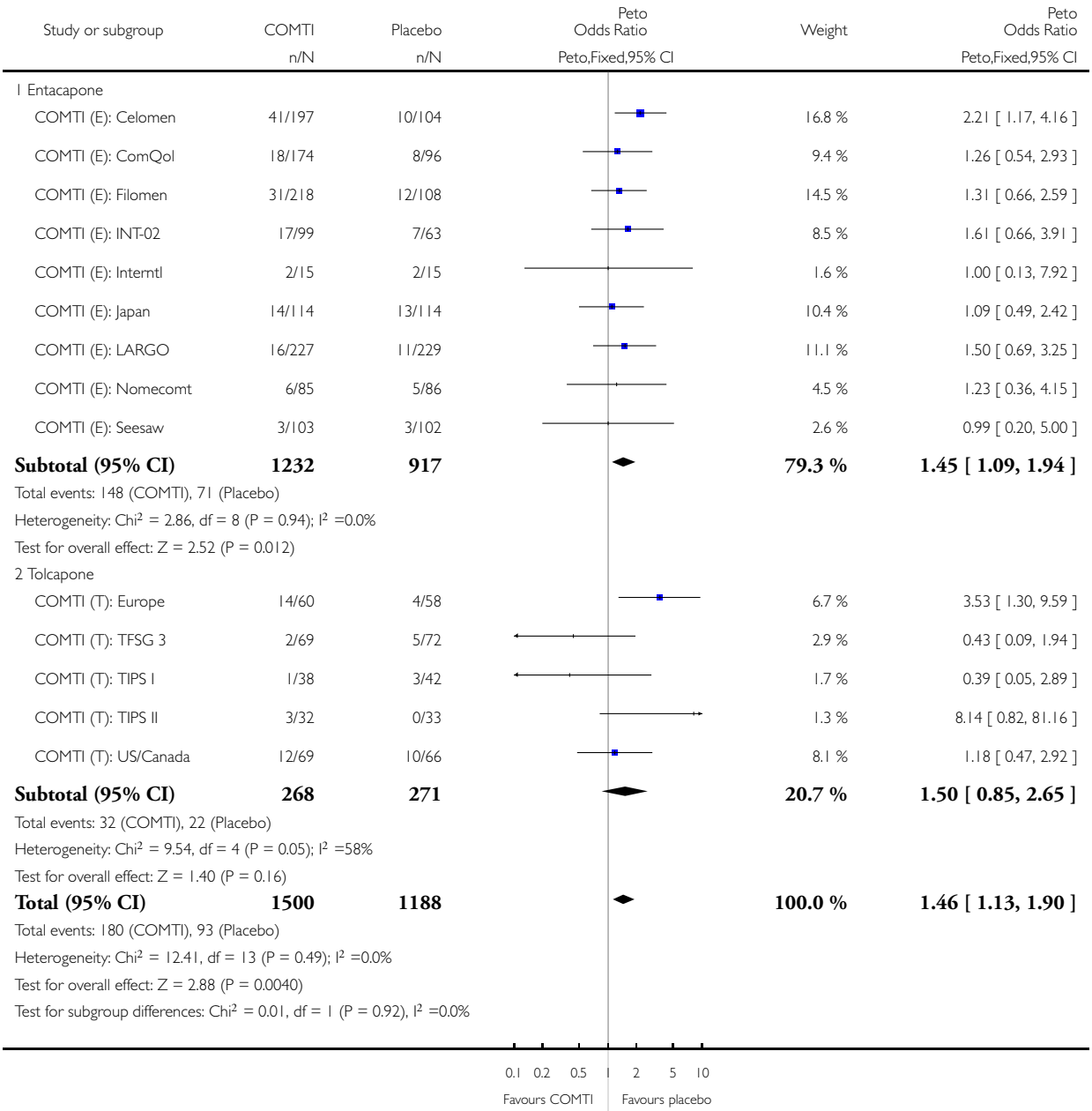


Analysis 7.8. Comparison 7 Patient Withdrawal, Outcome 8 Overall Patient Withdrawal due to Adverse Events (COMTI versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 7 Patient Withdrawal

Outcome: 8 Overall Patient Withdrawal due to Adverse Events (COMTI versus Placebo)



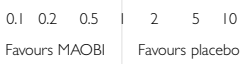
Analysis 7.9. Comparison 7 Patient Withdrawal, Outcome 9 Overall Patient Withdrawal due to Adverse Events (MAOBI versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 7 Patient Withdrawal

Outcome: 9 Overall Patient Withdrawal due to Adverse Events (MAOBI versus Placebo)

Study or subgroup	MAOBI n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Rasagiline					
MAOBI (R): LARGO	7/231	11/229		76.1 %	0.62 [0.24, 1.60]
Subtotal (95% CI)	**231**	**229**		**76.1 %**	**0.62 [0.24, 1.60]**
Total events: 7 (MAOBI), 11 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.98 (P = 0.33)					
2 Selegiline					
MAOBI (S): USA	0/50	2/49		8.7 %	0.13 [0.01, 2.11]
Subtotal (95% CI)	**50**	**49**		**8.7 %**	**0.13 [0.01, 2.11]**
Total events: 0 (MAOBI), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.44 (P = 0.15)					
3 Sublingual Selegiline					
MAOBI (ZS): USA	3/94	1/46		15.2 %	1.44 [0.17, 11.86]
Subtotal (95% CI)	**94**	**46**		**15.2 %**	**1.44 [0.17, 11.86]**
Total events: 3 (MAOBI), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.34 (P = 0.74)					
Total (95% CI)	**375**	**324**		**100.0 %**	**0.62 [0.27, 1.41]**
Total events: 10 (MAOBI), 14 (Placebo)					
Heterogeneity: Chi^2 = 1.82, df = 2 (P = 0.40); I^2 =0.0%					
Test for overall effect: Z = 1.15 (P = 0.25)					
Test for subgroup differences: Chi^2 = 1.82, df = 2 (P = 0.40), I^2 =0.0%					



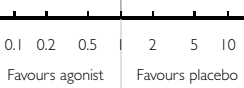
Analysis 7.10. Comparison 7 Patient Withdrawal, Outcome 10 Overall Patient Withdrawal due to Lack of Efficacy (Dopamine Agonist versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 7 Patient Withdrawal

Outcome: 10 Overall Patient Withdrawal due to Lack of Efficacy (Dopamine Agonist versus Placebo)

Study or subgroup	Dopamine Agonist n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Bromocriptine				
DA (B): Rotterdam	0/12	0/11		0.0 [0.0, 0.0]
DA (B): South Africa	0/22	0/18		0.0 [0.0, 0.0]
Subtotal (95% CI)	**34**	**29**		**0.0 [0.0, 0.0]**
Total events: 0 (Dopamine Agonist), 0 (Placebo)				
Heterogeneity: Chi² = 0.0, df = 0 (P<0.00001); I² =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 Cabergoline				
DA (C): Spain	0/23	5/20		0.09 [0.01, 0.59]
DA (C): UK	0/19	0/18		0.0 [0.0, 0.0]
DA (C): USA 1	2/123	5/65		0.19 [0.04, 0.90]
Subtotal (95% CI)	**165**	**103**		**0.14 [0.04, 0.46]**
Total events: 2 (Dopamine Agonist), 10 (Placebo)				
Heterogeneity: Chi² = 0.31, df = 1 (P = 0.58); I² =0.0%				
Test for overall effect: Z = 3.22 (P = 0.0013)				
3 Pergolide				
DA (Pe): N America	0/189	10/187		0.13 [0.04, 0.45]
Subtotal (95% CI)	**189**	**187**		**0.13 [0.04, 0.45]**
Total events: 0 (Dopamine Agonist), 10 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 3.22 (P = 0.0013)				
4 Pramipexole				
DA (Pr): Aust/Germ	0/33	0/44		0.0 [0.0, 0.0]
DA (Pr): CLEOPATRA	3/201	7/101		0.18 [0.05, 0.70]
DA (Pr): Europe	1/180	24/183		0.14 [0.06, 0.32]
Subtotal (95% CI)	**414**	**328**		**0.15 [0.08, 0.30]**
Total events: 4 (Dopamine Agonist), 31 (Placebo)				
Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² =0.0%				
Test for overall effect: Z = 5.32 (P < 0.00001)				
5 Ropinirole				



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Study or subgroup	Dopamine Agonist n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
DA (R): EASE-PD	6/202	27/191		0.24 [0.12, 0.48]
DA (R): France/Eng	1/23	2/23		0.50 [0.05, 5.04]
DA (R): USA	4/95	8/54		0.24 [0.07, 0.82]
Subtotal (95% CI)	**320**	**268**		**0.25 [0.14, 0.45]**
Total events: 11 (Dopamine Agonist), 37 (Placebo)				
Heterogeneity: Chi^2 = 0.37, df = 2 (P = 0.83); I^2 =0.0%				
Test for overall effect: Z = 4.59 (P < 0.00001)				
Total (95% CI)	**1122**	**915**		**0.18 [0.12, 0.28]**
Total events: 17 (Dopamine Agonist), 88 (Placebo)				
Heterogeneity: Chi^2 = 2.60, df = 7 (P = 0.92); I^2 =0.0%				
Test for overall effect: Z = 8.27 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 1.81, df = 3 (P = 0.61), I^2 =0.0%				

Analysis 7.11. Comparison 7 Patient Withdrawal, Outcome 11 Overall Patient Withdrawal due to Lack of Efficacy (COMTI versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 7 Patient Withdrawal

Outcome: 11 Overall Patient Withdrawal due to Lack of Efficacy (COMTI versus Placebo)

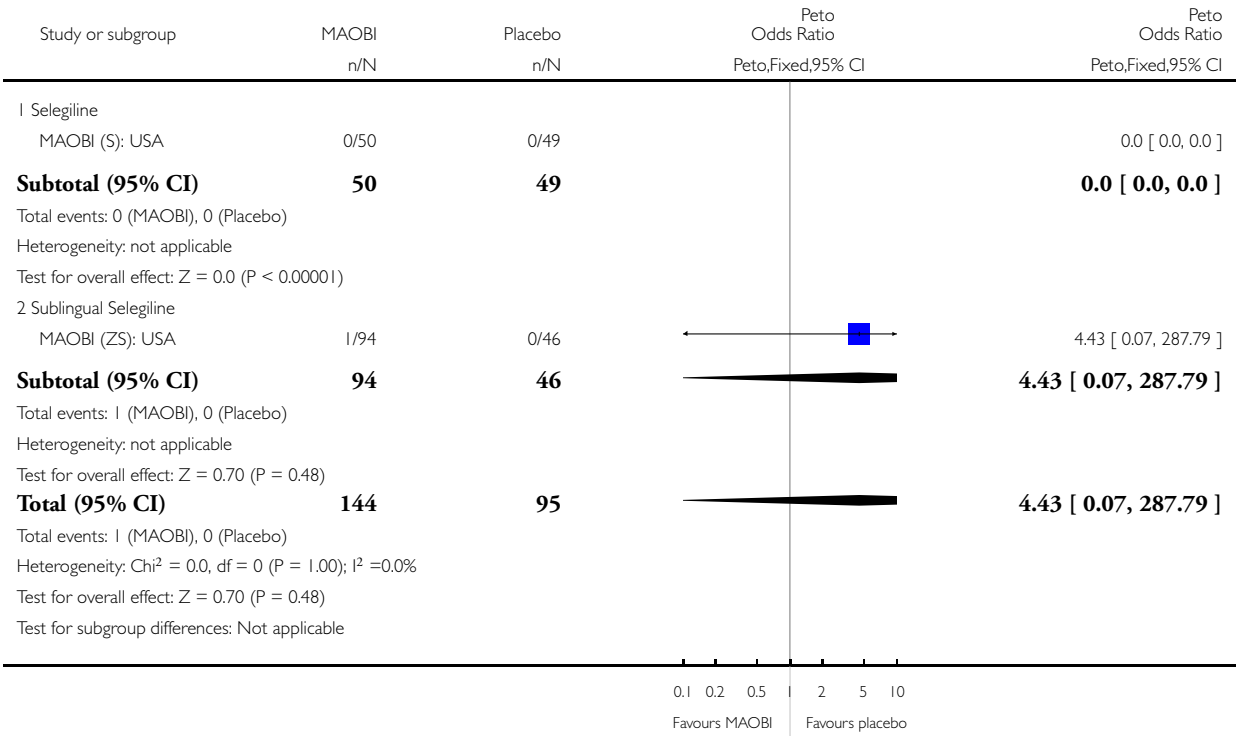
Study or subgroup	COMTI n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Entacapone				
COMTI (E): INT-02	3/99	9/63		0.20 [0.06, 0.65]
COMTI (E): Interntl	0/15	0/15		0.0 [0.0, 0.0]
COMTI (E): Seesaw	0/103	0/102		0.0 [0.0, 0.0]
Subtotal (95% CI)	**217**	**180**		**0.20 [0.06, 0.65]**
Total events: 3 (COMTI), 9 (Placebo)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 2.66 (P = 0.0079)				
2 Tolcapone				
COMTI (T): TFSG 3	0/69	0/72		0.0 [0.0, 0.0]
COMTI (T): TIPS II	0/32	2/33		0.14 [0.01, 2.21]
Subtotal (95% CI)	**101**	**105**		**0.14 [0.01, 2.21]**
Total events: 0 (COMTI), 2 (Placebo)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 1.40 (P = 0.16)				
Total (95% CI)	**318**	**285**		**0.18 [0.06, 0.56]**
Total events: 3 (COMTI), 11 (Placebo)				
Heterogeneity: Chi^2 = 0.06, df = 1 (P = 0.81); I^2 =0.0%				
Test for overall effect: Z = 3.00 (P = 0.0027)				
Test for subgroup differences: Chi^2 = 0.06, df = 1 (P = 0.81), I^2 =0.0%				

Analysis 7.12. Comparison 7 Patient Withdrawal, Outcome 12 Overall Patient Withdrawal due to Lack of Efficacy (MAOBI versus Placebo).

Review: Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications

Comparison: 7 Patient Withdrawal

Outcome: 12 Overall Patient Withdrawal due to Lack of Efficacy (MAOBI versus Placebo)



WHAT'S NEW

Last assessed as up-to-date: 29 March 2009.

Date	Event	Description
1 December 2009	Amended	Addressing reviewers comments

HISTORY

Protocol first published: Issue 2, 2008

Review first published: Issue 7, 2010

Date	Event	Description
20 March 2009	Amended	Addressing co-authors comments
24 July 2008	Amended	Converted to new review format
13 June 2008	Amended	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Rebecca Stowe contributed to the design of the protocol and was involved in data extraction, analysis and interpretation of the review.

Natalie Ives contributed to the design of the protocol and was involved in data extraction, analysis and interpretation of the review.

Carl Clarke contributed to the design of the protocol and was involved in data extraction, analysis and interpretation of the review.

Kelly Handley contributed to data extraction and analysis of the review.

Alexandra Furmston contributed to data extraction of the review.

Katherine Deane contributed to data extraction and analysis of the review.

JJ van Hilten contributed to the design of the protocol and was involved in data extraction, analysis and interpretation of the review.

Keith Wheatley contributed to the design of the protocol and was involved in data analysis and interpretation of the review.

Richard Gray contributed to the design of the protocol and was involved in data analysis and interpretation of the review.

All the authors reviewed and approved the final version of the paper.

DECLARATIONS OF INTEREST

Carl Clarke has received payments for consultancy, lecture fees and travel from Boehringer-Ingelheim, GlaxoSmithKline, Lundbeck, Orion, Teva, UCB and Valeant. Carl Clarke, Richard Gray, Natalie Ives and Keith Wheatley are either recruiting or involved in the running of the PD MED trial.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Parkinson's Disease Society, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Quality of life and health economic outcome data also assessed in the review.

INDEX TERMS

Medical Subject Headings (MeSH)

Antiparkinson Agents [adverse effects; *therapeutic use]; Catechol O-Methyltransferase [*antagonists & inhibitors]; Chemotherapy, Adjuvant; Dopamine Agonists [adverse effects; *therapeutic use]; Dyskinesias [*drug therapy; etiology]; Levodopa [therapeutic use]; Monoamine Oxidase Inhibitors [adverse effects; *therapeutic use]; Parkinson Disease [complications; *drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans