

2015

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Harrison, J. (2015) 'The efficacy of Levodopa+DDC inhibitor+Entacapone versus Levodopa+DDC inhibitor+Placebo in Parkinson's disease: an intervention review', The Plymouth Student Scientist, 8(2), p. 48-84.

<http://hdl.handle.net/10026.1/14097>

The Plymouth Student Scientist
University of Plymouth

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The efficacy of Levodopa+DDC inhibitor+Entacapone versus Levodopa+DDC inhibitor+Placebo in Parkinson's disease: an intervention review

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Abstract

Parkinson's disease (PD) has many possible treatment options. The main therapy uses a drug called levodopa. However after prolonged use, this drug begins to wear off and becomes less effective. Therefore additional drugs are needed to help ensure the patient is comfortable and to aid the relief of symptoms that can often occur. The addition of the COMT inhibitor, entacapone, aims to reduce motor symptoms and smooth out fluctuations that can sometimes be experienced with levodopa therapy. These can include bradykinesia, which is slowness of movement and help to control the resting tremor that is often associated with PD. The aim of this review is to determine if adding entacapone to existing levodopa therapy helps to improve patients motor symptoms and improve their ability to carry out every day activities; these outcomes will be measured using the unified Parkinson's disease rating scale UPDRS.

Background

Levodopa is known as the 'gold standard' in the treatment of Parkinson's Disease (PD). Levodopa is a precursor molecule of dopamine. It crosses the blood brain barrier (BBB) and is taken up by substantia nigra neurons and converted into dopamine through the dopa decarboxylase and catechol-O-methyltransferase pathway. Levodopa is practically always administered with a dopa-decarboxylase inhibitor (DDCI), usually carbidopa and sometimes benserazide. The addition of the DDCI prevents conversion of levodopa to dopamine in the periphery by blocking the enzymatic pathway (Chen 2007).

Levodopa/carbidopa is the most prescribed Parkinson's Disease (PD) medication, (Hauser 2009). A fundamental limitation of this treatment is the development of motor fluctuations and dyskinesias. This is thought to be due to the short half-life of levodopa which leads to pulsatile stimulation of postsynaptic dopamine receptors.

After prolonged use of Levodopa the efficacy of the drug is reduced, hence the need for additional drugs. A number of available drugs can be added to levodopa but one of the most effective is the addition of a catechol-O-methyltransferase inhibitor (COMT inhibitor). COMT inhibitors can smooth out fluctuations in plasma concentrations of levodopa after oral administration. Although there is a selection available, entacapone is thought to be tolerated the best. It is used as an adjunct to each daily levodopa/DDCI dose, it extends the half-life of levodopa and this increases the bioavailability of the drug; consequently prolonging each dose of levodopa (Maranis 2011).

By combining Levodopa/DDCI/Entacapone it prevents degradation of the agents in the plasma and therefore allowing prolonged therapeutic levels of the drugs in the brain.

Description of the condition

Parkinson's Disease (PD) is a chronic progressive neurodegenerative disease that affects the central nervous system (CNS). It was first identified by Dr James Parkinson in 1817 and was described as 'shakey palsy' due to the nature and symptoms that can be displayed during the disease (Lo 2007). Symptoms that can occur can be divided into 2 categories: motor and non-motor symptoms. Typical motor symptoms that can be experienced include: bradykinesia, rigidity, tremor, and postural instability with an asymmetric onset spreading to become bilateral with time. Other motor features include: gait and posture changes that can be seen as rapid shuffling steps with a forward-flexed posture when walking, speech and swallowing difficulties, masklike facial expression and micrographia (Korczyn 2010). Non-motor symptoms that can be observed can include: depression, sleep disturbance, sensory abnormalities, autonomic dysfunction, and cognitive decline.

PD affects over 6 million people worldwide making it the second most common neurodegenerative disease after Alzheimers (Ford 2010). PD has a significant impact on disability and quality of life, and its prevalence is thought to increase along with life expectancy (Braga 2014). Risk factors such as aging, genetic susceptibility, and environmental factors all play a role in the onset of the pathogenic process but how these interlink to cause neuronal loss is unknown (Dexter 2013). Currently, there is no known cure for PD, consequently, treatments available aim to reduce the symptoms and help patients to deal with their disease. PD is characterized by the presence of intracytoplasmic inclusions from Lewy bodies and the depletion of midbrain pigmented dopamine containing neurons in the region of the substantia

nigra. It is thought that 80% of dopaminergic neurons are already irreversibly destroyed when the first symptoms of PD become significantly visible (Singh 2007). PD cannot currently be diagnosed until there is extensive loss of the dopaminergic neurons from the substantia nigra pars compacta (snpc), however in recent years of research it has become apparent that pathology of PD doesn't actually begin in the snpc. It is thought that Lewy body pathology and the decomposition of a-synuclein originate in the olfactory bulb and lower brain stem and from there they spread to the mid brain and cortical regions, eventually reaching the snpc (Korczyn 2010).

As with many drugs there are often side effects produced. Many patients that are treated with levodopa often experience motor complications and fluctuations, as well as dyskinesias. If these symptoms arise clinicians may choose to add additional drugs to the patients existing therapy. With such a competitive market it can be difficult to conclude which drug is best from the vast variety available. This choice can often be dependent on each patient's individual circumstances as well as other factors. A selection of the drugs available are: Monoamine oxidase (MAO) inhibitors, dopamine agonists, catechol-O-methyltransferase inhibitor (COMT inhibitor). MAO inhibitors are thought to slow down the deterioration of dopamine and reduce oxidative stress in neurons, the most commonly used are selegiline and rasagiline. However in drug trials they have often produced contradictory findings that lack reproducible results (Williams 2010). Dopamine agonists are an option for the treatment of PD as an alternative to levodopa. Even though they do provide symptomatic benefit, they are associated with more side effects than standard levodopa therapy and can include: hallucinations, edema, impulse and control disorders and sudden sleep attacks. On the other hand, motor fluctuations and dyskinesias are less common from dopamine agonists compared to levodopa (Hickey 2011).

There are also non-pharmacological treatments available such as cognitive behavioural therapy, and deep brain stimulation. These two different approaches have been available for a while but recent advances and technologies are always being created.

Description of the intervention

It was in the 1990's that the structures of the 2 isoforms of the COMT enzyme and COMT gene were identified. The COMT gene is located on chromosome 22, band q11.2 and consists of 6 exons (Lee 2002). COMT enzyme is located throughout the body and can be found in high concentrations in peripheral organs such as the liver, kidney and intestines. The main function of COMT is to inactivate biologically active or toxic catechols. In the presence of Mg^{2+} it catalyses the transfer of the methyl group of S-adenosyl-Z-methionine to one of the hydroxyl groups of the catechol substrate; levodopa and dopamine are substrates of COMT.

COMT enzyme can catalyse the metabolism of levodopa to 3-O-methyldopa, therefore COMT inhibitor drugs prolong the maintenance of serum levodopa levels to produce a longer and more stable clinical levodopa response therefore leading to less frequent fluctuations in the patients' clinical condition. The 2 main COMT inhibitors that are used in practise are entacapone and tolcapone. Entacapone is thought to be best tolerated as tolcapone has been associated with liver toxicity and is currently only available in the USA (Maranis 2011).

Entacapone is a specific, potent and reversible COMT inhibitor with a half-life elimination of 1.5-3.5 hours after oral administration. The short half-life and

elimination combined with the reversible nature of this COMT inhibitor allows safe co-administration of entacapone with every levodopa/DDCI dose. It has been demonstrated in previous studies that entacapone significantly increases the average area under curve (AUC) of levodopa (Heikkinen 2002).

One of the main side effects of levodopa treatment is the development of motor complications; they develop from the progressive loss of dopaminergic nerve terminals on the striatum which leads to reduced dopamine storage capacity.

How the intervention might work

Inhibition of COMT by entacapone prolongs the half-life of levodopa, which is associated with improved clinical efficacy in PD patients. Extending the half-life of levodopa using entacapone allows delivery of the drug in a less pulsatile way, consequently allowing the benefit of levodopa with a decreased risk of motor complications compared to levodopa alone (Marin et al 2008). Although levodopa can cross the blood brain barrier when administered on its own, only 1% reaches the central nervous system; this is due to rapid metabolism by the enzymatic pathways dopa-decarboxylase and catechol-O-methyltransferase. Therefore, levodopa is almost always administered with a DDC inhibitor which increases the amount of levodopa that reaches the brain. The addition of the COMT inhibitor entacapone is used to prevent the levodopa metabolism to 3-O-methyldopa as this is a harmful metabolite of levodopa (Bugamelli 2011). Consequently it is thought that when the combination of the 3 drugs: Levodopa+DDCI+entacapone is administered there will be sustained plasma levels of levodopa result in more constant dopaminergic stimulation in the brain, leading to a greater reduction in the manifestations of parkinsonian syndrome. This intervention will analyse the efficacy of entacapone as an adjunct to levodopa+DDCI therapy through the primary outcome measuring UPDRS II+III.

Why it is important to do this review

It is important to do this review as the last meta-analysis in this area was by Stoewe 2010, therefore making it 4 years out of date. It was important to update this with more recent studies to see if the same results are still found. This review includes extremely recent data (Tolosa 2013); this paper has only been published online to date, and by including this article along with others that have not been included in previous meta-analyses it gives a new perspective. By combining UPDRS scores II and III it gives a collaboration of the patient and clinician viewpoints therefore producing a well-rounded overall score for improvement/effectiveness of the drug being tested.

Objectives

The objective of this meta-analysis is to determine if the COMT inhibitor, Entacapone, is a beneficial adjunct to Levodopa in the treatment of PD with regard to the UPDRS looking at combined scores II and III. Part II of the UPDRS is a self-evaluation of activities of daily life (ADL), part III is a clinician scored monitored motor evaluation.

Methods

Criteria for considering studies for this review

Types of studies

All randomised, double-blind trials comparing standard levodopa treatment (levodopa+DDCI) against levodopa with the addition of the adjunct entacapone (levodopa+DDCI+entacapone), a COMT inhibitor were considered for this study.

Types of participants

Patients with a clinical diagnosis of Idiopathic Parkinson's Disease were included in the study. All patients had been using levodopa treatments previously and needed smoothing out of the treatment as they were experiencing 'wearing off' and fluctuations. Their existing PD medications had to be stable for at least 4 weeks prior to randomisation of the experiment. Ages of the participants ranged from 30-80.

Types of interventions

Levodopa+DDCI+entacapone was compared to levodopa+DDCI+(placebo). Entacapone was administered with levodopa plus the DDCI. The DDCI was usually carbidopa, in some studies benserazide was used instead. Many of the studies used placebo in the control group; however, as all the studies were double blind and in both treatment groups the medication was administered in one pill the identity of the treatment group was concealed in all cases.

Types of outcome measures

The outcome measures were the UPDRS II+III scores combines. The adverse effect, dyskinesia, was also measured.

Primary outcomes

The primary outcome of this meta-analysis is the combined UPDRS II+III scores. The UPDRS was originally developed in the 1980s and is now the most widely used rating scale of PD (Gotez 2008). Part II of the UPDRS- activities of daily living is a self-assessed score completed by the patient. Filled out through a questionnaire the patient judges their own ability to successfully perform certain tasks. These include: speech, salivation, handwriting, cutting food, dressing, hygiene, moving in bed and altering bed clothes, walking, tremor, and any additional sensory complaints that are related to PD. Part III is a clinician scored motor analysis of the patient. The areas a physician would rate in each patient are: speech, facial expression, tremor at rest, rigidity, finger taps, hand movements, rapid alternating movements of hands, leg agility, rising from a chair, posture, gait, body bradykinesia and hyperkinesia. For both UPDRS II and III the rating is completed on a scale of 0-4. A score of zero indicates there is not a problem, whereas a score of 4 would indicate severe impairment of the task.

By choosing to combine scores II+III it demonstrates a broader picture of health of the patient from perspectives of the clinician and the patient creating a well-balanced score and opinion. There are other sections to the UPDRS, however they are not relevant to this meta-analysis in the outcomes and objectives that this analysis wishes to achieve and would not aid or effect the decision and efficacy of the treatment.

Secondary outcomes

The secondary outcome observes the adverse effect dyskinesia and how many patients experienced it.

Search methods for identification of studies

Electronic searches

All the studies were found online using either PUBMED or Primo.

Searching other resources

Studies that were unavailable were requested through the ILL (inter library loan system), and suitable studies that matched the criteria were used in the meta-analysis.

Data collection and analysis

In some of the articles UPDRS scores II and III were separate. I chose to combine the scores and not enter them as separate entities as I wanted to gain a realistic effect of the treatment. UPDRS III was a measurement taken by the clinician whereas UPDRS II is a patient evaluation of activities of daily life. By combining the scores it gives a broader overview from all perspectives and a true analysis.

There are two separate primary outcomes in this analysis. Analysis 1.1 (figure 1) is a dichotomous outcome; a risk ratio statistical analysis was carried out with fixed effects at a 95% confidence interval. Analysis 1.2 (figure 2) is a continuous analysis, the standard mean difference was the statistical method used with random effects and a confidence interval of 95%. Analysis 1.3 (figure 3) was a dichotomous outcome that used the statistical analysis risk difference with fixed effects at a 95% confidence interval.

Selection of studies

My first point of search was through the University of Plymouth's library search tool for journals, PRIMO. From there I accessed PubMed. My first criteria I looked for was COMT inhibitors in the treatment of PD. I narrowed my search to focus on the drug entacapone. To ensure my meta-analysis was original I searched for the most up to date studies I could find. I did this through requesting an inter-library-loan to receive journal articles that Plymouth University was not subscribed to. Through this method I was able to access the very recent Tolosa 2013 article which was critical to my analysis. When searching through journals and as I progressively narrowed my search to make it unique, I discarded studies that didn't match my specification, for example if they did not contain both UPDRS II and III scores.

Data extraction and management

Extracted data included the UPDRS II and III scores, also dyskinesia data in adverse effects for both control and placebo. All details of each experiment was recorded in the 'characteristics of study' tables and 'risk of bias' tables using the Review Manager 5.2 programme. I was careful to research and record every relevant detail to each study, including all decimal places and standard deviations.

Assessment of risk of bias in included studies

Any potential bias in the studies included in the analysis was recorded in the 'risk of bias' tables. Each section to the table covered a different aspect of the study where potential bias could occur. It was either rated as 'low, unclear or high risk' and relevant evidence to support this was included where required.

Measures of treatment effect

I used a number of different statistical assessments to present the data. Analysis 1.1 used dichotomous data which was analysed using a risk ratio (RR) with fixed effects at a 95% confidence interval (CI). The relative risk ratio (RRR) and the number needed to treat (NNT) were calculated from the data to provide an absolute measure of treatment effect.

Analysis 1.2 measured a continuous outcome. The mean difference was measured and random effects were used at a 95% CI as it weights the studies more evenly than fixed effects option. Random effects is more beneficial for smaller studies, analysis 1.2 has 2,656 participants making it quite small in number.

Analysis 1.3 used dichotomous data and examined the RD with fixed effects at a 95% CI. The NNT and absolute risk reduction were calculated.

All outcomes were assessed using Rev Man 5.2 at a 95% confidence interval.

Unit of analysis issues

All of the studies in this meta-analysis used consistent units throughout. Combined UPDRS II+III scores were used in the primary outcome. When the units were not already reported as a combined score UPDRS II scores were added to UPDRS III scores to create the final outcome measure I would be using. The number of patients experiencing dyskinesia side effects was the secondary outcome. This was consistent in all papers and was given as a number of patients who experienced this side effect.

Dealing with missing data

Myllyla 2001 was the only paper with reported unaccounted missing data. This paper did not state the baseline UPDRS II+III scores, it only stated the scores at the end of the study. I was therefore able to include this study in analysis 1.1 which just examined the UPDRS scores at the end of the study. In analysis 1.1 all the UPDRS II+III scores at the end of each individual study were compared. However this study was excluded from analysis 1.2 as there was no baseline UPDRS scores therefore I was unable to calculate an overall change in the study period.

Other studies reported excluded data, but there were no other cases of missing data without explanations. If any data had gone missing as the case in Olanow 2004, it was reported in the article. Olanow 2004 explained that those patients whose data had been lost were not analysed or included with any results in any aspect, and the patient was completely excluded and no partial data was included.

Assessment of heterogeneity

I^2 is a percentage that describes the variability of an effect to determine if it is due to heterogeneity rather than sampling error (due to chance). It is calculated using the chi squared statistic and degrees of freedom and is able to quantify inconsistencies across the range of studies. In the presence of heterogeneity a random effects outcome weighs the studies more equally than a fixed effects analysis. A 'fixed effects analysis' ignores heterogeneity, in this case as seen in analysis 1.1 and 1.3 the p value is interpreted instead. The p value for heterogeneity for analysis 1.1 of $p=0.005$ suggests that the observed effect is very unlikely to have arisen purely by chance. The P value for heterogeneity for analysis 1.4 of $p=0.00003$ also suggests that the observed effect is very unlikely to have arisen purely by chance. The I^2 value from analysis 1.2 (figure 2) =74%. When a value is between 50-90% it is thought

there may be substantial heterogeneity. Heterogeneity can be due to outliers in 1 or 2 studies that conflict with the other studies. The Tau^2 value is also reported in random effects analysis, it is an estimate of the variance between studies. In analysis 1.2 (figure 2) the $\text{tau}^2=11.0$.

Assessment of reporting biases

Myllyla (2001) was the only study to display incomplete outcome data (this can be seen clearly in Figure 4). Myllyla failed to include the UPDRS scores at the baseline; therefore this study was unable to be included in Figure 2 (analysis 1.2). Brooks did not state the age of the patients.

Data synthesis

I used dichotomous data for analyses 1.1 and 1.3 and continuous data for analysis 1.3. In analysis 1.1 the RR was calculated of benefit with 95% CI using a fixed effect model. Data is said to be significant compared to the control at 95%CI when the RR does not include the number 1.

Analysis 1.3 also used dichotomous data; however it examined the risk difference. This describes the actual difference in the observed risk of events between control and experimental interventions. This option can be used when considering both likely benefits and harms of an intervention. Analysis 1.3 focuses on adverse effects. The NNT and the absolute risk reduction were calculated, these figures allow us to determine the chance of adverse effects, this would be used by practitioners to analyse the risk of the treatment when prescribing the drug.

Analysis 1.2 measured a continuous outcome. Unlike dichotomous outcomes, continuous outcomes are measured both at the beginning of the study (the baseline) before the intervention was administered and then at the end of the study. Consequently continuous outcomes are expressed as a change in score from baseline to the end of study. The mean difference is measured (as opposed to the standardized mean difference as that option is used when outcomes are measured using different scales and this meta-analysis uses the same scale -UPDRS). 'Random effects' was used as it weights the studies more evenly than fixed effects option. Random effects is more beneficial for smaller studies, analysis 1.2 has 2,656 participants making it quite small in number.

Calculations that were used:

- Relative risk ratio (RRR)= $100\% * (1-RR)$
- Number needed to treat (NNT)= $1/ ACR * (1-RR)$, where ACR= the assumed control risk
- Absolute risk reduction was converted to a percentage by multiplying the data by 1000.

These additional calculations support the data and help to demonstrate the results allowing them to be more easily interpreted by practitioners.

The weight of each study is important in a meta-analysis and it is vital it is taken into account to prevent bias and causing skewed results. In analysis 1.1 the weighting of each study does slightly vary, however in analysis 1.2 they are more equally weighted with a small variation from 12.1-14.8%.

Subgroup analysis and investigation of heterogeneity

This review only looked at one primary outcome and there were no subgroups within this analysis. Therefore it was not necessary to perform a meta-regression analysis either. Heterogeneity can be determined from the forest plots (as seen in analysis 1.1, 1.2 and 1.3). The heterogeneity is represented by Chi^2 value, P value and I^2 value. These statistics help to gauge the heterogeneity of an analysis.

Sensitivity analysis

A sensitivity analysis can be carried out when there is suspicion or uncertainty whether to include a study in the meta-analysis. However all the studies used in this review are randomised and double blind and there are small amounts of bias (this is demonstrated in figures 4 and 5) Therefore it was not necessary to perform a full sensitivity analysis for this review.

Results

Description of studies

See characteristics of included studies tables.

A total of 8 studies fulfilled the selection criteria and were analysed in this meta-analysis with a total of 2,930 patients. 1,578 patients were randomly allocated to entacapone treatment and 1,353 were randomly assigned to control/placebo groups. All of the studies compared entacapone as an adjunct to levodopa treatment. All of the studies were randomised, double-blind and used 200mg of entacapone and examined patients with idiopathic PD. The length of the studies ranged from 13 weeks to 134 weeks with the average length of study approximately 40 weeks.

All of the studies prohibited previous use of COMT inhibitors.

Results of the search: included studies

A total of 8 studies fulfilled the inclusion criteria for this meta-analysis, with a total of 2930 participants. All of the studies except Brooks 2003, stated the age of the participants. Stoccho 2010 participants were aged between 30-70; all of the remaining studies used participants between ages 30-80. Every study was randomised and double blinded. All studies excluded patients that had any additional neurological disorders, such as dementia or any metal disorders . Non-selective MAO-inhibitors and any drugs that have dopaminergic action were prohibited in all studies. Previous use of COMT inhibitors was not permitted and all levodopa treatment had to be stable for at least 4 weeks prior to randomisation. All of the studies used the UPDRS for measuring the primary outcome and for the secondary outcome- side effect dyskinesia it was measured by the number of participants that experienced this effect.

The DDC inhibitor that is always administered with each levodopa dose was usually carbidopa. In some studies benserazide was allowed as an alternative. (Myllyla 2001), (Poewe 2002; Rinne 1998)

Dopamine agonists, selegiline, anticholinergics and amantadine were permitted in some studies; (Brooks 2003), (Haucer 2009- this study allowed dopamine agonists providing they had not been used 30 days prior to the study), (Myllyla 2001; Poewe 2002; Rinne 1998; Stocchi 2010 (permitted the above stated drugs except amantadine which was prohibited)).

Drugs that were prohibited were: Apomorphine, non-selective MAO-inhibitors and any drugs that have dopaminergic action (Brooks 2003; Hauser 2009; Myllyla 2001; Olanow 2004; Poewe 2002),

Brooks 2003:

A 6 month study of 172 fluctuating PD patients. This study also looked at non-fluctuating patients which were not included in this meta-analysis. Patients were already being treated with levodopa which was stabilized at least 4 weeks prior to the study. The experimental group of 115 patients were given 200mg of Entacapone with each of their daily levodopa doses. The 57 patients in the control group received their regular levodopa treatment and were given a placebo tablet. Apomorphine, non-selective MAO-inhibitors and any drugs that have dopaminergic action were prohibited. Anti PD drugs that were permitted were: dopamine agonists, selegiline, anticholinergics and amantadine.

Hauser 2009:

39 week study of 423 patients, some patients were excluded before randomisation making a total number of 392 patients. 177 patients were assigned to the experimental treatment and 215 were in the control group. 200mg of entacapone was administered to the experimental group in a combined pill which also contained the patients' regular levodopa treatment. The control group also received 1 pill that contained only their regular levodopa treatment. This study permitted the use of co-enzyme Q10, there was no mention of this co-enzyme in any of the other studies.

Myllyla 2001:

12 month study of 326 PD patients. 218 patients were randomised to experimental treatment and 108 to control. A 200mg entacapone tablet of identical placebo was administered with every levodopa dose. The DDC inhibitor that was administered with levodopa was either benserazide or carbidopa. Patients that had been treated with reserine or apomorphine within 6 months prior to randomisation were excluded from the study. This study permitted the standard or controlled release of levodopa and included fluctuating and non fluctuating patients.

Olanow 2004:

26 week study of 862 patients, however 112 were excluded before treatment allocation. Therefore 373 patients were randomly allocated to entacapone treatment and 377 were randomly allocated to the placebo treatment group. 200mg of entacapone or matching placebo was administered with every levodopa dose. Other antiparkinsonian drugs were permitted if they were stable for 1 month before study entry, but the individual specific drugs allowed were not stated.

Poewe 2002:

7 month study of 301 PD patients. 197 were randomly assigned to the entacapone treatment and 104 were assigned to the placebo treatment group. 200mg or placebo were administered with every levodopa dose. Controlled and immediate release preparations were permitted. The DDC inhibitor could either be carbidopa or benserazide. The primary outcome of this study was measuring proportion of daily 'on/off' time that can be experienced when taking PD medication. The secondary outcome measured UPDRS scores.

Rinne 1998:

24 week study of 171 patients. 85 patients were randomly assigned to entacapone treatment and 86 were assigned to the placebo treatment. Patients either took

200mg entacapone or identical placebo with each levodopa dose. Patients were able to take either carbidopa or benserazide as the DDC inhibitor. Controlled release levodopa was not permitted. Any additional anti PD medication had to be stable for at least 4 weeks before randomisation.

Stocchi 2010:

134 week study of 745 patients. 373 were randomised to the 200mg entacapone treatment group, 372 were assigned to the placebo group. Patients either took 200mg of entacapone with every levodopa dose or just levodopa. Each treatment group was administered in 1 combined pill. Previous use of COMT inhibitors was prohibited. Patients could not have taken amantadine within the preceding 270 days due to its anti-dyskinesia effects.

Tolosa 2013:

3 month study of 96 patients. 46 were randomised to 200mg entacapone (experimental group) and 49 patients were randomly assigned to the placebo group that received levodopa/carbidopa treatment with no entacapone. Both treatments were administered in 1 pill to eliminate chances of bias and to prevent un-blinding of the treatment groups. Previous use of COMT inhibitors was prohibited as was: any participants with a history of atypical or secondary parkinsonism, psychiatric disorders, dopaminergic treatments, patients with depression, treatment with neuroleptics, rotigotine or MAO inhibitors. This study examined immediate and slow release levodopa, I will only be using the data from the immediate release patients.

Excluded studies

The main reason for the exclusion of some studies was because they didn't include all of the relevant data that was required upon further inspection of the articles. (See characteristics of excluded studies for more detail).

Bet (2008) used the UPDRS as the primary outcome, however the study only analysed UPDRS III and did not include any data for UPDRS II therefore this study could not be included in my review as both UPDRS II+III were required to create an overall view from clinician and patients viewpoint. If this study was included it would cause potential bias towards the clinicians viewpoint and motor score rating because the patients self-assessment (UPDRS II was not reported). This was also true for Piccini (2000), and for Kieburtz (1997) only UPDRS II was measured and not UPDRS III

Durif (2001) was conducted as an open study, part of the specific criteria of this review ensured that the trials included were placebo controlled and double blinded to ensure bias is kept to a minimum where possible. Furthermore there was no control or placebo used in this study consequently there would be no baseline to compare results to. Gershanik (2003) also only had data for the experimental group of entacapone treatment with no control or placebo treatment group.

Larsen (2003) appeared to fit the selection criteria, however on further reading of the paper it became apparent that it was a follow up study to a trial that is already been included in this meta-analysis (Rinne 1998). Therefore this study was not needed in addition. Mizuno (2007) primary outcomes focused mainly on 'on/off time' of the treatment and didn't include enough data required for UPDRS for this analysis. Olanow (2013) was a review article of previous studies and did not contain any primary data, therefore was excluded. Reichmann (2005) did not use UPDRS as the

primary outcome, the study didn't include all of the standard deviations and data for the UPDRS scores that was required for this meta-analysis.

Risk of bias in included studies

All of the studies were randomised, the method for most of them was by randomised computer generation; however some of the studies did not state their randomisation methods.

Allocation (selection bias)

All of the studies used random allocation. Brooks (2003) carried out randomisation by the department of biostatistics of Orion Pharma, using a computerised method. Olanow (2004) used a computer generated randomised schedule to allocate participants to their treatment groups. Poewe (2002) used a computer generated randomisation procedure in a ratio of 2:1. Stocchi (2010) used a computer generated randomisation sequence to allocate participants to treatment groups. Tolosa (2013) used a randomised sequencing programme SAS version 9.1 statistical software, with random block sizes of 4.

Hauser (2009), Myllyla (2001) did not state the method they used to carry out randomisation, only that they were allocated randomly to treatment groups. Although the allocation concealment was definitely stated as random for Hauser (2009) and Myllyla (2001) the method is not stated and is therefore unknown. Consequently we cannot be entirely sure of the risk and on Figures 4 and 5 these 2 studies are highlighted in yellow as an 'unclear risk'.

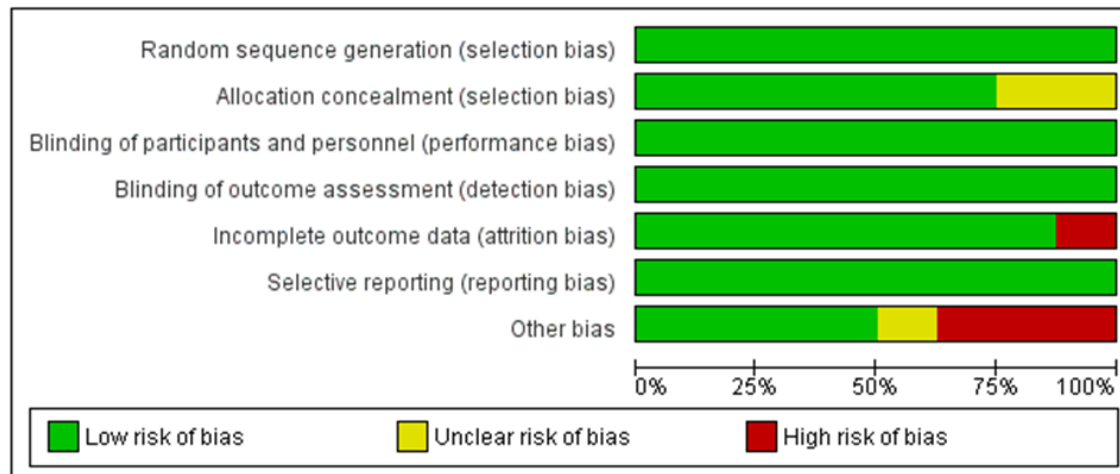


Figure 4: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

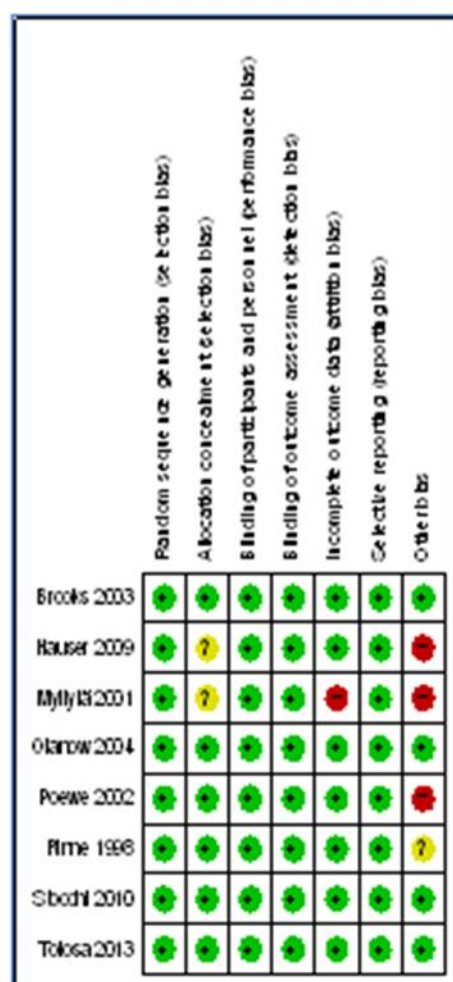


Figure 5: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Blinding (performance bias and detection bias)

All studies included in the meta-analysis were double blind to help reduce any forms of bias where possible.

Incomplete outcome data (attrition bias)

In all of the studies there were patients that did not complete the whole duration of the trial. In all cases the reason for withdrawal was explained. The main reason for withdrawal from the study was due to adverse effects. In some of the studies there were reported deaths of the patients, although in every case none were thought to be related to the study medication

Selective reporting (reporting bias)

For each of the 8 studies that are included in this meta-analysis a careful comparison was made between the primary objectives and the primary outcomes to ensure that the study reported what it set out to achieve. All of the 8 included studies reported the outcomes they had aimed to meet.

Other potential sources of bias

The Myllyla 2001 and Poewe studies permitted controlled and standard release levodopa. It also permitted fluctuating and non fluctuating patients. This may have caused potential bias as other studies did not permit these things. Both these studies permitted both carbidopa and benserazide as the DDC inhibitor. Other studies only allowed carbidopa.

A further potential source of bias could be due to finances. In many of the studies it does not state who funded the study. However the study by Stocchi 2010 was funded by Orion Pharma, this is also the company that manufactures the drugs being tested. Furthermore the authors of the paper have served as consultants to Orion. This raises the question to how reliable is this study, is this an unfair trial if it is the drug company themselves that is testing their own drug. They know what outcome they want to portray for their drug, why did they not use an independent unbiased outsource company to test the drug for them.

Financial gain can often be found at the heart of the pharmaceutical industry and it becomes increasingly difficult to judge validity of results. After all, it has been reported by Ben Goldacre (2012) in the book 'Bad Pharma' that very often drugs are tested by the people who manufacture them, often on unrepresentative patients, using techniques that may have been flawed by design in such a way that they exaggerate the benefits of treatments which then lead to results that favour the manufacture. It has also been shown that drug companies are more than entitled to abandon and hide results of trials from doctor and patients that the companies don't like; potentially producing a distorted image of any drug's true effects. Obviously this is not always or often the case, however it raises a thought of how often this may happen in this industry and is up to us as an independent opinion to carefully scrutinise the evidence that is available to make informed conclusions and decisions.

Effects of interventions

All 3 of the outcomes of this intervention analysed different comparisons based on the experimental treatment, entacapone, versus the control treatment of levodopa+DDCI.

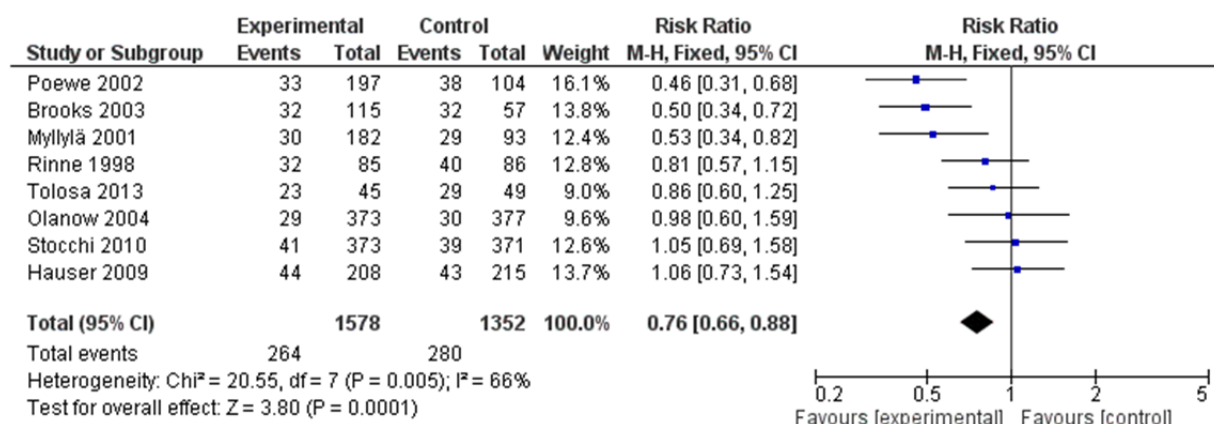


Figure 1 (Analysis 1.1): Forest plot of comparison: 1 Levodopa/DDCI/Entacapone versus Levodopa/DDCI/Placebo, outcome: 1.1 UPDRS II + III.

Figure 1 (Analysis 1.1) is a dichotomous analysis that compares levodopa+DDCI+entacapone versus levodopa+DDCI using a risk ratio (RR) with fixed effects at a 95% confidence interval (CI). The risk ratio is 0.76 with CI of 0.66-0.88. RR's describe the multiplication of the risk that occurs with use of the experimental intervention.

Poewe 2002, Brooks 2003 and Myllylä 2001 all strongly favour the experimental treatment, with RR's between 0.46-0.53, all 3 of these studies CI all favour the entacapone treatment also. Rinne 1998, Tolosa 2013 and Olanow 2004 also have RR that favour the experimental treatment, just not as strongly. Their RR range from 0.81- 0.98. Their CI all cross over into favouring the control. Stocchi 2010 and Hauser 2009 both slightly favoured the control with RR of 1.05 and 1.06, they also had CI that extended into both directions of favouring the experimental and the control.

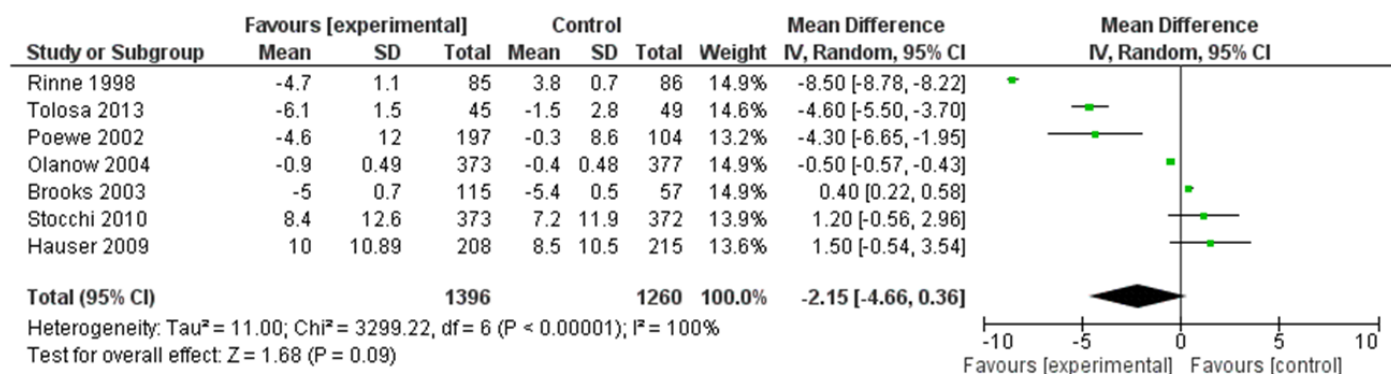


Figure 2 (Analysis 1.2): Forest plot of comparison: 1 Levodopa/DDCI/Entacapone versus Levodopa/DDCI/Placebo, outcome: 1.2 Change in UPDRS scores (II+III) from baseline to finish.

Figure 2 (Analysis 1.2) is a continuous outcome that examines the change in UPDRS scores II+III from baseline to finish. This analysis uses the statistical method mean difference with random effects at a 95% CI. Mean difference is used to give the absolute difference between the mean value of 2 groups. The standardized mean difference would be used if the outcomes were measured using different scales, however in this analysis all outcomes were measured using UPDRS II+III. By examining the change in UPDRS II+III scores from baseline to the end of each study this gives an overall score for improvement in the patients and reflects the success of each study. The total mean difference score for analysis 1.2 = -2.15 with CI= -4.66, 0.36. This indicates the average change in UPDRS was -2.15 which favours the experimental entacapone treatment. However it has large confidence intervals that slightly cross over 0 into favouring the control.

Rinne 1998 most favours the experimental treatment with an average mean difference of -8.50. This study had very small CI of -8.78,-8.22 therefore making the interval bars on the forest plot barely visible. Tolosa 2013, Poewe 2002, and Olanow 2004 also all completely favoured the experimental treatment. With mean difference scores of -4.60, -4.30 and -0.50. All of the CI also favoured the experimental treatment. Brooks 2003 had a mean difference of 0.4 which slightly favoured the control treatment. Stocchi 2010 and Hauser 2009 both favoured the control treatment with mean difference values of 1.20 and 1.50. However both of their upper CI did slightly favour the experimental treatment.

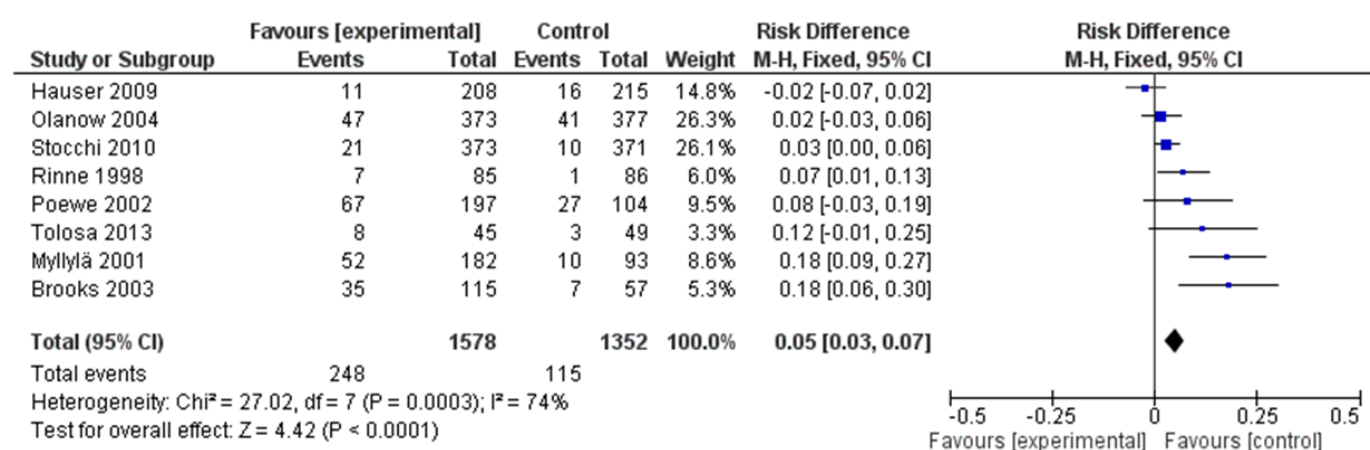


Figure 3 (Analysis 1.3): Forest plot of comparison: 1 Levodopa/DDCI/Entacapone versus Levodopa/DDCI/Placebo, outcome: 1.4 Adverse Effects- Dyskinesia.

Figure 3 (Analysis 1.3) is a continuous outcome that uses the statistical method mean difference (RD) with fixed effects at a 95% CI. Figure 3 analyses the side effect dyskinesia and compared the results of the experimental and control groups. RD explains the estimated difference in the probability of an individual experiencing an event- in this case the adverse effect. The average RD is 0.05 which indicates slight favour of the control group, with CI 0.03, 0.07. Hauser 2009 was the only study that favoured the experimental group, although this was by a very tiny amount of -0.02. all other studies favoured the control group. This is as expected and will be explored more in the discussion section.

From this analysis we could therefore reject the null hypothesis and conclude that the entacapone treatment does improve combined UPDRS scores II+III.

Discussion

Summary of main results

This review included 8 studies comparing entacapone 200mg as an adjunct to levodopa+DDCI therapy. Patients used their standard dose of levodopa+DDCI in both the experimental and control groups. Combined UPDRS scores II+III were the primary outcome this review focused on. The secondary outcome examined the adverse effect dyskinesia.

Figure 1 (Analysis 1.1) is a dichotomous outcome that examined all 8 studies with a total number of 2930 participants. 1578 were in the experimental group and 1352 participants were in the control group. The $RR=0.76$ CI [0.66,0.88]. The relatively small CI suggests the effect size is known precisely. The RR can be re-expressed as a relative risk ratio (RRR) by $= 100\% \times (1-RR)$. The RRR for analysis 1.1 is 24%. This can be interpreted as the entacapone experimental treatment decreases the risk of events by 24%. In the summary of results table it states the risk per 1000 patients. From this I was able to calculate the number needed to treat (NNT) of patients. For the study population, the assumed control risk was 207/1000, for the corresponding risk (entacapone) it was 157/1000. I was then able to calculate NNT by the following equation:

$NNT = 1 / ACR \times (1-RR)$, when the data for this analysis was entered: $NNT = 1 / 0.207 \times 24$, $NNT = 12.29$, which would be rounded to 13 (NNT is always rounded up). This can be interpreted that it is expected that one additional (or less) person will incur a reduction in UPDRS score for every 12 participants receiving the entacapone as an adjunctive treatment to levodopa+DDCI as opposed to the placebo (control treatment) over a given time frame (the studies ranged from 3-12 months). The P value for overall effect $P=0.0001$, therefore suggesting that the observed effect is very unlikely to have arisen purely by chance and provides evidence against the null hypothesis. From which we can interpret that entacapone treatment is preferable compared to placebo.

Figure 2 (Analysis 1.2) is a continuous outcome that examined 7 out of the 8 studies with a total of 2656 participants. 1369 belonged to the experimental treatment group and 1260 were in the control group. The mean difference for this analysis is -2.15 with CI [-4.66,0.36] The mean difference favours the experimental treatment group, however it has a wide CI. The outcome was measured using the same scale of change in UPDRS scores II+III from baseline to end of study. Consequently a pooled estimate was generated that can be seen in the summary of results table. There is a range of -6.1 to 10 in UPDRS II+III score differences over the studies that were between 3-12 months. On average the UPDRS II+III scores decreased by 2.15 points, this favours the entacapone treatment compared to placebo treatment as a lower score indicates an improvement in the patient. The summary of results table also suggests 'high grade' this indicated good quality data as all the studies were double blinded, randomised and placebo controlled. The P value for overall effect $P=0.09$, therefore this suggests there is not strong evidence that the intervention has an effect.

Figure 3 (Analysis 1.3) is a dichotomous outcome that examined all 8 of the studies with a total number of 2930 participants. 578 were in the experimental group and 1352 participants were in the control group. The risk difference (RD) was calculated in order to determine the probability of an individual experiencing the adverse effect dyskinesia in the experimental group compared to the control group. The RD= 0.05 [with CI=0.03-0.07]. The RD can be expressed as an absolute risk reduction, which is therefore 5%. The NNT can also be calculated by a slightly different method compared to RR. For RD NNT= 1/absolute value of risk difference, therefore $1/0.05=20$ participants needed to treat. This can be interpreted that 1 participant will incur the adverse effect dyskinesia for every 20 participants, when receiving entacapone treatment as an adjunctive treatment to levodopa+DDCI as opposed to the placebo (control treatment) over a given time frame (the studies ranged from 3-12 months). The P value for the test of overall effect $P=<0.0001$, this would suggest that the observed effect is very unlikely to have arisen purely by chance and provides evidence against the null hypothesis.

The risk of bias graph (Figure 4) demonstrates how every study was double blinded, this helps to remove any potential bias with patients guessing which treatment group they are in. Generally there is a low amount of bias throughout all of the meta-analysis.

Figure 4 demonstrates a graph highlighting the sources of potential bias in each individual study. From this figure it raises slight concern about Myllyla 2001 study which contains the most bias.

Overall completeness and applicability of evidence

All of the studies were completed and the quality of evidence is moderate to high. This is supported by the risk of bias figures (4 and 5) and further demonstrated in the summary of results table which categorised the grade of data as 'high' for every outcome. The table also states moderate quality, which can be interpreted as: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Quality of the evidence

The quality of the evidence in this meta-analysis is reasonably high, all the studies fit the criteria and have a good number of participants in each study to produce a well-balanced and reliable result. There are also relatively low levels of bias; this is shown in figures 4 and 5.

Potential biases in the review process

There is some potential biases in this review which may have had repercussions on the results and could explain the result seen in analysis 1.1. Myllyla 2001, Poewe 2002, Rinne 1998 all permitted an alternative DDC inhibitor, benserazide, in addition to carbidopa. Carbidopa is the only DDCI allowed in the other studies. The patients were assigned either DDCI according to the choice of the clinician based on previous levodopa treatment. However it is unlikely this caused bias considering that Rinne 1998 demonstrated results that significantly favoured entacapone treatment compared to control in analysis 1.1 and 1.2.

Other sources of bias could be the use of controlled release or immediate release levodopa. This was the case in Brooks 2003 and Poewe 2002. A potential source of bias that may explain why Myllyla consistently produced results that favoured the control treatment could be the allowance of fluctuating and non fluctuating patients in

the study, the rest of the studies used fluctuating patients. I still chose to include Mylly 2001 in the meta-analysis as it fitted the selection criteria and complied with all the other variables. It is also a case that may be seen in real practise.

Hauser 2009 produced results in analysis 1.1 and 1.2 that favoured the control treatment. One potential source of bias from this study could have been the use of coenzyme Q10, this was permitted in this study whereas in every other study in the meta-analysis Q10 was not mentioned. Another factor that may have caused bias in the study was the uneven gender distribution across the experimental and control groups. The experimenters acknowledged this and performed an additional analysis that incorporated gender into the model as a primary efficacy variable. The study then produced at p value of 0.023 which favoured the entacapone treatment group. Compared to analysis 1.1 where the average mean difference was 0.06 95% CI(-0.14, 0.25) and in analysis 1.2 an average standard mean difference of 0.14 95% CI(0.27,0.75). However in this additional analysis the experimenters did not report all the individual data values required to tabulate them in this review to create a new analysis. If this data was available the new analysis may have produced different conclusions favouring the entacapone treatment more.

UPDRS II is a self-assessed patient rating on activities of daily life. Even though there is a detailed questionnaire to guide the patient combined with thorough descriptions to help them categorise and determine their rating of a specific task there will always be slight discretions and inconsistencies that vary between patients own opinions of their ability to execute a given task. Therefore leaving a potential to bias, some patients may over or underestimate their capabilities. However this is why the UPDRS II and III scores are combined to given an overall rating. This will help to remove patient derived bias as the clinicians should be assessing patients UPDRS III scores with the same criteria and will be more experienced in analysing patients therefore producing consistent ratings as opposed to a patient themselves. Nevertheless it is good to get a fair and balanced viewpoint for the patient and clinician which is the aim of this meta-analysis.

Agreements and disagreements with other studies or reviews

The most previous meta-analysis that examined COMT inhibitors as potential adjuncts to levodopa therapy was from 2010, however the most recent study it included in the analysis was from 2004. This meta-analysis had a primary outcome of UPDRS II and UPDRS III but they were separate outcomes. They did include an outcome that looked at total UPDRS scores however this included UPDRS I,II,III,IV,V. In the individual UPDRS II and III scores they concluded that entacapone treatment was preferable, and therefore agreeing with the updated conclusions of this meta-analysis.

Authors' conclusions

Implications for practice

Entacapone is generally a well-tolerated drug and is an effective adjunct to levodopa treatment, dyskinesia is more common in entacapone compared to placebo, but not significantly and when compared to the benefits of entacapone treatment clinicians would most probably recommend the entacapone treatment as an adjunct to levodopa+DDCI therapy as the risk of dyskinesia is minimal.

Implications for research

More research needs to be done in this area to confirm the results. When more studies are carried out under the same conditions and new meta-analysis could be created to hopefully confirm the findings of this review, it would have the potential to be more significant and reliable if more participants are involved and if there is a greater number of studies available. Future research will look at drugs to stop the prevention of further depletion of the dopaminergic neurons and potentially reverse the damage,

At present, only symptomatic treatment exists and nothing can be done to halt the degenerative process, as its cause remains unclear.

Technology within science is rapidly evolving, nanotechnology is novel technology that helps to overcome some of the current problems that levodopa therapy currently faces. For example a major limitation to levodopa therapy is the minimal amount that can react to the CNS via the blood brain barrier (BBB). The BBB enables the passage of small lipophilic, large hydrophobic or charged particles that require facilitated transport. The CNS restricts the entry of dopamine because it is a polar compound. With the help of nanotechnology it would enable the packaging and transport of small molecules across the BBB in order to target specific structures, which would avoid degradation in the plasma and reduce systemic side effects (Linazasoro 2008) This therapy is still a far distance away, but in the future it may aid the pharmacological treatment of Parkinson's disease.

Characteristics of studies

Characteristics of included studies

Brooks 2003 Table 1.0

Methods	<p><u>Randomised:</u> Yes, patients were separated into fluctuating and non fluctuating and then randomly assigned within these two groups into the treatment groups. The randomisation was carried out by the department of biostatistics of Orion Pharma, using a computerised method.</p> <p><u>Blinded:</u> Double blind, placebo controlled</p> <p><u>Treatment period:</u> 6 months</p>
Participants	<p><u>Eligibility:</u> Patients were recruited from 29 neurology and movement disorder clinics from the UK and the Republic of Ireland. All patients were being treated already with levodopa, patients medication had to have remained stable for at least 4 weeks before randomisation. All patients were treated with either standard formulation of controlled release levodopa. Anti PD drugs that were permitted were: dopamine agonists, selegiline, anticholinergics, amantadine.</p> <p><u>Exclusion criteria:</u> Apomorphine, atypical PD, dementia and other neurological disorders were excluded. Non-selective MAO-inhibitors and any drugs that have dopaminergic action were prohibited in the study.</p> <p><u>Number of participants:</u> 172 fluctuating patients and 128 non</p>

	fluctuating patients <u>Distribution to treatment:</u> 115 fluctuating patients were assigned to Entacapone and 57 were randomly assigned to placebo.
Interventions	200mg of Entacapone was administered with each daily Levodopa dose, or placebo was administered with the daily Levodopa treatment.
Outcomes	<u>Primary:</u> Proportion of daily 'on time' compared to baseline and placebo <u>Secondary:</u> UPDRS I,II and III, adverse effects.
Notes	This study looked at fluctuating and non fluctuating patients, I will only be using the data from the fluctuating patients.

Risk of bias table Table 1.1

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was carried out by the department of biostatistics of Orion Pharma, using a computerised method.
Allocation concealment (selection bias)	Low risk	computerised method
Blinding of participants and personnel (performance bias)	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Low risk	Double-blind
Incomplete outcome data (attrition bias)	Low risk	No missing data/results
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Low risk	

Hauser 2009 Table 1.2

Methods	<u>Randomised:</u> Yes (Method not stated) <u>Blinded:</u> Double Blind, parallel group, multicentre study at 53 centres in Canada, Czech Republic, Israel, Italy, Poland, Portugal, Turkey and USA. <u>Treatment period:</u> 39 Weeks
Participants	<u>Eligibility:</u> Patients with PD that had at least two out of three cardinal signs (bradykinesia, rigidity and rest tremor). Patients were between ages 30-80 years at diagnosis. Patients were permitted to use amantadine, anticholinergics, selegiline,

	<p>rasagiline, and coenzyme Q10 providing they were a stable dosages at least 30 days prior to baseline.</p> <p><u>Exclusion criteria:</u> Previous use of COMT inhibitor and use of dopamine agonists for more than 30 days or within 4 weeks prior to baseline were excluded. Patients with atypical/secondary parkinsonism, patients prior to neurosurgery and patients with other neurological conditions or mental disorders were not included in the study.</p> <p><u>Number of participants:</u> 423</p> <p><u>Distribution to treatment:</u> 208 patients were given Levodopa/Carbidopa/Entacapone and there were 215 patients in the Levodopa/Carbidopa treatment group. 177 patients in the entacapone group completed the study, 190 in the control group completed. Entacapone treatment was a 200mg dose.</p>
Interventions	Patients were randomly assigned to either entacapone/levodopa/DDC inhibitor(carbidopa) or levodopa/DDC Inhibitor (carbidopa)
Outcomes	<p><u>Primary:</u> UPDRS II and III scores</p> <p><u>Secondary:</u> Hoehn-Yahr stage and Schwab and England ADL score</p>
Notes	There was no placebo administered in the levodopa/carbidopa group, however only 1 pill was administered in each group and the trial was double blind therefore patients had no way of knowing which test group they belonged to.

Risk of bias table Table 1.3

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, but method not stated.
Allocation concealment (selection bias)	Unclear risk	Although the allocation concealment was definitely stated as random the method not stated and is therefore unknown. Consequently we cannot be entirely sure of the risk.
Blinding of participants and personnel (performance bias)	Low risk	Double-blind trial
Blinding of outcome assessment (detection bias)	Low risk	Double-blind trial
Incomplete outcome data (attrition bias)	Low risk	Data was complete, where participants did not complete the trial it was stated reasons why, and only complete data was used in the

		analysis of the results.
Selective reporting (reporting bias)	Low risk	study reports all outcomes
Other bias	High risk	Coenzyme Q10 was permitted and this was not mentioned in any other studies.

Myllylä 2001 Table 1.4

Methods	<p><u>Randomised:</u> Yes (method not stated).</p> <p><u>Blinded:</u> Double-blind, placebo controlled, parallel-group design.</p> <p><u>Treatment period:</u> 12 months</p>
Participants	<p><u>Eligibility:</u> 'typical PD outpatients patients' levodopa-responsive, idiopathic PD that needed enhancement and or smoothening of Levodopa effects. Carbidopa and benserazide were permitted as the DDC inhibitor.</p> <p><u>Exclusion criteria:</u> Patients with secondary Parkinsonism, dementia or any other significant neurological disease were excluded. Patients with any psychiatric disorders, such as depression, were also excluded. Subjects that had been treated with neuroleptic agents, a-methyldopa, reserine or apomorphie within the last 6 months were excluded as well patients that had been treated with either MAO-A inhibitors and non-selective MAO-inhibitors within the last month. Levodopa treated had to be stable for at least 4 weeks prior to randomisation.</p> <p><u>Number of participants:</u> 326, 217 men and 109 women aged between 30-80.</p> <p><u>Distribution to treatment:</u> Two-thirds of patients (218) were randomised to entacapone and one third (108) to placebo treatment. However 51 patients discontinued, the number of patients that completed the Entacapone treatment was 182 and 93 patients completed the treatment in the placebo group.</p>
Interventions	An entacapone 200mg tablet or identical placebo was given with each scheduled levodopa/ddc inhibitor dose. the number of daily doses ranged from 2 to 10.
Outcomes	<p>UPDRS:</p> <p>Mentation, behaviour and mood (part 1)</p> <p>ADL (part 2)</p> <p>Motor Score (part 3)</p> <p>Total score (part 1,2 and 3)</p> <p>Side Effects</p>
Notes	The study permitted standard and controlled release of levodopa and soluble levodopa preparations and included fluctuating and non-fluctuating patients.

Risk of bias table Table 1.5

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	It states that patients were randomised to treatment groups but does not specifically state how or using what method
Allocation concealment (selection bias)	Unclear risk	Although the allocation concealment was definitely stated as random the method not stated and is therefore unknown. Consequently we cannot be entirely sure of the risk.
Blinding of participants and personnel (performance bias)	Low risk	Double-blind trial
Blinding of outcome assessment (detection bias)	Low risk	Double-blind trial
Incomplete outcome data (attrition bias)	High risk	Missing data, study does not report the baseline UPDRS scores and only states the end scores. Therefore an overall change cannot be calculated.
Selective reporting (reporting bias)	Low risk	Outcomes were all reported
Other bias	High risk	Study permitted the use of an alternative DDCl, patients could either use carbidopa or benserazide. The study also permitted fluctuating and non fluctuating patients.

Olanow 2004 Table 1.6

Methods	<p><u>Randomised</u>: Yes, method: computer-generated randomised schedule</p> <p><u>Blinded</u>: Double-blind, placebo-controlled, parallel group study</p> <p><u>Treatment period</u>: 26 weeks</p>
Participants	<p><u>Eligibility</u>: Male and female participants with idiopathic PD over age 30. Diagnosis of PD based on good response to Levodopa and at least two of the following: rigidity, resting tremor and bradykinesia. Other anti-parkinsonian medications were permitted providing the dose was stable for 1 month before the study entry.</p> <p><u>Exclusion criteria</u>: Previous exposure to COMT inhibitors, secondary or atypical parkinsonism, medical or psychiatric illnesses and any other neurological disorders were prohibited in the study.</p> <p><u>Number of participants</u>: 862</p> <p><u>Distribution to treatment</u>: 373 allocated to</p>

	Entacapone/Levodopa/Carbidopa, 377 allocated to Levodopa/Carbidopa/Placebo. (112 patients were excluded before patients were allocated groups, making the total number of participants 750.
Interventions	200mg of Entacapone or matching placebo was administered with every dose of Levodopa.
Outcomes	<u>Primary:</u> Changes in UPDRS III <u>Secondary:</u> UPDRS II
Notes	The dose of levodopa/carbidopa could not increase during the study and the levodopa/carbidopa could not switch formulations. It could however be decreased, any drug adjustments were performed by a blinded treatment investigator.

Risk of bias table Table 1.7

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computer-generated randomised schedule
Allocation concealment (selection bias)	Low risk	computer-generated randomised schedule
Blinding of participants and personnel (performance bias)	Low risk	Double-blind trial
Blinding of outcome assessment (detection bias)	Low risk	Double-blind trial
Incomplete outcome data (attrition bias)	Low risk	
Selective reporting (reporting bias)	Low risk	Study measures and records its outcomes that it states in its objectives.
Other bias	Low risk	

Poewe 2002 Table 1.8

Methods	<u>Randomised:</u> Yes, in a ratio of 2:1 by a computer generated randomisation procedure. Patients were from 30 centres in Germany and Austria. <u>Blinded:</u> Double blind, parallel group study. <u>Treatment Period:</u> 7 months
Participants	<u>Eligibility:</u> The study allowed a wide range of PD patients in order to gain more experience on the use of entacapone. Eligible patients may have had less advanced PD, patients without obvious motor fluctuations were also allowed. Use of 2-10 daily doses of standard or controlled release levodopa

	<p>preparations. Additional PD drugs that were permitted were: amantadine, memantine, anticholinergics, selegiline and dopamine agonists.</p> <p><u>Inclusion Criteria:</u> Patients were Levodopa responsive with idiopathic PD, aged between 30-80 and required enhancement or smoothening from the effects of Levodopa. Levodopa treatment had to be stable for at least 1 month before the study began.</p> <p><u>Exclusion Criteria:</u> Treatment with neuroleptics, antiemetics, catechol structured drugs, MAO-inhibitors and non-selective MAO inhibitors were prohibited. Patients with other major neurological, psychiatric or medical disorders were excluded.</p> <p><u>Number of Participants:</u> 301</p> <p><u>Distribution to treatment:</u> 197 patients were randomly assigned to entacapone treatment and 104 patients were assigned to the placebo treatment.</p>
Interventions	Entacapone 200mg or placebo was administered with the patient's standard levodopa/DDCI treatment.
Outcomes	<p><u>Primary:</u> Proportion of daily 'on and off time' recorded by the patient as a home diary.</p> <p><u>Secondary:</u> UPDRS scores (I,II and III)</p>
Notes	Controlled release and immediate release were permitted. Most studies have only used immediate release and only carbidopa not benserazide, however I have chosen to still include this study as all the other variables are maintained and also in the everyday life setting looking at typical PD patients there will always be slight variations within medications, this is because each individual has different needs and may have a preference with their existing medication. This study permitted the use of other antiparkinsonian drugs, this is to mimic current clinical practice as much as possible. The entacapone dose is 200mg (as identical to all the other articles) and it is compared against placebo and is double blind, therefore reducing the risk of bias.

Risk of bias table Table 1.9

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomisation procedure.
Allocation concealment (selection bias)	Low risk	Only the sponsor-employed person who generated the plan was aware of a given individuals assignment during the study.
Blinding of participants and	Low risk	Double-blind trial

personnel (performance bias)		
Blinding of outcome assessment (detection bias)	Low risk	Double-blind trial
Incomplete outcome data (attrition bias)	Low risk	There was no instance that required unblinding of the assignment during the study, however during a post-study visit one of the investigators had to open one envelope because the patient had diarrhoea and his family doctor insisted on knowing the medication. The independent safety monitoring committee identified no safety concerns and had no reason to either break the code or terminate the study prematurely.
Selective reporting (reporting bias)	Low risk	The primary outcome measuring 'on/off time' by method of patients home diary was originally measuring both 'observed case' and 'last observation carried forward' (LOCF), however due to a considerable amount of missing recording OC was the only outcome analysed. However there were no reported problems with the UPDRS scores which is the outcome I am interested in.
Other bias	High risk	Controlled release and immediate release levodopa were permitted in this study, also the DDCI used was either benserazide or carbidopa.

Rinne 1998 Table 2.0

Methods	<u>Randomised:</u> Yes (method not stated) <u>Blinding:</u> Double blind, conducted in 16 neurologic departments in the Nordic countries <u>Treatment period:</u> 24 weeks
Participants	<u>Eligibility:</u> Levodopa responsive with idiopathic PD that were experiencing motor fluctuations. Patients treated with amantadine, anticholinergics, selegiline, or dopamine agonists were permitted. Any anti-parkinsonian drugs had to be stable for at least 4 weeks before randomisation <u>Number of participants:</u> 171 <u>Exclusion criteria:</u> Control release levodopa was not permitted. <u>Distribution to treatment:</u> 85 patients were allocated to the Entacapone group and 86 to the placebo group. 152 patients completed the study, 77 from the entacapone group and 75 in the placebo group.
Interventions	Patients either took 200mg Entacapone or identical placebo with each daily Levodopa/DDC inhibitor dose.
Outcomes	<u>Primary:</u> Mean daily 'on and off' times, measured from home

	diaries. <u>Secondary:</u> UPDRS I, II, III
Notes	Patients were could either take carbidopa or benserazide as their DDC inhibitor with Levodopa.

Risk of bias table Table 2.1

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised but not stated how.
Allocation concealment (selection bias)	Low risk	Randomised but not stated how.
Blinding of participants and personnel (performance bias)	Low risk	Double-blind trial
Blinding of outcome assessment (detection bias)	Low risk	Double-blind trial
Incomplete outcome data (attrition bias)	Low risk	
Selective reporting (reporting bias)	Low risk	Study reports all of its objectives.
Other bias	Unclear risk	Benserazide preparations of levodopa were permitted.

Stocchi 2010 Table 2.2

Methods	<u>Randomised:</u> Yes, using computer generated randomisation sequence. <u>Blinded:</u> Double blind, Multicentre study; patients were from 77 centres in 14 countries in Europe and North America. <u>Treatment period:</u> 134 weeks
Participants	<u>Eligibility:</u> Men or women aged 30-70 with a diagnosis of PD based on UK brain bank criteria and a disease duration of <5 years from time of diagnosis. <u>Exclusion Criteria:</u> Patients were excluded if they had taken amantadine within the preceding 270 days. Previous use of COMT inhibitors was not permitted. Patients with secondary parkinsonism, concomitant use of neuroleptic agents and any medical and psychiatric conditions were excluded from the study. <u>Number of participants:</u> 745 <u>Distribution to treatment:</u> 373 patients were in the entacapone group and 372 in the placebo group. However 541 patients completed the study, 265 in the entacapone group and 276 in the control group. Withdrawal was mainly due to adverse

	effects and unsatisfactory therapeutic effect.
Interventions	Participants were randomised to either 200mg entacapone with every levodopa/DDC inhibitor dose or just levodopa/DDC inhibitor. The DDC inhibitor used was carbidopa. There was no placebo pill given, but both treatment groups were given their medication in 1 pill, and as the study was double blind there was no way of knowing which treatment group the patient was in
Outcomes	<u>Primary Outcome:</u> Time to onset of dyskinesia. <u>Secondary Outcome:</u> Frequency of dyskinesia, change from baseline in total UPDRS parts II and III, time and frequency of wearing off episodes.
Notes	Patients were allowed to be taking stable doses of a dopamine agonist or other antiparkinson's medications as long as it had been stable for at least 4 weeks previous to the trial. They could not have taken amantadine within the preceding 270 days due to its anti-dyskinesia effects.

Risk of bias table Table 2.3

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computer generated randomisation sequence
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias)	Low risk	Double-blind trial
Blinding of outcome assessment (detection bias)	Low risk	Double-blind trial
Incomplete outcome data (attrition bias)	Low risk	
Selective reporting (reporting bias)	Low risk	All outcomes are reported.
Other bias	Low risk	

Tolosa 2013 Table 2.4

Methods	<u>Randomised:</u> Yes, using randomised sequencing programme SAS version 9.1 statistical software, using random block sizes 4. <u>Blinding:</u> Double-blind, multicentre, parallel-group study. <u>Treatment Period:</u> 3 months
Participants	<u>Eligibility:</u> Patients were male and female between ages 30-80 and had idiopathic PD as diagnosed by the UK Parkinson's Disease society brain bank criteria, patients had to be stable

	<p>on Levodopa treatment for at least 1 month before the study. Patients had mild or minimally disabling motor complications. Patients were permitted to have used selegiline or rasagiline, providing treatment was stable for at least 60 days prior to the screening visit.</p> <p><u>Exclusion criteria:</u> Patients who had previously or were currently being treated with entacapone, symptoms or a history with atypical or secondary Parkinsonism, hallucinations or psychiatric disorders related to dopaminergic treatments, major depression, treatment with neuroleptics, rotigotine or monoaminooxidase inhibitors .</p> <p><u>Number of Participants:</u> 96</p> <p><u>Distribution to treatment:</u> 46 patients were randomly assigned to treatment Levodopa/Carbidopa/Entacapone and 49 patients were randomly assigned to Levodopa/Carbidopa treatment.</p>
Interventions	<p>Patients were randomly assigned to either treatment group and told to take their medication the same time each day. Patients were either given Levodopa/Carbidopa/Entacapone in the following dose 100/25/200mg or Levodopa/Carbidopa 100/25mg</p>
Outcomes	<p>Primary: UPDRS III</p> <p>Secondary: UPDRS I,II and III</p>
Notes	<p>This study looked at both immediate release and slow release, I will only be using the immediate release data.</p>

Risk of bias table Table 2.5

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used randomised sequencing programme
Allocation concealment (selection bias)	Low risk	Study medication was over encapsulated by Farmasierra (Spain) to prevent unblinding of the treatment.
Blinding of participants and personnel (performance bias)	Low risk	Double-blind trial
Blinding of outcome assessment (detection bias)	Low risk	Double-blind trial
Incomplete outcome data (attrition bias)	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Characteristics of excluded studies

Bet 2008

Reason for exclusion	This article didn't compare Entacapone to placebo or use any control. It also only looked at UPDRS III and didn't include II.
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Durif 2001

Reason for exclusion	This article didn't compare Entacapone to placebo or a control, also it was conducted as an open study therefore if this study was included in the meta-analysis there would be bias.
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Gershanik 2003

Reason for exclusion	This article only had data for Entacapone and no control or placebo.
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Kieburtz 1997

Reason for exclusion	This article only had data for UPDRS II (ADL) and no data for UPDRS III.
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Larsen 2003

Reason for exclusion	This was a follow up to a study that was carried out by Rinne 1998 which I have already included.
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Mizuno 2007

Reason for exclusion	The outcomes of this article were not consistent with the other papers, it focused on 'on time' rather than UPDRS scores.
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Olanow 2013

Reason for exclusion	This was a review type article, and although it focused on the correct subject, it didn't contain primary data, only a review of previous existing studies.
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Piccini 2000

Reason for exclusion	This article only looked at UPDRS score III and did not include UPDRS score II.
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Reichmann 2005

Reason for exclusion	UPDRS was not the primary outcome of this paper, they reported the baseline scores but did not include them as final scores in the detail I needed.
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Footnotes

Summary of findings tables

1 Levodopa+DDCI+Entacapone versus Levodopa+DDCI+Placebo in the treatment of Parkinson's disease Table 2.6

Levodopa+DDCI+Entacapone versus Levodopa+DDCI+Placebo in the treatment of Parkinson's disease						
Patient or population: Parkinson's disease						
Settings:						
Intervention: Levodopa+DDCI+Entacapone versus Levodopa+DDCI+Placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Levodopa+DDCI+Entacapone versus Levodopa+DDCI+Placebo				
UPDRS II + III UPDRS II+III Follow-up: 3-12 months	Study population		RR 0.76 (0.66 to 0.88)	2930 (8 studies)	⊕⊕⊕⊕ high	
	207 per 1000	157 per 1000 (137 to 182)				
	Moderate					
	339 per 1000	258 per 1000 (224 to 298)				
Change in UPDRS scores (II+III) from baseline to finish Scale from: -6.1 to 10. Follow-up: 3-12 months ¹	The mean change in updrs scores (ii+iii) from baseline to finish ranged across control groups from -6.1 to 10 UPDRS II+III	The mean change in updrs scores (ii+iii) from baseline to finish in the intervention groups was 2.15 lower (4.66 lower to 0.36 higher) ²		2656 (7 studies)	⊕⊕⊕⊕ high	
Adverse Effects- Dyskinesia UPDRS II+III Follow-up: 3-12 months	Study population		See comment	2930 (8 studies)	⊕⊕⊕⊕ high	Risks were calculated from pooled risk differences
	85 per 1000	135 per 1000 (115 to 155)				
	Moderate					
	91 per 1000	145 per 1000 (123 to 166)				
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio;						
GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the						

estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Footnotes

¹ The range has been used to demonstrate the variety of the scores from both ends of the spectrum.

² A lower score indicates a positive improvement and favours the treatment group in the analysis 1.2 (change in UPDRS scores II+III from baseline to end of study).

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Data and analyses

1 Levodopa/DDCI/Entacapone versus Levodopa/DDCI/Placebo Table 2.7

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 UPDRS II + III	8	2930	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.66, 0.88]
1.2 Change in UPDRS scores (II+III) from baseline to finish	7	2656	Mean Difference (IV, Random, 95% CI)	-2.15 [-4.66, 0.36]
1.4 Adverse Effects- Dyskinesia	8	2930	Risk Difference (M-H, Fixed, 95% CI)	0.05 [0.03, 0.07]