

Parkinson's disease

Synopses of Cochrane systematic reviews

1. Anticholinergics for symptomatic management of Parkinson's disease

Anticholinergic drugs can improve movement symptoms of Parkinson's disease, but with adverse mental effects, and there is not enough evidence to compare the different drugs.

Anticholinergics were the first drugs available for Parkinson's disease and they are still widely used. They are believed to work by counteracting an imbalance which exists in Parkinson's disease between two chemicals in the brain which transmit messages between nerve cells. However, anticholinergic drugs have been associated with unfavourable side effects. They are used alone, or with other anti-Parkinson's drugs. The review of trials found that anticholinergics can improve movement problems in people with Parkinson's disease, but also cause adverse mental effects (such as confusion, memory problems, restlessness and hallucinations). There is not enough evidence to compare the different anticholinergic drugs.

2. Monoamine oxidase B inhibitors for early Parkinson's disease

Parkinson's disease is a disabling condition of the brain characterized by slowness of movement, shaking (tremor), stiffness, and in the later stages, loss of balance. Many of these symptoms are due to the loss of certain groups of nerves in the brain, which results in the lack of a chemical called dopamine. Currently, the best treatment for Parkinson's is levodopa (Sinemet or Madopar) which is converted in the brain into dopamine. Although a very good treatment, levodopa does not slow the progression of the underlying condition and after a while drug use can cause involuntary movements (dyskinesia), painful leg cramps (dystonia) and a shortened response to each dose (motor fluctuations). Monoamine oxidase B (MAO-B) inhibitors such as selegiline (Eldepryl or Selgene) boost the levels of dopamine by a different mechanism which may reduce the risk of these complications and slow disease progression. We reviewed ten controlled trials (in a total of 2422 patients) that compared giving MAO-B inhibitors with not giving them in people with early Parkinson's to see if it was safe and effective. The results show that, although MAO-B inhibitors do improve symptoms of Parkinson's and delay the need for levodopa by a few months, they are too weak to have a major effect and do not seem to delay the progression of the condition. They may, however, reduce motor fluctuations although more information is needed to be certain of this. Although they can cause some side-effects, these are generally mild.

3. Bromocriptine versus levodopa in early Parkinson's disease

Bromocriptine delays movement fluctuations in patients with Parkinson's disease who can tolerate the drug.

Parkinson's disease is a disabling disease characterized by slowness of movement, trembling (tremors) and stiffness. Currently, the best treatment for Parkinson's disease is levodopa. However, with the number of levodopa treatment years, new disabling fluctuations of movement occur. To overcome this problem, bromocriptine has been tried as an alternative drug. The review of trials found that bromocriptine may be helpful in delaying such fluctuations of movement problems in patients with Parkinson's disease who can tolerate the drug.

4. Bromocriptine/levodopa combined versus levodopa alone for early Parkinson's disease

Bromocriptine/levodopa combination therapy does not prevent or delay movement fluctuations in Parkinson's disease.

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trials found no evidence that early use of combined bromocriptine/levodopa prevents or delays such fluctuations of movement in patients with Parkinson's disease.

5. Amantadine for dyskinesia in Parkinson's disease

There is not enough evidence about the safety and effectiveness of amantadine for people with dyskinesia in Parkinson's disease.

Levodopa is regarded as the most effective treatment for Parkinson's disease but in many patients it causes abnormal involuntary movements known as dyskinesias. It is thought that amantadine may be added to levodopa to reduce dyskinesias in patients with Parkinson's disease without worsening Parkinsonian symptoms. This review found that there is not enough evidence from trials about the effects of amantadine for people with dyskinesia in Parkinson's disease. Adverse effects in trials so far have included confusion, worsening of hallucinations, the re-emergence of palpitations, nausea, dry mouth, swelling of feet and constipation.

6. Amantadine in Parkinson's disease

There is not enough evidence about the safety and effectiveness of amantadine for people with Parkinson's disease.

Parkinson's disease causes progressive muscle rigidity, tremors and other symptoms. The most common drug used to try and relieve these symptoms is levodopa, but serious physical and psychiatric adverse effects are common. Amantadine is another option, used alone or with levodopa. Amantadine can have serious adverse effects (including psychiatric problems), and people can become resistant to the drug. The review found that there is not enough evidence from trials about the effects of amantadine for people with Parkinson's disease. Adverse effects in trials so far have not been severe, and included skin rash, dry mouth and blurred vision.

7. Bromocriptine for levodopa-induced motor complications in Parkinson's disease

This review identified important shortcomings regarding the methodological quality of eight trials. All studies failed to describe adequately their randomization procedure. Consultation with the trialists revealed that three trials adequately randomized their patients. Contrary to the information of the published report, one placebo-controlled trial appeared to be carried out as an open study and was therefore excluded. The remaining seven trials were reported to be carried out according to a double-blind design, although one was unblinded after five weeks. There was a conspicuous variability in the duration of trials: four to forty weeks (mean 14 weeks). None of the included trials was performed according to the intention-to-treat principle. With regard to the inclusion criteria, it frequently remained unclear if PD patients actually suffered from motor complications. Prominent differences between studies regarding the baseline characteristics and the rate by which BR was introduced during the titration phase were found. Major differences between studies emerged concerning the applied outcomes. The various methods used to evaluate the occurrence and/or severity of motor complications lacked a sound clinimetric basis. A great diversity of scales to evaluate impairment and disability was applied. None of the included trials reported whether scores on impairment and disability level referred to the "on"- or "off"-phase.

This review highlights major methodological problems and sources of heterogeneity that not only hamper the comparability of trials but also preclude a conclusion on the efficacy of BR in the adjunct treatment of PD patients with motor complications.

8. Cabergoline for levodopa-induced complications in Parkinson's disease

In the later stages of Parkinson's disease, side effects occur because of the use of levodopa treatment. These consist of involuntary writhing movements (choreoathetosis), painful cramps in the legs (dystonia) and a shortened response to each dose referred to as 'end-of-dose deterioration' or the 'wearing-off effect'. Dopamine agonist drugs act by mimicking levodopa in the brain, but they

do not cause these long-term treatment complications when used as initial therapy. For this reason, dopamine agonists have for some years been added once these problems develop in the hope of improving them. Cabergoline is a new dopamine agonist recently licensed in the UK for the treatment of later Parkinson's disease. In this review, we will examine the trials performed with this drug to see how effective it is and what side effects it causes.

Cabergoline has been compared with inactive placebo in two smaller and shorter (6 - 12 weeks) studies and one larger, medium term trial (24 weeks). These trials included 268 patients with Parkinson's disease and motor complications. The average reduction in the time patients spent in the immobile off state was 1.1 hours greater with cabergoline compared with placebo, although this was not statistically significant. Inadequate data on dyskinesia was collected to allow a conclusion to be drawn. A small but significant advantage of cabergoline over placebo was seen in one study for activities of daily living and physical functioning. No such advantage was seen in one other study due to small numbers of patients and the comparatively low doses of cabergoline used. Levodopa dose reduction was greater with cabergoline by 145 mg per day. There was a trend towards more side effects with cabergoline but towards fewer withdrawals from cabergoline treatment.

In the management of the motor complications seen in Parkinson's disease, cabergoline can be used to reduce levodopa dose and modestly improve motor function and activities of daily living with an acceptable side effect profile. This is based on, at best, medium term evidence. Further long term trials are required to compare the newer with the older dopamine agonists, particularly in terms of quality of life and cost.

9. Cabergoline versus bromocriptine for levodopa-induced complications in Parkinson's disease

In the later stages of Parkinson's disease, side effects occur because of the use of levodopa treatment. These consist of involuntary writhing movements (dyskinesia), painful cramps in the legs (dystonia) and a shortened response to each dose referred to as 'end-of-dose deterioration' or the 'wearing-off effect'. Dopamine agonist drugs act by mimicking levodopa in the brain, but they do not cause these long-term treatment complications when used as initial therapy. For this reason, dopamine agonists have for some years been added once these problems develop in the hope of improving them. Cabergoline is a new dopamine agonist recently licensed in the UK for the treatment of later Parkinson's disease. In this review, we will examine the trials performed with this drug to see how effective it is compared with the older drug bromocriptine and what side effects it causes.

Cabergoline has been compared with the older agonist bromocriptine in five studies including 1071 patients. Only one of the smaller studies was medium term (36 weeks), the others all being short term (12 -15 weeks). The time patients spent in the immobile off state was reduced with both agonists but slightly more by cabergoline compared with bromocriptine. This small advantage of cabergoline did not reach statistical significance. Dyskinesia reported as a side effect was significantly increased with cabergoline compared with bromocriptine. Physical impairment and disability were measured in four of the studies but no statistically significant advantage for cabergoline was found. The number of patients rated as much or very much improved on a clinician's global impression scale was similar with both agonists. Levodopa dose reduction was no different between cabergoline and bromocriptine. There was significantly more confusion with cabergoline. Otherwise, dopaminergic side effects were comparable with these agonists and no significant difference in the withdrawal rate from the trials was found.

Cabergoline produces similar benefits to bromocriptine in off time reduction, physical impairment and disability ratings, and levodopa dose reduction over the first three months of therapy. The frequency of side effects and withdrawals from treatment were similar with the two agonists apart from increased dyskinesia and confusion with cabergoline.

10. Catechol-O-methyltransferase inhibitors for levodopa-induced complications in Parkinson's disease

The COMT inhibitors entacapone and tolcapone show similar benefits in relieving levodopa-induced complications in Parkinson's disease but more data on the safety of tolcapone is required. As Parkinson's disease progresses the control of the symptoms often requires the addition of other drugs to levodopa. The principle aim of COMT inhibitor therapy is to increase the duration of effect of each levodopa dose and thus reduce the time patients spend in the relatively immobile 'off' phase. Tolcapone and entacapone can be used to reduce off time, reduce levodopa dose, and modestly improve motor impairment and disability. This is based on, at best, medium term evidence. However some participants on tolcapone had raised liver enzymes. Post-marketing surveillance identified three cases of fatal hepatic toxicity in patients treated with tolcapone. As a result, tolcapone has been withdrawn from some countries and severe restrictions on its use have been imposed in others.

11. Catechol-O-methyltransferase inhibitors versus active comparators for levodopa-induced complications in Parkinson's disease

Insufficient data are available on the benefits of the COMT inhibitor tolcapone compared with the dopamine agonists bromocriptine and pergolide in relieving the symptoms of later Parkinson's disease.

As Parkinson's disease progresses the control of the symptoms often requires the addition of other drugs to levodopa. The principle aim of COMT inhibitor therapy is to increase the duration of effect of each levodopa dose and thus reduce the time patients spend in the relatively immobile 'off' phase. However other drugs such as dopamine agonists can also be used at this stage of the disease. This review found that the COMT inhibitor tolcapone as an adjuvant to levodopa treatment had a similar level of benefits as two dopamine agonists, bromocriptine and pergolide. There was no significant difference in efficacy between the adjuvant tolcapone and adjuvant bromocriptine or pergolide in the medium-term. Tolcapone produced nausea less often than these agonists but there was some evidence of liver function abnormalities with tolcapone. Post-marketing surveillance identified three cases of fatal hepatic toxicity in patients treated with tolcapone. As a result, tolcapone has been withdrawn from some countries and severe restrictions on its use have been imposed in others. No evidence was found comparing entacapone with other adjuvant drugs for Parkinson's disease.

12. Lisuride for levodopa-induced complications in Parkinson's disease

No randomised controlled trials comparing lisuride with placebo in advanced Parkinson's disease with motor complications were found.

Well designed randomised controlled trials demonstrating efficacy and safety are required before the use of lisuride in later Parkinson's disease can be supported.

13. Lisuride versus bromocriptine for levodopa-induced complications in Parkinson's disease

Only one randomised cross-over trial including 20 patients has compared lisuride with bromocriptine as adjunct therapy in Parkinson's disease. Both lisuride and bromocriptine improved motor fluctuations with no significant differences between the agonists. However, this conclusion is based on an unvalidated 4 point rating scale which could only record positive outcomes. This, combined with the small size of the trial, suggests that firm conclusions on motor fluctuations should not be drawn. Lisuride and bromocriptine produced similar benefits in parkinsonian impairments according to the Columbia Rating Scale. Adverse events were similar with the two agonists and no withdrawals were reported from either drug.

The small size of this study and other methodological problems do not allow any firm conclusions to be drawn regarding the efficacy and safety of lisuride compared with bromocriptine in advanced

Parkinson's disease with motor complications.

14. Pergolide for levodopa-induced complications in Parkinson's disease

A large number of small RCTs were identified, but these were part of a large multicentre trial which was eventually published in full. The final publication was used as the only subject for this review. The time patients spent 'off' was reduced by 1.8 hours with pergolide compared with 0.2 hours with placebo ($p < 0.001$). Dyskinesia developed or deteriorated in 62% of pergolide-treated compared with 25% placebo-treated patients ($p < 0.05$). The excess in dyskinesia prevalence and severity resolved by the end of the study with levodopa reduction. Levodopa dose was reduced more in those receiving pergolide (235 mg v 51 mg; $p < 0.001$). Pergolide produced significant improvement in Hoehn and Yahr stage ($p < 0.05$) and both the motor and activities of daily living parts of a modified Columbia rating scale (both $p < 0.001$). Significantly more patients suffered nausea (24% v 13%; $p < 0.001$) and hallucinations (14% v 3%; $p < 0.01$) on pergolide. No difference was found in the numbers remaining on treatment at the end of the study (pergolide 84% v placebo 82%) but withdrawals due to adverse events were greater in those taking pergolide (10% v 4%).

Based on this single large multicentre study, pergolide reduces 'off' time and improves impairment and disability due to Parkinson's disease whilst allowing a reduction in levodopa dose. This is at the expense of dopaminergic adverse events. Further trials are required to compare pergolide with the newer dopamine agonists.

15. Pergolide versus bromocriptine for levodopa-induced complications in Parkinson's disease

Three short-term trials fulfilled the inclusion criteria for the review. Pergolide was superior to bromocriptine regarding UPDRS and NYPDS motor and NYPDS ADL scores in two trials. More patients recorded a 'marked' or 'moderate improvement' in clinician's global impression score with pergolide than bromocriptine in two studies. Insufficient evidence on fluctuations and dyskinesia was available to draw any conclusions. No significant differences between the agonists were seen in levodopa dose reduction, drop outs or adverse events. Although pergolide is superior to bromocriptine in reducing motor impairments and disability, no firm conclusions regarding levodopa-induced motor complications can be reached. Levodopa dose reduction, adverse events and withdrawals from treatment are similar for the two agonists. The small advantage of pergolide in efficacy does not take into account its additional cost compared with bromocriptine.

16. Pramipexole for levodopa-induced complications in Parkinson's disease

In the later stages of Parkinson's disease, side effects occur because of the use of levodopa in its treatment. These consist of involuntary writhing movements (dyskinesia), painful cramps in the legs and a shortened response to each dose referred to as 'end-of-dose deterioration' or the 'wearing-off effect'. Dopamine agonist drugs act by mimicking levodopa in the brain, but they do not cause these long-term treatment complications. For this reason, dopamine agonists have for some years been added once these problems develop in the hope of improving them. Pramipexole is a new dopamine agonist recently licensed in the UK for the treatment of later Parkinson's disease. In this review, we will examine the trials performed with this drug to see how effective it is and what side effects it causes.

Four trials have compared pramipexole with placebo in 669 patients with later Parkinson's disease. Two studies were medium term (24 weeks) and 2 studies were short term (4 weeks). Pramipexole significantly reduced the time patients spent in the immobile off state compared with placebo by an average of 1.8 hours. No changes occurred in a dyskinesia rating scale in any of the studies, but

dyskinesia recorded as a side effect was reported more frequently with pramipexole. A significant improvement occurred in the Unified Parkinson's Disease Rating Scale (UPDRS) complication score in 2 studies but not in the remaining trials. Significant improvements in UPDRS activities of daily living score occurred with pramipexole in all studies. Significant improvements in UPDRS motor scores in the mobile on state were reported in 3 of the 4 studies. Levodopa dose reduction was allowed in 3 studies and meta-analysis showed a significant difference in favour of pramipexole. There was a suggestion of more side effects such as nausea, vomiting and dizziness with pramipexole and a definite increase in hallucinations in those given pramipexole. There were significantly fewer withdrawals from pramipexole.

In conclusion, pramipexole can be used to reduce off time, improve motor impairments and disability and reduce levodopa dose at the expense of increased dyskinetic side effects. This is based on short and medium term trials (up to 24 weeks). Further trials are required to directly compare the newer with the older dopamine agonists.

17. Pramipexole versus bromocriptine for levodopa-induced complications in Parkinson's disease

In the later stages of Parkinson's disease, side effects occur because of the use of levodopa in its treatment. These consist of involuntary writhing movements (dyskinesia), painful cramps in the legs and a shortened response to each dose referred to as 'end-of-dose deterioration' or the 'wearing-off effect'. Dopamine agonist drugs act by mimicking levodopa in the brain, but they do not cause these long-term treatment complications. For this reason, dopamine agonists have for some years been added once these problems develop in the hope of improving them. Pramipexole is a new dopamine agonist recently licensed in the UK for the treatment of later Parkinson's disease. In comparison, bromocriptine has been available since the late 1970s and is a well established agonist. In this review, we will examine the trials performed to see whether pramipexole is better than bromocriptine in terms of effectiveness and side effects.

One trial compared pramipexole with bromocriptine but this was not designed to examine differences between the two treatments as there were too few patients included. However, there was a larger reduction in the time patients spent in the immobile off state with pramipexole therapy compared with bromocriptine by an average of 1.4 hours. No differences occurred in dyskinesia rating scale, dyskinesia as a side effect or Unified Parkinson's Disease Rating Scale (UPDRS) complication score. The UPDRS activities of daily living and motor scores showed similar improvements compared to placebo with both agonists. Levodopa dose reduction was similar with both agonists. Subscales of a quality of life measure, the Functional Status Questionnaire, showed significant improvements compared to placebo with both agonists. The finding that another quality of life scale, the EuroQol, improved significantly compared with placebo with pramipexole but not bromocriptine should be treated with caution. Side effects such as nausea, vomiting, and faintness were similar with each agonist, as was the withdrawal from treatment rate.

No conclusions regarding the comparative effectiveness and safety of pramipexole versus bromocriptine can be drawn as this single trial did not have adequate numbers of patients to assess such differences. Further larger trials are required to examine this issue in the future.

18. Ropinirole for levodopa-induced complications in Parkinson's disease

In the later stages of Parkinson's disease, side effects occur because of the use of levodopa treatment. These consist of involuntary writhing movements (dyskinesia), painful cramps in the legs (dystonia) and a shortened response to each dose referred to as 'end-of-dose deterioration' or the 'wearing-off effect'. Dopamine agonist drugs act by mimicking levodopa in the brain, but they do not cause these long-term treatment complications. For this reason, dopamine agonists have for some years been added once these problems develop in the hope of improving them. Ropinirole is a new dopamine agonist recently licensed in the UK for the treatment of early and later Parkinson's disease. In this review, we will examine the trials performed with this drug to see how effective it is

and what side effects it causes.

Three trials have compared ropinirole with an inactive placebo in 263 patients in the later stages of Parkinson's disease. Two studies were relatively small, were conducted over the short term (12 weeks), and used relatively low doses of ropinirole (maximum allowed 8 and 10 mg/d) in a twice daily administration regime. For these reasons, the results of these trials have not been included in a statistical overview. The other study was medium term (26 weeks) and used ropinirole doses in line with the current UK licensed maximum (24 mg/d) in a three times a day regime. The conclusions of this review are based on this single trial and thus should be viewed with some caution.

No clear difference in the time patients spent in the immobile off state was found between ropinirole and placebo. However, this was probably due to there being too few patients in the trial. Measurements of physical difficulties and problems with activities of daily living (such as bathing, shopping, etc.) were poor in these studies with incomplete information available. Levodopa dose reduction was greater with ropinirole than placebo by 180 mg/d. However, dyskinesia was increased in those who received ropinirole (2.9 times more common with ropinirole than placebo). No other differences in side effects or withdrawals from treatment were found.

Ropinirole reduces levodopa dose but at the expense of increased dyskinetic side effects. No clear effect on off time reduction was found in this single trial. Side effects were similar with ropinirole and placebo. These conclusions apply to short and medium term treatment, up to 26 weeks. Further longer term trials are required, with measurements of quality of life and costs, and also studies to compare the newer with the older dopamine agonists.

19. Ropinirole versus bromocriptine for levodopa-induced complications in Parkinson's disease

In the later stages of Parkinson's disease, side effects occur because of the use of levodopa treatment. These consist of involuntary writhing movements (dyskinesia), painful cramps in the legs (dystonia) and a shortened response to each dose referred to as 'end-of-dose deterioration' or the 'wearing-off effect'. Dopamine agonist drugs act by mimicking dopamine in the brain, but they do not cause these long-term treatment complications. For this reason, dopamine agonists have for some years been added once these problems develop in the hope of improving them. Ropinirole is a new dopamine agonist recently licensed in the UK for the treatment of early and later Parkinson's disease. In this review, we will examine the trials performed with this drug to see how it compares with one of the older agonists bromocriptine.

Three trials have compared ropinirole with bromocriptine in 482 patients in the later stages of Parkinson's disease. Two studies were conducted over the short term (8 and 16 weeks), and used relatively low doses of ropinirole (9 mg/d) and bromocriptine (17.5 and 22.5mg/d). The other study was medium term (25 weeks) and used ropinirole doses in line with the current UK licensed maximum (24 mg/d).

No significant differences were found between the agonists in the time patients spent in the immobile off state, in dyskinesia reported as a side effect, in measurements of physical difficulties and problems with activities of daily living (such as bathing, shopping, etc.), or in levodopa dose reduction. No differences in side effects or withdrawals from treatment were found apart from less nausea with ropinirole.

In patients with Parkinson's disease and motor complications, ropinirole has similar effects to bromocriptine in terms of improving off time and reducing levodopa dose, without increasing adverse events including dyskinesia. However, these comparator studies may have been underpowered to detect clinically meaningful differences between the agonists.

20. Cholinesterase inhibitors for Parkinson's disease dementia

Rivastigmine appears to moderately improve cognition and to a lesser extent activities of daily living in patients with PDD.

Dementia is frequently associated with Parkinson's Disease. While a number of neurotransmitters

appear to be involved, loss of cholinergic functioning is particularly associated with Parkinson's Disease Dementia (PDD) suggesting a potential utility for cholinesterase inhibitors. Rivastigmine appears to moderately improve cognition and to a lesser extent activities of daily living in patients with PDD. There was a clinically meaningful benefit in 15% of patients. Efficacy in other domains requires confirmation. Tolerability in particular nausea, vomiting and tremor appear problematic.

21. Therapies for Depression in Parkinson's Disease

Anti-depressant therapies may be able to help relieve depression in people with Parkinson's disease but more research is needed on safety and effectiveness.

Parkinson's disease can lead to psychiatric as well as physical symptoms, the most common of which is depression. Oral antidepressants, electroconvulsive therapy or behavioural therapy are currently used in the treatment of depression in Parkinson's disease. No trials were found examining the efficacy of electroconvulsive therapy or behavioural therapy. We identified three trials which examined antidepressant drugs. The review found that there is not enough evidence from the trials about the effects of antidepressant drugs for the treatment of depression in people with Parkinson's disease. Adverse effects in trials so far have not been severe, and included visual hallucinations and confusion.