Pramipexole for Parkinson's disease

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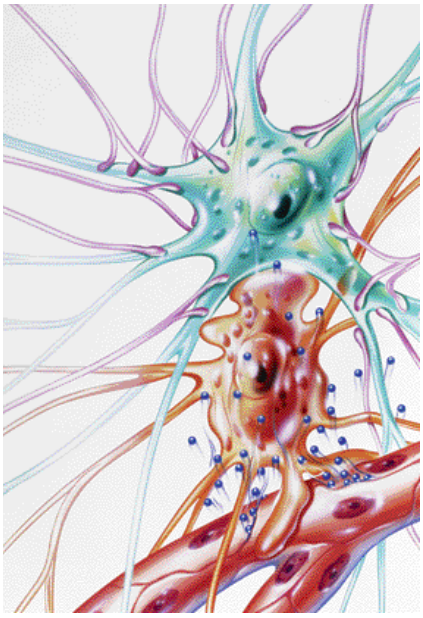
Pramipexole (Sifrol) is a highly potent dopaminergic drug that is useful for the treatment of both early and mid-to-late stage Parkinson's disease.



PHOTOLIBRARY

What is pramipexole?

Pramipexole (Sifrol) is a nonergoline dopamine agonist that was PBS listed (restricted benefit) on 1 June 2008 as adjunctive treatment for patients with Parkinson's disease who are treated with levodopa–decarboxylase inhibitor combinations. Pramipexole has Therapeutic Goods Administration (TGA) approval for use as monotherapy and adjunctive therapy with levodopa for Parkinson's disease. Pramipexole is also TGA approved for the symptomatic treatment of restless legs syndrome.

Pramipexole has been used in the USA and Europe for approximately 10 years for the treatment of Parkinson's disease. It has not been available for use in Australia because of pricing issues rather than concerns about side effects or risks.

What is the evidence?

The gold standard in the treatment of Parkinson's disease remains levodopa combined with a dopa-decarboxylase inhibitor. This is the most potent drug combination in terms of reduction in impairment, and it also has one of the best safety profiles. However, levodopa has the disadvantage of a relatively short half-life of 60 to 90 minutes and therefore requires periodic dosing throughout the day.

In the normal state, dopaminergic neurons provide an almost continuous flow of dopamine to receptors in the striatum, allowing control of movement via the selection of desired movement and rejection of undesired movement.[1] In early Parkinson's disease, the short half-life of levodopa, together with the usual practice of administering the drug three to four times daily in patients with nonfluctuating Parkinson's disease, exposes the brain to pulsatile dopaminergic stimulation. In animal models, pulsatile dopaminergic stimulation is one of the main determinants of whether a drug causes drug-induced dyskinesias. In patients with mid-stage Parkinson's disease who are experiencing motor fluctuations, the short half-life of levodopa also contributes to wearing off (end-of-dose deterioration). Another major problem with levodopa is that it is absorbed only through the small intestine but not through the stomach. Therefore, unpredictable and delayed gastric emptying can further contribute significantly to disabling motor fluctuations.

Dopamine agonists are synthetic dopaminergic drugs. They confer benefits compared with levodopa because of their relatively long half-life. With pramipexole, the half-life is about eight hours in young healthy volunteers and 12 hours in elderly volunteers. Steady state concentrations are achieved within two days of dosing. In comparison, the half-life of one of the currently available ergot dopamine agonists, cabergoline (Cabaser), is about 65 hours.

In early Parkinson's disease, using pramipexole as the initial therapy (with levodopa rescue in patients with incomplete symptom relief) as opposed to levodopa alone has been shown to significantly reduce the risk of developing wearing off, mild dyskinesias and on-off motor fluctuations over a two-year period.[2] In this study, 28% of patients treated with

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pramipexole developed motor complications, in comparison with 51% of patients initially treated with levodopa. The absolute risk reduction of 23% means that four to five patients need to be treated over two years with pramipexole as initial therapy to prevent one patient developing motor complications.[2] This study showed that patients with Parkinson's disease initially treated with levodopa had significantly better motor responses and reduction in their disease severity than the pramipexole group, but there was no difference between the groups in the quality of life reported. When these groups were compared at four years, 52% of patients assigned to pramipexole treatment developed mild dyskinesias, wearing off or on-off fluctuations compared with 74% of the levodopa group, although there was no difference between groups for disabling dyskinesias.[3]

Approximately 30 to 40% of patients will be able to remain on monotherapy with pramipexole even after three years. In patients with more advanced Parkinson's disease who are experiencing motor fluctuations, pramipexole has been shown to reduce 'off' time by an average of two hours per day.[4]

Pramipexole can be used in patients with early Parkinson's disease as initial therapy with the aim of reducing the risk of motor fluctuations and dyskinesias in the short to medium term. In mid-stage Parkinson's disease, pramipexole can be used to reduce the severity of motor fluctuations, which are a significant contribution to motor disability in these patients. When pramipexole is used as add-on therapy, especially if the intention is to reduce dyskinesia, a reduction of levodopa of between 25 and 40% may be required.

There have been no head-to-head comparisons of pramipexole and cabergoline, currently the most widely prescribed ergot dopamine agonist in Australia. In our experience of treating 30 to 40 patients with pramipexole over the past decade, we have found pramipexole to be at least as effective as cabergoline.

How is it administered?

In patients starting pramipexole for the first time, our practice is to introduce the drug slowly, with an initial dose of 0.125 mg (half a 0.25 mg tablet) daily, increasing weekly by half a tablet to a dose of 0.25 mg three times per day. Thereafter, the drug can usually be increased more quickly by 0.25 mg (one tablet) per week to a maintenance dose of 0.5 to 1 mg three to four times per day. In our experience patients usually require a dose of 0.5 to 1 mg three to four times per day to obtain maximal clinical benefit.

When switching a patient from a stable dose of cabergoline to pramipexole, 0.75 mg pramipexole equals approximately 1 mg cabergoline. Given the long half-life of cabergoline, it can be ceased one day, and then the dose of pramipexole incremented fairly quickly within one to two weeks to the equivalent dose of cabergoline. As cabergoline is administered as one to two doses per day, the new dose of pramipexole needs to be divided into three to four doses per day. The dosing schedule of pramipexole is the same when used as initial or add-on therapy for Parkinson's disease. Both GPs and specialists are able to prescribe pramipexole in accordance with the PBS guidelines.

If discontinuation of pramipexole is required, this should be done with a gradual dose reduction. Sudden withdrawal of dopaminergic agents can place patients at risk of Parkinsonism-hyperpyrexia syndrome and/or neuroleptic malignant syndrome.

What are the side effects?

The side-effect profile of pramipexole is similar to that of most dopamine agonists. There are the usual side effects related to increased dopaminergic therapy such as nausea, vomiting, hallucinations, confusion and precipitation or worsening of dyskinesia.

In addition, it is increasingly recognised that patients treated with dopaminergic therapy, particularly dopamine agonists, are at risk of developing impulse-control disorders, including pathological gambling, hypersexuality, compulsive eating, compulsive shopping, kleptomania and impulsive aggressive disorder. These disorders often do not appear until patients have been taking treatment for at least three to six months. It is therefore essential that patients are warned about this possibility and questioned on repeat visits, as well as given instructions to alert their treating physician immediately if symptoms occur to avoid social or financial harm. Estimates of the lifetime prevalence of impulse-control disorders in Parkinson's disease may be as high as 14%.[5] Immediate management is essential to avoid the major adverse outcomes associated with these behaviours. Discontinuation will result in marked reduction or cessation of these behaviours, usually within days to weeks. Dose reduction and/or switching to an alternative dopamine agonist have been recommended by some but in our experience has not been a reliable intervention.

Another side effect that can be triggered by the use of pramipexole is excessive sleepiness, which can manifest simply as mild excessive daytime somnolence. However, in its most extreme form it can cause sleep attacks (sudden onset of sleep). Sleep attacks can be sufficiently rapid in onset and unpredictable so that they can cause motor vehicle accidents. This side effect tends to emerge during the dose escalation phase.[2] Patients need to be carefully warned when commencing therapy that should symptoms of increased sleepiness occur while taking the medication, driving should be ceased altogether. Patients should also be warned that this side effect may be influenced by external factors such as sleep deprivation, driving long distances and use of other medications. Patients may therefore be required to modify their driving habits on a situational basis.

Finally, we have found ankle oedema and, rarely, generalised oedema to be a more common side effect in patients taking pramipexole compared with cabergoline or other dopaminergic drugs. Oedema is more commonly encountered in the maintenance phase of treatment.[2,3]

Pramipexole does not carry the risk of fibrosis and valvular heart disease that are encountered with ergot dopamine agonists.

Summary

In summary, pramipexole is a highly potent dopaminergic drug that is useful for the treatment of both early and mid-to-late stage Parkinson's disease. It is generally well tolerated and effective in many patients with Parkinson's disease. It has a predictable side-effect profile that, although potentially serious, can be managed if patients are given clear instructions and warnings about these potential side effects and how they can deal with them.

Pramipexole is currently only PBS listed as add-on therapy for patients already taking levodopa–decarboxylase inhibitor combinations. A private script can be given to patients who wish to commence pramipexole monotherapy for early Parkinson's disease, as it is TGA approved for this indication. MT

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COMPETING INTERESTS: Dr Fung is on Advisory Boards for Allergan, Boehringer Ingelheim (including the Sifrol Advisory Board), Ipsen, Novartis, Solvay and UCB Pharma. Drs Parratt and Hely: None.