

# RGH Pharmacy E-Bulletin

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A joint initiative of the Patient Services Section and the Drug and Therapeutics Information Service of the Pharmacy Department, Repatriation General Hospital, Daw Park, South Australia. The RGH Pharmacy E-Bulletin is distributed in electronic format on a weekly basis, and aims to present concise, factual information on issues of current interest in therapeutics, drug safety and cost-effective use of medications.

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## Pramipexole in Parkinson's Disease and RLS

Pramipexole is a recently released drug that is used for the treatment of Parkinson's disease. In Australia, supply as a subsidised benefit through the Pharmaceutical Benefits Scheme (PBS) is restricted to use as an adjunctive therapy for patients being treated with levodopa-decarboxylase inhibitor combinations. In addition to its use for Parkinson's disease, pramipexole is also being used as therapy to treat Restless Legs Syndrome (RLS).

Pramipexole is a non-ergot dopamine agonist with high relative in vitro specificity and full intrinsic activity at the D2 subfamily of dopamine receptors, binding with higher affinity to D3 rather than D2 or D4 receptor subtypes. Its mechanism of action in the treatment of Parkinson's disease is via stimulation of dopamine receptors in the striatum, inhibiting dopamine synthesis, and its release and turnover.

Long term use of levodopa combinations in patients with Parkinson's disease is associated with development of motor complications including abnormal involuntary movements and the wearing off phenomenon. It is thought that dopamine agonists can reduce the duration of immobile off periods whilst maintaining or improving motor impairments and only minimally increasing dopaminergic side effects.

A Cochrane review to compare efficacy of adjuvant pramipexole vs. placebo for levodopa-induced complications of Parkinson's disease showed pramipexole significantly reduced the time patients spent in an immobile "off" state by an average of 1.8 hours. Significant improvements in motor scores were also noted. This is based on trials up to 24 weeks. Comparisons of pramipexole with older dopaminergic agents have been inconclusive.

In RLS patients complain of limb discomfort at rest and an urge to move the affected limb and unpleasant sensations that are often described as itching, burning aching and painful. The nature of the association between RLS and Parkinson's disease is unclear but both conditions will respond to dopaminergic agents.

The dose of pramipexole for the treatment of Parkinson's disease is 125 microgram three times a day, and can be increased to a maximum of 4.5mg daily. For restless legs syndrome the recommended dose is 125 microgram 2 to 3 hours before bed up to a maximum dose of 750 microgram.

Pramipexole is rapidly absorbed and it undergoes little pre-systemic metabolism. Food does not affect extent of absorption but delays maximum plasma concentrations by one hour when the drug is taken with a meal. In patients with severe renal impairment dose adjustment is necessary.

Common adverse events include nausea and dizziness, sedation, constipation, confusion, dry mouth and headache. Impulse disorders including pathological gambling and hypersexuality are also increasingly being reported. Patients should be alerted to other potentially dangerous side effects such as hallucinations and pathological somnolence during the day, with the possibility of falling asleep whilst engaged in daily living activities such as driving or operating machinery being of some considerable concern.

Augmentation of symptoms of RLS is a phenomenon which may be encountered in patients on dopaminergic agents. Symptoms of augmentation include increased severity of RLS, changes in time of onset to earlier in the day and commencement of symptoms in previously uninvolved limbs. Increasing the dose of the dopaminergic agent can aggravate symptoms, so switching to another dopaminergic agent or temporary use of opioids whilst reducing dose of dopaminergic drug is recommended.

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