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Treatment of early Parkinson's disease

Ropinirole may improve function, while minimising involuntary movements

Parkinson's disease, a progressive neurodegenerative disorder, affects about 1% of the population over the age of 50. While it has no cure, it is the only neurodegenerative disorder with a range of medical and neurosurgical treatments that substantially reduce clinical symptoms.[1] However, medical management of early Parkinson's disease is controversial because of the potential risks and benefits to patients. Some clinicians prefer to use levodopa, a dopamine precursor, since it promptly relieves symptoms. Others prescribe dopamine agonists and withhold levodopa because of its long term complications, namely abnormal involuntary movements and potential neurotoxicity. Inevitably, managing the side effects of antiparkinsonian drugs becomes a therapeutic focus along with treating the primary motor abnormalities.[1] Extended controlled clinical trials are the only means of obtaining evidence based guidance on the use of dopamine agonists or levodopa for the management of early Parkinson's disease.

The results of a recent multisite, five year, randomised, double blind study comparing the incidence of dyskinesia with levodopa or ropinirole, a dopamine D_2 receptor agonist,[2] should sway practitioners towards initial treatment with agonists for early Parkinson's disease. In contrast to the hypokinesis that characterises Parkinson's disease, dyskinesias related to antiparkinsonian drugs involve hyperkinetic choreoathetoid, lurching, and jerky movements. These movements are thought to be related to the underlying severity of the disease and alterations in postsynaptic receptors, as well as pulsatile stimulation of dopamine receptors resulting from the shorter half life of levodopa.[3] For many patients, these abnormal involuntary movements are unsightly if not distracting, disfiguring, exhausting, painful, or frankly disabling. They tend to coincide with peak effects of each levodopa dose, which is often when the desired relief of the motor symptoms of Parkinson's disease (tremor, rigidity, gait disturbances, bradykinesia, and akinesia) occurs. Accordingly, antiparkinsonian treatments that avoid or delay the onset of motor complications are needed.

Of 268 patients with mild to moderately severe Parkinson's disease (Hoehn and Yahr stages I-III) in the trial, 179 took ropinirole up to 24 mg/day and 89 took levodopa up to 1200 mg/day.[2] If motor symptoms were not adequately controlled, participants were given supplemental, open label levodopa (51% of patients receiving ropinirole and 35% of those receiving levodopa). At the end of five years, motor deficits were slightly but significantly greater in the patients given ropinirole, but functional abilities were similar in the two groups. However, the length of time until dyskinesia developed in the 25% of patients remaining in the study was 214 weeks for those given ropinirole and 104 weeks for those given levodopa alone. Further, dyskinesias developed at a rate nearly three times slower in the ropinirole treated patients compared with the levodopa only group. Moreover, the dyskinesias were disabling in 23% of the levodopa treated patients compared with 8% of ropinirole treated patients. Before addition of supplementary levodopa, only 5% of patients receiving ropinirole had dyskinesia compared with 36% of those receiving levodopa. Thus, although levodopa remains the optimal treatment for Parkinson's disease, associated dyskinesia is a serious concern.

The results for those patients who completed the five year trial indicate that initial treatment with ropinirole in early Parkinson's disease adequately controls symptoms (based on functional abilities) and delays onset of problematic motor complications. However, since about half of each group withdrew during the study, neither ropinirole nor levodopa is an ideal treatment for many patients. Many adverse effects not involving dyskinesia occurred, causing nearly a third of participants to withdraw from the trial. Nausea, a leading reason why patients in our practice stop taking ropinirole, was reported by almost half of the participants in both groups. However, domperidone, used to counteract nausea, presumably allowed all but about 5% of participants who were affected by nausea to finish the trial. Hallucinations were a more serious complication of ropinirole (17% affected, causing 4% to quit the study) compared with levodopa alone (6% affected, causing 2% to quit the study). Other adverse events and variables were similar in the two groups.

Several other issues warrant consideration in interpreting and applying the results from this study. Firstly, initial treatment for early Parkinson's disease is not restricted to levodopa or dopamine agonists. Amantadine, anticholinergic drugs, selegiline, and non-pharmacological treatments (such as physical therapy) provide symptomatic relief in mildly affected patients. Thus, use of levodopa and dopamine agonists can be delayed until symptoms are clinically disabling.[4] Whether initial treatment with these alternative agents influences subsequent development of motor complications is unknown.

Secondly, the study did not examine the effects of disease severity or duration on the incidence of dyskinesia and other adverse effects. Such information would influence treatment, since the six month interim

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analysis of the study patients showed that levodopa was associated with significantly better motor function compared with ropinirole in patients with more advanced disease (Hoehn and Yahr stage >II) but that motor function was similar with either drug among less affected patients.[5]

Finally, the role of concurrent psychiatric illnesses was not addressed. Depressive and anxiety disorders affect at least half of patients with Parkinson's disease but are underrecognised and inadequately treated.[6] Thus, they potentially contribute to the perceived inefficacy of antiparkinsonian drugs and heighten the risk of premature withdrawal of the drug or the development of dyskinesias with increases in drug dose.

Despite the remaining unanswered questions, ropinirole seems to be an effective treatment for early Parkinson's disease. Although levodopa remains the optimal treatment for Parkinson's disease, ropinirole provides similar improvements in functional abilities while minimising abnormal involuntary movements.

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Ropinirole is made by SmithKline Beecham.

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The research needs of primary care

Trials must be relevant to patients

A health service that is led by primary care must be able to inquire into the practice of primary care; let research in primary care blossom. In England, at least, this logic now seems to be backed by political will. The Mant report (from a subcommittee of the health service's Central Research and Development Committee in 1997) states that there is an urgent need for both research and researchers in primary care.[1] The full committee later challenged universities to support this recommendation.[2] It is now government policy to develop research capacity through primary care research networks.[3]

Two papers, one in this week's *BMJ*, the other recently published in the journal, point the way towards conducting randomised controlled trials that are relevant to primary care. Both papers argue that it is difficult for researchers to gather a sample that is representative of the whole population. Wilson et al (p 24) point out that clinical trials must be conducted in primary care rather than secondary care or else the sample will include only those who have reached secondary care.[4] Rogers et al argue that trials must be relevant to a wide range of practices if a variety of practices are to be encouraged to participate in research.[5]

I experienced the difficulty of recruiting a representative sample of practices recently when coordinating recruitment for a large randomised controlled trial on the management of hypertension in primary care in west London. Altogether, 106 general practices—one fifth of the total practice pool—sent personalised letters to eligible patients inviting them to take part. However, as in Wilson et al's study, only one tenth of the potential sample was recruited. Nine out of 10 patients in west London were excluded, or excluded themselves, from this study. The reasons relate to understandable everyday factors. Firstly, patients and doctors often have medical reasons for preferring a particular way of managing a condition and do not want it changed—for example, a β blocker may help someone's panic as well as their hypertension. Secondly, people may be motivated to use some treatments and not others—they may trust one drug over another because a relative derived some benefit from it. Thirdly, there may be difficulties in following a research protocol: people forget to take tablets, don't want to attend for follow up, want to choose which arm of the study they are enrolled in, or their hypertension is compounded by heart failure, asthma, or fear.

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Comprehensive representation of the population matters only if we decide that randomised controlled trials are the last word in research. Randomised controlled trials are designed to address one or two issues and make sense of them in isolation. But these trials represent only one way of looking at things. General practitioners often have to manage multiple, interacting factors.[6 7] Occasionally patients do present with a simple symptom that requires a simple diagnosis and cure, but more often they have a multitude of interwoven issues that need unravelling.[8]

The challenge is to develop "real world" research that can capture something of these complexities.

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