Parkinson's disease

# Cholinesterase inhibitors for treatment of dementia associated with Parkinson's disease

J L Cummings

## Improving cognitive function and reducing neuropsychiatric symptoms

Patients with Parkinson's disease (PD) have a significant risk of developing dementia in the course of their illness. Cross sectional studies suggest a dementia prevalence rate of 30% to 40%.[1] Longitudinal studies indicate that the cumulative frequency of dementia in patients with PD is 60% to 80%.[1] The risk of dementia for individuals with PD is approximately six fold greater than that of age matched controls. The increased rate of dementia in PD reflects the substantial elevation of risk for dementia in patients with PD above the risk posed by Alzheimer's disease in this same population. Recent studies demonstrate a strong correlation between the occurrence of Lewy body pathology and severity of dementia in patients with PD.[2] The sensitivity, specificity, positive predictive value, and negative predictive value of cortical Lewy bodies for dementia exceeds that of senile plaques or neurofibrillary tangles,[2] again suggesting that the dementia of PD is related to the unique pathology of PD and in most cases does not reflect co-occurring Alzheimer's disease. There is a marked cholinergic deficit in patients with PD and dementia indicating that there is a cholinergic contribution to the cognitive decline.[3]

The presence of a cortical cholinergic deficit in patients with PD and dementia suggests that treatment with a cholinesterase inhibitor (ChE-I) may be beneficial. In this issue, Ravina and colleagues (***pp 934–9***)[4] report the results of a small double blind placebo controlled crossover study of donepezil for treatment of dementia in PD. Twenty-two patients participated in the study, which consisted of two treatment periods of 10 weeks separated by a 6 week wash out interval. The primary outcome measure was the Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAScog). While receiving donepezil, patients evidenced a mean 1.9 point improvement on the ADAScog, a change that did not reach statistical significance. The secondary outcome measures included the Mini Mental State Examination (MMSE), Mattis Dementia Rating Scale (MDRS), Clinical Global Impression of Change (CGI), and Brief Psychiatric Rating Scale (BPRS). There was a significant 2 point benefit on the MMSE and a significant 0.37 point improvement on the CGI. No beneficial or detrimental changes were observed on either the MDRS or the BPRS. All but three patients completed the trial (two dropouts during the donepezil treatment period and one dropout during placebo treatment), and no statistically significant differences in adverse events were found. Donepezil did not worsen parkinsonism. The authors concluded that donepezil may produce a modest cognitive benefit in patients with PD and dementia. Although the primary outcome measure did not distinguish the two groups there was a trend for improvement following treatment with donepezil and two secondary measures including the MMSE showed a statistically significant benefit. The power to detect differences of small magnitude is compromised by the limited sample size.

This study with donepezil must be seen in the context of the much larger double blind placebo controlled parallel group study of rivastigmine for the treatment of PD with dementia recently reported by Emre and colleagues.[5] This trial enrolled 541 patients of whom 410 completed the study. Statistically significant benefit was seen for both primary measures (ADAScog and the CGI) as well as the secondary measures including the Alzheimer's Disease Cooperative Study Activities of Daily Living Scale, the Neuropsychiatric Inventory, MMSE, Cognitive Drug Research power of attention test, verbal fluency test, and clock drawing test. No worsening of parkinsonism was noted on formal rating scales but adverse event reporting suggested an increase in tremor in the patients treated with rivastigmine. Tremor was rarely sufficient to lead to treatment discontinuation. The more favourable outcome of this study compared to that reported by Ravina et al[4] may be ascribed to the larger size and greater power of the trial, the use of rivastigmine rather than donepezil for acetylcholinesterase inhibition, or other differences in trial design and analysis. The study by Emre and colleagues[5] adds substantial weight to the suggestion that cholinesterase inhibitors may be beneficial in the treatment of dementia associated with PD.

A major caveat in clinical trials for the treatment of dementia associated with PD concerns the measurement of cognitive deficits. In this patient group executive deficits predominate and are more marked than the classical instrumental deficits involving memory, language, and praxis characteristic of Alzheimer's disease. The MMSE and ADAScog are relatively sensitive to the cognitive changes of Alzheimer's disease but both instruments lack executive measures. Use of these instruments to render comparison with treatment responses in Alzheimer's disease feasible may compromise detection of the impact of cholinesterase inhibitors on executive functions mediated by frontal subcortical circuits. Ravina and colleagues[4] included the MDRS—an instrument with measures of executive function—and noted no effect from treatment with donepezil. Emre *et al*[5] included verbal fluency and clock drawing tasks that require executive function and observed improvement in both measures following treatment with rivastigmine. Inclusion of measures of executive function is critical to a comprehensive assessment of the effects of cholinesterase inhibitors and other agents potentially useful in the treatment of dementia associated with PD.

The two recent studies discussed above add to a growing literature suggesting that cholinesterase inhibitors improve cognitive function in patients who have dementia associated with PD.[6–8] Several studies also indicate that cholinesterase inhibitors may reduce neuropsychiatric symptoms in PD, particularly hallucinations and delusions.[7 8] Dementia is a significant risk factor for neuropsychiatric symptoms in PD.

The growing literature on the potential utility of cholinesterase inhibitors in dementia associated with PD suggest that these agents may be helpful in improving cognitive function and reducing neuropsychiatric symptoms. Additional research is needed to determine whether all cholinesterase inhibitors are of equal efficacy in this setting, the duration of benefit to be expected, and the interaction with dopaminergic

agents and psychotropic drugs commonly used in this patient population.

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Correspondence to: Dr Jeffrey L Cummings, Reed Neurological Research Center, 710 Westwood Plaza, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095-1769, USA; jcummings@mednet.ucla.edu

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Movement disorders

# Surgery for movement disorders: new applications?

**P Limousin-Dowsey, S Tisch**

## The effect of basal ganglia surgery on Tourette syndrome, tardive dyskinesias, and myoclonus–dystonia

The last 15 years have been a period of significant advances in functional neurosurgery for movement disorders largely due to the development of the technique of deep brain stimulation (DBS) and the refinement of the targeting procedure. Deep brain stimulation is now well established for the treatment of Parkinson's disease, tremor, and primary dystonia, and is progressively being used for new applications. In this issue, Houeto *et al*[1] (***pp 992–5***) present a case report on the effect of basal ganglia surgery on Tourette syndrome, Lenders *et al*[2] (***p 1039***) on tardive dyskinesias, and Magarinos-Ascone *et al*[3] (***pp 989–91***) on myoclonus–dystonia.

Tourette syndrome is a disabling movement disorder—the signs include motor and vocal tics and various behavioural dysfunction. Ablative procedures have been carried out in the frontal area or the thalamus. An earlier report has shown an improvement of tics in three patients following thalamic DBS.[4] In the present study Houeto *et al*[1] compared the effect in two targets—the centromedian-parafascicular complex of the thalamus (Ce-Pf) and the antero-medial part of the internal globus pallidus (GPi)—both part of the limbic basal ganglia-thalamo-cortical loop.[1] They conducted a double blind study of four periods with different conditions of stimulation: off-stimulation, GPi stimulation, Ce-Pf stimulation, and GPi and Ce-Pf stimulation. GPi stimulation or Ce-Pf stimulation improved tic severity by 70%, improved coprolalia, and eliminated self injuries. Emotions and depression were improved with Ce-Pf stimulation. Lenders *et al*[2] report on a patient with tardive dyskinesias, predominantly dyskinetic in the right hemibody treated by left pallidotomy with 5 years follow up of good improvement.[2] Few cases had been previously reported. Magariños-Ascone *et al*[3] report the improvement of a myoclonus–dystonia syndrome by GPi stimulation, confirming earlier reports.

These studies are all case reports and although encouraging the results are limited by virtue of the sample size. In rare disorders such as these a multicentre study would allow a larger number of patients to be followed. The best target for Tourette syndrome certainly needs additional data to support this early finding. Other issues exist with Tourette syndrome and tardive dyskinesias that often include debilitating psychiatric problems. Patients with psychiatric problems may become preoccupied with the DBS implanted system and could even develop delusions that DBS is exerting ''mind control''. Therefore it is particularly important in those patients to have a multidisciplinary team to discuss the specific ethical issues, establish strict criteria of selection, and evaluate the impact of surgery on all aspects of the disease. For some conditions improved rating scales may need to be developed to better quantify clinical outcome after surgery. The impact on cognitive and behaviour functions also need to be carefully documented. Unilateral pallidotomy involves a one off procedure and no implanted equipment, and might still have a place in experienced hands and selected cases like Lenders *et al*.[2] Many questions remain on the mechanism of action of basal ganglia and thalamic surgery, and in particular how can they improve such a variety of conditions.

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**Authors' affiliations**
**P Limousin-Dowsey, S Tisch,** Institute of Neurology, London, UK

Correspondence to: P Limousin-Dowsey, Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, Box 146, Queen Square, London WC1N 3BG, UK; p.limousin@ion.ucl.ac.uk

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