intention-to-treat analysis. Compared with trials of surgery versus nonsurgical management, clinical trials that compare two surgical techniques in the same condition will experience fewer problems of patient crossover and patient recruitment, and these types of studies are crucial. The RCT remains the gold standard for investigating causality, but perhaps we should start to consider alternative statistical models that have greater validity than cohort studies, yet are more feasible than RCTs. This topic is gathering momentum[7] and is starting to permeate into the literature on spinal surgery.[8]

Ultimately, if we as spinal surgeons can be convinced that our patients do just as well, or better, with a less invasive surgical technique, justifying a more invasive approach would be extremely difficult. But as we stand, although evidence from studies such as that of Lee *et al.*[1] are encouraging, the question as to whether size matters in spinal surgery remains open.

Cambridge University Hospitals NHS Trust, Academic Neurosurgery Unit, Box 166, Hills Road, Cambridge CB2 2QQ, UK.
richard.mannion@nhs.net

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PARKINSON DISEASE

Serotonin reuptake inhibitors for depression in PD

Santiago Perez-Lloret and Olivier Rascol

A recent study to investigate the safety and efficacy of serotonin reuptake inhibitors suggests that these drugs are beneficial for the treatment of depressive disorders in Parkinson disease. Whether these treatments will offer such benefits in the long term compared with other pharmacological and nonpharmacological approaches remains to be determined.

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Depression affects 30–50% of individuals with Parkinson disease (PD), often preceding the appearance of motor symptoms, and reducing health-related quality of life.[1,2] The diagnosis and assessment of depression in PD is difficult owing to the overlap of symptoms between depression and parkinsonism, and to cognitive impairment and fluctuations of mood, which can hinder the patient's capacity to report their symptoms. The classical definition of major depression in the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) does not capture many features of PD-associated depression, and no rating scale is fully satisfactory for assessment of depression in the context of PD.[2] Furthermore, the pathophysiology of depression in PD is poorly understood, with roles suggested both for endogenous abnormalities of central dopamine, norepinephrine and serotonin systems, and for the patient's response to physical handicap.

Objective assessments of antidepressant therapies in PD are lacking. A recent evidence-based medicine review concluded that the dopamine agonist pramipexole was the sole medication to be deemed "efficacious" for depression in this condition.[3] Imipramine derivatives, such as nortriptiline and desipramine, were considered as only "possibly useful" owing to paucity of evidence, and "insufficient evidence" was available to determine the efficacy of any other antidepressant. Similar conclusions were reached in a meta-analysis of randomized controlled trials (RCTs) to investigate selective serotonin reuptake inhibitors (SSRIs) that are frequently used for depression in PD.[4] Consequently, the treatment of millions of depressed patients with PD worldwide is based on extrapolation of empirical data from patients without PD. Major concerns remain regarding the efficacy and safety of antidepressants in PD, as these drugs can induce or worsen parkinsonism.[5] In this context, a study by Richard and colleagues,[6] published in *Neurology*, is most welcome. The researchers report outcomes from an RCT to assess the efficacy and safety of the SSRI paroxetine and of extended-release venlafaxine, a serotonin and noradrenaline reuptake inhibitor (SNRI), for the treatment of depressive disorders in PD. They conclude that these drugs are safe and efficacious in the treatment of depression in PD.

> "...diagnosis and assessment of depression in PD is difficult..."

The overall quality assessment of the trial reveals a good score (>80%) according to international standards.[3] The trial used a double-blind, randomized, placebo-controlled parallel-group design, thereby minimizing selection and confounding biases, and analyses were performed on an intention-to-treat basis, with correction factors for multiple comparisons.[6] Drop-out rate was not trivial (12–19%), but sensitivity analyses with imputation techniques for missing data supported the robustness of the findings. For inclusion, patients were required to meet DSM-IV criteria for a depressive disorder or operationally defined 'subsyndromal depression'. Inclusion of patients with subsyndromal depression was a pragmatic approach, providing evidence of treatment effect on a frequently observed disease subtype. Such inclusion criteria, however, have not been universally validated,[2] reflecting the challenge of defining PD-related depression.

Of the 195 patients who were screened by Richard *et al.*,[6] only 115 were eligible for

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inclusion, which is fewer than the number initially estimated to provide adequate power for the study. Other trials in this field have faced the same problem of achieving suitable patient numbers, as recruiting depressed patients with PD who are not already receiving antidepressant medication is difficult.[7] Fortunately, the treatment effect observed by Richard *et al.*[6] was large enough to reach the statistical threshold despite reduced power. Primary outcome was the change from baseline in the 17-item Hamilton Depression (HAM-D) rating scale, which is considered the most suitable scale for use in clinical trials[2] even though somatic symptoms are heavily represented. Nonspecific motor changes were, however, unlikely to explain changes in HAM-D scores, as secondary outcomes showed consistent results, and Unified Parkinson Disease Rating Scale scores remained stable.

After 12 weeks of treatment, HAM-D scores were reduced by an average of 13 units in the paroxetine group, 11 units in the venlafaxine group, and 6.8 units in the placebo group. Notably, a minimum change in HAM-D score that defines a clinically important difference has not been established.[2] Richard *et al.* suggested a HAM-D score of ≤7 be used to define remission, with a 50% reduction in score defined as response to treatment.[6] 36% of patients receiving the SSRI, and 32% given the SNRI, were classed as being in remission at 12 weeks, compared with 28% of individuals in the placebo group. Tolerability was acceptable for both active drugs, and no major signal of concern was reported. Interestingly, insomnia was observed less frequently with paroxetine treatment than with either venlafaxine or placebo.

> “Objective assessments of antidepressant therapies in PD are lacking”

As the follow-up period was only 4 months and the number of patients was small, neither the long-term benefit of paroxetine or venlafaxine nor the profile of responders could be explored. Furthermore, the risk of treatment-related worsening of parkinsonism cannot be ruled out. As patients with cognitive impairment and those receiving antidepressants or monoamine oxidase inhibitors were excluded, the results cannot be extrapolated to all patients with PD. Nonetheless, considering the paucity and limitations of previous trials, the study by Richards and colleagues is an important contribution, as it provides the first class I evidence for the efficacy of frequently prescribed classes of SSRIs and SNRIs for treatment of depression in PD.

> “...the study by Richards and colleagues is an important contribution...”

In a previous RCT of antidepressants in PD, paroxetine showed no benefit over placebo, whereas nortriptyline did have beneficial effects.[7] The duration of follow-up and/or management of missing data could account for such inconsistency between trials. Another hypothesis is that the antimuscarinic effects of nortriptyline might have unblinded treatment and artificially inflated effect size, thereby leading to ascertainment bias.[8] Direct comparisons of antidepressant strategies in PD are still missing. Theoretically, SSRIs could differ from SNRIs in terms of mechanism of action and, therefore, clinical outcome, but this possibility could not be assessed in the small trial by Richards and colleagues. The risk–benefit ratio can also vary in individual patients; for example, the antimuscarinic effects of imipramine derivatives may improve features such as hypersalivation, tremor, pain or insomnia, while worsening others such as orthostatic hypotension (owing to α-adrenoceptor-blocking effects) or cognitive impairment.

Pramipexole has been shown to improve mood in depressed patients with PD,[9] but how the effect of this drugs compares with that of other antidepressants is unknown. Many other questions remain with regard to antidepressant treatment in PD, such as whether dopaminergic medications should be optimized to improve mood before the administration of antidepressants, or vice versa, and why response to a given drug varies between patients. Furthermore, whether the concomitant use of multiple antidepressant drugs has cumulative or synergistic effects is also unclear. Monoamine oxidase-B inhibitors are commonly used in patients with PD, and these drugs have antidepressant effects in non-PD patients. However, when combined with other antidepressant medications, these inhibitors increase the risk of serotonin syndrome owing to excessive serotonergic activity in the CNS.[10] Nonpharmacological interventions for the treatment of depression in PD also require consideration and testing.

In summary, the trial by Richard and colleagues[6] is one of the first attempts to specifically assess the treatment of depression in PD using modern scientific standards. For this reason, the importance of this study must be acknowledged despite its limitations, but many crucial questions remain to be answered before we can provide better patient management.

*Department of Clinical Pharmacology and Neuroscience, University Hospital, University of Toulouse III, Toulouse, France (**S. Perez-Lloret, O. Rascol**).*
Correspondence to: O. Rascol
olivier.rascol@univ-tlse3.fr

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