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Pharmacotherapy of neuropsychiatric symptoms: opportunities, challenges and current prospects

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Neuropsychiatric symptoms (NPS) are highly prevalent in diseases characterized by CNS pathology, and are a major source of disability, cost and carer burden. For example, one study has shown that 60% of patients with Alzheimer's disease (AD) in a community-based sample experienced NPS during a 1-month period [Lyketsos CG *et al.* (2002) *JAMA* 288: 1475–1483], and over 80% experienced NPS during the course of their illness.

Two Practice Point articles in this issue discuss recent studies that have highlighted the promise of pharmacotherapy for NPS in AD and Parkinson disease (PD), but have also identified the challenges of designing such studies and of interpreting their results.

In the first Practice Point, Ballard *et al.* comment on the CATIE-AD study [Schneider LS *et al.* (2006) *N Engl J Med* 355: 1525–1538], which examined the effectiveness of the second-generation antipsychotic drugs olanzapine, quetiapine and risperidone for the treatment of psychosis and agitation in AD by using a design intended to capture 'usual practice'. The primary outcome utilized the speed with which treatment was switched to the next phase as a measure of whether the physicians thought the therapy was helping. Although this was a practical design and innovative choice, in retrospect this design might have led clinicians to switch to the next phase of therapy early because the presence of a placebo arm raised the possibility that nonresponders were receiving no treatment. Nonetheless, the trial found no difference in overall time to switch between the three drugs and placebo, whereas switching caused by adverse events was less common in the placebo group. Schneider *et al.* concluded that these drugs were modestly effective, but the benefits were offset by adverse effects. Schneider reached the same conclusion more than a decade ago with regard to first-generation antipsychotics.

These findings are worrying because there are no proven alternative options for treating agitation and aggression in AD. For example, there has been no randomized clinical trial (RCT) in which patients with clinically significant psychosis or agitation were randomized to a cholinesterase inhibitor or memantine versus placebo. Without such RCT evidence, claims that these agents have efficacy for these symptoms [e.g. Sink KM *et al.* (2005) JAMA 293: 596–608] are unfounded. Likewise, the few data suggesting efficacy of selective serotonin reuptake inhibitors for the treatment of agitation need replication before efficacy can be accepted.

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Competing interests
The authors declared associations with the following companies and organizations: Adlyfe, Associated Jewish Federation of Baltimore, AstraZeneca, Bristol-Myers Squibb, Eisai, Forest Laboratories, GlaxoSmithKline, Pfizer, Janssen Pharmaceutica, Eli Lilly, National Institute on Aging, National Institute of Mental Health, Novartis, Ortho-McNeil, Supernus. See the article online for full details of the relationship.

www.nature.com/clinicalpractice
doi:10.1038/ncpneuro0492

In the second Practice Point, Williams-Gray and Barker comment on a secondary analysis of a trial of rivastigmine for dementia [Burn D *et al.* (2006) *Mov Disord* 21: 1899–1907]. Like the CATIE-AD trial, this study must be interpreted with caution and even regarded with concern. This subanalysis found better response on the AD Assessment Scale (ADAS-cog) in participants with hallucinations than in those without hallucinations. The difference on the ADAS-cog between rivastigmine and placebo in patients without hallucinations was only 2.09 points, an improvement that is unlikely to have clinical significance. Furthermore, this difference between rivastigmine and placebo was not statistically significant. The better response observed in the patients with hallucinations raises the possibility that some individuals with PD and hallucinations had dementia with Lewy bodies rather than PD, and that the dementia of PD is minimally responsive to this cholinesterase inhibitor.

The authors of the original studies are to be commended for advancing our knowledge of NPS. Their results demonstrate the importance of carefully designed and powered RCTs, and the need for placebo controls. The prevalence and negative impact of NPS highlight the need for continued research, and innovative trial designs, better measurement paradigms, testing of prospectively stated hypotheses, and etiology-linked therapeutics are the best hopes for advancement in the field.

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