Clinical Trials and Tribulations

Three articles in this issue of *The Journal of Clinical Psychiatry* call attention to challenges faced by researchers and clinicians seeking to establish and provide the best possible care for patients and families afflicted by Alzheimer's disease.

Here's one challenge: As the number of promising treatments to slow down Alzheimer's-related clinical decline grows, it is increasingly difficult, time-consuming, and expensive to enroll and properly study the required number of patients in clinical trials. Compounding this mounting problem, several randomized clinical trials have recently reported an unexpectedly slow rate of clinical decline in their placebo groups, reducing the statistical power of these studies and leading researchers to suggest the need for larger sample sizes, longer treatment durations, and even greater funding for clinical trials. Possible explanations for the lack of decline in the placebo group include (1) the inclusion of more mildly affected patients who decline more slowly; (2) a shorter study duration, reducing the time needed to observe decline; (3) a larger number of clinical trial sites, required to provide larger samples or compensate for slower enrollment rates, perhaps leading to more heterogeneity in subject selection and clinical ratings; (4) more numerous clinical evaluations, increasing the possibility of practice effects; and (5) a possible publication bias, such that negative trials may be published later, if they are published at all, and may be less likely than earlier published findings to show clinical decline in the placebo group.

In this "Focus on Alzheimer's Disease and Related Disorders," Michael Gold describes an analysis of publicly available clinical trials over the past 14 years. He confirms the suggestion of less placebo-related clinical decline in recently reported clinical trials and finds that longer study duration was the best predictor of placebo decline. Also noting that clinical trials with more mildly affected patients, a larger number of investigational sites, or more numerous clinical evaluations were associated with less placebo decline, he suggests that this information could be used to help inform the size, design, and duration of clinical trials, and he calls for study sponsors to be more transparent in reporting the relevant variables. Further, he suggests the need for ways to increase subject enrollment at individual sites and establish clinical endpoints least likely to be confounded by practice effects.

Here's another challenge: When one considers the extremely high prevalence of noncognitive psychiatric symptoms in patients with Alzheimer's disease and their impact on patients and families, there is an urgent need to identify effective and well-tolerated treatments for these conditions. While antipsychotic medications are commonly used for the treatment of agitation, aggression, and psychotic symptoms in patients with Alzheimer's disease, their efficacy is not well established, they may have intolerable side effects, and they may be associated with a small but measurably increased risk of death in these patients.

In this month's special section, Huertas and colleagues describe a small randomized clinical trial comparing the efficacy and tolerability of the antiandrogenic medication cyproterone to haloperidol. Their preliminary findings suggest the need for larger, randomized, placebo-controlled studies to confirm the suggested efficacy and tolerability of this approach to the time-limited treatment of aggression in patients with Alzheimer's disease and other dementias. Meantime, what is the clinician to do for these patients? First, identify and try to address the possible contribution of environmental factors, delirium, other medical illnesses, or unrecognized pain to the patient's symptoms. Second, if a cholinesterase inhibitor or memantine is already prescribed for a patient's cognitive symptoms, empirically determine its beneficial effects, if any, on the patient's noncognitive symptoms. Third, if an antipsychotic or other suggested but

not well-established medication is prescribed for the time-limited treatment of an Alzheimer's patient's neuropsychiatric symptoms, monitor the patient's response and adjust the medication accordingly. As recently suggested by a large study evaluating the cost-effectiveness of atypical antipsychotics in community-dwelling patients with Alzheimer's disease,[1] these and other medications may help some patients but not others, harm some patients but not others, or, of course, produce a combination of beneficial or adverse effects that need to be monitored and managed accordingly.

Finally, there is this challenge, too often ignored or inadequately addressed: How does one best help patients and families facing the most advanced stages of Alzheimer's disease? In this issue, Paul Kettl reviews several commonly confronted end-of-life care challenges, along with the important roles that the psychiatrist can play in working with families and other medical and nonmedical caregivers. He suggests how the psychiatrist can help patients and families anticipate and proactively address some of these challenges, and he reminds us of the extraordinary opportunity to maximize the comfort and quality of life of patients and families during this difficult time. His review emphasizes the importance of communicating with the family throughout the course of the patient's illness, helping them find appropriate resources for their nonmedical needs, facilitating advanced care directives when the patient may be able to participate in medical decisions and proxy decisions by family members later on, addressing commonly encountered physical problems in the most palliative way, and considering the possibility of hospice care.

For every challenge, there is an opportunity: the opportunity to evaluate slowing and prevention therapies for Alzheimer's disease in the most productive, rigorous, and cost-effective way; the opportunity to find more effective and better tolerated treatments for our patients' neuropsychiatric symptoms and use them in the most thoughtful and empirically individualized way; and the opportunity to address the unmet nonmedical needs of patients and families throughout the course of their illness. If you have suggestions or comments regarding "Focus on Alzheimer's Disease and Related Disorders," please feel free to contact me at Eric.Reiman@bannerhealth.com.

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REFERENCE

1. Schneider LS, Tariot PN, Dagerman KS, et al, and the CATIE-AD Study Group. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. N Engl J Med 2006;355:1525–1538