

## EDITORIALS



## Alzheimer's Disease — Clinical Trials and the Logic of Clinical Purpose

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Agitation, aggression, delusions, and hallucinations are among the most common and disabling symptoms of Alzheimer's disease. These problems diminish the quality of life for both the patient and caregiver.<sup>1</sup> They are also costly.<sup>2</sup> Treatments for these symptoms include the second-generation, or "atypical" antipsychotic medications.

The Food and Drug Administration (FDA) labels for antipsychotic medications state bluntly that they are not approved for the treatment of dementia-related psychosis, and they display a "black-box" warning: "Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo."<sup>3</sup> Yet, clinicians, including me, continue to prescribe these drugs.<sup>4</sup> Although the results of several clinical trials suggest this practice has some evidence base,<sup>5</sup> we have done this without clear evidence of the nature and extent of the clinical value of antipsychotic medications — until now.

The article by Schneider et al. in this issue of the *Journal* reports the results of the Clinical Antipsychotic Trials of Intervention Effectiveness—Alzheimer's Disease (CATIE-AD).<sup>6</sup> The trial substantially informs clinicians about the clinical value of three second-generation antipsychotic drugs (olanzapine, quetiapine, and risperidone) in a community-dwelling study population with a broad spectrum of dementia severity and behavioral problems that were severe enough to disrupt their functioning. Schneider and colleagues report that the main outcomes of their study "were the time from initial treatment to the discontinuation of treatment for any reason and the number of patients with at least minimal im-

provement on the Clinical Global Impression of Change (CGIC) scale at 12 weeks."

The balance of the results on the primary and secondary end points suggests that olanzapine and risperidone were equally effective and were superior to placebo and quetiapine in treating behavioral problems, but this benefit was limited to a subgroup of patients who either tolerated or did not have side effects such as parkinsonism and sedation. These results and the evidence that behavioral problems in Alzheimer's disease can be reduced by specialized care that stresses non-pharmacologic management<sup>7</sup> suggest that these drugs have a limited, but at times necessary, role in the care of patients with Alzheimer's disease. They are perhaps best prescribed in systems of care that can provide the skills and expertise needed to ensure that the risks associated with the drugs are justified by their potential benefits.

The study by Schneider and colleagues addresses a number of the problems with previous clinical trials of atypical antipsychotic medications. For instance, the designs of previous trials did not reflect clinical practice. Hence, their results could not directly change clinical practice. In contrast, the study by Schneider et al. adhered to the "logic of clinical purpose." This scientific and ethical model asserts that clinical trials are logically grounded in and ethically justified by the way in which they reflect and contribute to clinical practice.<sup>8</sup>

Many of the randomized and controlled trials for behavioral problems in persons with Alzheimer's disease assign patients to fixed doses of a drug and measure efficacy at prespecified time points with the use of a measure of symptom se-

verity such as the Neuropsychiatric Inventory. This design predominates among trials of treatments for Alzheimer's disease for many reasons. These scales are generally thought to represent a valid measure of the syndrome under study. In addition, studies in which outcomes are measured at multiple time points accrue a large volume of data; this approach, in turn, increases the likelihood that any change measured will be statistically, though not necessarily clinically, significant. Clearly, these designs are particularly valuable to companies seeking an FDA label or reprints of reports to distribute to clinicians.

However, these designs are not as valuable for clinicians, for many reasons. A clinical trial with a primary end point that is a measure not used in clinical practice will generate results that are difficult to interpret and, hence, not likely to lead to appropriate changes in clinical practice.<sup>9</sup> In addition, a fixed time of end-point assessment makes less sense for clinical trials that are intended to guide clinical decisions about treatments that may be discontinued at any time because the disorder varies substantially among patients and the intervention has side effects.

The study by Schneider et al. addresses these problems. Its primary end point is based on a real-world measure of clinical practice: the decision to change treatment after a reasonable time to allow titration to a therapeutic dose of the drug. In defining effectiveness, the investigators determined whether the time from the initiation of treatment to a decision to change the medication because of either lack of effectiveness or side effects would be longer for persons receiving the study drug than for persons receiving placebo.

This end point also addressed another common problem of the dominant model of studies of the treatment of symptoms in Alzheimer's disease: how to use data from patients who drop out before the end-point assessment. The typical solution regarding dropouts is to impute the missing data with the use of the "the last observation carried forward" method. But these data incorporate into the analysis different durations of exposure to both the drug and the study. This is a substantial problem when the condition under study involves variable decline or change, which is characteristic of the behavioral and cognitive problems in persons with Alzheimer's disease. The method also typically overestimates the precision of the effect and introduces bias.<sup>10</sup>

The primary end point in the study by Schneider et al. is an accurate reflection of a clinical event: the decision to change treatment because the patient's condition is worsening or not improving sufficiently. This portmanteau measure nicely mimics clinical practice and it obviates the problem of missing data. Moreover, the decision regarding how to administer the drugs well reflected clinical practice. Schneider and colleagues used flexible dosing of the drugs while maintaining blinded study conditions. Each of the medications was dispensed as identically appearing small and large capsules containing the appropriate lower and higher doses. The investigators chose the starting dose and were expected to adjust the dose on the basis of the patient's response. Although the assignment of patients to a fixed dose of a drug has considerable statistical efficiency, it does not reflect how these drugs are administered in clinical practice. Flexible dosing ensures one of the core principles of geriatric pharmacology: "start low and go slow, but go," meaning that the clinician should start a drug at a dose that is on the lower end of the plausible therapeutic index but then increase the dose until there is efficacy or intolerable side effects.

The CATIE-AD study is an exemplar of the clinical trial's revolutionary role in shaping therapeutics. Recent remarks by FDA officials support wider use of these kinds of adaptive designs.<sup>11</sup> This trial, funded by the National Institutes of Health, is also a model for how to spend our taxes on research, particularly now that taxes also pay for prescriptions.

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1. Steele C, Rovner B, Chase GA, Folstein M. Psychiatric symptoms and nursing home placement of patients with Alzheimer's disease. *Am J Psychiatry* 1990;147:1049-51.
2. Murman DL, Colenda CC. The economic impact of neuropsychiatric symptoms in Alzheimer's disease: can drugs ease the burden? *Pharmacoeconomics* 2005;23:227-42.
3. FDA Public Health Advisory: death with antipsychotics in elderly patients with behavioral disturbances. Rockville, MD: Food and Drug Administration, 2005.
4. Thomason C, Babic T, Margolin R, Schaeffer J, Riordan H. A review of atypical antipsychotic prescribing practices in a large, managed care database of elderly patients in the United States prior to and after black-box warnings. *Alzheimer's and Dementia* 2006;2:S4-S5.
5. Schneider LS, Dagerman K, Insel PS. Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. *Am J Geriatr Psychiatry* 2006;14:191-210.

6. Schneider LS, Tariot PN, Dagerman KS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med* 2006;355:1525-38.
7. Callahan CM, Boustani MA, Unverzagt FW, et al. Effectiveness of collaborative care for older adults with Alzheimer disease in primary care: a randomized controlled trial. *JAMA* 2006; 295:2148-57.
8. Freedman B. Placebo-controlled trials and the logic of clinical purpose. *IRB* 1990;12(6):1-6.
9. Karlawish JHT. The search for a coherent language: the science and politics of drug testing and approval. In: Kapp MB, ed. *Ethics, law and aging review*. Vol. 8. New York: Springer, 2002: 39-56.
10. Murphy SA. An experimental design for the development of adaptive treatment strategies. *Stat Med* 2005;24:1455-81.
11. Gottlieb S. Prepared remarks. Presented at the Conference on Adaptive Trial Design, Washington, DC, July 10, 2006. (Accessed September 21, 2006, at <http://www.fda.gov/oc/speeches/2006/trialdesign0710.html>.)

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## Rapid Detection of Tuberculosis and Drug-Resistant Tuberculosis

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Tuberculosis remains one of the major unresolved global health problems, and the situation is worsening in many parts of the world, primarily because of the association between tuberculosis and the epidemic of human immunodeficiency virus (HIV) infection and AIDS and the growing prevalence of drug resistance. The highest prevalence of both tuberculosis and drug resistance is found in countries with limited resources, which cannot afford to implement modern methods of epidemic control of tuberculosis. The detection of new cases of tuberculosis in these areas is based on provisional diagnosis by means of direct acid-fast bacilli testing of sputum smears, a diagnostic tool that can provide positive results in less than 50% of patients with newly diagnosed pulmonary tuberculosis confirmed on culture. Furthermore, the sputum-smear test does not address detection of persons with drug-resistant strains of *Mycobacterium tuberculosis*.

The most common method of detecting drug-resistant strains of tuberculosis in many countries (even those with a moderate economic level) is often limited to use in patients with no response to the initial standard treatment regimen. Therefore, detection of drug resistance is attempted only when there is a clinical suspicion of drug resistance. The loss of 9 to 12 (or more) months of the provision of appropriate tuberculosis therapy has several potentially critical consequences: patients with multidrug-resistant tuberculosis may have progressive disease or may die while receiving ineffectual treatment; the presence of amplified drug resistance, including the loss of pyrazinamide and ethambutol, may create the next level of an extensively drug-resistant tuberculosis

pathogen; and, most important, ongoing transmission is likely to occur.

A more efficient and cost-effective alternative to that expensive so-called strategy would be the implementation of culture isolation for more complete detection of new cases of tuberculosis and the testing of all initial culture isolates for susceptibility to isoniazid and rifampin. Such an alternative would be feasible and effective under two conditions: the method should be inexpensive and easy to implement and the turnaround time of laboratory testing should be short enough that providers could make timely adjustments to the treatment regimens when drug resistance is detected. For many years, the implementation of testing for drug susceptibility has been one of the most neglected aspects of health care, despite the large number of bacteriologic and molecular methods developed for testing.<sup>1</sup> The situation today demands further development in this area, with a focus on methods that can be implemented in countries with limited resources.

In this issue of the *Journal*, Moore and colleagues<sup>2</sup> attempt to address these problems. They have evaluated a method called the microscopic-observation drug-susceptibility (MODS) assay, which is considered an inexpensive tool for the bacteriologic diagnosis of tuberculosis and the detection of drug resistance. This method, originally described in 2000,<sup>3</sup> with additional data reported in 2004,<sup>4</sup> is based on direct inoculation of the selective 7H9 liquid culture medium in 24-well plates with a sputum specimen subjected to the digestion–decontamination procedure with the use of a mixture of two reagents, *N*-acetyl-L-cysteine and sodium hydroxide, for two pur-