Alzheimer’s Disease — Clinical Trials and the Logic of Clinical Purpose

Jason Karlawish, M.D.

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. They are also costly. 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.” Yet, clinicians, including me, continue to prescribe these drugs. Although the results of several clinical trials suggest this practice has some evidence base, 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 Anti-psychotic Trials of Intervention Effectiveness—Alzheimer’s Disease (CATIE-AD). 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 improvement 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 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.

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-
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. 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.

No potential conflict of interest relevant to this article was reported.

From the Department of Medicine, Division of Geriatric Medicine, Alzheimer’s Disease Center, Institute on Aging, University of Pennsylvania, Philadelphia.

Rapid Detection of Tuberculosis and Drug-Resistant Tuberculosis

Michael D. Iseman, M.D., and Leonid B. Heifets, M.D.

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. 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 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, with additional data reported in 2004, 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-