Atypical Antipsychotic Medications in Alzheimer's Disease: Effectiveness Versus Expectations

Eagerly awaited findings are presented this month from the Clinical Antipsychotic Trials of Intervention Effectiveness—Alzheimer's Disease (CATIE-AD) project. The management of dementia is a challenging endeavor, fraught with potential treatment adversities that have been underscored by a warning from the Food and Drug Administration regarding increased mortality among patients with dementia receiving atypical antipsychotic medications (1). The warning has understandably incurred greater wariness regarding their use, with little comfort to be gained from the modest evidence for their efficacy. This problem is unfortunately compounded by a lack of alternative medication choices. A recent update by Jeste et al. (2) sums up this difficult state of affairs quite well with the following comment: "The serious consequences of psychosis and agitation in dementia, the problematic risk-benefit profile of antipsychotic medications for such symptoms, and the paucity of data on other treatment alternatives combine to create a clinical conundrum for which there are no immediate or simple solutions."

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In this month's issue of the *Journal,* results are presented regarding the comparative treatment effects of olanzapine, quetiapine, risperidone, and placebo in patients with Alzheimer's disease. The CATIE-AD study was specifically designed to compare the effectiveness of these interventions for the management of psychosis or agitated/aggressive behaviors among noninstitutionalized adults with Alzheimer's disease (3). The primary outcome measure in the original study design involved time to discontinuation of study medication for any reason, to best reflect the overall clinical benefits relative to adverse effects. In a previous report on this all-cause discontinuation outcome, there were no differences observed among patients receiving olanzapine, quetiapine, risperidone, and placebo (4).

The report by Sultzer et al. in the current issue provides a closer look at symptom responses that occurred during phase 1 of the study (5). The CATIE-AD procedures permitted flexibility in choosing a starting dosage, and adjustments could be made on the basis of clinical judgment. Clinicians could choose to discontinue phase 1 at any time after the first 2 weeks if clinically indicated for any reason. If they chose to discontinue, the patient would be reassigned to phase 2, involving either a different atypical antipsychotic or citalopram, but there was no placebo assignment in phase 2. The new results from Sultzer et al. examined symptom ratings at the time of discontinuation in phase 1, which occurred after a median treatment duration of 7.1 weeks.

The authors report the intriguing observation that when the decision was made to end phase 1 and stop the first assigned drug in favor of a reassignment, some patients were experiencing clinical benefits at the time. Specifically, those patients receiving risperidone demonstrated improvement in the Neuropsychiatric Inventory total score, Brief Psychiatric Rating Scale (BPRS) hostile suspiciousness factor, and Clinical Global Impression of Change compared to placebo at the time of discontinuation in phase 1. Furthermore, patients taking olanzapine were observed to have improvements on the Neuropsychiatric Inventory total and BPRS hostile suspiciousness factor, but they demonstrated a worsening of symptoms on the BPRS withdrawn depression factor when

compared to placebo. Overall, these findings are consistent with the main findings of a 2006 Cochrane Collaboration review of placebo-controlled trials (6), which concluded that risperidone and olanzapine may improve aggression compared to placebo and that risperidone may improve psychosis relative to placebo.

As we reflect on these findings, we are left to mull over the observation that when phase 1 treatment was deemed unsatisfactory, symptom severity was concurrently improving. To place these observations in context, it may be helpful to bear in mind two important features of this study that were external to the patients themselves. The first of these features is that only phase 1 included a placebo arm and the other phases had active comparators, so the clinician and family caregivers were aware that if the patient was switched to the next phase of treatment, there would be a guarantee of active drug. The second important feature of this study is that the patients were residing in the community, i.e., the participants were dwelling in either their own homes or assisted living settings, but not nursing homes. The community caregiving setting could be considered a more precarious environment in many ways, as spouse and family caregivers are often acutely aware of the need to maintain adequate behavioral control to ensure the safety of the patient and avoid nursing home placement. Hence, the expectations for behavioral control may be much greater, with a relative lack of tolerance for only minimal gains.

The authors have appropriately concluded that treatment decisions are influenced in part by symptomatic change but also by expectations of the clinicians and the family caregivers. This role of expectations was discussed by Sultzer et al.: "…clinical symptom ratings reveal some beneficial antipsychotic effects, despite the frequent coincident decision to change treatment. This distinction suggests that clinicians were seeking a level of clinical improvement that was greater than the change detected on the clinical scales, were mindful of possible placebo assignment in phase 1, or were balancing symptom change with other clinical considerations, such as adverse effects. Treatment expectations and patient circumstances likely contributed to the perception of effectiveness."

If treatment expectations played a role in the choice to discontinue phase 1, it is also possible that the concern about a potential placebo assignment may have attenuated the perception of improvement in phase 1. It follows, then, that future analyses may potentially reveal greater treatment effects in phase 2 due to the anticipation of active drug. Indeed, active comparator trials have been shown to demonstrate significantly higher response rates than placebo-controlled trials in late-life depression (7). Whether such an enhanced effect occurs for phase 2 patients will be important to look for in future reports from this study.

What about patients who were perceived to be doing well enough to continue with the phase 1 drug? In a second analysis presented in this article, the authors examined patients who continued to take their initially assigned study medicine and continued through week 12. This group had the additional information gained from a reassessment of cognition and functional abilities obtained at 12 weeks. They were observed to be faring better symptomatically than those who had discontinued within phase 1, which is not surprising as they had been determined to be sufficiently responsive to continue their initial treatment. The comparisons across the different antipsychotic medications for these patients did not reveal significant differences in outcomes on the Clinical Global Impression of Change. Similarly, there were no differences across the medications on measures of daily function or cognitive outcome, with the exception that olanzapine was associated with a reduction in functional skills as measured by the Alzheimer's Disease Cooperative Study Activities of Daily Living Scale.

The observation that functional outcome measures largely did not differ from placebo is consistent with the conclusion in another recent publication from this study by Rosenheck et al., addressing the cost-effectiveness of second-generation antipsychotics, that there was no difference between the active treatment groups and placebo in

quality-adjusted life-years (8). It is possible that this absence of drug effects on quality of life or daily function added to the propensity for medication switching in search of a response, as the clinicians were simply not seeing the desired result from current treatments. Understanding the clinical environment is essential to conceptualizing these findings; perhaps more than in any other clinical condition, the care of the dementia patient is complicated by urgent and fluctuating care needs, significant caregiver distress, vulnerability to social/environmental factors, and significant medical burden.

Among these many factors and competing demands on the clinician's attention, it is challenging not to lose sight of the patient's symptoms in the mix, as subtle improvements may pale in the face of overall expectations and care needs. Clinicians using atypical antipsychotics are well aware of the warnings associated with them, which may contribute to the perception that the stakes are high in exposing patients to potential risk. However, it is important to realize that the stakes are truly highest of all for family members, when failure to maintain behavioral control may result in nursing home placement, with potentially severe financial consequences as well as the emotional distress of separation from the patient. Many spouses have pledged never to put their loved one in a nursing home. Considering this social context helps us to understand how much hope is placed in these medications to do something that they frankly cannot always do. Our challenge, then, is to develop more innovative approaches to care, including both the development of novel drug compounds as well as multimodal interventions that address caregiver needs. The best intervention strategies are likely to be derived through maximal input from families, nursing care providers, and others who are truly doing heroic jobs with the minimal benefits of the pharmacologic support we currently afford them.

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