Consequences of Antipsychotic Medications for the Dementia Patient

The management of agitation and psychosis in dementia is a complex undertaking because one side effect of antipsychotic drugs is the risk of worsening confusion. This interplay among cognitive symptoms, psychosis, and behavioral disturbance creates challenges in determining the best clinical outcomes. For example, agitation may be successfully reduced with sedation, but this is certainly not the desired result if quality of life and functional status are harmed. Consequently, there is value in understanding not only the behavioral effects of antipsychotic treatment in dementia patients but also the potential adverse effects on cognitive status and daily functioning.

The Clinical Antipsychotic Trials of Intervention Effectiveness–Alzheimer's Disease study (CATIE-AD) reported in this issue (1) finds lower cognitive performance in dementia patients who received atypical antipsychotic medications compared with placebo. These results broaden our understanding of the effects of atypical antipsychotics in patients with Alzheimer's disease. Data from CATIE-AD are particularly noteworthy in view of the study sample of more than 400 participants. Neuropsychological testing across a range of domains in this study offers a powerful look at the progression of Alzheimer's disease in the context of treating neuropsychiatric symptoms. Participants in the CATIE-AD study were community-dwelling patients with a mean Mini-Mental State Examination (MMSE) score of 15.2 (SD=5.7), reflecting a group with moderate to severe dementia who were enrolled after fulfilling criteria for agitation or psychosis warranting a pharmacologic intervention.

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Earlier studies examining the cognitive effects of antipsychotic medications have produced conflicting results that are partly related to the difficulty in accurately evaluating cognition among patients who are severely impaired as a direct result of their underlying brain disease. The CATIE-AD design also allowed for the comparison of different atypical antipsychotics (olanzapine, quetiapine, and risperidone) in order to detect individual drug effects, although the analyses reported in this issue required combining the three atypical antipsychotics to detect a statistically significant difference from placebo on the outcome measures of MMSE and cognitive summary scores. From a theoretical perspective, there are differences in the anticholinergic and sedative properties of atypical antipsychotics that may result in different outcomes across cognitive domains, but such findings were not evident here. It is likely that individual vulnerabilities to specific antipsychotics are mediated by a variety of factors, including concomitant medications, medical comorbidity, and underlying frailty, that are beyond the scope of this analysis, but such factors presumably affect clinical decisions on a case-by-case basis. Dose titration is also individualized, and while dose effects were not addressed in this analysis, adverse events in this population are dose related, and treatment dropouts occur more frequently with risperidone doses above 2 mg and olanzapine doses above 5 mg (2).

Readers should consider additional caveats when interpreting the findings and their potential impact on clinical practice. The CATIE study design allowed nonresponding

patients to switch to another antipsychotic or to citalopram at any time after the first 2 weeks of treatment, and therefore any patient who received an antipsychotic for 2 weeks was included in the analyses, including the analyses of changes in slopes over time. This duration is short compared to the usual duration of antipsychotic treatment in clinical practice, and the possibility exists that a harmful short-term effect on cognition may not be sustained with longer exposures. Analyses restricted to the subgroups that received antipsychotic medication for more prolonged periods would have been very helpful in this 36-week study. Clinically, it is well known that among the elderly there is a risk for reduced cognitive performance after receiving any medication with CNS effects; virtually all anxiolytics, antidepressants, and anticonvulsants have this liability as well. Consequently, the clinician is left in a position in which most, if not all, pharmacologic treatment choices may pose a risk for cognitive change, and alternatives such as benzodiazepines offer riskier cognitive liabilities.

In the clinical setting, there is the added complication that switching or crossing over from one active medication to another or switching from placebo to an active medication may also incur a change in mental status. Crossover effects such as these were not addressed explicitly in the article analyses. The removal of data from patients who were sedated at intake and during the trial was presumably related to the possible effect of sedation on the patients' ability to perform the cognitive tests, but removing this subgroup from the analyses decreases the clinical relevance of the findings given that sedation commonly occurs in the dementia population and may influence the selection and monitoring of antipsychotic medication.

Significant effects on cognition did not clearly emerge with individual antipsychotics in spite of moderately large sample sizes for each type of medication. Difficulty in obtaining clear outcome signals is not new in this complex patient population. For example, the Food and Drug Administration (FDA) analyses of atypical antipsychotic safety in dementia did not find statistically significant differences in mortality in any single trial of antipsychotic medication compared with placebo, so the FDA black box mortality warning was generated on the basis of pooled data from 17 studies, which permitted the detection of a mortality risk. After the black box warning was issued, several large-scale naturalistic studies conducted in nursing homes failed to show a greater mortality rate with antipsychotic use in patients with dementia (3, 4) while others suggest that the risk is greater with conventional antipsychotics (5). Much like the mortality signal, any change in cognitive course incurred by medications is likely to be an issue requiring multiple studies with various populations to fully understand the differential effects of care settings and the individual patient vulnerabilities that confer the greatest risk.

Despite the FDA black box warning, antipsychotic use in dementia has remained remarkably frequent; a recent study of 16,586 nursing home patients reported that 29% receive at least one antipsychotic medication (6). Evidence showed a decline in prescribing initially after the FDA warnings (7), but Valiyeva et al. (8) note that while the warnings slowed the rate of increase in new prescriptions for atypical antipsychotics in patients with dementia, they did not reduce the overall prescription rate. Despite the widespread awareness of adverse consequences, we can only infer that atypical antipsychotics continue to be prescribed for dementia treatment because there is a lack of alternatives and there is a perceived clinical benefit by care providers. Furthermore, agitated behaviors may cause patients and caregivers to feel that imminent danger has a higher precedence than issues such as declining cognition. These complex issues will require a thoughtful and balanced evaluation with an appreciation of the care setting, individual patient vulnerabilities, and goals of care. Treatment decisions about real-world agitation in dementia include shared decision making with severely impaired loved ones about end-of-life quality that is difficult to fully capture in study trial designs. Nonetheless, this study reminds us that when antipsychotic drugs are used for management of psychosis and behavioral complications, increased cognitive disability may be an unintended consequence. Risk-benefit analysis is always part of the decision

to use psychotropic medication. The aged are a particularly vulnerable group, and this study strongly underscores that vulnerability.

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