Antipsychotics and Mortality in Dementia

Dementia represents a significant clinical challenge, with an estimated 35.6 million people with dementia in the world, of whom 4.38 million reside in the United States (1, 2). Ninety percent of people with dementia experience behavioral and psychological symptoms of dementia at some point during their illness. Behavioral and psychological symptoms of dementia commonly manifest as agitation, aggression, depression, or psychosis (hallucinations and delusions), which can cause significant distress to the person and their caregiver as well as have a direct effect on the person's quality of life and likelihood of institutionalization. Although the majority of best practice guidelines emphasize the importance of nonpharmacological treatments and judicious short-term use of pharmacological treatment for behavioral and psychological symptoms of dementia, antipsychotic drugs are commonly used as a first-line approach for managing these symptoms. It is therefore a critical issue to understand the clinical efficacy and safety profile of individual antipsychotics to inform guidance on prescribing practice and choice of antipsychotic medication in situations where a prescription is deemed necessary. In this issue of the *Journal*, the cohort study conducted by Kales et al. (3) provides extremely valuable new knowledge pertinent to these key treatment decisions.

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A substantial number of trials have focused on the effectiveness of atypical antipsychotics for the treatment of behavioral and psychological symptoms of dementia. In total, 18 placebo-controlled randomized controlled trials conducted over a 6- to 12-week period have been undertaken in people with Alzheimer's disease. The best evidence of efficacy for the treatment of agitation, aggression, and psychosis relates to risperidone. Five trials have indicated a modest but significant improvement in aggression and psychosis, equating to a small treatment effect size (Cohen's d=0.2 at the optimal dose) (4, 5). However, this must be considered in the context of the widely reported side effects of atypical antipsychotics, which include extrapyramidal symptoms, sedation, gait disturbances, and falls. Many agents also lead to anticholinergic side effects, including delirium (4). Tardive dyskinesia with atypical antipsychotics appears to occur less frequently than with typical antipsychotics, but QTc prolongation has been reported as a significant problem associated with several atypical antipsychotics. A meta-analysis also identified a significant increase in respiratory and urinary tract infections as well as peripheral edema in people treated with risperidone, compared with placebo (4). These are likely to be class effects of atypical antipsychotics. It has also become clear that other, more serious adverse outcomes, such as stroke and related cerebrovascular events, accelerated cognitive decline, and death, are significantly increased in people with dementia who are prescribed antipsychotics, compared with people with dementia not treated with these agents. Deaths related to bronchopneumonia, thrombo-embolic events (including stroke and pulmonary embolism), and sudden cardiac arrhythmias are all significantly increased in people with dementia receiving antipsychotic treatment (6).

The most significant clinical issue has been the increased mortality associated with antipsychotic use among people with dementia. An initial meta-analysis completed

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by the Food and Drug Administration (7), which has been confirmed by independent analyses, highlighted a 1.5- to 1.7-fold increase in mortality risk for people with Alzheimer's disease receiving antipsychotics, compared with placebo, over 6–12 weeks in randomized clinical trials. Subsequent work has demonstrated that this significant risk is elevated and persistent in cases of longer-term exposure to antipsychotics (8). Key questions for clinical practice include whether there are differences in mortality risk between different antipsychotics, what the mechanisms leading to increased mortality are, and whether aspects of mortality can be prevented.

The Kales et al. study contributes valuable new evidence regarding the safety of antipsychotics. The study examined the relative risk of mortality associated with newly commenced prescriptions of olanzapine, quetiapine, and haloperidol, compared with risperidone as the reference compound, in a cohort of more than 30,000 veterans with dementia, ages 65 years and older. Importantly, haloperidol was associated with significantly greater mortality than risperidone (relative risk=1.54). Several studies have suggested that haloperidol confers a greater mortality risk than atypical antipsychotics (9), but the Kales et al. report is one of the few to have systematically compared mortality risk between different atypical antipsychotic agents. Olanzapine and risperidone had similar mortality risk, while the risk for quetiapine was significantly lower (relative risk=0.73). A key observation is that the highest increase in mortality risk was in the first 120 days, particularly in the first 30 days for haloperidol. In addition to the important findings of the study, it also has several key methodological advantages that add to its value. The study population was specifically older people with dementia, and there was a focus on new prescriptions of antipsychotics. Both these design elements help to remove many of the potential confounding factors.

One important consideration in implementing the evidence from this study into clinical practice is to balance safety and efficacy. Kales et al. report that the lowest mortality risk was associated with quetiapine. However, three randomized controlled trials of quetiapine did not demonstrate any effectiveness in the treatment of aggression, agitation, or psychosis (4, 5). The best evidence of efficacy is for risperidone, with consistent evidence of a modest but significant benefit over 12 weeks in the treatment of both aggression and psychosis. There is also evidence of a similar level of benefit with aripiprazole, olanzapine, and haloperiodol, but only a few studies have examined other agents. Through balancing the mortality data from this study and efficacy data from previous randomized controlled trials, risperidone and olanzapine emerge as the best evidence-based options.

The growing body of evidence regarding the safety risks associated with antipsychotics has led to considerable pressure to reduce prescribing practice. It is imperative that this is conducted within a framework to improve the overall management of behavioral and psychological symptoms of dementia, including appropriate use of nondrug treatments, effective treatment of pain (10), and judicious short-term use of antipsychotics when their use is clinically indicated. In this regard, the Kales et al. study provides further evidence to support the use of risperidone and olanzapine where an antipsychotic is deemed necessary.

Another major clinical imperative is to deliver treatment and care to proactively reduce the mortality associated with antipsychotics when they are appropriately prescribed. In addition to the aforementioned causes of mortality, meta-analyses of randomized controlled trials have reported significant incidence of sedation, chest-infection, and dehydration (4), offering insight into the mediating pathways of more escalating events leading to death. It is likely that better care of people who are prescribed antipsychotics, for example, by monitoring fluid intake and promoting vigilance for early detection and treatment of chest infections, may offer important potential opportunities to reduce excess mortality. The potential role of ECG monitoring for prolonged QTc interval should perhaps also be considered, although this is more challenging in routine clinical practice. Practical approaches for these elements of clinical practice are outlined in a

new evidence-based best practice guide for preventing and managing behavioral and psychological symptoms of dementia (11).

The Kales et al. study provides important data for a better understanding of optimal and safer clinical use of antipsychotics. Their findings should be considered within the context of data on antipsychotic efficacy and incorporated into the implementation of improved treatment and care for people with dementia who are experiencing behavioral and psychological symptoms of dementia.

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Dr. Corbett has received honorarium from Acadia Pharmaceuticals; she has also received speaker's fees from Lundbeck and Novartis. Dr. Ballard has received research grants from Acadia Pharmaceuticals and Lundbeck; he has also received honoraria or consultancy fees from Acadia Pharmaceuticals, Eisai, Janssen, Lundbeck, and Novartis. Dr. Freedman has reviewed this editorial and found no evidence of influence from these relationships.

The authors thank the Alzheimer's Society, London.