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Treating Dementia and Agitation

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Age is the greatest single risk factor for developing dementia. When people reach age 65, their risk of dementia is 10%, and by age 85, approximately one-third will develop Alzheimer

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mer disease, the most common cause of dementia.¹ With 76 million US baby boomers entering or having entered this period of risk, a new wave of dementia cases can be anticipated—instead of today's approximate 5 million people with dementia, nearly 14 million in the United States are expected to have dementia by 2050.²

These major neurocognitive disorders impair memory, language, and other cognitive abilities to the point that affected persons depend on assistance from others.³ As the disease progresses, agitation, aggression, irritability, disinhibition, and other behavioral disturbances emerge and pose a tremendous burden that severely limits social functioning, disrupts households, and triggers institutionalization.⁴

Such symptoms often present in primary care settings, where interdisciplinary nonpharmacological strategies have demonstrated some benefits.⁵ Despite the need for more effective treatments for agitation, multiple clinical trials have yielded mixed results and pharmacological options are limited: The US Food and Drug Administration (FDA) has not yet approved any medication for treating the agitation associated with dementia.

Physicians have used antipsychotics, antidepressants, cholinesterase inhibitors, anticonvulsants, and other classes of drugs for treating agitation. In recent years, atypical antipsychotic drugs (aripiprazole, olanzapine, quetiapine, and risperidone) often have been used to treat behavioral disturbances associated with dementia, but a meta-analysis of randomized, placebo-controlled trials concluded that such medications may be associated with an increased risk of death primarily from cardiac-related events or infections.⁶ In 2005, the FDA issued a black box warning and health advisory on the use of atypical antipsychotic medications in the treatment of behavioral disorders in elderly patients with dementia because of a 1.6- to 1.7-fold higher death rate in those taking such drugs compared with those taking placebo.⁷ Thus, physicians have no clear treatment algorithms for agitation in dementia and face the challenge of managing these disturbing behaviors using drugs that pose life-threatening adverse effects.

In this issue of *JAMA*, Porsteinsson and colleagues⁸ report new results of an alternative drug treatment for agitation. In their multicenter, double-blind, placebo-controlled randomized trial of 186 patients with dementia and agitation, participants randomized to receive the selective serotonin

reuptake inhibitor citalopram and a psychosocial intervention for 9 weeks demonstrated less agitation compared with those randomized to the psychosocial intervention and placebo. The 2 primary outcome measures, agitation, as measured by the 18-point Neurobehavioral Rating Scale-Agitation (NBRS-A) subscale, and change in dementia, as measured by the 7-point modified Alzheimer Disease Cooperative Study-Clinical Global Impression of Change [ADCS-CGIC] score, and several secondary measures yielded significant results, including a reduction in caregiver stress, favoring the citalopram intervention. The effect size associated with the drug appeared clinically relevant—an approximate 1-point between-group improvement on the NBRS-A favoring citalopram. In addition, 40% of the patients receiving citalopram had moderate or marked improvement from baseline on the ADCS-CGIC score compared with 26% of the placebo-treated patients.

Although the adverse effects of citalopram were relatively modest, 2 years after the trial began the FDA issued an advisory stating that citalopram prolonged the QT interval of the electrocardiogram (ECG) and should no longer be used at doses greater than 40 mg per day.⁹ The investigators thus amended their protocol to increase the frequency of ECG monitoring and to exclude volunteers who are at higher cardiac risk. As expected, citalopram treatment was associated with a significant increase in the QTc interval compared with placebo, and the authors expressed their concern about use of citalopram at 30 mg per day, which was the trial's target dose based on response and tolerability. The study did not include a large enough sample to determine if a 20-mg dose of citalopram reduced symptoms of agitation and affected the QT interval.

Cardiac effects of antidepressants have been documented in several investigations. A cross-sectional study including 38 397 patients showed that citalopram, escitalopram, and amitriptyline were associated with dose-related QTc prolongations.¹⁰ Other research, however, has raised questions about the FDA warning. For example, Veterans Health Administration data¹¹ derived before the FDA warning (2004-2009) indicated that patients with depression who received a prescription for citalopram (N = 618 450) in daily doses greater than 40 mg had lower risks for ventricular arrhythmia, all-cause mortality, and noncardiac mortality compared with patients receiving daily doses of 1 to 20 mg. Similar findings were observed regarding ventricular arrhythmia risks in the sertraline cohort (N = 365 898) in that study. Although these studies identified cardiac risks in a different patient population, those with depression rather than dementia, they still raise questions about how to interpret the potential dose-related cardiac effects of these drugs.

In the trial by Porsteinsson et al,⁸ in addition to cardiac effects, citalopram worsened cognitive functioning compared with placebo as measured by the Mini-Mental State Examination (MMSE). Performance on the MMSE in the citalopram-treated group declined, whereas the placebo-treated group improved after 9 weeks, but the mean between-group treatment difference was only 1 point on this 30-item MMSE cognitive scale. The sensitivity of this instrument is limited in patients with more severe dementias and the clinical relevance of the group difference in scores is difficult to interpret. In practice, individual patients often fluctuate on this measure by several points depending on the time of day, minor distractions during an examination, level of fatigue, or variations in methods of administering the scale.

Although the results from this study support a role for citalopram in the management of agitation in dementia, when and how to prescribe the drug so that benefits are optimized and risks minimized are not straightforward. Clinicians who have treated patients who have both dementia and agitation know the considerable challenge and potential danger of these symptoms. These disturbing behaviors can lead to physical harm to the patient, caregiver, and anyone who comes in contact with the patient. The symptoms may contribute to caregiver depression, which can lead to further functional decline in patients, perhaps having a greater effect than a slight cognitive decline associated with citalopram treatment. The finding that citalopram reduced caregiver distress suggests that the drug may mitigate the risk for caregiver depression.

More research is needed to answer the many remaining questions about using citalopram for agitation in patients with

Alzheimer disease. Such studies should determine the duration of adverse effects and benefits beyond 9 weeks, dose ranges that influence mortality risk as well as QT prolongation, and predictors of response. These new data suggest that a subgroup of patients may be robust responders; 40% of patients receiving citalopram showed moderate or marked improvement in the global impression measure of agitation. The identification of predictors of response would help clinicians decide whether citalopram is a reasonable medication choice for certain patients with agitation.

In addition, all study participants received a psychosocial intervention, which probably contributed to the high proportion (90%) of patients completing the study. Until more informative criteria are available for choosing a particular drug treatment for agitation, clinicians should continue to emphasize such nonpharmacological strategies and opt for medications with caution. In addition to educating caregivers and family members about the potential risks and benefits of particular medications, physicians should carefully document their treatment plans and aim for short-term treatment to minimize the possible added risks of long-term use. As demonstrated by the results of this study of citalopram, when behavioral interventions fail to improve agitation, multiple factors need consideration for selecting the best medication for an individual patient, including cardiac safety issues and evidence of efficacy from randomized controlled trials. Until more definitive treatments are available, the careful selection and monitoring of pharmacologic agents may help optimize the level of functioning and quality of life for some patients with dementia.

ARTICLE INFORMATION

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Conflict of Interest Disclosures: Dr Small has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of interest. Dr Small reports that he is among the inventors of FDDNP-PET; the University of California, Los Angeles, owns a US patent (6 274 119) for FDDNP-PET, which has been licensed to TauMark, LLC. Dr Small reports having a financial interest in TauMark, LLC and having served as an advisor and receiving lecture fees from Lilly, Herbalife, Janssen, Novartis, and Pfizer.

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