

Dextromethorphan and Quinidine for Treating Agitation in Patients With Alzheimer Disease Dementia

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Among patients with Alzheimer disease, more than 90% experience neuropsychiatric symptoms during the course of their illness¹ with agitation one of the most frequent and clinically important symptoms. Agitation is not only distressing for the patient but often confers risk both to patients and to others (such as family members and caregivers). Agitation also represents a common trigger for institutionalization and presents a major management challenge for clinicians. Effective treatment options for agitation in patients with Alzheimer disease are limited, so clinical innovation in this area is a high priority.

Current practice guidelines²⁻⁴ promote nonpharmacological interventions as the first-line approach for treatment of agitation, and an increasing evidence base supports the value of this approach.⁵⁻⁷ Despite considerable variability between studies, a 2014 meta-analysis highlighted the benefit associated with interventions involving social interaction and pleasant activities, such as at least 60 minutes a week of enjoyable activities.⁷ However, implementation of nonpharmacological interventions can be difficult, especially for patients with severe symptoms, for whom pharmacological interventions are often required.

Some evidence supports modest symptomatic benefit associated with short-term treatment of patients with severe aggression using atypical antipsychotic agents,⁸ particularly risperidone, olanzapine, and aripiprazole. However, benefits for nonaggressive agitation and for longer-term treatment are less clear.⁸⁻¹⁰ Moreover, the modest benefits must be balanced against significant safety concerns associated with these drugs, including risks of accelerated cognitive decline, stroke, and death, particularly with longer-term use.^{8,9} Therefore, even though nonpharmacological strategies provide a useful first-line treatment approach, pharmacological interventions that are more effective, are safer, and confer longer-term benefits are needed.

The combination of dextromethorphan hydrobromide and quinidine sulfate has been proposed as a candidate treatment of agitation among patients with Alzheimer disease. The treatment is approved in the United States and the European Union for the treatment of pseudobulbar affect, the involuntary or uncontrollable episodes of crying and/or laughing usually occurring secondary to a neurological disease or brain injury. Dextromethorphan-quinidine has several mechanistic actions that are potentially relevant for the treatment of agitation,¹¹ including low-affinity *N*-methyl-D-aspartate an-

tagonism, serotonin and norepinephrine reuptake inhibition, and nicotinic $\alpha_3\beta_4$ receptor antagonism. Emerging evidence also suggests analgesic action,¹² which may directly affect agitated behavior. However, it is unclear whether any of these actions occur at therapeutically relevant doses. Anecdotal observations of improvement in agitation among patients without dementia were the main rationale for the randomized clinical trial (RCT) by Cummings and colleagues¹³ reported in this issue of *JAMA*.

Cummings et al conducted a parallel-group, phase 2, double-blind RCT to evaluate the effect of dextromethorphan hydrobromide-quinidine sulfate on clinically significant agitation among patients with mild to moderately severe Alzheimer disease. This 10-week study used a sequential parallel comparison design in which patients allocated to placebo were rerandomized after 5 weeks. With this design, 220 patients initially were randomized 3:4 to receive dextromethorphan/quinidine ($n = 93$) or placebo ($n = 127$). After 5 weeks, patients receiving dextromethorphan-quinidine continued that therapy, whereas those receiving placebo were stratified by response and rerandomized 1:1 to receive dextromethorphan/quinidine ($n = 59$) or placebo ($n = 60$). The primary outcome was change from baseline in the Agitation/Aggression domain of the Neuropsychiatric Inventory (NPI; which ranges from a score of 0 [absence of symptoms] to 12 [symptoms occur daily and with marked severity]), as rated by the patient's caregiver.

Of the 220 randomized patients, 194 completed the study, including a total of 152 patients who had received dextromethorphan-quinidine and 127 who had received placebo at some point during the study. In the primary sequential parallel comparison design analysis, dextromethorphan-quinidine, compared with placebo, significantly improved the NPI Agitation/Aggression score (ordinary least squares z statistic, -3.95 ; $P < .001$), and results for each stage of randomization also favored dextromethorphan-quinidine. In the analysis after the first randomization, mean NPI Agitation/Aggression scores were reduced from 7.1 to 3.8 with dextromethorphan-quinidine and from 7.0 to 5.3 with placebo, for a least squares mean between-group treatment difference of -1.5 (95% CI, -2.3 to -0.7 ; $P < .001$). In the analysis including placebo nonresponders who were rerandomized after 5 weeks to either dextromethorphan-quinidine or placebo, mean NPI Agitation/Aggression scores were reduced from 5.8 to 3.8 with dextromethorphan-quinidine and from 6.7 to 5.8 with placebo, for a least squares mean treatment difference of -1.6 (95% CI, -2.9 to -0.3 ; $P = .02$).

There also were substantial improvements in the clinical impression of change related to agitation, favoring the group receiving dextromethorphan-quinidine, along with statistically significant but less marked improvements in aberrant motor behavior and depression.

The study by Cummings et al has several strengths. The magnitude of benefit for reducing agitation/aggression observed with dextromethorphan-quinidine compares favorably with previous studies.¹⁴⁻¹⁶ The sample size was similar to other major studies focusing on neuropsychiatric symptoms in patients with dementia,^{14,16} and use of the NPI ensures that a well-validated instrument was used as the primary outcome measure.¹⁷ In addition, the authors used a sequential parallel comparison design to minimize the placebo response, which is substantial in studies involving agitation in patients with Alzheimer disease. Even though the treatment periods were only 5 weeks for the placebo group, the analyses for each of the periods separately and the combined overall analysis all show statistically significant benefit, suggesting that the outcome is robust.

The RCT by Cummings et al is also one of the few studies focusing on neuropsychiatric symptoms in patients with Alzheimer disease to also directly evaluate quality of life, although this outcome showed no improvement with dextromethorphan-quinidine. It is possible that the length of the study, 10 weeks, was too short to demonstrate improvement in quality of life. Yet this finding highlights the imperfect correlation between neuropsychiatric symptoms and quality of life in these patients. Randomized clinical trials of pharmacological and nonpharmacological interventions for patients with these symptoms have struggled to demonstrate a benefit to quality of life, and further work is needed to understand the additional elements beyond symptoms that require attention to improve overall well-being.

However, the study by Cummings et al also has several important limitations. Although the total NPI is well validated, the primary outcome measure focused on the single NPI domain of Agitation/Aggression, which has a more limited potential range and for which a minimum clinically important difference (MCID) has not been established. The apparently modest numerical benefit, as evidenced by the approximately 1.5-point between-group difference for the primary outcome measure, is therefore difficult to interpret. However, this numerical difference was greater than 0.4 SD, which is the most common threshold used to determine MCID.^{18,19} In addition, the benefit on the total NPI score, while statistically significant, did not achieve the threshold that has been suggested for MCID, although this may be explained by differential effects on individual neuropsychiatric symptoms. Accordingly, the data from the study by Cummings et al are important, but not overwhelming, and a second independent study with longer duration is needed to confirm the treatment effect.

As dextromethorphan-quinidine is already licensed for the treatment of pseudobulbar affect, the safety profile is reasonably well understood. The most important concerns are the potential for prolongation of QTc, falls, fatigue, dizziness, diarrhea, and precipitation of serotonergic syndrome if this drug is combined with selective serotonin reuptake inhibi-

tors. Quinidine has potential anticholinergic effects that could result in adverse events but are probably not relevant at the dosage used in this study. In the study by Cummings et al, dextromethorphan-quinidine, compared with placebo, apparently was well tolerated with no reported increase in sedation and no prolongation of QTc, no significant increase in falls and diarrhea, no detrimental effects on cognition or activities of daily living, and no increase in mortality. Although this adverse event profile represents a significant advantage compared with studies of atypical antipsychotics, an important caveat is that the significant detrimental effects of atypical antipsychotics on cognition and mortality became evident only from meta-analysis; therefore, the adverse events reported from this single short-term trial need to be treated very cautiously.

The most important clinical questions currently pertain to the overall efficacy and safety of dextromethorphan-quinidine as a treatment for agitation in patients with Alzheimer disease. Although the results of the study by Cummings et al are encouraging, it will be important for future studies to carefully consider the mechanisms of action. Agitation is a broad syndrome, and specific symptoms may have different neurobiological substrates. For example, alterations in noradrenergic receptors may be more specifically related to aggression. A better understanding of the biology of agitation and candidate therapies will enable improved targeting of treatment in the future.

There are several additional candidate treatments for agitation in patients with Alzheimer disease. Along with some smaller studies of carbamazepine, oxycarbazine, and prazosin,¹⁵ recent larger RCTs of citalopram¹⁶ and stepped analgesia²⁰ have begun to provide a more informative evidence base, with further small RCTs and secondary analyses identifying additional potential candidate therapies. These studies represent new territory for investigation, where it will become increasingly important to prioritize potential treatments in terms of further research and potential clinical use.

Currently, pharmacological treatments for agitation in patients with dementia in the United States, and almost all treatments for these patients in the European Union, involve off-label prescription of atypical antipsychotics. Emerging evidence indicates that several other treatment approaches such as stepped analgesia and citalopram may have equivalent or better efficacy than antipsychotic agents, although adverse events including the prolongation of QTc may be a challenge with citalopram. Within this clinical treatment environment, pending further evidence, there is a reasonably strong case to prioritize dextromethorphan-quinidine as an off-label treatment for agitation, possibly as a safer alternative to atypical antipsychotics. However, while further studies are conducted to verify the efficacy and safety of this approach, it will be important to achieve a robust international expert consensus regarding the prioritization of potential treatments for agitation in patients with dementia to improve the consistency of clinical practice. This approach also must understand and incorporate patient and caregiver views regarding the evaluation of risk and benefits in relation to these treatments.

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