Evidence for using dextromethorphan-quinidine for the treatment of agitation in dementia

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Abstract
Behavioral and psychological symptoms including agitation are common in dementia, and are associated with decreased quality of life, increased risk of institutionalization, and greater patient and caregiver distress. Pharmacological agents used for management of behavioral and psychological symptoms of dementia are limited by their tolerability, prompting a need for identifying efficacious and safe pharmacological treatments for managing agitation in dementia. The combination of dextromethorphan and quinidine sulfate is approved for pseudobulbar affect, and may be effective in managing agitation in dementia. A review of literature found only one randomized controlled trial that evaluated the use of dextromethorphan-quinidine for the management of agitation in dementia when compared to placebo. Data from this trial demonstrated that dextromethorphan-quinidine decreased agitation in dementia, and was well tolerated. Although promising, further research is needed before dextromethorphan-quinidine combination can be accepted as a standard treatment for agitation in dementia.

Key words: Dextromethorphan; Quinidine; Agitation; Dementia; Behavioral and psychological symptoms of dementia
Core tip: Dextromethorphan-quinidine is approved for the treatment of pseudobulbar affect and may be effective in managing agitation in dementia. There is only one published trial that has evaluated the use dextromethorphan-quinidine for agitation in dementia. The study was of good quality and found that dextromethorphan-quinidine decreases severity of agitation when compared to placebo. Additionally, dextromethorphan-quinidine was fairly well tolerated and did not appear to cause significant sedation or worsen cognitive symptoms among individuals with dementia.

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INTRODUCTION

Behavioral and psychological symptoms of dementia (BPSD) are a group of psychological reactions, psychiatric symptoms and behaviors including agitation and aggression that are unsafe, disruptive, and impair the care of the individual in a given environment[1]. BPSD is seen in one-third of individuals with dementia who live in the community and in up to 80% of individuals with dementia who live in skilled nursing facilities[2]. The prevalence of agitation in dementia can be up to 46%, and is associated with decreased quality of life and increased risk of institutionalization for these individuals, in addition to greater caregiver burden and higher social and economic burden of caring for these individuals[3,4].

Non-pharmacological interventions are recommended as first-line for management of agitation in dementia. Pharmacotherapy including antipsychotics, antidepressants, anticonvulsants and cognitive enhancers are used when non-pharmacological interventions are ineffective[5]. Unfortunately, these medications are burdened with a significant side effect profile including QTc interval prolongation, weight gain, anticholinergic effects and cardiovascular adverse effects that carry substantial risks for the geriatric population[5]. Therefore, there is a great need for identifying efficacious and safe pharmacological treatments that are suitable for managing agitation in dementia.

Dextromethorphan is a low-affinity, uncompetitive N-methyl-D-aspartate receptor antagonist, σ1 receptor agonist, serotonin and norepinephrine reuptake inhibitor, and neuronal nicotinic α3β4 receptor antagonist[6]. Dextromethorphan has low and variable bioavailability when administered alone because of its rapid first-pass metabolism and subsequent elimination. The addition of quinidine, a potent inhibitor of the cytochrome P450 (CYP) liver enzyme CYP2D6, inhibits dextromethorphan metabolism and yields greater bioavailability[6]. The combination of dextromethorphan and quinidine sulfate is approved for the treatment of pseudobulbar affect in the United States and European Union. Evidence suggesting a potential effect of dextromethorphan-quinidine for agitation in dementia comes from controlled clinical trial data in non-demented patients with pseudobulbar affect[6].

The aim of this editorial is to review the literature on published randomized control trials (RCTs) that evaluated the efficacy and tolerability of dextromethorphan-quinidine for the management of agitation in dementia.

EVIDENCE FOR USING DEXTROMETHORPHAN-QUINIDINE FOR AGITATION IN DEMENTIA

A review of literature found only 1 RCT that evaluated the use of dextromethorphan-quinidine for the management of agitation in dementia (Table 1)[6]. The study was assessed as being of good quality based on JADAD criteria (Table 2). The details of the study are described in Table 3.

DISCUSSION

Available data from RCTs on the use of dextromethorphan-quinidine for the
management of BPSD is extremely limited. The only trial that we found in our literature review evaluated the efficacy of dextromethorphan-quinidine in reducing severity of agitation among individuals with Alzheimer’s disease when compared to placebo. This is the first dementia-related trial to use a sequential parallel comparison design\[8\]. In studies using this design, the first stage randomizes more patients to placebo than to active treatment. In the second stage, placebo non-responders from stage 1 are rerandomized and are included in the primary analysis. Pooled analysis of both stages maximizes the power to detect treatment differences and reduces the required sample size\[8\].

In this trial, treatment with dextromethorphan-quinidine demonstrated statistically significant decrease in agitation and aggression when compared to placebo. The reduction in agitation was considered clinically significant as measured by clinician rated scales. While the Alzheimer disease-related agitation characteristics of patients in this study were generally consistent with the International Psychogeriatric Association definition of agitation\[8\], patient emotional distress in patients was not directly measured.

Dextromethorphan-quinidine was generally well tolerated in this elderly population and was not associated with cognitive impairment. Most adverse events, including dizziness and diarrhea, were consistent with those observed in dextromethorphan-quinidine trials for pseudobulbar affect\[8\]. Falls were more common among patients receiving dextromethorphan-quinidine when compared to placebo. This may be explained by greater duration of exposure to dextromethorphan-quinidine and the lack of randomization to groups based on fall risk.

The strengths of the study include the use of the sequential parallel comparison design; inclusion of stable concomitant medications, including psychotropic medications, high retention rate, blinding of study sites to all aspects of the study, use of prespecified sensitivity analyses to corroborate the primary efficacy end point, and consistent results among multiple secondary outcomes and primary end point. Limitations of this trial include a short duration (10 wk), and a dose-escalation schedule that limited evaluation of dose-response relationships. Exclusion of concomitant drugs related to quinidine, tricyclic antidepressants, monoamine oxidase inhibitors, or phenothiazines, as well as cardiac parameters limit the generalizability of study findings. Finally, the patient population was predominantly outpatient, with only 5.5% of study participants domiciled in nursing homes. The treatment response may not be generalizable to patients in nursing homes and should be further explored.

In the study reviewed, the combination of dextromethorphan-quinidine was clinically efficacious for agitation and was generally well tolerated. However, evidence-based trials are limited, as is the generalizability of the results to wider clinical and nursing home populations. This highlights the need for further research on both the efficacy and safety of dextromethorphan-quinidine and other pharmacological interventions for agitation in dementia.

**CONCLUSION**

This review indicates that there is a scarcity of evidence for the use of dextromethorphan-quinidine for the management of agitation in dementia. There is only one available trial, which demonstrated a decrease in agitation and aggression compared with placebo. However, the trial had a limited number of participants and low representation of patients in nursing home, which further restricts the generalizability of the results. The need to further investigate the effectiveness of different pharmacotherapeutic modalities for the management of agitation in dementia is, therefore, essential.
Table 2  Quality of included studies

| Ref. | Randomization | Similar groups initially? | Equal treatment? | Analyzed groups in which they were randomized | Objective/“blind” treatments? | Overall quality of study |
|------|---------------|--------------------------|------------------|---------------------------------------------|-----------------------------|-------------------------|
| Cummings et al[8], 2015 | Yes | Yes | Yes | Yes | Yes | Good |

Table 3  Results summary from included studies

| Ref. | Outcomes | Tolerability | Limitations |
|------|----------|--------------|-------------|
| Cummings et al[8], 2015 | In stage 1, 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, P < 0.001. In stage 2, 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, P = 0.02. The prespecified comparison of NPI Agitation/Aggression scores between patients who were randomized to receive only dextromethorphan-quinidine vs only placebo for the entire 10 weeks of the trial also favored dextromethorphan-quinidine over placebo, P = 0.003. Response to dextromethorphan-quinidine compared with placebo did not appear to differ by disease stage. The additional prespecified analysis that included both placebo responders and non-responders who were rerandomized in stage 2 did not alter the significance or magnitude of effect of the primary analysis. Sequential parallel comparison design analysis of prespecified secondary outcomes showed significant improvement favoring dextromethorphan-quinidine on global rating scores. Results for changes in the quality of life-Alzheimer disease score, ADCS activities of daily living Inventory, MMSE, and ADAS-Cog were not significant vs placebo. Post hoc analyses showed similar improvement in NPI Agitation/Aggression scores with dextromethorphan-quinidine in patients taking concomitant acetylcholinesterase inhibitors, memantine, antidepressants, or antipsychotics n when compared with those not receiving these agents. Lorazepam rescue medication was used by 6.6% of patients in the dextromethorphan-quinidine group during treatment and by 10.4% during treatment with placebo. Treatment-emergent adverse events were reported by 61.2% of patients in the dextromethorphan-quinidine group and 43.3% with placebo group. The most commonly occurring treatment-emergent adverse events were falls (8.6% vs 3.9%), diarrhea (5.9% vs 3.1%), urinary tract infection (5.3% vs 3.9%), and dizziness (4.6% vs 2.4%). Serious adverse events occurred in 7.9% patients receiving dextromethorphan-quinidine and in 4.7% of patients receiving placebo. Serious adverse events in patients receiving dextromethorphan-quinidine included chest pain (n = 2), anemia, acute myocardial infarction, bradycardia, kidney infection, femur fracture, dehydration, colon cancer, cerebrovascular accident, aggression, and hernia. Serious adverse events in patients receiving placebo included idiopathic thrombocytopenic purpura, vertigo, pneumonia, gastroenteritis, confusion, transient ischemic attack, and agitation. Eight patients (5.3%) receiving dextromethorphan-quinidine and 4 (3.1%) receiving placebo discontinued treatment owing to adverse events. No deaths occurred during the study. No clinically meaningful between-group differences in electrocardiographic findings were observed. The duration was limited to 10 wk. The dose-escalation schedule limited evaluation of dose-response relationships. Exclusion of concomitant drugs related to quinidine and specific electrocardiographic/cardiac parameters that restricted patient enrollment, may limit the generalizability of study findings. Treatment at experienced trial sites by specialized clinicians under a clinical protocol prescribing frequent assessments may not reflect general practice. The patient sample consisted predominantly of outpatients; agitation in nursing home residents was underrepresented. | The most commonly occurring treatment-emergent adverse events were falls (8.6% vs 3.9%), diarrhea (5.9% vs 3.1%), urinary tract infection (5.3% vs 3.9%), and dizziness (4.6% vs 2.4%). Serious adverse events occurred in 7.9% patients receiving dextromethorphan-quinidine and in 4.7% of patients receiving placebo. 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NPI: Neuropsychiatric inventory; ADCS: Alzheimer’s disease cooperative study; MMSE: Mini mental state examination; ADAS-Cog: Alzheimer disease assessment scale–cognitive subscale.

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