Off-Label Uses of Nuedexta®
(Dextromethorphan/Quinidine)

By Darren Hein, PharmD

Introduction:

Nuedexta® is a fixed combination of dextromethorphan, an uncompetitive N-methyl-d-aspartate (NMDA) receptor antagonist and sigma-1 receptor agonist, and quinidine, a class IA antiarrhythmic agent and competitive inhibitor of the cytochrome P450 2D6 (CYP2D6) enzyme. Dextromethorphan/quinidine is FDA-approved for the treatment of pseudobulbar affect (PBA), the first and only drug to carry this indication.1,2

While PBA is currently the only indication for which dextromethorphan/quinidine is approved, clinical research on the safety and efficacy of dextromethorphan/quinidine for other indications has been conducted. Phase 2 clinical trials assessing the safety and effectiveness of dextromethorphan/quinidine for central neuropathic pain in multiple sclerosis (MS), levodopa-induced dyskinesia in Parkinson’s disease, agitation in Alzheimer’s disease, bulbar function in amyotrophic lateral sclerosis (ALS), and treatment-resistant depression have been completed with some results published, and phase 2 clinical trials evaluating the effects of dextromethorphan/quinidine in patients with autism or migraine are ongoing. A phase 3 clinical trial on the use of dextromethorphan/quinidine for diabetic neuropathic pain has also been completed with study results published.3 In addition to this clinical research, lower quality clinical evidence on the use of dextromethorphan/quinidine for other conditions has been published. This article will provide an overview of this evidence to determine if dextromethorphan/quinidine is safe and effective for off-label use.

Agitation in Alzheimer’s Disease

Cummings et al. conducted a randomized, double-blind, placebo-controlled, phase 2 clinical trial assessing the safety and effectiveness of dextromethorphan/quinidine in 220 patients with probable Alzheimer’s disease and clinically significant agitation. In the first stage of this study, subjects were randomized to receive dextromethorphan/quinidine or placebo for 5 weeks. For week 1, dextromethorphan/quinidine was dosed at 20 mg/10 mg once daily. This dose was given twice daily for weeks 2 and 3 and then increased to 30 mg/10 mg twice daily for weeks 4 and 5. In the second stage of this study, approximately half of the subjects receiving placebo in the first stage were randomized to receive dextromethorphan/quinidine based on the dosing regimen described. Subjects receiving the study drug during the first stage continued taking dextromethorphan 30mg/quinidine 10 mg twice
daily. A statistically significant difference between dextromethorphan/quinidine and placebo with respect to the primary outcome, Neuropsychiatric Inventory (NPI) Agitation/Aggression domain score, was found. Subjects receiving the study drug in the first stage of the study saw NPI Agitation/Aggression scores decrease by an average of 3.3 points on a 12 point scale while those receiving placebo saw scores decrease by only 1.7 points ($p<0.001$). In the second stage of the study, NPI Agitation/Aggression scores decreased by 2 points and 0.9 points with dextromethorphan/quinidine and placebo, respectively ($p=0.02$). Dextromethorphan/quinidine also appeared to improve global rating scales, symptoms of irritability and depression, and caregiver strain; however, significant differences in quality of life were lacking. Falls were reported in 8.6% of subjects receiving the study drug versus 3.9% for placebo. More subjects receiving the study drug also reported diarrhea and urinary tract infections vs. placebo.\(^4\)

It is unclear if the differences in NPI Agitation/Aggression scores are clinically significant, as a minimum clinically important difference (MCID) for this domain has not been established.\(^5\) Additionally, the increased incidence of falls with dextromethorphan/quinidine is concerning in this patient population.\(^6\) However, the authors note that 3 of the 13 subjects experiencing falls did so after study completion when they were not taking the study drug, and more subjects in the treatment group had a history of falls at baseline.\(^7\) Overall, due to the potential fall risk and lack of clarity with respect to the clinical significance of these results, more research is needed before dextromethorphan/quinidine should be recommended for treating agitation in patients with Alzheimer’s disease.

**Bipolar Disorder**

Kelly and Lieberman conducted a retrospective chart review to assess Clinical Global Impression-Improvement (CGI-I) scores after 90 days of treatment with dextromethorphan 20 mg/quinidine 10 mg once or twice daily in 77 patients with treatment resistant bipolar II or bipolar not otherwise specified (NOS) diagnoses. All of these patients suffered from depressive symptoms for at least two years and had failed an average of 21.2 medications per patient. After 90 days of treatment, the average CGI-I score was 1.66, suggesting that symptoms were slightly improved (score of 1) or much improved (score of 2). CGI-I scores could range from -3 (very much worse) to +3 (very much improved); however, only three subjects showed worsening bipolar symptoms (score of -1 for each). Of the 19 patients who discontinued the treatment early, 16 did so due to nausea.\(^8\) Due to the high discontinuation rate and lack of control group, more evidence is needed before dextromethorphan/quinidine should be recommended for the treatment of bipolar disorder.

**Bulbar Function in ALS**

Smith et al. conducted a randomized, double-blind, placebo-controlled, crossover trial to assess whether dextromethorphan/quinidine improves bulbar function (e.g., speech, swallowing, and salivation) in patients with ALS. Sixty patients with ALS were randomized to receive either dextromethorphan 20 mg/quinidine 10 mg or placebo for 28-30 days followed by a 10-15 day washout period before crossing over. The study drug was given once daily for the first week and twice daily thereafter for each study period. The primary endpoint was change in the Center for Neurologic Study Bulbar Function Scale (CNS-BFS) score. The CNS-BFS includes 21 questions with 7 questions assessing each domain (salivation, speech, swallowing). Each question is rated on a scale of 1-5, with lower ratings suggesting less severe symptoms. Patients
unable to speak are given a score of 6 for each question in the speech domain. The global CNS-BFS score ranges from 21-112, with domain scores ranging from 7-35 for salivation and swallowing and 7-42 for speech.\textsuperscript{9}

A statistically significant difference between the study drug and placebo was reported for both the global and domain scores on the CNS-BFS. Compared to placebo, treatment with dextromethorphan/quinidine decreased CNS-BFS global score by 5.8 points ($p<0.001$), salivation by 1.5 points ($p=0.004$), speech by 2.4 points ($p=0.003$), and swallowing by 1.8 points ($p=0.009$). While statistically significant, it is unclear if these improvements in bulbar functioning are clinically significant. Additionally, more patients reported dizziness (12\% vs. 2\%), constipation (9\% vs. 4\%), diarrhea (9\% vs. 2\%), and nausea (7\% vs. 0\%) when taking dextromethorphan/quinidine.\textsuperscript{9} While these results appear promising, higher quality research is needed before dextromethorphan/quinidine can be safely recommended for the enhancement of bulbar function long-term in ALS patients.

**Diabetic Peripheral Neuropathy**

Thisted et al. conducted a 29-day, open-label dose escalation study to assess the tolerability of dextromethorphan/quinidine in 36 patients with painful diabetic neuropathy. While adverse events, clinical parameters, and laboratory tests were the primary endpoints, some preliminary efficacy outcomes focusing on pain, quality of life, and sleep were reported. Subjects were initiated on dextromethorphan 30 mg/quinidine 30 mg once daily with doses increased up to a maximum of four capsules daily (dextromethorphan 120 mg/quinidine 120 mg). Nearly 70\% of the subjects completed the study on the maximum dose. Nausea (27.8\%), dizziness (25.0\%), and headache (25.0\%) were the most commonly reported adverse events. Statistically significant improvements in pain relief, quality of life, sleep scores, and other efficacy measures compared to baseline were reported.\textsuperscript{10} It is important to note that this study assessed a combination of dextromethorphan/quinidine at a higher dose than is currently available. Despite the high rate of adverse reactions and a lack of control group, the preliminary efficacy data prompted the following phase 3 clinical trial.

Shaibani et al. conducted a randomized, double-blind, placebo-controlled, phase 3 trial assessing dextromethorphan 30 mg/quinidine 30 mg and dextromethorphan 45 mg/quinidine 30 mg twice daily for 13 weeks in 379 patients with painful diabetic neuropathy. Both doses of dextromethorphan/quinidine showed statistically significant improvements in pain, sleep, and activity scores compared with placebo, with numerically greater improvements noted in patients on the higher dextromethorphan dosage. Treatment-related dizziness, nausea, diarrhea, and headache were reported in >10\% of subjects and more frequently than with placebo. Of note, 27.5\% of subjects receiving high dose dextromethorphan/quinidine reported dizziness vs. 11.4\% with placebo.\textsuperscript{11}

While the results from both studies in patients with diabetic peripheral neuropathy appear promising, the currently approved dextromethorphan/quinidine product is not available in the doses studied. Additionally, the larger doses evaluated in these studies appear to be associated with a higher risk for adverse events. It is currently unclear if dextromethorphan 20 mg/quinidine 10 mg will be efficacious for the treatment of diabetic peripheral neuropathy. Until more is known, dextromethorphan/quinidine should not be recommended for these patients.

**Heroin Detoxification**

Preliminary clinical research assessing the effects of dextromethorphan/quinidine in patients undergoing heroin detoxification suggests that dextromethorphan/quinidine is not effective for reducing withdrawal symptoms, self-administration of heroin, or other subjective effects of heroin use.\textsuperscript{12,13} Dextromethorphan/quinidine should not be recommended for this purpose.
In addition to the clinical research described above, a number of reports describing the use of dextromethorphan/quinidine for specific conditions have been published. The table below briefly summarizes these cases.

**Table. Off-label use of dextromethorphan/quinidine: case reports.**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Case Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitation associated with cerebellar injury¹⁴</td>
<td>A 47 year old male presented with emotional lability and agitation after suffering from a cerebellar stroke. Neither olanzapine nor valproate significantly improved his condition. A trial of dextromethorphan 20 mg/quinidine 10 mg twice daily was started, and improvement in agitation and other behavior was noted within 48 hours. After discharge, the patient could no longer afford this medication and stopped taking it, resulting in readmission for agitation. His agitation improved within 24 hours of restarting dextromethorphan/quinidine.</td>
</tr>
<tr>
<td>Agitation associated with traumatic brain injury (TBI)¹⁵</td>
<td>Four patients with moderate TBIs presented with agitation and confusion which did not respond to behavioral therapy. In lieu of antipsychotic treatment, dextromethorphan/quinidine (dosage unknown) was initiated in each patient. Within 1-2 days each patient showed decreased agitation and improved social interaction. Eventually all patients progressed through their rehabilitation and were discharged.</td>
</tr>
<tr>
<td>Catatonia¹⁶</td>
<td>A 65 year old male with a history of schizoaffective disorder and PBA was admitted for urologic infection. During his hospital stay, dextromethorphan 20 mg/quinidine 10 mg was held. Within one day he developed catatonia which persisted during a 2-week course of ciprofloxacin and one week thereafter. His catatonia did not respond to re-initiation of dextromethorphan/quinidine, so the dosing frequency was increased to twice daily. He was free of catatonic symptoms within one week of this change and discharged soon thereafter.</td>
</tr>
<tr>
<td>Chorea¹⁷</td>
<td>Ten patients with chorea of mixed etiologies received dextromethorphan 20 mg/quinidine 10 mg twice daily for 2-18 weeks. Eight of the 10 patients reported marked, moderate, or mild improvement in chorea, while two patients reported no improvement.</td>
</tr>
<tr>
<td>Emotional lability associated with depression¹⁸</td>
<td>A 32 year old female with five admissions for major depressive disorder in the past six years presented with difficulty controlling affective expressions, in particular crying outbursts. A range of antidepressants, psychotherapy, and electroconvulsive therapy sessions did not help with these symptoms. Dextromethorphan 20 mg/quinidine 10 mg daily was initiated and led to significant improvement in crying spells and overall mood lability.</td>
</tr>
<tr>
<td>Wilson’s disease¹⁹</td>
<td>A 34 year old female with a long history of Wilson’s disease presented with neuropsychiatric manifestations of the disease, including mood lability, depression, impulsivity, and parkinsonian features. Initiation of dextromethorphan 20 mg/quinidine 10 mg twice daily led to a marked improvement in mood lability and impulsivity, with no worsening of extrapyramidal symptoms.</td>
</tr>
</tbody>
</table>
Avanir Pharmaceuticals, the manufacturer of Nuedexta® (dextromethorphan/quinidine), is conducting research on a similar dextromethorphan/quinidine combination product (AVP-786) in which the dextromethorphan component is deuterated. Incorporating deuterium and dextromethorphan has been shown to reduce first-pass metabolism of dextromethorphan, allowing for a lower dose of quinidine and thus reducing the risk for adverse cardiovascular effects and drug-drug interactions. This product is being investigated for the treatment of agitation in Alzheimer’s disease, residual schizophrenia, disinhibition in dementia, and behavioral dysfunction post-TBI.

Summary

While Nuedexta® (dextromethorphan/quinidine) is only approved for the treatment of PBA, research on its off-label use in a variety of conditions is promising. Of note, dextromethorphan/quinidine seems to improve agitation in Alzheimer’s disease, decrease symptoms of bipolar II/NOS disorder, enhance bulbar function in ALS, and improve symptoms of painful diabetic peripheral neuropathy. However, these studies only showed benefit compared to placebo or baseline measurements; the effectiveness of dextromethorphan/quinidine compared to active treatment is unclear. Overall, due to safety concerns in the long-term care population, such as dizziness, and limitations of the published studies described above, higher-quality clinical research is warranted before dextromethorphan/quinidine should be recommended for conditions other than PBA.

References:


References continued.


