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Dextromethorphan/quinidine for pseudobulbar affect

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The combination of dextromethorphan and quinidine reduced the number of daily PBA episodes in 3 randomized trials

In October 2010, the FDA approved a combination of dextromethorphan (DM) and quinidine for the treatment of pseudobulbar affect (PBA)—also called pathological laughing and crying, affective lability, emotional dyscontrol, emotional incontinence, and involuntary emotional expression disorder—in patients with neurologic disorders and brain injuries (*Table*). Despite receiving an approvable letter in 2006, the compound was not approved at that time because of concerns about the arrhythmogenic potential of quinidine, which prolongs the QT interval. The manufacturer conducted another study using one-third of the previous quinidine dose, which ameliorated this concern and led to approval.

Table

Dextromethorphan/quinidine: Fast facts

Brand name: Nuedexta
Indication: Pseudobulbar affect
Approval date: October 29, 2010
Availability date: First quarter of 2011
Manufacturer: Avanir
Dosage forms: Dextromethorphan, 20 mg, plus quinidine, 10 mg
Starting dose: 1 capsule per day
Target dose: 2 capsules per day

Clinical implications

PBA is manifested by involuntary labile, shallow affect with sudden and unpredictable laughing, crying, or other emotional displays that are not appropriate to the social setting and may not be congruent with the patient's prevailing mood.[1] Episodes are often paroxysmal and cannot be interrupted voluntarily.[2] PBA seems to be caused by a loss of descending cortical control of brainstem motor nuclei and possibly the cerebellum, disrupting inhibitory mechanisms and resulting in inappropriate and involuntary emotional display.[3] Several studies have demonstrated involvement of subcortical areas, particularly the anterior limb of the internal capsule and the bulbar area. The pathophysiology of PBA may involve excessive release of glutamate by injured neurons, disrupting systems for motor control of emotional expression.[4,5]

PBA is most common in diseases that interfere bilaterally with the corticohypothalamic and corticobulbar tracts that control voluntary and involuntary faciorespiratory mechanisms. However, PBA occurs in unilateral disease as well. The reported prevalence of PBA is:

- 49% in amyotrophic lateral sclerosis (ALS)
- 18% to 39% in Alzheimer's disease
- 11% to 34% in stroke
- 10% to 11% in multiple sclerosis (MS) and traumatic brain injury.[6,7]

PBA also has been reported in patients with Parkinson's disease, brain tumors, Wilson's disease, syphilitic pseudobulbar

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palsy, and various encephalitides.[1] An estimated 880,000 U.S. patients exhibit PBA.[8]

Previously, there was no FDA-approved treatment for PBA. However, small controlled trials suggest that selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs)—usually in doses lower than those used to treat depression—may effectively reduce symptoms within 2 to 3 days.[1] Although dopaminergic agents such as levodopa and amantadine have shown benefit in open trials, results of controlled studies using objective measurements have not been positive.

How it works

DM is a serotonergic substance that also is an agonist of 1-sigma receptors and a low-affinity, uncompetitive antagonist of *N*-methyl-D-aspartate (NMDA) receptors, which are important in glutamate signaling, through binding at the phencyclidine site on the NMDA complex.[7,9] The 1-sigma receptor was thought to be an opioid receptor subtype, but unlike opioid receptors it is not blocked by narcotic antagonists and does not have an endogenous ligand. However, the 1-sigma receptor does modulate activity of opioid mu receptors in addition to altering dopamine release and possibly reducing glutamate release.[9] Sigma receptors are densely distributed in the limbic system and in systems related to motor control of affective expression and seem to be involved in learning, responses to stress, mood regulation, and drug dependence.[1] Because DM preferentially binds to brain regions that regulate emotional expression,[10] it could normalize glutaminergic neurotransmission and other relevant systems in these regions.[1] However, DM's exact mechanism of action is unknown.

Quinidine is a sodium channel antagonist usually used as a type Ia antiarrhythmic.[5] DM is subject to extensive first-pass metabolism by cytochrome P (CYP) 450 2D6 to dextrorphan, which after being glucuronidated cannot cross the blood-brain barrier. In doses 10 to 25 times lower than those used to treat cardiac arrhythmias, quinidine inhibits 2D6 and increases DM bioavailability.[10] DM blood levels increase linearly with dose following coadministration with quinidine but are undetectable in most patients given DM alone.[7,9]

Efficacy and tolerability

A combination of DM and quinidine (DMQ) reduced Center for Neurologic Study-Lability Scale (CNC-LS) scores and the number of daily PBA episodes in 3 randomized trials.[5,7,10] Visit this article at CurrentPsychiatry.com for a table summarizing these studies.

An 85-day randomized, double-blind, placebo-controlled study of 150 patients with PBA associated with MS found that DM, 30 mg, plus quinidine, 30 mg, (DMQ 30-30) was twice as effective as placebo within a week in reducing CNC-LS scores.[10] DMQ 30-30 patients also had approximately half as many episodes of inappropriate laughing, crying, or combined laughing and crying and a 2-fold greater decrease in pain intensity.[10] Twenty-one percent of DMQ 30-30 patients experienced complete remission—no PBA episodes—compared with 7% of placebo patients. There were no significant differences in QT prolongation between DMQ 30-30 and placebo.

A 3-arm, double-blind, 28-day, phase III multicenter trial of 140 ALS patients with PBA compared DM monotherapy, quinidine monotherapy, and DMQ 30-30.[5] Compared with either drug alone, DMQ 30-30 showed greater reduction of CNC-LS scores, as well as improved quality of life and quality of relationships scores, with equal benefit in poor and extensive DM metabolizers. However, the control conditions may not have been adequate. Quinidine alone would not be expected to have an effect on PBA, and the DM dose, which was the same in combination and monotherapy, may have been too low to be effective by itself. In support of this hypothesis, the DM plasma level was 18 times higher in patients taking DMQ 30-30 than those taking DM monotherapy.

In a manufacturer-sponsored, multicenter, 12-week randomized trial, 326 pa-

Clinical Point

In doses 10 to 25 times lower than those used to treat cardiac arrhythmias, quinidine inhibits 2D6 and increases DM bioavailability

tients with ALS or MS and clinically significant PBA were randomly assigned to DM, 30 mg, plus quinidine, 10 mg (DMQ 30-10), DM, 20 mg, plus quinidine, 10 mg (DMQ 20-10), or placebo, each administered twice daily.[7] Patients with comorbid psychiatric disorders or significant depressive symptoms were excluded. Although daily PBA episodes decreased in all groups, the daily rate of PBA episodes was 47% lower for patients taking DMQ 30-10, and 49% lower with DMQ 20-10 compared with placebo (both $P < .001$). The mean decrease in the number of daily PBA episodes was 3.9 to 4.1 with active treatment and 3.0 with placebo. Side effects were more common with active drug than placebo and included dizziness, nausea, diarrhea, and urinary tract infection. There were no serious adverse cardiac events and no active drug recipients showed a QTc interval >480 msec or a change from baseline >60 msec.[11] Discontinuation rates in this study were lower than in studies of DMQ 30-30. In an open-label extension of 253 patients who completed the double-blind phase and were assigned to DMQ 30-10 for 12 weeks, the incidence of treatment-related adverse events was 28%, with a 5.5% rate of serious adverse events.[12]

Safety

Because the 10 mg dose of quinidine in the approved formulation of DMQ is 10 times lower than the antiarrhythmic dose, substantial ECG changes and adverse cardiac effects with DMQ have not been reported. The most common side effects of DM are nausea, somnolence, dizziness, and headache. Thrombocytopenia, QT prolongation, hepatotoxicity, allergic reactions, and anticholinergic side effects can occur.

In high doses and combined with other substances, DM has been used as a recreational drug. When taken in high doses, adverse effects include nausea, vomiting, malaise, dilated pupils, difficulty urinating, increased urination frequency, fever, tachycardia, loss of appetite, shakiness, seizures, and potentially coma and death. DMQ may have a greater potential for serious adverse effects than DM alone because quinidine increases DM bioavailability and blood levels. The abuse potential of DMQ is not clear.

Psychosis has been reported with higher DM doses. The psychotomimetic effects of phencyclidine (PCP) are related to binding to the PCP site on the NMDA receptor complex—to which DM also binds—with reduced glutamate signaling in information processing systems. Therefore, caution is indicated when prescribing DM to patients with psychosis.

Because DM, a CYP2D6 substrate, is combined with quinidine, a 2D6 inhibitor, administering DMQ with other 2D6 inhibitors could lead to toxicity. When DMQ is combined with SSRIs and similar agents, the serotonergic properties of DM could result in serotonin syndrome, which could be fatal if DM is combined with monoamine oxidase inhibitors.[10] Combinations of DM and acetaminophen and antihistamines can be dangerous at higher doses.[10] Because quinidine is metabolized by CYP3A, inhibitors of this enzyme such as ketoconazole, nefazodone, and grapefruit juice should be avoided. Similarly, inhibition of CYP2D6 by quinidine could raise levels of coadministered 2D6 substrates.

Contraindications. DMQ is contraindicated in patients with:

- heart failure
- prolonged QT interval
- congenital long QT interval
- history of torsades de pointes
- complete atrioventricular (AV) block without implanted pacemakers.[13]

DMQ also is contraindicated in patients at high risk for complete AV block.[13]

Dosing

DMQ is available as a capsule containing DM, 20 mg, and quinidine, 10 mg. The recommended starting dose is 1 capsule by mouth for 7 days, then 1 capsule every 12 hours.

Although DMQ is convenient, its advantage over starting with DM alone and adding a small dose of a non-serotonergic 2D6 inhibitor if DM is not effective remains to be demonstrated. In view of the

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Substantial ECG changes and adverse cardiac effects with DMQ have not been reported

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unknown potential for abuse and toxicity as well as the cost of the proprietary drug ($3,000 to $5,000 a year), it would seem prudent to consider using an SSRI or a TCA first.[8] These medications also act on 1-sigma receptors,[14,15] which may account in part for their reported benefit.

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Related Resource

- Neudexta [package insert]. Aliso Viejo, CA: Avanir Pharmaceuticals; 2010.

Drug Brand Names

Amantadine • Symmetrel
Dextromethorphan/quinidine • Neudexta
Ketoconazole • Nizoral
Levodopa • Sinemet
Nefazodone • Serzone
Quinidine • Quinidex

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Clinical Point

When DMQ is combined with SSRIs and similar agents, the serotonergic properties of DM could result in serotonin syndrome

Bottom Line

As a result of NMDA antagonism, 1-sigma agonism, and serotonergic effects, dextromethorphan/quinidine ameliorates pseudobulbar affect in patients with chronic neurologic disease. Addition of quinidine enhances dextromethorphan levels, with the potential for both greater therapeutic and toxic effects.

Table 2

Dextromethorphan/quinidine for PBA: Evidence shows efficacy

Study	Patients	Dosages	Results
Panitch et al, 2006[10]; 85-day, randomized, double-blind, placebo-controlled	150 MS patients with PBA	DMQ 30-30 or placebo, given twice a day	DMQ 30-30 was associated with greater reductions in CNC-LS scores, fewer PBA episodes, improvement in QOL and QOR, and decrease in pain intensity
Pope, 2006[5]; 3-arm, double-blind, 28-day phase III multicenter trial	140 ALS patients with PBA	DMQ 30-30, DM, 30 mg, or quinidine, 30 mg, given twice daily	DMQ 30-30 was associated with greater decreases in CNC-LS scores and number of laughing and crying episodes and improvements in QOL and QOR compared with DM or quinidine alone
Pioro et al, 2010[7]; 12-week, randomized, double-blind, placebo-controlled trial	326 ALS and MS patients with clinically significant PBA	DMQ 30-10, DMQ 20-10, or placebo, given twice daily	CNC-LS scores decreased in all groups but the daily rate of PBA episodes was 47% lower for DMQ 30-10 and 49% lower for DMQ 20-10 compared with placebo

ALS: amyotrophic lateral sclerosis; CNC-LS: Center for Neurologic Study-Lability Scale; DM: dextromethorphan; DMQ 20-10: dextromethorphan, 20 mg, plus quinidine, 10 mg; DMQ 30-10: dextromethorphan, 30 mg, plus quinidine, 10 mg; DMQ 30-30: dextromethorphan, 30 mg, plus quinidine, 30 mg; MS: multiple sclerosis; PBA: pseudobulbar affect; QOL: quality of life; QOR: quality of relationships