CLINICAL INVESTIGATION

Dextromethorphan/quinidine for pseudobulbar affect

Dextromethorphan/quinidine (DM/Q; NUEDEXTA) is approved by the US FDA for the treatment of pseudobulbar affect (PBA) associated with chronic neurological disorders such as multiple sclerosis, stroke, traumatic brain injury and amyotrophic lateral sclerosis. Studies of applications in other illnesses and for behavioral disinhibition are currently underway. The primary active agent is dextromethorphan, with quinidine added to inhibit its metabolism by CYP450 2D6 and increase the bioavailability of dextromethorphan. Published studies suggest reduction of episodes of PBA and improved quality of life with reasonable tolerability. However, the combination has the potential to interact with a number of other medications used by older patients. Some antidepressants may also be helpful in low doses for PBA and are easier to use, but more controlled studies with validated outcome measures are available for DM/Q. This article reviews published studies of DM/Q and addresses its use in clinical practice.

Keywords: dextromethorphan • neurological disease • quinidine • pseudobulbar affect

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Pseudobulbar affect (PBA), also known as involuntary emotional expression disorder (IEED), *Zwangslachen* (forced laughter) and *Zwangsweinen* (forced crying), emotional incontinence, and forced laughing and crying, has been described in the neurological literature for more than a century [1]. This syndrome, which is always due to neurological disease, is manifested by paroxysmal, involuntary outbursts of labile, shallow affect with unpredictable stereotyped laughing, crying, or mixtures of the two that are not appropriate to the social setting and may or may not be congruent with the prevailing mood of the patient [1,2]. Episodes often appear to be provoked by minor interactions or events but cannot be interrupted voluntarily [3]. The emotional disorder is called pseudobulbar because of the discrepancy between loss of voluntary control of muscles innervated by motor nuclei of the lower pons and medulla (pseudobulbar palsy) resulting, for example, in inability to articulate and the preservation of those muscles for involuntary movement such as spasmodic laughing and crying [1]. Laughing and crying may accompany or alternate with each other because the same pontomedullary mechanisms and facial, vocal and respiratory muscles are involved in both forms of affective display [1]. However, 'pseudobulbar' affect can exist without pseudobulbar palsy and *vice versa*.

Pathophysiology & differential diagnosis

PBA appears to be associated with bilateral lesions, which may involve subcortical areas that interfere with corticohypothalamic and corticobulbar inhibitory and facilitatory tracts that control voluntary and involuntary faciorespiratory mechanisms [1,4], although in a small number of cases an isolated brainstem or cerebellar lesion may be present [5]. The pathophysiology of pseudobulbar affect may involve excessive release of glutamate by injured neurons, disrupting systems for motor control of emotional expression [6,7].

Disorders in which PBA is common are listed in Box 1 [1,8,9]. The reported prevalence of PBA is 49% in amyotrophic lateral sclero-

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sis (ALS), 18–39% in Alzheimer's disease, 11–34% in stroke, and 10–11% in multiple sclerosis and traumatic brain injury [8,9]; it has also been reported in Parkinson's disease, brain tumors, Wilson's disease, and syphilitic and other encephalitides [2]. It has been estimated that there are 880,000 patients with PBA in the USA [10].

PBA should be differentiated from other disorders associated with inappropriate, labile affect. Primary psychiatric disorders in this category include bipolar disorder, especially with ultradian cycling, and schizophrenia. In unstable bipolar disorder, very rapid mood swings can result in abrupt shifts from hilarity to tearfulness that seem unprovoked and inappropriate. In contrast to PBA, even brief emotional expression is consistent with underlying happy or sad mental content. Schizophrenia is often associated with inappropriate, shallow affect, but thinking is characterized by a consistent disorder of the form of thought (e.g., dereistic thinking, loos associations) that is not present in PBA. Illicit drug intoxications that can produce emotional outbursts include amphetamines and phencyclidine. Such states are less labile and more intense than is the affective dysregulation of PBA. The expression of major depression can be altered by right-sided brain disease (aprosodia), resulting in disturbances of recognition and expression of one's own emotions, so that depressed mood is manifested as labile, shallow affect, while psychological dimensions of depression are not obvious. A past and family history of depression, as well as other depressive features such as withdrawal and appetite disturbance, can often be observed. Le fou rire prodromique of Féré (prodromal laughing madness) is a syndrome of abrupt uncontrollable laughter followed by hemiplegia associated with vascular occlusion. Protracted laughing or occasionally crying may also be a manifestation of partial complex seizures (gelastic seizures) [1].

Previous treatment options

Seven placebo-controlled trials, only two of which involved more than 100 patients, suggest that serotonin reuptake inhibitor (SSRI) and tricyclic (TCA) antidepressants reduce PBA symptoms within 2–3 days, usually in doses lower than those used to treat depression [1,2,11]. Although methodologies differed, only one small study used a validated measure of PBA [11,12]. For example, the Pathological Laughter and Crying Scale demonstrated significantly more improvement with nortriptyline than placebo beginning at week 2 in a double-blind study of stroke and post-stroke patients [13]. Similarly, in 152 post-stroke patients, self-ratings of PBA-associated crying decreased by 69% with fluoxetine versus 21% with placebo, although there were no differences in reduction of laughing [14]. While dopaminergic agents such as L-dopa and amantadine (which also has NMDA antagonist properties) have seemed useful in open trials, controlled studies using objective measurements have not been positive.

Box 1. Disorders associated with pseudobulbar affect.

- Recurrent bilateral strokes in cerebral hemispheres or pons
- Binswanger diffuse leukoencephalopathy
- Parkinson's disease
- Alzheimer's disease
- Amyotrophic lateral sclerosis with pseudobulbar palsy
- Progressive supranuclear palsy
- Multiple sclerosis with corticobulbar demylelination
- Bilateral traumatic brain injury
- Wilson's disease
- Ischemic/hypoxic encephalopathy
- Gliomatosis cerebri
- Pontine myelinosis
- Tertiary syphilis

Actions of dextromethorphan/quinidine

Because of the presumed role of excessive glutamate signaling in PBA, as well as the role of serotonergic signaling in inhibiting abnormally released behavior, the apparent benefit of dextromethorphan, a serotonergic substance that is an agonist of sigma-1 receptors and a low-affinity, uncompetitive antagonist of *N*-methyl-D-aspartate (NMDA) glutamate receptors (through binding at the phencyclidine site on the NMDA complex) [9,15], noted in attempts to use it to slow neuronal apoptosis in ALS, seems logical. The sigma-1 receptor was once thought to be an opioid receptor subtype, but unlike opioid receptors it is not blocked by narcotic antagonists and it does not have a known endogenous ligand. However, the receptor does weakly modulate activity of opioid mu receptors in addition to altering dopamine release and possibly reducing release of glutamate [15]. Sigma receptors are densely distributed in limbic circuits and systems involved in motor control of affective expression, and seem to be involved in mood regulation, among other things [2]. Because dextromethorphan preferentially binds to brain regions that regulate emotional expression [16], it may have the potential to normalize glutaminergic neurotransmission there and possibly in other relevant regions [2]. However, the exact mechanism of action is unknown.

Dextromethorphan is subject to extensive first-pass metabolism by CYP450 2D6 to the active metabolite dextrorphan, which after being glucuronidated cannot cross the blood–brain barrier. In doses 10–25-times lower than those used to treat cardiac arrhythmias, quinidine, a type Ia sodium channel antagonist antiarrhythmic, inhibits 2D6 and increases dextromethorphan bioavailability [7,16]. Blood levels of dextromethorphan increase linearly with dose following coadministration with quinidine but are undetectable

in most subjects given dextromethorphan alone [9,15]. However, quinidine will not affect dextromethorphan levels in the 5–10% of people who are poor CYP2D6 metabolizers because they have insufficient enzyme activity for enzyme inhibition to be important. Quinidine may enhance the psychoactive properties of dextromethorphan [17]. For example, a study of postoperative pain found that 12 h after 50 mg of quinidine, biotransformation of 50 mg of dextromethorphan to dextrorphan was reduced by 50% compared with placebo, while use of NSAIDs was 5.5-times greater when dextromethorphan followed placebo versus quinidine [18]. Some of the putative actions of DM/Q are summarized in Figure 1.

In the first quarter of 2011, Avanir Pharmaceuticals released NUEDEXTA (formerly referred to as ZENVIA and NEURODEX), available in the USA as a twice-daily, fixed-dose combination of 20 mg dextromethorphan hydrobromide (DM) and 10 mg quinidine sulfate (Q), for the treatment of pseudobulbar affect in patients with neurological disorders and brain injuries. Approval was granted in October 2010 after the manufacturer lowered the original dose of quinidine to one-third of the dose that was originally studied because of concerns about its arrhythmogenic effect at higher doses. The lower dose did not appear to reduce efficacy of the combination for PBA. The cost is approximately US$3000–5000/year. The EU approved DM/Q in 2013 as fixed dose combinations of 20 or 30 mg dextromethorphan and 10 mg quinidine (labeled as 15/9 and 23/9).

This article reviews published studies of the dextromethorphan/quinidine combination (DM/Q) for pseudobulbar affect and addresses the role of this combination in clinical practice.

Phase II & III studies

An 85-day randomized, double-blind, placebo-controlled study in 150 patients with pseudobulbar affect associated with multiple sclerosis (MS) found that DM/Q in doses of 30 mg of each drug was about twice as effective as placebo in reducing scores on the Center for Neurologic Study-Lability Scale (CNS-LS) [16]. DM/Q patients also had about half as many episodes of inappropriate laughing, crying, or combined laughing and crying, and a twofold greater decrease in pain intensity [16]. Complete remission (no episodes of PBA from weeks 1 to 12) was achieved in 21% of DM/Q patients and 7% of placebo patients. There were no significant differences in QT prolongation between DM/Q and placebo.

A three-arm, double-blind, 28-day Phase III multicenter trial in 140 amyotrophic lateral sclerosis (ALS) patients with pseudobulbar affect compared monotherapy with 30 mg each of dextromethorphan or quinidine, with DM/Q 30/30 [7]. The combination was significantly better than either drug alone on reduction of CNS-LS scores, as well as on scores on the visual analogue Quality of Life (QOL) and Quality of Relationships (QOR) scales, with equal benefit in poor and extensive DM metabolizers. The fact that the DM plasma level was 18-times higher in the combination than in DM monotherapy, despite the identical dose, implies that a higher DM level with DM/Q explained the better result.

In a multicenter 12-week randomized trial, 326 patients with ALS or MS and clinically significant PBA were randomly assigned to DM 30 mg + Q 10 mg (DM/Q 30/10), DM 20 mg + Q 10 mg (DM/Q 20/10) or placebo [9]. Patients with comorbid psychiatric disorders or significant depressive symptoms were excluded. Although episodes of PBA decreased in all groups, reduction in the number of daily episodes of PBA was 47% greater than with placebo on DM/Q 30/10 and was 49% greater with DM/Q 20/10 (both $p < 0.001$). The mean decrease in number of PBA episodes was 3.9–4.1 with active treatment and 3.0 with placebo. There were no serious adverse cardiac events and no recipients of active drug had a QTc interval >480 ms or a change from baseline >60 ms [19]. Discontinuation rates were lower than in studies of the higher dose quinidine formulations. In an open-label extension [20], 253 patients who completed the double-blind phase were assigned to DM/Q 30/10 for 12 weeks and 235 of them completed the trial [21].

A Phase III study of PBA in MS and ALS (reviewed above) has been published [9]. Although a placebo-controlled randomized study of the safety and efficacy of DM/Q in 100 patients with ALS; ClinicalTrials.gov identifier: NCT00021697) ended in 2002, results were not posted at ClinicalTrials.gov as of March 2014 (last posting 2009). A Phase IV open-label safety study of PBA in Alzheimer's disease, stroke, Parkinson's disease and traumatic brain injury (TBI) was completed in August 2009, but results thus far have only been presented in abstracts. A Phase IV study of PBA in stroke, dementia and TBI, and a Phase IV study of PBA in Alzheimer's disease, both of which began in early 2013, are still recruiting subjects.

Clinical safety data

The incidence of treatment-related adverse events with DM/Q was 28%, with a 5.5% rate of serious adverse events in the 12-week open-label extension mentioned above [20]. The manufacturer reports that diarrhea, dizziness, vomiting, cough, weakness, ankle swelling, flu-like symptoms and flatulence occur in 10–13% of patients. According to Medscape, the most common

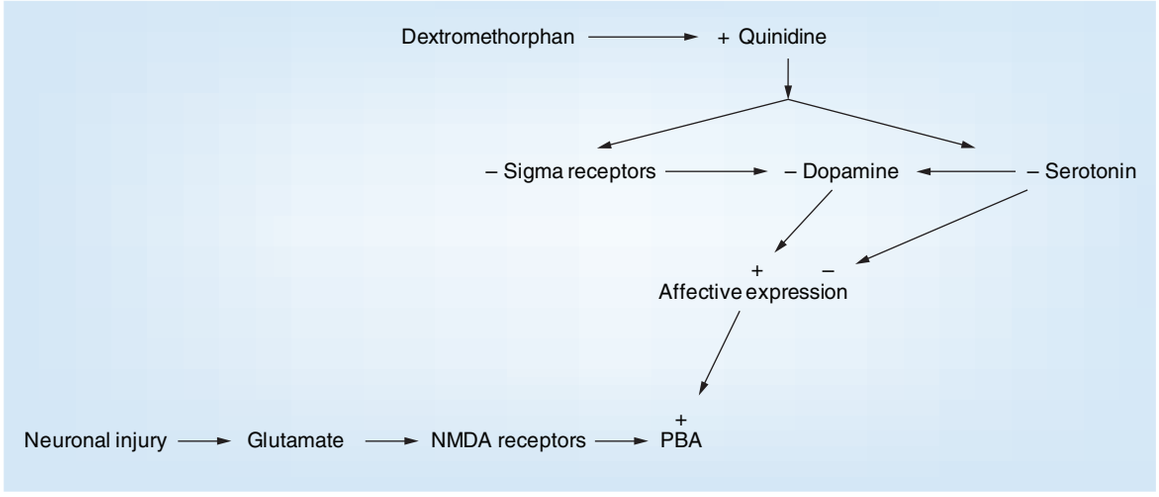

Figure 1. Putative actions of dextromethorphan/quinidine in pseudobulbar affect.
NMDA: *N*-methyl-D-aspartate; PBA: Pseudobulbar affect.

side effects of dextromethorphan/quinidine are nausea, somnolence, dizziness and headache. Thromobcytopenia, QT prolongation, hepatotoxicity, allergic reactions and anticholinergic side effects can occur with higher doses of quinidine. Because dextromethorphan binds to the same site as phencyclidine on the NMDA receptor, it can cause psychosis, especially in higher doses. Any dextromethorphan preparation therefore should be used very cautiously if at all in psychotic patients.

Dextromethorphan is sometimes used as a recreational drug, often in high doses and combined with other substances. When taken in high doses, adverse effects can include dilated pupils, difficulty urinating, increased urinary frequency, fever, tachycardia, loss of appetite, shakiness, seizures, and eventually coma and death. The consequences of abuse of DM/Q, which because of higher dextromethorphan levels should have a greater potential for serious adverse effects, is not clear.

Inhibition of the potassium rectifier current by quinidine prolongs depolarization, extending the window for ventricular re-entry and creating a possible a proarrhythmic effect [22]. Therefore, DM/Q should be avoided in patients with heart block without pacemakers, congenital long QT syndrome, a history of torsades de pointes or heart failure. Additive cardiac effects can occur with concomitant medications that also prolong the QT interval, including many antipsychotic drugs (e.g., haloperidol), tricyclic antidepressants, some antibiotics (e.g., erythromycin) and antifungal drugs. Quinidine inhibits intestinal CYP4503A4 and P-glycoprotein, resulting in excessive levels of lovastatin and some other 3A4 substrates, with a risk of myopathy. Inhibition of CYP2D6 interferes with the metabolism of codeine to morphine, and could antagonize the analgesic effect of codeine; increased levels levels of cholinesterase inhibitors such as donepezil and galantamine may also occur. Combining the serotonergic substance dextromethorphan with other serotonergic drugs such as the serotonin reuptake inhibitors could cause milder forms of serotonin syndrome, which are characterized by headaches, nausea, myoclonus and confusion, while combining dextromethorphan with monoamine oxidase inhibitors can result in life-threatening serotonin syndrome and is contraindicated. Combining quinidine with digoxin can result in digitalis toxicity as a result of inhibition of P-glycoprotein and competition for renal tubular clearance.

In healthy subjects, 20 mg of paroxetine added to DM/Q increased plasma dextromethorphan and quinidine exposure by 50 and 40%, respectively, and decreased dextrorphan exposure by 12%, while DM/Q increased plasma paroxetine exposure by 30% [23]. Conversely, there do not seem to be meaningful pharmacokinetic or pharmacodynamic interactions between DM/Q and memantine, at least in normal subjects [24].

Conclusion

PBA can be a significant problem in a variety of chronic neurological illnesses. In patients without major comorbidities, DM/Q appears to be effective and reasonably well tolerated. The strategy of combining dextromethorphan with a low dose of quinidine seems to have increased the central effect of the former drug without producing excessive QT prolongation in the absence of other drugs with the same cardiac effect, and this approach is probably at least as safe as combining dextromethorphan with another kind of CYP2D6 inhibitor while permitting substantial 2D6 inhibition at a low dose of the companion drug. Interactions with most antiparkinsonian drugs have not been reported, and combinations of DM/Q with memantine seem not to

be problematic. However, interactions with other drugs used for Alzheimer's disease such as the cholinesterase inhibitors requires caution and DM/Q may have the potential to interact with medications that are commonly used in older patients for other conditions such as serotonin reuptake inhibitors, antipsychotic drugs, digoxin and lovastatin.

Two new Phase IV trials of DM/Q were begun in 2013 and are still recruiting subjects. One of these (ClinicalTrials.gov identifier: NCT01799941) plans to enroll 750 patients with PBA associated with stroke, dementia or TBI in an open-label 12-week study of 20 mg dextromethorphan/10 mg quinidine. The primary end point is change from baseline in a seven-item caregiver-administered rating scale. The second study (ClinicalTrials.gov identifier: NCT01832350) will enroll 60 patients with Alzheimer's disease in a 26-week open-label study of reduction in frequency and severity of PBA episodes with DMQ 20/10. No results of clinical trials have been posted at ClinicalTrials.gov or published since the proprietary compound was released, even though one of these studies was completed a year before the drug was approved. Until more data are available, published studies involving a little over 600 patients (946 patients with PBA in total manufacturer experience [AVANIR PHARMACEUTICALS, FEBRUARY 2014; PERS. COMM.]) suggest that DM/Q is a reasonable treatment option for PBA in patients without significant comorbid medical illnesses or concomitant medications that might interact adversely with either dextromethorphan or quinidine. This is a greater number of patients than were studied in older antidepressant trials, which were not designed to obtain regulatory approval. Insofar as the small positive trials of antidepressants suggest possible benefit of low doses in a few days, it may be reasonable to consider one of these medications, which are simpler to use if less well studied, prior to instituting therapy with DM/Q. It remains to be seen whether DM/Q will prove useful for other dimensions of diffuse neurological disease such as behavioral disinhibition.

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Executive summary

Introduction

- NUEDEXTA is a fixed dose combination of 20 mg of dextromethorphan and 10 mg of quinidine (DM/Q) in the USA, and both 20/10 and 30/10 in the EU that is approved for the treatment of pseudobulbar affect (PBA) in patients with chronic neurological disease and traumatic brain injury.
- Published research has primarily involved PBA associated with amyotrophic lateral sclerosis and multiple sclerosis.
- The primary action of DM/Q probably involves a serotonergic effect combined with NMDA receptor antagonism of dextromethorphan, possibly mediated in part by actions on sigma receptors.
- Quinidine is used in a low dose to inhibit metabolism of dextromethorphan and increase its central availability.
- DM/Q is initiated in a once-daily dose and the dose is raised to a twice-daily schedule after 1 week.

Phase II & III studies

- Studies of approximately 600 patients have demonstrated reduction of PBA symptoms and improved quality of life.
- DM/Q appears to be relatively well tolerated by neurologically ill patients, but components of the combination have the potential for interactions with other medications.

Clinical safety data

- Common adverse effects include gastrointestinal distress, nausea and dizziness. Higher doses of dextromethorphan can be psychotogenic.

Conclusion

- DM/Q can be useful for PBA associated with other neurological disorders such as traumatic brain injury and Alzheimer's disease, but no published data are available yet.
- Studies are underway of potential uses of DM/Q for behavioral as well as affective disinhibition, but no results have been published so far.
- DM/Q is the only medication approved for the treatment of PBA, but a few small studies suggest that low doses of serotonin reuptake inhibitor and tricyclic antidepressants may be helpful.
- More data are needed before drawing definitive conclusions about the role of DM/Q in the treatment of neurological disease. In particular, comparative studies are necessary before concluding that DM/Q is the best treatment for PBA.

References

1 Samuels MA. Chapter 25. The limbic lobes and the neurology of emotion. In: *Adams and Victor's Principles of Neurology (9th Edition).* Samuels MA (Ed.). McGraw-Hill, NY, USA (2009).

2 Schiffer R, Pope LE. Review of pseudobulbar affect including a novel and potential therapy. *J. Neuropsychiatry Clin. Neurosci.* 17, 447–454 (2005).

3 Rosen HJ, Cummings J. A real reason for patients with pseudobulbar affect to smile. *Ann. Neurol.* 61, 92–96 (2007).

4 Miller AH. Pseudobulbar affect in multiple sclerosis: toward the development of innovative therapeutic strategies. *J. Neurol. Sci.* 245, 153–159 (2006).

5 Parvizi J, Coburn KL, Shillcutt SD, Coffey CE, Lauterbach EC, Mendez MF. Neuroanatomy of pathological laughing and crying: a report of the American Neuropsychiatric Association Committee on Research. *J. Neuropsychiatry Clin. Neurosci.* 21, 75–87 (2009).

6 Mattson MP. Excitotoxic and excitoprotective mechanisms: abundant targets for the prevention and treatment of neurodegenerative disorders. *Neuromol. Med.* 3, 65–94 (2003).

7 Pope LE. AVP-923 as a novel treatment for pseudobulbar affect in ALS. In: *Progress in Neurotherapeutics and Neuropsychopharmacology.* 1, 91–104 (2006).

8 Arciniegas DB. A clinical overview of pseudobulbar affect. *Am. J. Geriatr. Pharmacother.* 3(Suppl. A), 4–8 (2005).

9 Pioro EP, Brooks BR, Cummings J *et al.* Dextromethorphan plus ultra low-dose quinidine reduces pseudobulbar affect. *Ann. Neurol.* 68, 693–702 (2010).

10 Johnston SC, Hauser SL. Marketing and drug costs: who is laughing and crying? *Ann. Neurol.* 61, 11A–12A (2007).

11 Pioro EP. Current concepts in the pharmacotherapy of pseudobulbar affect. *Drugs* 71, 1193–1207 (2011).

12 Miller AH, Pratt H, Schiffer R. Pseudobulbar affect: the spectrum of clinical presentations, etiologies and treatments. *Expert Rev. Neurother.* 11, 1077–1088 (2011).

13 Robinson RG, Parikh RM, Lipsey JR, Starkstein SE, Price TR. Pathological laughing and crying following stroke: validation of a measurement scale and a double-blind treatment study. *Am. J. Psychiatry* 150, 286–293 (1993).

14 Choi-Kwon S, Han SW, Kwon SU, Kang DW, Choi JM, Kim JS. Fluoxetine treatment in poststroke depression, emotional incontinence, and anger proneness: a double-blind, placebo-controlled study. *Stroke* 37, 156–161 (2006).

15 Brooks BR, Thisted RA, Appel SH. Treatment of pseudobulbar affect with dextromethorphan/quinidine: a randomized trial. *Neurology* 63, 1364–1370 (2004).

16 Panitch HS, Thisted RA, Smith RA. Randomized, controlled trial of dextromethorphan/quinidine for pseudobulbar affect in multiple sclerosis. *Ann. Neurol.* 59, 780–787 (2006).

17 Zawertailo LA, Tyndale RF, Busto U, Sellers EM. Effect of metabolic blockade on the psychoactive effects of dextromethorphan. *Hum. Psychopharmacol.* 25, 71–79 (2010).

18 Ehret GB, Daali Y, Chabert J *et al.* Influence of CYP2D6 activity on pre-emptive analgesia by the *N*-methyl-D-aspartate antagonist dextromethorphan in a randomized controlled trial of acute pain. *Pain Physician* 16, 45–56 (2013).

19 Kaye R, Pratt C. Summary of cardiac safety from a randomized, placebo-controlled, trial of dextromethorphan/quinidine (STAR) for treatment of pseudobulbar affect. Presented at: *American Academy of Neurology Annual Meeting.* Toronto, Canada, 15 April 2010.

20 Pioro EP, Brooks BR, Cummings J *et al.* Safety and tolerability of dextromethorphan/quinidine for pseudobulbar affect in a 12-week, open-label extension study. Presented at: *American Academy of Neurology Annual Meeting.* Toronto, Canada, 15 April 2010.

21 ClinicalTrials.gov: NCT00021697. http://clinicaltrials.gov/ct2/show/NCT00021697?term=dextromethorphan+and+quinidine&rank=8

22 Osadchii OE. Quinidine elicits proarrhythmic changes in ventricular repolarization and refractoriness in guinea pig. *Can. J. Physiol. Pharmacol.* 91, 306–315 (2013).

23 Schoedel KA, Pope LE, Sellers EM. Randomized open-label drug-drug interaction trial of dextromethorphan/quinidine and paroxetine in healthy volunteers. *Clin. Drug Invest.* 32, 157–169 (2012).

24 Pope LE, Schoedel KA, Bartlett KA, Sellers EM. A study of potential pharmacokinetic and pharmacodynamic interactions between dextromethorphan/quinidine and memantine in healthy volunteers. *Clin. Drug Invest.* 32, e1–e15 (2012).