Dextromethorphan Plus Ultra Low-Dose Quinidine Reduces Pseudobulbar Affect

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Objective: To evaluate dextromethorphan combined with ultra low-dose quinidine (DMq) for treating pseudobulbar affect (PBA) in patients with amyotrophic lateral sclerosis (ALS) or multiple sclerosis (MS).
Methods: In a 12-week randomized, double-blind trial, ALS and MS patients with clinically significant PBA (a baseline score $\geq$13 on the Center for Neurologic Studies–Lability Scale [CNS-LS]) were maintained, twice daily, on placebo, DMq at 30/10mg (DMq-30), or DMq at 20/10mg (DMq-20).
Results: In 326 randomized patients (of whom 283, or 86.8%, completed the study), the PBA-episode daily rate was 46.9% ($p < 0.0001$) lower for DMq-30 than for placebo and 49.0% ($p < 0.0001$) lower for DMq-20 than for placebo by longitudinal negative binomial regression, the prespecified primary analysis. Mean CNS-LS scores decreased by 8.2 points for DMq-30 and 8.2 for DMq-20, vs 5.7 for placebo ($p= 0.0002$ and $p= 0.0113$, respectively). Other endpoints showing statistically significant DMq benefit included, for both dosage levels, the likelihood of PBA remission during the final 14 days and, for the higher dosage, improvement on measures of social functioning and mental health. Both dosages were safe and well tolerated.
Interpretation: DMq markedly reduced PBA frequency and severity, decreasing the condition's detrimental impact on a patient's life, with satisfactory safety and high tolerability. The findings expand the clinical evidence that DMq may be an important treatment for patients suffering from the socially debilitating symptoms of PBA.
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Introduction

Pseudobulbar affect (PBA) is a neurologic condition characterized by involuntary outbursts of laughing and/or crying incongruous or disproportionate to the patient's emotional state.[1] The condition, hypothesized to arise from disconnection of brainstem structures from cortical inhibition, is associated with underlying central nervous system disorders, including stroke,[2] traumatic brain injury,[3] Alzheimer disease,[4] amyotrophic lateral sclerosis (ALS),[5–7] and multiple sclerosis (MS).[8] Prevalence studies have reported that it affects 11% of patients 1 year after a stroke,[2] 11% of patients during the first year after traumatic brain injury,[9] 18% of patients with Alzheimer disease,[4] 10% of patients with MS,[8] and 49% of patients with ALS.[10] In addition to the effects of the underlying disorder, PBA can have a severe impact on well-being and social functioning and can be highly disabling, owing in part to the stigma attached to loss of emotional control.[11] Yet even with such a significant burden of illness, PBA appears to be poorly recognized and consequently is undertreated.[11,12]

In settings of ALS or MS, dextromethorphan plus quinidine (DMQ) has been found to be beneficial in reducing PBA.[13,14] Dextromethorphan (DM) is known to be a low-affinity, noncompetitive antagonist of the *N*-methyl-d-aspartate glutamate receptor,[15] and also a sigma-receptor agonist.[16] To block its first-pass metabolism, it was originally coadministered with low-dose quinidine (Q), a potent cytochrome P450 2D6 inhibitor,[17] at DMQ dosage of 30/30mg in a capsule taken twice daily. Without such blockade, DM blood levels in some ALS patients have been undetectably low even following DM dosage as high as 750mg/day.[17] In

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atrial fibrillation and flutter, Q is utilized for conversion as well as reduction in frequency of relapse. However, Q doses are often in excess of 1,000 to 1,600mg/day and may affect cardiac function in ways that include prolongation of the QTc interval,[18] which in turn may be associated with risk of ventricular arrhythmias.[19] In the treatment of PBA, a formal pharmacokinetic/pharmacodynamic analysis has predicted that the Q dosage can be reduced to 10mg per capsule (ultra low dosage, q), as a treatment referred to as DMq, with maintained efficacy and a decreased potential for proarrhythmic risk.[20] The present 12-week trial was designed to evaluate DMq at 30/10mg and at 20/10mg twice daily versus placebo for treating PBA in patients with ALS or MS. An additional objective was to determine the pharmacokinetic parameters of each DMq formulation in a subset of the study population, as will be reported separately.

Patients and Methods

Design

This was a 12-week, randomized, double-blind, placebo-controlled, 3-arm, parallel-group study conducted at 60 centers in the United States and South America between December 2007 and March 2009. Patients completed screening procedures 1 to 4 weeks before their baseline visit. At the screening visit, those meeting all inclusion/exclusion criteria (see below) were randomized (1:1:1) to receive placebo, DM 30mg + Q 10mg (DMq-30), or DM 20mg + Q 10mg (DMq-20). For the first treatment week, patients took a single capsule of study drug in the morning. During weeks 2 through 12, they took study drug once in the morning and once in the evening. Follow-up visits occurred at 2, 4, 8, and 12 weeks. In addition, for 1 week prior to baseline and throughout the trial, patients were required to maintain a diary recording the daily number of laughing and/or crying episodes experienced, the medications they took, and any adverse experiences. Patients completing the study were eligible to continue treatment in a 12-week open-label phase with DMq-30 twice daily.

The study protocol was approved by local institutional review boards or independent ethics committees and was conducted in accordance with Good Clinical Practice Consolidated Guidance, as approved by the International Conference on Harmonization (1997), and also with local or national laws and regulations. Prior to entry, study procedures and risks were explained to each subject, and written informed consent was obtained. The study's randomization code (blocked by center and by underlying neurological disorder) was computer-generated, and study drug was supplied in blister packs of identical-looking capsules. The sponsor, all patients, and all investigators were blind to treatment identification and allocation.

Patients

For entry, men or women 18 to 80 years old were required to have clinically significant PBA, with a score $\geq$13 on the Center for Neurologic Study–Lability Scale (CNS-LS),[21] and a diagnosis either of ALS (by El Escorial criteria[22]) within the past 30 months or of MS or probable MS (by McDonald criteria[23]). Patients were excluded for any evidence of clinically significant abnormality on screening electrocardiogram, a family history of congenital QT-interval prolongation syndrome, a resting respiratory rate outside the range of 12 to 20/min, or a resting diurnal oxygen saturation <95%. Patients were also excluded for any presence or history of major psychiatric disturbance, including current symptoms of a depressive disorder (or a score >19 on the Beck Depression Inventory–II [BDI-II][24]); major systemic disease or organ dysfunction capable of interfering with study assessments or putting the patient at risk; and exacerbation of the patient's underlying ALS or MS within the previous 2 months. Women with childbearing potential were required to use a medically acceptable form of birth control; pregnant or lactating women were excluded.

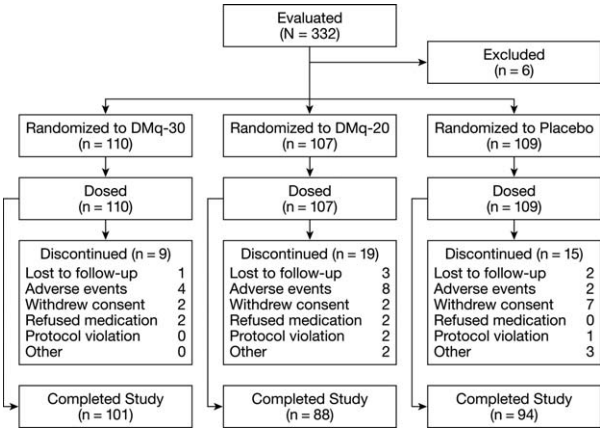

FIGURE 1: Subjects' disposition. DMq-30 = dextromethorphan combined with ultra low-dose quinidine at 30/10mg; DMq-20 = DMq at 20/10mg.

Efficacy Assessments

The primary efficacy outcome was a patient's change from baseline in the number of PBA episodes (laughing and/or crying) per day, as recorded in the patient's diary. Diary data also yielded, as secondary outcomes, a responder analysis (the proportion of patients with an improvement from baseline PBA rate, assessed across all degrees of improvement); number of episode-free days; and occurrence of remission from PBA (defined by absence of episodes during the study's final 14 days). Additional secondary outcomes were a patient's change from baseline on CNS-LS, which was administered at baseline and at each follow-up visit, and on BDI-II, the Neuropsychiatric Inventory (NPI),[25] and the Medical Outcomes Study 36-Item Short-Form Health Survey Version 1.0 (SF-36),[26] which were administered at baseline and at 12 weeks.

The CNS-LS is a 7-item self-assessment of PBA severity, validated for measuring PBA in ALS[21] and MS.[27] Total scores range from 7 to 35; a score $\geq$13 is the instrument's range for clinical PBA. The BDI-II is a 21-item self-assessment of symptoms of depression. A total score of 14–19 is considered mild, 20–28 is moderate, and 29–63 is severe. The NPI is a questionnaire covering 12 neuropsychiatric symptom domains; it

TABLE 1: Patients' Baseline Characteristics (ITT Population)

Characteristic	DMq-30	DMq-20	Placebo
No.	110	107	109
Age, mean yr (SD)	53.1 (11.0)	50.8 (11.1)	50.3 (11.9)
Females, No. (%)	64 (58.2)	54 (50.5)	59 (54.1)
Ethnic origin, No. (%)			
White	80 (72.7)	80 (74.8)	83 (76.1)
Hispanic	21 (19.1)	21 (19.6)	21 (19.3)
Black	6 (5.5)	2 (1.9)	4 (3.7)
Other	3 (2.7)	4 (3.7)	1 (0.9)
Diagnosis, No. (%)			
ALS	65 (59.1)	68 (63.6)	64 (58.7)
MS	45 (40.9)	39 (36.4)	45 (41.3)
Time since ALS diagnosis, mean mon (SD)	22.7 (29.8)	16.3 (22.9)	13.4 (18.0)
PBA episodes/day, mean (SD)			
All	4.7 (9.5)	6.8 (12.9)	4.5 (7.6)
Laughing	1.7 (3.4)	4.1 (11.8)	2.5 (7.4)
Crying	3.0 (6.7)	2.8 (4.2)	2.0 (2.0)
CNS-LS score, mean (SD)	19.8 (4.9)	21.0 (5.0)	19.9 (4.7)
BDI-II score, mean (SD)	9.4 (6.1)	10.9 (5.8)	10.5 (5.4)
NPI score, mean (SD)			
Frequency	6.2 (6.3)	7.8 (6.7)	7.0 (6.7)
Severity	5.8 (3.9)	7.0 (4.5)	6.3 (4.5)
SF-36 score, mean (SD)			
Mental Summary	44.0 (10.9)	44.6 (11.2)	44.9 (10.6)
Physical Summary	40.1 (10.1)	37.0 (10.4)	38.5 (9.8)

ITT = intent-to-treat; DMq-30 = dextromethorphan combined with ultra low-dose quinidine at 30/10mg; DMq-20 = DMq at 20/10mg; SD = standard deviation; ALS = amyotrophic lateral sclerosis; MS = multiple sclerosis; PBA = pseudobulbar affect; CNS-LS = Center for Neurologic Study–Lability Scale; BDI-II = Beck Depression Inventory Second Edition; NPI = Neuropsychiatric Inventory; SF-36 = Medical Outcomes Study 36-Item Short-Form Health Survey.

provides a brief, informant-based assessment of neuropsychiatric symptoms and caregiver distress. The SF-36 is a 36-item health-status assessment, with subdomains for Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health. Each of 2 summary scores (Mental Component and Physical Component) is standardized so that 50 represents the US general population norm (for 1998).

Safety/Tolerability Assessments

At all visits, vital signs were measured, 12-lead electrocardiography was performed, and reports of adverse events (AEs) were obtained. Serious AEs were defined as fatal, life-threatening, significantly disabling, or requiring hospitalization. Resting diurnal oxygen saturation and nocturnal oxygen saturation were measured (with pulse oximetry) at screening and at 2 weeks. Resting diurnal oxygen saturation was also measured at 12 weeks. Clinical laboratory testing was performed at screening and at 4 and 12 weeks.

Statistical Analyses

In the intent-to-treat population, comprising all randomized patients, change from baseline in laughing/crying episode rate was analyzed using longitudinal negative binomial regression,[28] with adjustment for baseline rate, diagnosis, and study site. As a sensitivity analysis, change in episode rate was also assessed by a nonlongitudinal negative binomial model. In addition, 12-week change in episode rate was analyzed using the Wilcoxon rank sum test. For number of episode-free days, a 2-sample *t*

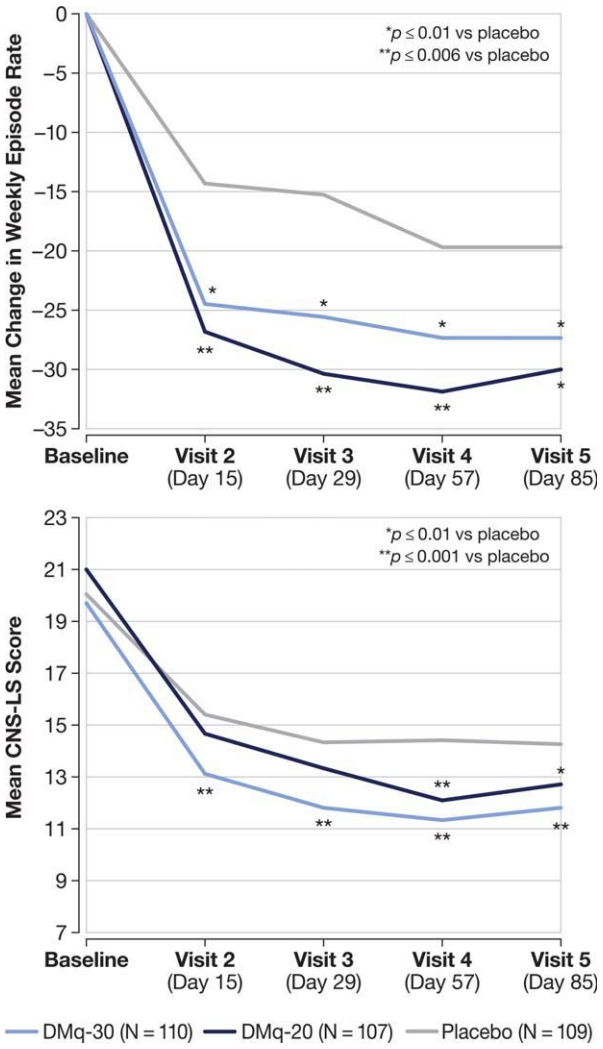

FIGURE 2: Twelve-week time course of pseudobulbar affect weekly episode rate and Center for Neurologic Study–Lability Scale (CNS-LS) score (intent-to-treat population). Weekly rates (top chart) are shown as change from baseline at each visit in mean daily rates × 7. CNS-LS scores (bottom chart) are the means at each visit. DMq-30 = dextromethorphan combined with ultra low-dose quinidine at 30/10mg; DMq-20 = DMq at 20/10mg.

test was used. Changes on CNS-LS, SF-36, BDI-II, and NPI were analyzed with analysis of covariance, using the method of Frison and Pocock.[29] Baseline value, study site, and diagnosis were covariates. Observed cases were used in the sensitivity analyses, with no imputation for missing data. All analyses were 2-sided hypothesis tests at the 0.05 significance level.

The safety population comprised all patients who took at least 1 dose of study medication. Their AE rates, for types reported by ≥5% of patients in any treatment group, were compared among groups, and mean change in resting nocturnal oxygen saturation (from baseline to day 15) was assessed by 2-sample *t* test.

Sample Size Calculation

Based on PBA episode rates in previous studies of DMq for PBA in ALS[13] and in MS,[14] a sample size of approximately 90 patients (60 with ALS and 30 with MS) per treatment group was planned. This size was expected to be sufficient to detect a 36% reduction in mean episode rate for DMq-30 vs placebo with at least 90% power. The study was not powered to test a difference between DMq-30 and DMq-20.

Results

Subjects

In all, 332 patients were screened, and among them 326 were randomized, 110 to DMq-30, 107 to DMq-20, and 109 to placebo (Fig 1). The main reasons for screening failure were unwillingness to discontinue disallowed medications, CNS-LS score <13, and BDI-II score >19. In all, 283 patients (86.8% of 326) completed the study, including 101 (91.8% of 110) in the DMq-30 group, 88 (82.2% of 107) in the DMq-20 group, and 94 (86.2% of 109) in the placebo group. Demographically and in baseline PBA characteristics, the treatment groups were well matched (Table 1), except for a higher baseline PBA episode rate in the DMq-20 group than in the other groups, and a longer time since ALS diagnosis in the DMq-30 group. At entry, no patient had clinical depression.

Efficacy

Over the course of the study, all 3 groups showed substantial reduction in daily PBA episode rates relative to baseline. However, the reduction in daily PBA episode rate was significantly greater in each of the DMq groups than in the placebo group. By longitudinal negative binomial model (predefined primary efficacy analysis), the

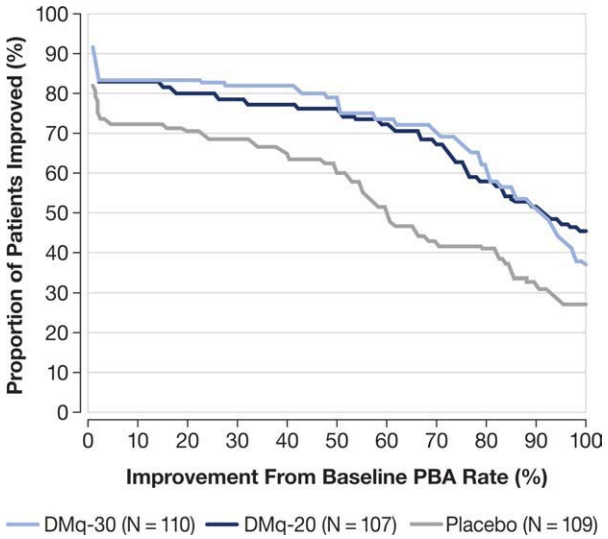

FIGURE 3: Responder analysis by treatment group (intent-to-treat population). Each curve graphs the proportion of patients improved with a given degree of improvement from baseline pseudobulbar affect (PBA) rate at endpoint. DMq-30 = dextromethorphan combined with ultra low-dose quinidine at 30/10mg; DMq-20 = DMq at 20/10mg.

TABLE 2: Twelve-Week Mean Change on CNS-LS, NPI, and BDI-II

Endpoint	DMq-30	DMq-20	Placebo
CNS-LS			
No.	103	96	101
Mean change (p vs placebo)	−8.2 (0.0002)	−8.2 (0.0113)	−5.7
BDI-II			
No.	103	97	101
Mean change (p vs placebo)	−1.6 (0.0368)	−1.0 (0.2707)	0.02
NPI (frequency)			
No.	74	79	66
Mean change (p vs placebo)	−1.6 (0.6558)	−2.6 (0.0938)	−1.3
NPI (severity)			
No.	46	54	48
Mean change (p vs placebo)	−0.7 (0.510)	−1.6 (0.207)	−1.0

CNS-LS = Center for Neurologic Study-Lability Scale; NPI = Neuropsychiatric Inventory; BDI-II = Beck Depression Inventory Second Edition; DMq-30 = dextromethorphan combined with ultra low-dose quinidine at 30/10mg; DMq-20 = DMq at 20/10mg.

treatment effect in each DMq group over that seen in the placebo group was an incremental reduction in PBA episode rate of 46.9% ($p < 0.0001$) for DMq-30 compared to placebo and 49.0% ($p < 0.0001$) for DMq-20 compared to placebo. By nonlongitudinal negative binomial model with constant dispersion (predefined efficacy sensitivity analysis), the additional improvement over placebo at both dosage levels was also statistically significant ($p < 0.0001$ and $p = 0.0370$, respectively). The 12-week mean change in daily episode rate was −4.1 for DMq-30 and −3.9 for DMq-20, vs −3.0 for placebo ($p = 0.0099$ and $p = 0.0048$, respectively). Weekly rates (daily rates × 7) showed significant decrease at all time points assessed, beginning with day 15 (Fig 2, top).

Among secondary outcomes, the 12-week mean reduction from baseline CNS-LS score was significantly greater at both DMq dosage levels than for placebo (Table 2), and for DMq-30, the mean reduction was significant at all time points assessed, beginning with day 15 (see Fig 2, bottom). Among secondary outcomes derived from diary data, the proportion of patients with an improvement from their baseline PBA rate was higher for both DMq-30 and DMq-20 than for placebo, across all degrees of improvement (Fig 3). The proportion of patients' episode-free days was significantly greater for DMq-30 than for placebo at all time points assessed, and for DMq-20 vs placebo at all time points except day 15 (Fig 4, left). Lastly, the proportion of patients reporting remission of PBA was significantly greater at both DMq dosage levels than for placebo (see Fig 4, right).

On BDI-II, mean improvement was significantly greater for DMq-30 than for placebo (see Table 2). On NPI, total scores showed no significant change for either dosage vs placebo (see Table 2). On SF-36, improvement was significant for DMq-30 vs placebo on the Mental Summary score and on its subdomains for social functioning and mental health (Table 3).

Safety and Tolerability

The proportion of patients reporting at least 1 AE was similar in all treatment groups, at 82.7% of DMq-30 recipients, 79.4% of DMq-20 recipients, and 82.6% of

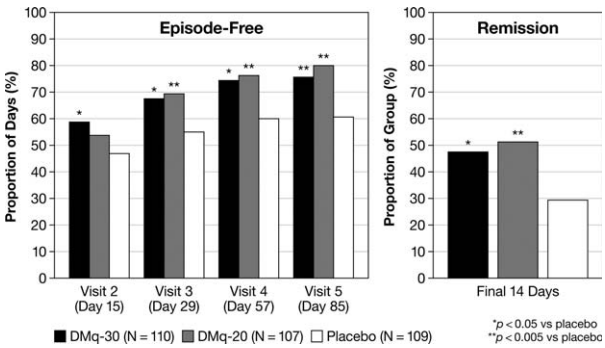

FIGURE 4: Decrease of pseudobulbar affect, as assessed by freedom from episodes and by remission (intent-to-treat population). Freedom from episodes (left) was defined as the percentage of episode-free days since the preceding visit. Remission (right) was defined by absence of episodes throughout the study's final 14 days. DMq-30 = dextromethorphan combined with ultra low-dose quinidine at 30/10mg; DMq-20 = DMq at 20/10mg.

TABLE 3: Twelve-Week Mean Changes on SF-36 (ITT Population)

SF-36 Domain, Mean Change (*p* vs placebo)	DMq-30 (n = 110)	DMq-20 (n = 107)	Placebo (n = 109)
Mental Summary	4.5 (0.0193)	1.8 (0.6792)	0.3
Vitality	−0.9 (0.2972)	−5.3 (0.7510)	−4.1
Social Functioning	9.3 (0.0033)	1.4 (0.5544)	−3.1
Role Emotional	11.6 (0.3658)	−1.8 (0.6838)	2.4
Mental Health	5.5 (0.0028)	3.1 (0.4457)	−0.3
Physical Summary	−0.8 (0.5877)	−1.0 (0.9967)	−1.3
Physical Functioning	−0.9 (0.2972)	−5.3 (0.7510)	−4.1
Role Physical	3.5 (0.3063)	−4.3 (0.2292)	−1.8
Bodily Pain	4.1 (0.0740)	5.8 (0.0678)	−1.1
General Health	−1.5 (0.8703)	−3.0 (0.3583)	−1.3

SF-36 = Medical Outcomes Study 36-Item Short-Form Health Survey; ITT = intent-to-treat; DMq-30 = dextromethorphan combined with ultra low-dose quinidine at 30/10mg; DMq-20 = DMq at 20/10mg.

placebo recipients. Overall, AE incidence was distributed evenly throughout the study, except for slightly higher rates in the DMq-30 and placebo groups during the initial treatment week. The proportion of patients reporting serious AEs was also similar across groups, at 7.3% (8 patients) in the DMq-30 group, 8.4% (9 patients) in the DMq-20 group, and 9.2% (10 patients) in the placebo group. Two serious AEs, both in the DMq-20 group, were reported as possibly treatment related. In 1 of these patients, the event was reported as respiratory depression and ALS progression. The other patient had worsening muscle spasticity. Seven deaths were reported, all in ALS patients: 3 in the DMq-30 group, 3 in the DMq-20 group, and 1 in the placebo group. All deaths were classified by an independent mortality adjudication committee as having a respiratory cause likely to be the result of progression of the underlying neurologic disease. No acute decompensation of respiratory function after initiation of study drug was observed, and no deaths were ascribed to a cardiac cause. Discontinuations due to AEs were more frequent in the DMq-20 group, at 9.3% (10 patients), than in the DMq-30 group, at 5.5% (6 patients), or the placebo group, at 1.8% (2 patients). Among frequently reported AEs (Table 4), dizziness, nausea, diarrhea, and urinary tract infection were more frequent for DMq-30 than for placebo, whereas falls, headache, somnolence, fatigue, and other AEs occurred at rates resembling those for placebo.

Vital signs, physical-examination findings, resting diurnal oxygen saturation, and clinical laboratory values showed no significant changes from their baseline means in any treatment group. For resting nocturnal oxygen saturation, Table 5 compares baseline and day-15 findings. At day 15, the mean change was −0.2 percentage points in the DMq-30 group and −0.7 percentage points in the DMq-20 group, vs −0.1 for placebo (p= 0.794 and

TABLE 4: Adverse Events Reported by ≥5% of Any Group (Safety Population)[a]

Event Type, No. (%)	DMq-30 (n = 110)	DMq-20 (n = 107)	Placebo (n = 109)
Fall	22 (20.0)	14 (13.1)	22 (20.2)
Dizziness	20 (18.2)	11 (10.3)	6 (5.5)
Headache	15 (13.6)	15 (14.0)	17 (15.6)
Nausea	14 (12.7)	8 (7.5)	10 (9.2)
Diarrhea	11 (10.0)	14 (13.1)	7 (6.4)
Somnolence	11 (10.0)	9 (8.4)	10 (9.2)
Fatigue	9 (8.2)	11 (10.3)	10 (9.2)
Nasopharyngitis	9 (8.2)	6 (5.6)	8 (7.3)
Urinary tract infection	8 (7.3)	4 (3.7)	3 (2.8)
Constipation	7 (6.4)	7 (6.5)	9 (8.3)
Muscle spasms	7 (6.4)	4 (3.7)	10 (9.2)
Muscle weakness	6 (5.5)	5 (4.7)	4 (3.7)
Dysphagia	5 (4.5)	6 (5.6)	4 (3.7)
Pain in extremity	5 (4.5)	2 (1.9)	8 (7.3)
Depression	0	1 (0.9)	6 (5.5)

[a]By MedDRA preferred term, listed by frequency in the DMq-30 group.
DMq-30 = dextromethorphan combined with ultra low-dose quinidine at 30/10mg; DMq-20 = DMq at 20/10mg.

TABLE 5: Summary of Nocturnal Oxygen-Saturation Data (Safety Population)

Data	DMq-30 (n = 108 or 106[a]), n = 110	DMq-20 (n = 102 or 100[a]), n = 107	Placebo (n = 108 or 109[a]), n = 109
Saturation, mean % (SD)			
At baseline	94.1 (5.4)	94.9 (2.0)	94.6 (2.2)
At day 15	94.4 (2.1)	94.1 (2.5)	94.4 (2.2)
Mean change (p vs placebo)	−0.2 (2.0) (0.794)	−0.7 (2.0) (0.039)	−0.1 (2.1)
Number of events <88%, mean (SD)			
At baseline	6.9 (12.6)	6.4 (13.9)	6.4 (12.2)
At day 15	5.0 (16.0)	5.0 (16.1)	9.0 (17.7)
Total time in minutes <88%, mean (SD)			
At baseline	11.2 (39.2)	9.9 (39.1)	9.1 (23.1)
At day 15	4.1 (19.7)	11.0 (41.7)	11.2 (20.9)

[a]For saturation and desaturation analyses, respectively.
DMq-30 = dextromethorphan combined with ultra low-dose quinidine at 30/10 mg; DMq-20 = DMq at 20/10 mg; SD = standard deviation.

$p = 0.039$, respectively). The differences between groups were not clinically significant. Descriptive analyses of desaturation data identified no substantial differences between groups (see Table 5). QTc-interval changes are summarized in Table 6. At all time points assessed, no DMq recipient had a QTc-interval absolute value >480 milliseconds (with Fridericia correction) or a change from baseline >60 milliseconds.

TABLE 6: Summary of QTc-Interval Data (Safety Population)

Data	DMq-30 (n = 110)	DMq-20 (n = 107)	Placebo (n = 109)
QTcB/QTcF at baseline, mean ms	418.2/406.6	416.4/404.2	416.1/404.7
QTcB/QTcF at day 84, mean ms	420.6/411.8	413.8/405.1	416.8/405.8
QTcB/QTcF change from baseline, mean ms	3.0/4.8	−1.9/1.0	1.6/1.0
Proportion of postbaseline ECGs with absolute QTcB/QTcF			
>450 ms	6.3%/1.9%	4.9%/1.2%	6.1%/2.4%
>480 ms	0.2%/0.0%	0.0%/0.0%	0.9%/0.0%
>500 ms	0.0%/0.0%	0.0%/0.0%	0.2%/0.0%
Proportion of postbaseline ECGs with change from baseline QTcB/QTcF			
30–60 ms	7.0%/7.2%	3.9%/2.9%	6.6%/3.5%
>60 ms	0.5%/0.0%	0.2%/0.0%	0.5%/0.5%
>90 ms	0.0%/0.0%	0.0%/0.0%	0.0%/0.0%

DMq-30 = dextromethorphan combined with ultra low-dose quinidine at 30/10mg; DMq-20 = DMq at 20/10mg; QTcB = QT interval corrected for heart rate (Bazett's formula); QTcF = QT interval corrected for heart rate (Fridericia's formula); ECG = electrocardiogram.

Discussion

In this large, double-blind, placebo-controlled study, both dosage levels of DMq were significantly superior to placebo for reducing PBA episode frequency among patients with underlying ALS or MS, as assessed by longitudinal and nonlongitudinal statistical models and also by mean change in daily PBA episode rate. At both dosage levels, DMq also significantly reduced the severity of PBA, as represented by CNS-LS score. For reduction in episode rate, a prespecified responder analysis showed, at both dosage levels, a substantial difference from placebo across all degrees of improvement, despite a strong placebo effect (resembling those seen in previous studies[13]). The differences between DMq and placebo included, at both dosage levels, a significantly higher likelihood of PBA remission on DMq than on placebo, suggesting that for large proportions of patients, the active treatment's amelioration of PBA may be marked.

Numerically, the responses to the higher DMq dosage were more robust than those to the lower dosage in several ways, including an earlier improvement in CNS-LS score, an earlier time to significant difference vs placebo in number of episode-free days, and a slightly greater 12-week mean change vs placebo in PBA daily episode rate. At the higher dosage, DMq was also associated with significant improvement in mental-health measures, by BDI-II and SF-36. Because none of the subjects in this study was clinically depressed, and because PBA can result in substantial reduction of quality of life,[11] this improvement may have been in well-being. Specific improvements on SF-36 subdomains for social functioning and mental health are further evidence that the social and psychological disability associated with PBA may have been reduced. However, the possibility that DMq may have direct antidepressant properties cannot be excluded, and would require further study. Overall, the efficacy reported for DMq containing Q at ultra low dosage—10mg per capsule—resembled the benefits reported by measures including CNS-LS scores and PBA episode counts in studies of DMq in its original formulation, in which the Q content per capsule was 30mg.[13,14]

In the present study, both dosage levels were safe. In particular, cardiovascular safety was satisfactory, with mild QTc prolongation and no proarrhythmic events. Respiratory findings appeared to be consistent with ALS progression. However, physicians should always exercise caution in managing a patient population that has compromised respiratory function. Both dosage levels were also well tolerated, with only 13% of DMq recipients discontinuing during 12 weeks of double-blind treatment. The overall discontinuation rate was lower for DMq-30, at 8%, than for DMq-20, at 18%. In studies of DMQ as originally formulated, with DM at 30mg per capsule and Q at 30mg, the 12-week discontinuation rate had been much higher, at 28% in ALS patients[13] and 25% in MS patients.[14] The implication is that the improved tolerability demonstrated in the present study may reflect ultra low dosing of Q. Usage of dose escalation (with once-daily dosing during week 1) may also have contributed.

A body of published evidence suggests that PBA may be ameliorated pharmacologically,[1] but the trials assessing current agents, all of which are being utilized off-label, have limitations. In 1979, dopaminergic treatment, specifically L-dopa, was reported to be effective for "emotional incontinence,"[30] but in a follow-up uncontrolled study of L-dopa or amantadine, only 10 of 25 recipients responded.[31] Since then, reports have centered on antidepressants, notably tricyclic agents (eg, amitriptyline[32] or nortriptyline[33]) and selective serotonin reuptake inhibitors (eg, fluoxetine,[34] citalopram,[35,36] paroxetine,[36] or sertraline[37]). Overall, the trials have been hampered by small size (12 to 28 subjects, among those referenced above) and by methodological problems, such as their definitions of PBA improvement. Substantial placebo effects, as demonstrated in the present study, make uncontrolled findings all the more difficult to interpret. In brief, well-controlled data to support current options are scarce, and no option is currently approved by the US Food and Drug Administration. In addition, antidepressants are associated with incompletely elucidated AE profiles (including QT-interval prolongation[19]).

In interpreting the present study's findings, the trial's limitations should be taken into account. Because its subjects were carefully selected, the findings should be generalized to a broader spectrum of PBA with caution. The study required, for instance, a baseline CNS-LS score of at least 13. Accordingly, the effects of DMq-30 or DMq-20 on milder forms of PBA are unknown. In addition, the study enrolled only patients with underlying ALS or MS. Because the pathophysiologic mechanisms causing PBA are probably similar regardless of the underlying CNS pathology, DMq will likely be effective in reducing symptoms of PBA arising in various brain disease or injury states, much in the same way that antispastic medication reduces spasticity, irrespective of the underlying condition. Even so, additional studies of the effect of DMq on PBA in various neurological disorders could provide enhanced safety, efficacy, and health outcome insight. Hence, further clinical studies of PBA are warranted.

Nevertheless, the present study represents the largest and longest double-blind, randomized, placebo-controlled trial of DMq conducted to date in PBA, and also the first to test DMq in PBA patients at ultra low Q dosage. Its findings expand the clinical evidence that with

satisfactory safety and high tolerability, DMq markedly reduces PBA frequency and severity, decreasing the condition's detrimental impact on a patient's life.

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Potential Conflicts of Interest

E.P.P. has received research support and compensation for consulting from Avanir Pharmaceuticals. B.R.B. has received compensation for consulting from Avanir Pharmaceuticals, Bayer Healthcare Pharmaceuticals, Biogen Idec, Genentech, and Teva Neuroscience, and has received research support from Avanir Pharmaceuticals, Biogen Idec, National Institutes of Neurological Disorders and Stroke Clinical Research Consortium, Novartis, and Teva Neuroscience. J.C. has received compensation for consulting from Abbott, Acadia, Accera, ADAMAS, Astellas, Avanir Pharmaceuticals, Bristol-Myers Squibb, CoMentis, Eisai, Elan, EnVivo, Forest, GlaxoSmithKline, Janssen, Lilly, Lundbeck, Medivation, Merck, Merz, Myriad, Neuren, Novartis, Pfizer, Prana, Schering Plough, Sonexa, Takeda, Toyama, and Wyeth, and owns the copyright of the Neuropsychiatric Inventory. A.H. and R.K. are employees of and own stock options in Avanir Pharmaceuticals. R.S. has received compensation for consulting from Teva and Avanir Pharmaceuticals and owns 300 shares of common stock in Johnson & Johnson Corporation. R.A.T. is a statistical consultant to Avanir Pharmaceuticals, and has been an expert witness on behalf of Eli Lilly, Forest Laboratories, Wyeth, Otsuka, GlaxoSmithKline, and Hoffmann-LaRoche. D.W. has received compensation for consulting from Teva Neurosciences, Pfizer, Serono, Acorda Therapeutics, GlaxoSmithKline, Avanir Pharmaceuticals, and Eli Lilly, and has received research support from Biogen Idec, Serono, Pfizer, Teva, UCB Pharma, PDL BioPharma, BioMS, Sanofi-Aventis, Opexa Therapeutics, Genzyme, GlaxoSmithKline, XenoPort, Avanir Pharmaceuticals, Eli Lilly, and Shire Laboratories.

Appendix

AVP-923 in PBA Trial Investigators

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