Randomized, Controlled Trial of Dextromethorphan/Quinidine for Pseudobulbar Affect in Multiple Sclerosis

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Objective: To evaluate the efficacy and safety of DM/Q (capsules containing dextromethorphan [DM] and quinidine [Q]) compared with placebo, taken twice daily, for the treatment of pseudobulbar affect over a 12-week period in multiple sclerosis patients.
Methods: A total of 150 patients were randomized in a double-blind, placebo-controlled study to assess pseudobulbar affect with the validated Center for Neurologic Study-Lability Scale. Each patient also recorded the number of episodes experienced between visits, estimated quality of life and quality of relationships on visual analog scales, and completed a pain rating scale.
Results: Patients receiving DM/Q had greater reductions in Center for Neurologic Study-Lability Scale scores than those receiving placebo ($p < 0.0001$) at all clinic visits (days 15, 29, 57, and 85). All secondary end points also favored DM/Q, including the number of crying or laughing episodes ($p \leq 0.0077$), quality of life ($p < 0.0001$), quality of relationships ($p = 0.0001$), and pain intensity score ($p = 0.0271$). DM/Q was well tolerated; only dizziness occurred with greater frequency than with placebo.
Interpretation: Results in multiple sclerosis patients were similar to those of a previous study in amyotrophic lateral sclerosis, demonstrating that DM/Q may be beneficial in treating potentially disabling pseudobulbar affect in a variety of neurological disorders.

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Pseudobulbar affect (PBA), also known as emotional lability, is characterized by frequent and inappropriate episodes of crying, laughing, or both and is associated with neurological disorders such as stroke, amyotrophic lateral sclerosis (ALS), Alzheimer's disease, Parkinson's disease, and traumatic brain injury. It occurs in approximately 10% of patients with multiple sclerosis (MS).[1] The cause of PBA is unknown, but recent evidence implicates the disruption of neural pathways emanating from the brainstem and cerebellum that normally control the expression of emotions.[2] Although tricyclic antidepressants, selective serotonin reuptake inhibitors, and L-dopa are sometimes used to treat PBA,[3–6] no drug has been rigorously studied or approved for this purpose.

Dextromethorphan (DM), the dextrorotatory analogue of levorphanol, is a σ-1 receptor agonist, suppressing the release of excitatory neurotransmitters,[7] and is an uncompetitive antagonist of the *N*-methyl-D-aspartate–sensitive[8,9] ionotropic glutamate receptor. The potential for useful pharmacology is limited, however, because DM is extensively metabolized by cytochrome P450 2D6 to dextrorphan (DX), which is rapidly glucuronidated[10] and unable to cross the blood–brain barrier.[11]

Quinidine (Q) is one of the most potent inhibitors of cytochrome P450 2D6 activity.[12] Concomitant dosing with Q at doses 10- to 20-fold lower than antiarrhythmic doses increases and sustains the concentration of DM in plasma, and thereby enhances its potential for therapeutic efficacy.[13]

A study conducted to test the hypothesis that the antiglutamate excitatory properties of DM/Q would be

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neuroprotective in ALS patients suggested that DM/Q had a beneficial effect on PBA. This observation was then extended in a crossover study of PBA in ALS.[14] In a recent phase III study in ALS patients with PBA, the combination of 30mg DM with 30mg Q given twice daily for 29 days significantly reduced the severity of PBA; reduced the incidence of crying or laughing episodes, or both; and improved quality of life compared with DM or Q alone.[15] This report describes a 3-month study to assess the safety and efficacy of DM/Q compared with placebo in MS patients with PBA.

Patients and Methods

Patients

Patients were enrolled and treated between December 2002 and June 2004 at 18 centers in the United States and 4 centers in Israel in this multicenter, randomized, double-blinded, placebo-controlled study. Patients were required to have MS according to the International Panel (McDonald) criteria,[16] a clinical diagnosis of PBA, and a score of 13 or more on the Center for Neurologic Study-Lability Scale (CNS-LS) at the day 1 clinic visit. The CNS-LS is a seven-item self-report questionnaire that provides a score for PBA ranging from 7 to 35. The CNS-LS has been validated in ALS[17] and is the only instrument validated for the measurement of PBA in MS.[18]

Patients were also required to have a normal electrocardiogram (ECG); normal hematological, hepatic, and renal function tests; no current or prior history of major psychiatric disturbance; and no coexistent systemic diseases that would interfere with interpretation of the results of the study. Patients with any of the following ECG abnormalities were excluded: heart block (any degree); prolongation of QTc interval (≥450 milliseconds for male patients; ≥470 milliseconds for female patients); sinus bradycardia (<50 beats/min) or history of sick sinus syndrome; ventricular tachycardia, multifocal ventricular ectopic beats (any frequency), or frequent unifocal ventricular ectopic beats (>5 per minute). Female patients had to practice an acceptable method of birth control for at least 1 month before entry and during the study, or be surgically sterile or postmenopausal.

Patients were not to take antidepressants, monoamine oxidase inhibitors, anticoagulants, certain other inhibitors or substrates for P450 2D6 or P450 3A4, and over-the-counter or prescription medications containing DM or Q during the study. Treatment with concomitant disease-modifying drug for MS (eg, interferon-β or glatiramer acetate) must have been established at least 1 month before enrollment and had to be maintained at a constant dose throughout the study. Patients who experienced MS exacerbations were withdrawn from this study, because exacerbations themselves or treatment with corticosteroids could confound the efficacy assessments. The procedures for the final study visit were conducted at the time of withdrawal.

Randomization and Blinding

Patients were randomized in a 1:1 ratio to receive capsules containing either DM/Q (30mg/30mg) or placebo. Study medications were formulated in identical capsules that were distributed in identical packaging and were dispensed in strict sequence. Randomization was done in blocks to ensure approximately equal representation within treatment centers (Quintiles, Mt Laurel, NJ), and study drug was shipped directly to the clinical sites. The sponsor, investigators, and patients were all blinded to treatment allocation.

Treatment and Evaluations

The study protocol and consent forms were approved by the institutional review boards of the participating institutions. Informed consent was obtained following the principles outlined in the Declaration of Helsinki.

Patients were instructed to take their study medication every 12 hours for 85 days and were given a diary to record the times when study medication was taken, the number of crying and/or laughing episodes experienced daily, and adverse events (AEs). Patients were seen for safety and efficacy assessments on days 1, 15, 29, 57, and 85. The CNS-LS questionnaire was administered at all clinic visits. The CNS-LS[18] includes questions regarding laughter and crying episodes and requires about 5 minutes to complete. Quality of life and quality of relationships were assessed at the same clinic visits using visual analog scales[19] consisting of 10cm lines anchored with "not at all" on the left and "continuously" on the right. A pain intensity rating scale also was administered at all clinic visits. Patients were asked to indicate the amount of pain experienced within the previous 24 hours using a five-point scale in which none = 0; mild = 1; moderate = 2, severe = 3; and extreme = 4.

Patients were questioned regarding AEs and vital signs were recorded at all clinic visits. ECGs and blood samples for laboratory testing were obtained at screening, day 29, and day 85; physical examination was performed at screening and day 85.

Cytochrome P450 2D6 genotyping to identify each patient's ability to metabolize DM was performed on isolated genomic DNA by polymerase chain reaction analysis (Genaissance Pharmaceuticals, Morrisville, NC). Based on the results, subjects were classified according to predicted phenotype as poor, intermediate, extensive, or ultrarapid metabolizers. These results were used for data evaluation only; patients were eligible to enter the study regardless of genotype.

Blood samples also were taken on days 29 and 85 (or the final visit) for the determination of concentrations of DM, the DM metabolite DX, and Q in plasma. Heparinized plasma samples were assayed (MDS Pharma Services, Lincoln, NE) using a validated high-performance liquid chromatography procedure for Q (limit of quantitation = 50ng/ml) and a validated liquid chromatography mass spectrometry/mass spectrometry procedure for DM (limit of quantitation = 0.200ng/ml) and DX (limit of quantitation = 2.5ng/ml).

The protocol-defined primary efficacy end point was change from baseline in the CNS-LS score. Secondary efficacy variables were the number of episodes of inappropriate crying and/or laughing per week, changes from baseline in visual analog scale scores for overall quality of life and quality of relationships, and change from baseline in the pain intensity rating scale score. Additional efficacy variables, not specified in the protocol, used to evaluate the data were the proportion of patients with complete remission (no episodes of PBA), proportion of patients who responded to treatment (at least a

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three-point decrease in CNS-LS), clinical effect by treatment period (proportion of patients with more than one episode per week), and the mean improvement in CNS-LS score by visit.

Statistical Methods

For analysis of continuous efficacy variables, mean change in each group's score was assessed using the analysis of covariance method of Frison and Pocock[20] with baseline CNS-LS measurement and indicator variables for center effect as covariates. Episode counts were analyzed separately using a negative binomial regression model with center effects.[21] Efficacy comparisons were tested with a two-sided, 5% significance level using SAS, Version 8.2 (SAS Institute, Cary, NC) or Stata, Version 8.2 (StataCorp, College Station, TX) to perform the analyses. Data analysis conformed to a protocol-defined statistical analysis plan.

Change scores were measured as the difference between baseline scores (day 1) and the average of the four scores on days 15, 29, 57, and 85. If any scores were missing, the nonmissing scores were averaged. All patients who took study medication were included in the intention to treat analysis.

AEs were recorded and included in the safety analysis regardless of their relationship to treatment. The original terms used by the investigators to identify AEs in the case report form were translated into dictionary-coded preferred terms by using the Medical Dictionary for Regulatory Activities (MedDRA, Version 3.3 Maintenance and Support Services (MSSO), Reston, VA). Fisher's exact test or likelihood ratio χ^2 tests, as appropriate, were used to compare the AE rates (preferred terms) between treatment groups for all AEs occurring in 5% or more of patients in a treatment group.

A sample size calculation determined that 48 patients in each randomized treatment group would be sufficient to detect a difference of 3 points in the CNS-LS score with 90% power. These calculations were based on an observed difference of 3.4 units in the adjusted average improvement in CNS-LS scores with a residual standard deviation of 4.5 in the phase III randomized study of DM/Q in ALS patients.[15]

Results

Disposition and Demography

The disposition of patients is illustrated in Figure 1. A total of 150 patients were randomized to treatment, 76 in the DM/Q group and 74 in the placebo group. The proportion of patients who discontinued treatment was 27.6% in the DM/Q group and 28.4% in the placebo group, with 11 patients (14.5%) in the DM/Q group and 8 patients (10.8%) in the placebo group discontinuing due to AEs (excluding MS exacerbations). The characteristics of the intention to treat population are given in Table 1. The treatment groups were comparable in baseline characteristics (all $p \geq 0.103$). Most patients in this study were extensive metabolizers of DM, and the treatment groups had similar frequencies of metabolizer phenotypes (Table 2).

Efficacy

PRIMARY EFFICACY MEASURE (CENTER FOR NEUROLOGIC STUDY-LABILITY SCALE). Efficacy results are summarized in Table 3. Patients who received DM/Q had a greater decrease in CNS-LS score during study compared with patients who received placebo ($p < 0.0001$); on average, the improvement for patients receiving DM/Q was more than twice that of placebo patients.

The adjusted mean improvements in CNS-LS score were also compared for each visit separately. The estimated treatment effect by study day is shown in Figure 2. Patients receiving DM/Q had a greater decrease in CNS-LS score than patients receiving placebo at each assessment (all $p < 0.0001$, t test for the linear regression coefficient), and more patients receiving DM/Q responded to treatment with a three-point or greater decrease in mean CNS-LS than did patients receiving placebo ($p < 0.0001$; see Table 3).

SECONDARY EFFICACY MEASURES (EPISODE COUNTS, VISUAL ANALOG SCALE, AND PAIN INTENSITY RATING SCALE). Patients treated with DM/Q experienced about half as many episodes of inappropriate crying, laughing, or crying and laughing combined (all $p \leq 0.0077$; see Table 3); had greater improvement in overall quality of life and quality of relationships ($p \leq 0.0001$); and had a twofold greater decrease in pain intensity ($p = 0.0271$) compared with patients treated with placebo.

Based on episode rates (see Table 3), DM/Q was statistically superior to placebo as early as the first week of treatment. Fewer DM/Q patients had more than one episode per week during every time period after beginning treatment, and in the final period analyzed (weeks 9–12), more than 65% of placebo patients had more than one episode per week, whereas only one-fourth of DM/Q patients did ($p < 0.001$). The proportion of patients with complete remission, that is, no episodes of inappropriate crying and/or laughing, was also significantly greater in the DM/Q group during every 2-week study period and over the entire duration of the study.

ADDITIONAL ANALYSES. To provide clinical interpretation of the CNS-LS score in patients with MS, we compared changes in CNS-LS scores with the rate of episodes. In a study of DM/Q in patients with ALS,[15] each increase of one point in the CNS-LS score corresponded to approximately a 12% higher episode rate. When the same model was applied to this study's results, each point on the CNS-LS corresponded to an increase of 11% in the episode rate, and a mean 7.7-point decrease in CNS-LS score in patients treated with DM/Q corresponded to an approximately 46% decrease in episode rate.

To assess whether the severity of PBA at baseline influenced the quantity or the timing of response, we classified patients as having either moderate or severe PBA

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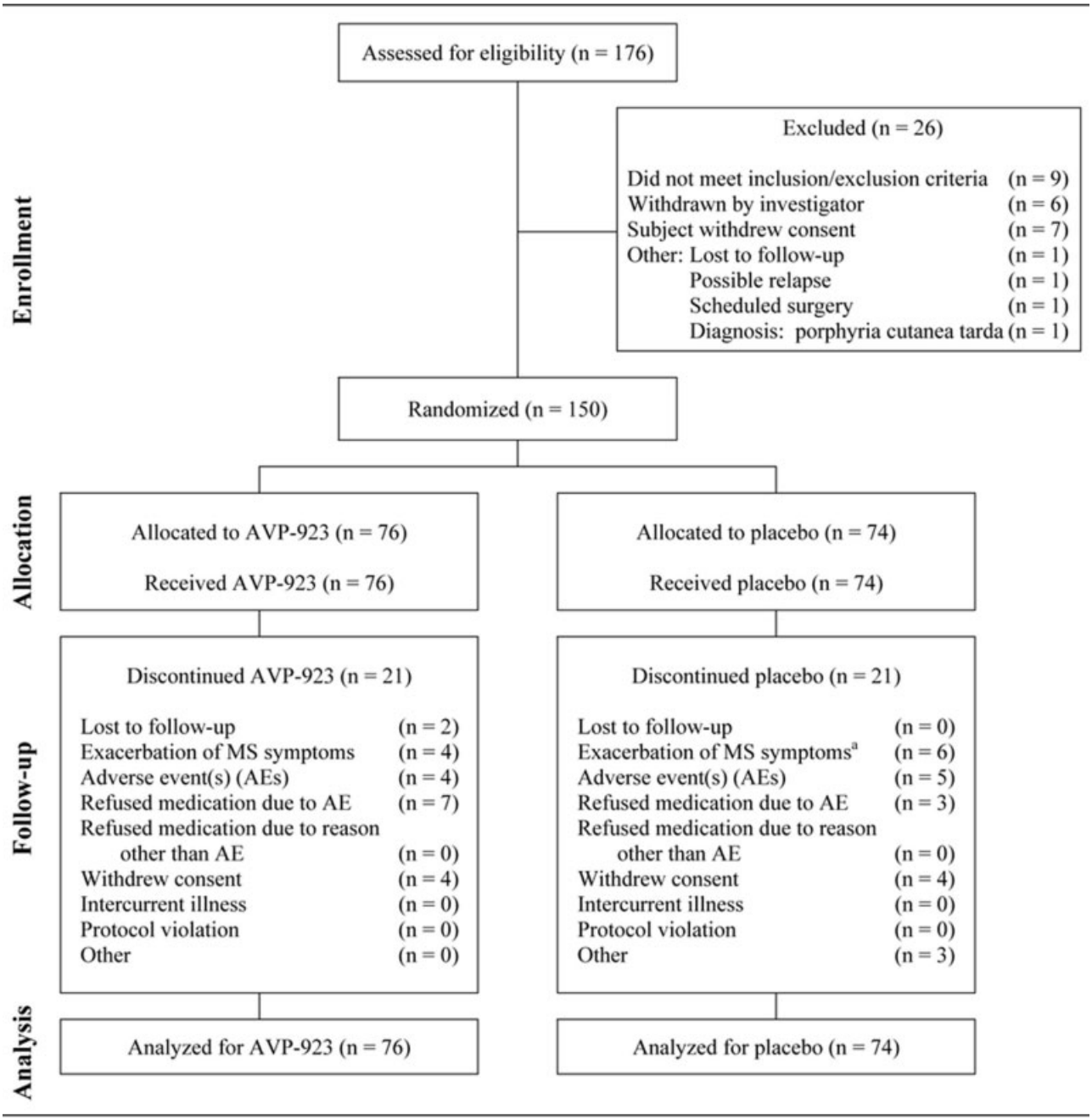

Fig 1. Disposition of patients. AVP-923 was the study code number for DM/Q (capsules containing dextromethorphan [DM] and quinidine [Q]).

at baseline by splitting the sample at the median baseline CNS-LS score. The effect of DM/Q on episode rate was tested by using the negative binomial regression model in each severity category over several time periods. There was no discernible interaction of baseline severity with response to treatment (all $p \geq 0.326$).

Sensitivity analyses for dropouts and missing data were performed. The number of patients with one or more missing observations was 29% overall and was approximately equal in the two treatment groups (21/76 for DM/Q and 22/74 for placebo). Two analyses were performed to examine this issue using Mallinckrodt and colleagues'[22] strategy for examining dropouts. A last observation carried forward analysis produced an adjusted mean difference between DM/Q and placebo of 3.8 points (standard error = 0.8; $p < 0.0001$). A repeated-measures generalized estimating equations model with exchangeable correlation structure, adjusting for center effects and common time trend, estimated a mean treatment difference of 4.6 points (standard error = 0.7; $p < 0.0001$). Both of these sensitivity analyses agreed with the primary effi-

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Table 1. Demographics, Multiple Sclerosis and Pseudobulbar Affect History, and Baseline Values

Characteristics	DM/Q (n = 76)	Placebo (n = 74)	p^a
Mean age, yr (SD)	46.3 (9.8)	43.7 (10.0)	0.1033
Female sex, n (%)	62 (81.6)	62 (83.8)	0.7214
Race, n (%)			0.7275
White	68 (89.5)	68 (91.9)	
Black	5 (6.6)	5 (6.8)	
Asian	1 (1.3)	0 (0.0)	
Hispanic	2 (2.6)	1 (1.4)	
Other	0 (0.0)	0 (0.0)	
Mean years with MS (SD)	10.3 (8.6)	9.6 (7.4)	0.5751
Mean weekly episodes of crying and laughing (patient estimate) (SD)	14.1 (20.4)	17.3 (25.2)	0.4048
Mean baseline (day 1) CNS-LS (SD)	20.3 (5.0)	21.4 (5.1)	0.1683
Mean baseline VAS, overall quality of life (SD)	50.4 (28.4)	54.1 (27.5)	0.4206
Mean baseline VAS, overall quality of relationships	45.6 (28.8)	49.2 (27.5)	0.4233
Mean baseline pain intensity rating scale	1.4 (1.0)	1.4 (1.0)	0.8206

[a] p values to compare means for continuous variables were computed by using t tests. p values for categorical variables were computed by using χ^2 tests.

DM/Q = capsules containing dextromethorphan and quinidine; SD = standard deviation; MS = multiple sclerosis; CNS-LS = Center for Neurologic Study–Lability Scale; VAS = visual analog scale.

cacy analysis and indicated that dropouts did not differentially bias the assessment of efficacy in this study.

Safety

ADVERSE EVENTS. The proportions of patients who had any AEs, had serious adverse events (SAEs), or had AEs that resulted in discontinuation were similar between treatment groups. Eleven (14.5%) patients in the DM/Q group and eight patients (10.8%) in the placebo group discontinued the study or stopped medication due to AEs. Four patients in the DM/Q group and six patients in the placebo group were dropped from the study because of MS exacerbations. At least 1 AE was reported by 62 (81.6%) DM/Q patients and 63 (85.1%) placebo patients. Six patients had SAEs, two (2.6%) in the DM/Q group and four (5.4%) in the placebo group; none of the SAEs was judged by the investigators to be related to study treatment. AEs experienced by at least 5% of patients within a treatment group are summarized in Table 4.

Headache was the most common AE, but it occurred in more placebo patients than DM/Q patients, although the difference was not significant. Nausea was reported for more DM/Q patients than placebo patients, but this difference also was not significant. The median duration of nausea was 1.5 days in DM/Q patients and 1.0 day in placebo patients. Dizziness was the only AE that occurred significantly more frequently in DM/Q patients than in placebo patients; but most instances of dizziness were mild or moderate, and only one patient, in the DM/Q group, reported severe dizziness. The number of patients reporting fatigue was 15 in both groups, although the median duration of fatigue was 1.5 days in DM/Q patients and 3.0 days in placebo patients.

OTHER SAFETY RESULTS. There was no significant difference between treatment groups for shifts in any laboratory value, and there was no significant shift within a treatment group for any laboratory value. There were no clinically relevant changes from baseline in vital signs or physical examination results for either treatment group. No significant difference between treatment groups was noted for the ECG parameters: HR, PR, QT, or QRS. The DM/Q group had a significantly greater change from screening to day 85 than the placebo group in QTc, but the QTc change was small (mean increase of 7.5 milliseconds in the DM/Q group vs 0.3 millisecond in the placebo group; $p = 0.0236$). No patient in either treatment

Table 2. Number (%) of Patients with Predicted Phenotype for Metabolism of Dextromethorphan

Predicted Phenotype	DM/Q (n = 76)	Placebo (n = 74)	Total (n = 150)
Total with phenotype data, n	50	53	103
Poor	1 (2.0%)	2 (3.8%)	3 (2.9%)
Intermediate	0 (0.0%)	1 (1.9%)	1 (1.0%)
Extensive	48 (96.0%)	50 (94.3%)	98 (95.1%)
Ultrarapid	1 (2.0%)	0 (0.0%)	1 (1.0%)

DM/Q = capsules containing dextromethorphan and quinidine.

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