

CME Treatment of pseudobulbar affect in ALS with dextromethorphan/quinidine

A randomized trial

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Abstract—*Background:* Patients with ALS commonly exhibit pseudobulbar affect. *Methods:* The authors conducted a multicenter, randomized, double-blind, controlled, parallel, three-arm study to test a defined combination of dextromethorphan hydrobromide (DM) and quinidine sulfate (Q) (AVP-923) for the treatment of pseudobulbar affect in ALS. Q inhibits the rapid first-pass metabolism of DM. The effects of AVP-923 (30 mg of DM plus 30 mg of Q) given twice daily for 28 days were compared with those of its components. Patients were evaluated on days 1, 15, and 29. The primary efficacy variable was the change from baseline in the Center for Neurologic Study Disability Scale (CNS-LS) score. Secondary efficacy variables were laughing/crying episode rates and changes in Visual Analog Scales for Quality of Life (QOL) and Relationships (QOR). Efficacy was evaluated in intention-to-treat subjects who were not poor metabolizers of DM (n = 65 for AVP-923, n = 30 for DM, and n = 34 for Q). Safety was assessed in all randomized subjects (n = 140). *Results:* AVP-923 patients experienced 3.3-point greater improvements in CNS-LS than DM patients ($p = 0.001$) and 3.7-point greater improvements than Q patients ($p < 0.001$). AVP-923 patients exhibited lower overall episode rates, improved QOL scores, and improved QOR scores ($p < 0.01$ for all endpoints). Adverse effects were mostly mild or moderate; treatment-related discontinuation was 24% for AVP-923, 6% for DM, and 8% for Q. *Conclusions:* AVP-923 palliates pseudobulbar affect in ALS. Overall benefits of treatment are reflected in fewer episodes of crying and laughing and improvements in overall quality of life and quality of relationships.

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Up to 50% of patients with ALS exhibit pseudobulbar affect,¹ and it is more prevalent in those with the bulbar form of ALS. There are currently no drugs approved by the Food and Drug Administration for the treatment of pseudobulbar affect associated with ALS or other neurologic disorders.

Dextromethorphan (DM) inhibits glutamate at the NMDA receptor site by acting as a weak, noncompetitive NMDA receptor antagonist²⁻⁴ by binding to the phencyclidine site within the receptor-associated ion channel,^{5,6} thereby directly blocking glutamate-mediated calcium influx through the channel.³ In ad-

dition, DM is proposed to act as an agonist at the high-affinity σ -1 receptor.^{7,8} σ ligands may indirectly modulate NMDA-induced neuronal activation^{3,9} and inhibit presynaptic release of glutamate,¹⁰ and DM has been shown to decrease potassium-stimulated glutamate release.¹¹ DM has also been shown to modulate dopamine release in the mesolimbic pathway,¹² an effect that may be, in part, mediated via its unique σ -neuromodulatory properties.^{9,13} Because of its inhibitory actions on glutamate, a number of investigators have treated ALS patients with DM in the hope of modifying or arresting the disease.¹⁴⁻¹⁶

See Commentary, page 1345

*See the Appendix on page 1370 for a list of Group members.

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These trials have failed to demonstrate any benefit, possibly owing to the rapid and extensive metabolism of DM that occurs in approximately 90% of the Caucasian population (referred to as extensive metabolizers).¹⁷

DM metabolism is primarily mediated by the cytochrome P450 2D6 enzyme (CYP2D6)¹⁸ in extensive metabolizers, the majority phenotype. Co-administration of quinidine (Q), a selective CYP2D6 inhibitor, at Q doses 1 to 1.5 logs below those employed for the treatment of cardiac arrhythmias¹⁸ circumvents DM metabolism. Blood levels of DM increase linearly with DM dose following co-administration with Q but are undetectable in most subjects given DM alone, even at high doses.¹⁹ The DM plasma levels in these extensive metabolizers co-administered Q thus mimic the plasma levels in individuals expressing the minority poor metabolizer phenotype where polymorphisms in the gene result in reduced levels of P450 2D6.

In a placebo-controlled, crossover study, concomitant administration of DM and Q to ALS patients was found to suppress pseudobulbar affect ($p < 0.001$ compared with placebo).²⁰ We evaluated the efficacy, safety, and tolerance of AVP-923 taken twice daily relative to its individual components (DM and Q).

Methods. Patients. At 17 academic centers across the United States, we conducted a multicenter, randomized, double-blind, controlled study of the treatment of pseudobulbar affect in ALS. Patients were enrolled between January 11, 2001, and April 30, 2002. The study protocol and informed consent document were approved by the institutional review boards of the participating institutions. Informed consent of the patients was obtained following the principles outlined in the Declaration of Helsinki.

Study inclusion required a diagnosis of probable or definite ALS according to the El Escorial (World Federation of Neurology) criteria.²¹ Patients had a history of pseudobulbar affect and were required to attain a score of ≥ 13 on the Center for Neurologic Study Lability Scale (CNS-LS) at screening. The CNS-LS is a seven-item self-administered scale that measures pseudobulbar affect and has been validated in a large population of ALS patients.²² Inclusion criteria included a score on the Hamilton Rating Scale for Depression (HRSD) of ≤ 16 (moderate depression), normal hematologic, hepatic, and renal function as determined by laboratory tests, and a vital capacity of at least 50% predicted. Patients were required to have a normal resting EKG as defined by prespecified criteria and obtained within 4 weeks of study randomization.

Patients were excluded from the study if they had been diagnosed with ALS within the last 2 months, to avoid enrolling subjects with reactive depression. Patients with a history of major psychiatric disturbance, substance abuse, or those receiving antidepressant medication were also ineligible. Participating patients agreed not to take prohibited medications during the study and for 1 week prior to entry. These medications included antidepressants, monoamine oxidase inhibitors, anticoagulants, certain inhibitors and substrates for P450 2D6 or P450 3A4, and medications containing components of the test drug mixture.

Treatment and drug dosing. This multicenter study had a parallel, three-arm design. Subjects were randomized by center to receive AVP-923, DM alone, or Q alone, with twice as many subjects receiving AVP-923 as either DM or Q alone (2:1:1 ratio). Capsules containing 30 mg of DM and 30 mg of Q (AVP-923) or 30 mg of each of the separate components were prepared. All were identical in appearance.

The study was randomized by center. Randomization was blocked to ensure approximately equal representation within treatment centers using a computer algorithm. Study drug was randomized by Sharp Clinicals (Conshohocken, PA) and shipped

directly to the clinical study sites. The sponsor and investigators were blinded to treatment allocation. Investigators were shipped AVP-923, DM, and Q in identical blister-pack cards that were dispensed in strict sequence.

Capsules were taken orally by the patients twice daily (approximately every 12 hours) for 28 days. Patients were asked to complete a diary logging the date and time each dose was taken, the number of laughing and crying episodes experienced, and the adverse events (AEs) experienced.

Evaluation. Patients were assessed prior to dosing on day 1 (baseline) and on days 15 and 29. On each of these days, subjects completed the CNS-LS questionnaire and two 10-cm Visual Analog Scales (VASs): one assessing quality of life (QOL) and one assessing quality of relationships (QOR).²³ The CNS-LS was also administered at a screening visit occurring within 4 weeks of enrollment on day 1. The HRSD was administered at screening and on day 29. Subjects who discontinued early were to return to the clinic as soon as possible to complete a "final visit," which included all evaluations scheduled for day 29. Safety was evaluated by monitoring AEs, physical examination results, vital signs, resting EKGs, and clinical laboratory values for serum chemistry, hematology, and urinalysis.

Blood samples were to be taken on day 1 for CYP2D6 genotyping. Genotyping was performed on isolated genomic DNA by PCR analysis by Genaisance Pharmaceuticals (Morrisville, NC). Based on the results, subjects were classified according to predicted phenotype as poor, intermediate, extensive, or ultrarapid metabolizer.

Blood samples were to be taken on day 29 within 8 hours following the last dose to determine concentrations of DM, its metabolite dextroprphan²⁴ (DX), and Q. Heparinized plasma samples were assayed at MDS Pharma Services (Lincoln, NB) using a validated high-performance liquid chromatography procedure for Q (limit of quantitation [LOQ] = 50 ng/mL) and a validated liquid chromatography mass spectrometry/mass spectrometry procedure for DM (LOQ = 0.200 ng/mL) and DX (LOQ = 2.5 ng/mL). Only samples that were taken within the 8-hour window specified by the protocol were included in the statistical analysis of the bioanalytic results.

The primary efficacy variable was based on the change from baseline in the CNS-LS score. Secondary efficacy endpoint variables were 1) the number of laughing or crying episodes per week

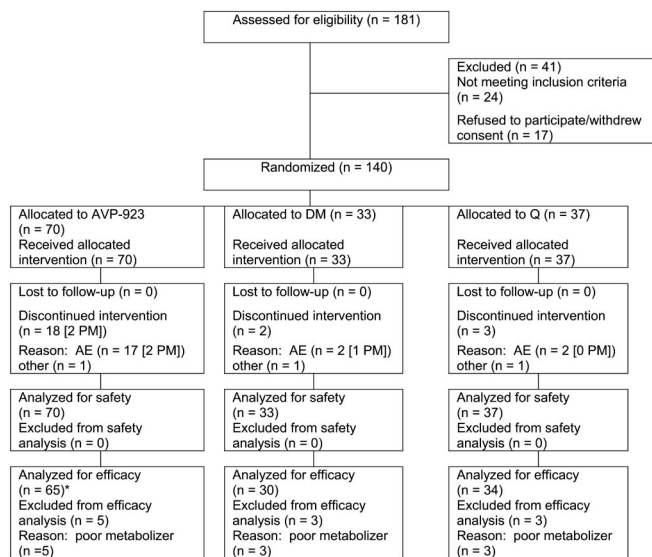


Figure. Subject disposition. *For the primary efficacy endpoint, CNS-LS, four additional subjects completed only the day 1 CNS-LS; therefore, a change in CNS-LS could not be calculated. As a result, the evaluable intention to treat is $n = 61$. DM = dextromethorphan hydrobromide; Q = quinidine; PM = poor metabolizer(s); AE = adverse event; CNS-LS = Center for Neurologic Study Lability Scale.

Table 1 Demographic characteristics: ITT cohort

Characteristic	AVP-923	DM	Q	<i>p</i> Value*	
				AVP-923 vs DM	AVP-923 vs Q
n	65	30	34		
Age, y	54.8 (12.8)	53.8 (11.2)	55.3 (9.5)	0.78	0.99
Female, %	35	47	35	0.15	0.81
Race, %				0.21	0.55
Black, n	3	0	0		
White, n	89	83	91		
Hispanic, n	8	10	9		
Other, n	0	7	0		
HRSD	5.4 (4.3)	4.3 (3.1)	5.8 (4.2)	0.14	0.71
CNS-LS	20.0 (5.5)	21.4 (6.2)	22.2 (5.2)	0.32	0.07
VAS-QOL	35.1 (26.7)	47.6 (27.2)	46.6 (26.9)	0.02	0.03
VAS-QOR	31.2 (28.5)	41.1 (28.2)	42.2 (29.9)	0.14	0.06

Quantities are means (SD), except as noted. HRSD, CNS-LS, and VAS scores are baseline values. Baseline measurements for HRSD were done at screening. Baseline measurements for CNS-LS, VAS-QOL, and VAS-QOR were done on day 1.

* *p* Values to compare means were computed by using analysis of variance with an adjustment for center.

ITT = intention to treat; DM = dextromethorphan hydrobromide; Q = quinidine sulfate; HRSD = Hamilton Rating Scale for Depression; CNS-LS = Center for Neurologic Study Liability Scale; VAS = Visual Analog Scale; QOL = Quality of Life; QOR = Quality of Relationships.

recorded in patient diaries, 2) change from baseline QOL scores, and 3) change from baseline in QOR scores. All efficacy variables involving a change were determined as the baseline score subtracted from the mean of the scores on days 15 and 29.

The intent of the study was to enroll both extensive and poor DM metabolizers (all phenotypes) to evaluate safety in all populations that might be prescribed the drug. Because, theoretically, Q should not be required for efficacy in poor metabolizers, the protocol specified that poor metabolizers, regardless of randomized group, would be omitted from the intention-to-treat (ITT) efficacy analysis. Thus, the ITT cohort included all randomized patients who were not poor metabolizers of DM as identified by *CYP2D6* genotyping.

Statistical analysis. Data analysis was performed by INC Research (Charlottesville, VA) as directed by a protocol-defined Statistical Analysis Plan. Results were confirmed by one of the authors, who also conducted additional exploratory analyses.

Changes from baseline in CNS-LS, QOL, and QOR scores were assessed using linear regression models. For these variables, the average of the day 15 and day 29 measurements was used. If either measurement was missing, the nonmissing value was used. Patients who completed no postrandomization evaluations were omitted from the primary analysis, but they were included in sensitivity analyses by carrying their baseline values forward. In each case, the baseline score and study center were used as covariates.²⁵ Episode counts were evaluated using a negative binomial regression model to control for site differences and substantial patient-to-patient heterogeneity. We used this model to compare episode rates between the treatment groups and to estimate the relationship between episode rates and CNS-LS. Comparisons are made between AVP-923 and each constituent. Because it was necessary that both comparisons favor AVP-923 for the combination to be considered superior, a multiple comparison adjustment within efficacy measure was not appropriate. Secondary efficacy variables were also combined and analyzed simultaneously by using the O'Brien rank sum method²⁶ to account for multiple comparisons of endpoints. Adverse experience comparisons used the Fisher exact test. All *p* values reported are two sided. An α value of 0.05 was used for significance.

Sample size calculations indicated that 48 patients in the AVP-923 group and 24 patients in each of the DM and Q groups would be sufficient to detect a difference in CNS-LS score of 5.5 between

the AVP-923 group and each component, assuming SDs of 7, 5, and 3 for AVP-923, DM, and Q. These calculations were based on variance and effect size estimates drawn from a small 14-patient crossover study.²⁰ A computer simulation was used to incorporate the feature that statistical significance was required against each active control.

Results. Patients were enrolled between January 2001 and March 2002, with the last subject completing treatment on April 30, 2002. One hundred forty patients were randomized; 11 were identified by genotyping to be poor metabolizers of DM. Of the remaining 129 ITT patients, 125 were evaluable in that they had completed at least one of the scheduled on-study evaluations, and 108 (84%) completed the study (figure).

Key demographic and baseline characteristics for the ITT cohort are shown in table 1. The ITT cohort included 80 men and 49 women. The mean age was approximately 55 years with a range of 33 to 82 years, and about 88% of patients were white. Significant differences between the AVP-923 group and the DM and Q groups were not observed for any of the demographic variables. The only statistical difference noted was that subjects in the AVP-923 group rated their QOL better at baseline than did the subjects in either of the other two treatment groups. This difference at baseline did not affect the study outcome primary endpoint.

The *CYP2D6* genotypes in each randomized treatment group were similar ($p = 0.94$). Of all eligible patients, 7.9% were poor metabolizers, consistent with previously reported values.¹⁷

Effects of treatment. Inhibition of DM metabolism: bio-analytical results. The purpose of Q is to inhibit the rapid first-pass metabolism of DM. The mean DM plasma concentration was 18-fold higher in the AVP-923 group (96.4 ± 46.7

Table 2 Efficacy assessments: ITT cohort

Parameter	AVP-923		DM		Q		p Value	
	Mean*	SE	Mean	SE	Mean	SE	AVP-923 vs DM	AVP-923 vs Q
CNS-LS	7.4	0.6	4.1	0.9	3.7	0.8	0.001	<0.001
QOL	24.1	2.5	11.2	3.6	12.2	3.3	0.002	0.001
QOR	22.6	2.4	6.6	3.4	8.6	3.2	<0.001	<0.001

Episode rates	DM vs AVP-923		Q vs AVP-923		p Value	p Value
	Ratio	95% CI	Ratio	95% CI		
Combined	1.89	1.23–2.90	2.13	1.44–3.16	0.004	<0.001
Crying	1.98	1.20–3.27	3.32	2.06–5.33	0.007	<0.001
Laughing	1.49	0.87–2.54	1.63	1.00–2.67	0.142	0.050

For CNS-LS, QOL, and QOR, values listed are least-squares means, adjusting for baseline levels and center effects. In each case, larger scores represent greater improvement. For each patient, the change in score was evaluated as the baseline score subtracted from the mean of the scores for day 15 and day 29. Values for episode rates show the ratio between DM or Q and AVP-923 rates. Ratios for combined and laughing episode rates omit one outlier in the DM group (see text).

ITT = intention to treat; DM = dextromethorphan hydrobromide; Q = quinidine sulfate; CNS-LS = Center for Neurologic Study Liability Scale; QOL = Quality of Life; QOR = Quality of Relationships.

ng/mL, mean \pm SD, n = 35) than in the DM group (5.2 \pm 5.0 ng/mL, n = 23), and the mean concentration of DX was 3.3-fold lower in the AVP-923 group (89.5 \pm 52.3 ng/mL) than in the DM group (295.9 \pm 143.2 ng/mL). These differences between AVP-923 and the DM-only group were significant for both DM and DX ($p < 0.0001$). The reduced n value for the bioanalytical results reflects the fact that many of the pharmacokinetic samples were drawn >8 hours after the last dose.

Analysis of Q revealed a median level of 150.0 ng/mL in the AVP-923 group (range, < LOQ to 2,210 ng/mL) and a median level of 80 ng/mL (range, < LOQ to 200 ng/mL) in the Q group. In the AVP-923 group, 4 of 35 subjects had Q values less than the LOQ, and in the Q group, 7 of 23 subjects had Q values less than the LOQ. The bioanalytical results indicated good compliance with respect to dosing, with the exception of one subject in the Q group whose blood sample showed measurable amount of DM and DX (it is suspected that this subject was noncompliant with respect to avoiding over-the-counter cough medicines). The nonquantifiable levels of Q in these patients are not an indication of noncompliance. Based on previously completed pharmacokinetic studies by the sponsor, Q levels with this dose regimen often dip below the LOQ of 0.050 μ g/mL during the 8-hour window of collection ($T_{\max} = 2$ hours).²⁷

Improvement of CNS-LS score. One hundred twenty-five patients were included in the primary efficacy end-point analysis (ITT) cohort, as four subjects in the AVP-923 group discontinued study drug and declined to return for any follow-up assessments. The unadjusted decrease in CNS-LS in the AVP-923 group was greater (7.39 \pm 5.37, mean \pm SD) than that in the DM group (5.12 \pm 5.56) or the Q group (4.91 \pm 5.56).

For statistical comparison, as predefined in the statistical plan, the difference in mean CNS-LS improvement (table 2) was adjusted for two important, prospectively defined covariates: baseline CNS-LS score and study center. Indeed, patients with higher levels of baseline CNS-LS

tended to show greater improvements, regardless of assigned treatment. The mean reduction of CNS-LS in the AVP-923 group was 3.29 points greater than in the DM group ($p = 0.001$) and 3.71 points greater than in the Q group ($p < 0.001$). There was no significant treatment-by-center interaction.

Decreased laughing/crying episodes. Diary records of episodes were evaluated for the number of crying episodes, laughing episodes, and laughing plus crying episodes per week. Episode rates are highly variable (table 3). To account for this variability, a negative binomial regression model was used to compare rates across treatment groups, shown in the lower portion of table 2.

A single outlier in the DM group reported 10 times more episodes (primarily laughing) than any other patient in the study—an average of >100 episodes/day. Omitting this outlier from the analysis, the average episode rate recorded in the AVP-923 group was 1.9 times lower than in the DM group ($p = 0.004$) and 2.1 times lower than in the Q group ($p < 0.001$). Corresponding ratios for crying and for laughing were similar (see table 2). Of the AVP-923 patients, 52% were symptom-free over the last 2 weeks of the study compared with 23% for DM and 12% for Q ($p < 0.001$).

Improved QOL and QOR. The adjusted mean changes in VAS scores for QOL and QOR in the ITT group treated with AVP-923 were greater than those in either of the other two treatment groups at all time points examined (see table 2). The significance level of improvement increased with longer duration of drug treatment.

Simultaneous analysis of secondary efficacy variables. To account for multiple comparisons, all secondary efficacy variables were combined and analyzed using the non-parametric method of O'Brien.²⁶ The results showed that subjects treated with AVP-923 had a reduction in laughing/crying episodes and improved QOL and QOR scores relative to subjects treated with DM ($p = 0.004$) or Q ($p < 0.001$).

Poor metabolizers. The ITT cohort for the primary analysis was prospectively defined as randomized patients

Table 3 Distribution of episode rates

Episode	Percentile				
	10	25	50	75	90
Crying					
AVP-923	0.0	0.0	0.3	1.9	6.0
DM	0.0	0.2	0.6	8.5	14.0
Q	0.0	1.7	3.8	8.3	14.2
Laughing					
AVP-923	0.0	0.0	0.8	4.8	24.4
DM	0.0	0.0	2.0	9.6	46.3
Q	0.0	0.2	2.0	9.0	20.0
Total					
AVP-923	0.0	0.5	2.4	8.6	24.8
DM	0.0	1.2	9.0	19.0	46.9
Q	0.8	3.0	6.0	16.2	36.1

Episode rates are expressed as episodes/week, measured over the course of study treatment. For example, 75% of AVP-923 patients had ≤ 1.9 crying episodes/week during treatment. Similarly, 25% of Q patients had ≤ 1.7 crying episodes/week during treatment.

DM = dextromethorphan hydrobromide; Q = quinidine sulfate.

who were not poor metabolizers of DM. Although the poor metabolizer subgroup was small (five AVP-923, three DM, three Q), the results were consistent with expectation. Mean improvements in adjusted CNS-LS for AVP-923, DM, and Q, in order, were 9.9, 7.0, and 0.8 (SD = 4 for all groups); mean improvements in adjusted VAS-QOL were 26, 25, and -7 (SD = 10, 12, 11), and mean improvements in adjusted VAS-QOR were 21, 3, and 4 (SD = 18, 21, 19).

Sensitivity analyses. When all randomized patients are included in the analysis ($n = 140$), the substantial findings—including significance—do not change. Similar results are also obtained when missing values are replaced with the last observed value rather than being omitted from the analysis. When all missing values are replaced by baseline values ($n = 129$), the mean reduction in CNS-LS is 2.5 points greater for AVP-923 than for DM ($p = 0.013$) and 3.1 points greater than for Q ($p = 0.002$).

Safety assessments. All 140 patients receiving drug were monitored for AEs. AEs were reported by 89% of patients dosed with AVP-923, 70% of patients dosed with DM, and 65% of patients dosed with Q. Most AEs were mild or moderate. AEs reported in $\geq 5\%$ of subjects are listed in table 4.

Drug treatment discontinuations due to AEs included 24% ($n = 17$) of AVP-923 patients, 6% ($n = 2$) of DM patients, and 5% ($n = 2$) of Q patients. One AVP-923 patient died of ALS complications unrelated to study treatment. In AVP-923 patients that discontinued, most AEs were judged to be at least possibly related to treatment; however, 46 of 50 AEs in these subjects were mild or moderate. The largest proportion comprised AEs related to the nervous system. Only 2 of the 17 subjects had severe AEs (headache, nausea, and vomiting), all of which resolved without sequelae. The two DM patients that discontinued experienced seven AEs, all judged to be related to treatment; all AEs except one were mild or moderate. One DM

Table 4 Number (%) of subjects ($\geq 5\%$ in any treatment group) with adverse events: safety population ($n = 140$)

Adverse event preferred term	AVP-923, n = 70	DM, n = 33	Q, n = 37
Anorexia	4 (5.7)	1 (3.0)	0 (0.0)
Anxiety NEC	3 (4.3)	0 (0.0)	3 (8.1)
Arthralgia	2 (2.9)	3 (9.1)	2 (5.4)
Constipation	5 (7.1)	2 (6.1)	0 (0.0)
Confusion	1 (1.4)	2 (6.1)	0 (0.0)
Diarrhea NOS	11 (15.7)	7 (21.2)	4 (10.8)
Dizziness (excluding vertigo)*	14 (20.0)	5 (15.2)	1 (2.7)
Dyspnea NOS	2 (2.9)	0 (0.0)	3 (8.1)
Edema lower limb	0 (0.0)	1 (3.0)	2 (5.4)
Fall	6 (8.6)	2 (6.1)	0 (0.0)
Fatigue	13 (18.6)	3 (9.1)	4 (10.8)
Flatulence	1 (1.4)	2 (6.1)	0 (0.0)
Headache NOS	11 (15.7)	4 (12.1)	4 (10.8)
Hypertonia	5 (7.1)	0 (0.0)	1 (2.7)
Joint stiffness	7 (10.0)	0 (0.0)	1 (2.7)
Localized infection	0 (0.0)	0 (0.0)	2 (5.4)
Loose stools*	0 (0.0)	3 (9.1)	0 (0.0)
Muscle cramps	5 (7.1)	2 (6.1)	1 (2.7)
Muscle spasms	2 (2.9)	2 (6.1)	0 (0.0)
Nasopharyngitis	1 (1.4)	3 (9.1)	1 (2.7)
Nausea*	23 (32.9)	2 (6.1)	3 (8.1)
Pruritus NOS	0 (0.0)	0 (0.0)	2 (5.4)
Sinus congestion	2 (2.9)	2 (6.1)	1 (2.7)
Sleep disorder NOS	0 (0.0)	0 (0.0)	2 (5.4)
Somnolence*	9 (12.9)	1 (3.0)	0 (0.0)
Sweating increased	4 (5.7)	0 (0.0)	1 (2.7)
Upper respiratory tract infection NOS	3 (4.3)	1 (3.0)	2 (5.4)
Vomiting NOS	4 (5.7)	0 (0.0)	0 (0.0)
Weakness	4 (5.7)	1 (3.0)	4 (10.8)

* Number reported significantly different between groups.

DM = dextromethorphan hydrobromide; Q = quinidine sulfate; NEC = not elsewhere classified; NOS = not otherwise specified.

patient experienced severe diarrhea, which resolved without sequelae. Three Q patients discontinued and experienced five AEs, four of which were judged unrelated to treatment and were mild or moderate. One patient had severe muscle cramping that was judged to be related to treatment, and the AE resolved without sequelae.

Significant differences between treatment groups in the number of subjects experiencing an AE were observed for nausea, dizziness, somnolence, and loose stools. Nausea ($p = 0.003$ vs DM, 0.004 vs Q), dizziness ($p = 0.017$ vs Q), and somnolence ($p = 0.03$ vs Q) were reported more frequently in the AVP-923 group, and loose stools were reported more commonly in the DM group ($p = 0.03$ vs AVP-923). Nausea, dizziness, and somnolence are established side effects of DM, and as Q enhances the bioavailability of

DM by inhibition of its metabolism, one would expect the incidence of DM-related AEs to be increased in the AVP-923 group. Nausea was experienced by 32.9% of AVP-923 patients compared with 6.1% of DM patients and 8.1% of Q patients. Dizziness was experienced by 20.0% of AVP-923, 15.2% of DM, and 2.7% of Q subjects. Somnolence was experienced by 12.9% of AVP-923 and 3.0% of DM patients, and it was not reported by Q patients. Loose stools were experienced only in the DM group (9.1%).

No significant changes were observed in hematology, clinical chemistry, or urinalysis from baseline to day 29 in any treatment group. There were no clinically relevant changes from baseline to day 29 in vital signs or physical examination results. In the EKG, there was a significant difference in the change from baseline to day 29 in ventricular rhythm and in the QT interval between the AVP-923 and Q groups but not between the AVP-923 and DM groups; the changes in the AVP-923 group were small and not judged to be clinically relevant (change in ventricular rhythm = -3.8 beats/min, change in QT = 7.5 milliseconds). There was no significant difference among the treatment groups in QT_c, PR, or QRS duration.

To help quantify and understand how changes in CNS-LS score compare to the number of episodes, the "effect" of a 1-point change on the CNS-LS score on the episode rate during the previous 2 weeks was estimated. For each 1-point increase in CNS-LS score, the average episode rate increased 12%. Thus, the approximate 3.5-point decrease in CNS-LS score of AVP-923 compared with either agent alone corresponds to a 50% decrease in episode rate. This is true for both laughing and crying episodes.

Discussion. The results demonstrate that AVP-923 effectively palliates pseudobulbar affect in ALS patients and is significantly more effective than either of its components. Improvement indicated by the validated self-assessment tool (CNS-LS) is correlated with decreased episodes of laughing or crying. Further, this benefit significantly improved qualities of life and relationships for these patients with ALS.

Results of the study indicate that AVP-923 is safe; AEs reported were as expected based on previous use of DM and Q (e.g., nausea, dizziness, and gastrointestinal complaints), and many appeared to be specific for ALS patients (e.g., muscle cramps, muscle spasms, weakness). More subjects in the AVP-923 group had AEs and discontinued because of AEs than in either of the other two groups; however, most AEs (92%) in subjects who discontinued were mild or moderate, and the effects were reversible. Discontinuations appeared to occur early in the trial (of the 117 patients in the trial who received >5 days of treatment, the discontinuation rates were 9% for AVP-923, 3.5% for DM, and 9% for Q). A dose titration schedule of administration utilized during a recently completed open-label study in patients with diabetic neuropathic pain (manuscript in preparation) suggests that some intolerance can be avoided by increasing dosage from an initial low dose. This issue requires further investigation. There was no evidence for cardiac effects of Q, and the bioanalytic results demonstrated very low exposure levels. There were no

treatment-related serious AEs. Based on the evidence for improved qualities of life and relationships, most ALS patients who were treated with AVP-923 benefited and were able to tolerate the side effects.

AVP-923 represents a novel treatment option for pseudobulbar affect in ALS and is the first agent proven effective in a controlled, multicenter, randomized study. Currently, patients with pseudobulbar affect may be treated with selective serotonin reuptake inhibitors^{28,29} and tricyclic antidepressants.^{30,31} These agents have been reported to palliate inappropriate emotional expression to varying degrees, although some patients remain unresponsive to treatment.³⁰

Patients in this study did not experience depression. This is evidenced by mean HRSD scores of <6 at baseline and at the end of the experimental treatment. At baseline, the correlation between HRSD and CNS-LS was -0.004 . These observations underscore the clear distinction between depression and pseudobulbar affect.³¹

The neurochemical pathology of pseudobulbar affect is poorly understood but may be similar in pseudobulbar affect associated with such disorders as stroke and multiple sclerosis. AVP-923 is currently being evaluated in a placebo-controlled, multicenter study of pseudobulbar affect in patients with multiple sclerosis.

The basis for the effect of AVP-923 on inappropriate emotional displays remains conjectural. Whereas DM and riluzole, the only approved treatment of ALS, share an inhibitory action on NMDA receptor-related events and glutamate release,^{2-4,11,32} riluzole has not been reported to relieve pseudobulbar affect. DM differs from riluzole in its ability to act as a σ ligand,^{7,8} suggesting that this property of DM may be important for its therapeutic benefit. Furthermore, DM binding sites are preferentially localized to brainstem and cerebellum,^{2,33} brain regions with particularly high concentrations of σ -1 receptors,^{7,9} which are believed to mediate emotional motor expression.^{34,35} It is possible that the therapeutic benefit of AVP-923 results from a σ -agonist effect on brainstem motor nuclei involved in emotional expression and regulatory neurons that project to the cerebral cortex.

The medical uses of DM have been limited primarily to its use as an antitussive agent. Recently, there has been renewed interest in exploring its pharmacology in the treatment of a variety of disorders including seizures, neuropathic pain, Parkinson disease, and Huntington disease. Study results with DM alone have been mixed. This may be because researchers have generally ignored the pharmacokinetic characteristics of orally ingested DM, failed to genotype or phenotype patients for metabolizer type, and failed to assess blood levels following administration of the drug. Based on the results of this study in ALS patients, reports of a failure to benefit from DM need to be evaluated more rigorously and consideration given to treatment with AVP-923, which of

fers the promise of attaining predictable and sustained blood levels of DM.^{19,32}

Appendix

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References

1. Gallagher JP. Pathologic laughter and crying in ALS: a search for their origin. *Acta Neurol Scand* 1989;80:114–117.
2. Tortella FC, Pellicano M, Bowery NG. Dextromethorphan and neuro-modulation: old drug coughs up new activities. *Trends Pharmacol Sci* 1989;10:501–507.
3. Maurice T, Lockhart BP. Neuroprotective and anti-amnesic potentials of sigma (σ) receptor ligands. *Prog Neuropsychopharmacol Biol Psychiatry* 1997;21:69–102.
4. Ebert B, Thorikildsen C, Andersen S, Christrup LL, Hjeds H. Opioid analgesics as noncompetitive N-methyl-D-aspartate (NMDA) antagonists. *Biochem Pharmacol* 1998;56:553–559.
5. Murray TF, Leid ME. Interaction of dextrorotatory opioids with phen-cyclidine recognition sites in rat brain membranes. *Life Sci* 1984;34:1899–1911.
6. DeCoster MA, Klette KL, Knight ES, Tortella FC. Sigma receptor-mediated neuroprotection against glutamate toxicity in primary rat neuronal cultures. *Brain Res* 1995;671:45–53.
7. Maurice T, Urani A, Phan VL, Romieu P. The interaction between neuroactive steroids and the sigma 1 receptor function: behavioral consequences and therapeutic opportunities. *Brain Res Rev* 2001;37:116–132.
8. Klein M, Musacchio JM. High affinity dextromethorphan binding sites in guinea pig brain. Effect of sigma ligands and other agents. *J Pharmacol Exp Ther* 1989;251:207–215.
9. Debonnel G, de Montigny C. Modulation of NMDA and dopaminergic neurotransmissions by sigma ligands: possible implications for the treatment of psychiatric disorders. *Life Sci* 1996;58:721–734.
10. Ellis Y, Davies JA. The effects of sigma ligands on the release of glutamate from rat striatal slices. *Naunyn-Schmiedeberg Arch Pharmacol* 1994;350:143–148.
11. Annels SJ, Ellis Y, Davies JA. Non-opioid antitussives inhibit endogenous glutamate release from rabbit hippocampal slices. *Brain Res* 1991;564:341–343.
12. Steinmiller CL, Maisonneuve IM, Glick SD. Effects of dextromethorphan on dopamine release in the nucleus accumbens: interactions with morphine. *Pharmacol Biochem Behav* 2003;74:803–810.
13. Weatherspoon JK, Gonzalez-Alvear GM, Frank AR, Werling LL. Regulation of [3H] dopamine release from mesolimbic and mesocortical areas

- of guinea pig brain by sigma receptors. *Schizophrenia Res* 1996;21:51–62.
14. Askmark H, Aquilonius SM, Gillberg PG, Liedholm LJ, Stalberg E, Wuopio R. A pilot trial of dextromethorphan in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* 1993;56:197–200.
15. Hollander D, Pradas J, Kaplan R, McLeod HL, Evans WE, Munsat TL. High-dose dextromethorphan in amyotrophic lateral sclerosis: Phase 1 safety and pharmacokinetic studies. *Ann Neurol* 1994;36:920–924.
16. Blin O, Azulay JP, Desnuelle C, et al. A controlled one-year trial of dextromethorphan in amyotrophic lateral sclerosis. *Clin Neuropharmacol* 1996;19:189–192.
17. Hildebrand M, Seifert W, Reichenberger A. Determination of dextromethorphan metabolizer phenotype in healthy volunteers. *Eur J Clin Pharmacol* 1989;36:315–318.
18. Schadel M, Wu D, Otton SV, Kalow W, Sellers EM. Pharmacokinetics of dextromethorphan and metabolites in humans: influence of the CYP2D6 phenotype and quinidine inhibition. *J Clin Psychopharmacol* 1995;15:263–269.
19. Zhang Y, Britto MR, Valderhaug KL, Wedlund PJ, Smith RA. Dextromethorphan: enhancing its systemic availability by way of low-dose quinidine-mediated inhibition of cytochrome P4502D6. *Clin Pharmacol Ther* 1992;51:647–655.
20. Smith RA, Moore SR, Gresham LS, Manley PE, Licht JM. The treatment of affective lability with dextromethorphan. *Neurology* 1995;45:A330.
21. Brooks BR. El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. Subcommittee on Motor Neuron Diseases/Amyotrophic Lateral Sclerosis of the World Federation of Neurology Research Group on Neuromuscular Diseases and the El Escorial “Clinical Limits of Amyotrophic Lateral Sclerosis” Workshop contributors. *J Neurol Sci* 1994;124:96–107.
22. Moore SR, Gresham LS, Bromberg MB, Kasarkis EJ, Smith RA. A self report measure of affective lability. *J Neurol Neurosurg Psychiatry* 1997;63:89–93.
23. Huskisson EC. Pain: mechanisms and measurement. In: Hart FD, ed. *The treatment of chronic pain*. Philadelphia: Davis, 1974:1–38.
24. Vetticaden SJ, Cabana BE, Prasad VK, et al. Phenotypic differences in dextromethorphan metabolism. *Pharm Res* 1989;6:13–19.
25. Frison L, Pocock SJ. Repeated measures in clinical trials: analysis using mean summary statistics and its implications for design. *Stat Med* 1992;11:1685–1704.
26. O'Brien PC. Procedures for comparing samples with multiple endpoints. *Biometrics* 1984;40:1079–1087.
27. Pope LE, Khalil MH, Berg JE, Stiles M, Yakatan GJ, Sellers EM. Pharmacokinetics of dextromethorphan after single or multiple dosing in combination with quinidine in extensive and poor metabolizers. *J Clin Pharmacol* 2004 (in press).
28. Mukand J, Kaplan M, Senno RG, Bishop DS. Pathological crying and laughing: treatment with sertraline. *Arch Phys Med Rehabil* 1996;77:1309–1311.
29. Nahas Z, Arlinghaus KA, Kotrla KJ, Clearman RR, George MS. Rapid response of emotional incontinence to selective serotonin reuptake inhibitors. *J Neuropsychiatry Clin Neurosci* 1998;10:453–455.
30. Schiffer RB, Herndon RM, Rudick RA. Treatment of pathologic laughing and weeping with amitriptyline. *N Engl J Med* 1985;312:1480–1482.
31. 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* 1993;150:286–293.
32. Doble A. The pharmacology and mechanism of action of riluzole. *Neurology* 1996;47:S233–S241.
33. Musacchio JM, Klein M, Canoll PD. Dextromethorphan and sigma ligands: common sites but diverse effects. *Life Sci* 1989;45:1721–1732.
34. Wilson SAK. Some problems in neurology. II: pathological laughing and crying. *J Neurol Psychopathol* 1924;4:299–333.
35. Parvizi J, Anderson SW, Martin CO, Damasio H, Damasio AR. Pathological laughter and crying/a link to the cerebellum. *Brain* 2001;124:1708–1719.