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Dextromethorphan/Quinidine Improved Symptoms of Pseudobulbar Affect Irrespective of Concomitant Antidepressant Use

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Abstract

INTRODUCTION: Pseudobulbar affect (PBA) can occur secondary to certain neurological diseases or brain injury. It is characterized by frequent, uncontrollable laughing/crying episodes that can be exaggerated or incongruent to mood or social context. PBA may be mistaken for, or occur comorbidly with depression and many patients receive antidepressant therapy. Dextromethorphan/quinidine (DM/Q) is currently the only approved PBA treatment (US and EU). This exploratory analysis evaluated outcomes from a DM/Q effectiveness trial for PBA stratified by antidepressant use at baseline (BL).

METHODS: PRISM II was an open-label trial enrolling persons with a clinical diagnosis of PBA secondary to dementia, stroke, or traumatic brain injury (TBI) and a Center for Neurologic Study Lability Scale (CNS-LS) Score ≥13. All participants received DM/Q 20/10 mg BID for 90 days. Patients taking antidepressants were allowed to enroll provided doses were stable (2 months). Outcome measures evaluated included the CNS-LS score (primary), PBA episode counts, PBA episode quality of life impact (QoL-Visual Analog Scale), Patient Health Questionnaire (PHQ-9) and Mini-Mental State Examination (MMSE). Comparisons of LS mean change from BL to Day 90 for antidepressant users vs non-users were analyzed for each cohort (TBI, dementia, and stroke) with a 2-sample t-test using an ANCOVA model with BL score as covariates. Safety data were analyzed descriptively.

RESULTS: A total of 367 patients enrolled, including 120, 113, and 134, with TBI, stroke, and dementia, respectively. Of these, 48.5% [42.5%, 45.1%, and 56.7%, respectively] were using antidepressants. At Day 90/endpoint, significant improvement was observed for all outcome measures compared to BL, regardless of antidepressant use. Reductions in CNS-LS score were similar for antidepressant users vs non-users: LS mean change -8.2 vs. -7.2 [$P_{=}$.08] and were similar within disease cohorts: TBI -8.9 vs. -8.2 [$P_{=}$.56], stroke -8.5 vs. -6.9 [$P_{=}$.16], and dementia -7.6 vs. -6.7 [$P_{=}$.36]. Likewise, there were no significant differences in other outcome measures by antidepressant use, with the exception of MMSE score in the stroke cohort [improvement of 0.6 for antidepressant users vs. 1.6 for nonusers, $P_{=}$.02]. The overall incidence of AEs was 37.6% for antidepressant users and 34.4% for non-users. Adverse events occurring in ≥2% of overall patients were: diarrhea 4.9% (2.8% antidepressant users vs. 6.9% non-users), headache 3.0% (4.5% vs. 1.6%), dizziness 2.2% (4.5% vs. 2.6%), and UTI 2.2% (1.7% vs. 2.6%). Serious AEs were reported in 6.3% (5.6% vs. 6.9%) and 9.8% (7.9% vs. 11.6%) discontinued for AEs.

CONCLUSIONS: In this analysis, DM/Q was associated with PBA symptom improvement, and reduced depressive symptoms, regardless of concomitant AD use at BL. These findings were observed across a range of disease subgroups associated with PBA.

Introduction

- Pseudobulbar affect (PBA) occurs secondary to certain neurologic diseases or brain injury (such as ALS, MS, dementia, stroke, or traumatic brain injury [TBI]) and is characterized by frequent, uncontrollable outbursts of laughing and/or crying that are excessive and/or incongruent to mood or social context[1,2]
- PBA may occur comorbidly with depression[3–8]
- Currently, the only FDA-approved treatment for PBA is the fixed-dose combination of dextromethorphan and quinidine (DM/Q 20/10 mg)[9,10]
  - DM is the active component in the CNS
  - Low dose quinidine (10 mg) inhibits the normally rapid metabolism of DM to dextrorphan, thereby providing therapeutic DM concentrations without undesirably high levels of dextrorphan
- Phase III studies supporting approval of DM/Q were conducted in patients with PBA secondary to ALS or MS, and excluded patients with major depression
- The PRISM II study investigated the effectiveness of DM/Q treatment for PBA secondary to dementia, stroke, or TBI, and allowed patients with depression or using stable doses of antidepressants to enroll

Objective

- Evaluate the effectiveness and safety of DM/Q treatment for PBA in patients who were using vs. not using antidepressants at baseline

Methods

Study Design

- PRISM II was an open-label, 90-Day, multicenter trial conducted in the United States (NCT01799941)
- All patients received DM/Q 20/10 mg twice daily (once daily during Week 1)
- Stable doses (≥2 months) of concomitant neuropsychiatric medications were allowed

Participants

- Adults with a clinical diagnosis of PBA[11] and a Center for Neurologic Study-Lability Scale (CNS-LS) score of ≥13[10]
- Diagnosis of dementia (AD or vascular, Lewy body, or frontotemporal dementia), stroke (ischemic or hemorrhagic, stable ≥3 months and non-evolving), or TBI (non-penetrating, stable ≥3 months)
- Patients with unstable or severe dementia (MiniMental State Examination [MMSE] score <10), severe depression, history of psychosis or bipolar disorder, unstable medical illness, DM/Q contraindication, or DM/Q use during the prior 6 months were excluded

Assessments

Efficacy

- Outcome measure assessments were performed at baseline, Day 30, and Day 90
  - Primary outcome:
    - Mean change from baseline to Day 90 (or final visit) in CNS-LS score (scale range, 7 [no symptoms] to 35 [maximum]), a patient-reported measure assessing PBA episode frequency and severity validated in ALS and MS[12,13]; not validated in dementia, stroke or TBI
  - Secondary outcomes:
    - Change in PBA episode count (past 7 days)
    - Impact of PBA episodes on quality of life (0 [not at all] to 10 [significantly]) on a visual analog scale (QOL-VAS)
      - 9-item Patient Health Questionnaire (PHQ-9) assessing prior 2-week frequency of depressive symptoms (0 [not at all] to 3 [nearly every day])
    - MMSE (assessment of cognition scored from 0 to 30, with lower scores indicating greater impairment)
- Caregivers could complete the efficacy measures for any participants who were unable, with the exception of MMSE

Safety

- Safety measures included adverse events (AEs) and vital signs
  - AEs were reported through 30 days following the last medication dose

Statistical Analysis

- The safety set included all patients who received ≥1 DM/Q dose
- The effectiveness analysis set included all safety set patients who met study eligibility criteria and had at least 1 post-baseline CNS-LS assessment
- All efficacy outcomes were analyzed descriptively
  - For rating scale measures (CNS-LS, QOL-VAS, MMSE, and PHQ-9), changes from baseline were analyzed inferentially using one-sample t-tests
  - Changes from baseline in PBA episode counts per week were estimated using a mixed-effects Poisson regression model (number of episodes in past 7 days was dependent variable)
  - Comparisons between antidepressant users and non-users for all outcomes were evaluated using an ANCOVA model with baseline score as covariate
  - All tests utilized the α=.05 level of significance
- For missing data, the patient's Final Visit data was included as the Day 90 visit (if there was no Final Visit, Day 30 was not carried forward as the patient's Final Visit)

Results

Baseline Demographics and Characteristics

- The patient demographic and baseline clinical characteristics are shown in **Table 1**
- Overall, 367 patients with PBA were enrolled; 134 (37%) had a diagnosis of dementia; 113 (31%) stroke, and 120 (33%) TBI
- Approximately half [178 (48.5%)] were taking antidepressants at baseline (**Figure 1**)

Figure 1. PRISM II Patient Cohorts

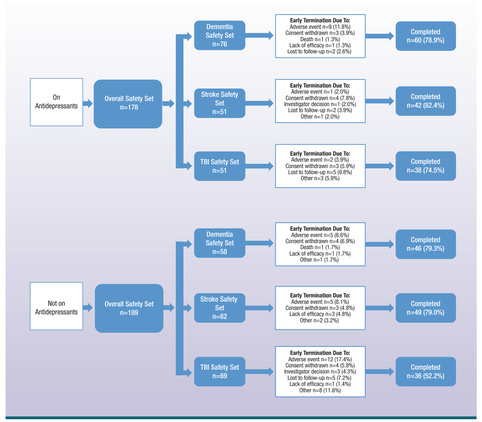


Table 1. Baseline Demographics and Clinical Characteristics—Safety Population

	On Antidepressants (n=178)	Not on Antidepressants (n=189)
Mean age, years (SD)	60.5 (16.0)	58.4 (17.0)
Male, n (%)	75 (42.1)	90 (47.6)
Race, n (%)		
White/Caucasian	156 (87.6)	148 (78.3)
Black/African American	20 (11.2)	30 (15.9)
Asian	1 (0.6)	2 (1.1)
Other*	0	4 (2.1)
Unknown	1 (0.6)	5 (2.6)
Concomitant Psychotropic Medications, n (%)		
Antipsychotics	41 (23.0)	25 (13.2)
Antidepressants	178 (100.0)	0
Non-selective	14 (7.9)	0
SSRI	103 (57.9)	0
Other	83 (46.6)	0
Sedative/Hypnotics	31 (17.4)	29 (15.3)
Anxiolytics	54 (30.3)	33 (17.5)
Any benzodiazepine†	67 (37.6)	42 (22.2)
Psychostimulants, (ADHD and nootropics)	10 (5.6)	10 (5.3)
Antidementia drugs	62 (34.8)	37 (19.6)
Antiepileptics	57 (32.0)	35 (18.5)
Mean CNS-LS score, (SD)‡	21.1 (4.7)	19.8 (3.9)
Mean PBA episode count (per week), (SD)§	24.6 (24.6)	18.0 (25.0)
Median PBA episode count (per week), (range)§	15.5 (0, 100)	10.0 (0, 240)
Mean MMSE score, (SD)‖	23.1 (6.2)	24.8 (5.4)
Mean QOL-VAS score, (SD)‡	6.4 (2.6)	5.4 (2.5)
Mean PHQ-9, (SD)‖	14.1 (5.6)	12.8 (6.1)

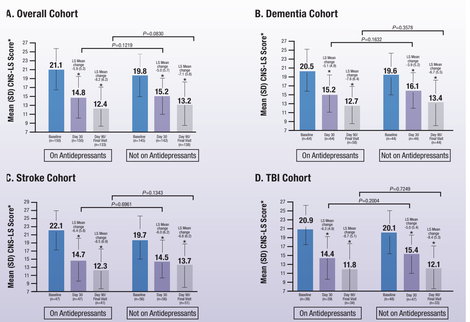
*Other includes American Indian, Alaskan Native, Native Hawaiian, or other Pacific Islander.
†Also includes clonazepam as an antiepileptic.
‡n=177 set; n=153 (on antidepressants); n=155 (not on antidepressants); and n=308 (overall population).
ADHD=attention deficit/hyperactivity disorder; CNS-LS=Center for Neurologic Study-Lability Scale; PHQ-9=Patient Health Questionnaire-9; QOL-VAS=quality of life visual analog scale; SD=standard deviation; SSRI=selective serotonin reuptake inhibitor.

Effectiveness Measures

Primary Outcome

- CNS-LS score improved significantly at Day 30 and 90 compared to baseline (all $P_{<}$.001) regardless of antidepressant use or neurological disease cohort
- The magnitude of improvement between antidepressant users and nonusers was not statistically different overall or by cohort, suggesting similar efficacy of DM/Q regardless of baseline antidepressant use (**Figure 2A-D**)

Figure 2. Mean CNS-LS Scores by Antidepressant Use at Baseline

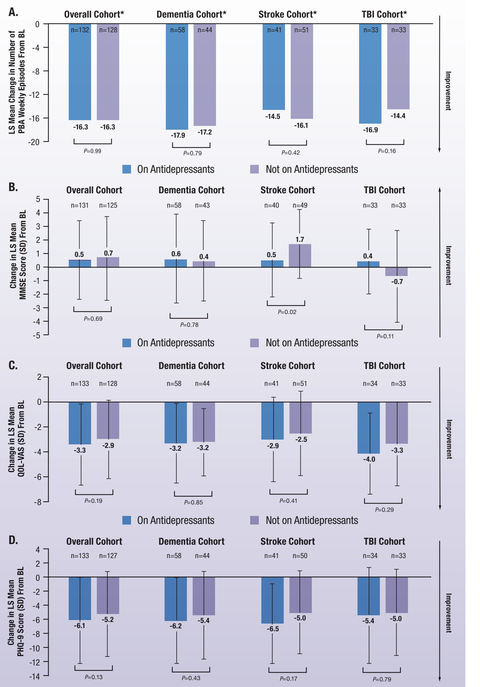


*Indicates $P_{<}$.001 vs. baseline CNS-LS score using one-sample t-test.
†P values between antidepressant use groups are based on the change in score from baseline using an ANCOVA model with baseline score as covariate.
CNS-LS=Center for Neurologic Study–Lability Scale; LS=least squares; SD=standard deviation.

Secondary Outcomes

- All secondary outcomes showed improvement with statistical differences from baseline (all $P_{<}$.0001) both overall and by disease cohort, with the exception of MMSE which showed small improvements that were significant for the overall group and stroke cohorts only
- There were no statistically significant differences between antidepressant users and nonusers for any secondary outcome, [with the exception that MMSE scores showed statistically greater improvement in antidepressant nonusers in the stroke group, that may be an anomalous finding and requires further study] suggesting DM/Q was effective regardless of baseline antidepressant use (**Figure 3A-D**)

Figure 3. Change From Baseline in PBA Episodes per Week, MMSE, QOL-VAS and PhQ-9 Scores by Antidepressant Use at Baseline



Statistical comparisons between subgroups performed by two-sample t-tests of change in score from baseline using ANCOVA model with baseline score as covariance.
*PBA episodes were estimated for the 7 days prior to each study visit. Analysis using a mixed effects Poisson regression model on PBA episode count controlling for antidepressant use also showed no significant effect of concomitant antidepressant use on episode count.
BL=baseline; LS=least squares; MMSE=mini-mental state exam; PHQ-9=Patient Health Questionnaire-9; PBA=pseudobulbar affect; QOL-VAS=quality of life-visual analogue scale; SD=standard deviation.

Safety

- The incidence of AEs in each cohort are summarized in **Table 2**
  - AEs were reported by 36.0% of overall patients; the most common AEs overall were diarrhea (5.4%), headache (4.1%), urinary tract infection (2.7%), and dizziness (2.5%) and AEs were mostly mild or moderate in severity
  - The incidence of AEs was too small to allow meaningful statistical between-group comparisons; the incidence of AEs appeared similar for antidepressant users/nonusers within each neurologic condition, with the exception that diarrhea was more frequently reported by antidepressant nonusers
  - Serious AEs occurred in 6.3% overall (dementia 10.4%; stroke 4.4%; TBI 3.3%), and were similar in frequency among antidepressant users (5.6%) vs nonusers (6.9%); no serious AE was considered related to DM/Q treatment
  - Overall 9.8% discontinued for AEs (dementia 11.9%; stroke 5.3%; TBI 11.7%), including 7.9% of antidepressant users vs. 11.6% of nonusers

Table 2. Summary of Adverse Events—Safety Population

Antidepressant Use	Dementia		Stroke		TBI	
	On Antidepressant n=76	Not on Antidepressant n=58	On Antidepressant n=51	Not on Antidepressant n=62	On Antidepressant n=51	Not on Antidepressant n=69
Any AE, n (%)	28 (36.8)	21 (36.2)	21 (41.2)	19 (30.6)	18 (35.3)	25 (36.2)
Mild	11 (14.5)	14 (24.1)	11 (21.6)	11 (17.7)	7 (13.7)	13 (18.8)
Moderate	21 (27.6)	7 (12.1)	12 (23.5)	10 (16.1)	5 (9.8)	17 (24.6)
Severe	6 (7.9)	3 (5.2)	1 (2.0)	3 (4.8)	4 (7.8)	5 (7.2)
Unknown	0	2 (3.4)	0	1 (1.6)	3 (5.9)	1 (1.4)
Most common AEs*, n (%)						
Diarrhea	2 (2.6)	3 (5.2)	1 (2.0)	4 (6.5)	2 (3.9)	8 (11.6)
Headache	6 (7.9)	4 (6.9)	4 (7.8)	0	0	1 (1.4)
Somnolence	3 (3.9)	0	0	1 (1.6)	0	1 (1.4)
Urinary tract infection	2 (2.6)	4 (6.9)	0	1 (1.6)	2 (3.9)	1 (1.4)
Dizziness	0	3 (5.2)	2 (3.9)	1 (1.6)	1 (2.0)	2 (2.9)
Serious AEs, n (%)	6 (7.9)	8 (13.8)	2 (3.9)	3 (4.8)	2 (3.9)	2 (2.9)
AEs leading to discontinuation, n (%)	10 (13.2)	6 (10.3)	1 (2.0)	5 (8.1)	3 (5.9)	11 (15.9)

*Occurring in ≥3 patients in any group.
AE=adverse event.

Conclusions

- Patients with PBA may suffer from concomitant psychiatric conditions and many are treated with psychotropic medications, including antidepressants
- The persistence of PBA symptoms and the common use of antidepressants in this study population, irrespective of the underlying neurological disorder, suggest antidepressants did not adequately treat PBA in these patients
- DM/Q therapy appeared effective in reducing PBA and depressive symptoms regardless of concomitant antidepressant use or causative neurologic condition
- DM/Q was generally well-tolerated in this trial and antidepressant use did not appear to have a negative impact on safety and tolerability measures
- Results of this analysis show that DM/Q may provide effective treatment of PBA regardless of prior or concomitant antidepressant use

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