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Neurological and Psychiatric Comorbidities Assessment in the PRISM II Study of Dextromethorphan/Quinidine for Treatment of Pseudobulbar Affect

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Abstract

INTRODUCTION: Pseudobulbar affect (PBA) can occur secondary to certain neurological diseases or brain injury and is characterized by frequent, uncontrollable laughing/crying episodes. While PBA is distinct from mood disorders in which feelings of happiness or sadness can also lead to laughing or crying, persons with PBA may often have psychiatric comorbidities (e.g., depression or anxiety). A recently completed study (PRISM II) evaluated the effectiveness of dextromethorphan/quinidine (DM/Q) for the treatment of PBA in persons with dementia, stroke and traumatic brain injury (TBI); we assessed the prevalence of comorbid neurological and psychiatric disorders among PRISM II patient cohorts.

METHODS: Patients with PBA secondary to either dementia, stroke, or TBI, with a Center for Neurologic Study–Lability Scale (CNS-LS) score ≥13 were enrolled and treated with DM/Q 20/10 mg BID, open-label for 90 days. Persons with severe dementia, stroke within ≤3 months, penetrating TBI, severe depressive disorders, or psychotic disorders were excluded. Concomitant medications for neuropsychiatric conditions were allowed provided doses were stable, and there were no contraindications to DM/Q use. Baseline assessments included PBA and depression ratings (CNS-LS, episode count and PHQ-9) concomitant diseases and medications.

RESULTS: A total of 367 patients were enrolled (n=120 TBI, n=113 stroke, n=134 dementia), 70.8% were receiving ≥1 psychiatric medication at baseline, most commonly antidepressants (48.5%), antipsychotics (17.7%) and sedatives/anxiolytics/hypnotics (33.8%). A total of 57.5% reported a depression diagnosis at baseline, including 61.7%, 50.4% and 59.7% of the TBI, stroke, and dementia populations, respectively; other reported CNS diagnoses included: anxiety disorders 42.2% (50.0% TBI, 36.3% stroke and 40.3% dementia, respectively); sleep disorders 34.1% (40.8%, 29.2%, and 32.1%); cognitive impairment 28.9% (25.8%, 18.6% and 40.3%); headache disorder 20.4% (37.5%, 15.9% and 9.0%); seizures 14.7% (17.5%, 16.8%, and 10.4%); and post-traumatic stress disorder 4.6% (13.3%, 0.9%, 0.0%). The baseline mean PHQ-9 score was 13.5 (13.9, 13.4, and 13.2, respectively), suggesting moderate depression.

CONCLUSIONS: Persons enrolling in this study of DM/Q for treatment of PBA subsequent to TBI, stroke or dementia often had other CNS comorbidities, most commonly, depression and anxiety disorders. These findings underscore the importance of considering both neurologic and psychiatric causes in the differential diagnosis of affective symptoms such as uncontrollable laughing and crying. The fact that over 70% of our study population were already being treated for psychiatric comorbidity suggests that specific PBA treatment may still be required.

Introduction

- Pseudobulbar affect (PBA) occurs secondary to certain neurologic diseases or injuries affecting the brain and is characterized by frequent, uncontrollable outbursts of laughing and/or crying that are excessive and/or disconnected to mood or social context[1-3]
- Such outbursts are often embarrassing, leading to social isolation and negatively impacting quality of life[1-3]
- Patients with PBA may have psychiatric comorbidities and many receive antidepressants or other neuropsychiatric treatments[5,6]; however, PBA often goes undiagnosed or may fail to be differentiated from other neuropsychiatric conditions[4]
- Dextromethorphan (DM) and quinidine (Q) in the fixed combination NUEDEXTA® (DM/Q) is currently the only FDA-approved treatment for PBA
- Controlled studies supporting DM/Q approval were conducted in patients with PBA secondary to ALS or MS[7,8,9]
- The open-label PRISM II trial provides additional DM/Q effectiveness data in patients with dementia, stroke, or TBI; PRISM II had less restrictive enrollment criteria than the Phase III trials, including patients with psychiatric comorbidities and those taking neuropsychiatric medications at stable doses

Objective

- Evaluate the prevalence of comorbid neurological and psychiatric disorders with PBA among PRISM II patient cohorts

Methods

Design

- Open-label, 90-day, US multicenter trial (NCT01799941)

Eligibility

- Clinical diagnosis of PBA and Center for Neurologic Study Lability Scale (CNS-LS) score ≥13
- Clinical diagnosis of dementia (AD, vascular, frontotemporal or Lewy body), stroke (ischemic or hemorrhagic), or TBI (non-penetrating) that was stable and not rapidly changing (≥3 months prior to baseline)
- No contraindications to DM/Q use, severe depression, severe dementia (Mini-Mental State Examination (MMSE) <10), psychotic disorder or substance abuse (last 3 years)
- Stable doses of neuropsychiatric medications (≥2 months) and anticholinesterases/memantine (≥6 weeks) were allowed

Treatment

- All patients received DM/Q 20/10 mg twice daily for 90 days (once daily during Week 1)

Outcomes

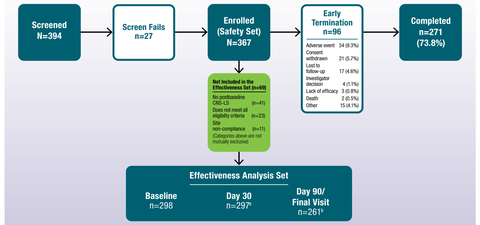
- Psychiatric comorbidities were obtained from the medical history in the study report
- The primary efficacy outcome was the change from baseline in CNS-LS score at Day 90/Final Visit[10]
  - The CNS-LS is an established PBA rating instrument (scale range 7 [no symptoms] to 35) validated in patients with MS and ALS[11,12] and used as an outcome in DM/Q Phase 3 trials[7,8,9]
- Secondary outcomes included PBA episode counts (assessed over the 7 days prior to a study visit) and the 9-item Patient Health Questionnaire (PHQ-9) an assessment of depressive symptoms with items rated (0 [not at all] to 3 [nearly every day]) over the prior 2-week period[13]
- Changes from baseline for the CNS-LS and PHQ-9 were analyzed inferentially using one-sample t-tests
- Adverse events (AE) were recorded through ≥30 days following last dose

Results

Participants

- 367 patients with PBA enrolled (134 with dementia, 113 with stroke, and 120 TBI)
  - 271 (73.8%) completed the study through Day 90 (**Figure 1**)
  - Most common reasons for discontinuation were AEs (9.3%) and withdrawal of consent (5.7%)

Figure 1. PRISM II Study Consort Diagram



[a]n=1 patient in the MITT did not have a Day 30 visit score (but did have a valid Day 90/Final visit score).
[b]n=37 patients in the MITT had no Day 90/Final Visit score.
CNS-LS=Center for Neurologic Study–Lability Scale. The safety set comprised all patients who received ≥1 DM/Q dose and included all enrolled patients. The effectiveness set comprised participants in the safety set with at least 1 post-baseline CNS-LS assessment who met all eligibility criteria.

- Baseline demographics and clinical characteristics are shown in **Table 1**; neurologic disease cohorts differed by age, and baseline cognition

Table 1. Baseline Demographics and Clinical Characteristics—Safety Analysis Set

Characteristic	Overall (n=367)	Dementia (n=134)	Stroke (n=113)	TBI (n=120)
Age, mean (SD), y	59.4 (16.5)	70.7 (12.1)	60.5 (12.2)	45.7 (14.1)
≥75 years, n (%)	75 (20.4)	58 (43.3)	14 (12.4)	3 (2.5)
Gender, n (%)				
Male	165 (45.0)	55 (41.0)	47 (41.6)	63 (52.5)
Female	202 (55.0)	79 (59.0)	66 (58.4)	57 (47.5)
Race, n (%)				
White/Caucasian	304 (82.8)	118 (88.1)	88 (77.9)	98 (81.7)
Black/African American	50 (13.6)	12 (9.0)	21 (18.6)	17 (14.2)
Asian	3 (0.8)	1 (0.7)	2 (1.8)	-
Other*	4 (1.1)	-	2 (1.8)	2 (1.7)
Unknown	6 (1.6)	3 (2.2)	-	3 (2.5)
Ethnicity, n (%)				
Hispanic/Latino	71 (19.4)	34 (25.4)	26 (23.0)	11 (9.2)
Place of Residence, n (%)				
Home	303 (82.6)	87 (64.9)	101 (89.4)	115 (95.8)
Assisted living	35 (9.5)	31 (23.1)	4 (3.5)	-
Skilled nursing facility	29 (7.9)	16 (11.9)	8 (7.1)	5 (4.2)
Overall MMSE score, mean (SD)[†§]	23.9 (5.9)	20.2 (5.6)	24.9 (5.7)	27.3 (3.6)

*Other includes American Indian, Alaskan Native, Native Hawaiian, or other Pacific Islander. †Based upon effectiveness analysis set (n=298). ‡MMSE ranges from 0-30 with higher scores indicating increasing cognitive impairment.
MMSE=Mini-Mental State Examination; SD=standard deviation; TBI=traumatic brain injury.

- In the safety population, approximately 90% of patients had other recorded CNS disorders at baseline, with a slightly lower percentage among the stroke cohort (**Table 2**)
- At baseline, psychotropic medications were used by 70.8% of patients in the overall safety population; antidepressants were used by 48.5% of patients across all cohorts (**Table 2**)

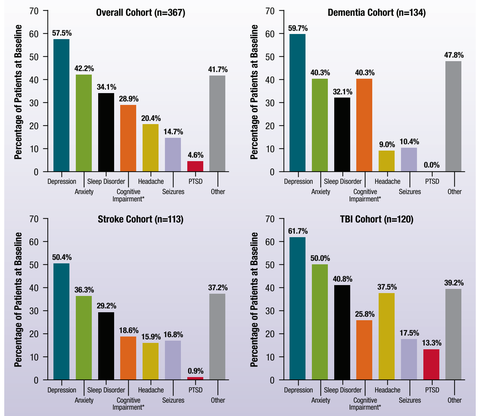
Table 2. Baseline CNS Disorders and Concomitant CNS Medication Use

	Overall (n=367)	Dementia (n=134)	Stroke (n=113)	TBI (n=120)
Any CNS Disorder, n (%)	325 (88.6)	124 (92.5)	90 (79.6)	111 (92.5)
Concomitant medications at baseline				
Mean	8.4	9.3	9.2	6.5
Median (min, max)	7.0 (0, 27)	8.0 (0, 27)	9.0 (0, 23)	5.5 (0, 23)
Concomitant psychiatric or anti-dementia medication use, n (%)				
Any psychotropic medication[a]	260 (70.8)	109 (81.3)	67 (59.3)	84 (70.0)
Anticonvulsants	92 (25.1)	31 (23.1)	26 (23.0)	35 (29.2)
Antidepressants	178 (48.5)	76 (56.7)	51 (45.1)	51 (42.5)
Antipsychotics	65 (17.7)	39 (29.1)	9 (8.0)	17 (14.2)
Sedative/hypnotic/anxiolytics	124 (33.8)	48 (35.8)	30 (26.5)	46 (38.3)
Benzodiazepines[b]	109 (29.7)	47 (35.1)	25 (22.1)	37 (30.8)
Anti-dementia drugs	99 (27.0)	73 (54.5)	16 (14.2)	10 (8.3)

[a]Psychotropic medications include: antiepileptics (anticonvulsants), antipsychotics, antidepressants, sedatives/hypnotics or anxiolytics, and benzodiazepines.
[b]Also includes clonazepam as an anticonvulsant.
CNS=central nervous system; TBI=traumatic brain injury.

- Depression (57.5%) and anxiety disorders (42.2%) in overall cohort were the most commonly reported (>40%) neuropsychiatric comorbidities (**Figure 2**)
- Sleep disorders, cognitive impairment and headache were also commonly reported across cohorts; headache and PTSD were most frequent in the TBI cohort. Seizure disorders were reported by 14.7%, most commonly in the stroke and TBI cohorts (**Figure 2**)

Figure 2. PRISM II: CNS Comorbidities in Patients Overall and by Disease Cohort—Safety Set

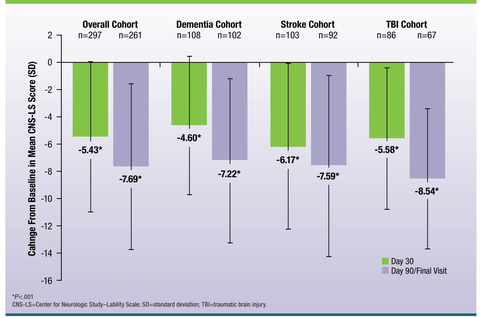


*Noted as an additional diagnosis.
CNS=central nervous system; PTSD=post-traumatic stress disorder; TBI=traumatic brain injury.

Primary Endpoint

- CNS-LS scores improved significantly at Day 30 and 90 compared with baseline (all *P*<.001), regardless of neurological disease cohort (**Figure 3**)

Figure 3. PRISM II Primary Outcome: Improvement in CNS-LS Score—Effectiveness Set

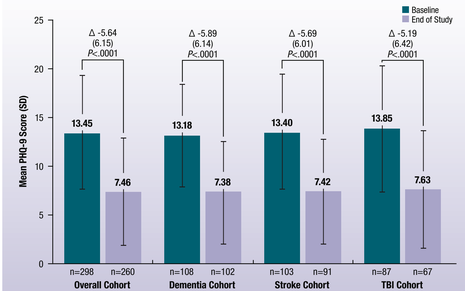


*P<.001
CNS-LS=Center for Neurologic Study–Lability Scale; SD=standard deviation; TBI=traumatic brain injury.

Secondary Endpoints

- PBA episode counts were significantly reduced from baseline at Day 90 in the overall cohort and the individual disease cohorts (overall cohort: 72.3% reduction; dementia: 67.7%; stroke: 74.5%; TBI: 78.5%; all *P*<.0001)
- The 9-item Patient Health Questionnaire showed moderate depressive symptoms at baseline across all cohorts (**Figure 4**)
- Mean PHQ-9 scores improved at Day 90 with statistical difference from baseline (all *P*<.0001) both overall and by disease cohort (**Figure 4**)

Figure 4. PHQ-9 at Baseline and Endpoint—Effectiveness Set



PHQ-9=9-Item Patient Health Questionnaire-9; SD=standard deviation; TBI=traumatic brain injury.

Safety Measures

- A summary of safety outcomes is shown in **Table 2**

Table 3. Summary of Adverse Events—Safety Population

	Overall (n=367)	Dementia Cohort (n=134)	Stroke Cohort (n=113)	TBI Cohort (n=120)
Any AE	132 (36.0)	49 (36.6)	40 (35.4)	43 (35.8)
Mild	67 (18.3)	25 (18.7)	22 (19.5)	20 (16.7)
Moderate	72 (19.6)	28 (20.9)	22 (19.5)	22 (18.3)
Severe	22 (6.0)	9 (6.7)	4 (3.5)	9 (7.5)
Unknown	7 (1.9)	2 (1.5)	1 (0.9)	4 (3.3)
Most common AEs[a]				
Diarrhea	20 (5.4)	5 (3.7)	5 (4.4)	10 (8.3)
Headache	15 (4.1)	10 (7.5)	4 (3.5)	1 (0.8)
Urinary tract infection	10 (2.7)	6 (4.5)	1 (0.9)	3 (2.5)
Dizziness	9 (2.5)	3 (2.2)	3 (2.7)	3 (2.5)
Serious AEs	23 (6.3)	14 (10.4)	5 (4.4)	4 (3.3)
Treatment-related AEs	55 (15.0)	16 (11.9)	16 (14.2)	23 (19.2)
Treatment-related serious AEs	0	0	0	0
AEs leading to discontinuation	36 (9.8)	16 (11.9)	6 (5.3)	14 (11.7)

[a]Occurring in ≥2% patients in Overall Group.
AE=adverse event.

Conclusions

- The majority of patients in this study of DM/Q for treatment of PBA secondary to TBI, stroke, or dementia had psychiatric comorbidities, most commonly, depression and anxiety disorders, and were taking concomitant psychiatric medications, including antidepressants, antipsychotics and sedatives/anxiolytics/hypnotics
- These findings underscore the importance of careful neurologic and psychiatric evaluation and treatment of patients with PBA secondary to neurologic diseases or injuries
- In this study, DM/Q was shown to be effective for treating PBA, even in patients with clinically significant symptoms of PBA, despite concomitant treatment with commonly used psychiatric medications, which suggests that a more specific treatment may still be required
- Concomitant use of DM/Q with commonly used psychiatric medications, including serotonergic antidepressants, by the majority of patients evaluated in this study, was generally safe and well-tolerated

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