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Dextromethorphan/Quinidine for Treatment of Pseudobulbar Affect in Patients With Dementia: Examination of CNS-LS Outcomes in a 12-Week Open-Label Trial (PRISM II)

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Introduction

- Pseudobulbar affect (PBA) is characterized by frequent, uncontrollable episodes of crying and/or laughing that are exaggerated or incongruous with mood or social context[1,2]
- PBA occurs when neurologic diseases or brain injuries damage neuronal pathways coordinating expression of affect[1–3]
- PBA episodes are disruptive, are often distressing, impair social function and quality of life (QOL), and may contribute to nursing home placement[1,2,4]
- Results of prevalence surveys suggest that approximately 6% to 10% of patients with Alzheimer's disease or other dementias have moderate to severe symptoms of PBA; however, PBA often goes unrecognized and may be mistaken for depression or other psychiatric condition[2,3,5,6]
- Dextromethorphan hydrobromide and quinidine sulfate (DM/Q; NUEDEXTA®) is the only treatment approved for PBA (FDA and EMA); approval was based on efficacy in patients with PBA secondary to amyotrophic lateral sclerosis (ALS) or multiple sclerosis (MS)[7-9]
- This study (PRISM II) was conducted to provide additional DM/Q effectiveness, safety, and tolerability data in patient cohorts with PBA secondary to stroke, traumatic brain injury, or dementia
- Final results from the dementia cohort have been previously presented[10]; we report here an additional analysis of the item distribution and response of the Center for Neurologic Study—Lability Scale (CNS-LS) scores, the primary effectiveness measure

Methods

Study Design

- Open-label, multicenter (~120 US sites), 12-week trial (NCT01799941)

Eligibility

- Adults with a clinical diagnosis of PBA[11] and baseline CNS-LS[12,13] score ≥13
- Clinical dementia diagnosis (Mini Mental State Examination [MMSE] score ≥10)
- Stable doses (≥6 weeks) of dementia medications (memantine/cholinesterase inhibitors) or other neuropsychiatric medications (≥2 months) were allowed
- No history of psychosis or delirium or contraindications to DM/Q; medical/neurologic condition stable and not rapidly changing

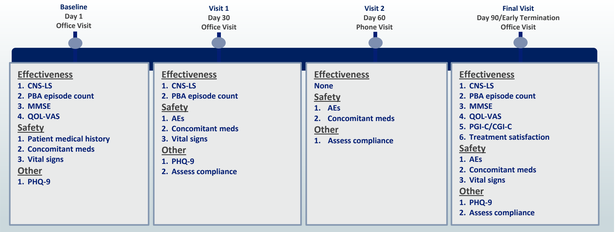
Treatment

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

Assessments

- Study visits and measures are shown in **Figure 1**. Caregivers completed ratings as proxies for patients who were unable (except for MMSE)

Figure 1. Study Visits and Outcome Measures



AE=adverse event; CGI-C=Clinical Global Impression of Change; CNS-LS=Center for Neurologic Study-Lability Scale; MMSE=Mini-Mental State Examination; PBA=pseudobulbar affect; PGI-C=Patient Global Impression of Change; PHQ-9=Patient Health Questionnaire-9; QOL-VAS=quality-of-life visual analog scale.

Statistical Analysis

- Primary analysis: Change from baseline in CNS-LS (1-sample *t*-test) for the effectiveness population that included patients meeting eligibility criteria with postbaseline CNS-LS
  - The CNS-LS (**Figure 2**) is an established PBA rating instrument (range, 7–35) validated in patients with MS and ALS[11,12] and used as an outcome measure in DM/Q phase 3 trials[7–9]
  - A planned analysis also compared the change in CNS-LS score in PRISM II with DM/Q pivotal phase 3 trial[9]
- This post-hoc exploratory analysis compares: change from baseline in CNS-LS Labile Laughter (CNS-LS-L) score (4 items, range 4–20), CNS-LS Labile Crying (CNS-LS-C) score (3 items, range 3–15), and the 7 individual CNS-LS item scores

Figure 2. CNS-LS[13]

Instructions: Using the scale below, please write the number that describes the degree to which each item applies to you *DURING THE PAST WEEK*. Write only one number for each item.

Applies never	Applies rarely	Applies occasionally	Applies frequently	Applies most of the time
1	2	3	4	5

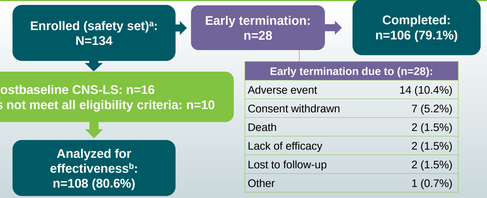
Assessment questions	Answer
1. There are times when I feel fine one minute and then I'll become tearful the next over something small or for no reason at all.	
2. Others have told me that I seem to become amused very easily or that I seem to become amused about things that really aren't funny.	
3. I find myself crying very easily.	
4. I find that even when I try to control my laughter, I am often unable to do so.	
5. There are times when I won't be thinking of anything happy or funny at all, but then I'll suddenly be overcome by funny or happy thoughts.	
6. I find that even when I try to control my crying, I am often unable to do so.	
7. I find that I am easily overcome by laughter.	
Total Score:	__

Results

Patient Disposition and Baseline Characteristics

- 134 patients with PBA and dementia were evaluated for safety; 108 (81%) were included in effectiveness analyses; 106 (79%) completed the trial (**Figure 3**)
- Patient characteristics are shown in **Table 1**

Figure 3. PRISM II Patient Disposition



Early termination due to (n=28):	
Adverse event	14 (10.4%)
Consent withdrawn	7 (5.2%)
Death	2 (1.5%)
Lack of efficacy	2 (1.5%)
Lost to follow-up	2 (1.5%)
Other	1 (0.7%)

[a]Safety analysis set consisted of all enrolled patients who received ≥1 dose of DM/Q.
[b]The effectiveness analysis set includes patients who received ≥1 dose of DM/Q, had ≥1 postbaseline CNS-LS measurement, and met all eligibility criteria.
CNS-LS=Center for Neurologic Study-Lability Scale.

Table 1. Patient Characteristics—Safety Population (N=134)

Characteristic	n (%)	Characteristic	n (%)
Age		Type of dementia	
Mean, years (SD)	71 (12)	Alzheimer's disease	86 (64)
≥75 years, n (%)	58 (43)	Vascular dementia	21 (16)
Gender		Frontotemporal lobe dementia	12 (9)
Male	55 (41)	Lewy body dementia	5 (4)
Female	79 (59)	Other[a]	10 (7)

[a]Other dementia included dementia due to multiple sclerosis (n=4), Parkinson's disease (n=1), alcohol-induced (n=1), brain cell deterioration (n=1), subcortical (n=1), unspecified (n=1), and mild cognitive impairment (n=1). SD=standard deviation.

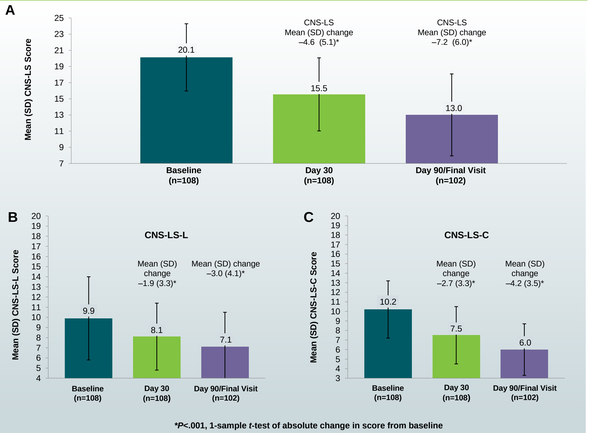
CNS-LS: Overall and Laughing/Crying Sub-scores

- Mean (SD) CNS-LS score reduction (i.e., improvement) was significant at Day 30 and Day 90/Final Visit (*P*<.001 for both; **Figure 4A**) compared with baseline
- The mean CNS-LS [SD] reduction from baseline (–7.2 [6.0]) was consistent with that seen for DM/Q in the phase 3 pivotal trial (–8.2 [6.1]) and represents improvement over the change in the placebo group from that trial (–5.7 [5.3])[9]
- Significant improvement from baseline was seen for both CNS-LS laughing and crying subscores at Day 30 and Day 90/Final Visit (*P*<.001 for all; **Figure 4B and 4C**)
- Mean (SD) baseline CNS-LS scores were higher for the 3 item CNS-LS-C (10.2 [3.0]) than for the 4 item CNS-LS-L (9.9 [4.1]), indicating that pathologic crying symptoms were more common than pathologic laughing symptoms

CNS-LS: Individual Item Scores

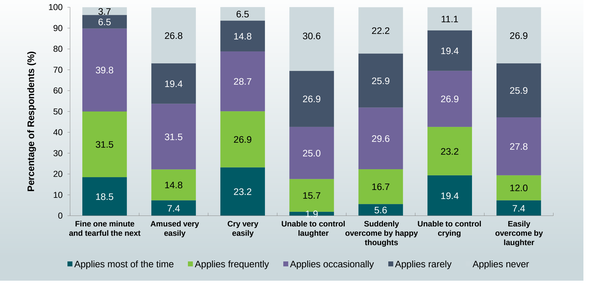
- The distribution of baseline CNS-LS Item scores is presented in **Figure 5**
- All individual CNS-LS item scores improved significantly from baseline to Day 90/Final Visit (*P*<.001; **Figure 6**), with largest reductions for those items with higher baseline scores

Figure 4. Primary Outcome, Change in CNS-LS Score (A) and Change in CNS-LS Laughing (CNS-LS-L) Subscore (B) and Crying (CNS-LS-C) Subscore (C)



CNS-LS scores range from 7 to 35, with higher scores indicating increased frequency and severity of PBA episodes. CNS-LS-L scores range from 4 to 20 and CNS-LS-C scores range from 3 to 15, with higher scores indicating increased frequency and severity.
PBA=pseudobulbar affect; CNS-LS=Center for Neurologic Study–Lability Scale; SD=standard deviation.

Figure 5. Distribution of Responses to CNS-LS Items at Baseline (n=108)

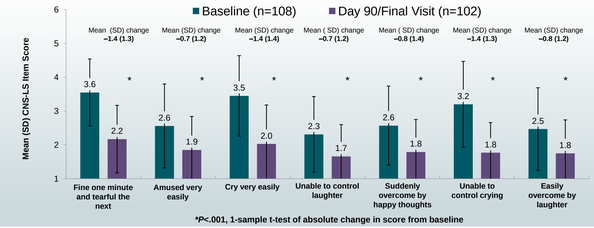


Percentages within an item may not sum to 100 due to rounding.
CNS-LS=Center for Neurologic Study–Lability Scale.

Secondary Outcomes

- Reduction in CNS-LS was consistent with reduction in PBA episode counts. Median (range) PBA episodes per week decreased from 21 (0, 90) at baseline to 6 (0, 77) at Day 30 and 3 (0, 80) at Day 90/Final Visit
- Estimated PBA weekly episode counts were reduced by 50.2% at Day 30 and 67.7% at Day 90/Final Visit vs baseline (*P*<.001 for both; mixed-effects Poisson regression model)
- 77% and 76% of patients were deemed to be "much improved" or "very much improved" with respect to PBA symptoms, based on clinician CGI-C, and patient or caregiver PGI-C ratings, respectively

Figure 6. Change in CNS-LS Individual Item Scores



CNS-LS item scores each range from 1 to 5, with higher scores indicating increased frequency and severity of PBA episodes.
CNS-LS=Center for Neurologic Study–Lability Scale; SD=standard deviation.

Safety

- 49 (36.6%) patients reported ≥1 adverse event (AE; **Table 2**); most were mild to moderate in intensity
- AEs were considered at least possibly related to DM/Q treatment in 16 (11.9%) patients
- Serious AEs occurred in 14 (10.4%) patients; none were considered treatment related by clinical investigators
- AEs led to study discontinuation in 16 (11.9%) patients

Table 2. AEs Occurring in ≥2% Patients

AE Category, n (%)	Safety Population (n=134)
Headache	10 (7.5)
Urinary tract infection	6 (4.5)
Diarrhea	5 (3.7)
Nausea	3 (2.2)
Fall	3 (2.2)
Dizziness	3 (2.2)
Somnolence	3 (2.2)

AE=adverse event.

Conclusions

- PRISM II is the first clinical trial of PBA treatment in patients with dementia
- Patients with dementia who were taking DM/Q experienced significantly reduced PBA symptoms of both uncontrollable laughing and uncontrollable crying over this 12-week open-label trial
- Improvement in the CNS-LS (including overall score, laughing and crying sub-scores, and individual CNS-LS item scores) was accompanied by reductions in the number of PBA episodes/week and global improvements (PGI-C/CGI-C)
- DM/Q appeared well tolerated in this largely elderly population with dementia, with low rates of treatment-related AEs; AEs were consistent with DM/Q prescribing information
- Despite open-label limitations, reduction in overall CNS-LS scores were similar to that observed in the DM/Q phase 3 pivotal trial in patients with PBA secondary to ALS or MS, supporting the CNS-LS as a metric for assessing PBA symptoms and the effectiveness of DM/Q in PBA secondary to dementing conditions

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