Sublingual Dexmedetomidine Demonstrates Significant Reduction in Agitation Across Baseline Severity in Patients With Bipolar Disorders

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INTRODUCTION

Sublingual dexmedetomidine is an orally dissolving film formulation of dexmedetomidine, a selective alpha-2 adrenergic receptor agonist. Acute agitation in individuals with bipolar disorders requires urgent management to relieve distress and to prevent escalation.[1] Previously, a single 120 mcg or 180 mcg dose of sublingual dexmedetomidine was effective at reducing agitation in adults with mild or moderate agitation associated with bipolar disorder I or II.[2]

OBJECTIVE

Evaluate the efficacy of a single 180 mcg or 120 mcg dose of sublingual dexmedetomidine in adults with baseline mild-moderate or severe symptoms of acute agitation associated with bipolar disorder I or II.

METHODS

Design

Post hoc analysis of a Phase 3, randomized, placebo-controlled study

Subjects

Adults (18-75) diagnosed with DSM-5 bipolar I or II

Stratified by baseline agitation, as measured by total score on the Positive and Negative Syndrome Scale (PANSS)-Excited Component (PEC)

- Mild-moderate (14-19)
- Severe (>19)

Treatment

Single-dose of self-administered sublingual dexmedetomidine 180 mcg or 120 mcg, or matching placebo

Primary Endpoint

Mean change from baseline on **PEC Scale** total score at 2 hours after the first dose

5 PEC Items

1. Poor impulse control
2. Tension
3. Hostility
4. Uncooperativeness
5. Excitement

7-point Scale

1=minimum 7=maximum

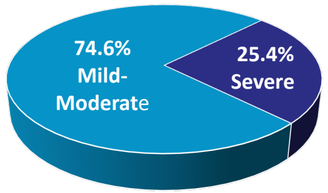
Total Score

Sum of the 5 item scores (range 5-35)

RESULTS

Subjects

Of the 378 subjects who received study drug, 282 (74.6%) had mild-moderate agitation and 96 (25.4%) had severe agitation at baseline.



Compared with the mild-moderate agitation group, subjects in the severe agitation group were more likely to be male (56% vs 41%) and Black (67% vs 52%) and to have mania (54% vs 45%); they also reported slightly longer current agitation (22.0 vs 20.5 days) and more hospitalizations (3.8 vs 2.8).

Primary Endpoint: Mean Change from Baseline in PEC Total Score at 2 Hours Postdose in Subjects With Mild-Moderate or Severe Agitation at Baseline

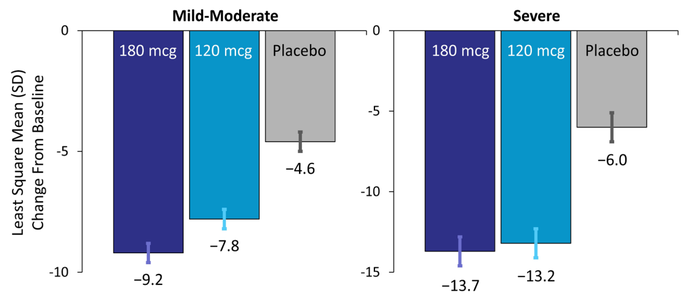
In the **mild-moderate group,** least square mean 2-hour change from baseline PEC scores were −9.2 for sublingual dexmedetomidine 180 mcg, −7.8 for sublingual dexmedetomidine 120 mcg, and −4.6 for placebo.

In the **severe group**, least square mean 2-hour change from baseline PEC scores were −13.7 for sublingual dexmedetomidine 180 mcg, −13.2 for sublingual dexmedetomidine 120 mcg, and −6.0 for placebo.

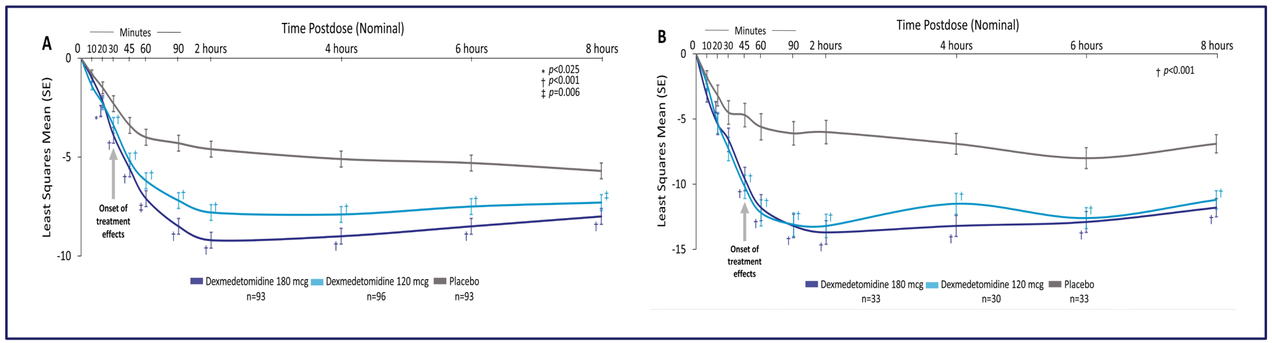
Both doses of sublingual dexmedetomidine were significantly different from placebo (*P*<.001).

Significant separation from placebo was evident as early as 30 minutes postdose in the **mild-moderate baseline agitation** group and as early as 45 minutes postdose in the **severe baseline agitation** group.

The separation from placebo was maintained in both groups through 8 hours for both doses of sublingual dexmedetomidine.



Change from Baseline in PEC Total Score Through 8 Hours Postdose in Subjects With Mild-Moderate (A) or Severe (B) Agitation at Baseline



Adverse Events

There were no serious or severe treatment-related adverse events.

The most commonly reported adverse events in the sublingual dexmedetomidine treated groups were:

Mild-Moderate Baseline: Somnolence (15.9%) Dizziness (4.8%), Dry Mouth (4.2%), Headache (2.1%), Hypotension (2.1%), Oral Hypoesthesia (2.1%)

Severe Baseline Agitation: Somnolence (4.8%), Headache (3.2%), Hypotension (3.2%), Nausea (3.2%), Oral Hypoesthesia (1.6%), Oral Paresthesia (1.6%)

KEY FINDINGS

In this post hoc analysis of Phase 3 clinical trial data, 2-hour PEC change scores were stratified by baseline PEC agitation severity: mild-moderate (14-19) and severe (>19)

Sublingual dexmedetomidine significantly reduced acute agitation in adults with bipolar disorders at 2 hours in patients with either mild-moderate or severe agitation at baseline

Rates of treatment-emergent adverse event reporting were lower in the group with baseline PEC scores in the severe range compared to those in the mild-moderate range

The most commonly reported adverse events in the baseline mild-moderate group were somnolence, dizziness, dry mouth, headache, hypotension and oral hypoesthesia and somnolence, headache, hypotension, and nausea in the baseline severe group.

Demographics and Baseline Characteristics

	Mild-Moderate Agitation n=282	Severe Agitation n=96	Total Population N=378
Age, years, mean (SD)	46.1 (11.4)	44.2 (12.1)	45.6 (11.6)
BMI, kg/m², mean (SD)	31.7 (7.2)	34.7 (9.8)	32.5 (8.1)
Sex, n (%)			
Female	165 (59)	42 (44)	207 (55)
Male	117 (41)	54 (56)	171 (45)
Race, n (%)			
Black	148 (52)	64 (67)	212 (56)
White	124 (44)	31 (32)	155 (41)
Other	10 (4)	1 (1)	11 (3)

	Mild-Moderate Agitation n=282	Severe Agitation n=96	Total Population N=378
Diagnosis, n (%)			
Depressed	61 (22)	13 (14)	74 (20)
Hypomania	23 (8)	6 (6)	29 (8)
Mania	128 (45)	52 (54)	180 (48)
Mixed episodes	55 (20)	24 (25)	79 (21)
Unspecified	15 (5)	1 (1)	16 (4)
Current agitation, days, mean (SD)	20.5 (53.6)	22.0 (27.6)	20.9 (48.3)
Sleep, hours this week, mean (SD)	5.3 (1.5)	4.8 (1.6)	5.2 (1.6)
Hospitalizations, n, mean (SD)	2.8 (4.2)	3.8 (4.5)	3.0 (4.3)

Adverse Events

	Moderate n=282 (74%)				Severe n=96 (26%)			
	180 mcg n=93	120 mcg n=96	Placebo n=93	Total N=282	180 mcg n=33	120 mcg n=30	Placebo n=30	Total N=96
Any TEAE, n (%)	36 (38.7)	37 (38.5)	15 (16.1)	88 (31.2)	9 (27.3)	7 (23.3)	7 (21.2)	23 (24.0)
Any related TEAE, n (%)	32 (34.4)	36 (37.5)	10 (10.8)	78 (27.7)	7 (21.2)	5 (16.7)	5 (15.2)	17 (17.7)
TEAE severity, n (%)								
Mild AEs	23 (24.7)	29 (30.2)	13 (14.0)	65 (23.0)	7 (21.2)	6 (20.0)	6 (18.2)	19 (19.8)
Moderate AEs	13 (14.0)	8 (8.3)	2 (2.2)	23 (8.2)	2 (6.1)	1 (3.3)	1 (3.0)	4 (4.2)
Severe AEs	0	0	0	0	0	0	0	0

References 1. Citrome L. *Ther Clin Risk Manag.* 2013;9:235-245; 2. Preskorn SH et al. *JAMA*. 2022;327:727-736.

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