Number Needed to Treat (NNT) and Number Needed to Harm (NNH) from Two Phase 3 Studies of Sublingual Dexmedetomidine for Treating Acute Agitation in Patients with Schizophrenia and Bipolar Disorder

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INTRODUCTION

- Sublingual dexmedetomidine is an orally dissolving film formulation of dexmedetomidine, a selective alpha$_2$ adrenergic receptor agonist
- It is approved for sublingual or buccal administration for the treatment of adults with acute agitation associated with schizophrenia or bipolar disorder I or II
- In Phase 3 studies, sublingual dexmedetomidine significantly reduced acute agitation in adults with schizophrenia or bipolar disorder at 2 hours postdose, on the Positive and Negative Syndrome Scale-Excited Component (PEC)
- Number Needed to Treat and Number Needed to Harm can facilitate formulary and prescribing decisions[1] during new drug evaluations
- In general, medications with a low NNT (≥10% better than placebo resulting in an NNT <10) and a high NNH (no more than a 10% disadvantage, resulting in an NNH >10) are preferred

OBJECTIVE: Calculation of NNT and NNH through post hoc analysis of Phase 3 data using the metrics of Number Needed to Treat (NNT) and Number Needed to Harm (NNH)[2]

METHODS

Design: Post hoc analysis of data from two phase 3 studies in adults with schizophrenia or bipolar disorder experiencing acute agitation[3-5]

Participants: Adults (18-75) diagnosed with DSM-5 schizophrenia, schizoaffective disorder, or bipolar disorder I or II

Treatment: Participants self-administered 1 dose of sublingual dexmedetomidine 180 mcg, 120 mcg, or placebo

Primary Endpoint

Mean change from baseline on total score on the Positive and Negative Syndrome Scale (PANSS)-Excited Component (PEC)[6] at 2 hours postdose

Therapeutic response defined as ≥40% reduction in PEC total at 2 hours. NNT was calculated as 1/absolute risk reduction for PEC response rate versus placebo. NNH was determined from the incidence of adverse events versus placebo.

Secondary Endpoint: Earliest time of a statistically significant separation from placebo on the PEC

PEC Scale

5 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)

Participants in This Analysis

≥14 PEC total score
≥4 on at least 1 PEC item

Participant Demographics and Baseline Characteristics

	Sublingual Dexmedetomidine		
	180 mcg (n=251)	120 mcg (n=255)	Placebo (n=252)
Age, years, mean (SD)	45.9 (11.6)	45.9 (11.4)	45.0 (11.6)
Age range, years	18, 71	19, 70	18, 68
Gender, self-identified, n (%)			
Female	110 (44)	119 (47)	117 (46)
Male	141 (56)	136 (53)	135 (54)
Race, self-identified, n (%)			
Black or African American	174 (69)	160 (63)	174 (69)
White	70 (28)	89 (35)	71 (28)
Other[a]	7 (3)	6 (2)	7 (3)
Body mass index, kg/m^2, mean (SD)	32.9 (8.3)	31.4 (7.8)	32.5 (7.4)
Number of hospitalizations, mean (SD)	3.6 (7.6)	4.1 (5.1)	3.4 (4.5)
Hours of sleep/night this week, mean (SD)	5.3 (1.6)	5.6 (1.7)	5.4 (1.7)
Current smoker, n (%)	160 (64)	193 (76)	185 (73)
PEC total score, mean (SD)	17.8 (2.9)	17.7 (2.6)	17.8 (2.6)

CGI, Clinical Global Impressions, severity of illness rated on a 7-point scale from 1 (normal) through to 7 (among the most severely ill patients); PEC, Positive and Negative Syndrome Scale-Excited Component, comprised of 5 items with a range of 5 (absence of agitation) to 35 (extremely severe); SD, standard deviation.
[a]Includes Native American, Alaska Native, Asian, Native Hawaiian or other Pacific Islander, and Multiple.

Table 1. PEC Response, Absolute Risk Reduction, & Number Needed to Treat in Pooled Participants with Schizophrenia or Bipolar Disorder

	PEC Response[a] n (%)				Absolute Risk Reduction[b] %, (95% CI)			Number Needed to Treat (95% CI)		
	Sublingual Dexmedetomidine			Placebo	Sublingual Dexmedetomidine			Sublingual Dexmedetomidine		
Time postdose	180 mcg n=251	120 mcg n=255	120 or 180 mcg n=506	n=252	180 mcg n=251	120 mcg n=255	120 or 180 mcg n=506	180 mcg n=251	120 mcg n=255	120 or 180 mcg n=506
10 min	30 (12.0)*	22 (8.6)	52 (10.3)*	14 (5.6)	6.4 (1.5, 11.3)	3.1 (−1.4, 7.5)	4.7 (.8, 8.6)	16 (9, 68)	33 (ns)[c]	22 (12, 118)
20 min*	72 (28.7)	53 (20.8)	125 (24.7)	33 (13.1)	15.6 (8.6, 22.6)	7.7 (1.2, 14.2)	11.6 (6.0, 17.2)	7 (5, 12)	14 (8, 84)	9 (6, 17)
30 min*	106 (42.2)	94 (36.9)	200 (39.5)	64 (25.4)	16.8 (8.7, 25.0)	11.5 (3.5, 19.5)	14.1 (7.3, 21.0)	6 (5, 12)	9 (6, 29)	8 (5, 14)
45 min*	152 (60.6)	131 (51.4)	283 (55.9)	83 (32.9)	27.6 (19.2, 36.0)	18.4 (10.0, 26.9)	23.0 (15.8, 30.2)	4 (3, 6)	6 (4, 11)	5 (4, 7)
1 hr*	186 (74.1)	170 (66.7)	356 (70.4)	95 (37.7)	36.4 (28.3, 44.5)	29.0 (20.6, 37.3)	32.7 (25.5, 39.8)	3 (3, 4)	4 (3, 5)	4 (3, 4)
1.5 hrs*	217 (86.5)	187 (73.3)	404 (79.8)	99 (39.3)	47.2 (39.8, 54.5)	34.0 (25.9, 42.2)	40.6 (33.6, 47.5)	3 (2, 3)	3 (3, 4)	3 (3, 3)
2 hrs*	**225 (89.6)**	**199 (78.0)**	**424 (83.8)**	**109 (43.3)**	**46.4 (39.2, 53.6)**	**34.8 (26.8, 42.7)**	**40.5 (33.6, 47.4)**	**3 (2, 3)**	**3 (3, 4)**	**3 (3, 3)**
4 hrs*	219 (87.3)	178 (69.8)	397 (78.5)	100 (39.7)	47.6 (40.3, 54.9)	30.1 (21.9, 38.4)	38.8 (31.8, 45.8)	3 (2, 3)	4 (3, 5)	3 (3, 4)
6 hrs*	221 (88.0)	187 (73.3)	408 (80.6)	112 (44.4)	43.6 (36.3, 50.9)	28.9 (20.7, 37.1)	36.2 (29.2, 43.2)	3 (2, 3)	4 (3, 5)	3 (3, 4)
8 hrs*	223 (88.8)	185 (72.5)	408 (80.6)	131 (52.0)	36.9 (29.6, 44.2)	20.6 (12.3, 28.8)	28.6 (21.6, 35.7)	3 (3, 4)	5 (4, 9)	4 (3, 5)
24 hrs*	147 (58.6)	135 (52.9)	282 (55.7)	86 (34.1)	24.4 (16.0, 32.9)	18.8 (10.3, 27.3)	21.6 (14.3, 28.9)	5 (4, 7)	6 (4, 10)	5 (4, 7)

PEC, Positive and Negative Syndrome Scale-Excited Component; CI, confidence interval.
*Nominal P<.05 in the main studies, indicating treatment response rates significantly different from placebo, based on Fisher's exact test. [a]Defined as a ≥40% reduction from baseline as measured by the 5-item Positive and Negative Syndrome Scale-Excited Component; [b]Sublingual dexmedetomidine vs placebo; [c]Not statistically significant.

Safety

- **Treatment-emergent adverse events** were experienced by 32.9%, 34.1%, and 11.9% of participants in the sublingual dexmedetomidine 180 mcg, 120 mcg, and placebo groups, respectively
- The **most common** treatment-emergent adverse event was **somnolence**, which affected 22.2%, 21.2%, and 6.3% in the 180 mcg, 120 mcg, and placebo groups, respectively
- **No severe AEs** were reported

Efficacy

Primary: At 2 hours postdose, the mean (SD) change from baseline in PEC total score was −10.4 (4.39) for sublingual dexmedetomidine 180 mcg, −8.7 (5.05) for sublingual dexmedetomidine 120 mcg, and −4.8 (4.67) for placebo. Both sublingual dexmedetomidine doses were more effective than placebo (*P*<.001) at reducing symptoms of agitation.

Secondary: The onset of treatment effect was 10 minutes postdose in the sublingual dexmedetomidine 180 µg group (−1.8 (3.13) vs −1.2 (2.02), *P*<.001) and 20 minutes postdose in the sublingual dexmedetomidine 120 µg group (−2.9 (3.92) vs −2.2 (3.11), *P*<.001).

Table 2. Adverse Events[a] and Number Needed to Harm in Participants With Schizophrenia or Bipolar Disorder

	Bipolar Disorder					Schizophrenia				
	Incidence n (%)			Number Needed to Harm[b] (95% CI)		Incidence n (%)			Number Needed to Harm[b] (95% CI)	
	180 mcg n=126	120 mcg n=126	Placebo n=126	180 mcg n=126	120 mcg n=126	180 mcg n=126	120 mcg n=129	Placebo n=126	180 mcg n=126	120 mcg n=129
AE of Special Interest										
Cardiac/vascular disorder	6 (4.8)	4 (3.2)	3 (2.4)	42 (ns)[e]	126 (ns)[e]	7 (5.6)	6 (4.7)	0	18 (11, 65)	22 (13, 99)
Hypotension/ bradycardia(s)	6 (4.8)	4 (3.2)	0	21 (12, 96)	32 (17, 883)	5 (4.0)	6 (4.7)	0	26 (14, 179)	22 (13, 99)
Bradycardia(s)	2 (1.6)	1 (.8)	0	63 (ns)[e]	126 (ns)[e]	0	2 (1.6)	0	ND	65 (ns)[e]
Hypotension	5 (4.0)	3 (2.4)	0	26 (14, 179)	42 (ns)[e]	5 (4.0)	4 (3.1)	0	26 (14, 179)	33 (17, 914)
Adverse Event										
Somnolence	26 (20.6)	25 (19.8)	5 (4.0)	6 (5, 12)	7 (5, 13)	25 (19.8)	26 (20.2)	9 (7.1)	8 (5, 23)	8 (5, 22)
Dry mouth	4 (3.2)	8 (6.3)	1 (.8)	42 (ns)[e]	18 (10, 98)	5 (4.0)	9 (7.0)	1 (.8)	32 (ns)[e]	17 (10, 66)
Dizziness	4 (3.2)	4 (3.2)	1 (.8)	42 (ns)[e]	42 (ns)[e]	6 (4.8)	2 (1.6)	1 (.8)	26 (ns)[e]	133 (ns)[e]
Hypoesthesia oral	5 (4.0)	2 (1.6)	1 (.8)	32 (ns)[e]	126 (ns)[e]	7 (5.6)	5 (3.9)	0	18 (11, 65)	26 (14, 184)
Paresthesia oral	-	-	-	-	-	3 (2.4)	5 (3.9)	1 (.8)	63 (ns)[e]	33 (ns)[e]
Headache	1 (.8)	4 (3.2)	3 (2.4)	−63 (ns)[e]	126 (ns)[e]	1 (.8)	1 (.8)	3 (2.4)	−63 (ns)[e]	−62 (ns)[e]
Nausea	2 (1.6)	1 (.8)	3 (2.4)	−126 (ns)[e]	−63 (ns)[e]	-	-	-	-	-
Orthostatic hypotension	1 (.8)	1 (.8)	0	126 (ns)[e]	126 (ns)[e]	1 (.8)	0	0	126 (ns)[e]	ND

CI, confidence interval; NNH, number needed to harm; AE, Adverse Event; ND, no difference.
[a]Occurring within the first 2 hours postdose. [b]A negative NNH denotes an advantage for sublingual dexmedetomidine relative to placebo and is not interpretable as a harm. [c]Using NNT for response at 2 hours postdose (refer to Table 1). [d]Reported by at least 2% of participants in the safety population (all participants who received a dose of study drug). [e]Not statistically significant.

KEY POINTS

- **Post hoc NNT/NNH analysis of pooled data from 2 Phase 3 Clinical Trials (N=506) of sublingual dexmedetomidine for the treatment of adults with acute agitation associated with schizophrenia or bipolar disorder I or II**
- 2-hour PEC Change was significantly greater than placebo for both doses
- Onset of treatment effect (Key Secondary Endpoint):
  - 10 minutes postdose for 180 mcg
  - 20 minutes postdose for 120 mcg
- Number Needed to Treat (95% confidence interval) for response at 2 hours postdose was:
  - 3 (2, 3) NNT for 180 mcg dose
  - 3 (3, 4) NNT for 120 mcg dose
- Number Need to Harm was greater than 10 for all AEs except somnolence
- The most common adverse events from pooled Phase 3 trials were somnolence, dry mouth, hypotension, dizziness, orthostatic hypotension, and oral hypoesthesia
- Post hoc calculations of NNT and NNH for sublingual dexmedetomidine support a favorable benefit-risk profile for the treatment of acute agitation in adults with DSM-5 diagnoses of schizophrenia or bipolar disorder

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