# Dexmedetomidine Sublingual Film for the Treatment of Acute Agitation Associated with Schizophrenia or Bipolar Disorder: Effect Size and Pooled Efficacy

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## INTRODUCTION

Acute agitation is frequently managed in psychiatric and emergency care settings. Verbal de-escalation, environment management, and collaborative care are recommended to improve patient outcomes. When needed, pharmacological treatment should ideally be noninvasive, have rapid onset, and produce calming without oversedation.[1]

Previously, two randomized, placebo-controlled clinical trials showed that a single 180 mcg or 120 mcg dose of sublingual dexmedetomidine film effectively reduced agitation in adults with schizophrenia, schizoaffective disorder, or bipolar disorder I or II.[2,3]

Dexmedetomidine sublingual film is an orally dissolving formulation of dexmedetomidine, a selective alpha$_2$ adrenergic receptor agonist. It is approved for sublingual or buccal administration for the treatment of acute agitation associated with schizophrenia or bipolar disorder I or II in adults.

## OBJECTIVE

Cohen's d effect sizes and pooled efficacy data are presented from post hoc analyses of data from two clinical trials evaluating a single dose of dexmedetomidine sublingual film for the treatment of acute agitation associated with schizophrenia (Serenity I) or bipolar disorder (Serenity II) in adults.

## METHODS

**Design:** Post hoc analysis of pooled data from two Phase 3 randomized, controlled studies in adults with schizophrenia or bipolar disorder experiencing acute agitation[2,3] Acute agitation was defined as a score of ≥14 on the PANSS-Excited Component (PEC) scale and ≥4 on at least 1 of 5 PEC items.

**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 matching placebo **(Fig 2).**

**Primary Endpoint:** Mean change from baseline on total score on the Positive and Negative Syndrome Scale (PANSS)-Excited Component (PEC)[4] at 2 hours postdose.

Therapeutic response was defined as a ≥40% reduction in PEC total at 2 hours.

**Secondary Endpoint:** Earliest time of a statistically significant separation of active drug from placebo on the PEC.

**Cohen's d Effect Sizes**: Cohen's d effect sizes for active treatment versus placebo were calculated for both doses in each trial.

## PARTICIPANTS

The 758 adults in the pooled population were treated with dexmedetomidine 180 mcg (n=251), dexmedetomidine 120 mcg (n=255), or placebo (n=252). The study population had a mean (SD) age of 45.0 (11.5) years and 54% self identified as male and 59% as Black or African American **(Table 1**).

At baseline, mean (SD) PEC total scores were 17.8 (2.9) for sublingual dexmedetomidine 180 mcg, 17.7 (2.6) for sublingual dexmedetomidine 120 mcg, and 17.8 (2.6) for placebo.

### Table 1. Participant Demographics and Baseline Characteristics

| | Sublingual Dexmedetomidine | | |
|---|---|---|---|
| | 180 mcg (n=251) | 120 mcg (n=255) | Placebo (n=252) |
| **Age, years, mean (SD)**<br>**Age range, years** | 45.9 (11.6)<br>18, 71 | 45.9 (11.4)<br>19, 70 | 45.0 (11.6)<br>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/m², 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) |

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.

## Safety

**Treatment-emergent adverse events** (AE) were experienced by 36.5%, 37.3%, and 16.3% of participants in the sublingual dexmedetomidine 180 mcg, 120 mcg, and placebo groups, respectively **(Table 2).**

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 **(Table 2).**

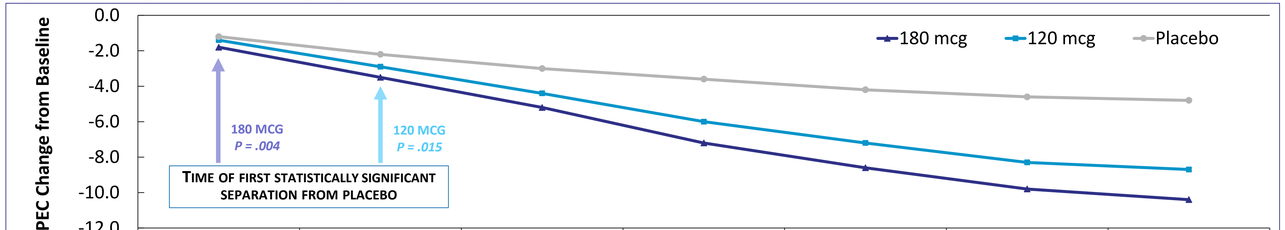
There were no severe or serious **treatment-related** AEs reported.

### Table 2. Pooled Adverse Events (AE) by Treatment Group

| | Sublingual Dexmedetomidine | | |
|---|---|---|---|
| | 180 mcg (n=252)* | 120 mcg (n=255) | Placebo (n=252) |
| **Any Treatment Emergent AE** | 92 (36.5) | 95 (37.3) | 41 (16.3) |
| **Serious AE** | 0 | 1 (0.4) | 0 |
| **Discontinuation due to AE** | 0 | 3 (1.2) | 0 |
| Somnolence | 56 (22.2) | 54 (21.2) | 16 (6.3) |
| Dry Mouth | 11 (4.4) | 19 (7.5) | 3 (1.2) |
| Hypotension | 13 (5.2) | 14 (5.5) | 0 |
| Dizziness | 15 (6.0) | 10 (3.9) | 2 (0.8) |
| Orthostatic Hypotension | 13 (5.2) | 7 (2.7) | 1 (0.4) |
| Oral Hypoesthesia | 12 (4.8) | 7 (2.7) | 1 (0.4) |
| Headache | 6 (2.4) | 12 (4.7) | 12 (4.8) |
| Nausea | 7 (2.8) | 6 (2.4) | 4 (1.6) |
| Oral Paresthesia | 6 (2.4) | 7 (2.7) | 1 (0.4) |

Subjects were counted once within each adverse event preferred term. *Data for 1 subject enrolled in the study at two different sites in error (in the 120 mcg and the 180 mcg treatment groups) are reported in the 120 mcg and 180 mcg columns for adverse events.

### Figure 1. Efficacy: Pooled PEC Change by Dose and Time – Baseline to 2 Hours Postdose




| | 10 mins Postdose | 20 mins Postdose | 30 mins Postdose | 45 mins Postdose | 1 hour Postdose | 1.5 hours Postdose | 2 hours Postdose |
|---|---|---|---|---|---|---|---|
| 180 mcg | -1.8 | -3.5 | -5.2 | -7.2 | -8.6 | -9.8 | -10.4 |
| 120 mcg | -1.4 | -2.9 | -4.4 | -6.0 | -7.2 | -8.3 | -8.7 |
| Placebo | -1.2 | -2.2 | -3.0 | -3.6 | -4.2 | -4.6 | -4.8 |

## Efficacy

**Primary:** At 2 hours postdose, the mean (SD) change from baseline in PEC total score was −10.4 (4.4) for sublingual dexmedetomidine 180 mcg, −8.7 (5.0) for sublingual dexmedetomidine 120 mcg, and −4.8 (4.7) for placebo. Both sublingual dexmedetomidine doses were more effective than placebo (*P*<.001) at reducing symptoms of agitation **Fig 1**

**Secondary:** The onset of treatment effect was 10 minutes postdose in the sublingual dexmedetomidine 180 µg group (−1.8 (3.1) vs −1.2 (2.0) for placebo, *P<.01*) and 20 minutes postdose in the sublingual dexmedetomidine 120 µg group (−2.9 (3.9) vs −2.2 (3.1), *P*<.05) **Fig 1**

**Cohen's D Effect Size:** Cohen's D effect sizes for the 180 mcg doses in Serenity I and Serenity II were 1.25 and 1.21, respectively, and for the 120 mcg doses in Serenity I and Serenity II were 0.78 and 0.83, respectively.

| Trial | 180 mcg | 120 mcg |
|---|---|---|
| Serenity I – Schizophrenia | 1.25 | 0.78 |
| Serenity II – Bipolar Disorder | 1.21 | 0.83 |

## 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 at Baseline**

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

### Figure 2. Sublingual Dexmedetomidine Film

- Blue rectangular 22 mm x 13 mm thin film
- 2 micro-deposited spots (darker blue) containing dexmedetomidine hydrochloride in a polymer matrix
- Muco-adhesive
- Sucralose and peppermint oil

## KEY POINTS

- Sublingual dexmedetomidine is an orally dissolving film formulation of dexmedetomidine, a selective alpha$_2$ adrenergic receptor agonist (**Fig 2**)
- Post hoc analysis of pooled data from 2 Phase 3 Clinical Trials (N=506) of sublingual dexmedetomidine film for the treatment of adults with acute agitation associated with schizophrenia or bipolar disorder I or II
- Reduction in PEC total was significantly greater than placebo from 20 minutes through 2 hours for both doses (**Fig 1**)
- Onset of treatment effect (**Key Secondary Endpoint, Fig 1**)
  - 10 minutes postdose for 180 mcg
  - 20 minutes postdose for 120 mcg
- Cohen's d Effect Sizes were 1.25 and 0.78 for the 180 mcg dose and 1.21 and 0.83 for the 120 mcg dose for the Serenity I and Serenity II trials, respectively. Cohen's d values of 0.8 or greater are generally considered to represent large effect sizes.[5]
- The most common adverse events were somnolence, dry mouth, dizziness, hypotension, orthostatic hypotension, oral hypoesthesia, headache, nausea, oral paresthesia (**Table 2**)

**References** 1. Zeller SL, Citrome L. *West J Emerg Med*. 2016 Mar;17(2):165-72; 2. Preskorn SH, Zeller S, Citrome L, et al. *JAMA*. 2022;327:727-736; 3. Citrome L, Preskorn SH, Lauriello J, et al. *J Clin Psychiatry*. 2022; 83(6); 4. Montoya A et al. *Health Qual Life Outcomes*. 2011;9:18; 5.Lakens D. *Front Psychol*. 2013 Nov 26; 4:863.

**Disclosures** This study was supported by funding from BioXcel Therapeutics. HR, LR, BP, and RR are employed by BioXcel Therapeutics.

Presented at the American Association of Psychiatric Pharmacists, April 16-19, 2023
Previously presented at the Academy of Consultation Liaison Psychiatry, November 9-12, 2022, Atlanta, GA