Review
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Sublingual Dexmedetomidine for the Treatment of Agitation in Patients with Schizophrenia and Bipolar Disorder

Colin M. Smith[1], Morgan Santalucia[2], Hannah Bunn[2], Andrew Muzyk[3]

[1]Department of Behavioral Health, Phoenix Indian Medical Center, Indian Health Service, Phoenix, AZ, [2]Doctor of Pharmacy Program, Campbell University College of Pharmacy and Health Sciences, [3]Department of Pharmacy Practice, Campbell University College of Pharmacy and Health Sciences, Buies Creek, NC, USA

Acute agitation is common amongst individuals with bipolar disorder and schizophrenia and represents a medical emergency. Commonly used medications for agitation, such as benzodiazepines and antipsychotics, are often delivered intramuscularly and may cause adverse effects. Non-invasive, effective, and safe alternative treatment options are needed. The purpose of this review article is to describe the efficacy and safety of sublingual formulation of dexmedetomidine (Igalmi), a selective α2-adrenergic receptor agonist, U.S. Food and Drug Administration approved for the treatment of acute agitation in adults with schizophrenia or bipolar I and II disorder. In two phase 3 trials, two dose strengths of sublingual dexmedetomidine 180 μg and 120 μg were safe and effective in managing acute agitation in patients with bipolar disorder or schizophrenia. Both doses significantly reduced Positive and Negative Syndrome Scale-Exited Component scores two hours after receiving a single dose as compared to placebo, indicating a substantial improvement in agitation. The beneficial effects of sublingual dexmedetomidine were achieved without serious adverse events with the most common side effect being mild somnolence. The clinical trial data suggest that sublingual dexmedetomidine represents a safe and effective treatment option in the armamentarium for acute agitation for people with schizophrenia or bipolar disorder.

KEY WORDS: Clonidine; Psychosis; Anxiety; Mania; Aggression; Irritable mood.

INTRODUCTION

Schizophrenia and bipolar disorder are commonly associated with acute episodes of agitation in emergency settings [1]. Of the 1.7 million emergency department visits per year involving agitation, approximately 21% are due to schizophrenia and 13% are due to bipolar disorder [2-4]. Given that agitation can result in injury to patients and staff, safe and effective treatment of patients presenting with agitation is essential.

Guidelines for acute agitation management are heterogenous, but recommend prioritizing safety, behavioral interventions, and verbal de-escalation as first line interventions and contend that physical restraint should be used as a last resort. Psychopharmacological therapy should be reserved for when behavioral interventions fail to prevent physical restraint. For acute agitation as a result of schizophrenia or bipolar disorder, oral antipsychotics and/or oral benzodiazepines are first line, followed by intramuscular antipsychotics and/or benzodiazepines [5-10]. With high prevalence of acute agitation in emergency care settings, combined with recent shortages of medications commonly used for agitation and concerns related to current therapies, there has been an increasing interest in new treatment options for acute agitation management [11,12].

A sublingual formulation of dexmedetomidine (Igalmi), a novel therapeutic, was approved by the U.S. Food and Drug Administration (FDA) in 2022 for the treatment of acute agitation associated with schizophrenia or bipolar I or II disorder in adults [13]. In this article, we review the

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Address for correspondence: Andrew Muzyk
Department of Pharmacy Practice, Campbell University College of Pharmacy and Health Sciences, Room 237, JP Riddle Pharmacy Center, Buies Creek, NC 27506, USA
E-mail: Andrew.Muzyk@duke.edu
ORCID: https://orcid.org/0000-0002-6904-2466

safety and efficacy of sublingual dexmedetomidine in the treatment of agitation of these patient populations.

CLINICAL PHARMACOLOGY

Dexmedetomidine, a highly selective α2-adrenergic receptor agonist, is thought to treat acute agitation associated with schizophrenia or bipolar disorder by activating presynaptic α2-adrenergic receptors to suppress the hypersympathetic activity and decrease the firing of locus coeruleus neurons [14]. The mucoadhesive film is rapidly absorbed into the bloodstream via the sublingual or buccal route. In pharmacokinetic studies after a single dose of dexmedetomidine, the absolute bioavailability of the sublingual and buccal administration was 72% and 82% respectively and plasma concentrations were quantifiable 5 to 20 minutes after oral administration [13]. Tables 1 and 2 provide key pharmacodynamic and pharmacokinetic properties and dosing in special populations.

Table 1. Pharmacodynamic and pharmacokinetic properties of sublingual dexmedetomidine [13]

Class	α2-adrenergic receptor agonist
Formulation	120 μg and 180 μg sublingual films
Flavor	Mint
Route	Sublingual or buccal
Metabolism	Glucuronidation and hydroxylation (primarily by CYP2A6)
Half-life	2.8 hr
Elimination	Urine (95%), feces (4%)
Drug interactions	Opioids, hypnotics, sedatives, anesthetics, QT prolonging medications.
Pregnancy	Crosses the placenta. There is no available data to evaluate maternal or fetal adverse effects.
Lactation	Infant risk cannot be ruled out.

Revised from the article of BioXcel Therapeutics. (U.S. Food and Drug Administration; 2022) [13].

CLINICAL TRIALS

Sublingual dexmedetomidine was assessed for efficacy in treating acute agitation in two phase 3 randomized, double-blind, placebo-controlled trials [15,16]. One study evaluated its use in patients with bipolar I or II disorder (n = 378), while the other included patients with schizophrenia or schizoaffective disorder (n = 381). For both trials, patients were between the ages of 18−75 and had a diagnosis of one of the aforementioned disorders, respective for the trial they were enrolled in, along with current agitation. After screening, patients were assessed beginning on the day of treatment (day 1) through day 3, as well as an end of study visit on day 7. Patients had a baseline score of ≥ 14 on the 5 items of the Positive and Negative Syndrome Scale-Excited Component (PEC) and a score of ≥ 4 on at least one of the 5 PEC items. Patients were recruited from a variety of settings including hospitals; outpatient clinics; and mental health, psychiatric, or emergency medical services. Common medications that patients were on at baseline include second generation antipsychotics, antidepressants, and sedatives/hypnotics/anxiolytics. Key baseline demographics for both studies are found in Table 3. Notable exclusion criteria were the use of antipsychotics or benzodiazepines within 4 hours of treatment, intoxication with alcohol or other drugs of abuse, current use of α1-blockers, and pregnancy or breastfeeding.

The primary endpoint was the change from baseline in PEC total score 2 hours after receiving a single dose of the

Table 2. Dosing of sublingual dexmedetomidine in adults and special populations [13]

Patient population	Agitation severity	Initial dose[a]	2nd or 3rd doses[a]
Adults (μg)	Mild or moderate	120	60
	Severe	180	90
Mild or moderate hepatic impairment[b] (μg)	Mild or moderate	90	60
	Severe	120	60
Severe hepatic impairmentb (μg)	Mild or moderate	60	60
	Severe	90	60
Geriatrics, ≥ 65 yr (μg)	Mild, moderate, or severe	120	60

[a]Ifagitation persists after the initial dose, up to two additional doses may be administered at least two hours apart. Prior to any additional doses, assess vital signs including orthostatic measurements; [b]Hepatic impairment: mild (child-pugh class A), moderate (child-pugh class B), severe (child-pugh class C).
Adapted from the article of BioXcel Therapeutics. (U.S. Food and Drug Administration; 2022) [13].

Table 3. Key baseline demographics reported in clinical trials with sublingual dexmedetomidine

Demographic	Bipolar disorder study (n = 378) [15]			Schizophrenia study (n = 381) [16]		
	180 μg (n = 126)	120 μg (n = 126)	Placebo (n = 126)	180 μg (n = 126)	120 μg (n = 129)	Placebo (n = 126)
Age (yr)	45.9 ± 11.3	46.1 ± 11.5	44.8 ± 12.1	46.0 ± 11.9	45.7 ± 11.3	45.1 ± 11.1
Female	67 (53.2)	67 (53.2)	73 (57.9)	44 (34.9)	52 (40.3)	44 (34.9)
Race						
Asian	1 (0.8)	0	2 (1.6)	-	-	-
Black or African American	72 (57.1)	68 (54.0)	72 (57.1)	103 (81.7)	92 (71.3)	102 (81.0)
Multiple	3 (2.4)	1 (0.8)	1 (0.8)	-	-	-
White	49 (38.9)	56 (44.4)	50 (39.7)	21 (16.7)	33 (25.6)	21 (16.7)
Other	1 (0.8)	1 (0.8)	1 (0.8)	2 (1.6)	4 (3.1)	3 (2.4)
Hispanic or Latino	15 (11.9)	12 (9.5)	11 (8.7)	13 (10.3)	17 (13.2)	7 (5.6)
Diagnosis						
Schizophrenia	-	-	-	101 (80.2)	113 (87.6)	108 (85.7)
Schizoaffective disorder	-	-	-	25 (19.8)	16 (12.4)	18 (14.3)
Mania	59 (46.8)	58 (46.0)	63 (50.0)	-	-	-
Depressed	28 (22.2)	20 (15.9)	26 (20.6)	-	-	-
Mixed episodes	30 (23.8)	27 (21.4)	22 (17.5)	-	-	-
Hypomania	5 (4.0)	14 (11.1)	10 (7.9)	-	-	-
Unspecified	4 (3.2)	7 (5.6)	5 (4.0)	-	-	-
PEC total score[a]	18.0 ± 3.0	18.0 ± 2.7	17.9 ± 2.9	17.6 ± 2.7	17.5 ± 2.5	17.6 ± 2.3

Values are presented as mean ± standard deviation or number (%).
PEC, Positive and Negative Syndrome Scale-Exited Component; -, not available.
[a]PECscale is comprised of 5 items: poor impulse control, tension, hostility, uncooperativeness, and excitement. Each item is rated from 1 (lowest) to 7 (highest), with the total score being the sum of the 5 items and ranging from 5 (no agitation) to 35 (extremely severe agitation).

Table 4. Study outcomes reported in clinical trials with sublingual dexmedetomidine

Study	Treatment	Change from baseline in PEC score at 2 hr[a] (standard error)	Least squares mean difference from placebo (95% confidence interval)	Time to treatment effect (min)[c]
Bipolar disorder [15]	Dexmedetomidine 180 μg	−10.4 (4.4)	−5.4 (−6.6 to −4.2)[b]	20
	Dexmedetomidine 120 μg	−9.0 (5.3)	−4.1 (−5.3 to −2.9)[b]	20
	Placebo	−4.9 (4.7)	-	-
Schizophrenia [16]	Dexmedetomidine 180 μg	−10.3 (0.4)	−5.5 (−6.7 to −4.3)[b]	20
	Dexmedetomidine 120 μg	−8.5 (0.4)	−3.7 (−4.9 to −2.5)[b]	30
	Placebo	−4.8 (0.4)	-	-

PEC, Positive and Negative Syndrome Scale-Exited Component; -, not available.
[a]PEC scale is comprised of 5 items: poor impulse control, tension, hostility, uncooperativeness, and excitement. Each item is rated from 1 (lowest) to 7 (highest), with the total score being the sum of the 5 items and ranging from 5 (no agitation) to 35 (extremely severe agitation); [b]$p < 0.001$; [c]Defined as the earliest time at which the change from baseline in PEC score statistically significantly separated from placebo.

study medication. Two strengths of sublingual dexmedetomidine (180 μg and 120 μg) were compared to placebo; patients were randomized in both studies in a 1-1-1 fashion and stratified based on age < 65 or ≥ 65 years old. In the trials, both doses of sublingual dexmedetomidine significantly reduced PEC scores at 2 hours post-dose compared to placebo; the magnitude of effect was greatest with the 180 μg dose. In the schizophrenia and schizoaffective disorder trial, 180 μg produced significantly reduced agitation within 20 minutes compared to 30 minutes with 120 μg, while both doses produced this effect within 20 minutes in the bipolar disorder study. Table 4 contains results for the primary endpoint.

The bipolar disorder study had one secondary endpoint which was the earliest point at which the change in PEC score from baseline statistically significantly separated from placebo, the results of which are mentioned above. The secondary endpoint for the schizophrenia study was the absolute change from baseline in PEC total score at 10, 20, 30, 45, 60, and 90 minutes post dose. In both

treatment groups, PEC scores continuously decreased from baseline at all of these time points. Redosing of sublingual dexmedetomidine 2 hours after initial treatment was permitted at half of the first dose (90 μg or 60 μg) if necessary. Patients could receive a maximum of 2 subsequent doses in the 12 hours following the initial dose. In the bipolar disorder study, the number of patients requiring more than one dose were as follows: 10.3% of the 180 μg group, 23.8% of the 120 μg group, and 46% of the placebo group. In the schizophrenia study, the amount of patients requiring redosing were: 4% of the 180 μg group, 21.7% of the 120 μg group, and 42% of the placebo group. Rescue medication was also permitted for persistent agitation, defined as oral or intramuscular lorazepam 0.5−5 mg. For the bipolar disorder study, rescue medication was needed in 2.4% of the 180 μg group and 1.6% of both the 120 μg and placebo groups. For the schizophrenia study, rescue medication was needed in 0.8% of the 180 μg group, 3.1% of the 120 μg group, and 0.8% of the placebo group.

The authors of both studies investigated numerous prespecified post dose exploratory endpoints focused on agitation including Agitation-Calmness Evaluation Scale (ACES) scores at 15 minutes, 2, 4, and 8 hours; and PEC response rate defined as a ≥ 40% reduction in total score from baseline at or before 2 hours. In both trials, there was a greater percentage of patients whose agitation was resolved (ACES score ≥ 4 at 2, 4, and 8 hours) in the 180 μg and 120 μg groups than in the placebo group. In the bipolar disorder study, PEC response rates were 90.5% for the 180 μg group, 77% for the 120 μg group, and 46% for the placebo group. In the schizophrenia study, PEC response rates were 88.8% for the 180 μg group, 79.1% for the 120 μg group, and 40.5% for the placebo group.

Adverse events were minimal across the studies, with the most common side effect being somnolence that was rated as mild in many cases (Table 5). No patients were unarousable. Other adverse effects included hypotension, dizziness, and dry mouth. Only one serious adverse event occurred in the 120 μg group of the bipolar disorder study, though this was determined to not be related to dexmedetomidine. In the bipolar disorder study, two patients - one in each sublingual dexmedetomidine group - experienced suicidal ideation lasting for one day. One patient in the schizophrenia study, belonging to the 120 μg group, experienced this adverse event. All patients reporting suicidal ideation completed the study. Overall, 3 patients dropped out of the study due to adverse events, all of which belonged to the 120 μg group.

Instances of hypotension, orthostatic hypotension, and bradycardia were reviewed by an external board-certified cardiologist. Generally, these events occurred more frequently in the 180 μg group than in the 120 μg group. Most of these cases were rated as mild. Patients were monitored via ECG through 24 hours post dose, and no relevant findings were noted.

POST HOC ANALYSIS

A post hoc analysis of the two phase 3 trials with sub-

Table 5. Adverse events reported in clinical trials with sublingual dexmedetomidine

Adverse event	Bipolar disorder study (n = 378) [15]			Schizophrenia study (n = 381) [16]		
	180 μg (n = 126)	120 μg (n = 126)	Placebo (n = 126)	180 μg (n = 126)	120 μg (n = 129)	Placebo (n = 126)
Any treatment-emergent AE	45 (35.7)	44 (34.9)	22 (17.5)	47 (37.3)	51 (39.5)	19 (15.1)
Any drug-related AE	39 (31.0)	41 (32.5)	15 (11.9)	44 (34.9)	46 (35.7)	15 (11.9)
Somnolence	27 (21.4)	26 (20.6)	6 (4.8)	29 (23.0)	28 (21.7)	10 (7.9)
Hypotension	8 (6.3)	6 (4.8)	0	5 (4.0)	10 (7.8)	2 (1.6)
Dizziness	7 (5.6)	7 (5.6)	1 (0.8)	8 (6.3)	3 (2.3)	1 (0.8)
Dry mouth	6 (4.8)	9 (7.1)	1 (0.8)	5 (4.0)	10 (7.8)	2 (1.6)
Orthostatic hypotension	6 (4.8)	5 (4.0)	1 (0.8)	7 (5.6)	2 (1.6)	0
Hypoesthesia oral	5 (4.0)	2 (1.6)	1 (0.8)	7 (5.6)	5 (3.9)	0
Nausea	5 (4.0)	3 (2.4)	3 (2.4)	2 (1.6)	3 (2.3)	1 (0.8)
Bradycardia	3 (2.4)	2 (1.6)	0	-	-	-
Headache	-	-	-	4 (3.2)	6 (4.7)	6 (4.8)
Paresthesia oral	3 (2.4)	2 (1.6)	0	3 (2.4)	5 (3.9)	1 (0.8)

Values are presented as number (%).
AE, adverse event; -, not available.

lingual dexmedetomidine was conducted to calculate the numbers needed to treat (NNT), numbers needed to harm (NNH), and likelihood to be helped or harmed (LHH) [17]. The NNT was calculated based on the PEC response rate defined as a 40% or greater reduction in PEC score from baseline. The LHH metric is found by dividing NNH by NNT. A value of greater than 1 indicates the treatment is more likely to help than to harm. The authors' intent with this analysis was to translate the findings from the two phase 3 studies into clinically meaningful metrics of the efficacy and tolerability.

In the schizophrenia and schizoaffective disorder study, the NNT versus placebo was 3 for the 180 μg and 120 μg doses, while in bipolar disorder study it was 3 for the 180 μg dose and 4 for the 120 μg dose. In both studies, the NNH values were greater than 10 for all adverse events except a NNH of 7 for somnolence. The LHH values were greater than 1 for all adverse effects. The calculated NNT, NNH, and LHH provide values indicating a favorable benefit-risk profile of sublingual dexmedetomidine in the treatment of acute agitation in the studied patient populations. A limitation of this post hoc analysis is the NNT of PEC response was an exploratory endpoint and was not adjusted for multiplicity.

PLACE IN THERAPY

Sublingual dexmedetomidine represents the first drug approved by the FDA in the last decade for the treatment of acute agitation in people with schizophrenia or bipolar I disorder and the first approved for agitation associate with bipolar II disorder [18]. Emerging evidence suggests that this novel drug has a role in agitation management in these patient populations.

There are several potential advantages to sublingual dexmedetomidine as a treatment option in the management of acute agitation in people with schizophrenia and bipolar disorders. First, sublingual medications are inherently less coercive and more collaborative than the intramuscular options that have been commonly used in agitation management despite recommendations to first offer oral alternatives [19]. Sublingual formulations pose less physical and psychological risk to patients experiencing agitation, leading to improved patient experience [20, 21]. Second, sublingual dexmedetomidine lacks dopamine receptor activity, avoiding extrapyramidal side effects including dystonia, akathisia, and tremor resulting from antipsychotic use [22]. Third, the use of sublingual dexmedetomidine avoids the potential stigma associated with antipsychotic use [23]. Finally, dexmedetomidine is familiar to those in the field of psychopharmacology given its unique sedative and anxiolytic properties. Although the intravenous formulation was first approved by the FDA in 1999 for sedation and analgesia in intensive care settings [24], it has since been used by some psychiatrists in the management of agitation in delirium [25], alcohol withdrawal [26,27], and catatonia [28].

Despite the potential unique advantages of sublingual dexmedetomidine, there are several concerns that may affect its clinical utility in acute agitation management. First, the primary α2-adrenergic receptor agonist activity may not address the underlying mechanism of illness in either schizophrenia or bipolar disorders, as the pathophysiology of these disease states is currently understood, which is the primary reason antipsychotics are used as first line for this population [20]. Second, the safety and effectiveness for the drug has not been evaluated beyond 24 hours of first use [13]. Ten percent (10%) or less and approximately 20% of patients in the clinical trials (180 μg and 120 μg respectively) required a second dose of sublingual dexmedetomidine. Third, medications delivered sublingually limit their use in patients who are severely agitated requiring involuntary medication. Indeed, one criticism of the available data on sublingual dexmedetomidine is that participants may not represent the full spectrum and severity of patients presenting with acute agitation since participants were able to consent to and self-administer treatment [29]. The wholesaler acquisition cost (WAC) in the United States is $105 per dose. The WAC price represents a published list price, but may not represent an actual transactional price for this medication [30].

Taken together, the available evidence suggests that sublingual dexmedetomidine is a safe and effective treatment for acute agitation in patients with schizophrenia or bipolar I and II disorder. Sublingual dexmedetomidine represents a novel medication in the agitation treatment armamentarium due to its quick onset of action, minimal need for repeat dosing, and a favorable side effect profile that is unique from current treatments, namely extrapyramidal side effects from antipsychotics and excessive sedation with benzodiazepines. Future studies will need to assess the clinical utility of sublingual dexmedetomidine

in the real world setting and its impact on important healthcare outcomes including hospital admission rates, hospital length of stay, concomitant medication use for agitation, and restraint use. Studies exploring the use of sublingual dexmedetomidine for treatment of agitation in other patient populations will be useful to clinicians.

DISCLAIMER

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■ **Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

■ **Author Contributions**

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■ **ORCID**

Colin M. Smith	https://orcid.org/0000-0002-5758-4698
Morgan Santalucia	https://orcid.org/0009-0000-2941-5224
Hannah Bunn	https://orcid.org/0009-0000-8373-9916
Andrew Muzyk	https://orcid.org/0000-0002-6904-2466

REFERENCES

1. San L, Marksteiner J, Zwanzger P, Figuero MA, Romero FT, Kyropoulos G, *et al. State of acute agitation at psychiatric emergencies in Europe: the STAGE study. Clin Pract Epidemiol Ment Health 2016;12:75-86.*
2. Holloman GH Jr, Zeller SL. *Overview of project BETA: best practices in evaluation and treatment of agitation. West J Emerg Med 2012;13:1-2.*
3. Hazlett SB, McCarthy ML, Londner MS, Onyike CU. *Epidemiology of adult psychiatric visits to US emergency departments. Acad Emerg Med 2004;11:193-195.*
4. Sankaranarayanan J, Puumala SE. *Epidemiology and characteristics of emergency departments visits by US adults with psychiatric disorder and antipsychotic mention from 2000 to 2004. Curr Med Res Opin 2007;23:1375-1385.*
5. Allen MH, Currier GW, Carpenter D, Ross RW, Docherty JP; Expert Consensus Panel for Behavioral Emergencies 2005. *The expert consensus guideline series. Treatment of behavioral emergencies 2005. J Psychiatr Pract 2005;11 Suppl 1:5-108; quiz 110-112.*
6. Garriga M, Pacchiarotti I, Kasper S, Zeller SL, Allen MH, Vázquez G, *et al. Assessment and management of agitation in psychiatry: expert consensus. World J Biol Psychiatry 2016;17:86-128.*
7. Raveesh BN, Munoli RN, Gowda GS. *Assessment and management of agitation in consultation-liaison psychiatry. Indian J Psychiatry 2022;64(Suppl 2):S484-S498.*
8. Roppolo LP, Morris DW, Khan F, Downs R, Metzger J, Carder T, *et al. Improving the management of acutely agitated patients in the emergency department through implementation of Project BETA (best practices in the evaluation and treatment of agitation). J Am Coll Emerg Physicians Open 2020;1:898-907.*
9. Wilson MP, Pepper D, Currier GW, Holloman GH Jr, Feifel D. *The psychopharmacology of agitation: consensus statement of the American Association for Emergency Psychiatry project beta psychopharmacology workgroup. West J Emerg Med 2012;13:26-34.*
10. Wood B. *Clinically significant acute agitation: consensus update. US Pharm 2010;35:HS-9-HS-15.*
11. Lin J, Figuerado Y, Montgomery A, Lee J, Cannis M, Norton VC, *et al. Efficacy of ketamine for initial control of acute agitation in the emergency department: a randomized study. Am J Emerg Med 2021;44:306-311.*
12. Miller J. *Managing acute agitation and aggression in the world of drug shortages. Ment Health Clin 2021;11:334-346.*
13. BioXcel Therapeutics. *IGALMI™ (dexmedetomidine) sublingual film, for sublingual or buccal use [Internet]. Silver Spring (MD): U.S. Food and Drug Administration; 2022 [cited at 2022 Nov 27]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215390s000lbl.pdf*
14. Preskorn SH. *How an understanding of the function of the locus coeruleus led to use of dexmedetomidine to treat agitation in bipolar disorder: example of rational development of psychiatric medications. J Psychiatr Pract 2022;28:227-233.*
15. Preskorn SH, Zeller S, Citrome L, Finman J, Goldberg JF, Fava M, *et al. Effect of sublingual dexmedetomidine vs placebo on acute agitation associated with bipolar disorder: a randomized clinical trial. JAMA 2022;327:727-736.*
16. Citrome L, Preskorn SH, Lauriello J, Krystal JH, Kakar R, Finman J, *et al. Sublingual dexmedetomidine for the treatment of acute agitation in adults with schizophrenia or schizoaffective disorder: a randomized placebo-controlled trial. J Clin Psychiatry 2022;83:22m14447.*
17. Citrome L, Risinger R, Rajachandran L, Robison H. *Sublingual dexmedetomidine for agitation associated with schizophrenia*

or bipolar disorder: a post hoc analysis of number needed to treat, number needed to harm, and likelihood to be helped or harmed. Adv Ther 2022;39:4821-4835. Erratum in: Adv Ther 2023;40:391.

18. Alexza Pharmaceuticals. *ADASUVE™ (loxapine) inhalation powder, for oral inhalation use [Internet]. Silver Spring (MD): U.S. Food and Drug Administration; 2012 [cited at 2022 Nov 27]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022549s000lbl.pdf*
19. Dundar Y, Greenhalgh J, Richardson M, Dwan K. *Pharmacological treatment of acute agitation associated with psychotic and bipolar disorder: a systematic review and meta-analysis. Hum Psychopharmacol 2016;31:268-285.*
20. Zeller SL, Citrome L. *Managing agitation associated with schizophrenia and bipolar disorder in the emergency setting. West J Emerg Med 2016;17:165-172.*
21. Day JC, Bentall RP, Roberts C, Randall F, Rogers A, Cattell D, *et al. Attitudes toward antipsychotic medication: the impact of clinical variables and relationships with health professionals. Arch Gen Psychiatry 2005;62:717-724.*
22. Zareifopoulos N, Panayiotakopoulos G. *Treatment options for acute agitation in psychiatric patients: theoretical and empirical evidence. Cureus 2019;11:e6152.*
23. Townsend M, Pareja K, Buchanan-Hughes A, Worthington E, Pritchett D, Brubaker M, *et al. Antipsychotic-related stigma and the impact on treatment choices: a systematic review and framework synthesis. Patient Prefer Adherence 2022;16:373-401.*
24. Hospira. *Precedex (dexmedetomidine hydrochloride) label [Internet]. Silver Spring (MD): U.S. Food and Drug Administration; 2013 [cited at 2022 Nov 27]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021038s021lbl.pdf*
25. Nelson S, Muzyk AJ, Bucklin MH, Brudney S, Gagliardi JP. *Defining the role of dexmedetomidine in the prevention of delirium in the intensive care unit. Biomed Res Int 2015;2015:635737.*
26. Muzyk AJ, Fowler JA, Norwood DK, Chilipko A. *Role of α2-agonists in the treatment of acute alcohol withdrawal. Ann Pharmacother 2011;45:649-657.*
27. Muzyk AJ, Revollo JY, Rivelli SK. *The use of dexmedetomidine in alcohol withdrawal. J Neuropsychiatry Clin Neurosci 2012;24:E45-E46.*
28. Almeida M, Cicolello K, Hanso A, DeCavalcante G, DeOliveira GS. *Treatment of acute agitation associated with excited catatonia using dexmedetomidine: case series and literature review. Prim Care Companion CNS Disord 2021;23:20cr02899.*
29. Hsiao JK. *Sublingual dexmedetomidine as a potential new treatment for agitation. JAMA 2022;327:723-725.*
30. *Dexmedetomidine sublingual film (Igalmi) for acute agitation. Med Lett Drugs Ther 2022;64:203-205.*