THE JOURNAL OF
CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: Sublingual Dexmedetomidine for the Treatment of Acute Agitation in Adults With Schizophrenia or Schizoaffective Disorder: A Randomized Placebo-Controlled Trial

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DOI Number: 10.4088/JCP.22m14447

List of Supplementary Material for the article

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Supplementary Box 1. Results – Exploratory Endpoints

At 2 hours postdose, mean Positive and Negative Syndrome Scale-Excited Component (PEC) response (≥40% reduction from baseline) rates were 88.8% and 79.1% with sublingual dexmedetomidine 180 µg and 120 µg compared with 40.5% with placebo (Supplementary Figure 1).

On the Clinical Global Impression-Improvement (CGI-I) scale, improvements in agitation (ie, lower CGI-I scores) relative to baseline were observed at 30 minutes to 4 hours postdose (Supplementary Table 3). The least squares mean (standard error [SE]) differences from placebo at 30 minutes, 1, 2, and 4 hours were −0.5 (0.1), -1.1 (0.1), -1.3 (0.1), and -1.3 (0.1) with sublingual dexmedetomidine 180 µg and −0.3 (0.1), -0.6 (0.1), -0.8 (0.1), and -0.8 (0.1) with sublingual dexmedetomidine 120 µg. At 4 hours postdose, mean CGI-I response (score of 1 [very much improved] or 2 [much improved]) rates were 86.9% and 76.2% with sublingual dexmedetomidine 180 µg and 120 µg compared with 50.0% with placebo (Supplementary Figure 2).

ACES change from baseline through 8 hours postdose are presented in Supplementary Table 3 and Supplementary Figure 4. At 2 hours postdose, Agitation-Calmness Evaluation Scale (ACES) differences from placebo were observed in the sublingual dexmedetomidine 180 µg and 120 µg groups (least squares mean [SE] difference: 2.6 [0.2] and 1.6 [0.2], respectively). At 2, 4, and 8 hours postdose, the percentage of patients who had their agitation resolved (ACES score ≥4) was greater in the sublingual dexmedetomidine 180 µg and 120 µg groups than in the placebo group (Supplementary Figure 3).

The respective percentages of patients experiencing calmness (improvement in ACES of ≥1 vs baseline) at 2, 4, and 8 hours postdose were 95%, 93%, and 91% in the 180 µg group, 81%, 87%. and 88% in the 120 µg group, and 49%, 70%, and 66% with placebo.

Patient-reported medication acceptability (as defined by "strongly agree" or "agree" on a 1-5 Likert Scale, administered 20 minutes after dosing) was 84.1% with sublingual dexmedetomidine 180 µg, 84.4% with sublingual dexmedetomidine 120 µg, and 74.6% with placebo. Overall, 67.5% of patients treated with sublingual dexmedetomidine 180 µg, 66.5% of patients treated with sublingual dexmedetomidine 120 µg, and 64.3% of those treated with placebo liked the flavor of the medication (as defined by "strongly agree" or "agree" on a 1-5 Likert Scale). About 99% of study patients judged sublingual dexmedetomidine to have no unpleasant aroma, and the majority of participants judged the study medication to have no unpleasant aftertaste (91.3%, 90.6%, 90.5%) and were satisfied with the time to dissolution (90.1%, 84.9%, 88.4%) in the sublingual dexmedetomidine 180 µg, 120 µg, and placebo groups, respectively, based on yes/no questions.

Supplementary Table 1. Antipsychotic, antidepressant, mood stabilizer, and sedative/hypnotic/anxiolytic concomitant medications

Medication	180 mcg (n=126)	120 mcg (n=129)	Placebo (n=126)	Overall (N=381)
First Generation Antipsychotics	**8**	**10**	**6**	**24**
Chlorpromazine	0	1	0	1
Fluphenazine	1	0	1	2
Haloperidol	6	8	3	17
Loxapine	1	0	0	1
Perphenazine	0	1	2	3
Second Generation Antipsychotics	**99**	**105**	**83**	**287**
Aripiprazole	9	9	9	27
Brexpiprozole	3	2	1	6
Cariprazine	1	1	2	4
Iloperidone	0	1	0	1
Lurasidone	7	6	2	15
Olanzapine	17	14	13	44
Paliperidone	6	4	2	12
Quetiapine	29	37	23	89
Risperidone	26	27	25	78
Ziprasidone	1	4	6	11
Antidepressants	**57**	**42**	**50**	**149**
Amitriptyline	2	0	1	3
Bupropion	5	4	5	14
Citalopram	3	4	5	12
Doxepin	3	2	4	9
Duloxetine	2	2	5	9
Escitalopram	2	1	1	4
Fluoxetine	5	3	7	15
Imipramine	0	1	0	1
Mirtazapine	5	3	1	9
Paroxetine	1	0	0	1
Sertraline	15	6	8	29
Trazodone	14	11	12	37
Venlafaxine	0	4	1	5
Vortioxetine	0	1	0	1

Medication	180 mcg (n=126)	120 mcg (n=129)	Placebo (n=126)	Overall (N=381)
Lithium & Anticonvulsants	**18**	**20**	**12**	**50**
Gabapentin	4	1	0	5
Lamotrigine	1	2	0	3
Lithium	1	3	5	9
Oxcarbazepine	1	0	0	1
Topiramate	0	1	1	2
Valproate, Valproic Acid	10	13	6	29
Zonisamide	1	0	0	1
Sedatives, Hypnotics, Anxiolytics	**28**	**41**	**22**	**91**
Alprazolam	0	1	1	2
Buspirone	2	3	1	6
Clonazepam	1	2	2	5
Diazepam	1	0	0	1
Diphenhydramine	1	3	3	7
Hydroxyzine	8	5	5	18
Lorazepam	9	14	6	29
Temazepam	2	7	2	11
Zolpidem	4	6	2	12

Supplementary Table 2. Frequency of Repeat Dosing by Group

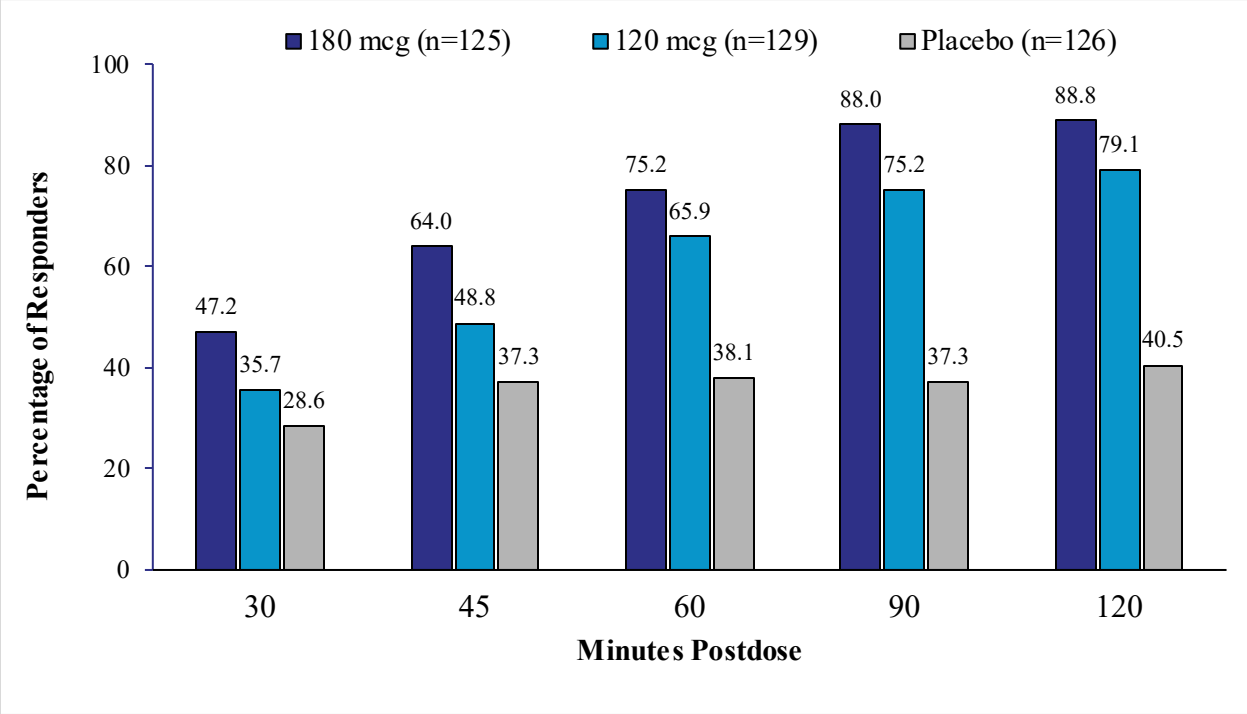
Doses Received	180 mcg (n=126)	120 mcg (n=129)	Placebo (n=126)
1	121 (96.0%)	101 (78.3%)	73 (57.9%)
2	5 (4.0%)	16 (12.4%)	29 (23.0%)
3	0	12 (9.3%)	24 (19.0%)

Supplementary Table 3. Exploratory efficacy endpoints: CGI-I and ACES Scales

	Sublingual Dexmedetomidine				Placebo	
	180 mcg		120 mcg			
CGI-I	**Mean**	**Standard Deviation**	**Mean**	**Standard Deviation**	**Mean**	**Standard Deviation**
30 minutes	2.7	1.2	3.0	1.2	3.4	0.9
1 hour	1.9	1.1	2.4	1.1	3.1	1.1
2 hours	1.5	0.9	2.0	1.2	2.9	1.2
4 hours	1.5	0.9	1.8	1.1	2.5	1.2
ACES						
2 hours	6.0	1.6	4.9	2.0	3.3	1.5
4 hours	5.6	1.6	5.2	1.8	3.8	1.6
8 hours	4.8	1.4	4.4	1.5	3.3	1.3

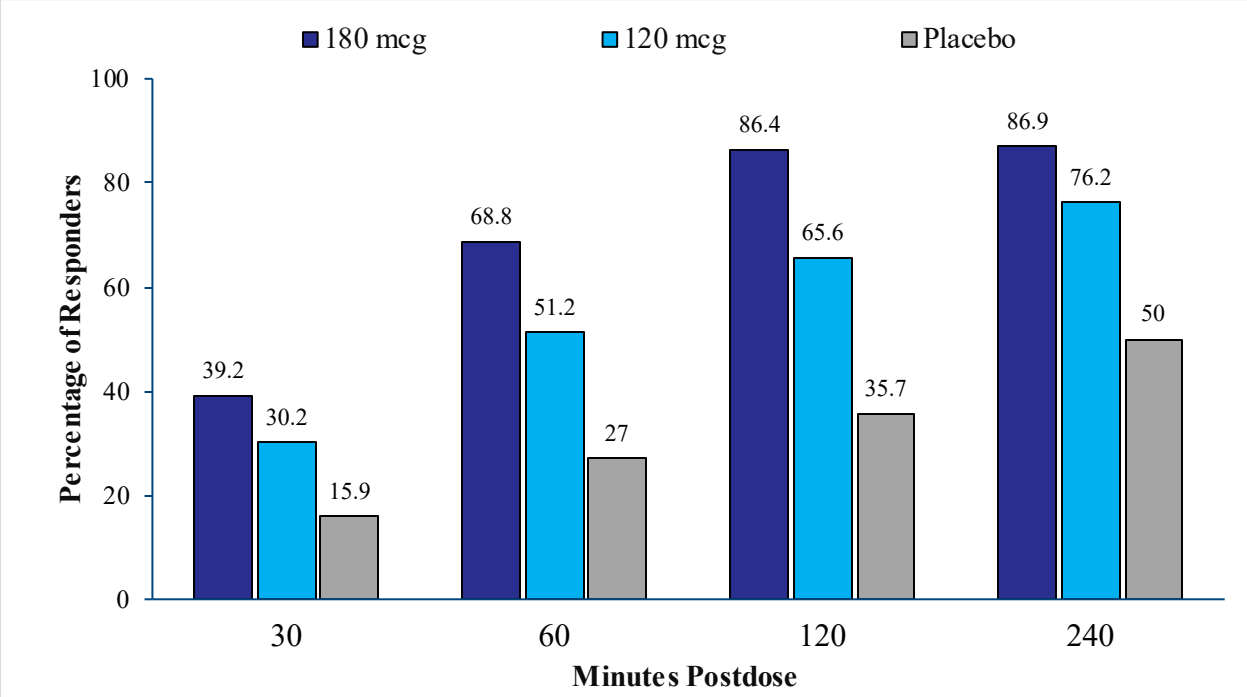
ACES, Agitation-Calmness Evaluation Scale, a single-item measure used to rate overall agitation and calmness where 1=marked agitation, 2=moderate agitation, 3=mild agitation 4=normal behavior, 5=mild calmness, 6=moderate calmness, 7=marked calmness, 8=deep sleep, and 9=unarousable;
CGI-I, Clinical Global Impressions – Improvement with possible scores ranging from 1 (very much improved) to 7 (very much worse).

Supplementary Figure 1. Percentage of patients with a response[a] on the PEC total score



PEC, Positive and Negative Syndrome Scale-Excited Component
[a] Defined by ≥40% reduction from baseline

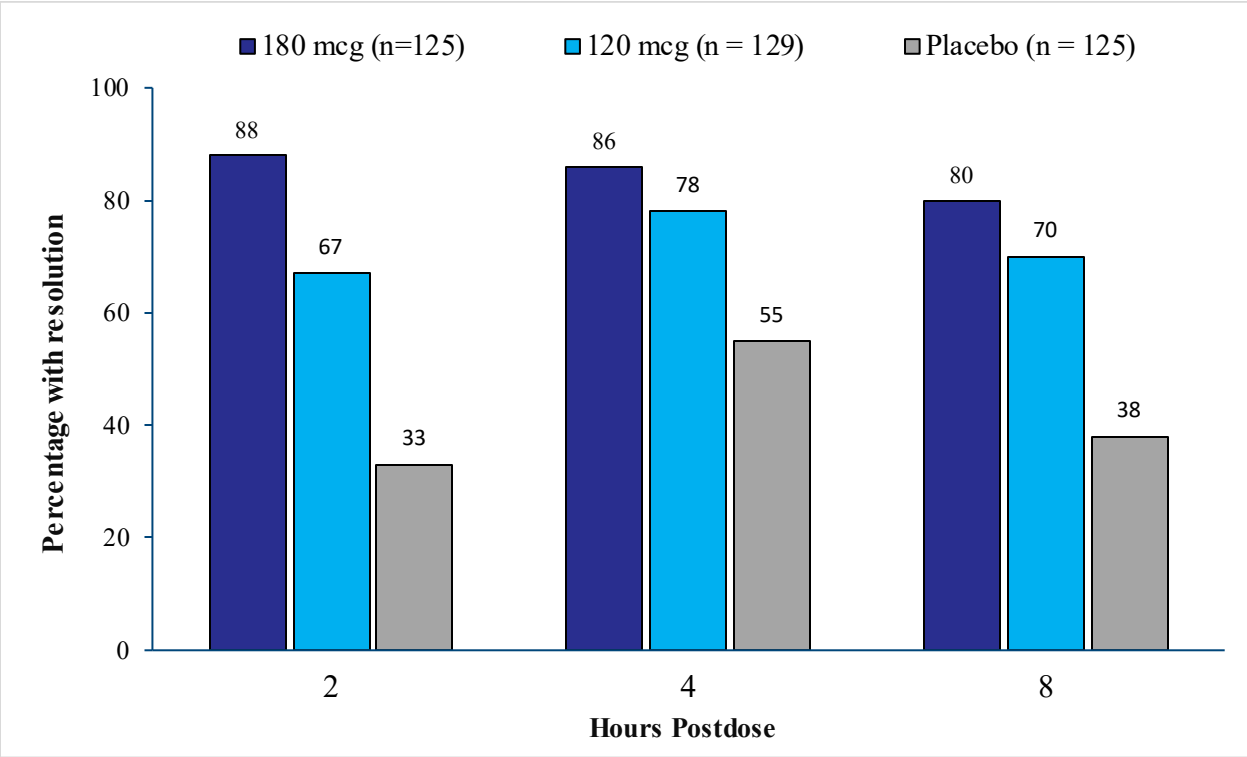
Supplementary Figure 2. Percentage of patients with a response[a] on the Clinical Global Impression-Improvement[b] scale



Minutes Postdose	180 mcg		120 mcg		Placebo	
	n	N	n	N	N	N
30	49	125	39	129	20	126
60	86	125	66	129	34	126
120	108	125	84	128	45	126
240	106	122	80	105	41	82

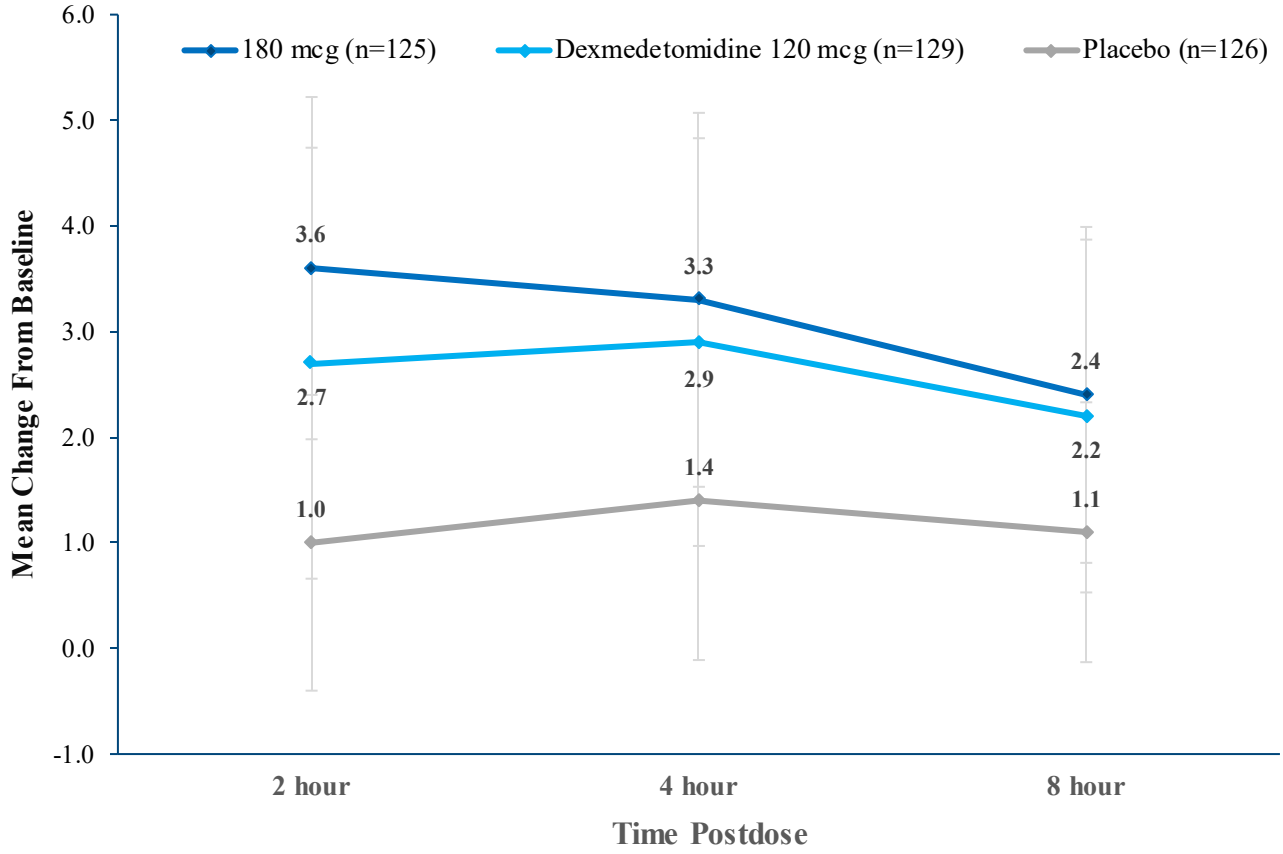
[a]Defined by a score of 1 (very much improved) or 2 (much improved)
[b]Clinical Global Impression-Improvement evaluated drug response on agitation. Scores range from 1 to 7: 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, 7=very much worse.

Supplementary Figure 3. Percentage of patients with resolution of agitation[a] on the Agitation-Calmness Evaluation Scale[b]



[a]Defined by a score of ≥4 on the Agitation-Calmness Evaluation Scale
[b]The Agitation-Calmness Evaluation Scale (ACES) is a single item measure used to rate overall agitation and calmness, where 1=marked agitation, 2=moderate agitation, 3=mild agitation, 4=normal behavior, 5=mild calmness, 6=moderate calmness, 7=marked calmness, 8=deep sleep, and 9=unarousable.

Supplementary Figure 4. Mean change from baseline on the Agitation-Calmness Evaluation Scale[a]



[a]The Agitation-Calmness Evaluation Scale (ACES) is a single item measure used to rate overall agitation and calmness, where 1=marked agitation, 2=moderate agitation, 3=mild agitation, 4=normal behavior, 5=mild calmness, 6=moderate calmness, 7=marked calmness, 8=deep sleep, and 9=unarousable.