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## Challenges in Testing Intranasal Ketamine in Obsessive-Compulsive Disorder

**To the Editor:** Given prior reports that a single intravenous (IV) dose of ketamine, a glutamate receptor modulator, rapidly decreases symptoms in unmedicated patients with obsessive-compulsive disorder (OCD),<sup>1-4</sup> we explored whether an intranasal delivery system is a practical alternative (eg, lower cost and easier administration) to IV infusion. Lapidus et al<sup>5</sup> reported that intranasal ketamine was tolerable and effective in major depression. Thus, we hypothesized that intranasal ketamine administration in OCD patients would be similarly tolerated and yield a greater proportion of treatment responders than midazolam at 1 week post-administration.

**Methods.** OCD outpatients (aged 18–55) were recruited (September 2014 to May 2015) with institutional review board approval. Eligible patients met criteria for OCD (both *DSM-IV* and *DSM-5*), were at least moderately symptomatic (Yale-Brown Obsessive Compulsive Scale [YBOCS<sup>6,7</sup>] score  $\geq 16$ ), and were on stable psychotropic medication doses for at least 6 weeks prior to enrollment. Exclusion criteria included severe depression (Hamilton Depression Rating Scale 17-item [HDRS]<sup>8</sup> score  $> 25$ ) or comorbid psychiatric or medical conditions that made participation unsafe.

Patients were randomized 1:1 to receive intranasal ketamine 50 mg or intranasal midazolam 4 mg. Ketamine was delivered using the administration protocol of a prior intranasal ketamine study in depression.<sup>5</sup> An independent evaluator, blind to treatment, evaluated OCD and depression symptoms at baseline and 1 week after drug administration.<sup>6-8</sup> Treatment response was defined a priori as  $\geq 35\%$  YBOCS score reduction.<sup>9</sup> Patients randomized to midazolam were offered open-label intranasal ketamine 50 mg after study completion.

**Results.** Of the 23 adults with OCD who contacted the clinic to participate in pharmacologic studies, 20 (87%) were screened and determined eligible for study participation. Of those 20 adults, 15 (75%) refused study participation due to not wanting intranasal medication, 6 (40%) of whom endorsed fear of contamination from the nasal applicator. After 2 participants completed the study, we discontinued it due to low enrollment rate and poor tolerability as detailed below.

Subject 1 was a 36-year-old African-American man who had moderate OCD without depression (YBOCS = 21; HDRS = 1) and was taking no medications at baseline. He was randomized to 50 mg intranasal ketamine. Upon administration, he showed visible signs of discomfort (eg, wrinkled nose, upper lip retraction, recoiling); he stated, “This is very unpleasant in my nose—isn’t there another way for me to get this?” but wanted to continue the study. Side effects included dissociation (eg, body feeling unusually large, colors seemed brighter than expected, and time slowed) that lasted for 45 minutes after administration. One week after administration, he did not meet treatment response criteria (YBOCS score = 19; HDRS score = 0).

Subject 2 was a 20-year-old white woman (on stable dose of sertraline 125 mg daily for OCD and divalproate 250 mg daily for migraines) with severe OCD and moderate depression (YBOCS score = 33 and HDRS score = 18). She was randomized to midazolam 4 mg. She wrinkled her nose and complained of an unpleasant “bitter taste” and “stinging” in the nose but wanted to continue the study. She reported lightheadedness and perceptual changes (ie,

sensation of having shrunk) 30 minutes after administration, which resolved by 60 minutes after administration; she also reported headache that resolved by 180 minutes after administration. One week after midazolam administration, she did not meet OCD response criteria, but her depressive symptoms improved from moderate to mild (YBOCS score = 35; HDRS score = 10). She was offered and accepted open treatment with intranasal ketamine. Upon administration, she frowned, wrinkled her nose, opened her mouth with tongue extension, and complained of unpleasant taste, stating, “I would much prefer this in my vein than in my nose.” She also reported nausea and headache that resolved 110 minutes post-administration. One week after ketamine administration, she did not meet OCD response criteria, although her depressive symptom severity met criteria for remission (YBOCS score = 32, HDRS score = 2).

Contrary to our hypotheses, (1) nasal delivery was poorly tolerated in the first 2 study participants, and (2) neither patient met OCD response criteria 1 week after ketamine administration. As a result of observed verbal and physical cues indicating patient discomfort during nasal delivery and difficulty enrolling study participants, the study was discontinued. The discomfort reactions to intranasal ketamine were specific to the insertion of the nasal applicator and the spray method of delivery rather than to medication side effects. In contrast, in prior studies<sup>1-4</sup> of ketamine conducted by the first author of this case report (C.I.R.), placement of the IV and ketamine administration were well tolerated. Enrollment rates for this study were very low (of the 20 screened eligible participants, only 2 [10%] agreed to participate over 9 months), compared to significantly higher rates in C.I.R.’s studies in the same clinic with IV ketamine. Regarding our finding that neither patient met OCD treatment response criteria, our results may simply reflect subgroups of OCD patients that do and do not respond to ketamine (as indicated by contrasting prior publications on the efficacy of IV ketamine in OCD).<sup>1-4,10</sup> By chance, the study participants (n = 2) may be in the subgroup that does not respond to ketamine. Approaches to properly assessing efficacy of intranasal ketamine in OCD in future studies may require utilizing a more comfortable self-administration device (as investigated in a recent Janssen-sponsored study [NCT01998958]).

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**Potential conflicts of interest:** Drs Steinman and Kalanthroff and Miss Zwerling, Levinson, and Mahnke report no additional financial or other relationships relevant to the subject of this letter. Dr Rodriguez received rapastinel for another study at no cost from Naurex (since drug donation, Naurex has been acquired by Allergan); she was reimbursed for travel and time to present these findings to Allergan after the results were submitted for publication. Dr Rodriguez is also a consultant for BlackThorn Therapeutics. Dr Lapidus has received research support from the Brain and Behavior Research Foundation, Le Foundation, Education and Research Foundation for Nuclear Medicine and Molecular Imaging, Simons Foundation, and NIMH; serves on the advisory board for Halo Neuroscience; has received devices, meals, travel, and research support from Medtronic, Halo Neuroscience, Neuronetics, Brainsway, and Roche; has consulted for FCB Health, SmartAnalyst, Cipla, and LCN Consulting, Inc; provides clinical treatment with ketamine; founded New York Neuromodulation; and has been named on a patent application for an intranasal medication administration device. Dr Simpson receives royalties from Cambridge University Press and UpToDate, Inc.

**Funding/support:** This investigation was supported by grants from Columbia University Provost's Grant Program for Junior Faculty Who Contribute to the Diversity Goals of the University (Dr Rodriguez) and the National Institute of Mental Health (K23MH092434, to Dr Rodriguez, and K24MH09155, to Dr Simpson).

**Role of the sponsor:** None.

**Acknowledgments:** We thank those individuals with OCD who generously donated their time to participate in this research study.

**Trial registration:** ClinicalTrials.gov identifier: NCT02206776.

*J Clin Psychiatry* 2017;78(4):466–467

<https://doi.org/10.4088/JCP.16cr11234>

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