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Open-Label Trial on the Effects of Memantine in Adults With Obsessive-Compulsive Disorder After a Single Ketamine Infusion

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LETTER TO THE EDITOR

The only first-line pharmacological treatments recommended for obsessive-compulsive disorder (OCD) are serotonin reuptake inhibitors (SRIs).¹ We found that a single intravenous (IV) dose of ketamine, an N-methyl-D-aspartate (NMDA) glutamate receptor antagonist, rapidly decreases symptoms in unmedicated patients with OCD,² demonstrating that a drug affecting glutamate transmission can reduce OCD symptoms without an SRI. After study participation, patients often requested a drug with similar effects to ketamine that could be taken as an outpatient. Memantine shares a similar mechanism of action as ketamine, ie, NMDA glutamate receptor antagonism, albeit with less affinity³ to the receptor than ketamine. It has been shown to decrease OCD symptoms in some when given orally over 12 weeks.^{4–11} Given memantine is available in oral dosing and may be easier to access than ketamine in outpatient treatment, we explored in an open-label pilot trial whether response to one NMDA receptor antagonist (IV ketamine) might predict response to a second NMDA receptor antagonist (oral memantine) in a sample of convenience - unmedicated adults with

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OCD who had recently finished participation in a trial of IV ketamine. We also sought to explore memantine's clinical effects and tolerability when given after ketamine.

Methods

To accurately document history of ketamine effects, we recontacted (with institutional review board approval) 15 adults with OCD who participated in a prior ketamine study in which half met response criteria (35% reduction on Yale-Brown Obsessive-Compulsive Scale [Y-BOCS]¹²) seven days post a single 0.5mg/kg intravenous (IV) dose. Twelve agreed to participate and provided informed consent. At the time of the ketamine study, all met DSM-IV and DSM-5 criteria for OCD with at least moderate symptoms (Y-BOCS score 16). At the time of the memantine trial, all were unmedicated and 2 had symptoms of mild to moderate depression. As shown in Table 1, the weeks since their ketamine infusion varied as did their OCD severity as measured by the Y-BOCS prior to starting memantine. Ketamine responders averaged 38.8 days (SD = 32.0) and ketamine non-responders averaged 26.1 days (SD = 26.4) before memantine administration; there was no significant difference in the time since prior ketamine treatment between the two ($t(10)=0.615$, $p=0.552$).

Open-label memantine was started at 5mg daily and titrated by 5mg weekly to 10mg twice daily for up to 6 weeks. Memantine was continued to 12 weeks in those with treatment response¹³ either to ketamine (35% Y-BOCS reduction one week after IV ketamine) or current response to memantine (35% Y-BOCS reduction from pre- to post- 6 weeks of memantine). At baseline, 6, and 12 weeks, an independent evaluator, blind to study design, evaluated OCD symptoms (Y-BOCS), depression (HDRS-17), and anxiety (Hamilton Anxiety Inventory [HAM-A]). Paired t-tests assessed change from pre-memantine (baseline) to post-memantine (6 weeks) using the last available observation.

Results

Of the 12 who started memantine, 8 completed six weeks and 3 completed 12 weeks. Overall, the 12 patients showed no significant changes 6 weeks post-memantine on YBOCS ($t(11)=1.28$, $p=.23$), HDRS-17 ($t(11)=1.85$, $p=.09$), and HAM-A ($t(11)=-.09$, $p=.93$). In those who did not respond to IV ketamine ($n=8$), they did not respond to oral memantine either (Table 1). However, they did report side effects of dizziness ($n=2$) and anxiety ($n=3$), which led 3 to drop out early. In those who did respond to IV ketamine ($n=4$), the story was more complex. Subject 1 lost his ketamine response at the time of starting memantine and regained his treatment response after six weeks of memantine but not after 12 weeks of memantine. Subject 2 seemed to maintain his response to ketamine (although it is not clear how long the beneficial effects of ketamine would have lasted without the memantine) and by his verbal report after 12 weeks of memantine; however, when he discontinued his memantine at week 12, he relapsed two weeks later. Subject 3 also seemed to maintain his ketamine response after six weeks of memantine (34% decrease from initial score of 29 on the YBOCS). Subject 4 responded so robustly to ketamine that it was impossible to assess further benefit from memantine.

Conclusions/Discussion

In ketamine nonresponders, none responded subsequently to oral memantine. In ketamine responders, memantine may have helped 1 patient temporarily regain the ketamine effects and 2 two maintained the ketamine effects, although it is not possible to rule out whether ketamine's effect would have persisted without memantine. Another responded so well to ketamine it was not possible to assess memantine's effects. In this sample of convenience with variable time between treatments, we learned that in ketamine responders, ketamine affects individuals in unique trajectories. How these trajectories intersect with memantine's effects awaits a confirmatory large randomized trial.

This sample had a low rate of response to memantine compared to prior studies,^{4–11} which could have occurred for 2 reasons: (1) in contrast to prior trials, our sample was not on an SRI, and 2) 8 of the 12 participants had no response to ketamine, which means we may have selected patients unresponsive to NMDA modulation, the putative mechanism of ketamine and memantine.

Limitations of this exploratory open-label pilot study include small sample size, lack of randomization and blinding, and high drop rate due to side effects and nonresponse. It is also important to highlight that ketamine and memantine have similar (but not identical) mechanisms of action via NMDA receptor antagonism.

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Clinical Characteristics and History of Ketamine Response^a in Unmedicated OCD patients (n=12) Treated with Open-Label Memantine for 6 to 12 Weeks

Table 1

History of Ketamine Response by Patient	Age/Sex/Ethnicity	Duration of Illness	No. of Prior SRI Trial	Prior EX/RP Trials	KETAMINE		Days Post Ketamine Infusion	Memantine Start			
					Pre-Baseline Y-BOCS	Post-1-Week Y-BOCS		Pre-Baseline Y-BOCS	Y-BOCS at Drop ^b	Post-6-Week Y-BOCS	Memantine Continuation 12-Week ^c Y-BOCS
Ketamine Responders	1. 47/M/AA	19	3	Yes	26	14	84	25		14	22
	2. 53/M/W	15	1	No	29	12	28	11		12	^d
	3. 32/M/H	25	3	Yes	29	17	21	21		19	25
	4. 24/F/AA	12	0	Yes	25	7	14	0	0	-	-
Ketamine Non Responders	5. 24/M/H	5	0	No	24	27	73	27		23	-
	6. 32/M/W	11	3	Yes	23	19	62	18	23	-	-
	7. 38/F/A	22	2	No	36	31	25	31		28	-
	8. 29/F/AA	14	4	No	29	30	14	31		23	-
	9. 33/M/W	30	5	No	24	26	14	26		21	-
	10. 22/F/AA	10	0	No	25	24	7	24	24	-	-
	11. 33/M/AA	21	0	No	20	23	7	23		26	-
	12. 36/M/W	20	1	Yes	23	20	7	20	23	-	-

^aHistory of ketamine response in a prior study (see Koran et al¹) was defined as a 35% Y-BOCS reduction one week after intravenous ketamine.

^bY-BOCS score at drop visit. Participant 4 dropped at week 4 due to no longer having OCD symptoms. Participants 6, 10, 12, dropped at week 2 due to increased anxiety.

^cMemantine was continued to 12 weeks in those with treatment response (see Goodman et al¹²) either to ketamine (35% Y-BOCS reduction one week after intravenous ketamine) or to memantine (35% Y-BOCS reduction from pre- to post- 6 weeks of memantine).

^dParticipant 2 reported continued low OCD symptoms while on his medication, but was unable to have week 12 independent evaluation until 2 weeks after his medications ran out. His Y-BOCS score at week 14 was 26.

Abbreviations: A = Asian, AA = African American; EX/RP = Cognitive Behavioral Therapy with Exposure and Response Prevention; F = female; H = Hispanic; M = male; OCD = obsessive-compulsive disorder; SRI = serotonin reuptake inhibitor; W = white; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale.

Symbol: - = not applicable.