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

To the Editor: The only first-line pharmacologic 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 affinity[3] to the receptor than ketamine. It has been shown to decrease OCD symptoms in some patients when given orally over 12 weeks.[4–11] Given that 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 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]) 7 days after a single 0.5 mg/kg 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 36.8 days (SD = 32.0) before memantine administration, and ketamine nonresponders averaged 26.1 days (SD = 26.4) ($t_{10} = 0.615$, $P = .552$).

Open-label memantine was started at 5 mg daily and titrated by 5 mg weekly to 10 mg twice daily for up to 6 weeks. Memantine was continued to 12 weeks in those with treatment response,[13] either previous response to ketamine (≥ 35% Y-BOCS reduction 1 week after IV ketamine) or current response to memantine (≥ 35% Y-BOCS reduction from pre– to post–6 weeks of memantine). At baseline and 6 and 12 weeks, an independent evaluator blinded to study design evaluated OCD symptoms (Y-BOCS), depression (17-item Hamilton Depression Rating Scale [HDRS-17][14]), and anxiety (Hamilton Anxiety Rating Scale [HARS][15]). 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 6 weeks and 3 completed 12 weeks. Overall, the 12 patients showed no significant changes 6 weeks after memantine initiation on Y-BOCS ($t_{11} = 1.28$, $P = .23$), HDRS-17 ($t_{11} = 1.85$, $P = .09$), and HARS ($t_{11} = -0.09$, $P = .93$). In those who did not respond to IV ketamine (n = 8), they did not respond to oral memantine either (Table 1).

Table 1. Clinical Characteristics and History of Ketamine Response[a] in Unmedicated Adult OCD Patients (n = 12) Treated With Open-Label Memantine for 6 to 12 Weeks

					KETAMINE		Memantine Start ↓	MEMANTINE			
History of Ketamine Response by Patient	Age/Sex/ Ethnicity	Duration of Illness (y)	No. of Prior SRI Trials	Prior EX/RP Trials	Pre-Baseline Y-BOCS	Post–1-Week Y-BOCS	Days Post-Ketamine Infusion	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 nonresponders											
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	…	…

[a]History of ketamine response in a prior study (see Koran et al[1]) was defined as a ≥ 35% Y-BOCS reduction 1 week after intravenous ketamine.
[b]Y-BOCS score at drop visit. Participant 4 dropped at week 4 due to no longer having OCD symptoms. Participants 6, 10, and 12, dropped at week 2 due to increased anxiety.
[c]Memantine was continued to 12 weeks in those with treatment response (see Goodman et al[12]) either to ketamine (≥ 35% Y-BOCS reduction 1 week after intravenous ketamine) or to memantine (≥ 35% Y-BOCS reduction from pre– to post–6 weeks of memantine).
[d]Participant 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 independent evaluation 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.

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 6 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, continued to maintain it after 12 weeks of mematine; however, when he discontinued his mematine at week 12, he relapsed 2 weeks later. Subject 3 also seemed to maintain his ketamine response after 6 weeks of memantine (34% decrease from initial score of 29 on the Y-BOCS). Subject 4 responded so robustly to ketamine that it was impossible to assess further benefit from memantine.

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 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 taking an SRI, and (2) 8 of the 12 participants had no response to ketamine, which means we may have selected patients unresponsive to NMDA receptor 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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