ROLE OF KETAMINE IN OBSESSIVE COMPULSIVE DISORDER: A REVIEW OF LITERATURE

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Background

OCD is a chronic neuropsychiatric disorder characterised by obsessions and/or compulsions that are ego-dystonic. It is associated with significant disability, poor quality of life and high family burden, often comparable to schizophrenia and other severe mental illnesses (Gururaj et al., 2008). The National Mental Health Survey of India (2015-2016) reported the prevalence of anxiety disorders (including PTSD and OCD) to be 2·94% in the country. With its varied aetiology, autoimmunity was initially implicated in the OCD pathophysiology in the early 1990s, with the paediatric autoimmune neuropsychiatric disorder associated with group A beta-hemolytic streptococcus (GABHS), initially named PANDAS, then renamed paediatric acute neuropsychiatric syndrome (PANS) (Swedo et al., 2012). There is a fivefold higher rate of anti-basal ganglia antibodies in both paediatric and adult OCD patients compared to controls (Pearlman et al., 2014). Studies confirmed the presence of inflammatory markers in the adult OCD brain, specifically within the cortico-striatal-thalamo-cortical regions implicated in OCD pathophysiology (Attwells et al., 2017; Cosco et al., 2019). Raised levels of Interleukins (IL-2,4,6,10), and TNF-alpha were found in comorbidity-free OCD (Rao et al., 2015). Raposo-Lima and colleagues in 2021 found raised serum levels of Neutrophil Gelatinase Associated Lipocalin (NGAL) in OCD patients compared to healthy controls (Raposo-Lima at al., 2021).

Only about 40-70% of OCD patients treated with first line treatments (SRI's/CBT) show an adequate response with a remission rate of 10-40% (Skapinakis et al., 2016). The remaining 30-60% are either partial responders or non-responders (Reddy et al., 2017). Beyond the anti-inflammatory agents such as Celecoxib, Rituximab (a monoclonal antibody that binds Naproxen, Memantine, Troriluzole, Minocycline, Lamotrigine and Topiramate, ketamine too has found its application in OCD.

KETAMINE

Ketamine is a non-competitive N-methyl-d-Aspartate (NMDA) receptor agonist with well-established safety and efficacy as an analgesic and anaesthetic. It has been found to produce profound analgesia combined with an unconsciousness in which the patient appears disconnected rather than asleep. Thus, pharmacologically, Ketamine is categorised as a dissociative anaesthetic agent.

Reports of Ketamine's rapid antidepressant action first appeared in 2000 in a case study by Berman and colleagues, in which patients with major depressive disorder underwent two test days involving intravenous administration of ketamine hydrochloride (0.5 mg/kg) or saline solutions, under randomised, double-blind conditions. Subjects with depression evidenced significant improvement in depressive symptoms within 72 hours after ketamine but not placebo infusion. Thereafter, several studies across the globe have confirmed the rapid antidepressant actions of ketamine. One Indian study found rapid alleviations of depressive symptoms following each of a series of 6 bolus injections of Ketamine starting at 1 hour post infusion and lasting up to a month of the last injection (Mandal et al., 2018). Another study found rapid improvement in both depressive symptoms and suicidal ideations from 6th hour till 1 week following ketamine infusions (Pathak et al., 2021).

Post-Traumatic Stress Disorder (PTSD): There is little research in this field, despite the hypothesis that ketamine may be helpful in reducing the onset of PTSD by promoting stress resilience (Brachman et al., 2016). (Li and Vlisides, 2016). Feder and colleagues discovered in

2014 that ketamine may lessen the severity of PTSD symptoms more quickly than midazolam; however, they did not exclude patients who had experienced depression in the past, and the results may have been partially explained by ketamine's well-known antidepressant properties. A case study by Donoghue et al. (2015) describing the remission of disruptive symptoms and PTSD in a kid due to ketamine administration offers conflicting evidence on the effects of ketamine on PTSD.

Ketamine in OCD

The complete impact of ketamine on OCD has not yet been determined. Ketamine's rapid antidepressant effectiveness is thought to be due to the inhibition of presynaptic NMDA receptors, which increases glutamate release from nerve terminals and activates postsynaptic AMPA receptors. Following these occurrences, calcium influx, voltage-sensitive calcium channel activation, and the release of brain-derived neurotrophic factor occur (BDNF). The mTOR and its downstream signalling pathways are activated by the BDNF-TrkB signalling, which results in increased synaptic protein synthesis and synaptogenesis (neuroplasticity) (Scheuing et al., 2015). It is unknown whether such a mechanism contributes to the purported effectiveness of ketamine in treating OCD, and further research is necessary (Marinova et al., 2017).

Rodriquez and colleagues, in 2015, hypothesised that ketamine infusion significantly increases medial Prefrontal Cortex (MPFC) Glutamate + Glutamine (Glx) level in unmedicated adult OCD participants over time. **However, in their study ketamine did not bring about such an increase in the levels of Glx, instead it significantly increased MPFC GABA levels over time. The change in GABA/W levels was positively correlated with changes in OCD symptoms, but not correlated with (and thus unlikely to be manifestations of) psychotic or dissociative symptoms.** Such findings were in line with the findings by others who proposed the role of **abnormalities in cortical inhibitory processes in OCD**, observed using transcranial magnetic stimulation paradigms with untreated OCD patients who displayed baseline GABA impairments in MPFC compared to matched healthy controls (Richter et al., 2012). (Simpson et al., 2012). The post-ketamine increase in GABA is consistent with recent studies suggesting that **ketamine simultaneously stimulates a subpopulation of GABAergic interneurons and projection neurons.** (Whittington et al., 2000). Nonetheless, some authors exercise caution in this regard, speculating the possibility that greater GABA changes during ketamine infusion may only be a reflection of greater underlying GABAergic abnormalities in OCD and not a mechanism of action (Rodriquez et al., 2015).

1.3.2. Previous Studies of Ketamine in Obsessive Compulsive Disorder:

The use of Ketamine in the treatment of OCD was first made by Rodriguez and colleagues in a 2011 case report. In this, a 24-year-old woman with history of obsessions of exactness/symmetry and compulsive repetition and checking had a history of failure of trials of three previous anti-obsessives: Fluoxetine 60 mg, Escitalopram 30 mg and Clomipramine 200 mg, each lasting for three months. She had also had poor adherence to ERP and had refused antipsychotic augmentation for fear of weight gain. She had a positive family history of OCD in her sister and depression in her mother. Prior to the trial, she had a baseline Y-BOCS score of 30 (severe OCD) and HDRS score of 7 (mild depressive symptoms).

The trial consisted of a double-blind crossover of ketamine and saline. This involved two intravenous (IV) infusions given to the patient over a 40-minute period, separated by seven days. She originally received a saline infusion as a placebo, but there was no improvement in her compulsive symptoms. **After the second infusion (ketamine at 0.5 mg/kg), however, the obsessive symptoms were totally eliminated, with a partial return between 40 and 230**

minutes following intervention. And the symptoms only returned to their baseline level after 7 days. The patient showed no symptoms of mania, psychosis or intoxication with scores on YMRS, BPRS AND Visual Analog scale for Intoxication scales being 0. Feeling of unreality with CADSS score of 1, resolved after 5 minutes of stopping the infusion. **The trial was limited by the small sample size and the difficulties of blinding due to the psychoactive effects of ketamine.**

Figure 1: Proposed mechanisms of Ketamine (adapted from Motta et al., 2021)

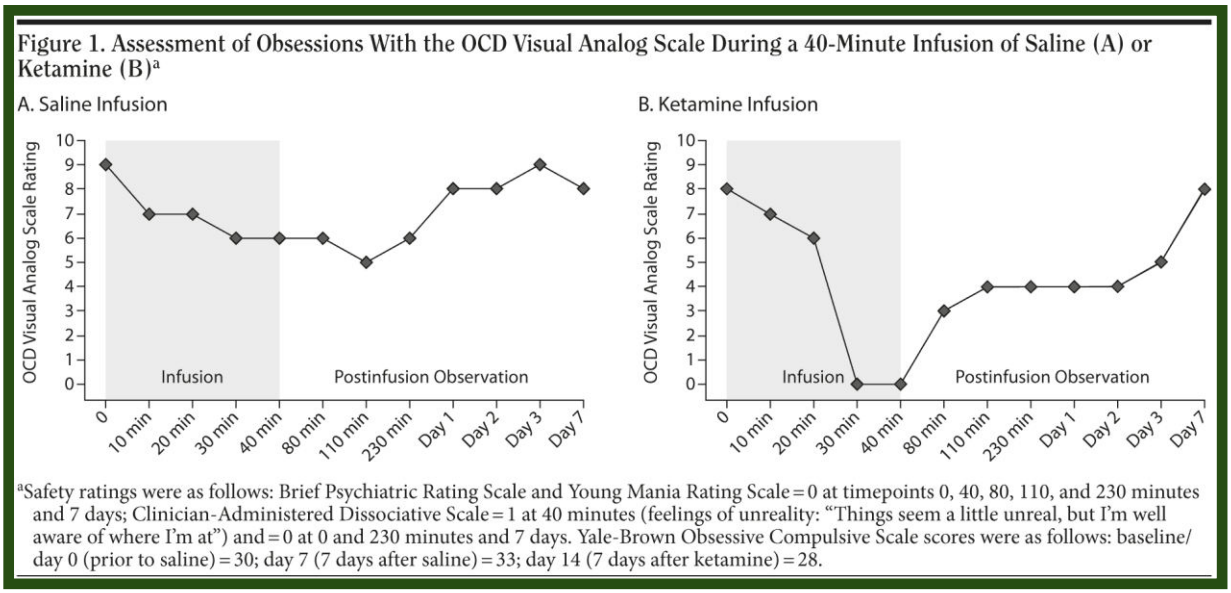
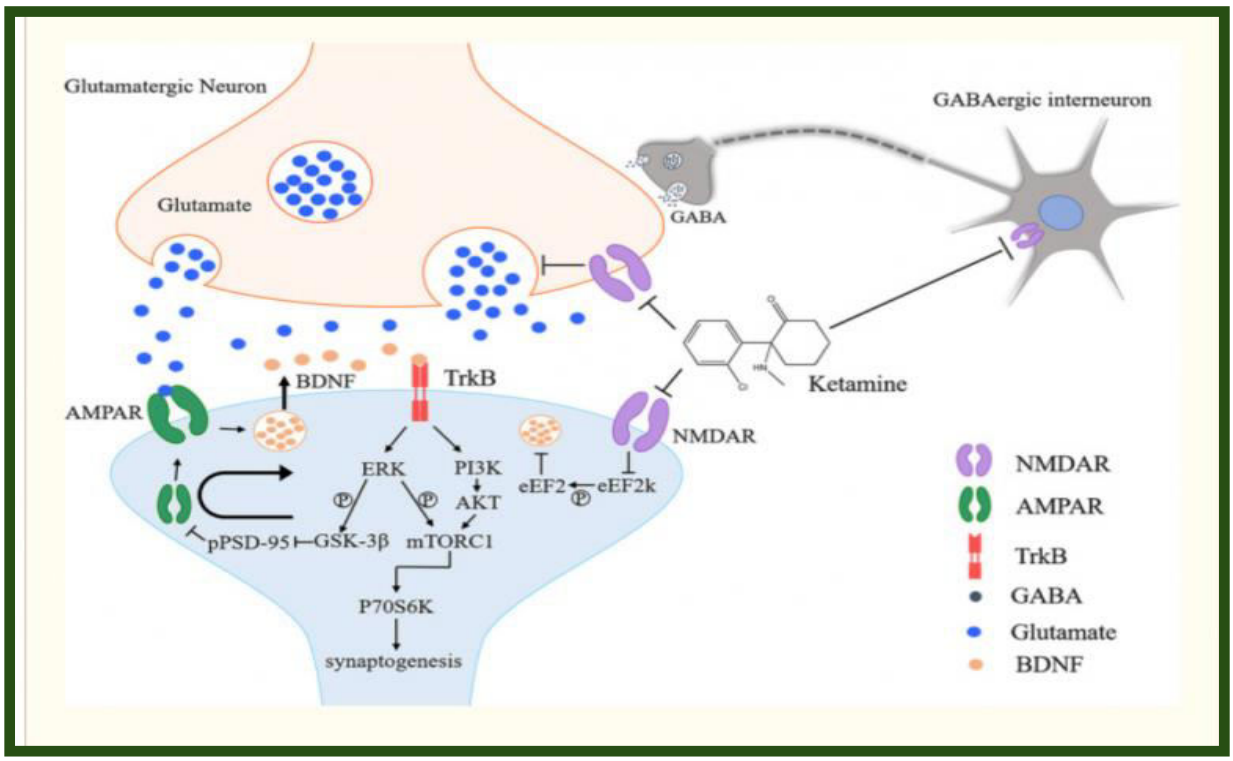


Figure 2: Adapted from Rodriquez et al., 2011.



Following this, an open labelled clinical trial was conducted by Bloch and colleagues in 2012. Ten patients of refractory OCD (defined as Y-BOCS score >24 after 2 trials of SSRIs and having been offered CBT previously) who were on stable doses of medications for 2 months prior, were each given a 40-minute continuous infusion of a single dose of intravenous ketamine (0.5 mg/kg body weight). They were rated at 1, 2, 3 hours and 1, 2, 3, 5 and 7 days following infusion using Y-BOCS, HDRS, CADSS, CGI scales. The patients had severe baseline OC symptoms with Y-BOCS range of 31-36. Six subjects had major depressive disorder. Seven of the patients were on anti-obsessives, six on high doses. Four were on antipsychotic augmentation. 1 patient was on glutamate modulating agents - both Riluzole and N-Acetyl cysteine.

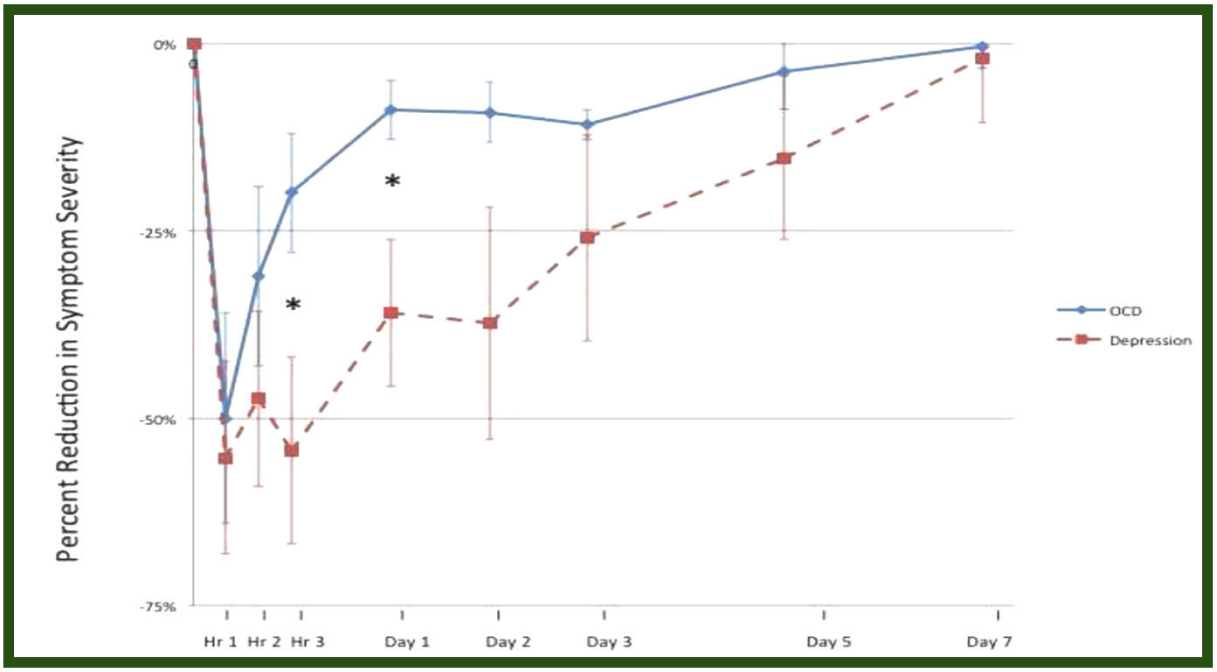


Figure 3: Adapted from Bloch et al., 2012

Following infusion, OC symptoms reduced by a maximum of 11% within 3 hours of the infusion but did not meet the response criteria at any time, defined a priori as reduction of symptoms by 35% or more. Even this minimal reduction did not continue as the effect largely dissipated the day following the infusion. There was also no significant difference in the pattern of reduction in the obsession and compulsion sub-scales. Four of the seven patients with co-morbid major depressive disorder showed response (>50% reduction in HDRS) within the 1st three days of the infusion. There was a substantial association between the two in the first three days, with the percentage reduction in depressed symptoms being significantly bigger than the percentage reduction in OC symptoms. **There were significant limitations to the trial. It was small, uncontrolled and unblinded. This was designed as such because the time course of OCD response to ketamine was yet unknown and establishing this time-course was a critical task for future controlled trials.** Moreover, **it was problematic to establish a credible placebo for ketamine,** given the predictable and common acute physiologic (increase in heart rate and blood pressure) and psychological (dissociative symptoms, euphoria, peri-oral paraesthesias, nausea etc.) effects of ketamine. Their conclusion was that there was insufficient data for the use of Ketamine therapeutically.

In 2013, Niciu and colleagues published a case report of two female OCD patients (aged 25 years and 64 years) with comorbid PTSD in both, unspecified personality disorder and Trichotillomania in one, and past history of major depressive disorder in both. A 40-minute

continuous infusion of a single dose of intravenous ketamine (0.5 mg/kg body weight) resulted in late onset dysphoria, worsening of anxiety and suicidal ideation peaking at 24 hrs after infusion.

With 15 patients with moderate to severe OCD (Y-BOCS > 16), Rodriquez and colleagues conducted their first randomised, double-blind, placebo-controlled cross-over trial in 2013. All participants in the trial had been on stable doses of medications for 1 year prior to the trial and were required to be off medications for 7 days before the trial began. They were divided into 2 arms. In Arm A, 8 patients were first given intravenous Ketamine infusion, followed by saline infusion after 1 week of the 1st infusion. In Arm B, 7 participants were first given saline infusion and were supposed to be given Ketamine infusion after 1 week of the saline infusion. Three key conclusions emerged: (1) In contrast to participants who got saline infusion initially, those who first received ketamine infusion experienced a quick drop in obsessions that lasted for one week after the infusion. (2) One week after the ketamine infusion, 50% of the subjects had already met the criteria for therapeutic response. (3) Considerable carryover effects were seen, indicating that the effects of ketamine on OCD symptoms may continue considerably longer than indicated by prior studies. It was the first randomised controlled trial to demonstrate that Ketamine reduced obsessive symptoms when serotonin reuptake inhibitors are not used. They proposed that the disparity between their results and those of Bloch and colleagues was due to 1) sampling preference (patients with near constant intrusions of > 8 hrs/day vs no such requirement by Bloch and colleagues), 2) requirement to be medication free (Bloch and colleagues enrolled those that were on medications), 3) higher scores on dissociation scale (22 vs 1.4 on CDSS) and, 4) lesser number of patients with co-morbid depression in their study than the previous study (2 out of 15 vs 7 out of 10) leading the authors to even hypothesise that OCD with co-morbid depression may perhaps be the sub-population that responds minimally to Ketamin.

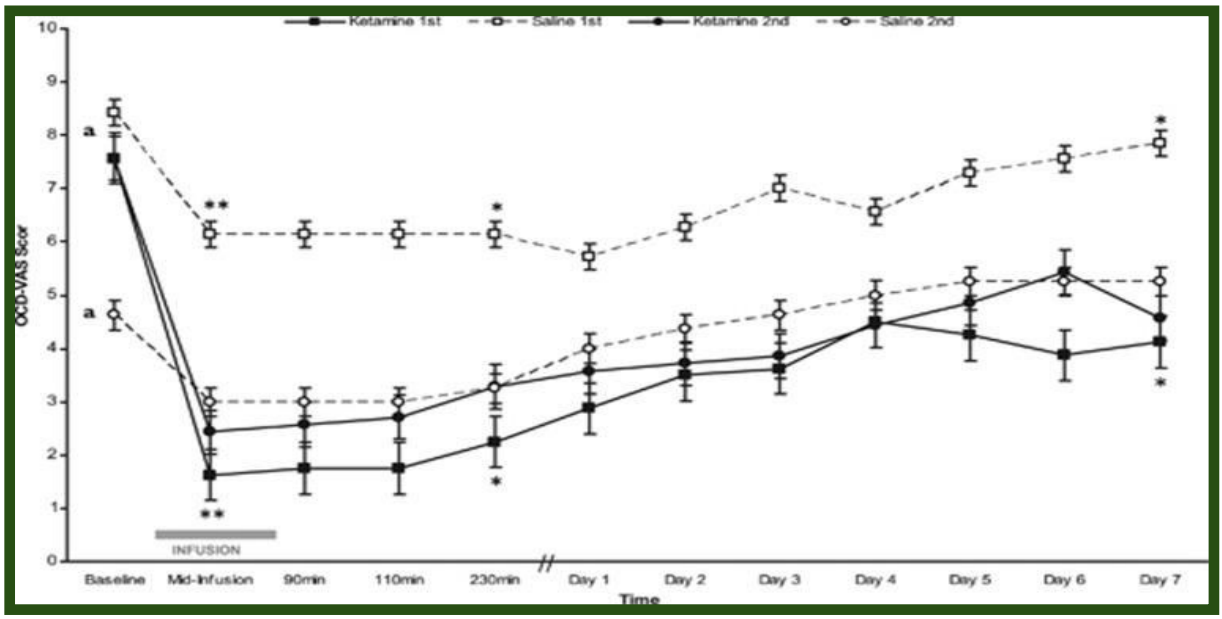
There were three main limitations to the study. First, the sample size was small. Second, blinding of patients was difficult due to the characteristic psychomimetic effects of Ketamine. Third, despite ketamine's NMDA receptor binding affinity being several times higher than at other sites, it remains unproven if the anti-obsessional effects are indeed due to NMDA receptor binding and not other receptors. In 2016, the same group conducted an open label trial on ten untreated OCD outpatients (aged 18 to 55) with intrusive obsessions that are nearly persistent (>8 hours per day) and a Y-BOCS score under 16. Participants got a single IV infusion of 0.5 mg/kg ketamine in a 40 minutes period, followed by 10 CBT sessions with the same therapist lasting an hour each, spread over two weeks.

Of the ten, nine finished the infusion. OCD-VAS scores from eight patients showed a sharp decline, though seven patients' scores continued to rise up to 230 minutes after the infusion. Within two weeks of the infusion, eight people finished the 10 hours of CBT. The mean estimated Y-BOCS score was significantly lower at weeks 2 and 4 compared to the baseline (difference=10.75 and 6.88 points, respectively), and there was a modest increase between weeks 2 and 4 (difference=3.63). 63% of patients continued to meet response criteria (a 35% Y-BOCS reduction) after the conclusion of CBT (week 2). It's interesting how differently the subjects responded: one person saw no improvement, the majority did so for up to two weeks, and one person experienced remission up to six months after the infusion.

Again in 2017, Rodriquez and colleagues presented a case report of 2 OCD patients. They were a 36 year old man with moderate OCD (Y-BOCS=21) without depression (HDRS=1) and on no medications, and a 20 year old woman with severe OCD (Y-BOCS=33) and moderate depression (HDRS=13) on 125 mg of Sertraline and 250 mg of Divalproex for migraines. Both received 50 mg of intranasal Ketamine spray. Both complained of wrinkled nose, upper lip retraction and unpleasant taste which were specific to the nasal applicator insertion and the spray

method rather than the medication itself. Neither met response criteria for OCD at 1 week after the administration (Y-BOCS=19 and 32 respectively) but had significant reductions in depressive symptoms (HDRS=0 and 2 respectively).

Figure 4: Adapted from Rodriquez et al., 2013.

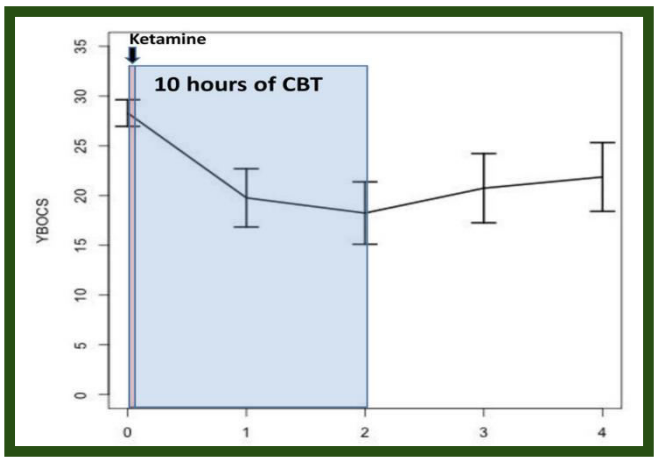


In a case report by Adams and colleagues in 2017, a male patient in his late twenties, with multiple co-morbidities-OCD (Y-BOCS=28), MDD (MADRS=33), suicidal ideation, social phobia, and bulimia- and a string of unsuccessful treatments, received ketamine intra-nasally (50 mg), twice a week for four weeks along with CBT-ERP, which was started 2 weeks prior to Ketamine administration. The patient showed a reduction in OCD symptoms (Y-BOCS=23) after two weeks of the CBT, with an additional reduction (Y-BOCS=20) after 1 week of ketamine application. It is challenging to say whether intensive CBT and ketamine worked together to achieve therapeutic benefit. Improvements in OCD symptoms were noted after two weeks of CBT and prior to the administration of ketamine, suggesting that the patient may have benefited purely from inpatient CBT. The absence of relevant OCD triggers on the inpatient unit may possibly be responsible for these improvements. However, there are reasons to think that the patient benefited from ketamine, including additional symptom reductions that occurred after the start of ketamine treatments, improved compliance with ERP soon after starting ketamine, which suggests that ketamine may enhance the process of ERP for OCD, and the patient's report of a rapid and significant decline in suicidal ideation after the first week of the treatments.

In 2020, Sharma and colleagues reviewed the clinical charts of 14 adult patients (7 male, 7 female) who received ketamine infusions during their inpatient care at a premiere neurosciences institute in India between June 2014 and January 2019. Patients resistant to SRIs were chosen: twelve of the fourteen had not responded to at least 2 adequate trials and one had failed a single trial. One patient could not take oral medication due to contamination fears and was not amenable for CBT as well. Overall, nine of 14 (64 %) had failed to respond to CBT. All subjects received serial ketamine infusions ranging from 2 to 10 in number. Infusions were given either twice or thrice a week.Tools used to evaluate patients were the Mini International Neuropsychiatric Interview (MINI), Y-BOCS and HAM-D. **There was a statistically significant reduction in the YBOCS total score with ketamine infusions [YBOCS baseline = 31.4 vs. YBOCS post ketamine 26.9; Friedman chi squared = 8.4, df = 2, p = 0.01].** The improvement persisted [YBOCS baseline = 31.8 vs. YBOCS post ketamine 29, even after the exclusion of the dramatic responder whose Y-BOCS dropped to 0. The patient was a 55 year old

male with a 20-year history of chronic refractory OCD and moderate depression of relatively new onset. His primary obsessions were related to aggressions. He had received a previous trial of CBT-ERP, without benefit. He had failed 6 adequate SRI trials as well as 2 augmentation strategies for OCD. At the time of receiving ketamine, he was on a combination of paroxetine, clonazepam, and N-acetyl cysteine.

Figure 5: Adapted from Rodriquez et al., 2016.



He received a total of 6 ketamine infusions, following which his YBOCS total score dropped from 25 to 0, and his HAM-D reduced from 15 to 2. His illness remained in remission for 3 months following ketamine. He returned with a relapse of obsessions 3 months later, for which he was given additional 3 infusions of ketamine. Following this, his OCD remained in remission for 6 months. Two other patients showed partial response (Y-BOCS reduction by 25 to 35%), while the rest did not respond to the infusions. There was significant reduction in depressive symptoms as well (HAM-D=17.8 at baseline vs 12.8 after the infusions).

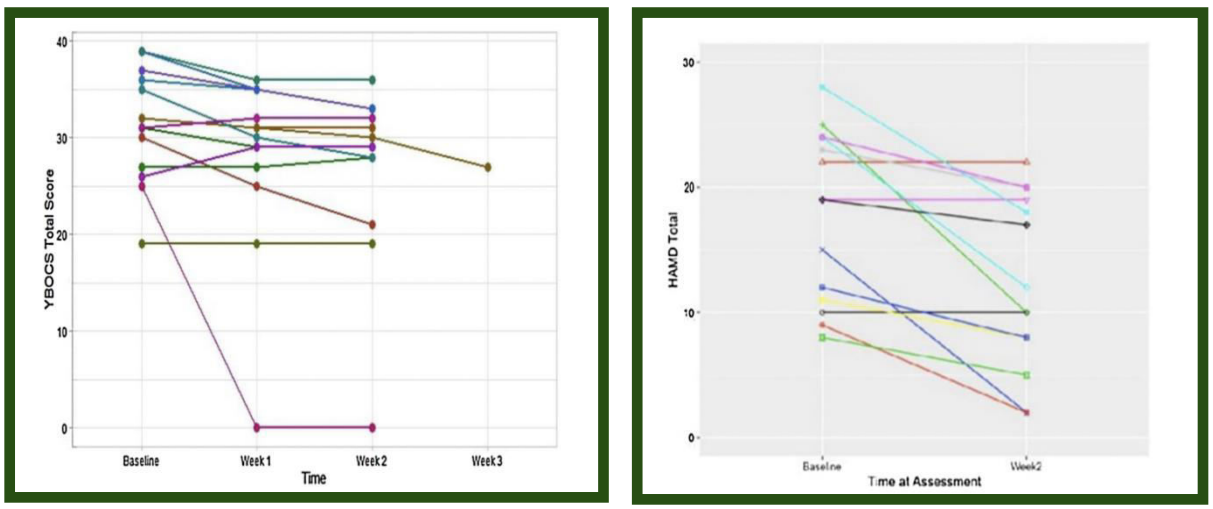


Figure 6: Adapted from Sharma et al., 2020.

Table 1: *Summary of Previous Trials of Ketamine in Obsessive Compulsive Disorder*

Study	Sample Size	Mean Age	Comorbidities	Scale	Type of Study	Dose/Route	Results	Limitations
Rodriguez et al. (2011)	1	24 years	mild depression (HDRS = 7)	OCD-VAS	Case report of double blind cross-over trial	0.5 mg/kg, single session, IV over 40 mins	Reduction in obsessions until day 7.	Small sample size and the difficulties of blinding due to the psychoactive effects of ketamine.
Bloch et al. (2012)	10	41.7 years	Current MDD (7), previous MDD (3), social phobia (3), trichotillomania (2), PTSD (2), eating disorder (2), skin picking (1), previous tic disorder	Y-BOCS	Open-label trial	0.5 mg/kg, single session, IV over 40 mins	No patients experienced a response. OCD symptoms significantly reduced in the first three days following the injection. Bigger decrease in depressive symptoms than in OCD symptoms.	Study was small, uncontrolled and unblinded.
Niciu et al. (2013)	2	25, 64 years	Previous MDD (2), PTSD (2), trichotillomania (1), personality disorder not specified (1	Y-BOCS	Case report	0.5 mg/kg, single session, IV over 40 mins	Both patients presented late-onset dysphoria, worsening anxiety, and suicidal ideation peaking 24 hours after infusion.	Small sample size
Rodriquez et al. (2013)	15(8+7)	34.2 years	Social anxiety disorder (3), current MDD (2), previous MDD (1), specific phobia (1)	OCD-VAS, Y-BOCS	Randomised, double-blind, placebo-controlled, crossover trial	0.5 mg/kg, single session, IV over 40 mins	Response in 50% (n=8)after 1 week compared to 0% in placebo (n = 7). Significant carryover effects of ketamine ($p < .005$). Significant improvement in obsessions	Small sample size, difficulty blinding due to Ketamine's psychotomimetic effect and carry over, anti-obsessive effect whether due to NMDAR antagonism or due to other receptors could not be ascertained.
Rodriguez et al. (2015)	16	32.9 years	MDD (2), social anxiety disorder (3), specific phobia (1)	OCD-VAS, Y-BOCS	Randomised, double-blind, placebo-controlled, crossover trial	0.5 mg/kg, single session, IV over 40 mins	Significant increase in MPFC GABA levels but not in glutamate/ glutamine levels	Small sample size, less statistical power to rule out type-1 error or confounds like gender. J-editing cannot differentiate glutamate and glutamine.

Rodriquez et al. (2016)	10	No report	No report	OCD-VAS, Y-BOCS	Open-label trial	0.5 mg/kg, single session, IV over 40 mins, followed by 10 sessions of CBT (over 2 weeks	63% showed response after 2 weeks of the infusion	Small sample size, uncontrolled.
Rodriquez et al. (2017)	2	20, 36 years	Current MDD (1)	Y-BOCS	Case Report	50 mg, single session, intranasal	Neither met OCD response after 1 week. The patient with MDD met criteria for remission after 1 week. Intranasal administration was poorly tolerated by both patients.	Study discontinued due to poor enrollment and poor tolerability.
Adams et al. (2017)	1	Late 20s	MDD, social anxiety disorder, previous bulimia nervosa	Y-BOCS	Case Report	50 mg, 8 sessions, intranasal	Reduction in OC and depressive symptoms, rapid reduction of suicidal ideation, well tolerated.	Small sample size
Sharma et al. (2020)	14	36.2 years	MDD (9), personality disorder (4), generalised anxiety disorder (1)	Y-BOCS)	Retrospective Chart Review	0.5 mg/kg, multiple sessions,e IV over 40 mins.	Significant reductions in mean total Y-BOCS, HDRS scores. Response with posterior remission after 6 months in 1 patient. Partial response in 2 patients.	Retrospective study, heterogeneity in the administration of ketamine infusions (ranging from 2 to 10), small sample size and lack of a control group. Illness severity after each infusion was not measured.

OCD, obsessive-compulsive disorder; PTSD, post traumatic stress disorder; MDD, major depressive disorder;
Y-BOCS, Yale-Brown Obsessive Compulsive Scale; OCD-VAS, OCD Visual Analog Scale; HDRS, Hamilton Depression Rating Scale;
MPFC, medial prefrontal cortex; GABA, gamma aminobutyric acid; NMDAR, N-methyl-D-aspartate Receptor;
CBT, cognitive-behavioural therapy;
IV, intravenous; min, minute; SD, standard deviation;

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