REVIEW

Ketamine in the Treatment of Obsessive-Compulsive Disorder: A Systematic Review

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Introduction: First-line treatment for obsessive-compulsive disorder (OCD) includes exposure and response prevention behavioral therapy and serotonin reuptake inhibitors, particularly in combination. New and more effective treatments are needed, give that recent studies suggest that glutamatergic neurotransmission contributes to the pathophysiology of the disorder. In these circumstances, ketamine, as a potent N-methyl-D-aspartate receptor antagonist and glutamate modulator, offers alternative possibilities for OCD treatment.

Methods: This systematic review aims to investigate the effects of ketamine in OCD, following the Preferred Reporting Items for Systematic Review and Meta-analyses Protocols (PRISMA-P). Searches were carried out using the PubMed/MEDLINE, Embase, and PsycINFO databases.

Results: Nine articles were included, of which three were randomized controlled trials, three case reports, two open-label trials, and one a retrospective chart review. Reported data have shown a potential for fast onset of action and good tolerability of ketamine for OCD, even though the principal studies used only single-session racemic ketamine treatments, administered intravenously, and the results have been erratic. In addition, none of the available evidence demonstrates whether racemic ketamine, S-ketamine, or R-ketamine has the best efficacy in controlling OCD symptoms, and only sparse evidence suggests that a combination of ketamine and psychotherapy could benefit patients with OCD.

Conclusion: In order to advance clinical practice regarding the use of ketamine in treating OCD, future randomized, double-blind, placebo-controlled trials are required. These trials need to use larger samples to explore ketamine and its enantiomers, with different methods of administration, multiple sessions, and appropriate washout periods.

Keywords: glutamate, ketamine, N-methyl-D-aspartate, obsessive-compulsive disorder

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INTRODUCTION

According to the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5),[1] obsessive-compulsive disorder (OCD) is characterized by the presence of repetitive and persistent thoughts, images, or urges (obsessions), or by repetitive behaviors or mental acts (compulsions). Typically, compulsions correspond to responses to obsessions or subjective experiences (e.g., the need to relieve a tactile sensation or to achieve a "just right" feeling),[2–4] which are described as unpleasurable and involuntary.

First-line treatments for OCD include exposure and response prevention behavioral therapy (ERP) and serotonin reuptake inhibitors (SRIs), both selective and nonselective (e.g., clomipramine), often in combination.[5–8] However, approximately 20% of OCD cases are refractory to these approaches.[9] In these patients, augmentation strategies such as the use of antipsychotics combined with SRIs are frequently used.[9] In some OCD patients (less than 1% of treatment-seeking individuals), the condition is severe and considered "intractable." In these cases neurosurgery is considered a viable option.[10]

Another limitation of the current pharmacological treatment options (in addition to the high number of refractory patients) is the delayed onset of therapeutic response, given that it typically takes six to ten weeks for clinical improvement to occur. Therefore, new and more effective treatments are needed.

Taking into consideration the role of the N-methyl-D-aspartate receptor (NMDAR) and the glutamatergic pathways in the pathophysiology of OCD,[11–13] ketamine has emerged as a potential therapeutic option with rapid onset of action. To the best of our knowledge, this is the first systematic review aiming to explore the current evidence for the use of ketamine in OCD.

METHODS

This systematic review follows the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P).[14]

Eligibility Criteria and Sources

The articles included in this systematic review presented original data investigating the use of ketamine for treating OCD in humans, were published (in any language) up to July 2021, and were indexed in PubMed/MEDLINE, Embase, or PsycINFO. We included case reports, case series, randomized clinical trials, and pilot studies that used ketamine or its enantiomers (e.g., esketamine or arketamine) alone or as major adjuvant treatment, in any route of administration and in single or multiple interventions. Reviews, editorials, and conference abstracts were excluded. Moreover, articles that used no validated OCD scale to measure symptoms after intervention were also excluded.

Search Strategy

Search term descriptors were based on terms used in Medical Subject Headings (MeSH) for PubMed/MEDLINE, Embase subject headings (Emtree) for Embase, and APA Thesaurus of Psychological Index Terms for PsycINFO. Database searches used a combination of descriptors and Boolean operators. Two researchers (IDB and DHLS) independently selected articles based on the titles. Reviewers then read the abstracts from articles that at least one researcher had selected. Articles deemed eligible by at least one reviewer were then chosen, and those that fully met the eligibility criteria were included in the study.

Risk of Bias in the Studies

Methodological quality and risk of bias were evaluated using the Cochrane risk-of-bias tool (RoB 2).[15] Pilot searches revealed both randomized clinical trials (RCTs) and open-label pilot studies; the risk of bias assessment was measured using RCT standards. If an included study reported secondary findings from a published clinical trial, we referred to its parent articles for a more precise assessment of method and risk of bias. Title, abstract, full-text screening, and bias estimation were independently conducted by IDB and DHLS, with discrepancies resolved by consensus.

RESULTS

We found a total of 249 studies via our database search strategy: 195 in EMBASE, 47 in PubMed/Medline, and 7 in PsycINFO. We then read the titles in order to exclude duplicates and read the abstracts of the 206 remaining studies to select the 14 articles eligible for full-text reading. Finally, nine studies were included in qualitative synthesis: three RCTs,[16–18] three case reports,[19–21] two open-label trials,[22,23] and one retrospective chart review.[24] Notably, four studies used overlapping samples (Supplemental Figure 1, http://links.lww.com/HRP/A189).[17–19,22]

Study Design and Sample Characteristics

Some of the evaluated studies had defined inclusion and exclusion criteria to select eligible patients for the trial. In three studies, DSM criteria (IV, IV-TR, or 5) were used to confirm the diagnosis of OCD.[20,22,23] All studies used the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score as an inclusion criterion: three studies stipulated the inclusion of patients with a score greater than or equal to 16,[17,20,23] and one study included participants with a score greater than 24.[22] In addition, two studies included only patients with near-constant intrusive obsessions (>8 hours a day).[17,23] Two studies selected patients with treatment-resistant OCD, variously defined as (1) therapeutic failure after two selective serotonin reuptake inhibitor trials of adequate dose and duration and after having previously been offered cognitive-behavioral therapy (CBT)[22] and (2) failure in at least one trial of SSRI or CBT.[17] In the latter case, patients who refused these treatments were also included. Regarding exclusion criteria, three studies excluded patients with severe depression, defined as a score greater than 25 on the Hamilton Depression Rating Scale (two articles)[20,23] or greater than or equal to 25 (one article).[17]

Among the nine studies assessed, we evaluated a total of 55 OCD patients. One patient did not complete the ketamine infusion, however, and another did not complete the CBT sessions anticipated in the study.[23] In addition, seven of these participants were assigned to receive a placebo,[17] and one to receive midazolam, in their respective studies.[20] Thus, 46 OCD patients were treated with ketamine according to the established protocols. One of the studies reported a carryover effect.[17]

Risk of Bias

We used the Cochrane risk-of-bias tool to assess the selected studies (Supplemental Table 1, http://links.lww.com/HRP/A190). Following analysis, two studies were considered to have a low risk of bias.[18,20] Additionally, six studies had some concerns regarding risk of bias because of the difficulties encountered when measuring the outcome.[16,17,21–24] Only one study presented a high risk of bias.[19]

Obsessive-Compulsive Assessment Strategies

Among the studies investigated, two evaluated the effects of multiple ketamine infusions,[21,24] while the remaining studies investigated the effects of a single administration of the drug. The studies assessed obsessive-compulsive symptoms using the

OCD Visual Analog Scale (OCD-VAS) (three articles)[16,17,23] and the Y-BOCS (six articles).[17,20–24] The time of the scales' application was inconsistent between the studies, however, with the one-week time point being most evaluated. Also, this one-week period was the follow-up interval for participants' obsessive-compulsive symptoms in four studies.[16,17,20,22] The other studies followed the patients' symptoms for 2,[24] 4,[23] and 17 weeks.[21] In addition, six other scales were used to assess secondary outcomes: Hamilton Depression Rating Scale (four articles);[17,20,22,24] Clinician-Administered Dissociative State Scale (four articles);[16,17,21,22] Young Mania Rating Scale (two articles);[16,17] Clinical Global Impression (one article);[22] Brief Psychiatric Rating Scale (one article);[22] and Montgomery-Åsberg Depression Rating Scale (one article).[21] Studies with overlapping samples were counted only once.

CURRENT EVIDENCE IN CLINICAL STUDIES

The first description of human ketamine use for the treatment of OCD was made by Rodriguez and colleagues[16] in a 2011 case report. A 24-year-old patient had a history of failure of three previous therapeutic regimens, each lasting three months, as well as poor adherence in a previous clinical trial using ERP. The study consisted of a double-blind crossover trial of ketamine and saline, in which the patient received two intravenous (IV) infusions over 40 minutes with a seven-day interval between them. Following placebo infusion, no reduction in obsessive symptoms was found. Following 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. It is worth noting that symptoms only returned to their original levels seven days after ketamine infusion.

Following these findings, in 2012 Bloch and colleagues[22] conducted an open-label clinical trial with ten individuals with OCD, seven of whom had major depressive disorder (MDD) as a comorbidity. The researchers employed the same IV regimen (0.5 mg/kg of ketamine over 40-minute infusions) and found that OCD and depression symptoms showed a (statistically) significant reduction three days after a single ketamine infusion. This improvement was not sufficient, however, to meet clinical response criteria, which, for OCD, is defined as a reduction greater than 35%. Regarding the patients with MDD, four experienced an improvement in depressive symptoms in the first three days following infusion, leading the authors to conclude that patients with comorbidities had longer and more lasting responses to depressive symptoms than OCD symptoms. The authors did not find a prolonged response to ketamine in any patient, however, contrary to the previous case report.[16] In addition, two patients with similar comorbidity profiles presented late-onset dysphoria, as well as a worsening of anxiety symptoms, suicidal ideation, and certain depressive symptoms. Therefore, the authors concluded that insufficient data were available to warrant the use of therapeutic ketamine outside of research for patients with comorbid psychiatric disorders.[19]

Rodriguez and colleagues[17] published the first randomized, placebo-controlled, double-blind, crossover trial of ketamine for the treatment of OCD and demonstrated a reduction in obsessive symptoms. This study involved 15 subjects diagnosed with moderate to severe OCD (Y-BOCS ≥16), who had been on the same medication regimen for more than one year prior to the study and had completed a seven-day washout from their standard oral medications. Unfortunately, a carryover effect occurred in this clinical trial, making it impossible to undergo crossover of the two groups. The group of eight subjects that received IV ketamine (0.5 mg/kg) during the first infusion showed significant improvement in obsessive symptoms compared to the placebo group of seven subjects. In addition, one week after the ketamine infusion, half of the subjects in the intervention group met response criteria, versus no patients in the placebo group. The authors hypothesized that this prolonged response to ketamine could be due to the small number of patients with comorbid MDD in their sample (3 of 15), compared to the Bloch and colleagues study (7 of 10).[22] For Rodriguez and colleagues,[17] it is possible that patients with OCD-MDD comorbidity might have been less responsive to ketamine's therapeutic effects on OCD.

Rodriguez and colleagues[18] conducted a secondary analysis of the study, investigating the neurochemical effects of ketamine versus saline infusions using proton magnetic resonance spectroscopy. This study demonstrated that ketamine did not significantly increase glutamate and glutamine (Glx) levels in the medial prefrontal cortex but that it increased levels of gamma-aminobutyric acid (GABA) over time. Ketamine was also found to affect oscillatory activity consistent with the evolution of cortical microcircuits. The results suggest that the pathophysiological models of OCD should also consider potential pathophysiological changes within the GABAergic system in relation to the symptoms of this disease and the modulatory role of ketamine in the GABAergic pathways.

The same group also conducted two open-label trials using IV ketamine, although one of the studies selected participants from the crossover trial cited above. In addition, the group tried to carry out an RCT with intranasal ketamine, which had to be discontinued. The first trial,[23] involving 10 patients, tested whether a single session of ketamine followed by ten sessions of exposure-based CBT could sustain the previously demonstrated therapeutic effects on OCD. Of 10 selected patients, only 9 undertook the IV ketamine infusion, and only 8 completed the ten CBT sessions. At the end of the tenth session, 5 of those 8 patients (63%) met response criteria (≥35% decrease in Y-BOCS score at week 2), with responses varying from complete remission of OCD symptoms (one patient, lasting for the six months of follow-up analysis) to no benefit at all (one patient). In the second open-label trial,[25] the researchers tested whether response to an NMDA antagonist (IV ketamine) could also predict response to a second NMDA antagonist (oral memantine). The same patients from a previous trial[17] were contacted, and 12 agreed to participate in this second study. Eight patients completed 6 weeks of memantine

treatment and 3 completed 12 weeks. Although limited in size, the study suggested that patients who did not respond well to ketamine also did not respond well to memantine (≥35% decrease in Y-BOCS score). However, within the group that showed a ketamine response, the findings for memantine varied considerably, suggesting that ketamine may affect individual subjects differently, making it difficult to predict a clinical response. In an attempt to test a route other than IV for OCD, Rodriguez and colleagues[20] demonstrated the difficulties of conducting a trial with intranasal racemic ketamine in this population. The majority (75%) of the selected participants were unwilling to receive ketamine intranasally, and as only two subjects were enrolled, the study was discontinued.[20]

Two studies evaluated repetitive ketamine infusions compared to administration of a single dose. In a case report by Adams and colleagues,[21] a male patient in his second decade of life, with multiple comorbidities (OCD, MDD, suicidal ideation, social phobia, and bulimia) and a history of unsuccessful treatments, received ketamine intranasally (50 mg), twice a week for four weeks. The patient manifested an additional reduction in OCD symptoms after ketamine application, in combination with CBT, along with a substantial increase in the acceptance of response-prevention techniques and a rapid reduction in suicidal ideation. Sharma and colleagues[24] performed a retrospective chart review of 14 adult inpatients with SRI-resistant OCD treated with multiple IV infusions of 0.5 mg/kg ketamine over 40 minutes. They found a significant decrease in Y-BOCS total scores over 2–3 weeks of treatment, although only one patient, with the Y-BOCS total score decreasing from 25 to 0, met the defined response of >35% decrease on the Y-BOCS. This patient remitted for three months until relapsing with obsessional behavior, which was controlled with three additional infusions of ketamine, resulting in remission for the full six months of follow-up. Additionally, two other patients presented with partial responses, defined as a 25%–35% decrease in Y-BOCS total scores, although no follow-up information is available. Moreover, the authors reported a significant reduction in Hamilton Depression Rating Scale scores and no major adverse effects. These results raise the question of whether a subgroup of OCD patients may respond well to ketamine.

In respect of control for depressive symptoms, some of the studies included in this review did not include patients with MDD[16] or included only a small percentage with MDD.[17] One study reported a correlation between OCD and depressive symptoms (Pearson r = .82; p = .02), with no patient considered responsive to ketamine infusion (>35% in Y-BOCS reduction between days 1 and 3 following intervention).[22] The other trials included here did not report controlling for a possible reduction in depressive symptoms, which might have indirectly reduced OCD symptoms. A summary of the current clinical evidence for ketamine in treating OCD is included in Table 1.

With regard to ongoing studies, a registered RCT on the clinicaltrials.gov site is comparing a single infusion of ketamine (0.5 mg/kg) with midazolam (0.045 mg/kg), with the aim of testing the mechanism of ketamine action on OCD pathophysiology (ClinicalTrials.gov Identifier: NCT02624596).

DISCUSSION

Glutamate in OCD

Glutamate plays an important role in the cortico-striato-thalamo-cortical (CSTC) circuitry and also influences other neurocircuitry important to the pathophysiology of OCD, involving the dorsal anterior cingulate cortex as well as the amygdalo-cortical and medial orbitofrontal cortex brain structures.[26] Regarding glutamatergic dysfunction, some biochemical and genetic indications show an association between this dysregulation and OCD. Two studies found elevated levels of glutamate in the cerebrospinal fluid of OCD patients, but neither could explain the reason behind these findings or ascertain the origin of excess glutamate.[27,28] In the field of genetics, the first study to support a glutamatergic role on OCD was conducted by Welch and colleagues.[29] That research identified behaviors similar to OCD in homozygous mice by deleting the protein-associated striatal gene *Sapap3*, a gene with high striatal expression, associated with NMDAR and AMPAR proteins.[29] Since then, different genetic studies suggested an association between OCD and mutations in genes coding for *EAAT3*, a glutamate transporter, *GRIK2*, a glutamate receptor, and *PTPRD*, a protein-tyrosine phosphatase receptor present within glutamatergic synapses.[30] In addition, genome-wide association studies identified areas significantly associated with OCD that involved glutamatergic genes.[31–33] Further studies are needed to better establish the strength of the associations.

Other Glutamatergic Treatments Studied in OCD

Considering that ketamine may have a therapeutic role in OCD through its action on glutamatergic circuits, it is reasonable to expect that other drugs that act on these circuits could also bring clinical benefits to these patients. Several such substances have already been tested in clinical trials, usually with mixed results.[11,34] The drug with the most favorable evidence to date is memantine, a noncompetitive NMDAR antagonist. A 2019 meta-analysis of eight trials comparing augmentation with memantine to placebo found an overall significant mean reduction of 11.73 points in Y-BOCS scores; those treated with memantine were considered 3.61 times more likely to be responders than those receiving the placebo.[35] Riluzole, an inhibitor of glutamate release, was evaluated for OCD in three clinical trials, two of which found no significant benefit,[36,37] and one demonstrating a significant reduction in obsessive-compulsive symptoms in the group that received riluzole in addition to fluvoxamine.[38] A meta-analysis of these three studies found small, nonsignificant positive effects of riluzole on obsessive-compulsive symptoms.[39] Other substances such as glycine, an NMDAR co-agonist, and D-cycloserine, a partial co-agonist at the glycine site of the NDMAR, have also been tested for treating OCD, with the latter producing negative results[40–42] and glycine showing a trend toward therapeutic effects.[43]

Table 1

Characteristics of Clinical Studies of Racemic Ketamine for Obsessive-Compulsive Disorder

Study	Sample size	Percentage female	Mean age (SD)	OCD assessment instrument	Comorbidities (n)	Methods	Dosage, no. sessions, route	Results
Rodriguez et al. (2011)[16]	1	100%	24	OCD-VAS	Minimal depressive symptoms (HDRS = 7)	Case report	0.5 mg/kg, single session, IV over 40 mins	Reduction in obsessions until day 7
Bloch et al. (2012)[22]	10[a]	40%	41.7 (13.5)	Y-BOCS	Current MDD (7), previous MDD (3), social phobia (3), trichotillomania (2), PTSD (2), eating disorder (2), skin picking (1), previous tic disorder (1)	Open-label trial	0.5 mg/kg, single session, IV over 40 mins	No patients experienced response[a] Significant improvement in OCD symptoms in the first 3 days after infusion Reduction in depressive symptoms greater than reduction in OCD symptoms
Niciu et al. (2013)[19]	2[a]	100%	25 and 64	Y-BOCS	Previous MDD (2), PTSD (2), trichotillomania (1), personality disorder not specified (1)	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
Rodriguez et al. (2013)[17]	15[c]	44%	34.2 (9)	OCD-VAS and Y-BOCS	Social anxiety disorder (3), current MDD (2), previous MDD (1), specific phobia (1)	Randomized, 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
Rodriguez et al. (2015)[18]	16[b]	43.7%	32.9 (7.5)	OCD-VAS and Y-BOCS	MDD (2), social anxiety disorder (3), specific phobia (1)	Randomized, placebo-controlled, double-blind, crossover trial	0.5 mg/kg, single session, IV over 40 mins	Significant increase in MPFC GABA levels but not in glutamate/glutamine levels
Rodriguez et al. (2016)[23]	10[d]	Not reported	Not reported	OCD-VAS and 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

Table 1

Continued

Study	Sample size	Percentage female	Mean age (SD)	OCD assessment instrument	Comorbidities (n)	Methods	Dosage, no. sessions, route	Results
Rodriguez et al. (2017)[20]	2	50%	20 and 36	Y-BOCS	Current MDD (1)	Case report	50 mg, single session, intranasal	Neither patient 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
Adams et al. (2017)[21]	1	0%	Late 20s	Y-BOCS	MDD, social anxiety disorder, and previous bulimia nervosa	Case report	50 mg, 8 sessions, intranasal	Reduction in OCD symptoms Rapid reduction on suicidal ideation Improvement in depressive symptoms Intranasal administration was well tolerated
Sharma et al. (2020)[24]	14	50%	36.2 (12.9)	Y-BOCS	MDD (9), personality disorder (4), general anxiety disorder (1)	Retrospective chart review	0.5 mg/kg, multiple sessions,[e] IV over 40 mins	Significant reduction in Y-BOCS and HDRS mean total scores One patient presented response with posterior remission after 6 months of follow-up Two patients presented partial response

CBT, cognitive-behavioral therapy; HDRS, Hamilton Depression Rating Scale; IV, intravenous; MDD, major depressive disorder; min, minute; MPFC, medial prefrontal cortex; OCD, obsessive-compulsive disorder; OCD-VAS, OCD Visual Analog Scale; PTSD, posttraumatic stress disorder; SD, standard deviation; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

[a] I.e., major decrease in relevant scale for assessing OCD symptoms (here, >35% decrease in Y-BOCS).

[b] Overlapping samples.

[c] Overlapping samples.

[d] Nine patients completed ketamine infusion; eight patients completed all CBT sessions.

[e] Mean (SD) = 5.4 (2.5).

Bitopertin is a glycine reuptake inhibitor studied mainly for negative symptoms of schizophrenia. A study involving OCD was registered in 2012 (NCT01674361), but no results have been reported (https://www.clinicaltrials.gov/ct2/show/record/NCT01674361). Finally, medications already widely used in other scenarios, such as the anticonvulsants topiramate and lamotrigine, exert complex effects on glutamatergic synapses but mainly inhibit glutamate release. Trials for treatment enhancement in OCD have generally demonstrated beneficial effects for lamotrigine[44,45] and mixed results for topiramate, with one study demonstrating overall positive effects,[46] another showing benefits to compulsions,[47] and a third finding no difference to placebo at the conclusion of the study.[48]

Ketamine as a Glutamate Modulator Agent

Ketamine binds to NMDAR at the phencyclidine site of the calcium channel and acts as a potent noncompetitive antagonist of glutamate.[49,50] It also has a lower affinity for the following: σ-1 receptor, related to function and behavioral actions in the central nervous system;[51] opioid receptor μ, linked by some authors to ketamine's antidepressant and antisuicidal effects;[52] and norepinephrine and serotonin transporters.[51]

Current models suggest that when ketamine blocks NMDAR at GABAergic interneurons in the prefrontal cortex, it prevents them from being excited by glutamate (released by pyramidal neurons) and thus restrains the release of GABA, an inhibitory neurotransmitter. It is worth noting that the release of GABA inhibits another glutamatergic pyramidal neuron. The absence of GABA results in an increased release of glutamate downstream.[50] Glutamate then binds to the AMPAR and triggers the depolarization process. The AMPAR activation triggers a biochemical cascade activating the mammalian target of rapamycin protein (mTOR) pathway, which stimulates the expression of new dendritic spines.[53] It is not yet clear whether these ketamine effects are due to its direct antagonism of the NMDAR, to AMPAR stimulation (resulting in an increase in dendritic spines), or to the modulation of the σ-1 receptor. Indeed, it is not clear whether its likely indirect effects on the opioid system are necessary or sufficient to grant it efficacy in treating mental disorders,[51] given that the opioid system may be a clinical target in OCD, as has been suggested in prior literature.[54]

Neurobiological Substrates and Possible Mechanisms of Ketamine in OCD

KETAMINE'S EFFECTS ON THE CORTICO-STRIATAL GLUTAMATERGIC TRANSMISSION It is not yet known how ketamine reduces OCD symptoms. A well-established OCD model is based on an imbalance in the cortico-striato-thalamo-cortical circuitry. Several regions comprise CSTC circuitry, and neuroimage studies corroborate this hypothesis. During task switching, fMRI shows reduced activation in ventral frontostriatal regions in patients with OCD, which may be related to cognitive inflexibility. In addition, abnormalities in the parietal cortex have been reported, and metabolism in this region appears to be decreased in patients with OCD.[55] A possible explanation for the ketamine mechanism on OCD symptoms is that in targeting NMDA GABA interneurons in hypo-functioning regions, such as parietal and frontostriatal regions, a secondary glutamate release provokes activation in these areas. The downstream synaptic plasticity alterations could also have a role in the rearrangement of CSTC circuitry.

KETAMINE'S EFFECTS ON THE FEAR CONDITIONING/EXTINCTION/ANXIETY SYSTEM The response of fear seems to be regulated by different neurobiological approaches, such as fear conditioning and fear extinction. Notably, patients with OCD exhibit impaired fear extinction.[56] Preclinical investigations suggest NMDARs on the basolateral amygdala play a major role in extinguishing fear. Moreover, NMDAR antagonism was found to block the fear extinction process, while D-cycloserine, an NMDAR partial agonist, enhanced fear extinction retention.[57] It would therefore be reasonable to assume that ketamine, as an NMDAR antagonist, would also impair the fear extinction process. Ketamine's effects seem to depend, however, on the duration and route of administration: while intravenous ketamine infusions delayed fear extinction in rats, intraperitoneal ketamine injections enhanced fear-memory extinction.[58]

Additionally, fear conditioning and extinction play a major role in posttraumatic stress disorder (PTSD). A literature review of preclinical and clinical studies concerning the use of ketamine for the treatment of PTSD found that the drug produced an immediate clinical improvement that lasted for several weeks.[59] Thus, the robust effect of ketamine on PTSD symptoms supports the drug's role in the fear-conditioning and fear-extinction network, a neural circuitry also relevant for the treatment of OCD. It is not yet clear, however, whether the effect of ketamine on PTSD symptoms is mediated by the modulation of the neuronal circuits involved in fear-conditioning and -extinction processes.

KETAMINE'S RAPID ANTIDEPRESSANT EFFECTS Concerning ketamine's antidepressant effects, several clinical examples have already been mentioned, and these are important to keep in mind because of the substantial comorbidity between OCD and depression. A recent international collaborative study reported that MDD was the most common comorbid disorder in OCD patients, with a frequency of current and lifetime MDD of 28.4% and 50.5%, respectively.[60]

Despite the important overlap between these disorders, the mechanism of this association is largely unknown: it is still not clear whether the functional impairment of OCD is a trigger for depressive symptoms, or whether depressive symptoms themselves can be a trigger for OCD symptoms. This information would clearly be of great help in clinical settings in order to establish priorities, since an improvement in the "causative" symptomatic cluster of OCD would generate greater benefits in the longer term.

Longitudinal studies point to different conclusions: there is evidence to suggest that depression is a predictor for OCD,[61]

that OCD is a predictor of depression,[62,63] and that the relationship is bidirectional.[64] Ascertaining ketamine's effects on OCD is further complicated by the failure of most of these studies to control for its antidepressant properties, as discussed earlier.

Because of the association between MDD and OCD, the need to control for ketamine's antidepressant effects is crucially important. Future clinical trials of ketamine on OCD treatment should follow the steps of Bloch and colleagues[22] and control—in both trial design and data analysis, when feasible—for the effects of reduced depressive symptoms as OCD symptoms improve.

Additionally, regarding the neurobiological basis for ketamine's rapid antidepressant effects, some studies point to a neurotrophic hypothesis, in which increased expression of brain-derived neurotrophic factor in the medial prefrontal cortex and hippocampus lead to increased synaptic activity in these areas.[65] Data about BDNF and ketamine in humans is still controversial, however.[66] It is worth noting that early evidence points to similar mechanisms for the rapid antidepressant effects of serotonergic psychedelics, such as psilocybin and LSD.[67]

FUTURE DIRECTIONS

No data are currently available comparing the capacity of the different enantiomers of ketamine (S-ketamine and R-ketamine) to control OCD symptoms, and also few data to suggest an optimal anti-obsessive-compulsive dose. To date, studies have evaluated the effects of IV racemic ketamine at 0.5 mg/kg,[16–19,22,23,25] the same protocol used by most studies in treatment-resistant depression,[68–77] while others have administered intranasal ketamine at 50 mg.[20,21] Therefore, it is possible that the most appropriate anti-obsessive-compulsive dose of ketamine is different from the antidepressant one.[16–19,22,23,25] Regarding the number of treatments, only one case report[21] and one retrospective chart review[24] examined the effect of multiple administrations of ketamine for OCD. This aspect of therapeutic application deserves scrutiny, given differences in how ketamine is used in off-label clinical practice versus evidence-based practice, which has typically emphasized single-infusion treatments.

Also, alternatives such as subcutaneous, intramuscular, and oral administration have not yet been explored for OCD.

Another therapeutic alternative for ketamine treatment of OCD involves combining the drug with psychotherapy, such as CBT, which has been evaluated for treating other conditions such as depression, PTSD, alcoholism, and heroin dependence.[78–80] Ketamine administration in conjunction with CBT has produced promising results for prolonging the effect of the drug in patients with treatment-resistant depression.[81] For the treatment of OCD, however, the only evidence available is that of a previously discussed clinical trial[23] and case report,[21] in which ketamine associated with CBT resulted in a wide range of response levels.[21,23] New clinical trials with larger samples could better elucidate whether concomitant psychotherapy, especially CBT and ERP, could potentiate or prolong the ketamine effect on OCD. Moreover, RCTs investigating ketamine augmentation in SRI-refractory population are also needed. Previous studies with other glutamate modulators such as memantine report amelioration of OCD symptoms. Additionally, head-to-head studies of ketamine with other augmentation strategies or with neuromodulation approaches for treatment-resistant OCD would be beneficial; advances along these lines could help to elucidate OCD neurobiology and to identify better therapeutic targets. It is important to take into account, however, that the risk of addiction to ketamine could be higher among OCD patients.[82] According to Ruscio and colleagues,[83] a statistical analysis of the National Comorbidity Survey Replication indicated that 38.6% of the sample of OCD patients met the criteria for lifetime substance use disorder.

As shown in this review, the mechanism through which ketamine reduces OCD symptoms is not yet known; advances in the studies of biological and clinical markers will surely move things forward. Much depends on a better understanding of the neurochemical mechanisms behind OCD itself, and progress is being made in that direction.[55] This knowledge should be linked with future data on clinical predictors of ketamine response in OCD such as comorbidities, degrees of treatment refractoriness, and Y-BOCS dimensions. Understanding the linkages would potentially enable the development of biological markers for guiding the use of ketamine and other glutamatergic modulators in the treatment of OCD patients. In this context, the growing number of genetic studies connecting the glutamatergic pathway to OCD[29–33] may shape future pharmacogenetic studies, which could also help us understand the previously reported erratic effects of ketamine and thus identify individuals who might respond better to treatment. Certain studies have already suggested an association between glutamatergic genes and the response to antidepressant treatment for OCD,[84] although larger studies are required. These studies should be complemented by trials comparing the effects of pharmacological intervention with antidepressants and glutamatergic drugs, such as ketamine, in patients with the same genetic profile. Biochemical studies that help to elucidate the mechanisms of action of ketamine may contribute to therapeutic advances in treating OCD; an accurate understanding of the ketamine mechanism that relieves the disorder's symptoms may assist the development of new, more potent drugs, with fewer side effects.

LIMITATIONS

It is important to highlight the heterogeneity between studies: the study designs ranged from case reports to randomized clinical trials; the psychiatric comorbidity profiles differed from study to study, especially regarding MDD; the studies followed different therapeutic schemes, including multiple doses of ketamine, intranasal ketamine, and adjuvant CBT; and different instruments—Y-BOCS or OCD-VAS—were used to evaluated responses. These differences are summarized in Table 1. Furthermore, more and better instruments are needed to assess rapid changes to obsessive-compulsive symptoms. It is possible that the negative results seen in some

studies may reflect their use of an inadequate OCD assessment tool. Finally, few studies evaluated ketamine's anti-obsessive-compulsive effects, and those that did used small sample sizes.

CONCLUSIONS

Given the current therapeutic limitations in treating OCD, coupled with the emerging evidence that glutamate may play a role in its pathophysiology, ketamine has emerged as an alternative agent in the field. However, we need further randomized, double-blind, placebo-controlled trials, with larger samples, exploring ketamine and its enantiomers, and using different routes of administration and regiment protocols (single or multiple sessions), with appropriate washout periods. We also need further studies involving the use of ketamine with existing evidence-based therapies. Advances along these directions will enable us to determine the potentially extensive uses of ketamine for the treatment of OCD.

Declaration of interest: Dr. Sanacora has received consulting fees from Allergan, Alkermes, AstraZeneca, Avanir, Axsome Therapeutics, Biohaven Pharmaceuticals, Bristol-Myers Squibb, Clexio Biosciences, Epiodyne, Intra-cellular Therapies, Janssen Pharmaceutica, Merck & Co., Naurex, Navitor, NeuroRx, Novartis, Noven Pharmaceuticals, Otsuka, Perception Neuroscience, Praxis Pharmaceutical, Sage Therapeutics, Servier Pharmaceuticals, Taisho Pharmaceutical, Teva, Valeant, and Vistagen Therapeutics over the last 24 months. He has also received additional research contracts from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Johnson & Johnson, Hoffmann-La Roche, Merck & Co., Naurex, and Servier over the last 24 months. Free medication was provided to Dr. Sanacora by Sanofi-Aventis for a National Institutes of Health–sponsored study. In addition, Dr. Sanacora holds equity in Biohaven Pharmaceuticals, and he is a coinventor on a U.S. patent (no. 8,778,979) held by Yale University and on U.S. Provisional Patent Application no. 047162-7177P1 (00754), filed on 20 August 2018 by Yale University Office of Cooperative Research, OCR 7451 US01, Abdallah C, Krystal JH, Duman R, Sanacora G, entitled "Combination Therapy for Treating or Preventing Depression or Other Mood Diseases." Yale University, Dr. Sanacora's employer, has a financial relationship with Janssen Pharmaceutica and may in the future receive financial benefits from this relationship. The university has put multiple measures in place to mitigate this institutional conflict of interest. Questions concerning the details of these measures should be directed to Yale University's Conflict of Interest office.
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