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REVIEW ARITICLE

Efficacy and safety of ketamine in the management of anxiety and anxiety spectrum disorders: a review of the literature

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Anxiety disorders are among the most prevalent psychiatric conditions. Despite many proven pharmacological and non-pharmacological treatments available, high rates of partial response and low rates of long-term remission remain. Ketamine has been receiving increasing attention as an interventional treatment modality in psychiatry, especially among refractory conditions, including major depressive disorder. There is limited yet growing evidence to support the use of ketamine in anxiety disorders. In this review of the literature, we present case reports, case series, and controlled trials demonstrating proof-of-concept for its potential role in the treatment of anxiety and anxiety spectrum disorders. Its unique mechanism of action, rapid onset, and high rate of response have driven its use in clinical practice. Ketamine is generally well tolerated by patients and has a limited side effect profile; however, the effects of long-term use are unknown. While there is a growing body of research and increasing clinical experience to suggest ketamine may have clinical applications in the treatment of refractory anxiety disorders, further research to determine long-term safety and tolerability is indicated.

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Background

The use of sub-anesthetic doses of ketamine in the management of treatment-refractory psychiatric disorders is receiving increasing attention. The rapid onset of response, unique mechanism of action, and demonstrated benefits in patients who have not responded to traditional therapies are the primary drivers of the growing interest and use of ketamine in clinical psychiatry.[1] Furthermore, ketamine has been shown to dramatically reduce acute suicidal ideations, which could theoretically prevent hospitalizations and decrease mortality.[2] Most of the published literature on ketamine in psychiatry has focused on depressive symptoms. A recent review found five well-controlled studies in unipolar depression and two in bipolar depression. The total sample size in unipolar depression in these trials was $n = 152$. Intravenous administration was the route of delivery used in all but one study. In bipolar depression studies, the total sample size was $n = 33$.[3] There are even fewer well-powered, controlled trials supporting the use of ketamine in anxiety-related conditions. Funding for ketamine trials is hampered by the medication's off-patent status. However, increasing evidence suggests that ketamine may also reduce anxious symptoms and possibly play a role in the management of treatment-resistant anxiety disorders. Here, we review the limited controlled studies that are available, as well as case reports and case series that demonstrate proof-of-concept of the potential efficacy of ketamine in the management of anxiety disorders.

Anxiety disorders are among the most prevalent psychiatric conditions and, like depression, are associated with high rates of morbidity, mortality, and disease burden. The 12-month prevalence rates for anxiety disorders are estimated to be between 10.3% and 19.1%, compared to 6.7% of US adults with depression.[4] In the most recent update of the *Diagnostic and Statistical Manual* (DSM-5), the classification of previous anxiety disorders was revised into three categories: anxiety disorders, obsessive compulsive disorder (OCD), as well as trauma

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and stressor-related disorders. While OCD and post-traumatic stress disorder (PTSD) were re-classified into their own category, we will include them in our review of ketamine effects on anxiety spectrum disorders. The DSM-5 still acknowledges that anxiety is a significant component of both these conditions.[5]

Several of the published reports on ketamine in the management of anxious symptoms are in patients exhibiting comorbid depression and anxiety symptoms. While anxiety is not considered a symptom of depression, the most recent updated DSM-5 added the specifier "with anxious distress" to major depressive disorder acknowledging the effect of anxiety on treatment choices and patient response. Additionally, 50–60% of adults with lifetime major depression also have a history of an anxiety disorder, with anxiety and depressive disorders often co-occurring.[6] In the Sequenced Treatment Alternatives to Relieve Depression (STAR-D) Trial, nearly 50% of those treated for depression had clinically significant levels of anxiety. Patients with anxiety took longer to respond to treatment, were less likely to achieve remission, and experienced more side effects to medication.[7] Similarly, other studies have demonstrated that comorbid anxiety and depression is associated with worsening symptom severity, longer duration of illness, increased rates of suicidal behavior, higher rates of mental health utilization, greater medical costs, and increased risk of re-occurrence.[8]

Current pharmacologic therapies for anxiety disorders primarily target the monoaminergic system. Unfortunately, their use is limited by a delay in onset to action (6–8 weeks), low rates of remission (25–35%), and high rates of non-response (40–50%).[9] Additionally, true rates of non-response may be underreported because these data do not reflect those individuals who may have initially responded to treatment but experienced a relapse.[10] Benzodiazepines are well known to provide immediate relief of symptoms of anxiety, but these are associated with long-term concerns about dependence and tolerance. GABA-ergic anti-epileptic drugs and atypical antipsychotic agents have also shown some effectiveness in reducing anxiety symptoms, but there is limited data supporting their use, and concerns over tolerability and side effect profile with these classes exist.[11]

There is increasing evidence that glutamate dysfunction plays a significant role in depression, anxiety, and trauma-related disorders. Glutamate is the major excitatory neurotransmitter in the brain, and 80–90% of cortical synapses are glutamatergic. Glutamate is important in fear extinction, regulating neuropeptides in the stress response, and in several second messenger and downstream effects that may affect anxious symptoms and the development of anxiety disorders.[12-14] The glutamate system also exerts a role in synaptic and neural plasticity. In anxiety disorders, there is substantial evidence of neuronal damage induced by stress. This includes neuronal atrophy, reduced synaptic density, reductions in dendritic complexity and spine density in prefrontal cortex (PFC) neurons and CA3 pyramidal cells of the hippocampus, diminished neurogenesis in the hippocampus, and decreased number of glia in the medial PFC.[15]

Ketamine has been used in clinical practice for over 50 years as an anesthetic agent and has a favorable safety profile. The antidepressant and antianxiety properties of ketamine were recognized in the 1990s in both preclinical studies and clinical observations.[16] Linking a pharmacological mechanism to its observed clinical effect is a challenge for many pharmacologic therapies, particularly in the field of behavioral health. The antidepressant effects of ketamine are often attributed to its selective antagonistic effects on the NMDA receptor, one of the four subtypes of inotropic glutamate receptors located throughout the central nervous system that regulate signaling at excitatory synapses.[17,18] A preclinical study evaluating chronic administrations of 17 different antidepressants showed adaptive changes in radioligand binding to NMDA receptors in the cerebral cortex. Two antidepressants (imipramine and citalopram) and electroconvulsive therapy were studied in detail, and the authors observed that changes developed slowly over time and persisted after treatment was stopped.[19]

However, NMDA receptor antagonism alone may not fully explain the psychiatric benefits of ketamine since other NMDA antagonists have not consistently demonstrated antidepressant effects.[20] There are a number of other immediate and delayed effects of ketamine that may account for its efficacy in mood and anxiety disorders. Ketamine induces a hyperglutamatergic state, which also impacts AMPA receptors, kainate receptors, and delta-opioid receptors.[21] In the central nervous system, these receptors mediate excitatory synaptic transmission and play a role in synaptic plasticity, which impacts learning and memory.[22] Although an increased synaptic availability of glutamate is short-lived following ketamine administration, its antidepressant effects persist long after blood levels of ketamine have diminished. There is evidence that ketamine produces a hyperglutamatergic state, leading to changes in synaptic connectivity and downstream signaling, which may contribute to synaptogenesis through the inhibition of eukaryotic elongation factor kinase and increases in BDNF levels.[23] In animal models, ketamine has been shown to reverse structural and functional changes, including a deficit in dendritic spine density associated with anhedonia and chronic stress exposure.[24] Ketamine also impacts regulators of protein translation, mediators of translation and synaptic plasticity, and elevations of synaptic proteins.[25]

Anxious Symptoms in Depressed Patients

Some of the earliest published reports of ketamine's effects in anxiety were provided in a case series of

patients in hospice care, a setting in which depression and anxiety are highly prevalent. Up to 42% of hospice patients have depression and 70% have anxiety related to their terminal condition. Conventional antidepressant treatments often do not provide rapid relief of symptoms or are ineffective in this population. This particular case series reported on two patients who were given one dose of oral ketamine (0.5 mg/kg) and showed rapid improvements in symptoms of depression and anxiety (within an hour), with a sustained effect up to 1 week.[26]

In a larger open-label, proof-of-concept study, oral ketamine (0.5 mg/kg) was given to 14 patients with life-limiting illness receiving hospice care, who also suffered from depression and anxiety symptoms. The Hospital Anxiety and Depression Scale (HADS), which is used to rate overall depression and anxiety symptoms at baseline, was administered on days 3, 7, 14, 21, and 28. All subjects who completed the trial had a reduction in both anxiety and depression symptoms when given ketamine treatment. The mean time to response for anxiety symptoms with ketamine was 8.6 days ($n = 8$, median 7, SD = ±6 days), while the mean time to response for depressive symptoms was 14.4 days ($n = 8$, median 10.5, SD = ±19.1 days). All subjects maintained this response to ketamine treatment through day 28 on both measures. There were no serious adverse events reported. In addition to the open-label design, limitations of this study included that although the subjects had prominent depressive and anxious symptoms, they were not formally diagnosed with depressive or anxiety disorders.[27]

The effect of ketamine on anxiety symptoms in patients diagnosed with treatment-resistant depression has been examined in several small studies. Ionescu *et al.* (2014) treated 26 inpatients with treatment-resistant depression with a single dose of 0.5 mg/kg of intravenous ketamine and performed a post hoc analysis of efficacy in anxious vs. non-anxious depression based on the Montgomery-Asberg Depression Rating Scale (MADRS). Anxious patients had significantly fewer depressive symptoms compared with non-anxious depressed patients at days 1 through 5, 9 through 12, 15 through 17, and 25. There were no differences in dissociative, psychotic, or other side effects between the groups.[28]

Ballard *et al.* (2014) analyzed data from four previously published clinical trials on ketamine in treatment-resistant depressed patients to determine whether the improvement in suicidal ideation was related or independent to the effect on depressive and anxious symptoms. A group of 133 subjects diagnosed with major depression ($n = 98$) or type I ($n = 19$) or II ($n = 16$) bipolar depression were administered 0.5 mg/kg ketamine intravenously over 40 min. Outcome measures included the Hamilton Depression Rating Scale (HAMD), Scale for Suicidal Ideation (SSI), Beck Depression Inventory (BDI), and Hamilton Anxiety Rating Scale (HAM-A) at 230 min post-infusion. Suicidal ideation has been shown to diminish within the first hour of ketamine administration. While depression and anxiety also improved with ketamine treatment, the reduction in suicidal ideation could not be completely explained by reductions in those symptoms. The authors concluded that changes in suicidal ideation were related but also independent of the antidepressant and antianxiety effects of ketamine. They acknowledge the relationship between depression and suicidal ideation but suggest that reductions in anxiety may be just as important in decreasing suicidal risk.[29] In fact, anxiety has been associated with immediate and long-term risk of suicide and is purported to play a role in transitioning from suicidal ideation to behavior.[30,31]

Generalized Anxiety Disorder

Ray *et al.* (2016) reported a single case of an adult woman with severe panic attacks, agoraphobia, and generalized anxiety disorder (GAD) whose anxiety failed to respond to high-dose SSRI medications, lamotrigine, electroconvulsive therapy (ECT), cognitive-behavioral therapy, and prolonged exposure response prevention (ERP) therapy, and she was homebound due to her anxiety symptoms. She was treated with a single dose of 0.5 mg/kg of intravenous ketamine for severe cervicalgia due to two herniated discs. Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder-7 (GAD-7) scores dramatically improved immediately after infusion, and the treatment exhibited continued benefit over 10 weeks. She also remained free of panic attacks in the 10-week follow-up.[32]

Glue *et al.* (2017) studied the efficacy and safety of subcutaneous administration of ascending does of ketamine (0.25, 0.5, 1 mg/kg) delivered at weekly intervals in patients with treatment-resistant GAD and/or social anxiety disorder (SAD). All 12 patients had a diagnosis of SAD, and only 2 patients did not have a comorbid diagnosis of GAD. Ten of 12 patients were treatment-responders at 0.5–1.0 mg/kg with reduced anxiety reported within 1 h of drug administration. Eight of 12 patients (67%) had a >50% reduction in HAM-A and/or Fear Questionnaire (FQ) after 0.5–1 mg/kg doses at 2 h post-infusion. Dose responses for anxiolytic effects, dissociative side effects, and changes in blood pressure and heart rate were observed, and ketamine was considered well tolerated in the study group without serious adverse events.[33]

The same authors examined the efficacy and safety of ketamine as maintenance therapy in treatment-refractory GAD and SAD. Twenty patients (10 men and 10 women) who responded to acute open-label ascending doses of ketamine (0.25, 0.5, 1 mg/kg) were given one or two weekly ketamine doses of 1 mg/kg subcutaneously. Fifteen patients had a diagnosis of GAD, and 18 were diagnosed with SAD, with some patients having both

anxiety disorders. FQ ratings decreased by ~50%, as did HAM-A ratings. Clinician-Administered Dissociative States Scale (CADSS) mean scores decreased from 20 points at week 1 to 8.8 points at week 14. Ketamine was considered well tolerated. There were mild side effects to ketamine treatment, including nausea, dizziness, and blurry vision, as well as non-clinically significant increases in systolic and diastolic blood pressures. Eighteen subjects reported improved social functioning and/or work-related functioning during maintenance treatment.[34]

Anxious Symptoms in Bipolar Disorder

Zarate *et al.* (2012) evaluated the antidepressant and anti-anxiety effects of a single intravenous dose of ketamine (0.5 mg/kg) vs. a placebo antidepressant in a double-blind, placebo-controlled study of 15 patients with bipolar disorder type I or II. All patients were maintained on therapeutic doses of lithium or valproic acid during treatment. Both depression and anxiety symptoms improved as early as 40 min post-infusion across various outcome measures, including the MADRS, Hamilton Rating Scale for Depression (HDRS), self-rated BDI, and Visual Analog Scale (VAS)-Depression, as well as the HAM-A and VAS-Anxiety scales. The population studied was notable for frequent hospitalizations, failing multiple medication trials, history of suicide attempts, high rates of comorbid anxiety, and significant disability.[35]

Another study of 18 treatment-resistant bipolar disorder patients using a randomized, double-blind, crossover design of a single intravenous ketamine (0.5 mg/kg over 40 min) infusion vs. saline given 2 weeks apart showed significant antidepressant effects with high response and remission rates after day 1. HAM-A was performed as a secondary measure and showed significant improvement after the first post-infusion observation and at 230 min through day 3. Significant differences in ketamine compared to placebo occurred at day 10, but not at days 7 or 14. Improvements in ketamine-treated patients were also noted on VAS-Anxiety.[36]

Previous studies have demonstrated that comorbid anxiety predicts worse outcomes to treatment in bipolar depressed patients.[37] A post hoc analysis was published on the two above studies that combined data from two separate but identically performed randomized, crossover studies examining the antidepressant effects of a single infusion of intravenous ketamine (0.5 mg/kg over 40 min) in bipolar depression. The goal of the study was to evaluate if those patients with anxious vs. non-anxious bipolar depression were less likely to respond to ketamine treatment.

The analysis included 36 treatment-resistant inpatients who had not responded to traditional therapies and were treated concurrently with lithium or valproic acid. They had high anxiety symptoms with a HDRS Anxiety/Somatization Factor Score >7. Anxious patients ($n = 21$) had similar improvement in depression based on MADRS and HDRS to non-anxious patients ($n = 15$) and did not have a greater incidence of side effects, including dissociation or worsening anxiety.[38]

Social Anxiety Disorder

SAD is a highly prevalent condition and the third most common psychiatric disorder in the general population.[39] While often misconstrued with extreme shyness, SAD is associated with significant functional impairment, and nearly half of these patients report moderate to severe impairment in areas of education, work, family, and other social relationships. There is also a high association of SAD with other co-occurring psychiatric conditions.[40] Several SSRI and SNRIs are FDA-approved for SAD, but there are still high rates of non-response to medications ranging from 30% to 45%.[41,42,43]

One single-dose and one maintenance study were reviewed above since these included patients with GAD as well as SAD. In one double-blind, randomized, placebo-controlled crossover study on 18 adults with SAD, ketamine (0.5 mg/kg over 40 min) and placebo infusions were given in a random order with a 28-day washout between infusions. The primary self-report outcome measure was VAS-Anxiety, and the primary clinical reported scale was the Leibowitz Social Anxiety Scale (LSAS). Ratings were performed 3 h after dosing and days 1, 2, 3, 5, 7, 10, and 14 days post-infusion. Response was defined as 35% on LSAS and 50% on VAS-Anxiety. Those receiving ketamine were more likely to have a beneficial response on VAS (88.9% vs. 52.9%) vs. placebo, but this did not reach statistical significance. Subjects receiving ketamine were statistically more likely to show a response on LSAS (33.3% vs. 0%) vs. placebo in the first 2 weeks post-infusion. The authors discussed concerns about the use of saline as a placebo comparator, since most participants correctly identified they were on active medication, which could have affected the reliability of the study.[44]

Obsessive Compulsive Disorder

OCD is a severely disabling condition with low response and remission rates to standard therapies. Numerous studies have focused on the most common pharmacological therapies for this indication – SSRIs – which typically showed a 25–35% decrease in symptoms on the Yale Brown Obsessive Compulsive Scale (Y-BOCS) for approximately 60% of patients, but did not significantly improve their quality of life.[45] Studies of SSRIs demonstrated a significant delay in onset of action, and the durations of treatment benefits are short. In a 5-year longitudinal study, only 39% of patients had either a partial (22.1%) or full (16.9%) recovery.[46] Long-term follow-up of individuals treated for OCD indicated that 83% of them had improvement in

symptoms, with 20% being asymptomatic and 28% having only subclinical symptoms. Fifty-nine percent of participants showed a relapse during a follow-up of almost 50 years.[47] Glutamate abnormalities have been identified using neuroimaging, genetic, and neurochemical studies as indicators to the pathogenesis of OCD. Small published studies using pharmacological agents targeting glutamate such as riluzole, N-acetylcysteine, and memantine have demonstrated some benefits in OCD symptomology.[48]

One published case report examined the efficacy of intranasal ketamine given twice weekly in a Caucasian male in his mid-20s with treatment-resistant OCD under hospital admission. He was given 50 mg of ketamine delivered intranasally in 5–10-mg doses over 20 min. While OCD symptoms reduced following the first week of ketamine administration, suicidality rapidly decreased after the first dose. Compliance with ERP therapy markedly improved in this patient after starting ketamine treatment. The authors suggest that ketamine may augment the efficacy of ERP and encourage studying the concurrent use of ketamine and extinction-based ERP in OCD.[49]

Bloch *et al.* (2012) conducted an open-label clinical trial of intravenous ketamine (0.5 mg/kg over 40 min) in 10 patients with treatment-resistant OCD. Response to ketamine in reducing OCD symptoms was defined as >35% on the Yale Brown Obsessive-Compulsive Scale (Y-BOCS) and >50% on depressive symptoms using HDRS-17 measured between 1 and 3 days after infusion. No response in OCD symptoms was demonstrated in any of the 10 subjects. Four of the seven patients with comorbid depression had an antidepressant response in the first 3 days post-infusion. OCD symptoms did improve in the first few hours post-infusion, but some of the changes were postulated to be attributable to the dissociative and euphorigenic effects of ketamine. The improvement in OCD symptoms was <12%, and the reduction in depression scores was significantly greater than the improvement in OCD scores.[50] However, this group also reported in a separate case series that two patients showed a worsening in delayed suicidal ideation, dysphoria, and anxiety with ketamine infusion. While these patients had a history of major depression, their depressive symptoms were regarded as minimal at the start of infusion.[51]

Rodriguez *et al.* (2013) conducted the first randomized, placebo-controlled, crossover design study in OCD patients. A single dose of intravenous ketamine (0.5 mg/kg) or saline, given 1 week apart, was administered to 15 drug-free patients endorsing near-constant obsessional thoughts. Ketamine ($n = 8$) was associated with a significant improvement in obsessional thoughts as measured by OCD-VAS compared to receiving placebo ($n = 7$). Fifty percent of patients met the criteria for treatment response to ketamine (>35% Y-BOCS), 0% to placebo, 1 week post-infusion.[52] This study demonstrated rapid anti-obsessional effects that persisted for at least 1 week post-infusion. The authors hypothesized that their study may have yielded positive results because their subjects had more constant obsessions, suggesting that there may be a subtype of OCD more sensitive to ketamine. Participants in Bloch *et al.* were not required to have constant obsessional thinking as an entry criterion. Subjects in the Rodriguez *et al.* study had to be medication-free, whereas participants in the Bloch *et al.* study were allowed concomitant medications, including SSRIs, antipsychotics, and benzodiazepines, which may have affected the outcomes. Other differences in the two studies included higher levels of dissociation and lower rates of comorbid depression, suggesting that dissociation may predict response rates and that higher levels of comorbid depression with OCD may represent a subtype less responsive to ketamine.

Post-traumatic Stress Disorder

Currently, several SSRIs are FDA-approved therapies for the treatment of PTSD. As with other anxiety disorders, pharmacologic treatments for PTSD are also associated with low rates of remission and high rates of treatment non-response. Glutamate has been shown to modulate stress response, traumatic memory formation, and may impact PTSD symptoms. Glutamate also plays a role in the regulation of neurosteroids, such as corticotropin-releasing factor, which has been associated with the pathophysiology of PTSD.[53] While ketamine has been explored as a potential therapeutic option for treatment-resistant PTSD, there are concerns that possible side effects, including hyperarousal and dissociation, could exacerbate PTSD symptoms during ketamine administration.

Clinically, ketamine is often given in the emergency room setting for analgesia, or as a sedative. S-ketamine is an enantiomer of ketamine that has a fourfold higher affinity to the glutamate NMDA receptor than R-ketamine. It is thought to have a similar mechanism of action to ketamine and was recently approved via an intranasal delivery system for treatment-resistant depression.[54] There has been mixed data published from small, poorly controlled trials examining the potential risks of triggering or worsening PTSD symptoms, such as dissociation, in accident victims. One retrospective trial followed 56 moderately injured patients 1 year post-injury and found that those given peritraumatic S-ketamine experienced higher dissociative and acute stress disorder symptoms measured by the Peritraumatic Dissociative Experiences Scale (PDEQ), Acute Stress Disorder Scale (ASD), and Impact of Events Scale (IES-R). All received a single dose of S-ketamine, opioids, or racemic ketamine. Those given S-ketamine had elevated PTSD symptoms, while there was no difference between opioid- or racemic ketamine-treated patients.[55]

Table1. Studies on ketamine for anxiety disorders

Disorder	Author	Study design	Clinical population	*n*	Ketamine type and dose	Outcome measures	Follow-up	Results
Anxiety symptoms in depressed patients	Irwin *et al.* (2010)	Case series	Depression and anxiety in patients receiving hospice care	2	Single dose of 0.5 mg/kg oral ketamine hydrochloride	HDRS, HADS, ASC, BPRS	Baseline, 1, 2 h, and 2, 3, 8, and 15 days post-dose	Rapid improvement in anxiety symptoms within 1 h, with sustained effect up to 1 week
	Irwin *et al.* (2013)	Open-label, proof-of-concept study	Depression and anxiety in patients receiving hospice care	14	Daily oral doses of 0.5 mg/kg ketamine hydrochloride	HADS	Baseline, on days 3, 7, 14, 21, and 28	Significant reduction in anxiety symptoms occurred by day 3, mean time to response 8.6 days, maintained through day 28
	Ionescu *et al.* (2014)	Post hoc analysis of open-label trial	Inpatients with treatment-resistant depression	26	Single dose of 0.5 mg/kg of intravenous ketamine	MADRS and HDRS Anxiety/Somatization Factor Score; anxious depression defined as HDRS Anxiety/Somatization Factor Score ≥7	Baseline, 230 min post-infusion, and on days 1, 3, 7, 14, 21, and 28	Anxious patients responded better to ketamine than non-anxious depressed patients, with longer time to relapse
	Ballard *et al.* (2014)	Post hoc analysis of four prior studies, including an open-label trial and double-blind, placebo-controlled studies	Patients with major depression ($n = 98$) or type I ($n = 98$) or II ($n = 16$) bipolar disorder	133	Single dose of 0.5 mg/kg of intravenous ketamine	HDRS, SSI, BDI, HAM-A	Baseline, 40, 80, 120, 230 min and 1, 2 and 3 days post-infusion	Suicidal ideation diminished within first hour, reduction independent of antidepressant and antianxiety effects
GAD, SAD	Glue *et al.* (2017)	Ascending single-dose, uncontrolled, open-label study	Refractory GAD and/or SAD	12	Weekly subcutaneous 0.25, 0.5, or 1 mg/kg ketamine	FQ, HAM-A; response defined as ≥50% reduction in HAM-A or FQ total score after any dose	Pre-dose, 1, 2, 24, 72, and 168 h post-dose	Treatment response in 10/12 patients (83%) at 0.5–1 mg/kg
	Glue *et al.* (2018)	Uncontrolled, open-label, maintenance trial	Patients with GAD ($n = 15$) or SAD ($n = 18$) who had responded to acute open-label ascending doses of ketamine	20	Once or twice weekly subcutaneous 1 mg/kg ketamine	FQ, HAM-A	Pre-dose, 1, 2 h post-dose, then weekly to 14 weeks	FQ, HAM-A decreased by ~50%, improved social/work functioning in 18/20 subjects
	Taylor *et al.* (2018)	Randomized, placebo-controlled, double-blind, crossover trial	SAD	18	Single dose of 0.5 mg/kg of intravenous ketamine	LSAS, VAS-Anxiety, response defined as >35% LSAS reduction and 50% VAS-Anxiety reduction	Pre-infusion, 3 h and 1, 2, 3, 5, 7, 10 and 14 days post-infusion	Ketamine resulted in a significantly greater reduction in anxiety relative to placebo on LSAS but not VAS-Anxiety

(*Continued*)

Table1. (*Continued*)

Disorder	Author	Study design	Clinical population	*n*	Ketamine type and dose	Outcome measures	Follow-up	Results
Anxiety in bipolar disorder	Zarate *et al.* (2012)	Randomized, double-blind, placebo-controlled trial	Bipolar disorder type I or II	15	Single dose of 0.5 mg/kg of intravenous ketamine on 2 test days 2 weeks apart	MADRS, HDRS, BDI, VAS-Depression, VAS-Anxiety, HAM-A, BPRS, YMRS	Baseline, 40, 80, 110, and 230 min and 1, 2, 3, 7, 10, and 14 days post-infusion	Depression and anxiety symptoms across various outcome measures improved as early as 40 min post-infusion
	Diazgranados *et al.* (2010)	Randomized, placebo-controlled, double-blind, crossover trial	Treatment-resistant bipolar disorder	18	Single dose of 0.5 mg/kg of intravenous ketamine on 2 test days 2 weeks apart	MADRS, HDRS, BDI, VAS-Depression, VAS-Anxiety, HAM-A, BPRS, YMRS	Baseline, 40, 80, 110, and 230 min and 1, 2, 3, 7, 10, and 14 days post-infusion	Significant improvement post-infusion, sustained through day 3
	Ionescu *et al.* (2014)	Meta-analysis of two prior randomized, crossover studies	Treatment-resistant bipolar disorder	36	Single dose of 0.5 mg/kg of intravenous ketamine	MADRS, HDRS Anxiety/ Somatization Factor Score	Baseline, 40, 80, 110, and 230 min and 1, 2, 3, 7, 10, and 14 days post-infusion	Anxious patients had similar improvement in depression compared to non-anxious patients
OCD	Bloch *et al.* (2014)	Open-label trial	Treatment-resistant OCD	10	Single dose of 0.5 mg/kg of intravenous ketamine	Y-BOCS, HDRS; response defined as >35% change on Y-BOCS and >50% change on HDRS-17	Baseline, 1, 2, and 3 h, and 1, 2, 3, 5, and 7 days post-infusion	No significant change in OCD symptoms on Y-BOCS (<12%), 4/7 with comorbid depression had antidepressant response
	Rodriguez *et al.* (2013)	Randomized, placebo-controlled, double-blind crossover trial	Drug-free patients with OCD	15	Single dose of 0.5 mg/kg of intravenous ketamine	VAS-OCD, Y-BOCS; response defined as >35% change on Y-BOCS	Baseline, during infusion, 90, 110, 230 min and daily for 1 week post-infusion	Significant improvement in obsessional thoughts on VAS-OCD, 50% patients met criteria for response on Y-BOCS
PTSD	Schönenberg *et al.*(2005)	Retrospective cohort study	Moderately injured accident victims	56	Single or fractionated dose of S-ketamine, racemic ketamine, or opioids	PDEQ, ASD, IES-R	1 year post-exposure	Patients who received S-ketamine had elevated PTSD symptoms, no difference between opioid or racemic ketamine
	Schönenberg *et al.*(2008)	Naturalistic, prospective study	Moderately injured accident victims	50	Single or fractionated dose of racemic ketamine, opioids, or non-opioid analgesics	PDEQ, ASD, TLEQ	Within 3 days of admission	Patients who received ketamine had increased trauma-related symptoms
	McGhee *et al.* (2008)	Retrospective cohort study	Military service burn victims	147	Ketamine during surgery	PCL-M	Unknown	Patients who received perioperative ketamine had lower prevalence of PTSD

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Table 1. (*Continued*)

Disorder	Author	Study design	Clinical population	*n*	Ketamine type and dose	Outcome measures	Follow-up	Results
	Feder *et al.* (2014)	Proof-of-concept, randomized, active, placebo-controlled, double-blind, crossover study	Chronic PTSD	41	Single-dose of intravenous ketamine (0.5 mg/kg) vs. midazolam (0.045 mg/kg)	IES-R, CGI, CAPS-IV	Baseline, during infusion, 90, 110, 230 min and 1, 2, 3, and 7 days post-infusion	Patients who received ketamine had a significant reduction in PTSD symptoms after 24 h compared to controls, but no significant difference at 7 days
	Zeng *et al.* (2013)	Post hoc analysis of prior studies including three randomized controlled trials	Patients with treatment-resistant depression or bipolar disorder who had trauma history or comorbid PTSD	30	Single dose of 0.5 mg/kg of intravenous ketamine	BPRS, HDRS	40, 80, 110 and 230 min and 1, 2, 3, and 7 days post-infusion	No increase in psychosis, dissociation, or anxiety in those with depression along with a history of trauma or PTSD
	Albott *et al.* (2018)	Open-label trial	Comorbid PTSD and treatment-resistant depression	15	Six doses of intravenous ketamine (0.5 mg/kg) over 12 days	MADRS, PCL-5	Baseline, 24 h after each infusion and weekly for 8 weeks following the final infusion	Significant improvements in PTSD remission (80%) and depression response (93.3%)

Note: HDRS, Hamilton Depression Rating Scale; HADS, Hospital Anxiety and Depression Scales; ASC, Adverse Symptom Checklist; BPRS, Brief Psychiatric Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; SSI, Scale for Suicidal Ideation; BDI, Beck Depression Inventory; HAM-A, Hamilton Anxiety Rating Scale; FQ, Fear Questionnaire; LSAS, Liebowitz Social Anxiety Scale; YMRS, Young Mania Rating Scale; VAS-Anxiety, Visual Analog Scale-Anxiety; VAS-Depression, Visual Analog Scale-Depression; Y-BOCS, Yale Brown Obsessive-Compulsive Scale; VAS-OCD, Visual Analog Scale-Obsessive Compulsive Disorder; PDEQ, Peritraumatic Dissociative Experiences Questionnaire; ASD, Acute Stress Disorder Scale; IES-R, Impact of Events Scale-Revised; TLEQ, Traumatic Life Events Questionnaire; PCL-M, PTSD Checklist-Military; CGI, Clinical Global Impression Scale; CAPS-IV, Clinician Administered PTSD Scale; PCL-5, PTSD Checklist of DSM-5.

In a naturalistic, prospective study, accident victims admitted to a hospital were screened for ASD using PDEQ, ASD, and the Traumatic Life Events Questionnaire (TLEQ). Patients received racemic ketamine ($n = 13$), non-opioids ($n = 13$), or opioids ($n = 24$). There were no differences between the groups with regard to demographics, injury severity, or prior trauma. There was an association between ketamine administration and increased dissociation, re-experiencing, hyperarousal, and avoidance, which, the authors postulated, could contribute to long-lasting symptomology.[56]

A study examined the effects of PTSD development with ketamine administration in burn victims in military service using a PTSD Checklist-Military (PCL-M). Among the 147 soldiers who received surgery, 119 received ketamine and 28 did not. The prevalence of PTSD was 27% in those receiving ketamine during surgery and 43% in those who did not. The authors concluded that those receiving perioperative ketamine had lower rates of PTSD than those who did not receive ketamine, despite having larger burn areas, higher injury severity scores, more ICU time, and more surgeries.[57]

There is one published case report of a veteran given a single dose of intravenous ketamine (35 mg) and propofol (34 mg) over 20 min for the management of severe, treatment-resistant depression with suicidal ideation. His depression improved immediately post-infusion, and his PTSD scores dropped significantly on PCL-M. Unfortunately, he had a return of symptoms at 14-day follow-up.[58]

Feder *et al.* (2014) conducted a proof-of-concept, single-dose, randomized, double-blind, crossover study comparing intravenous ketamine (0.5 mg/kg) with active placebo midazolam (0.045 mg/kg) in 41 patients with chronic PTSD. Ketamine demonstrated a significant and rapid reduction in PTSD symptoms after 24 h of infusion compared to midazolam using IES-R. Both crossover and first-period analysis showed significant improvements in PTSD symptoms on IES-R and the Clinical Global Impression Scale (CGI) to ketamine even after adjusting for baseline and 24-h depression symptom severity. Comorbid depression symptoms also improved, and ketamine was well tolerated without persistent dissociative symptoms. Secondary measures, including MADRS and Quick Inventory of Depressive Symptomatology (QIDS-SR), at 24 h did not show a statistically significant benefit of ketamine vs. placebo. The Clinician-Administered PTSD Scale (CAPS-IV) at day 7 post-infusion did not show a significant change in symptom severity to ketamine vs. placebo. While the study demonstrated rapid improvements in chronic PTSD symptoms with ketamine treatment, a sustained response to the treatment was not demonstrated.[59]

Zeng *et al.* (2013) examined patients enrolled in one of three separately conducted intravenous ketamine trials for treatment-resistant depression and bipolar disorder type I or II. They found that 10 subjects had comorbid PTSD, another 12 and 8 had histories of sexual abuse and physical abuse, respectively. There were no differences in improvements in the positive symptom subscale of the Brief Psychiatric Rating Scale (BPRS) in those with or without comorbid PTSD or trauma history. The authors did not detect differences in symptoms of dissociation, psychosis, or anxiety between those with or without trauma and/or PTSD 1 week after ketamine infusion. While acknowledging the small sample size, the authors concluded that a history of trauma may not negatively impact the antidepressant effect of ketamine on depression.[60]

A study was conducted to evaluate the efficacy, safety, and durability of repeated ketamine treatments in 15 individuals with comorbid PTSD and treatment-resistant depression. Subjects received six intravenous infusions of 0.5 mg/kg of ketamine over 12 days and were assessed weekly for 8 weeks. MADRS and PTSD Checklists of DSM-5 (PCL-5) were both used as outcome measures. There were significant improvements in PTSD remission (80%) and depression response rates (93.3%). While repeated infusions were associated with transient worsening of dissociative symptoms, there was no worsening of overall PTSD symptoms throughout the study. A median time to relapse of depression in responders was 20 days post-infusion.[61]

Side Effects and Tolerability

Anxiety disorders are often associated with physical symptoms such as tachycardia, elevated blood pressure, shortness of breath, and gastrointestinal disorders. Many currently approved antidepressants have been associated with short-term worsening of anxiety, and ketamine may be no exception.[62,63] Dissociation as well as elevations in pulse and blood pressure, which can mimic anxious symptoms, can be common side effects of ketamine infusion.[64] Castle *et al.* (2017) reported on the use of CADSS in assessing dissociative symptoms after ketamine infusion. They found that CADSS is a reliable instrument in monitoring dissociative side effects and that dissociative ratings increased in a dose-dependent manner in patients with anxiety disorders.[65]

Other studies on ketamine in treatment-resistant depression also showed similar side effects of dissociative symptoms, mild elevations in pulse and blood pressure, dizziness, blurry vision, headache, nausea, poor coordination, and restlessness. There have been a few isolated cases of reported mania and little evidence for worsening of anxiety, OCD, PTSD, or panic symptoms.[66,67,68]

Safety and tolerability of ketamine in 97 treatment-resistant depressed patients undergoing a total of 205 infusions from three separate clinical trials was reviewed. The overall discontinuation rates due to side effects were

low at 1.95% (4 of 205 infusions). The most common side effects within the first 4 h post-infusion were drowsiness, poor coordination, blurry vision, and feeling strange and unreal. One-third had transient hemodynamic changes, including mild elevations in pulse and blood pressure. Fourteen percent received medication intervention for these changes. In all but two cases, blood pressure responded quickly to intervention. In the other two cases, blood pressure returned to normal within minutes of infusion discontinuation. There were small but significant increases in psychomimetic and dissociative symptoms, none of which persisted at long-term follow-up. There was no evidence of ketamine cravings, drug cravings, and substance abuse at follow-up.[69]

Conclusions

Anxiety disorders are the most prevalent of psychiatric conditions, and despite the availability of effective therapies, high rates of partial responders and treatment resistance exist. In addition, anxiety may be one of the most common coexisting psychiatric symptoms in a number of other psychiatric conditions, such as attention-deficit disorder, substance abuse, and bipolar disorder, but may not be severe enough to be considered an additional diagnosis. High rates of comorbid anxiety disorders also occur with other psychiatric conditions. Consequently, understanding the safety and efficacy of ketamine use in this population is important. The focus of ketamine research has primarily targeted treatment-resistant depression and acute management of suicidality. There are an increasing number of case reports, case series, and small but well-controlled trials demonstrating proof-of-concept for its efficacy in the treatment of anxiety and anxiety spectrum disorders.

There is no unifying genetic, psychosocial, neurobiological, neuroanatomical, or neuropsychological etiology that links all anxiety disorders together.[70] As such, the role of ketamine in managing anxious symptoms or specific anxiety disorders becomes even more challenging to decipher. There is sufficient evidence to show that glutamate plays an important role in the pathophysiology and treatment of depression as well as anxious symptoms and anxiety disorders.[71] Perhaps high rates of co-occurring depression and anxiety are a consequence of a shared etiology,[72] which may explain why a number of pharmacological interventions that are effective in depression also showed benefit in anxiety disorders. This begs the question of whether ketamine has a role in improving depressive symptoms, targeting a similar etiology of both conditions, or affecting pathophysiological changes unique to anxiety disorders. Interpreting the findings of studies presented here is complicated due to the fact that many of the subjects had comorbid depression and anxiety.

There is sufficient evidence to suggest that ketamine and other glutamatergic agents in development may offer novel strategies for the management of treatment-resistant patients who continue to experience significant symptomology and disability as a result of their anxious symptoms. Risks from ketamine treatment appear minimal in this population based on the current level of evidence, provided patient screening is appropriately performed. Caution should be employed in high-risk patients, including those with a psychotic disorder, active substance abuse, or health problems that might get aggravated by ketamine use, such as uncontrolled hypertension, aneurysms, or elevated intracranial pressure. More well-controlled studies with longer follow-up periods are needed to assess the long-term safety and tolerability of ketamine in difficult-to-treat patients with symptoms of anxiety or anxiety disorders.

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REFERENCES:

1. Grady S, Marsh T, Tenhouse A, *et al.* Ketamine for the treatment of major depressive disorder and bipolar depression: a review of the literature. *Mental Health Clin*. 2017; **7**(1): 16–23.
2. Diaz Granados N, Ibrahim L, Brutsche N, *et al.* Rapid resolution of suicidal ideation after a single infusion of an N-Methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. *J Clin Psychiatry*. 2010; **71**(12): 1605–1611.
3. Newport DJ, Carpenter LL, McDonald WM, *et al.* Ketamine and other NMDA antagonists: early trials and possible mechanisms in depression. *Am J Psychiatry*. 2015; **172**(10): 950–966.
4. Kessler R, Petukhova M, Sampson N, *et al.* Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. *Int J Methods Psychiatr Res*. 2012; **21**(3): 169–184.
5. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders* 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
6. Kaufman J, Charney D. Comorbidity of mood and anxiety disorders. *Depress anxiety*. 2000; **12**(S1): 69–76.
7. Fava M, Rush A, Alpert J, *et al.* Difference in treatment outcome in outpatients with anxious versus nonanxious depression: a STAR*D report. *Am J Psychiatry*. 2008; **165**(3): 342–351.
8. Wiethoff K, Bauer M, Baghai T, *et al.* Prevalence and treatment outcome in anxious versus nonanxious depression. *J Clin Psychiatry*. 2010; **71**(08): 1047–1054.

9. Gorman JM, Kent JM. SSRIs and SNRIs: broad spectrum of efficacy beyond major depression. *J Clin Psychiatry*. 1999; **60**(4): 33–38. discussion, 39.
10. Roy-Byrne P. Treatment-refractory anxiety; definition, risk factors, and treatment challenges. *Dialogues Clin Neurosci*. 2015; **17**(2): 191–206.
11. Cassano G, Rossi N, Pini S. Psychopharmacology of anxiety disorders. *Dialogues Clin Neurosci*. 2002; **4**(3): 271–285.
12. Davis M, Myers KM. The role of glutamate and gamma-aminobutyric acid in fear extinction: clinical implications for exposure therapy. *Biol Psychiatry*. 2002; **52**(10): 998–1007.
13. Madaan V, Wilson DR. Neuropeptides: relevance in treatment of depression and anxiety disorders. *Drug News Perspect*. 2009; **22**(6): 319.
14. Uys JDK, Stein DJ, Daniels WMU. Neuroproteomics: relevance to anxiety disorders. *Curr Psychiatry Rep*. 2006; **8**(4): 286–290.
15. Duman RS, Aghajanian GK. Synaptic dysfunction in depression: potential therapeutic targets. *Science*. 2012; **338**(6103): 68–72.
16. Trullas R, Skolnick P. Functional antagonists at the NMDA receptor complex exhibit antidepressant actions. *Eur J. Pharmacol*. 1990; **185**: 1–10.
17. Aguado L, Antonio AS, Pérez L, *et al.* Effects of the NMDA receptor antagonist ketamine on flavor memory: conditioned aversion, latent inhibition, and habituation of neophobia. *Behav Neural Biol*. 1994; **61**(3): 271–281.
18. Garcia LSB, Comim CM, Valvassori SS, *et al.* Acute administration of ketamine induces antidepressant-like effects in the forced swimming test and increases BDNF levels in the rat hippocampus. *Prog Neuro-Psychopharmacol Biol Psychiatry*. 2008; **32**(1): 140–144.
19. Skolnick P, Layer R, Popik P, *et al.* Adaptation of N-Methyl-D-Aspartate (NMDA) receptors following antidepressant treatment: implications for the pharmacotherapy of depression. *Pharmacopsychiatry*. 1996; **29**(01): 23–26.
20. Zarate CA, Jr, Singh JB, Quiroz JA, *et al.* A double-blind, placebo controlled study of memantine in the treatment of major depression. *Am J Psychiatry*. 2006; **163**: 153–155.
21. Autry AE, Adachi M, Nosyreva E, *et al.* NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. *Nature*. 2011; **475**(7354): 91–95.
22. Collingridge GL, Olsen RW, Peters J, *et al.* A nomenclature for ligand-gated ion channels. *Neuropharmacology*. 2009; **56**(1): 2–5.
23. Monteggia LM, Gideons E, Kavalali ET. The role of eukaryotic elongation factor 2 kinase in rapid antidepressant action of ketamine. *Biol Psychiatry*. 2013; **73**(12): 1199–1203.
24. Li N, Liu R-J, Dwyer JM, *et al.* Glutamate N-methyl-D-aspartate receptor antagonists rapidly reverse behavioral and synaptic deficits caused by chronic stress exposure. *Biol Psychiatry*. 2011; **69**(8): 754–761.
25. Murrough JW. Ketamine as a novel antidepressant: from synapse to behavior. *Clin Pharmacol Ther*. 2011; **91**(2): 303–309.
26. Irwin SA, Iglewicz A. Oral ketamine for the rapid treatment of depression and anxiety in patients receiving hospice care. *J Palliat Med*. 2010; **13**(7): 903–908.
27. Irwin SA, Iglewicz A, Nelesen RA, *et al.* Daily oral ketamine for the treatment of depression and anxiety in patients receiving hospice care: a 28-day open-label proof-of-concept trial. *J Palliat Med*. 2013; **16**(8): 958–965.
28. Ionescu DF, Luckenbaugh DA, Niciu MJ, *et al.* Effect of baseline anxious depression on initial and sustained antidepressant response to ketamine. *J Clin Psychiatry*. 2014; **75**(09): e932–e938.
29. Ballard ED, Ionescu DF, Vande Voort JL, *et al.* Improvement in suicidal ideation after ketamine infusion: relationship to reductions in depression and anxiety. *J Psychiatr Res*. 2014; **58**: 161–166.
30. Goldberg D, Fawcett J. The importance of anxiety in both major depression and bipolar disorder. *Depress Anxiety*. 2012; **29**(6): 471–478.
31. Nock MK, Hwang I, Sampson NA, *et al.* Mental disorders, comorbidity and suicidal behavior: results from the national comorbidity survey replication. *Mol Psychiatry*. 2009; **15**(8): 868–876.
32. Ray SM, Kious BM. Sustained resolution of panic disorder, agoraphobia, and generalized anxiety disorder with a single ketamine infusion. *Prim Care Companion CNS Disord*. 2016; **18**(4).
33. Glue P, Medlicott NJ, Harland S, *et al.* Ketamine's dose-related effects on anxiety symptoms in patients with treatment refractory anxiety disorders. *J Psychopharmacol*. 2017; **31**(10): 1302–1305.
34. Glue P, Neehoff SM, Medlicott NJ, *et al.* Safety and efficacy of maintenance ketamine treatment in patients with treatment-refractory generalised anxiety and social anxiety disorders. *J Psychopharmacol*. 2018; **32**(6): 663–667.
35. Zarate CA, Brutsche NE, Ibrahim L, *et al.* Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. *Biol Psychiatry*. 2012; **71**(11): 939–946.
36. Diazgranados N, Ibrahim L, Brutsche NE, *et al.* A randomized add-on trial of an n-methyl-d-aspartate antagonist in treatment-resistant bipolar depression. *Arch Gen Psychiatry*. 2010; **67**(8): 793–802.
37. El-Mallakh RS, Hollifield M. Comorbid anxiety in bipolar disorder alters treatment and prognosis. *Psychiatr Q*. 2008; **79**(2): 139–150.
38. Ionescu DF, Luckenbaugh DA, Niciu MJ, *et al.* A single infusion of ketamine improves depression scores in patients with anxious bipolar depression. *Bipolar Disord*. 2014; **17**(4): 438–443.
39. Grant BF, Hasin DS, Blanco C, *et al.* The epidemiology of social anxiety disorder in the United States. *J Clin Psychiatry*. 2005; **66**(11): 1351–1361.
40. Schneier FR. Social Phobia. *Arch Gen Psychiatry*. 1992; **49**(4): 282–288.
41. Stein MB, Liebowitz MR, Lydiard RB, *et al.* Paroxetine treatment of generalized social phobia (social anxiety disorder). *JAMA*. 1998; **280**(8): 708.
42. Katzelnick D, Kobak K, Greist J, *et al.* Sertraline for social phobia: a double-blind, placebo-controlled crossover study. *Am J Psychiatry*. 1995; **152**(9): 1368–1371.
43. van Vliet IM, den Boer JA, Westenberg HGM. Psychopharmacological treatment of social phobia; a double blind placebo controlled study with fluvoxamine. *Psychopharmacology*. 1994; **115**(1-2): 128–134.
44. Taylor JH, Landeros-Weisenberger A, Coughlin C, *et al.* Ketamine for social anxiety disorder: a randomized, placebo-controlled crossover trial. *Neuropsychopharmacology*. 2017; **43**(2): 325–333.
45. Haan E, Oppen P, Balkom AJLM, *et al.* Prediction of outcome and early vs. late improvement in OCD patients treated with cognitive behaviour therapy and pharmacotherapy. *Acta Psychiatr Scand*. 1997; **96**(5): 354–361.
46. Eisen JL, Sibrava NJ, Boisseau CL, *et al.* Five-year course of obsessive-compulsive disorder. *J Clin Psychiatry*. 2013; **74**(03): 233–239.
47. Skoog G, Skoog I. A 40-year follow-up of patients with obsessive-compulsive disorder. *Arch Gen Psychiatry*. 1999; **56**(2): 121–127.
48. Pittenger C, Bloch MH, Williams K. Glutamate abnormalities in obsessive compulsive disorder: neurobiology, pathophysiology, and treatment. *Pharmacol Ther*. 2011; **132**(3): 314–332.
49. Adams TG, Bloch MH, Pittenger C. Intranasal ketamine and cognitive-behavioral therapy for treatment-refractory obsessive-compulsive disorder. *J Clin Psychopharmacol*. 2017; **37**(2): 269–271.
50. Bloch MH, Wasylink S, Landeros-Weisenberger A, *et al.* Effects of ketamine in treatment-refractory obsessive-compulsive disorder. *Biol Psychiatry*. 2012; **72**(11): 964–970.
51. Niciu MJ, Grunschel BD, Corlett PR, *et al.* Two cases of delayed-onset suicidal ideation, dysphoria and anxiety after ketamine infusion in patients with obsessive–compulsive disorder and a history of major depressive disorder. *J Psychopharmacol*. 2013; **27**(7): 651–654.
52. Rodriguez CI, Kegeles LS, Levinson A, *et al.* Randomized controlled crossover trial of ketamine in obsessive-compulsive disorder:

proof-of-concept. *Neuropsychopharmacology*. 2013; **38**(12): 2475–2483.
53. Nair J, Ajit SS. The role of the glutamatergic system in posttraumatic stress disorder. *CNS Spectr*. 2008; **13**(07): 585–59.
54. Molero P, Ramos-Quiroga JA, Martin-Santos R, *et al.* Antidepressant efficacy and tolerability of ketamine and esketamine: a critical review. *CNS Drugs*. 2018; **32**(5): 411–420.
55. Schönenberg M, Reichwald U, Domes G, *et al.* Effects of peritraumatic ketamine medication on early and sustained posttraumatic stress symptoms in moderately injured accident victims. *Psychopharmacology*. 2005; **182**(3): 420–425.
56. Schönenberg M, Reichwald U, Domes G, *et al.* Ketamine aggravates symptoms of acute stress disorder in a naturalistic sample of accident victims. *J Psychopharmacol*. 2008; **22**(5): 493–497.
57. McGhee LL, Maani CV, Garza TH, *et al.* The correlation between ketamine and posttraumatic stress disorder in burned service members. *J Trauma*. 2008; **64**(Supplement): S195–S199.
58. D'Andrea D, Andrew Sewell R. Transient resolution of treatment-resistant posttraumatic stress disorder following ketamine infusion. *Biol Psychiatry*. 2013; **74**(9): e13–e14.
59. Feder A, Parides MK, Murrough JW, *et al.* Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: a randomized clinical trial. *JAMA Psychiatry*. 2014; **71**(6): 681–688.
60. Zeng MC, Niciu MJ, Luckenbaugh DA, *et al.* Acute stress symptoms do not worsen in posttraumatic stress disorder and abuse with a single subanesthetic dose of ketamine. *Biol Psychiatry*. 2013; **73**(12): e37–e38.
61. Albott CS, Lim KO, Forbes MK, *et al.* Efficacy, safety, and durability of repeated ketamine infusions for comorbid posttraumatic stress disorder and treatment-resistant depression. *J Clin Psychiatry*. 2018; **79**(3).
62. Gollan JK, Fava M, Kurian B, *et al.* What are the clinical implications of new onset or worsening anxiety during the first two weeks of SSRI treatment for depression? *Depress Anxiety*. 2011; **29**(2): 94–101.
63. Malhi GS, Byrow Y, Cassidy F, *et al.* Ketamine: stimulating antidepressant treatment? *BJPsych Open*. 2016; **2**(03): e5–e9.
64. Suleiman Z, Kolawole I, Bolaji B. Evaluation of cardiovascular stimulation effects after induction of anaesthesia with ketamine. *J West Afr Coll Surg*. 2012; **2**(1): 38–52.
65. Castle C, Gray A, Neehoff S, *et al.* Effect of ketamine dose on self-rated dissociation in patients with treatment refractory anxiety disorders. *J Psychopharmacol*. 2017; **31**(10): 1306–1311.
66. Serafini G, Howland R, Rovedi F, *et al.* The role of ketamine in treatment-resistant depression: a systematic review. *Curr Neuropharmacol*. 2014; **12**(5): 444–461.
67. Katalinic N, Lai R, Somogyi A, *et al.* Ketamine as a new treatment for depression: a review of its efficacy and adverse effects. *Aust N Z J Psychiatry*. 2013; **47**(8): 710–727.
68. Girish B, Prutha D, Prahlad P. Ketamine-induced affective switch in a patient with treatment-resistant depression. *Indian J Pharmacol*. 2015; **47**(4): 454–455.
69. Wan L-B, Levitch CF, Perez AM, *et al.* Ketamine safety and tolerability in clinical trials for treatment-resistant depression. *J Clin Psychiatry*. 2014; **76**(03): 247–252.
70. Krishnan V, Nestler EJ. The molecular neurobiology of depression. *Nature*. 2008; **455**(7215): 894–902.
71. Riaza Bermudo-Soriano C, Perez-Rodriguez MM, Vaquero-Lorenzo C, *et al.* New perspectives in glutamate and anxiety. *Pharmacol Biochem Behav*. 2012; **100**(4): 752–774.
72. Mathew AR, Pettit JW, Lewinsohn PM, *et al.* Co-morbidity between major depressive disorder and anxiety disorders: shared etiology or direct causation? *Psychol Med*. 2011; **41**(10): 2023–2034.