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REVIEW

Ketamine in Bipolar Disorder: A Review

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Abstract: Bipolar disorder (BD) is a psychiatric illness associated with high morbidity, mortality and suicide rate. It has neuroprogressive course and a high rate of treatment resistance. Hence, there is an unquestionable need for new BD treatment strategies. Ketamine appears to have rapid antidepressive and antisuicidal effects. Since most of the available studies concern unipolar depression, here we present a novel insight arguing that ketamine might be a promising treatment for bipolar disorder.

Keywords: ketamine, bipolar disorder, staging, neuroprogression, treatment resistance

Introduction

Bipolar disorder (BD) is a burdensome and recurrent psychiatric condition that affects more than 1% of the population. It has the highest lifetime risk of suicide among all psychiatric disorders.[1,2] Most patients with BD experience depression for a significant part of their lives.[3,4] The treatment failure rates of bipolar depression are higher than those of major depressive disorder (MDD).[5] A longer duration of bipolar depression leads to neuroprogression, which involves structural brain changes and neuropsychological deficits. Currently, there is an unmet need for both short- and long-term treatment options for patients with refractory bipolar depression.[4,6] The robust antidepressant and antisuicidal effects of ketamine in treatment-resistant patients, as well as its unique mechanism of action, may point to ketamine as an interesting treatment option for BD. There are currently 140 trials of ketamine and its enantiomers registered in psychiatric disorders. Most of them include MDD patients, only 0.7% include bipolar patients, and 5.7% include both MDD and bipolar patients.[7] Ketamine treatment in bipolar depression is clearly understudied; however, it is of great importance given the currently poor treatment outcomes for bipolar depression. This review describes current evidence regarding the potential benefits of ketamine for patients with BD and could serve to inform future clinical trials and clinicians on this subject.

Ketamine in Bipolar Disorder – Clinical Data

Single Administration

The rapid antidepressant effect of low-dose ketamine intravenous infusion was first reported by Berman et al in a placebo-controlled double-blind study conducted among patients with depression (including one bipolar patient); this effect was later confirmed by Zarate et al in a placebo-controlled, double-blind crossover study conducted among 18 patients with treatment-resistant MDD.[8,9] Subsequent controlled studies have demonstrated the effectiveness of single low-dose ketamine in treatment-resistant cases of bipolar depression.[10–12]

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The first randomized, placebo-controlled, double-blind, crossover study which administered ketamine to patients with bipolar depression reported an antidepressant effect when a single infusion was used as an adjunct to mood stabilizers.[10] The results were replicated in a double-blind, randomized, crossover, placebo-controlled study with 15 bipolar patients.[11] Similar results were obtained in another study.[13] In an open-label study of 42 patients with bipolar depression, Permoda-Osip et al found that 52% responded to a single infusion of ketamine;[14] the rapid antidepressant effect was replicated in a subsequent study conducted among 53 patients with bipolar depression.[15] In another study, 23 and 4 patients with unipolar and bipolar depression, respectively, were administered esketamine (0.25mg/kg); almost half of the patients (48.1%) showed a response within 1 week of treatment. Ten patients (37.0%) experienced remission in the same period.[16] Two meta-analyses including the above studies have also supported the effectiveness of a single ketamine infusion in the treatment of unipolar and bipolar depression.[17,18] Predictors of positive response to a single ketamine infusion in unipolar and bipolar patients are high BMI (body mass index) and lower baseline levels of adiponectin suggesting that metabolic imbalance might be related to ketamine's antidepressant effect.[19,20]

Multiple Administration

Data on multiple administration of ketamine in patients with bipolar depression are scarce. A very low dose of sublingual ketamine (administered every 2–3 days or weekly) was reported to produce rapid and consistent effects, which included the improvement of mood level and stability, cognition, and sleep in most patients (77%) with unipolar or bipolar depression; mild side effects were observed in 26 patients.[21] Another study administered multiple ketamine intravenous infusions (six 0.5mg/kg infusions) in patients with unipolar (n=77) and bipolar (n=20) depression, and reported response and remission rates of 68% and 50.5%, respectively; however, the results of the bipolar group were not analyzed separately.[22] A recent study on 6 low-dose ketamine infusions in 16 bipolar patients reported response and remission rate 73.7% and 63.2%, respectively, at 24 h after the 6th infusion.[23] The most recent study by McIntyre included 213 TRD patients including 30 patients with bipolar disorder, but this subgroup was not analyzed separately. The authors observed rapid antidepressive and antisuicidal effects.[24] The authors of the mentioned studies did not observe any significant side effects. It remains unclear as to how repeated ketamine infusions may affect the severity of subsequent episodes of bipolar depression. It is possible that this treatment regimen could decrease the severity of depressive symptoms, as well as improve quality of life and daily functioning.[25] A recent retrospective study on IV ketamine in unipolar and bipolar depression suggests that using ketamine to treat resistant depression has a rapid effect in reducing agitation, irritability, anxiety, and suicidal ideation. Therefore, the authors suggest that this treatment should be considered in depression with mixed features, which is particularly common in bipolar disorders (2.2 in MDD vs 14.3% in BD) and related to high suicidality.[26,27]

Rapid Antisuicidal Effect of Ketamine

Suicidality accounts for 15–20% of deaths in BD patients.[28–30] Risk of suicidal act in BD patients with mixed or psychotic symptoms is one of the highest of all psychiatric disorders.[31] Currently, there are no approved pharmacological interventions for suicidality in BD. Two open-label studies found that a single intravenous ketamine infusion significantly reduced suicidal ideation in subjects with treatment-resistant depression.[32,33]

A systematic review examining the effects of a single dose of ketamine on suicidal ideation concluded that it was able to rapidly reduce suicidal thoughts within 1 day.[18] While the majority of the included studies were conducted among patients with MDD, some of the studies also enrolled patients with BD.[34] Another meta-analysis revealed a significant and sustained decrease of suicidality within 4 h of a single ketamine infusion.[35] Such a rapid antisuicidal effect is in stark contrast to the delayed onset of currently available pharmacological treatment A recent open-label clinical trial that administered six intravenous doses of 0.5 mg/kg ketamine three times a week in patients with unipolar and bipolar depression reported a significant reduction in suicidal ideation 24 h after the first infusion in 57% of patients and in 65% after the sixth infusion.[36]

The antisuicidal mechanism of ketamine remains speculative. Plasma kynurenine levels have been implicated in the pathophysiology of suicidal behavior,[37] and it has been suggested that ketamine may play a role in their modification.[38] On the other hand, a post-mortem study of suicidal patients with BD, MDD, and schizophrenia suggested a possible role for microglia in the pathophysiology of these conditions.[39] This is notable, considering the evidence on the anti-inflammatory effect of ketamine

on microglia.[40] As suggested by studies investigating the antisuicidal effect of clozapine in patients with schizophrenia, suicidality may constitute a separate symptom dimension. It is, therefore, possible that ketamine also has an antisuicidal effect which is independent of its antidepressive effect.[41,42]

Risk of Affective Switch

Due to a lack of data, it is unclear whether ketamine induces an affective switch in treated patients. Current evidence suggests that the risk for affective switch is increased in patients treated with antidepressants, as well as in patients with a history of substance abuse, especially opioid use disorder.[41] Data from three studies, conducted among patients with treatment-resistant unipolar and bipolar depression, reported transient mood elevation in 7% and 10% of subjects administered placebo and subanesthetic doses of ketamine, respectively. As mood levels returned to baseline by the next day, the authors concluded that their results did not reflect a persistent substance-induced syndrome.[43] While the neurobiological basis of affective switch has not been fully elucidated, limited evidence suggests that brain-derived neurotrophic factor (BDNF) may play a major role. One study has reported that individuals with bipolar depression who also have the val/val BDNF genotype may be at a greater risk for either a spontaneous or antidepressant-related switch to mania.[42] Nevertheless, future studies are needed to confirm the risk factors for affective switch.

Ketamine in Bipolar Disorder – Molecular Data

Antidepressant Effect

Although the robust antidepressant effect of ketamine is known, the precise molecular and cellular mechanisms involved are unclear.[44] The blockade of N-methyl-D-aspartate receptors (NMDARs) at inhibitory interneurons causes the disinhibition of pyramidal cells; this leads to the activation of glutamatergic transmission.[44] As non-ketamine NMDAR antagonists do not exhibit such an effect in patients with depression, this suggests that mechanisms other than NMDAR inhibition play a key role in this disease. Maeng et al reported that α-amino -3-hydroxy-5-methyl-4 isoxazole propionic acid receptor (AMPAR) antagonists blocked the antidepressant effects of ketamine in rodents, implicating a role for AMPAR activation in mediating the antidepressant effect of ketamine.[45] In addition to NMDA and AMPA receptors, other pathways that may be involved in the antidepressant effect of ketamine include mechanistic target of rapamycin (mTOR) and BDNF-tyrosine kinase receptor B (TrkB).

Animal models suggest that long-lasting activation of the BDNF-TrkB cascade in the prefrontal cortex (PFC) and hippocampus may be responsible for the long-term antidepressant effects of ketamine.[44] Animal studies have also suggested that ketamine can increase the levels of BDNF, cyclic adenosine 3′, 5′-monophosphate response element binding (CREB), protein kinase C (PKC), and protein kinase A (PKA) in brain areas known to be involved in MDD, such as the PFC, hippocampus, amygdala, and nucleus accumbens.[46] Wei et al[47] suggested that increased CREB Ser133 phosphorylation, as well as expression of CREB and glutamate receptor 1 (GluR1), are crucial for the antidepressant effect of ketamine.

A study in mice showed that the metabolites of ketamine have rapid antidepressant effects, and that they do not act through NMDARs. Specifically, it was found that (2R, 6R)-hydroxynorketamine activated AMPARs and rapidly upregulated BDNF expression.[48] Additional studies are needed to confirm the effect of (2R, 6R) HNK on BDNF, and its potential to act as an antidepressant.

Neuroplasticity and BDNF

Neurotrophins are essential for the sprouting of neurites, differentiation of neurons, and synaptogenesis.[49] One of the neurotrophins involved in the pathophysiology of BD is BDNF.[50] In addition to its role in neuronal maturation, differentiation, and survival, BDNF is also involved in synaptic plasticity.[51] Preclinical evidence suggests that BDNF regulates the release of serotonin, glutamate, and gamma-aminobutyric acid (GABA).[52,53] A BDNF gene polymorphism (66 Val/Met) may be associated with a higher risk for early-onset BD, as well as rapid cycling, suicidality, and treatment response. Apart from its role in neuroplasticity, BDNF is also involved in intracellular signal transduction.[50] Several clinical studies have demonstrated decreased levels of BDNF in bipolar patients during depressive and manic episodes.[51] Other studies have shown that low levels of BDNF are associated with an increased severity of bipolar episodes.[54,55] This suggests the use of ketamine as a viable treatment option for bipolar patients, given that ketamine increases BDNF expression although the exact mechanism of BDNF effect in bipolar disorder needs to be elucidated.

Synaptogenesis

Evidence from preclinical studies has shown that ketamine rapidly induces synaptogenesis and reverses the synaptic changes caused by chronic stress, and that these actions are associated with its antidepressant effect.[56] Ketamine has also been reported to improve spine density in the medial PFC of chronic social defeat stress-susceptible mice 1 week after the administration of a single dose.[56,57] One recent animal study focusing on processes underlying acute and sustained effects of ketamine found that a single injection of ketamine caused in vivo restoration of spines in the PFC lost due to stress. The authors used the new technology of two-photon imaging to observe how chronic stress and ketamine effect dendritic spine modelling in PFC of living mice. Interestingly, behavioral improvement was observed prior to changes in spine formation. The authors suggest that maintaining the restored spines is necessary for maintaining behavioral remission and that dendritic spine formation in the PFC leads to long term, as opposed to acute, antidepressant effects of ketamine.[58] This is supported by in vitro studies which have shown that ketamine treatment is correlated with increased differentiation and maturation of new neurons in the dentate gyrus.[59,60] Furthermore, Yamada and Jinno have reported that ketamine increases the density of neuronal progenitors and newborn granule cells, and accelerates their maturation in the ventral hippocampus.[61] However, some studies have shown contrary evidence and do not support the beneficial effect of ketamine on synaptic plasticity and the proliferation of neurons in rats.[62,63] Taken together, it is likely that neurogenesis could have a role in the sustained actions of ketamine; nevertheless, this remains to be confirmed by future studies.

Epigenetics

Epigenetic changes probably play a role in the various phases of bipolar illness although this subject needs further investigation.[64,65] Evidence suggests differential gene expression in depression, euthymia, and mania. In depression expression of the circadian gene cryptochrome 2 (CRY2) and neural cell adhesion molecule gene (NCAM-140) was decreased compared to control. In euthymic bipolar patients, decreased expression of histone deacetylase (HDAC) genes was found compared to control. The elevation of the mitogen-activated protein kinase 6 gene (MAPK6) was reported in mania compared to patients in euthymia.[66,67] Manic episodes seem to cause oxidative damage to DNA, interfering with future DNA methylation.[68] For example, hypomethylation of the COMT gene has been reported in patients with BD.[69] One study found that ketamine produced an antidepressant effect by decreasing histone deacetylase activity in the nucleus accumbens of deprived rats; this suggested that ketamine may act via an epigenetic mechanism.[70]

Immunological Effects

Patients with BD present with several immunological alterations. Multiple proinflammatory cytokines, especially those responsible for innate immune hyperactivity (eg, Interleukin [IL] -1β, IL-4, IL-10, tumor necrosis factor alpha [TNF- α]) are elevated in bipolar patients.[71] Increased levels of IL-1β and kynurenic acid have been reported in the cerebrospinal fluid of BD patients.[72] In a post-mortem examination of brain tissue in patients with BD, PFC levels of IL-1β, IL-1R, myeloid differentiation factor 88, nuclear factor-kappa B subunits (IL-1 pathway), and astroglial and microglial neuroinflammatory markers were increased.[73] Patients with BD also have a high prevalence (48.1%) of autoimmune diseases.[74]

In general, data pertaining to the immunological effects of ketamine in bipolar patients are limited. Studies have indicated that proinflammatory cytokines (mainly IL-6, G-CSF, and IL-1α) are reduced 4 h after a single dose of intravenous ketamine.[75] One study has shown rapid decreases in levels of IL-6 and TNF-α, as well as a correlation between the decrease in TNF-α and a reduction in the Montgomery Asberg Depression Rating Scale (MADRS) score.[76] Another study found that ketamine influences the kynurenine pathway by increasing the level of kynurenine, kynurenic acid and decreases the level of quinolinic acid acting as a rapid anti-inflammatory agent in patients with bipolar depression.[77] No significant correlation has been found between the levels of inflammatory markers (C-reactive protein and intracellular adhesion molecule-1), before or after ketamine infusion in BD patients.[14]

In terms of the autoimmune effects of ketamine, in vitro studies have shown that it suppresses T-cell differentiation into Th17 cells. Th17 cells play a significant role in the autoimmunization of mice subjected to experimental autoimmune encephalomyelitis.[78] This effect may indicate an immunomodulatory role for ketamine in BD patients, who have a predisposition to autoimmune disease. Further studies are needed to elucidate a potential immunomodulatory effect of ketamine in this patient population.

Microbiota

The brain-gut-microbiota axis has a role in the pathophysiology of depression[79–81] through its involvement in the

immune system, endocrine system, and vagus nerve.[82,83] Moreover, it has been demonstrated that the gut microbiome modulates the level of central BDNF.[84,85] The composition of the gut microbiota is altered in BD patients[86] Negative correlations have been found between *Lactobacillus* counts and sleep, as well as between *Bifidobacterium* counts and serum cortisol levels, which are both altered in patients with depression compared to that of healthy controls.[87] According to Lu et al, the antidepressive effect of quetiapine in bipolar depression can be attributed to its effects on the gut microbiota and immune activation.[86]

Existing evidence also suggests that the antidepressant action of ketamine can be attributed to its effects on the microbiome. For instance, randomized placebo-controlled study examining chronic ketamine administration in rats reported significant increases in the levels of low-abundance bacterial genera (eg, *Lactobacillus, Turicibacter*, and *Sarcina*), and decreases in the numbers of opportunistic pathogens.[81] A study involving RNA sequencing of Chronic Social Defeat Stress (CSDS)-susceptible mice feces reported that (R)-ketamine, altered amounts of Bacteroidales, Clostridiales and Ruminococcaceae (R)-ketamine also reduced the stress-induced increases of Clostridium levels compared to control.[88] Another placebo-controlled study conducted with the use of the same animal model of depression reported that (R)-ketamine administration inhibited the reduction in bacteria levels from Mollicutes class. Furthermore, both (R)- and (S)- ketamine enantiomers diminished the decrease in Butyricimonas bacteria genus.[89] Furthermore, ketamine has been shown to positively affect the abnormal composition of gut microbiota in rodents with a depression-like phenotype.[90] Thus, current evidence indicates that ketamine treatment improves gut microbiota composition, and mediates antidepressant effects through this mechanism.

Lithium and Ketamine

Few mechanisms of ketamine's action are shared with one of the most efficient and widely used pharmacological agents for treating BD – lithium. One of the best known is glycogen synthase kinase-3 (GSK-3) inhibition, the enzyme which is involved in a wide range of signal transduction pathways.[91] GSK-3 has mainly proapoptotic effects, though its inhibition leads to neuroprotection due to the disinhibition of BDNF synthesis, long-term neuroplasticity and mood stabilization.[92] Studies with knocked-in mouse models of GSK-3beta S9A showed a lack of ketamine's antidepressant effect, although it is still unknown if ketamine inhibits GSK-3 directly,[93] The final effect of GSK-3 inhibition, which is increased synthesis of BDNF, is also similar for lithium and ketamine. Ketamine's NMDA antagonism causes activation of mTOR pathway, which increases the BDNF synthesis due to increased eukaryotic elongation factor 2 (eEF2) levels.[94] Lithium can also prolong the activation of mTOR/BDNF-TrkB pathways and maintain restoration of spine density induced by a single injection of ketamine, and as a consequence, increase the antidepressant-like effects of ketamine in mice;[95] this observation is particularly notable, considering the possibility of simultaneous ketamine and lithium use in BD.

Both ketamine and lithium modulate the glutamatergic system in the brain. Chronic administration of lithium causes an increase of glutamate reuptake, thus diminishes the concentration of glutamate in the synaptic cleft, preventing the excitotoxic effect of glutamate.[96] Another common mechanism of action of ketamine and lithium might be immunomodulation. Lithium's immunomodulatory effect in patients suffering from BD has been shown in several studies, both in vitro and ex vivo, and some of them seem to be similar to those found in ketamine studies. A study performed by Leu et al showed that the presence of lithium-reduced production of IL-6, TNF-α and increased secretion of IL-10 by cultivated and activated human monocyte-derived dendritic cells.[97] Lithium treatment increased IL-1β production and decreased IL-6 production by activated monocytes from BD patients, causing normalization of IL1b/IL-6 ratio, similar to healthy control.[98]

Staging and Neuroprogression in BD

BD may present with manic and depressive episodes, often with mixed features; its variable clinical manifestations can be described in stages.[99] These stages include cognitive deterioration and functional decline, changes in inflammatory and neuroanatomical biomarkers, lowered response to treatment, and a worsened self-reported quality of life, all of which have been linked to disorder progression.[100] To date, there has been a lack of staging models based on psychopathology.[101] Kapczinski et al.[102,103] suggested a model that accounted for functioning, cognitive performance, and blood biomarkers. Cosci and Fava subsequently proposed an integrative model emphasizing the lack of evidence for stage 0 (at-risk).[104] Duffy, in turn, suggested a staging model that took into consideration the natural history of BD and the heterogeneity of the different subtypes.[105]

Neuroprogression is a concept that describes the pathological processes in the brain as a consequence of the

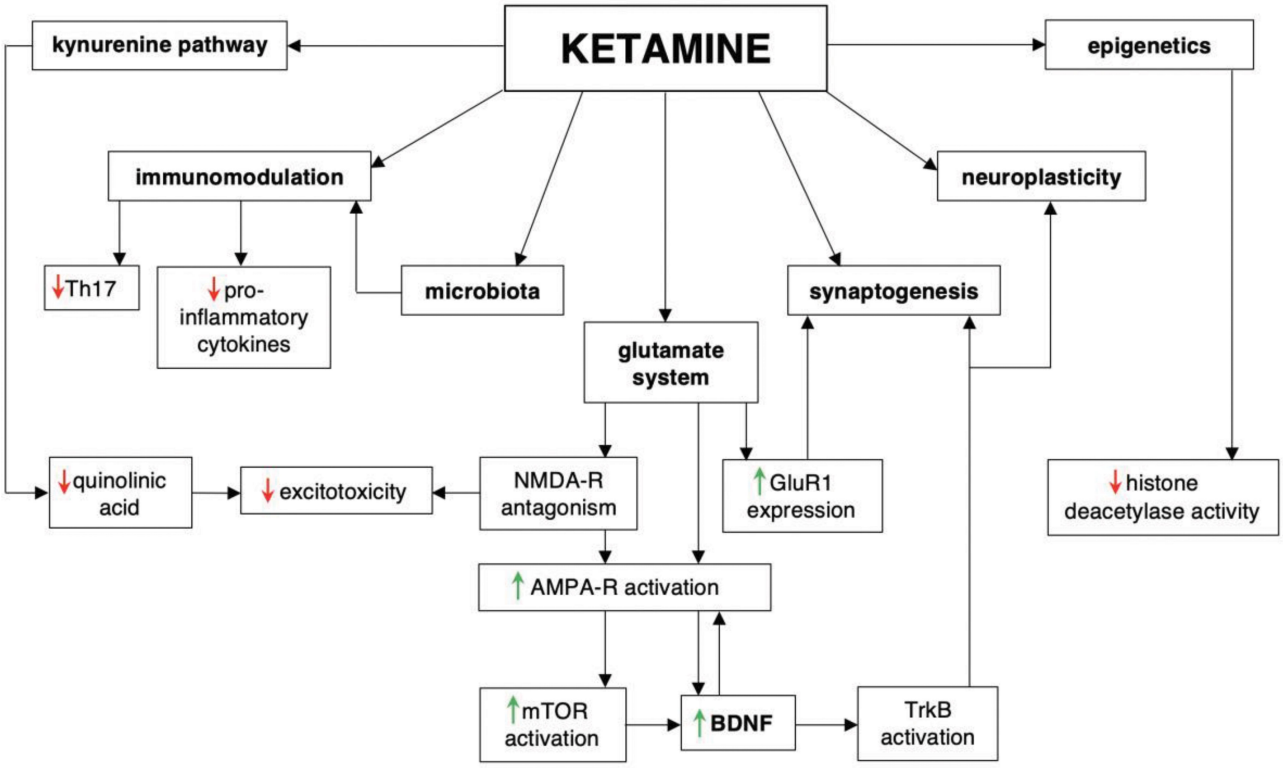

Figure 1 Ketamine's possible mechanisms of action in bipolar disorder. Proposed model summarizes multipotential properties of ketamine, including modulation of immune system, microbiota, epigenetics, kynurenine pathway and glutamate system as well as synaptogenesis and neuroplasticity.
Abbreviations: AMPA-R, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; BDNF, brain-derived neurotrophic factor; GluR1, glutamate receptor 1; mTOR, mammalian target of rapamycin; NMDA-R, N-methyl-D-aspartate receptor; Th17, T helper cells producing IL-17; TrkB, tyrosine receptor kinase B.

toxicity-associated mood episodes.[106] A large body of evidence supports the presence of structural brain abnormalities and reduced connectivity in bipolar patients.[107,108] The process underlying neuroprogressive changes in BD patients is still poorly understood. Fries et al suggested that the epigenetic modifications in individuals with BD appear earlier in life compared to healthy individuals.[109] Other correlates of aging and neuroprogression in mood disorders include reduced BDNF levels and oxidative stress imbalances.[103,110–113] A recent imaging study found that bipolar patients with extensive blood-brain barrier (BBB) leakage had more severe and chronic symptoms. Furthermore, the authors also found insulin resistance in this group of patients and suggest that it may increase BBB dysfunction in BD.[114] The role of insulin resistance in neuroprogression in BD has been previously described.[115] Moreover, dysregulated glucose metabolism (insulin resistance or type 2 diabetes mellitus) is present in more than half of patients with BD and appears more often in patients with poor treatment response, cognitive impairment, and poor functioning. Hence, the proposed mechanisms connecting insulin resistance and neuroprogression are oxidative stress, lipid peroxidation, and endothelial dysfunction.[115] The chronic and refractory nature of bipolar illness along with aging has a synergistic impact on the decline of neurotrophic signaling and an increase in inflammation.[113,116,117] Indeed, an imbalance between inflammatory cytokines (especially TNF-α), mediators of oxidative stress, and BDNF is associated with the progression of structural brain changes and neurocognitive decline.[117,118] Although this possibility requires further studies, ketamine could hypothetically influence the progression of BD by increasing BDNF levels through an epigenetic mechanism effecting histone acetylation and the induction of neuroplasticity. Furthermore, as mentioned previously, ketamine has demonstrated to have a better antidepressive effect in patients with high BMI and low adipokine levels,[19,20] suggesting that ketamine may interfere with the metabolic mechanisms of neuroprogression. Moreover, one aspect of neuroprogression is cognitive dysfunction; currently, some evidence show that single and multiple ketamine infusions in subanaesthetic dose improve cognitive functions in patients with unipolar and bipolar depression.[119,120] Possible mechanisms of ketamine's action in bipolar disorder are presented in Figure 1.

Discussion

We hypothesize that the use of ketamine as an adjunctive treatment can have beneficial short-term and long-term effects on the course of BD. Previous studies, although still scarce have demonstrated the short-term antidepressant and antisuicidal effects of ketamine in patients with BD, and its administration also appears to carry a low risk of affective switch.[7–36]

Studies on the molecular mechanism of action of ketamine indicate that it has effects on glutamatergic transmission, BDNF levels, and intracellular signal transduction, which are all perturbed in patients with BD. There is mounting evidence for the beneficial effect of ketamine on synaptogenesis and neuroplasticity; such long-term effects are particularly interesting, considering the neuroprogressive nature of BD.[38–55,121] There is some evidence for the modifying effects of ketamine on epigenetic processes present in BD,[64–70] as well as its ability to regulate inflammation.[62–69] Ketamine may also have favorable effects on gut microbiota, which have been shown to be disturbed in patients with BD.[71–78] The majority of the above-mentioned effects, however, are based on preliminary evidence and engage unipolar depression model, and therefore require confirmation by studies in bipolar disorder.

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