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# Ketamine Treatment for Depression in Patients With a History of Psychosis or Current Psychotic Symptoms: A Systematic Review

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## ABSTRACT

***Objective:*** Ketamine shows rapid and robust antidepressant effects in clinical studies. Psychotic features are an exclusion criterion in most ketamine treatment studies based on the assumption that psychosis will increase with ketamine administration. As patients with treatment-resistant depression (TRD) often have psychotic features, and treatment-resistant depressive symptoms are also common in patients with schizophrenia, the aim of this systematic review is to determine whether this assumption holds true.

***Data Sources:*** The literature was searched for data on ketamine treatment for depression or negative symptomatology in patients with a history of psychosis or current psychotic symptoms (PubMed/MEDLINE) from inception to March 2020 without date or language restrictions. The following terms were used: *ketamine* and *psychosis, psychotic* or *schizo**. A filter for human studies was applied.

***Study Selection:*** A total of 482 articles were identified; 473 articles were excluded because they did not report on the effect of ketamine treatment in patients with a history of psychosis or current psychotic symptoms.

***Data Extraction:*** The remaining 9 articles were reviewed.

***Results:*** Nine reports of pilot studies and case reports with a total of 41 patients have been published. These studies suggest that short-term ketamine treatment for depression and even negative symptoms in patients with a history of psychosis or current psychotic features can be both safe and effective, as side effects were mild and self-limiting.

***Conclusions:*** The currently available literature does not support the assumption that ketamine will exacerbate psychotic symptoms in predisposed patients. Data, however, are limited, and further trials are needed in this patient group.


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The *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine was initially synthesized in 1962 as a short-acting dissociative anesthetic with the ability to maintain cardiorespiratory stability. It has since then become one of the most versatile agents in the field of medicine, with a wide variety of applications, including as an analgesic for pain management in acute and chronic settings.[1] A study in 1973[2] described symptom relief and facilitation of psychotherapy in 100 psychiatric inpatients after intravenous (IV) ketamine administration. In 2000, rapid antidepressant effects of ketamine in patients with depression were reported.[3] Since then, robust antidepressant and antisuicidal effects of ketamine have been described in unipolar and bipolar depression.[4,5] Given the high disease burden of depression, and the fact that around 30% of patients are treatment resistant,[6] these findings provide hope in a field where the development of more effective treatments is urgently needed.

Side effects of ketamine include transient psychotomimetic phenomena such as perceptual disorders, hallucinations, feeling strange or unreal, abnormal sensations, and dissociation.[7] These effects are dose-related[8,9] and associated with higher peak blood levels of ketamine.[10] In a review[7] on the side effects of ketamine for depression, psychotomimetic effects were reported in 72% of IV studies and in 36% of non-IV (eg, intramuscular, subcutaneous, oral) studies investigating ketamine for depression. These effects, hypothesized to stem from an increase in glutamate concentration within the synaptic cleft following NMDA receptor blockage,[11,12] have made ketamine an interesting model for studying schizophrenia and related psychotic disorders in humans as well as in preclinical studies.[13–15]

The potential schizophrenia-like effects of ketamine have led to exclusion of patients with depression with current or past psychotic symptoms in the majority of studies investigating the antidepressant potential of ketamine. This exclusion has important clinical implications, as psychotic symptoms are common in depressed patients (psychotic symptoms were present in a median proportion of 19% in studies including both in- and outpatients or only outpatients and 42% in studies including only inpatients).[16] Psychotic symptoms occur especially in more severe depression, which is associated with poorer treatment outcome and higher relapse rates.[16,17] The concerns regarding the psychotomimetic

**Clinical Points**

- Due to fear of psychotic exacerbation, patients with vulnerability to psychosis are often excluded from studies investigating ketamine treatment for depression.
- Although data are limited, the currently available literature suggests that short-term ketamine treatment can be safe and effective in patients with a history of psychosis or current psychotic symptoms.

side effects of ketamine have also led to the exclusion of patients with schizophrenia or related psychotic disorders who experience treatment-resistant depressive symptoms. Depression is also associated with poor functional recovery, poor quality of life, and suicidality in these patients.[18,19] In addition, up to 60% of patients with schizophrenia suffer from negative symptomatology that has a clear phenomenological overlap with depression.[20] Common features include loss of motivation, affective blunting, anhedonia, and attentional deficits.[21] Neither patients with depression nor those with negative symptoms in schizophrenia respond well to treatment with currently available antidepressants and antipsychotics.[22,23] Anti-anhedonic effects of subanesthetic ketamine doses have been reported[24] without negatively affecting long-term psychotic symptomatology in patients with schizophrenia.[25,26]

Thus, questions arise as to whether future research on ketamine treatment for depression should carefully broaden the inclusion criteria to also investigate its actual effects in patients with a vulnerability to psychosis. In this review, we summarize the literature on the effects of ketamine for depression in patients with a history of psychosis or current psychotic symptoms. Studies investigating ketamine as a treatment for negative symptoms in patients with schizophrenia are also taken into account.

## METHODS

We searched the PubMed/MEDLINE database from inception to March 2020, without limits on year of publication or language. The search was conducted with the terms *ketamine* and *psychosis*, *psychotic* or *schizo**. A filter for humans was applied. Articles were included if they reported on the effect of ketamine as a treatment for depression or negative symptomatology in patients with a history of psychosis or current psychotic symptoms.

## RESULTS

Abstracts for a total of 482 articles were identified. Of these articles, 9 reported on ketamine treatment in patients with a history of psychosis or current psychotic symptoms and were included (Table 1). Five articles reported on the findings in patients with unipolar or bipolar depression or depression in schizoaffective disorder. The other 4 studies investigated patients with schizophrenia; in 3 of these studies, the patients suffered from concurrent depression. All studies were case reports or pilot studies. The total number of participants was 41. Treatment target of ketamine administration was to relieve depressive symptoms in all studies but one.[35] This latter trial studied the effects of ketamine administration on negative symptoms in 6 patients with schizophrenia.

Pennybaker et al[27] performed a post hoc analysis to investigate whether a lifetime history of psychosis had influenced how patients responded to ketamine in depression trials. They combined the data from 3 randomized, placebo-controlled crossover trials in patients with a current depressive episode receiving 0.5 mg/kg ketamine infusion over 40 minutes. Two of these studies included patients with bipolar disorder receiving lithium or valproate treatment, and the third trial included unmedicated patients. All patients were free of any other psychotropic medication, including antipsychotics. Of all 69 patients for whom information on history of psychosis was available, 2 patients had been diagnosed with a major depressive disorder with psychotic features and 10 patients with bipolar disorder with psychotic features in the past. Patients with a history of psychosis showed an improvement in depressive symptoms on the Montgomery-Asberg Depression Rating Scale (MADRS) from baseline up to 3 days after ketamine infusion ($P < .01$). When compared to placebo, the antidepressant effects of ketamine were significant in both groups but appeared to be less robust in the patients with a positive history of psychosis than in patients without a history of psychosis (Cohen $d = 0.35$ vs 1.17, $P < .001$ in both groups). Scores on the Clinician-Administered Dissociative States Scale (CADSS) were significantly higher in patients with a history of psychosis (Cohen $d = 0.23$, $P < .01$), but only 40 minutes post-infusion and not at later time points. Scores on the Brief Psychiatric Rating Scale–Positive Symptoms subscale (BPRS-P) did not significantly differ between the two groups ($P = .47$). In conclusion, this analysis suggests that a single infusion of ketamine in patients with a history of psychosis has antidepressant effects without causing psychotic symptoms.

The first use of ketamine as an antidepressant for patients with current psychotic features was described in 2 cases by Medeiros da Frota Ribeiro et al.[28,29] One patient, a 52-year-old woman with a long history of unipolar depression with psychotic features (auditory hallucinations and paranoid delusions) and treatment resistance for numerous antidepressant drugs, was treated with 0.5 mg/kg IV ketamine infusion over 40 minutes. There was a dramatic mood improvement, with Hamilton Depression Rating Scale (HDRS) score decreasing from 19 to 9, and the auditory hallucinations and paranoia ceased within hours. After 3 infusions, the patient was transitioned from concurrent venlafaxine to a monoamine oxidase inhibitor for relapse prevention. Over the course of a year, she received 12 monthly maintenance infusions of 0.5 mg/kg ketamine with good results.

The second patient, a 55-year-old woman with schizoaffective disorder, presented with depression, severe suicidal ideation, and catatonia. She previously showed a

**Table 1. Included Articles on Ketamine Treatment in Patients With a History of Psychosis or Current Psychotic Symptoms**

| Study | Sample, N | Diagnosis | Intervention | Outcome | Side Effects |
|---|---|---|---|---|---|
| Pennybaker et al 2017[27] | 12 | Unipolar (n = 2) or bipolar (n = 10) depression with psychotic features in the past | A single dose of 0.5 mg/kg IV ketamine | Improvement in depressive symptoms on the MADRS from baseline up to 3 days after ketamine infusion ($P < .01$). When compared to placebo, antidepressant effects of ketamine were significant in both groups but appeared to be less robust in patients with a positive history of psychosis than in patients without a history of psychosis (Cohen $d = 0.35$ vs 1.17) | The CADSS scores were significantly higher in patients with a history of psychosis (Cohen $d = 0.23$, $P < .01$), but only at 40 minutes postinfusion and not at later time points. The BPRS-P scores did not significantly differ between the two groups ($P = .47$) |
| Medeiros da Frota Ribeira et al 2016[28] and 2017[29] | 2 | Unipolar depression with psychotic features (n = 1) or schizoaffective disorder with current depression (n = 1) | 0.5 mg/kg IV ketamine, monthly infusions for a year | Mood improvement with HDRS scores changing from 19 to 9 and from 29 to 8. Auditory hallucinations and paranoia ceased within hours, and both patients became free of psychotic symptoms. Good results over the course of a year | Mild dissociative symptoms, fatigue, and a mild headache (n = 1) |
| Ajub and Lacerda 2018[30] | 4 | MDD with psychotic features (n = 2), bipolar depression with psychotic features (n = 1), or schizoaffective disorder, depressive type (n = 1) and psychiatric comorbidity | 0.5 mg/kg esketamine, IV (n = 1) or SC (n = 3). One infusion (n = 3) and 3 weekly infusions (n = 1) | Three patients showed marked improvement or complete remission of both depressive and psychotic symptoms 24 hours after administration and also at a 2- and 4-week follow-up evaluation. One patient showed no changes in depressive or psychotic symptoms after 24 hours nor after 3 weekly administrations | Side effects were mild (n = 2) or intense (n = 1) dissociative symptoms, nausea (n = 2), vomiting (n = 1), and light-headedness (n = 1), all of which remitted 2 hours after administration. No worsening of psychotic symptoms occurred |
| Zarrinnegar et al 2019[31] | 1 | Treatment-resistant adolescent depression with psychotic features | 0.5 mg/kg IV ketamine, 6 infusions over the course of 3 weeks, starting with 3 infusions a week and gradually tapering down to once a week | Gradual decrease in depressive symptoms on the MADRS and CDRS and in suicidality on the SSI. The patient subjectively denied improvement until 2 weeks after the final infusion. After more than 1 year of inpatient psychiatric hospitalization, the patient was successfully discharged 1 month after completion of ketamine infusions with the absence of depressive, psychotic, or suicidal symptoms. The patient continued to do well during follow-up of several months | Symptoms of derealization and nausea, managed with administration of low-dose chlorpromazine preinfusion |
| Bartova et al 2018[32] | 1 | Schizophrenia and TRD | 0.22 mg/kg IV esketamine, increased to 0.33 mg/kg thrice weekly for 3 weeks | A robust antisuicidal and antidepressant response that lasted for several days. A sustained remission was achieved | No relevant psychotic symptoms; discrete, well-tolerated, and self-limiting dissociative phenomena were induced by the esketamine administration |
| Ye et al 2019[33] | 15 | Schizophrenia and TRD | Twice weekly 0.5 mg/kg IV ketamine for 4 weeks | A significant reduction both in CDSS scores (64% decrease) and in general psychopathological symptom scores on the PANSS (30% decrease) from day 7 to day 14 after the first treatment. Despite maintenance treatment, the CDSS scores gradually increased to the point that they were statistically similar to the scores at baseline by day 28 | The positive scores on the PANSS did not significantly change from pre- to post-ketamine time points (0.06% decrease). Visual hallucinations within the first half hour after the first infusion (n = 1). No side effects that required medical intervention |
| Zhuo et al 2020[34] | 15[a] | Schizophrenia and TRD | The same treatment strategy was subsequently repeated 58 days after the pilot study by Ye et al[33] | No significant differences were observed between CDSS scores at baseline and at assessments on days 65, 72, and 79 | No significant differences between PANSS scores at baseline and at assessments on days 65, 72, and 79. No side effects requiring medical intervention were induced |
| Nunes et al 2018[35] | 6 | Schizophrenia | 0.5 mg/kg (first week), 0.75 mg/kg (second week), and 1 mg/kg (third and fourth weeks) SC esketamine weekly for 4 weeks | Significant improvement of negative symptomatology in 5 patients. The mean BNSS score decreased from 59.5 to 37.3 (−37.3%) | Side effects were reported in 2 patients, with transient sedation during infusions in 1 patient and nausea and vomiting during the second infusion in 1 patient |

[a]The study by Zhuo et al[34] used the same sample and treatment strategy as described in the study by Ye et al.[33]

Abbreviations: BNSS = Brief Negative Symptom Scale, BPRS = Brief Psychiatric Rating Scale, BPRS-*P* = Brief Psychiatric Rating Scale–Positive Symptoms subscale, CADSS = Clinician-Administered Dissociative States Scale, CDRS = Children's Depression Rating Scale, CDSS = Calgary Depression Scale for Schizophrenia, HDRS = Hamilton Depression Rating Scale, IV = intravenous, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder, PANSS = Positive and Negative Syndrome Scale, SC = subcutaneous, SSI = Scale for Suicidal Ideation, TRD = treatment-resistant depression.

robust antidepressant effect to electroconvulsive therapy with ketamine as the anesthetic agent, even though no seizure was induced.[36] Also in this patient, a dramatic mood improvement was observed after 0.5 mg/kg ketamine infusion, with HDRS score decreasing from 29 to 8. Furthermore, her psychotic symptoms disappeared after the ketamine infusion. The patient remained stable with monthly infusions over the course of a year.

Following the report on these 2 patients, Ajub and Lacerda[30] described the efficacy of esketamine in 4 patients with severe depression with psychotic features. Two patients had major depressive disorder with psychotic symptoms, 1 patient had bipolar depressive disorder with mixed features, and 1 patient had schizoaffective disorder, depressive type. Comorbid psychiatric disorders were social anxiety disorder (n = 1) and current alcohol abuse (n = 1) or dependence (n = 1). Esketamine 0.5 mg/kg was administered intravenously (n = 1) or subcutaneously (n = 3). Three patients showed marked improvement or complete remission of both depressive and psychotic symptoms 24 hours after administration and also at 2 and 4 weeks' follow-up evaluation. One patient showed no changes in depressive or psychotic symptoms after 24 hours or after 3 weekly esketamine administrations. Side effects that were reported were mild (n = 2) or intense (n = 1) dissociative symptoms, nausea (n = 2), vomiting (n = 1), and light-headedness (n = 1), all of which remitted 2 hours after administration. No worsening of psychotic symptoms occurred after esketamine administration in these 4 patients.

Zarrinnegar et al[31] present the case of a 15-year-old adolescent male with severe TRD with psychotic symptoms, suicidal ideation, generalized anxiety disorder, and posttraumatic stress disorder. He was hospitalized for more than 1 year and displayed a worsening of symptoms with psychotic features (auditory, visual, and tactile hallucinations and impairment in reality testing), regression, suicidality, muteness, and self-harm. He failed multiple adequate trials of antidepressants, anxiolytics, and antipsychotics. He was administered 6 ketamine infusions of 0.5 mg/kg during the course of 3 weeks. The clinicians observed a gradual decrease in depressive symptoms as measured by the MADRS and Children's Depression Rating Scale (CDRS) and in suicidality on the Scale for Suicidal Ideation (SSI). The patient subjectively denied improvement until 2 weeks after the final infusion. One month after the completion of ketamine infusions, depressive, psychotic, and suicidal symptoms were absent. The patient was successfully discharged into community care and continued to do well during follow-up of several months. Ketamine side effects consisted of derealization and nausea and were managed with the administration of a low dose of chlorpromazine.

A case report by Bartova et al[32] described treatment with IV esketamine (0.22 mg/kg) in a 30-year-old woman with severe and chronic schizophrenia. The patient showed full remission of positive symptoms with standard psychopharmacotherapy, but her depressive symptoms remained. Esketamine augmentation resulted in a robust antisuicidal and antidepressant response that lasted for several days. A sustained remission was achieved after increasing the dose to 0.33 mg/kg and infusion thrice weekly for 3 weeks. Discrete, well-tolerated, and self-limiting dissociative phenomena were induced by the esketamine administration, and psychotic symptoms did not occur.

A pilot study[33] investigated the effects of adjunct ketamine treatment on treatment-resistant depressive symptoms in 15 patients with treatment-resistant schizophrenia. Intravenous ketamine 0.5 mg/kg was administered every 3 days for 3.5 weeks. This resulted in a significant reduction in mean [SD] scores on the Calgary Depression Scale for Schizophrenia (CDSS) of 64% (baseline score = 16.50 [3.94], ) and a reduction in scores on the general psychopathological symptom subscale of the Positive and Negative Syndrome Scale (PANSS) of 30% (baseline score = 29.90 [5.41]) from day 7 to day 14 after the first treatment. Despite maintenance of the ketamine treatment strategy, the CDSS scores gradually increased, by day 28, to values that were statistically similar to the scores at baseline. The positive scores on the PANSS did not significantly change from pre- to post-ketamine time points (baseline score = 25.60 [9.23]; 0.06% decrease). One patient reported visual hallucinations within the first half hour after the first ketamine infusion.

The same treatment strategy was then repeated after 58 days in the same 15 patients.[34] No significant differences were observed between CDSS or PANSS scores at baseline and at assessments on days 65, 72, and 79. No psychotic symptoms or side effects requiring medical intervention were induced during the first and second treatment phases.

Nunes et al[35] studied the effects of esketamine on persistent negative symptoms in 6 patients with schizophrenia. The patients received subcutaneous esketamine weekly for 4 weeks in doses increasing from 0.5 mg/kg (first week) to 0.75 mg/kg (second week) and 1 mg/kg (third and fourth weeks). Five of 6 patients showed significant improvement of negative symptomatology at the end of the series of 4 esketamine infusions. The mean Brief Negative Symptom Scale (BNSS) score decreased from 59.5 to 37.3 (−37.3%). Psychotic symptoms did not increase in any patient, and the mean Brief Psychiatric Rating Scale (BPRS) score decreased from 21.2 to 17.3 (−18.1%). Side effects were reported in 2 patients, with transient sedation during infusions in 1 patient and nausea and vomiting during the second infusion in 1 patient.

## DISCUSSION

The aim of this review was to determine whether treatment with ketamine or esketamine in patients with a history of psychosis or current psychotic symptoms would lead to an increase of psychotic symptoms, in line with the current exclusion of such patients from most clinical trials. Our findings suggest that the outcome may be different from what is expected, as no psychotic exacerbation occurred in the patients from the included studies on this issue. In several cases, comorbid psychotic symptoms even improved or disappeared entirely after ketamine or esketamine

administration for depression. The article by Pennybaker et al[27] reporting on ketamine in depressed patients with and without a history of psychosis suggests that dissociative phenomena might occur more often in predisposed patients. This effect, however, rapidly dissipates, and, overall, ketamine seemed to be well tolerated. Moreover, the intensity of psychotomimetic effects may diminish with repeated ketamine dosing.[37] These results suggest that clinicians should not simply assume that treatment with subanesthetic doses of ketamine or esketamine will exacerbate psychotic symptoms in vulnerable or predisposed patients.

Good initial antidepressant effects were observed in most trials and in some patients were even maintained over the course of a year. Pennybaker et al,[27] however, found a lower effect size in patients with a history of psychosis when compared to patients without a history of psychosis (0.35 vs 1.17). This small effect size indicates that future randomized controlled trials including patients with a past history of psychosis would have to enroll larger numbers of patients to evaluate the antidepressant effects of ketamine. In the largest pilot study in patients with treatment-resistant schizophrenia and TRD,[33] the initial antidepressant effect was unsatisfactory during follow-up. The authors postulated that long-term tolerance might have occurred, which would be reason for great caution regarding ketamine administration in patients with TRD and treatment-resistant schizophrenia. The only case series investigating esketamine for the treatment of negative symptoms in schizophrenia without a diagnosis of depression[35] suggests promising effects by showing an improvement of negative symptomatology.

It should be noted that most patients described in the included studies received ketamine or esketamine augmentation to standard psychopharmacotherapy, including antipsychotic medication. Pharmacodynamic interactions between ketamine and antipsychotics have been demonstrated in humans for haloperidol,[38] risperidone,[39] and clozapine,[40] which complicates the interpretation of the results.

This review has several limitations. The number of identified studies and the sample sizes of those studies are small, and all trials were uncontrolled. There is also a risk of publication bias because negative results of observational trials are unlikely to be published. Nevertheless, this review shows that subanesthetic doses of ketamine or esketamine may have the potential to improve depressive symptoms in patients with MDD and psychotic features, schizoaffective disorder, and schizophrenia. Although these effects were not always lasting, treatment was well tolerated, and ketamine or esketamine use did not negatively influence the course of psychotic illness, as observed in the (short-term) follow-up periods after ketamine administration.

These observations may serve as an important first step toward broadening the indication for ketamine treatment studies. Further randomized controlled trials are needed to assess the efficacy and tolerability of repeated ketamine and esketamine treatment in depressed patients with vulnerability to psychosis.

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