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Ketamine and Psychosis History: Antidepressant Efficacy and Psychotomimetic Effects Postinfusion

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To the Editor

da Frota Ribeiro *et al.* (2016) reported successful treatment of two cases of psychotic depression with intravenous ketamine. Ketamine administration lessened both depressive and psychotic symptoms within hours (1). While ketamine has been shown to have rapid and robust antidepressant effects in numerous trials (2), it has also been associated with increased psychotic symptoms in healthy controls and in those with schizophrenia during and shortly after infusion (3,4). Because of a theoretical risk of exacerbating psychosis in predisposed patients, subjects with current psychotic symptoms or a past history of psychosis are typically excluded from ketamine trials. However, the findings of da Frota Ribeiro *et al.* draw attention to the lack of data regarding ketamine's efficacy in subjects with current or past psychosis.

This analysis primarily sought to investigate whether having a lifetime history of psychosis influenced how patients responded to ketamine. Our secondary goal was to determine whether a lifetime history of psychosis predicted increased psychotic or dissociative symptoms during infusion and postinfusion.

Our group has conducted three randomized, placebo-controlled, crossover ketamine trials in which patients with a lifetime history of psychosis were not excluded. The results of two of these studies—conducted on patients with bipolar disorder receiving concurrent lithium or valproate treatment—have been published (5,6); results of the third trial—which comprises mostly currently unmedicated patients with major depressive disorder—have not yet been published in full (National Clinical Trial No. 00088699, National Institutes of Health Protocol No. 04-M-0222, substudies 2 and 4). All subjects were free of other psychotropic medications, including antipsychotics, for 2 weeks prior to ketamine infusion. All subjects

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A patent application for the use of ketamine in depression has been submitted listing the corresponding author (CAZ) among the inventors. He has assigned his rights on the patent to the U.S. government but will share a percentage of any royalties that may be received by the government. All other authors report no biomedical financial interests or potential conflicts of interest.

were experiencing a current depressive episode and received a single 0.5 mg/kg ketamine infusion over 40 minutes, the same dose given by da Frola Ribeiro *et al.* (1). Depressive symptoms were assessed using the Montgomery–Åsberg Depression Rating Scale (MADRS). Psychotic symptoms were measured using the Brief Psychiatric Rating Scale–Positive Symptoms subscale (BPRS-P), which assesses conceptual disorganization, mannerisms and posturing, grandiosity, hostility, suspiciousness, hallucinatory behavior, unusual thought content, and excitement. Dissociative symptoms were measured using the Clinician-Administered Dissociative States Scale (CADSS). MADRS, BPRS-P, and CADSS scores were assessed at –60 (baseline), 40, 80, 120, and 230 minutes postinfusion as well as at 1, 2, 3, 10, and 14 days postinfusion.

In the combined data from the three studies, there were 69 subjects for whom information about history of psychosis was available. Of these, 12 subjects had a previous history of psychosis. They were diagnosed with either major depressive disorder with psychotic features ($n = 2$) or bipolar disorder with psychotic features ($n = 10$). Those with and without a previous history of psychosis did not differ significantly on previously reported predictors of response identified by our group, including baseline MADRS score, baseline BPRS-P, body mass index, family history of alcohol use disorder in a first-degree relative, and history of prior suicide attempts.

To determine whether those with a history of psychosis benefited from ketamine, we used a linear mixed model with restricted maximum likelihood estimation and a compound symmetry covariance structure where group, time, and drug were factors. Ketamine improved depressive symptoms (MADRS) from baseline in patients with a history of psychosis for up to 3 days postinfusion ($p < .01$). Next, we ran the same linear mixed model with baseline MADRS as a covariate to investigate whether ketamine had greater antidepressant effects than placebo and whether history of psychosis affected antidepressant effects. The drug by history interaction was significant ($F_{1,992} = 4.34$, $p = .04$). Compared with placebo, ketamine had significant effects in both groups ($ps < .001$), but the effect size (Cohen's d) appeared to be smaller for the group with a history of psychosis (0.35 vs. 1.17).

Our secondary aim was to investigate whether history of psychosis influenced dissociative (CADSS) or psychotic (BPRS-P) symptoms. Because prior research indicates that ketamine has only acute effects on these symptoms, planned comparisons were examined at 40 minutes postinfusion. CADSS score was significantly higher in subjects with a history of psychosis (Cohen's $d = 0.23$, $p < .01$), but BPRS-P score did not significantly differ between the patient groups ($p = .47$). This difference in CADSS score was not seen at any other time point. Because most patients in the sample with a history of psychosis had bipolar disorder, all analyses were repeated with only patients with bipolar disorder; no changes in outcome were found.

Consistent with results from the case series by da Frola Ribeiro *et al.* (1) that noted dramatic improvements in depressive symptoms, we found a significant improvement in depressive symptoms compared with placebo in patients with a history of psychosis who received ketamine; the effects appeared to be less robust than in those without a history of psychosis. In addition, patients with a history of psychosis had more dissociative but not psychotic

symptoms at 40 minutes postinfusion than those without a history of psychosis. However, while ketamine increased dissociative symptoms in those with a history of psychosis, this effect was not maintained past the 40-minute time point. Thus, we support the conclusion that clinicians should not assume that a single infusion of ketamine will exacerbate psychotic symptoms in predisposed patients.

Major limitations in our analysis include its post hoc design and small sample size. The fact that current psychosis was excluded in our sample also decreases its generalizability to patients with a significant degree of current psychotic symptomatology. Finally, concurrent treatment with a mood stabilizer in our participants with bipolar disorder may have confounded these results. Nonetheless, our findings support the idea that history of psychosis should not be used to exclude subjects from receiving ketamine in a clinical setting, although such patients may be at risk for experiencing greater short-term dissociative symptoms. Future studies should investigate how ketamine treatment affects depressed patients with current psychotic features given that these patients may benefit from a trial of ketamine.

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