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Subanesthetic Dose Ketamine Does Not Induce an Affective Switch in Three Independent Samples of Treatment-Resistant Major Depression

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To the Editor

In the August 15, 2011, issue of *Biological Psychiatry*, Ricke and colleagues (1) presented a 42-year-old female patient with a history of reflex sympathetic dystrophy, depression, and insomnia admitted for the treatment of intractable pain. Her outpatient medications (duloxetine, mirtazapine, quetiapine, and high-dose opioids) were held at admission, and she received intravenous ketamine (.1–.2 mg/kg for 5 days) for analgesia. During this time, she developed symptoms consistent with mania (euphoric mood, decreased need for sleep, grandiose ideas, and loose associations) that the authors attributed to ketamine. However, there are at least four other diagnostic possibilities that have not been conclusively ruled out. First, the authors stated that the patient "appeared over-sedated and admitted to self-administering opioids from a supply she kept in her purse, but when asked to, she was reluctant to turn these over to her physicians." In the context of potential opioid intoxication, delirium must be ruled out (her level of attention and cognition during the hospitalization were not reported). Second, if the patient was self-administering opioids and reluctant to relinquish them to her inpatient providers, she may also have been using other illicit substances with analgesic properties that explain her manic-like syndrome (e.g., cocaine use). Unfortunately, there was no report of urine toxicology. Third, excessive opioid administration can cause a substance-induced mood disorder analogous a to mania in some patients. Finally, Ms. M.'s manic-like presentation occurred in the context of multiple medication adjustments (including *increasing* duloxetine on Day 8 in the midst of purported mania). Thus, antidepressant-induced mania is another important diagnostic consideration.

Subanesthetic-dose ketamine has rapid and robust antidepressant effects in several open-label and randomized controlled trials, including three placebo-controlled studies from our group (2–4). Because ketamine causes transient psychotomimetic symptoms, there is a theoretical risk that it might induce mania. To this end, we analyzed data from our three completed studies for treatment-emergent manic-like symptoms via the Young Mania Rating Scale (YMRS). The more conservative definition from the International Society for Bipolar Disorders Task Force (5) defined a treatment-emergent affective switch as "likely" with at least two manic symptoms lasting more than 50% of the day for 2 days and a YMRS

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>12. The less stringent criteria of Keck *et al.* (6) is a YMRS less than 15 at baseline but 15 or greater during treatment. We opted for the more conservative assessment of a YMRS less than 12 at baseline and 12 or greater at any point during protocol, which is also consistent with the mild (type I) threshold of Young *et al.* (7). In our randomized, controlled, crossover studies in major depressive disorder (2) and bipolar depression (4,8), 3 of 44 (7%) subjects who received placebo and 5 of 52 (10%) subjects who received ketamine had maniclike worsening (7). There were 11 subjects who did not have a placebo phase and 3 who did not have a ketamine phase.

In the unipolar sample, 4 of 22 randomized patients scored greater than 12 on the YMRS. One patient scored greater than 12 on ketamine and placebo (14 on Day 2 postinfusion on placebo) but nil on the “elevated mood” item (which, with irritable mood, is mandatory for a diagnosis of hypomania or mania). All four patients randomized to ketamine with a YMRS greater than 12 peaked at the end of the 40-minute infusion and returned to baseline by the following day. Three also scored >2 on the YMRS “elevated mood” item. This transient mood elevation is inconsistent with a persistent substance-induced syndrome.

In the bipolar sample, 3 of 33 randomized patients had a YMRS greater than 12 in the 4-week crossover protocol. Two bipolar I patients (one on valproic acid and the other on lithium) had manic-like symptoms after placebo infusion. The first patient scored 13 at Day 7 and 21 at Day 21, leading to eventual protocol discontinuation. The second subject had an isolated score of 14 on Day 3 that returned to baseline. There was only one bipolar II subject with YMRS elevation after receiving ketamine. This lithium-treated subject had an isolated score of 15 at the end of the 40-minute infusion that decreased to three only 40 minutes later. These results again support acute, transitory effects as opposed to a persistent substance-induced syndrome.

In the ketamine-riluzole protocol (9), 3 of 43 patients had YMRS greater than 12 at any point during the 4-week follow-up period. Two of these patients had manic-like symptoms after receiving intravenous ketamine followed by oral placebo. The first had a YMRS of 14 at Day 1 that decreased to 6 the following day. The second scored a 13 on Day 18; this subject also returned to baseline the following day. Interestingly, both patients scored a zero on the elevated mood item during the entire protocol. The sole patient who had manic-like symptoms above threshold with intravenous ketamine followed by oral riluzole had elevated scores at Day 24 and 25. Even though the YMRS returned to 4 at Day 26, this subject dropped out of the study because of worsening anxiety. Nevertheless, this subject’s YMRS elevated mood item remained zero throughout the protocol as well.

An increase in manic symptoms in bipolar patients treated with traditional antidepressants has been validated in the real-world effectiveness trial Systematic Treatment Enhancement Program for Bipolar Disorder (10). The risk increases without adjunctive mood stabilizer(s) (11,12). The unipolar subjects were unmedicated for at least 2 weeks before and during the entirety of the protocol. The bipolar patients were maintained on either therapeutic lithium or valproic acid without adjunctive psychotropic medications on the same time scale. In the case presented by Ricke and colleagues, there were multiple medication changes without adjunctive mood stabilizer use (quetiapine was only restarted at Day 8 post-ketamine initiation), which could have substantially contributed to her manic-like presentation. The dose and duration of ketamine infusion was also dramatically different in our studies relative to this case report. Nonetheless, there is insufficient evidence to support mania induction with a single subanesthetic dose of ketamine in 98 treatment-resistant major depressed patients.

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References

1. Ricke AK, Snook RJ, Anand A. Induction of prolonged mania during ketamine therapy for reflex sympathetic dystrophy. Biol Psychiatry. 2011; 70:e13–14. [PubMed: 21529780]
2. Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, et al. A randomized trial of an *N*-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry. 2006; 63:856–864. [PubMed: 16894061]
3. Diazgranados N, Ibrahim L, Brutsche NE, Newberg A, Kronstein P, Khalife S, et al. A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. Arch Gen Psychiatry. 2010; 67:793–802. [PubMed: 20679587]
4. Zarate CA Jr, Brutsche NE, Ibrahim L, Franco-Chaves J, Diazgranados N, Cravchik A, et al. Replication of ketamine's antidepressant efficacy in bipolar depression: A randomized controlled add-on trial. Biol Psychiatry. 2012; 71:939–946. [PubMed: 22297150]
5. Tohen M, Frank E, Bowden CL, Colom F, Ghaemi SN, Yatham LN, et al. The International Society for Bipolar Disorders (ISBD) Task Force report on the nomenclature of course and outcome in bipolar disorders. Bipolar Disord. 2009; 11:453–473. [PubMed: 19624385]
6. Keck PE Jr, Corya SA, Altshuler LL, Ketter TA, McElroy SL, Case M, et al. Analyses of treatment-emergent mania with olanzapine/fluoxetine combination in the treatment of bipolar depression. J Clin Psychiatry. 2005; 66:611–616. [PubMed: 15889948]
7. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: Reliability, validity and sensitivity. Br J Psychiatry. 1978; 133:429–435. [PubMed: 728692]
8. DiazGranados N, Ibrahim LA, Brutsche NE, Ameli R, Henter ID, Luckenbaugh DA, 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; 71:1605–1611. [PubMed: 20673547]
9. Ibrahim L, Diazgranados N, Franco-Chaves J, Brutsche N, Henter ID, Kronstein P, et al. Course of improvement in depressive symptoms to a single intravenous infusion of ketamine vs add-on riluzole: results from a 4-week, double-blind, placebo-controlled study. Neuropsychopharmacology. 2012; 37:1526–1533. [PubMed: 22298121]
10. Goldberg JF, Perlis RH, Ghaemi SN, Calabrese JR, Bowden CL, Wisniewski S, et al. Adjunctive antidepressant use and symptomatic recovery among bipolar depressed patients with concomitant manic symptoms: Findings from the STEP-BD. Am J Psychiatry. 2007; 164:1348–1355. [PubMed: 17728419]
11. Salvi V, Fagiolini A, Swartz HA, Maina G, Frank E. The use of antidepressants in bipolar disorder. J Clin Psychiatry. 2008; 69:1307–1318. [PubMed: 18681751]
12. Salvadore G, Quiroz JA, Machado-Vieira R, Henter ID, Manji HK, Zarate CA Jr. The neurobiology of the switch process in bipolar disorder: A review. J Clin Psychiatry. 2010; 71:1488–1501. [PubMed: 20492846]