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CLINICAL CONUNDRUM

BIPOLAR DISORDERS WILEY

Hypomania associated with high dose ketamine treatment

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For more than 50 years, pharmacotherapy for major depressive disorder (MDD) has narrowly focused on enhancing monoaminergic neurotransmission resulting in more than 30 FDA-approved treatments. In contrast, the glutamatergic, non-competitive *N*-methyl D-aspartate (NMDA) receptor antagonist ketamine has been "repurposed" as a rapid acting antidepressant[1]; the enantiomer S-ketamine, or esketamine, is now FDA-approved for treatment-resistant unipolar depression (TRD). These drugs have fundamentally changed the landscape of community-based practice for TRD. A growing number of psychiatrists, anesthesiologists, Certified Registered Nurse Anesthetists, and sometimes even emergency department physicians, are providing off-label infusions to patients for a wide range of diagnoses including bipolar depression, posttraumatic stress disorder, obsessive-compulsive disorder (OCD), chronic pain, cocaine dependency, and suicidality. Poorly monitored use of this medication for varied indications and in unusual dosing schedules and formulations is increasing, given the wide availability of ketamine and esketamine.[2,3] We present a case of high-dose ketamine associated with the development of hypomania in a patient with Bipolar II disorder (BPII), emphasizing the importance of the appropriate use of ketamine and the risk of treatment-emergent mania.

1 | CASE PRESENTATION

Mr. L is a 28-year-old, single, employed, Caucasian male who sought consultation at the Mayo Clinic Depression Center in November 2019 for treatment-resistant depression and OCD. Mr. L. had one prior psychiatric hospitalization for depression with suicidal ideation in 2017 followed by a 4-month residential program. He experienced previous hypomanic episodes (decreased need for sleep, euphoric mood, increased energy, libido, and self-confidence) that had occurred spontaneously and preceding the use of any antidepressant pharmacotherapy, as well as hypomania possibly associated with prior treatment of sertraline (maximum dose of 200 mg). He had a history of an obsessional focus on his physical stature and the shape of his jaw to the point of contemplating surgery. His medical evaluation showed no evidence of substance use, anemia, vitamin-D deficiency, or thyroid disease. Prior medications focused primarily on selective serotonin reuptake inhibitors (SSRIs) for 7-8 years (sertraline 200 mg, fluoxetine 60 mg, escitalopram 20 mg daily, citalopram 40 mg daily), supporting diagnoses of MDD and OCD. There was no prior treatment with lithium, mood stabilizing anticonvulsants, or atypical antipsychotics, with the exception of aripiprazole, which was only used at 5 mg and discontinued due to akathisia. There was significant concern from the patient in using antipsychotics due to the potential extrapyramidal symptoms and weight gain that could cause more anxiety due to his focus on body image. He recently discontinued sertraline and started lamotrigine titrated to 200 mg. He received a series of 21 repetitive transcranial magnetic stimulation a year prior to presentation with some reported benefit. ECT was not trialed due to patient and family's concerns for side effects on memory.

After Mayo Clinic evaluation, the working diagnosis was treatment-resistant non-rapid cycling BPII depression. We recommended optimizing lamotrigine to 400 mg daily and to later consider higher dose SSRIs or clomipramine in combination with anti-manic mood stabilization. In January 2020, while on maintenance lamotrigine 400 mg daily, his referring psychiatrist started intranasal esketamine (Spravato®) (Table 1). Because of insurance limitations, he was switched to compounded intranasal racemic ketamine halfway through the course. Treatment consisted of 20 insufflations per session at his psychiatrist's clinic. Over the course of 12 weeks, the patient received a total of 21 intranasal treatments (8 esketamine and 13 racemic ketamine). He had no significant dissociative side

effects, rating them only 2-3/10, 10 = worst. Depressive symptom severity was assessed each session by the Montgomery Äsberg Depression Rating Scale (MADRS). Overall, he achieved a modest 25% reduction in depressive symptom severity as quantified by the MADRS (baseline 33, final 25). At the end of treatment week 9, Mr. L. experienced an episode of hypomania, with elevated mood, racing thoughts, being more talkative than usual, inflated self-esteem, increased libido, and increased spending. By mood analog scale (MAS; 0 = worst depression, 50 = euthymia, 100 = highest elevation), in retrospect, he reported an average score of MAS 75-80 the week after his last treatment. He reported feeling "up", confident, and relieved to have no intrusive anxiety. He acknowledged an increased sex drive, spending excessive time on pornographic websites, and financial indiscretion. Ketamine was discontinued and his symptoms of hypomania resolved 2 weeks later. He was subsequently psychiatrically hospitalized for a mixed BPII episode.

2 | DISCUSSION

TABLE 1 Ketamine/esketamine dosing per session for Mr. L

Session#	Day	Intranasal ketamine type	Dose (mg)
1	1	Esketamine	84
2	2	Esketamine	112
3-5	5, 7, 12	Esketamine	168
6-7	21, 23	Esketamine	140
8	27	Esketamine	168
9	32	Racemic ketamine	196
10	34	Racemic ketamine	168
11	39	Racemic ketamine	196
12-13	41, 48	Racemic ketamine	168
14-20	49, 53, 55, 60, 62, 65, 67	Racemic ketamine	196
21	75	Racemic ketamine	140

Off-label use of ketamine for the treatment of psychiatric illnesses, in various delivery models, is increasing in this country. This case illustrates the potential risks of ketamine in patients with underlying bipolar disorder. There are a number of clinical points of interest.

First, the esketamine dosing for Mr. L. was twice as high as recommended. The FDA-approved starting dose of Spravato® is 56 mg on day 1, then 56 or 84 mg twice a week during weeks 1-4, and for maintenance, 56 or 84 mg once weekly for weeks 5-8, then every 1-2 weeks thereafter. This patient received an average weekly esketamine dose of 229.6 mg for the first 5 weeks (given over two sessions for 3 of those weeks, and one session the other 2 weeks), and then switched to compounded racemic intranasal ketamine averaging 344 mg weekly (given over 2 sessions each week). This twice a week use, continued indefinitely in an "acute course" rather than once a week maintenance schedule, also exposed this patient to higher than usual doses of ketamine, for both esketamine and the off-label compounded racemic form.

Key Message

Intravenous and intranasal ketamine are being used more frequently for treatment-resistant depression. While there is off-label use in bipolar depression, adverse events such as hypomania can occur without an anti-manic mood stabilizer and close monitoring, especially with high dosages. More controlled studies are needed for ketamine treatment in bipolar depression.

Learning points

- Ketamine may be associated with treatment emergent hypomania/mania in bipolar disorder.
- It is important to monitor response and side effects when using ketamine off-label or in different forms.
- More controlled studies are needed for ketamine treatment in bipolar disorder.

The second clinical point is that it is unknown whether racemic ketamine can simply substitute for intranasal esketamine spray. Esketamine is twice as potent as (R,S)-ketamine, but the estimated bioavailability is only 45%. A 28 mg dose of intranasal esketamine is delivered in two sprays totaling 0.2 mL, and additional 28 mg doses require a 5-minute waiting period. In its most common concentration of 100 mg/mL, compounded racemic ketamine requires a higher number of insufflations, leading to nasal congestion and post nasal drip, which makes intranasal absorption less reliable. Higher concentrations of compounded ketamine are also less reliable because of sedimentation of the ketamine in the bottle. Additionally, compounded medications are not set to the same bioequivalence standards of commercially available prepared drugs. If we were to calculate a possible dose equivalence of IV to intranasal ketamine for this patient weighing 83.6 kg, using a standard IV dose for depression of 0.5 mg/kg (thus 41.8 mg) and the estimated 45% intranasal esketamine bioavailability, it would be 92.9 mg intranasally (almost 1 mL using the 100 mg/mL concentration). The compounded 196 mg dose the patient received was nearly 5× the conventional dosing of intravenous ketamine and 2.11× the estimated compounded intranasal dose.

The third clinical point is that ketamine may be associated with treatment emergent hypomania/mania in bipolar disorder, and that lamotrigine may not be a sufficient anti-manic agent. Although current knowledge can provide background to formulate hypotheses of the mechanisms of affective switch in bipolar disorder, further research is needed to validate these hypothesis before they can be used for clinical interpretation. Among these hypotheses, ketamine may be related to the change in cortical excitability related

to cortical disinhibition and reduced activity of inhibitory interneurons. There is also evidence suggesting that ketamine may act as a partial agonist of the dopamine D2 receptors and may increase the dopamine levels in the striatum. Several studies investigating the efficacy and safety of ketamine for bipolar depression showed significant response and minimal risk, although the number of publications and sample sizes were small, and even smaller for intranasal ketamine.[4] These studies had strict inclusion criteria, most notably requiring the presence of antimanic mood stabilization (i.e. lithium, valproic acid), beyond lamotrigine[5] and used standard IV dosing parameters of 0.5 mg/kg. While not proven, it is reasonable to infer that there is a dose correlation with the likelihood of treatment-emergent mania.

A fourth clinical point relates to the monitoring of response and side-effects to ketamine, especially for off-label use. Esketamine must be administered in a physician's office, but it is usually another health care professional (such as a nurse or medical assistant) who observes the patient for the treatment and 2-h waiting period. The psychiatrist must remain "in-house" during the treatment but does not have to be present with the patient. There is no standard recommendation for how frequently the physician should assess the patient's progress. For intravenous ketamine, sometimes there is not even a psychiatrist to guide the treatment course. While we do not propose any specific timeframes for in-person visits, we recommend that the physician closely and carefully reviews the patient's progress and side-effects, with regular in-person assessments. For bipolar depression, it is important to monitor for hypomanic or manic symptoms, and a rating scale such as the Young Mania Rating Scale could be used.

There are some limitations of this case. Being a case report, causal inference and generalization is not possible. More controlled studies are needed for the use of ketamine treatment of bipolar disorder. Second, this report is produced retrospectively and is subjected to recall bias. History from medical records may not contain all relevant data and clinicians' subjectivity might bias the interpretation of the observation.

In summary, intravenous and intranasal ketamine are being used more frequently for treatment-resistant depression and sometimes bipolar depression. While off-label practice occurs, we advocate adhering to evidence-based practice to minimize the chances of adverse effects such as the treatment-emergent hypomania. Close monitoring and use of an anti-manic mood stabilizer would also be recommendations when treating bipolar depression.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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