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Induction of Prolonged Mania During Ketamine Therapy for Reflex Sympathetic Dystrophy

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To the Editor

Clinical studies have demonstrated that ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, has mood-elevating and antidepressant properties (1–6). In light of these findings, we present a case report of a patient receiving ketamine therapy for reflex sympathetic dystrophy who subsequently developed manic and psychotic symptoms.

Ms. M is a 42-year-old Caucasian married woman with a history of chronic left gluteal and left leg pain diagnosed as reflex sympathetic dystrophy. She was disabled by refractory symptoms that had failed a number of interventions and required high-dose opioids. Ms. M was otherwise high functioning and had completed a professional degree. The patient elected to undergo experimental IV ketamine therapy for her symptoms. An admission note documented a history of depression and insomnia, for which the patient had been prescribed duloxetine 20 mg daily, mirtazapine 45 mg qHS, and quetiapine 100 qHS. These medications were held on admission. On Day 1, ketamine was started and titrated from 10 to 20 mg/hour over a period of 5 days in the intensive care unit. The patient immediately reported that her pain was much better and it was a “miracle,” but by Day 2 she again complained of considerable pain. On Day 3, duloxetine 20 mg and mirtazapine 45 mg were restarted. By Day 4, Ms. M reported significant pain relief and continued to get better by Day 5 and Day 6. In these first 6 days, some subtle behavioral changes were seen (e.g., sometimes being too optimistic about the therapy), but nothing extraordinary was documented, and the therapy continued because Ms. M seemed to benefit considerably from it. On Day 7 of the ketamine protocol, Ms. M started exhibiting notable changes in her mental status. She 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. On Day 8, Ms. M was irritable and emotionally labile and expressed the feeling that the team was withholding pain medications from her. Without any prompting, she detailed a series of past traumas that she had experienced, including the deaths of her parents. Therefore, on Day 8, quetiapine 100 mg qHS was restarted, and duloxetine was increased to 60 mg. However, her mania like symptoms did not get better, and on Day 10 Ms. M demonstrated pressured speech and sent her physicians a lengthy e-mail that was tangential with loosening of associations. The communication included statements like “Dear Doctors and Heroes” and “If we could treat RSD like jazz we could treat individuals according to specific needs at specific times.” Given her symptoms, a decision was made to

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discontinue the ketamine protocol, but the mania symptoms did not abate. On day 11, a psychiatry consult was requested, because the patient was expressing suicidal ideation. She repeatedly called 911 from her hospital room, believing she was having a stroke. On psychiatric examination, the patient was manic; emotionally labile; and noted to have pressured speech, racing thoughts, flight of ideas, and paranoia. Duloxetine was discontinued by psychiatry, and a sitter was ordered for suicidal precautions. The patient was less agitated but more euphoric and sleeping less by Day 12 and Day 13. She refused neuroleptics, including quetiapine, despite urging by the team. In the next few days, the patient continued to have pressured speech with flight of ideas, labile but mostly euphoric mode, and little insight into her condition. The patient was still exhibiting signs of mania on Day 18 and finally agreed to treatment with 200 mg of quetiapine. After 2 days of compliance with quetiapine, by Day 20, the signs and symptoms of mania began subsiding; however, she continued to display symptoms of hypomania at the time of discharge.

Past history revealed—that the patient might have possibly experienced 3–4 days of hypomania-like symptoms after surgery 3 years prior. However, the patient had never been diagnosed with bipolar disorder nor had any previous psychotic symptoms.

The propensity of ketamine to produce psychotic symptoms is well-known, and in fact, this drug has been used as a model of schizophrenia in research studies (5). Important recent studies have also documented its mood-elevating properties, lasting many days, in patients with both unipolar and bipolar depression (2,4,6). In psychiatric reports, usually a bolus dose of ketamine is given for treatment of depression (e.g., a bolus dose of .5 mg/kg has been reported to be effective) (4). For treatment of pain, as administered in this case, a continuous infusion with .1–.2 mg/kg over the course of many days has been recommended (7). However, we could not find— despite larger total doses of ketamine being administered in the pain setting—any previous report in the literature with regard to ketamine-induced mania, presumably because of the slow rate of infusion. Although other drugs such as duloxetine might also have contributed to the change in the mental status of the patient, the close association with treatment with ketamine suggests a causal role of ketamine in the induction of the manic symptoms. Another possibility is that the mania was induced as an interaction between ketamine and the antidepressant. In either case, this report suggests that IV ketamine use can be associated not only with euphoria and mood elevation but also with development of mania. The effect was particularly striking, because it was seen in a medical setting in a patient with no definite past diagnosis of bipolar disorder. The induction of prolonged mania and associated psychotic symptoms highlights a potential side effect that needs to be kept in mind if ketamine is used for treatment of patients with pain and mood disorders (8), many of whom are also being treated with conventional antidepressants.

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