Ketamine-induced affective switch in a patient with treatment-resistant depression

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ABSTRACT

There is growing evidence to support the rapid, albeit short-lived antidepressant effect of subanesthetic dose of ketamine, a noncompetitive glutamate N-methyl-D-aspartate receptor antagonist in treatment-resistant unipolar and bipolar depression. Ketamine is known to cause transient mood elevation or euphoria, psychotomimetic effects, and dissociative symptoms, but its use in unipolar or bipolar depression has not been reported to induce an affective switch amounting to persistent or prolonged hypomania/mania or manic-like syndrome. We report the case of a 52-year-old male with first episode, continuous, nonpsychotic, treatment-resistant, unipolar major depression of 10 years duration, who manifested a switch from depression to mania while being treated with subanesthetic dose of ketamine, given intramuscularly. This case suggests that polarity switch should be considered as a potential side effect while using ketamine for treatment-resistant depression.

KEY WORDS: Affective switch, ketamine, treatment-resistant depression

Case Report

A 52-year-old male presented with first episode, continuous, nonpsychotic, unipolar MDD of 10 years duration. Past and family history was unremarkable for any psychiatric or neurological illness. There was no history of substance use apart from tobacco chewing. He did not suffer from any chronic medical illness. Laboratory investigations (including serum vitamin B12 and D3 levels) were within the normal reference range. The brain magnetic resonance imaging was normal. Past treatment records revealed that he had received adequate treatment trials (in terms of doses, duration, and compliance) of fluoxetine, escitalopram, sertraline, imipramine, bupropion, moclobemide, lithium, lamotrigine, methylphenidate, fluoxetine-olanzapine combination, quetiapine, and aripiprazole, as mono-or combination therapy. In the 10 years of being on treatment, sleep, appetite, and concentration improved on medication in varying degrees, but depressed mood and...
diminished interest in most activities almost always persisted without much change. Throughout the duration of illness, he had experienced a feeling of passive death wish but never had suicidal ideation or attempts.

At the time of presentation to us, he scored 26 on the 17-item Hamilton Rating Scale for Depression (HRSD). We prescribed a combination of venlafaxine and mirtazapine, in doses of 300 mg and 30 mg respectively, up-titrated over a period of 3 weeks. At the end of 12 weeks, he scored 20 on HRSD. Electroconvulsive therapy was considered, but the patient and his family members denied consent. Feeling that the medications were not helping him much, he went off treatment for 22 days but did not report much worsening of symptoms, apart from mild headaches and impaired sleep.

We then administered ketamine intramuscularly in a dose of 0.3 mg/kg, as the patient consented for the same. None of the antidepressants was restarted. HRSD score before the injection was 24. Two hours postinjection, his mood was expansive on a clear sensorium. He reported mild nausea and dizziness but no other adverse effects. He scored 16 on HRSD and 17 on Young Mania Rating Scale (YMRS). Two more injections of ketamine were given in the same dose at an interval of 2 days each time. His scores before the second and third injections were 18 on HRSD, 13 on YMRS and 16 on HRSD, 14 on YMRS, respectively. After 2 h of the second and third injections, his scores were 12 on HRSD, 18 on YMRS and 10 on HRSD, 20 on YMRS respectively. He always scored ≥2 on the YMRS “elevated mood” item. Family members complained that he was unduly cheerful and energetic, talking more than usual, restless and fidgety, unusually grooming well, singing along, and picking fights in the neighborhood, especially after the third injection. In absence of any such past history or concurrent antidepressant or substance use, it was postulated that the patient had an affective switch from depression to mania induced by ketamine; the assertion supported by a score of 9 on the Naranjo Adverse Drug Reaction Probability Scale. Hence, ketamine was discontinued. Within the next 16–18 days, manic symptoms subsided, but depressive symptoms re-emerged. He scored 24 on HRSD and six on YMRS. He was then prescribed lithium 900 mg (in two divided doses), and paroxetine extended-release 25 mg. Lorazepam 2 mg was continued all through the course of these events.

Discussion

The International Society for Bipolar Disorders Task Force has 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 >12.18 Our patient clearly fulfilled this definition, and the polarity switch may thus be attributed to ketamine, in the absence of any concomitant antidepressant medication. Wada et al., reported the prevalence of manic/hypomanic switch during acute antidepressant treatment in their sample of admitted unipolar MDD patients to be 13.1%, and the manic/hypomanic episodes lasted from 1 to 8 weeks; the switch occurring more commonly in males.[3] Interestingly, our patient had never developed manic/hypomanic symptoms anytime in the past while receiving antidepressant treatment. In the 6 months following the subsidence of the switch episode, he did not present with manic/hypomanic symptoms again, but he was also taking lithium along with paroxetine. A study examining the long-term outcome of moderate/severe unipolar MDD patients with mood switch during acute antidepressant treatment found that no subject presented spontaneous mania/hypomania (once antidepressant maintenance treatment had finished) during 3 years of follow-up.[6]

Niciu et al., analyzed data from their three independent studies (constituting a total of 98 treatment-resistant unipolar or bipolar major depressed patients) for treatment-emergent manic-like symptoms as assessed using YMRS, while being administered subanesthetic dose ketamine.[7] They concluded that there was insufficient evidence to support that ketamine induces a switch of polarity from depression to mania. Furthermore, they critically evaluated the case presented by Ricke et al.,[8] which claimed induction of prolonged mania in a patient during ketamine therapy for reflex sympathetic dystrophy, with comorbid depression and insomnia, and questioned the authors’ attribution of the affective switch to ketamine.[7]

With the growing evidence and increasing use of ketamine for treatment-resistant unipolar MDD, our case report suggests that clinicians should consider affective switch as its potential side effect.

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Conflicts of Interest

There are no conflicts of interest.

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