

## CLINICAL CASE CONFERENCE

**Treatment of suicidal depression with ketamine in rapid cycling bipolar disorder**

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**Introduction**

Despite rapid advances in understanding the neurobiology of bipolar disorders, rapid cycling states continue to be the Achilles heel for psychiatrists. This is due to their elusive presentation, poor treatment response, frequent recurrences, high suicidality and overall poor prognosis (Wu and Dunner, 1993; Coryell *et al.*, 2003; Nierenberg *et al.*, 2010). The management of rapid cyclers, especially in the acute depressive phase with antidepressants remains a challenge, due to antidepressant induced mood switches (hypomanic, manic and mixed) and fear of worsening the overall course of illness (Ghaemi *et al.*, 2003). The scenario becomes more complicated in the setting of severe depression with suicidality, where electroconvulsive therapy is the only recommended treatment (Srisurapanont *et al.*, 1995). However, nonavailability, prohibitive costs, negative public perceptions and stigma limit the utility of electroconvulsive therapy (ECT) in clinical settings (Rose *et al.*, 2003). Ketamine, a widely used anaesthetic agent and N-methyl-D-aspartate receptor (NMDA) antagonist offers a way out of this conundrum with its rapid antidepressant and antisuicidal effects with better efficacy and tolerability. We present a case of a 19-year-old female with rapid cycling bipolar depression admitted after a suicide attempt, successfully treated with

ketamine when she failed to improve with standard treatment.

**Case report**

Miss P.B. was brought to the casualty in a state of acute confusion following a suicidal attempt by hanging. The patient was immediately stabilized and shifted to the intensive care unit for intensive medical care. A diagnosis of hypoxic encephalopathy due to suicidal hanging was made by the medical team. After two days, the patient was transferred to the medical ward after recovery with no permanent neurological deficits. Computed tomography scan brain, X-ray cervical spine, and blood parameters were within normal limits. The patient was transferred to psychiatric inpatient services for a detailed evaluation and psychiatric management.

History revealed that the total duration of illness was one and a half years which started with an episode of depression (moderate) without any precipitating factors. It lasted three to four weeks and remitted spontaneously without any treatment. A second episode of depression, four months after the index episode was severe in intensity and was precipitated by academic problems. During this episode, the



patient attempted suicide with a household cleaning solution. The patient was hospitalized during the episode where she had her first contact with psychiatric services (in a different center). A diagnosis of depressive episode was made and escitalopram 10 mg was started. The patient was discharged from that facility and was advised to follow up as an outpatient two weeks later. The patient did not refill her prescriptions and stopped antidepressants after a fortnight as she reportedly felt better.

About a month after the second episode of depression, the patient began experiencing elevated mood, increased energy levels, and over-talkativeness. She would go on spending sprees buying expensive items impulsively, spending more time and money on grooming than usual. She would come home late after school despite parental restrictions, and become unusually irritable and angry when her parents reprimanded her. The episode lasted one to two weeks following which the patient returned to her usual premorbid self.

After about a month of the "high," the patient's family could notice a distinct change in her attitude and behavior. During this period ("low") the patient became gloomy, overslept, refused to socialize with her friends, lost her appetite and even refused meals. She would complain of feeling tired all day, skipped her classes at school resulting in poor academic performance and expressed guilt over her behavior. The "low" lasted for two to three weeks which the patient felt was distinctly different from her usual premorbid self.

Her family reported that the "highs" and "lows" occurred almost every two months once, and in the last six months the duration of the "lows" had gradually become more troubling. Psychiatric consultation was not considered as her family interpreted her "highs" as rebellious adolescent behavior and her "lows" a guilt reaction to her behavior during the periods of "high."

The present depressive episode started three weeks ago and was especially bothersome to the family as the patient was exhibiting more symptoms than usual with refusal of meals and increasing social isolation by being confined to her room all day. The suicide hanging was without any apparent precipitating event.

Based on the longitudinal history, a Diagnostic and Statistical Manual, 5th Edition diagnosis of Bipolar II Disorder current episode depressed (severe) with rapid cycling was made (296.89). Hypothyroidism was ruled out by normal laboratory thyroid profile. Borderline personality disorder (BPD) was considered as a differential diagnosis and was ruled

out due to the following reasons. The onset of the illness was clear and distinct with an episode of depression one and a half years ago, prior to which there were no reports of any interpersonal adjustment problems or chronic impulsivity. The patient had maintained good relationships with friends and relatives and was known to have a stable mood. Though BPD exhibits mood swings that mirror bipolar disorder, they commonly switch from the poles of anger, anxiety and dysphoria rather than from the poles of elation and depression as exhibited by our patient. The episodes were distinct, not precipitated by external events (except for the second depressive episode), lasting longer than a week with normal inter-episodic functioning, which is highly unlikely in BPD. Lastly, this patient reported that her irritability, impulsivity and anger outbursts were only present during the episodes of "highs" which is quite uncharacteristic of BPD. Attention deficit hyperactivity disorder was ruled out clinically and by psychometric evaluation. Substance induced mood disorder was ruled out clinically and a normal drug screen panel on admission.

Bipolar depression rating scale (BDRS) designed specially to measure and rate the severity of depression in bipolar depression and mixed states (Berk *et al.*, 2007) was used to score the depression severity. It is a 20-item scale with 15 items for depression and five items for mixed states. The patient's BDRS score of 28 and a Montgomery Asberg Depression Rating Scale (Montgomery and Asberg, 1979) score of 36 indicated severe depression. Mini Mental Status Examination (Folstein *et al.*, 1975) score of 28 excluded any permanent cognitive impairment due to hypoxic encephalopathy.

After baseline investigations, the patient was started on lithium and quetiapine; the dose gradually titrated over the course of a week to 800 mg and 400 mg, respectively. Antidepressants were avoided to prevent a switch and worsening the course of rapid cycling bipolar illness. After 10 days of inpatient stay, the patient did not show any improvement in her depressive symptoms except for improved sleep (one week Montgomery Asberg Depression Rating Scale (MADRS) score of 34) and continued to express suicidal wishes, hopelessness and refusal of food. Blood lithium levels were optimal at 0.82 mEq/L.

The case was discussed in the clinical case conference as it posed a treatment challenge and necessitated expert psychiatric intervention. A second opinion was sought from two senior psychiatrists from the State Psychiatric hospital, who concurred with the diagnosis. Given that the patient did not show satisfactory improvement to the current line of



management and continued to express persistent suicidal ideation, it was decided that a change in treatment regimen was prudent. Three lines of management were suggested. The first was ECT to which the caregivers refused despite explaining its strong evidence base and its necessity in the situation. Despite being an effective treatment in the eyes of the psychiatric community, ECT has a bad reputation among the general public as a result of its incorrect portrayal in the media leading to its stigmatization in this part of the world. The second plan was to supplement the current treatment with cognitive behavior therapy. However, the patient's psychomotor retardation, anhedonia and low mood interfered with the active engagement in therapy since admission. It was agreed after much deliberation to initiate a trial of ketamine for the patient's severe suicidal depression. Despite evidence from case reports and case series of the efficacy of ketamine for depression in bipolar disorder, the treatment is still considered experimental due to apprehensions about the psychedelic status of ketamine and its abuse potential. The caregivers were involved in the treatment decision making and were explained in detail regarding the nature of ketamine and its less than robust clinical evidence. It was informed that during the ketamine infusion, temporary dissociative phenomenon were common, cardiovascular status monitoring was needed, and that there was a theoretical risk of switch to mania although it was not reported in literature. Ketamine's abuse potential was briefed to both the parents and the patient, although it was unlikely given ketamine's restricted availability (unlike benzodiazepines) and a negative history of substance abuse in our patient. It was also explained that ketamine infusion was only a temporary intervention (due to its rapid onset antidepressant effect) for the patient's suicidal ideation, and the main target was to bring about a meaningful reduction in the depressive symptoms and buy time for the psychological interventions and medications to stabilize the patient. After discussion, the caregivers agreed to a trial of ketamine on the condition that if there is no improvement after three infusions they would reconsider their consent for ECT.

Dr. H.S who has had an extensive experience in administering ketamine for unipolar and bipolar depression (more than 400 procedures over a period of four years) took charge of the patient. Ketamine at a dose of 0.5 mg/kg body weight in 100 ml saline over 40 minutes was administered under pulse oximeter monitoring. The patient was closely monitored during the procedure till she regained full consciousness. The patient had mild nausea, giddiness, dizziness and

apprehension during the infusion which disappeared within 30 minutes after the treatment. MADRS was administered 12th hourly to document changes in depression and Young Mania Rating Scale (Young *et al.*, 1978) to notice any switch to hypomania/mania. The patient showed remarkable improvement in her depressive symptoms with MADRS score of 18 (mild depression) within 12 hours of the ketamine infusion. Her mood, appetite, anhedonia, psychomotor retardation improved and suicidal ideation disappeared for the first time since admission. She did not display any symptoms of hypomania or mania (switch) after ketamine treatment.

A second infusion of ketamine was given after five days as she responded well to the first dose without any troublesome side-effects. The improvement was sustained this time and over the course of the third week her depression remitted with a MADRS score of 6 on discharge. The patient currently visits our outpatient services fortnightly and is adherent to the treatment plan. Since the last four months, the patient is well stabilized on lithium 800 mg and quetiapine 200 mg without experiencing a relapse.

## Discussion

Over the past decade, research has moved beyond the monoamine model of affective disorders to the glutaminergic (NMDA) hypothesis based on preclinical, clinical and postmortem studies (Sanacora *et al.*, 2008). Since Berman *et al.* (2000) reported the effects of ketamine, numerous well-designed studies have established the rapid antisuicidal and antidepressant effects of ketamine infusion in treatment-resistant major depressive disorder (Zarate *et al.*, 2006; Price *et al.*, 2009). However, it took almost a decade for the beneficial effect of ketamine to be reported in bipolar depression (Diazgranados *et al.*, 2010). Since then, there have been studies attesting to the efficacy of ketamine in treatment-resistant bipolar depression (Zarate *et al.*, 2012; Lara *et al.*, 2013). Some studies suggest that the brain-derived neurotrophin factor, vascular endothelial growth factor, nerve growth factor B12 may be involved in the antidepressant effects of ketamine in bipolar states (Permoda-Osip *et al.*, 2014).

Suicidal ideation and behavior is more common in rapid cyclers and is independently associated with a poorer outcome. In our case, we needed to act promptly to treat the severe suicidal depression in our patient. ECT, though an effective option in the treatment armament, cannot be readily administered



when it is most needed due to various factors that lie beyond the psychiatrist's control (consent, stigma and cost). In this scenario, ketamine offers rapid and effective relief of depressive suicidal ideation till the standard medications take effect.

## Conclusion

To our knowledge, this is the first case report of the efficacy of ketamine in a rapid cycling bipolar disorder. Rapid cyclers in their depressive phase pose a unique challenge to the clinician as they poorly respond to treatment, are extremely sensitive to antidepressant induced mood switches, and have high suicidal tendencies. Our patient showed a robust and rapid antidepressant and antisuicidal response to ketamine without a switch to mania. We suggest that ketamine be considered as a treatment option in the setting of depression in rapid cycling bipolar disorder especially in patients with suicidal ideation.

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