

Rapid Clozapine titration in a case of refractory bipolar disorder (mania) with compound tibia-fibula fracture

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ABSTRACT

Treatment refractory bipolar disorder (TRBD) cases are known to be notoriously difficult to manage. The problems further increase when a comorbid illness is associated with it. Traditionally clozapine has been used in a slow titration regime which takes two to three weeks for reaching the desired dose and thus duration of hospital stay is prolonged. Here we report a case of TRBD with comorbid tibia-fibula fracture successfully treated with rapid dose clozapine titration regime, without any overt side effects. We observed rapid dose titration regime to be extremely effective in fast control of agitated-violent behavior and superior mood stabilization. This suggests rapid titration of clozapine as a suitable alternative for hospitalized TRBD patients, especially when the severe manic symptoms cause hindrance to adequate management of a comorbid illness.

Key words: clozapine, bipolar disorder, mania, treatment resistant.

INTRODUCTION

Bipolar disorder particularly mania presents with agitation and violent behavior, which is a significant public health problem. The risk of injuries or death in such patients and their victims is high [1]. Also seen with progressively increasing episodes of bipolar disorder are the accumulating neurobiological changes which lead to an increase in burden of disease. Self-sensitization and cross-sensitization among multiple mood episodes, trauma and biological/psychosocial stressors account for impairment in mood regulation. This leads to treatment refractoriness and difficult management of such cases [2-3]. Care and management of bipolar mania patients which present with both agitated-violent behavior and treatment refractoriness is a challenging task requiring an intensive approach.

Literature supports clozapine use as the gold standard in treatment of refractory schizophrenia, suicidal patients of schizophrenia and schizoaffective disorder [4]. Also the use of clozapine, alone or in combination, in bipolar

disorder has shown significant association with reduction in psychiatric admissions and hospital contacts for self harm/ overdose, which suggests its strong mood-stabilizing properties [5]. A systematic review of 15 clinical trials of clozapine monotherapy or clozapine combined with other treatments for treatment refractory bipolar disorder (TRBD) concluded it to be both relatively safe and effective in such cases [6]. It also has superior efficacy over other atypical and typical antipsychotics, in reducing agitation and hostility [7-9]. There may be some serious side-effects like seizures [10], agranulocytosis and myocarditis [11]. Thus it presents as a double edged sword for optimizing its utilization. Close monitoring during early periods of starting clozapine can minimize these risks [12-13].

In view of risk of seizures and hypotension our current guidelines recommend slow clozapine dose titration with reaching the target dose over a 2-3 week period. However published literature supports the use of rapid clozapine titration, as it seems to be equally safe and effective when compared to standard clozapine titration. The hospital stay is significantly decreased with this approach [14-15]. We report here a case of TRBD with compound tibia-fibula fracture which showed minimal improvement over a combination treatment with antipsychotic and mood stabilizers and rapid improvement with complete remission when given a trial of rapid clozapine titration.

CASE REPORT

A 30 year old married female was brought by her mother with history of acute onset, progressive course manic behaviour since two months & a compound tibia-fibular fracture. The episode of mania began after the psychosocial stressor of her acknowledgement about the husband's extramarital affair. Initially she had disturbed sleep and irritability, while later within a week began with over-talkativeness, over-familiarity, singing and dancing. Gradually over time she was seen with demanding behaviour and spending sprees, expansive plans for future. She claimed to have a lot of power and that she was the reincarnation of goddess Laxmi. When contradicted she was seen to get abusive and assaultive with throughing stones over the people. During this acute phase of mania, in a state of manic excitement patient while running across the road met with a vehicular accident and sustained a compound lower limb fracture. She was then brought to the emergency department and assessed. Her longitudinal course of illness revealed five recurrent episodes of mania in past with progressively increasing duration and severity, precipitated by lack of adherence to treatment after recovery in each episode. On physical examination there was swelling and tenderness over left lower limb with 5 × 5 × 4cm lacerated wound. X-ray showed a compound grade IIIB mid-shaft comminuted fracture tibia-fibula (Gustillo Anderson classification).

On the day of admission her psychomotor activity was increased with decreased reaction time. Her speech was spontaneous, irrelevant at times, coherent with increased rate and volume. Her affect was elated with thinking revealing flight of ideas and mood congruent grandiose and persecutory delusions. Her judgment was impaired and insight was lacking. She was diagnosed with Bipolar Affective Disorder, current episode mania with mood congruent psychotic symptoms [F31.2], with Gustillo grade IIIB mid-shaft comminuted fracture tibia-fibula.

Initially in the emergency department, fracture was stabilised by a Plaster of Paris slab. Then the patient was shifted to orthopaedic ward where she was operated and an external fixator was applied. During stay in orthopaedic ward the patient was given injectable neuroleptics (Inj. Haloperidol 5mg with Inj. Promethazine 25mg) in view of marked activity. Many a times to keep her activity under control she also had to be given additional injection of lorazepam 4mg. But as the patient was getting unmanageable she was taken transfer to psychiatry ward and started on a combination of Tab Divalproex Sodium 500 mg/day and Tab Olanzapine 10 mg/day with gradual increase in dosage to 1500 mg/day and 20 mg/day respectively. Additionally Injectable lorazepam 4mg was given on as and when required basis to keep her activity under control. In view of the persistent manic behaviour tablet lithium 300 mg/day was added and gradually increased to 600 mg/day with serum lithium level monitoring which was 1.0mmol/l on fifth day. Her manic behaviour continued even after adequate trial of the above mentioned medications. The diagnosis was revised as TRBD in mania with a compound tibia-fibula fracture. The immobilization of fractured limb was getting difficult and healing was getting delayed. So after getting normal level of complete blood counts of the patient, tablet clozapine was added at a dosage of 50 mg with another 50 mg repeated after 12 hours on the first day. Later clozapine was rapidly increased by 50 mg per day so that clozapine dose of 300mg per day was achieved within 5 days. Regular monitoring of complete blood counts and electrocardiogram was done, which were seen to be in normal range throughout the treatment course. Also postural blood pressure monitoring was kept so as to rule out significant postural drop in blood pressure. No significant adverse effects were noticed and within two days of starting clozapine the activity of patient decreased significantly. Within two weeks the patient showed significant improvement on Young's Mania Rating Scale, which decreased from 36 to 10. The patient improved and was discharged after psychoeducation. The patient maintained improvement with no significant side effects over a follow-up period of 6 months.

(see Figure)

DISCUSSION

As per literature difficult to treat TRBD cases show improvement with the addition of electroconvulsive therapy (ECT) [16-18] or clozapine [4-5]. In view of fracture with metallic external fixator in this case, opting for ECT would have warranted a much greater amounts of muscle relaxant in pre-ECT work up and thus a risk of undesirable drug-drug interactions. Thus opting for clozapine combination treatment seemed more prudent, although clozapine combination is also not entirely free from the risk of serious-side effects. Complicating factors in prediction of side effects with clozapine treatment are the inter-individual and intra-individual variations in plasma levels of clozapine with the same dose. But when done under close monitoring of weight, blood pressure, electrocardiogram and blood parameters this risk can be mitigated [10-13]. To be highlighted in this case is the fact that along with TRBD, the patient presented with comorbid diagnosis of a fracture limb. The comorbid condition plays a major role in the refractoriness of affective disorder by cross-sensitization [2-3] and in turn the psychopathology may be a significant factor in deciding the healing time of fracture, as evident in this case. Thus in this case an urgent need for agitation and aggressive behavior control added to the treatment challenge. So as to avoid an undue delay, rapid clozapine titration was used instead of guideline based slow clozapine titration. The patient improved significantly within a short duration of 15 days after starting with rapid clozapine titration and developed none of the life-threatening adverse

effects. Although clozapine has long been known for its sedative effects, special about the rapid clozapine titration approach is the rapid sedation effect achieved within 2 days, as seen in this case. This is of benefit in controlling the markedly agitated-aggressive behavior, especially when agitation causes hindrance in adequate management of a comorbid diagnosis, like fracture in this case. Also evident in this case is the rapid control of manic symptoms which strengthens the literature evidences advocating the clozapine's mood stabilizing properties.

Thus the case report here suggest that rapid titration of clozapine might be an option for hospitalized TRBD patients having severe manic episode creating a hindrance for adequate management of a comorbid diagnosis. Our observation supports previous literature evidences showing clozapine effectiveness in TRBD and also that rapid titration of clozapine is effective in achieving rapid symptom control without any significant side effects. Contrary to this some studies recommend the use of slow clozapine titration [19] as the risk of seizures and myocarditis is maximum during the initiation phase [20]. Thus while considering rapid clozapine titration in TRBD patients pre-existing seizure and cardiac risk factors along with relevant neurological abnormalities should be ruled out. We advocate avoiding rapid clozapine titration approach in definite seizure disorder and/or cardiac disease patients. Also close monitoring with a high index of clinical suspicion during the first month can be of help in avoiding these complications [21]. Thus to be kept in mind while treating patient's with rapid clozapine titration is its potential for an increased risk of severe side effects [22].

So our case report advocates the prudent use of rapid dose clozapine titration in TRBD cases where activity and agitation control is an urgent need. We suggest a comprehensive assessment for the possible risks and benefits before starting the patient with rapid clozapine dose titration regime and an intensive monitoring for the possible life threatening adverse effects throughout the treatment. Further controlled clinical trials in this direction are needed so as to confirm our preliminary observations.

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Figure - X-Rays and photograph of the same patient with fracture

