

## CASE REPORT

# TREATMENT RESISTANT MANIA: A CASE REPORT

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### Abstract

**Objective:** The objective of this case report is to highlight the challenges faced in managing a patient with treatment resistant bipolar mania. **Methods:** We report a case of a young Chinese lady who was in the manic phase of bipolar mood disorder and though compliant, was found to be resistant to standard anti-manic medications that were given for a duration of 3 months. Clozapine was used as augmentation therapy. **Results:** Marked clinical improvement was shown after augmentation with clozapine. **Conclusions:** Clozapine appears to be effective augmentation therapy when dealing with cases of resistant bipolar mania. However, further in-depth studies are needed to substantiate its indication, safety and effectiveness in such cases. *ASEAN Journal of Psychiatry, Vol. 17 (1): January – June 2016: XX XX.*

**Keywords:** Treatment Resistant Mania, Augmentation, Clozapine

### Introduction

Bipolar mood disorder is a mental disorder with a lifetime prevalence rate of about 1% in the general population [1]. Recent advances in research have provided numerous effective treatments for bipolar mood disorder. However, there is still a proportion of individuals who suffer from bipolar mood disorders that are resistant to standard treatment. The aim of this study is to report challenges in the management of treatment mania.

### Case Report

This case report depicts Miss L, a 23-year-old Chinese lady who has been suffering from bipolar mood disorder. She was previously under the care of another hospital prior to visiting ours. Miss L first presented to us in October 2014 with a month's history of irritability, increased goal-directed activities, talkativeness, inflated self-esteem and engaging in spending sprees. During that time, she also had depressive symptoms such as low mood, weight loss, poor appetite and suicidal

thoughts. Miss L holds a clerical job at her grandfather's second-hand car dealer shop. Though she was still able to go to work daily, she was unable to function at work due to the symptoms she was experiencing then. Her symptoms rendered an admission into our hospital's psychiatric ward necessary for further management, and a diagnosis of bipolar I disorder in manic phase with mixed features was made.

Prior to admission, Miss L was compliant to her once daily medications given by the previous hospital, which was sodium valproate 1000 milligrams and quetiapine XR 800 milligrams. Her compliance to medications was evident with the therapeutic levels of sodium valproate found in her blood. We started her on lithium carbonate 600 milligrams per day and quetiapine XR 800 milligrams per day while her sodium valproate was discontinued. After a week of introducing these medications, her symptoms improved. However, just prior to discharge from our ward, her condition deteriorated. While her depressive symptoms largely disappeared, her manic symptoms re-emerged, and she was

noted to be disinhibited, talkative, irritable, having flight of ideas as well as pressured speech. She also experienced auditory hallucinations and persecutory delusions, which were not mood congruent. The dip in her condition warranted a course of ECT which managed to relatively improve her symptoms. She received a total of 6 sessions of ECT, and her symptoms then showed marked improvement.

Given Miss L's improved condition, she was given a trial of home leave. Unfortunately, her condition worsened at home despite being compliant to her medications, and she had to return prematurely to our hospital's psychiatric ward. An additional 6 sessions of ECT was given but unfortunately it did not yield the same results as it once did. Due to the poor response to ECT then, we withheld further sessions.

Miss L's manic symptoms did not improve despite being treated with a combination of different mood stabilizers and antipsychotics, which were adequate in both dosage and duration. She was given various combinations of medications such as lithium with quetiapine; quetiapine with asenapine and haloperidol; asenapine with sodium valproate and lithium as well as the combination of olanzapine, sodium valproate and lithium.

Thorough revision of diagnosis and medications deemed Miss L to be treatment resistant. After careful deliberation, a decision was made to augment her treatment with clozapine. Clozapine was commenced with the initial dose of 12.5 milligrams per day and subsequently titrated up to a daily dose of 300 milligrams. The schedule for the titration of clozapine can be seen in Table 1. Clozapine was used as an adjunct to her pre-existing medications of lithium carbonate 750 milligrams per day and sodium valproate 800 milligrams per day. Miss L was able to tolerate clozapine well and to date has not experienced any of its side effects. Plans are in place to monitor her full blood count results weekly for 18 weeks, then monthly thereafter. Her initial weekly full blood count results were normal where the range of total white blood cell count was  $6.2$  to  $8.4 \times 10^9/L$  and the absolute neutrophil count range was  $3.44$  to  $4.03 \times 10^9/L$ .

Miss L showed tremendous improvement with clozapine whereby her manic symptoms of irritability, pressured speech, flight of ideas and disinhibited behaviour resolved. She was given another trial of home leave after 2 weeks of augmentation with clozapine. A week later, we discharged a well Miss L after a grand total of 106 days stay in our psychiatric ward.

**Table 1. Clozapine titration schedule**

Day(s)	Clozapine (milligrams)	
	Morning	Evening
1	-	12.5
2	-	25
3-5	25	25
6-8	25	50
9-11	50	50
12-14	75	75
15-17	100	100
18-20	125	125
21-23	150	150

## Discussion

Though a common occurrence, identification of treatment resistant bipolar disorder cases are challenging as there seems to be a lack of consensus about its definition [2]. The general agreement would be that a lack of response or

rather no response to standard treatment therapies that are known to be effective, would best define treatment resistant bipolar disorder [2, 3].

Electroconvulsive therapy (ECT) and clozapine are non-standard treatment options

that have been suggested for use in treatment resistant mania [3]. Clozapine is the first atypical antipsychotic agent that acts on various neurotransmitters, and it appears to be an effective treatment. However, judicious use of clozapine is required due to the lack of thorough studies, and the serious side effects associated with its use. In the case of Miss L, she failed to respond to a combination of multiple first and second line therapies for the treatment of bipolar mania. She did however, respond well to ECT initially. Subsequently, though, her condition deteriorated and where ECT once worked for her, it now did not produce any clinical improvement for her.

There have been a few guidelines that have suggested using clozapine in cases of bipolar mania. According to the Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for bipolar, treatment with clozapine for acute bipolar mania is a third line option and should be reserved for use in treatment resistant patients due to safety concerns and the lack of double blinded randomized controlled trials [4]. Even the American Psychiatric Association's guidelines states that clozapine may be particularly effective in refractory cases of bipolar mania [5].

Although large-scale studies scale studies have been few and far between, there are certain studies that reveal clozapine to be effective in cases of treatment resistant mania. In a study by Green et al. (2000), it was found that 17 out of 22 treatment-refractory bipolar disorder manic type with psychotic features showed at least 20% improvement in the Brief Psychiatric Rating Scale, Young Mania Rating Scale, and the Clinical Global Impressions scale after treatment with clozapine [6]. Similarly, there have been other studies that show clozapine's effectiveness in treating refractory affective illness [7, 8]. Correspondingly, Miss L responded well after the augmentation with clozapine together with her existing medications of lithium and sodium valproate. Clozapine was gradually titrated to a total dose of 300 milligrams per day and within 3 weeks of starting clozapine. Miss L was discharged well from our psychiatric ward.

A recent study has found that rapid titration of clozapine is safe and is associated with a shorter hospital stay as compared to slow titration in the treatment of refractory bipolar disorder [9]. We, however, employed the slow titration method for Miss L as a more cautious approach. To date, the management of treatment resistant bipolar disorder remains a challenge. As mentioned earlier, the effectiveness of clozapine in treating Miss L was consistent with the findings of current literature. Thus, it is worthwhile to consider the use of clozapine as a treatment modality in resistant cases. It is with much hope that further studies will be done in this area so that better understanding can be obtained, and this will assist clinicians in better managing patients with treatment resistant mania.

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