Chlorpromazine as Prophylaxis for Bipolar Disorder with Treatment- and Electroconvulsive Therapy-Refractory Mania: Old Horse, New Trick

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ABSTRACT

A 22-year-old male diagnosed with bipolar affective disorder presented to us with a 3rd episode mania resistant to both olanzapine and haloperidol as well as electroconvulsive therapy. He, however, responded to chlorpromazine (CPZ) which was also effective as a mood stabilizer. The patient had a relapse of his illness when CPZ was stopped and responded again when it was started. The case demonstrates that CPZ may have a role in both an anti-manic agent and for the maintenance for bipolar disorders. The possible underlying mechanism for this role is also discussed.

Key words: Bipolar disorder, chlorpromazine, electroconvulsive therapy-resistant mania, mood stabilizer, treatment-resistant mania

INTRODUCTION

In addition to lithium and valproate, certain second-generation antipsychotic agents have prophylactic properties in bipolar disorder (BD).

However, a small, yet significant number of patients fail to respond to the first-line therapies, warranting the need to have diverse therapeutic options to choose from, especially for the management of refractory cases of BD. Clozapine is one useful option for acute control and long-term therapy but requires frequent blood monitoring.

Chlorpromazine (CPZ) is a first-generation antipsychotic (FGA) drug with a unique pharmacological profile among other FGAs. CPZ with respect to its greater effect at serotonin receptors than at D2 receptors is more similar to the atypical antipsychotics than to other typical antipsychotics.

There is absence of literature on the use of CPZ for prophylaxis of BD. Only a few small-scale studies exist on its use in BD, those too are limited to acute...
symptomatic control only. A PubMed/Medline search using terms “chlorpromazine” and “treatment resistant mania” or “ECT resistant mania” and “Chlorpromazine” and “mood stabilizer” did not identify any reports of CPZ used as an anti-manic agent and in long-term prophylaxis in treatment-resistant cases.

We report a case (under active follow-up for 1.5 years) of multiple drug-resistant and electroconvulsive therapy (ECT)-resistant manic episode, who remitted with CPZ, and relapsed after an attempt to take off CPZ from his regimen after 8 months of sustained remission.

CASE REPORT

The patient is a 22-year-old unmarried male, with the International Classification of Diseases-10 diagnosis of bipolar affective disorder (F31.7), who was the first admitted to the psychiatry ward, Department of Psychiatry, AIIMS, New Delhi, in September 2014 with an abrupt-onset manic episode of 2 weeks duration. In the past, he had two similar episodes at the age of 11 and 20 years (in the years 2004 and 2013 respectively) lasting for 3–6 months each time. There was no history of any depressive episode. His 2nd manic episode was treated with lithium 900 mg/day, which he continued regularly. After a year, he had a breakthrough episode, after which he was initiated on sodium valproate (1500 mg/day, serum levels - 95 mg/ml). In addition, tablet olanzapine (up to 30 mg/day) and clonazepam (6 mg/day) showed no significant response over next 4 weeks, after which tablet haloperidol (20 mg) was added for another 4 weeks with no symptom control. Eltroxin (25 µg) was added after a repeat thyroid function test showed marginally increased thyroid-stimulating hormone, with normal T3 and T4. Since the patient had failed to respond and difficult to manage on two antipsychotics in addition to valproate, after informed consent from family, he was taken up for modified ECT (MECT) for a total of 16 effective sessions (twice per week) with no clinically significant improvement. Clozapine was considered but was refused by family members reluctant of regular ECT. He continued regularly. After a year, he had a breakthrough episode was treated with lithium 900 mg/day, which he continued regularly. After a readmission, after which patient had clinical remission again over 3 weeks. Currently, the patient is in active outpatient follow-up with CPZ continuing in his treatment regimen. He is currently tolerating the medications well, compliant, and asymptomatic.

DISCUSSION

The case we report here is, to the best of our knowledge, the first report of CPZ as an anti-manic agent for achieving as well as sustaining a remission in a case with drug and ECT-resistant mania.

CPZ is on the WHO list of essential medications. Among FGAs, CPZ is associated with relatively less extrapyramidal effects compared to higher-potency drugs such as haloperidol. A recent systematic review and meta-analysis concluded that, with conservative dosing, the incidence of such effects for CPZ may be comparable to newer atypical agents such as risperidone.

Lithium, valproate, carbamazepine, and atypical antipsychotics are preferred as first-line options for control of acute mania as well as prophylaxis. Among antipsychotics, olanzapine, and aripiprazole are the only approved agents for acute and long-term use in BD. For treatment-resistant mania, MECT remains an effective choice, in addition to medications. This patient had failed all the above usually recommended pharmacological options in addition to MECT.

His initial response to CPZ, continued/sustained remission on CPZ, relapse after CPZ was taken off and response to reinstitution of CPZ points to the observation that CPZ was the effective agent in both terminating the acute episode as well as continuing to act as a prophylactic agent. Current research indicates a follow-up period of at least 6 months to call a drug effective for “maintenance.”

The mechanism for the mood-stabilizing properties of atypical antipsychotics is largely unknown with serotonin 5-HT2a receptor antagonism in addition to a dopamine D2 antagonism being implicated. Usually, the FGAs are not thought to possess 5-HT2a antagonism. In vitro, CPZ too has 5-HT2a antagonism though it lacks in vivo evidence and its receptor binding properties are similar to second-generation antipsychotics. Although CPZ and its metabolites had lesser 5HT2a antagonism than second-generation antipsychotics, it was more than haloperidol, the other antipsychotic in the study. It is possible that at adequate
doses CPZ might possess significant 5HT2a antagonism which would imply mood-stabilizing properties. There is some earlier evidence that FGAs may possess some prophylactic properties in BD.\footnote{15} While the adverse effect profile of CPZ does limit its wider or long-term usage in BD in otherwise treatment responsive cases; however, this case of treatment refractory BD might be a scenario where the use of CPZ led to sustained remission and improved quality of life, and therefore is being continued in this particular patient for nearly 2 years now.

In conclusion, the addition of CPZ to treatment regimen was successful for acute control as well as long-term treatment of extremely severe/refractory case of bipolar mania. Given its low cost and easy availability, it may be considered by the treating clinician, especially in resource-limited countries.

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Conflicts of interest
There are no conflicts of interest.

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