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Effectiveness of ultra-rapid dose titration of clozapine for treatment-resistant bipolar mania: case series

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***Abstract*:** Treatment of severe and refractory manic episodes in hospital settings can occasionally be very difficult. In particular, severely excited patients showing aggressive, hostile, impulsive behaviours frequently require physical restraint and seclusion, high doses of antipsychotics and benzodiazepines, and sometimes, electroconvulsive therapy. Hospital stay is generally prolonged and such patients cause great emotional distress for other patients in the ward and clinical staff involved in their care.

Here we report on three patients with a diagnosis of bipolar disorder and one patient with a diagnosis of schizoaffective disorder bipolar subtype, all of whom were hospitalized for severe manic episodes with psychotic features. These patients were extremely difficult to manage in the ward as no response could be obtained in the first week of treatment despite high doses of antipsychotics and benzodiazepine administration. The introduction and rapid titration of clozapine proved remarkably effective and was well tolerated in the acute management of these patients. We observed that clozapine had a superior and fast mood stabilization effect with rapid titration and could be extremely helpful in the management of such patients.

Keywords: clozapine, rapid titration, bipolar disorder, mania

Introduction

Clozapine's superior efficacy over other antipsychotics has been confirmed in previous studies in schizophrenia [Wahlbeck *et al.* 1999]. A growing number of reports show that it has proved to be useful in the treatment of mood disorders with psychotic features [Lindstrom, 1988, McElroy *et al.* 1991, Banov *et al.* 1994] and particularly treatment-resistant bipolar disorder (BD) [Li *et al.* 2015]. Use of clozapine for affective BD was found to be significantly associated with a reduction in psychiatric admissions, psychotropic comedications, and hospital contact for selfharm/overdose [Nielsen *et al.* 2012], which suggests that clozapine has strong mood-stabilizing properties.

Clozapine administration is usually started in hospital settings. Clinical guidelines recommend slow clozapine dose titration, generally starting with 12.5–25 mg/day, gradually increasing the dose by 25 mg within a week, and 25–50 mg thereafter in a 2–3-week period until the target dose is achieved [Safferman *et al.* 1991], particularly for decreasing the risk of seizures and hypotension. Hypotension and sedation are both dose dependent and may vary greatly among individuals. In addition, seizures are more common during the initiation period of clozapine treatment when doses are gradually increased [Sajatovic and Meltzer, 1996]. However, the long clozapine titration period could delay the adequate control of symptoms and prolong the duration of hospital stay [Ifteni *et al.* 2014a]. In a recent study, Ifteni and colleagues have shown that rapid clozapine titration was effective and safe in patients with schizophrenia [Ifteni *et al.* 2014b]. Recently they compared rapid with standard titration in patients with treatment-refractory BD and found that rapid clozapine titration was equally safe and effective for this condition [Ifteni *et al.* 2014a]. However, the mechanism of action of efficacy remains unclear.

We report here ultra-rapid titration of clozapine in four patients with treatment-refractory mania with psychotic features. These case histories support the findings of Ifteni and colleagues [Ifteni

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et al. 2014a] and suggest that rapid titration of clozapine may be safe, provide adequate and rapid control of symptoms, and shorten the duration of hospital stay. We also present some potential mechanisms of action which may be unique to the effects of clozapine on abnormal neurochemistry during a manic-psychotic episode in patients with BD.

Case 1

A 20-year-old boy was hospitalized for BD [diagnosed using the International Classification of Diseases (ICD-10) criteria] [WHO, 1992], acute manic episodes displaying symptoms of elevated mood, psychomotor agitation, increased restlessness, grandiose delusions, and logorrheic and pressured speech. His first affective episode in 2012 was hypomania when he was under chemotherapy for embryonal testicular carcinoma. This was followed by a depressive episode with psychotic features, which required his first hospitalization. He had been stable for 9 months on olanzapine 15 mg/daily, venlafaxine 150 mg/daily after being discharged. Then he had a manic episode during which he had two other hospitalizations in 1-month intervals without complete remission. During that episode, he had received 11 sessions of electroconvulsive therapy (ECT) and was discharged on 4 mg of risperidone, 200 mg of quetiapine, 6 mg of biperiden, and 1500 mg of valproate daily. One week after being discharged he was still extremely hyperactive; he was found by the police while running until he was exhausted. He was then immediately hospitalized. The manic symptoms did not subside for several months despite many antipsychotic treatments, including valproate. Valproate blood levels were 102–110 mg/liter during that time. Since he was still very agitated, clozapine was introduced on the first day, at a dose of 50 mg in the morning and 100 mg in the evening (total of 150 mg), after obtaining informed written consent from his family. On the second day, the dose was increased by 50 mg/day and clozapine was titrated to 350 mg in 5 days. Mania started to resolve quickly during the first few days of clozapine treatment. On the 11th day of hospitalization, clozapine was reduced gradually because of excessive sedation. He was discharged after 26 days in a euthymic state, on daily doses of clozapine 100 mg, aripiprazole 10 mg, and valproic acid 1000 mg. No serious side effects were observed during rapid titration of clozapine, except sedation, which was desired at the beginning of his hospitalization.

Case 2

A 23-year-old girl was hospitalized with the diagnosis of BD (diagnosis using ICD-10 criteria) and acute manic episodes. She had her first manic episode 4 years ago which required prolonged hospitalization. The episode was extremely severe as reported by her family. Since then, she was on lithium 900 mg/day (lithium levels were between 0.6 and 0.8 mEq/liter) and stable except for two short periods of hypomania. In 2013, she stopped her outpatient visits but continued to take lithium until 2 months ago. In November 2014, she was admitted to our inpatient clinic in a state of confusion. We found out that she had been off medication for 3 months and had a depressive episode immediately before her manic symptoms appeared. In her inpatient follow up, her mood was unrestrained, easily transitioning to irritability, and even weeping. She showed physical and verbal aggressive behaviour and was so severely excitable that she injured other patients in the ward. The same evening we started treatment with 20 mg of olanzapine. The same evening she hit another patient and was physically restrained. On the second day, she expressed religious delusions such as the imminent arrival of the Judgement Day. The next day the treatment was changed to injection of haloperidol 30 mg/day. Despite a 45 mg haloperidol injection on the third day, manic excitement was difficult to control; she was standing erect on her bed and saluting in religious fashion, and could not sit or lie for long. Upon obtaining informed written consent from her family on the fourth day, two doses of clozapine were administered (50 mg two times daily; 100 mg/day total dose) in addition to a 30 mg haloperidol injection. On the next day, haloperidol was discontinued and clozapine was increased by 50 mg, given three times daily. There was a significant recovery in her mental state on the first day we introduced clozapine. Her psychomotor agitation was noticeably reduced and her extremely rapid and loud talkativeness was alleviated within the first few days of clozapine treatment. At the end of the first week religious delusions gradually disappeared. During her inpatient follow up, lithium was added on the 11th day and titrated to 1200 mg/day in 6 days and clozapine was increased to 250 mg/day in 6 days. After 18 days of hospitalization, there was complete resolution of her affective symptoms and she was free from any side effects on her discharge. In her outpatient visit after 2 weeks of discharge she did not display any symptoms related to mood disturbance. However, she complained of hypersalivation and so clozapine was decreased to 150

mg/day and lithium 1200 mg/day (blood level was 0.8 mEq/liter) was continued.

Case 3

A 19-year-old boy was hospitalized with the diagnosis of acute manic episodes with psychotic features. Diagnosis of BD was based on ICD-10 criteria. The patient's need for sleep was lessened, he displayed increased psychomotor activity and restlessness, the flight of idea and pressure of speech were very marked, and grandiose delusions such as the belief of being a 'messiah' were observed. The patient was administered intramuscular injections of haloperidol 30 mg, biperiden 10 mg, 50 mg chlorpromazine, in two equal doses per day. Starting on the first day, the need for seclusion and frequent physical restraint were indispensable for the patient. He was extremely hyperactive and his mood easily fluctuated to irritability. During the first 7 days, the injection of haloperidol 30–45 mg/day was continued and biperiden 10 mg/day and chlorpromazine 50 mg/day were administered. Despite this treatment he was still severely excitable. The patient's family rejected ECT. Clozapine was initiated on the eighth day. Along with 30 mg/day haloperidol, clozapine was started at 50 mg followed by 50 mg as needed every 6 h (maximum 150 mg/day) on day 1, followed by increases of 50 mg/day. On the ninth day clozapine was increased to 200 and on the 12th day to 250 mg/day. Beginning on the first day, the patient was markedly sedated. There was no need for isolation and physical restraint after we introduced clozapine. On the third day of clozapine treatment, psychomotor activity decreased substantially. After 3 days of 250 mg clozapine, the total dose was increased to 300 mg/day. By this augmentation, elevated mood of the patient started to disappear. During treatment with clozapine, no serious side effects were observed. Apart from the sedation, which was desired during the treatment, hypersalivation disturbed the patient. After a 28-day period of hospitalization, on the 21st day of clozapine treatment, the patient was discharged in a euthymic mood with no psychotic symptoms.

Case 4

A 31-year-old man was hospitalized with the diagnosis of schizoaffective disorder, bipolar subtype (ICD-10). The mood disorder had begun 10 years previously and then he had a manic episode every year. In 2011, he had his first hospitalization with the diagnosis of BD, manic episode with psychotic features. Subsequently his mood disorder converted to schizoaffective disorder, bipolar subtype. He was hospitalized again in September 2013 with dysphoric mania with psychotic features; he had predominantly religious, paranoid, and grandiose delusions.

In his inpatient follow up, aripiprazole up to 30 mg/day, quetiapine 900 mg/day, and valproic acid 2000 mg/day were initiated in the first week. His mood was extremely elevated and he had severe excitations. To treat this patient, zuclopenthixol acuphase injection (50 mg/day) was administered three times every other day along with clonazepam 4 mg/day. He required frequent seclusion, physical restraint, or adjunctive intramuscular injections of haloperidol (20–30 mg/day) because of his physical aggression towards other patients and nurses. On the ninth day, valproic acid was discontinued and with the consent of his family ECT was started twice a week. After eight sessions of ECT, we introduced valproic acid 2000 mg/day (valproate levels were 115 mg/liter) again. There was no noticeable improvement in his mental state after 52 days of hospitalization, he was still extremely irritable and frequently hit or attacked staff/nurses. With the consent of his family, clozapine was introduced on the 52nd day, 50 mg followed by 50 mg as needed every 6 h (maximum 150 mg/day) on day 1, followed by increases of 50–100 mg/day and titrated to 400 mg in 4 days. There was no need for isolation and physical restraint after we introduced clozapine. No serious side effects were observed and he began cooperating with the medical team. His psychomotor agitation was noticeably reduced on the first day of clozapine administration, without extreme sedation. After 65 days of hospitalization and 13 days after we introduced clozapine 400 mg/day with quetiapine 600 mg/day he was discharged in a euthymic mood with no psychotic symptoms.

Discussion

Our observations in the cases reported here suggest that a rapid titration-dosing regimen of clozapine might be an option for hospitalized treatment-refractory patients having severe manic episodes with psychotic features. Our observations suggest the effectiveness of clozapine in refractory BD and support previous work in which rapid titration of clozapine was shown to achieve rapid symptom control and shorten the duration of hospital stay

without causing significant side effects in patients with refractory BD [Ifteni *et al.* 2014a].

Rapid titration was safe in our cases, as none of the patients developed life-threatening adverse effects such as neutropenia, symptoms suggestive of myocarditis, neuroleptic malignant syndrome, or delirium. Clozapine has a side-effect profile that is a cause for concern. In addition, significant variations were observed in plasma levels with any given dose, both between individuals (8–45-fold difference) and within each individual (18–53% variance) [Stark and Scott, 2012] which may complicate the prediction of the severity of side effects. The potential for an increased risk of orthostatic hypotension and seizures during rapid titration [Lee *et al.* 2003, Oyewumi *et al.* 2004] should certainly be considered for each patient. Schulte and colleagues have reported several patients with schizophrenia who did not tolerate clozapine despite the usual, prudent titration scheme; they observed severe orthostatic hypotension, collapse, sedation, and dizziness at the first days of treatment (with doses of 6.25—25 mg) [Schulte *et al.* 2014]. In addition, another report described a case with extreme sedation despite very low doses (6.25 mg/day) and very slow titration of clozapine which was not tolerated, suggesting that sedation, although usually regarded as a manageable side effect, may not be manageable in some cases [Rosenman, 2013].

The majority of case studies report clozapine-induced seizures in patients taking doses greater than 600 mg a day [Baker and Conley, 1991, Karper *et al.* 1992]; however a definite relationship between dose and occurrence of seizures was not found in a systematic review [Varma *et al.* 2011]. As seizures are more common during the initiation phase [Devinsky *et al.* 1991; Pacia and Devinsky, 1994] slow titration is recommended [Varma *et al.* 2011]. Nevertheless, the benefits of rapid clozapine titration should be balanced against the increased risk for seizures, and in patients who display other pre-existing seizure disorders or relevant neurological abnormalities, slow clozapine dose titration should be preferred.

Among the life-threatening side effects of clozapine, a relationship between a faster upward titration and the incidence of clozapine-induced myocarditis [Ronaldson *et al.* 2012] was described in a previous report. However, myocarditis is not considered a dose-dependent condition, as it has been observed in different dose ranges such as 100–450 mg/day [Haas *et al.* 2007] and 50–750 mg/day [Merrill *et al.* 2005].

Pharmacological or nonpharmacological interventions that positively influence seclusion or restraint are likely to have a major role in the treatment of patients with psychiatric disorders. Studies have reported that seclusion and restraint fell by more than 90% and 80%, respectively, among inpatients in state hospitals following clozapine initiation [Mallya *et al.* 1992; Chengappa *et al.* 2002]. A recent systematic review concluded that clozapine has 'specific' antiaggressive effects, to some extent, greater than both its more general antipsychotic and sedative effects [Frogley *et al.* 2012]. Clozapine may exert its antiaggressive effects through a number of pathways [Volavka and Citrome, 2008]. Although initial titration-related sedation may affect the acute reduction of aggression, in our patients despite no severe sedation, we obtained adequate controls of manic symptoms in the rapid titration. Therefore, the rapid mood-stabilizing effect of clozapine might be connected with its antiaggressive effect. In addition, the antiaggressive benefits of clozapine continue to occur for months after the titration phase [Chengappa *et al.* 2002].

As stated by Ifteni and colleagues [Ifteni *et al.* 2014a], we also believe that the titration rate of clozapine should be determined according to the patient's needs during acute management. We recommend rapid titration of clozapine, after an initial test dose of 25 mg, if this is well tolerated, especially in young patients in whom adequate control of symptoms is urgent. The rapid titration scheme may be indicated particularly for inpatients having severely agitated mania with psychotic symptoms requiring physical restraints and seclusion, with no response to high doses of antipsychotics generally given in parenteral form or ECT within the first weeks of treatment. We also suggest further controlled clinical trials to confirm our preliminary observations.

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here are preserved in the archives of the inpatient unit of Cerrahpaşa Medical School, Department of Psychiatry.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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