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Long acting paliperidone injection in patient with bipolar affective disorder, current episode manic with psychotic symptoms: A case report

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Abstract---*Bipolar Disorder is a chronic mental illness characterized by periods of mania, depression, and mixed episodes that often need lifelong medication. The first line of pharmacotherapy includes lithium, valproate, or second-generation antipsychotics. Paliperidone is a medication that works in the brain and is also known as a second-generation antipsychotic. Paliperidone is available as an oral extended-release tablet and a once-monthly extended-release suspension for intramuscular injection. Long-acting injectables (LAIs) are used to reduce the non-adherence of oral medication. Paliperidone is one of the LAI that could be used to treat manic, hypomanic, and mixed episodes in patients with bipolar disorder. Paliperidone LAI reduces the number of relapses, hospitalization, and length of stay. As reported in this case, a patient with a manic episode who received paliperidone LAI showed favourable results after a week-long observation with no signs of extrapyramidal symptoms.*

Keywords---*bipolar disorder, long-acting injectable, manic episode, paliperidone, second-generation antipsychotics.*

Introduction

Bipolar disorder (BD) is a chronic, episodic mental illness characterized by periods of mania, depression, and mixed episodes with an estimated lifetime prevalence of BD-I was 0.6%, BD-II 0.4%, subthreshold BD 1.4%, and bipolar spectrum 2.4% (Rowland & Marwaha, 2018). According to the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition, text revision (DSM 5), patients presenting with a manic episode must have an abnormally and persistently elevated or expansive mood for 1 week, or any duration if the patient is hospitalized (Chakrabarti, 2022; Sugiharta et al., 2022).

The first line of treatment for bipolar disorder is the use of pharmacotherapy. The first line of pharmacotherapy includes lithium, valproate, or second-generation antipsychotics. A meta-analysis conducted by Cipriani et al. (2011), proved that the use of second-generation antipsychotics is equally, if not more, effective than mood stabilizers for the treatment of mania.

Paliperidone is a medication that works in the brain to treat schizophrenia and schizoaffective disorder. It is also known as a second-generation antipsychotic (SGA) or atypical antipsychotic (American Association of Psychiatric Pharmacists (AAPP)). Chemically, paliperidone is the primary active metabolite of the antipsychotic risperidone (paliperidone is 9-hydroxy risperidone). The mechanism of action has not been fully elucidated but may involve antagonism of central dopamine type 2 (D2) and serotonin type 2 (5-hydroxytryptamine [5-HT_{2A}]) receptors (American Society of Health-System Pharmacists). Essentially medications

with properties of D2 antagonist/partial agonist are effective in the treatment of acute bipolar mania and in preventing recurrences of mania. Some drugs are better studied than others, and the therapeutic effects in acute bipolar mania are present whether the mania is psychotic or nonpsychotic (Stahl & Stahl, 2000).

Paliperidone is available as an oral extended-release tablet and a once-monthly extended-release suspension for intramuscular injection (National Center for Biotechnology Information). In 2009, *Paliperidone palmitate* (Invega sustenna®) was introduced as the first nanocrystal injection product. Because of extremely low water solubility, paliperidone esters such as paliperidone palmitate dissolve slowly after an intramuscular injection before being hydrolyzed to paliperidone and made available in the systemic circulation (Riebesehl, 2015).

The use of long-acting paliperidone injection is used to prevent non-compliance with medication usage and to minimise the number of medications in patients with bipolar disorder that often need lifelong treatment. In this paper, we report a case of long-acting paliperidone injection as a therapy for a patient with a current manic episode of Bipolar Affective Disorder with Psychotic Symptoms (Duffy et al., 2010; Quraishi & Frangou, 2002).

Case Report

A 26-year-old International tourist, female, was brought by her sister and brother-in-law to the clinic with agitation, talking irrelevantly, and non-compliance to commands since one day ago. The patient was taken by her family one day ago due to her conflict with the local citizen in Ubud. The patient was reported by the citizen and her video was taken and shared on social media which showed that she had a mental illness. During the interview at the clinic, the patient displayed hostility towards medical staff, was not cooperative and talked in a high tone. The initial assessment of the patient showed irritable mood, inappropriate affect, grandiose delusion, and elevated psychomotor.

The initial treatment for the patient was mood stabilizer 200mg lithium twice a day and combined with second-generation anti-psychotic 100mg quetiapine twice a day. Due to elevated aggression, the patient was given 10mg olanzapine and 10mg diazepam injections with a higher dose of lithium 200mg in the morning, 400mg in the evening and 200mg quetiapine twice a day. After a few days, no significant changes were observed in the patient thus the quetiapine dose was raised to 300mg twice a day and lithium to 400mg twice a day.

Three weeks after being admitted to the clinic, the patient could be more cooperative even though the mood was still unstable. The patient started to consume a 6mg paliperidone tablet for a few days as a preparation for the long-acting paliperidone injection. After being given 6mg of paliperidone tablet, the patient displayed a more stabilized mood. A week after the oral paliperidone, patients were given a 150mg long-acting paliperidone injection intramuscularly followed by a 100mg injection a week later. After the long-acting injection, the patient's condition was observed every day and improved significantly. The patient showed no hostility toward medical staff, was cooperative, had no delusion, and slightly elevated psychomotor. The patient also showed no signs of extrapyramidal symptoms (Zuddas et al., 2011; Fraguas et al., 2011).

Discussion

An important determinant of the clinical course in bipolar disorder is adherence or non-adherence to medications, estimated at 10–60 % in these patients even during their euthymic periods (Keramatian et al., 2019). Non-adherence to mood stabilizers and antipsychotics in the treatment of bipolar disorder increases the risk of suicide, relapse, and rehospitalization (Gentile, 2018). An alternative to reduce the non-adherence of oral medication is the usage of long-acting injectable (LAI) antipsychotics.

The use of LAI in a patient with bipolar disorder is widely used while the support for their use is rather limited. Second-generation antipsychotics (SGAs) are more common compared to first-generation antipsychotics (FGAs) in treating bipolar disorder (Misawa et al., 2016; Li et al., 2011). Studies for FGA long-acting injection usage in Bipolar Disorder are scarcely limited to open trials, case series and retrospective analyses. A study conducted with flupenxitol LAI showed neither effect nor superiority over lithium.¹⁵ Haloperidol LAI and fluphenazine LAI increase the risk of depressive episodes when the usage of lithium had been stopped before the LAI started (Gigante et al., 2012).

In a randomized controlled trial by Vieta et al. (2012), risperidone LAI is effective either as a sole treatment or as an adjunct to treat manic, hypomanic and manic-mixed episodes but does not affect depressive episodes ((Taylor et al., 2021). Another SGA, Paliperidone LAI has similar effects to risperidone LAI. The oral form of paliperidone is used to prevent manic relapse in bipolar disorder, while the LAI form of paliperidone according to case series by Buoli et al. (2015), also showed good outcomes in preventing manic relapse. However, there were no controlled studies that compared FGAs and SGAs LAI.

Paliperidone LAI leads to significantly fewer extrapyramidal symptoms than older-generation antipsychotics (Schreiner et al., 2015). Compared to oral SGAs, Paliperidone LAI showed a similar safety profile as oral SGAs, but with greater incidence of mild injection-site pain. A novel 3-monthly formulation of Paliperidone LAI has shown similar safety and efficacy as once-monthly Paliperidone LAI compared to placebo. This LAI may be most effective in patients with prior failed treatment of oral antipsychotics or other LAIs (Morris & Tarpada, 2017).

Paliperidone LAI reduced the number of medication non-compliance, relapse, number of hospital readmissions and length of inpatient stay by decreasing the number of manic and mixed episodes, thereby having a positive effect on the course of the disease. Paliperidone LAI as an adjunctive in patients with bipolar disorder are beneficial, safe, and could help in improving the prognosis of bipolar disorder (Caliskan et al., 2020).

Conclusion

The use of LAI in a patient with bipolar disorder is widely used while the support for their use is rather limited. Second-generation antipsychotics (SGAs) are more common compared to first-generation antipsychotics (FGAs) in treating bipolar disorder. In this case report, a patient with bipolar affective disorder, current episode manic with psychotic symptoms that received SGA paliperidone LAI showed favourable results (patient showed no hostility toward medical staff, cooperative, no delusion, and slightly elevated psychomotor) with no signs of extrapyramidal symptoms after a week-long observation. However, further controlled research for paliperidone action and efficacy on patients with secondary mental illness, different age groups and genders might be needed to make a definitive recommendation.

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Abbreviation :

- BD : Bipolar Disorder
 FGA : First Generation Antipsychotic
 SGA : Second Generation Antipsychotic
 LAI : Long-Acting Injectable