Two-injection start regimen of long-acting aripiprazole in three patients treated with bipolar affective disorder manic episodes: Review with case reports

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SUMMARY

Long-acting aripiprazole is used in the acute treatment of bipolar affective disorder (BAD) and schizophrenia as well as in maintenance treatment. There are few data on the use of long-acting aripiprazole initial double dose in BAD. Factors such as frequent hospitalizations, recurrent attacks, aggression, comorbid substance use, lack of insight, and poor medication compliance are influental in the choice of long-acting antipsychotics. Aripiprazole initial double dose may be a safe and effective option in patients with BAD. In this study, we will present 3 cases who were involuntarily hospitalized with BAD manic episode and treated with long-acting aripiprazole two-injection start regimen and review the literature on this subject.

Key words: Aripiprazole, bipolar affective disorder, long-acting injection, mania

INTRODUCTION

Aripiprazole is a third-generation antipsychotic with antagonist activity at serotonin 5-HT2A receptors and partial agonist activity at dopamine D2 and serotonin 5-HT1A receptors (1). The aripiprazole long-acting injection (LAI) has been approved by the European Medicines Agency (EMA) for the treatment of schizophrenia and manic episodes associated with bipolar affective disorder (BAD) in adults at a dose of 400 mg once a month (2). Aripiprazole is the first D2 receptor partial agonist with a long-acting form for the maintenance treatment of schizophrenia and BAD (3). In the initial administration of aripiprazole with a once monthly injection, it is recommended to take 10-20 mg oral aripiprazole concomitantly with the injection for 14 days to maintain therapeutic aripiprazole concentrations (4). The EMA recently approved an initial strategy of oral 20 mg aripiprazole followed by two-injection start (TIS) regimen aripiprazole LAI at separate gluteal and/or deltoid injection sites on the same day (5). With this simplified strategy, aripiprazole has been shown to reach therapeutic plasma concentrations on the first day of treatment, support consistent clinical efficacy throughout the dosing interval, have a safe and tolerable profile, and eliminate the need for 14-day oral tablet supplementation (5). This new starting option is thought to prevent compliance problems that may occur during treatment in patients (5). It has been shown that the aripiprazole LAI is more effective than the LAI forms of haloperidol and risperidone in patients with schizophrenia and BAD, delays the relapse period, and reduces relapse rates and hospitalizations (6). In patients who experience relapses related to treatment compliance or who have an inadequate response to treatment, it is thought that starting treatment with the aripiprazole TIS regimen will reduce relapses that may occur at the beginning of treatment, the length of hospital stay, and the burden of caregivers to control oral ari-piprazole intake (5). In a study conducted in Italy with 133 schizophrenia patients, it was found that the aripiprazole TIS regimen did not cause serious side effects in patients, was tolerable and safe, and the side effects were similar to those observed with a single injection (7). In a study conducted in Spain with schizophrenia patients, it was shown that patients were hospitalized largely due to non-compliance with treatment, and that the aripiprazole TIS regimen shortened the average

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length of stay and reduced the use of concomitant medications (8). In a systematic review of the use of LAI antipsychotics in BAD, second-generation LAI antipsychotics were shown to be effective in treating manic symptoms and preventing the recurrence of mood attacks (9). In the same study, multicenter randomized controlled studies using the same sample produced by Calabrese et al. on the use of aripiprazole LAI in BAD were mentioned in the literature (9). Calabrese et al. found that aripiprazole LAI therapy was safe and tolerable in the treatment of BAD maintenance period (10). In addition to limited information on the use of aripiprazole LAI in BAD, there is a single case report on the aripiprazole TIS regimen (11). In this case report, three patients with BAD who were treated with the aripiprazole regimen will be presented and the literature on this subject will be reviewed. The case report statement, checklist and guidelines were followed in the preparation of the case report (12).

Case presentations

Case 1: A 44-year-old male patient was admitted to the psychiatric ward with a decision for compulsory medical treatment, following his family's application. He presented with symptoms such as restlessness, insomnia, irritability, delusions of being a prophet, touchiness, taking out large amounts of credit, spending money, and unruliness. Diagnosed with BAD with a manic episode at the age of 39, the patient had received inpatient treatment only for his first episode in his five-year illness history. The patient also had diagnoses of cannabis use disorder and obesity accompanying BAD. Substance analysis performed on the day of hospitalization revealed positive cannabis. On the first day of hospitalization, the patient experienced psychomotor agitation and was administered benzodiazepine and intramuscular haloperidol. On the second day of hospitalization, valproate and 20 mg oral aripiprazole were initiated, and the aripiprazole TIS regimen was applied to two different gluteal regions on the same day. During follow-up, the patient exhibited a good safety and tolerability profile, with no akathisia or metabolic side effects observed. Throughout his stay in the ward, he demonstrated clinically increased insight, decreased irritability and exuberance, decreased substance cravings, and an overall improvement in functioning. The level of improvement was observed in the clinical scale scores. On the 32nd day of treatment, the patient was discharged with a LAI maintenance dose.

Case 2: A 42-year-old female patient presented with symptoms including euphoria, insomnia, restlessness, the initiation of numerous new projects, and rapid, pressured speech. Following a family application, she was admitted to the psychiatric ward under a compulsory medical treatment order. Her 12-year history revealed four depressive and two manic episodes. It was noted that these episodes typically occurred within three months of discontinuing her prescribed medications, resulting in three hospitalizations. She had no history of comorbid medical conditions. Her treatment history included various typical and atypical antipsychotics and mood stabilizers, but she had not previously received LAI antipsychotic treatment. Treatment was initiated with oral lithium 600 mg and aripiprazole 20 mg, and the aripiprazole regimen was administered via two separate deltoid injections. No significant adverse effects were observed during follow-up. During treatment, a reduction in psychomotor agitation and an increase in sleep duration were noted. A maintenance dose of aripiprazole LAI was administered within the first month of treatment. The patient, who demonstrated improved insight into her condition and enhanced functionality, was discharged on the 34th day of treatment.

Case 3: A 47-year-old female patient was admitted to the psychiatric ward under a compulsory medical treatment order following judicial proceedings. She presented with symptoms including increased libido and pressured speech, insomnia, excessive wandering, heightened energy, and extreme irritability. Her 17-year history included five manic and three depressive episodes, with six total hospitalizations, all of which were involuntary and preceded by medication discontinuation. Her past medical history revealed the use of various combinations of typical and atypical antipsychotics and mood stabilizers, such as haloperidol, zuclopenthixol, risperidone, olanzapine, and quetiapine. She had previously undergone dialysis for lithium intoxication. She had received all available

Table 1.

		Initation day of TIS regimen	1 week later	2 week later	3 week later	4 week later
Case 1	YMRS	31	22	13	10	5
	PANSS	72	52	43	35	33
	CGI-S	10	8	6	5	3
	BARS	2	1	0	0	0
	SAS	2	1	1	1	1
Case 2	YMRS	30	21	12	7	3
	PANSS	56	44	37	34	31
	CGI-S	10	9	6	4	2
	BARS	0	0	0	0	0
	SAS	1	1	1	0	0
Case 3	YMRS	33	17	8	4	2
	PANSS	78	58	40	32	30
	CGI-S	12	8	3	3	2
	BARS	3	1	0	0	0
	SAS	0	0	0	0	0

YMRS:Young mania rating scale, PANSS:Positive and negative syndrome scale, CGI:Clinical global impressions, BARS:Barnes akathisia scale, SAS:Simpson-angus scale

LAI treatments except aripiprazole LAI. Oral aripiprazole 20 mg, quetiapine 200 mg, and lorazepam 2 mg were initiated. On the same day, the aripiprazole TIS regimen was administered via bilateral gluteal injections. No adverse effects were observed during follow-up. The patient's sleep and libido normalized, her speech became less pressured, and her daily functioning improved. Sleep and restlessness symptoms subsided, and quetiapine and lorazepam were gradually tapered and discontinued after the second week of treatment. The Young Mania Rating Scale score, which was 33 at baseline, decreased to 8 by the second week. A maintenance dose of aripiprazole LAI was administered within the first month. The patient was discharged in remission on the 32nd day of treatment.

Patients' clinical symptoms were evaluated during hospitalization and follow-up using the Young Mania Rating Scale (YMRS), Clinical Global Impressions (CGI), and Positive and Negative Symptom Scale (PANSS) (13-15). The safety profile was assessed using the Barnes Akathisia Rating Scale (BARS) and the Simpson-Angus Scale (SAS) (16, 17). The YMRS measures the severity of manic states, with scores ranging from 0 to 60. The PANSS evaluates psychotic symptoms and patient functionality over the past week, with scores ranging from 30 to 210. The CGI is a three-dimensional scale designed to allow clinicians to record their impressions of patient functionality before and after treatment initiation. The scale's first dimension assesses disease severity, the second evaluates recovery, and the third assesses drug side effect severity. In this study, the first two dimensions, CGI-S, were used. The BARS assesses akathisia resulting from antipsychotic use, with scores ranging from 0 to 13. The SAS aims to identify extrapyramidal symptoms resulting from antipsychotic use, with scores ranging from 0 to 40. The scores from the scales administered before and during the four-week clinical follow-up prior to the aripiprazole TIS regimen are presented in Table 1.

DISCUSSION

As with many chronic diseases characterized by intermittent symptoms, medication non-adherence is frequently observed in BAD (18). One study found that 34% of patients diagnosed with BAD did not take at least one psychotropic medication within a 10-day period, and 20% missed all daily doses at least once (19). Another study demonstrated that nearly 49.5% of 1,052 BAD patients were non-adherent to treatment, and this high rate of medication non-adherence was associated with poorer treatment response and impaired functioning (20). In BAD, treatment adherence increases the duration of remission, while a decline in adherence shortens the interval between episodes and increases relapse rates (21). LAI antipsychotic treatment has been shown to significantly improve quality of life, functionality, disease prognosis, and reduce relapse rates in chronic mental illnesses compared to oral formulations (22, 23). A study conducted in Turkey showed that the use of LAI antipsychotics in BAD reduced the number of hospital days and hospitalizations (24). A randomized, double-blind study revealed that monthly aripiprazole LAI was effective in the maintenance treatment of BAD, significantly reducing overall symptoms and mania severity, with effects maintained

for one year (25). In BAD, Aripiprazole LAI treatment has been shown to reduce the proportion of individuals experiencing mood episodes, prolong the time to episode recurrence, and improve treatment adherence compared to placebo (26).

In a study conducted in China among patients with BAD, the prevalence of involuntary hospitalization was found to be 52%, with a strong correlation observed between manic episodes, aggression, low education level, poor insight, and involuntary treatment (27). Another study found that BAD patients receiving involuntary treatment exhibited lower treatment adherence, higher rates of comorbid substance use disorders, reduced insight, and increased aggressive behavior compared to those receiving voluntary treatment (28). It has been demonstrated that the use of LAI antipsychotics reduces hospitalizations by 45.2% compared to the pre-transition period when compared to oral antipsychotics, and also decreases the frequency of involuntary hospitalizations (29). A systematic review examining the effects of LAI antipsychotics in BAD and schizoaffective disorder concluded that aripiprazole LAI significantly delayed manic episode recurrence in BAD without triggering depression, while also demonstrating that all LAI antipsychotics were effective against mania, but first-generation antipsychotics worsened depressive symptoms (30). Second-generation LAI antipsychotics have been shown to improve treatment and patient adherence, enhance general functioning, and reduce the risk of relapse, psychiatric emergencies, and the rate and duration of rehospitalization compared to first-generation antipsychotics (31). Treatment adherence is a critical determinant of hospitalization status in BAD, with atypical antipsychotics demonstrating superiority over typical antipsychotics in terms of both voluntary and involuntary hospitalization status and treatment adherence (32).

The most commonly used medications in BAD include mood stabilizers, anticonvulsants, and second-generation atypical antipsychotics (33). Among second-generation antipsychotics, LAI forms of risperidone and aripiprazole are approved for the maintenance treatment of BAD (34). Studies have shown that weight gain and metabolic side effects are more prevalent during risperidone LAI monotherapy compared to placebo in patients with BAD (35). A study assessing the tolerability and safety of oral aripiprazole and aripiprazole LAI for the treatment of manic episodes and maintenance of BAD concluded that these medications exhibit a favorable tolerability profile, with reduced risks of weight gain, dyslipidemia, diabetes, and hyperprolactinemia, a lower propensity for extrapyramidal side effects than first-generation antipsychotics, and robust cardiovascular safety (36). In BAD, aripiprazole LAI monotherapy has been associated with a prolactin-sparing profile, minimal sexual dysfunction, and a favorable metabolic side effect profile, with transient and infrequent side effects leading to high patient satisfaction and reduced medication discontinuation rates (37). A prospective study demonstrated that after 6 months of aripiprazole treatment, patients' metabolic profiles remained unaffected, prolactin levels normalized, and the dosages of other antipsychotics in combination therapy could be decreased (38).

Aripiprazole has demonstrated effectiveness in treating acute mania symptoms in BAD when used as monotherapy or in combination with mood stabilizers (39). The addition of aripiprazole to lithium or valproate has been shown to rapidly improve mania symptoms within 1–2 weeks of treatment initiation, and this combination therapy is well-tolerated (40). In a randomized controlled trial involving patients with limited response to lithium and valproate monotherapy, adding aripiprazole to the treatment regimen resulted in improved patient symptoms and an increased time to any mood episode over a 1-year period (41). Aripiprazole LAI has been shown to reduce manic episode symptoms in BAD, prevent relapses, enhance quality of life and functionality, and exhibit a safe and tolerable profile (42).

The aripiprazole TIS regimen has recently become available (5). Two studies in the literature have examined its application in a schizophrenia patient group (7, 8). Patient non-compliance with treatment was identified as the primary reason clinicians chose this alternative regimen, with patients reporting high satisfaction, and psychiatrists stating that this practice reduces average hospitalization costs by enhancing treatment adherence and con-

serving healthcare resources (8). The successful treatment of a 16-year-old BAD patient with the aripiprazole TIS regimen, beyond its use in schizophrenia, demonstrated its favorable safety and efficacy profile. The case report further highlights the potential for this regimen to offer advantages in reducing treatment non-adherence and relapse in first-episode BAD patients. (15). However, when examining studies on aripiprazole LAI treatment in BAD, it is evident that many were conducted in multicenter settings and utilized data from the same sample, which limits the breadth of available information in this field (42).

In our study, three patients were admitted to the treatment clinic via involuntary hospitalization. One patient had a comorbid substance use disorder diagnosis. Another patient had a history of oral antipsychotic use only. No serious side effects that negatively impacted treatment were observed in two patients receiving aripiprazole with a mood stabilizer. Two patients received a combination of a mood stabilizer and aripiprazole LAI, while the third patient received aripiprazole LAI monotherapy. All three patients hospitalized with BAD manic episodes responded favorably to aripiprazole treatment. Our study demonstrates that the aripiprazole TIS regimen is a useful and effective treatment with a favorable safety and tolerability profile. This was observed in three patients with BAD manic episodes who exhibited low treatment adherence, required inpatient treatment, had comorbid substance use disorders, experienced frequent hospitalizations, and necessitated combination therapy. Further randomized controlled trials comparing the aripiprazole TIS regimen with single-dose initial administration in terms of efficacy, safety, and tolerability in clinical practice for patients with BAD will help elucidate the effect of this strategy in patients who are non-adherent to treatment, have additional diagnoses, are involuntarily admitted, and require combination therapy.

Informed consent: Written informed consent was obtained from the patients and her parents to publish this manuscript.

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