Aripiprazole Long-Acting Injectable for Maintenance Treatment of Bipolar I Disorder in Adults

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Abstract

Bipolar I disorder is a serious and disabling psychiatric illness. It is associated with a significant reduction in quality of life and an increased risk for suicide. Pharmacotherapy is essential for both the acute and maintenance treatment of bipolar I disorder. While multiple oral medications are recommended for the maintenance treatment, there are not many long-acting injectable medications approved for this indication. New treatments that would improve patient adherence have the potential for decreasing relapses and improving patients' ability to remain functional members of society. In this paper we discuss the available data for safety and efficacy of aripiprazole long-acting injectable in bipolar disorder.

Key Words: Bipolar I, Aripiprazole, Adherence, Psychopharmacology

Introduction

Bipolar I disorder is a serious and disabling psychiatric illness with an estimated lifetime prevalence of 2.1% (1). It is a lifelong, episodic illness characterized by one or more manic episodes and—in a vast majority of cases—major depressive episodes (2). Bipolar I disorder is associated with a significant reduction in quality of life (3) and an increased risk for suicide as high as 20 to 30 times than that for the general population (4). Pharmacotherapy is essential for both the acute and maintenance treatment of bipolar I disorder. While multiple oral medications are recommended for the maintenance treatment (5), until recently risperidone long-acting injectable (RLAI) was the only long-acting injectable (LAI) approved for this indication. There are two related aripiprazole LAI formulations currently available—Abilify Maintena® (AMLAI) and Aristada® (aripiprazole lauroxil LAI). While both of these formulations are approved for use in schizophrenia in adults (6), AMLAI was also approved by the U.S. Food and Drug Administration for the maintenance monotherapy treatment of bipolar I disorder in adults in July 2017. Table 1 compares the two LAIs that are currently approved for treatment of bipolar I disorder.

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Need for LAIs in Bipolar Disorder

When clinicians think of patients with bipolar disorder, they think of patients with an illness that has the potential to dramatically alter their lives. Patients go from having a seemingly normal level of functioning—holding a job, being a spouse and/or parent, managing their own finances, etc.—to being individuals who behave uncharacteristically. Episodes of unprotected sex with multiple partners, extravagant spending, and alienating family members and co-workers are products of their euphoric, bizarre or irritable behavior. Equally problematic, they can switch to a depressive state, meeting all the criteria for major depression including becoming suicidal.

In their analysis of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) (7), Parikh et al. stated that "bipolar disorder is a uniquely challenging disorder to treat, with the most lethality, the most recurrences, and the most varied clinical presentations of any major

Table 1 Comparison of AMLAI and RLAI (long-acting injectables currently approved for bipolar I disorder)

	AMLAI	RLAI
Injection interval	4 weeks	2 weeks
Dose range	200–400 mg	12.5–50 mg
Maximum recommended dose	400 mg every 4 weeks	50 mg every 2 weeks
Administration	Start at 400 mg. Overlap with oral aripiprazole required for the first 14 days.	Start at 25 mg. Overlap with oral risperidone required for the first 3 weeks.

AMLAI=Abilify Maintena Long-Acting Injectable; RLAI=Risperidone Long-Acting Injectable

psychiatric disorder." The World Health Organization report on Mental Health noted bipolar disorder as the ninth leading cause of disability adjusted life-years (DALYs) in those ages 15–44 years (8). DALYs for a disease are the sum of the years of life lost due to premature mortality and years lost due to disability (8). Despite this grim data, bipolar disorder can still be managed effectively and a substantial number of patients are able to return to a functional level. In a 4-year outcome study of first-episode mania/mixed mania, more than half of the patients returned to their previous level of functioning at initial assessment and were able to maintain this level of functioning at the 4-year follow-up mark (9).

Much of the recent data on outcomes with bipolar disorder suggests that effective treatment, as early in the illness as possible, will result in better outcomes (9-11). Relapse rates have been found to be very high, with data from the STEP-BD study, the largest prospective examination of bipolar disorder outcomes in the U.S. to date, revealing relapse rates at the 2-year mark of 48.5% (12). Early identification and treatment can be helpful in preventing relapse. It is also important to consider functional outcomes such as ability to maintain relationships, ability to sustain some type of productive work/activities and ability to have a degree of independent living, as these factors have been shown to produce better outcomes (13).

In the STEP-BD study, it was found that relapses occurred despite utilization of guideline-based treatment (7, 12). Another prospective study conducted by Montoya et al. showed the same findings (13). However, medication adherence could have been a major factor in this data as medication adherence in bipolar disorder patients has been found to be very poor, with rates in the literature reported to range from 20–64% (14). New treatments that would improve patient adherence have the potential for decreasing relapses and improving patients' ability to remain functional members of society.

Efficacy and Safety of Aripiprazole Long-Acting Injectable in Bipolar Disorder

Oral aripiprazole has been proven to be safe and effective in both acute and maintenance treatment of bipolar I disorder (15, 16). AMLAI has demonstrated safety and efficacy in adult patients with schizophrenia (17). Based on these results, AMLAI was evaluated for maintenance treatment of bipolar I disorder in a 52-week, double-blind, placebo-controlled, randomized withdrawal study (18).

Study Design

This was a multinational study (Canada, Japan, Republic of Korea, Poland, Romania, Taiwan and the United States) and comprised of four treatment phases. In the first phase, patients were required to be in a manic episode on entry and they were converted to oral aripiprazole monotherapy from others medications over 4–6 weeks; in the second phase, patients were stabilized on oral aripiprazole for 2–8 weeks. Stabilization was defined using clinical status (outpatient status and no suicidality) and rating scales (Young Mania Rating Scale [YMRS] and Montgomery Asberg Depression Rating Scale [MADRS]). In the third phase, patients stabilized on oral aripiprazole were subsequently stabilized on AMLAI in the next 12–28 weeks. Oral aripiprazole was permitted for the first 2 weeks in this phase. In the last phase of the study, eligible patient were randomized in a double-blind manner to AMLAI or placebo. This phase lasted up to 52 weeks. Overall, 1,175 patients were screened for the study, out of which 266 patients entered the randomized, double-blind, placebo-controlled phase and 102 patients completed the study. Majority of the randomized patients were female (57.5%), with a mean age of 40.6 years. Patients were predominantly white (54.1%) or black/African American (28.2%).

Efficacy Data

The primary efficacy end point of this study was time taken from randomization to recurrence of any mood episode and the study concluded that the time to recurrence of any mood episode was significantly longer with AMLAI compared to placebo and risk of recurrence of any mood episode over one year was reduced by almost half in the ALMAI group (hazard ratio=0.45; 95% CI, 0.30–0.68; p<.0001). The study also noted that the proportion of patients with the recurrence of any mood episode in the randomized phase was significantly lower in the AMLAI group (26.5%) than in the placebo group (51.1%, Fisher's exact test p<.0001); however, this difference was predominantly seen only for manic episodes but not for mixed or depressive episodes.

Safety Data

In the AMLAI stabilization phase (Phase 3), 68.5% patients experienced treatment-emergent adverse events (TEAE), which consisted of akathisia (17.4%), weight increase (11.1%), insomnia (9.6%), anxiety (7.1%), restlessness (5.6%), fatigue (5.2%) and nasopharyngitis (5.2%). In the randomized phase (Phase 4), 7.6% patients in the AMLAI group experienced serious adverse events (defined in the study as bipolar disorder, major depression or mania) as compared to 18.8% of patients in the placebo group. There were no clinically significant changes in prolactin levels, metabolic parameters, vital signs or extrapyramidal symptoms in either group. About half (51.9%) the patients in AMLAI group discontinued during the randomized withdrawal phase (as compared to 71.4% in the placebo group), which is consistent with withdrawal rates of study evaluating oral aripiprazole for maintenance treatment in bipolar I disorder (16). The most frequent reasons for withdrawal were recurrence of a mood episode, patients withdrawing consent and patients getting lost to follow-up.

Limitations of the Study

A major limitation of the study is that randomized patients were already stabilized on AMLAI monotherapy, which resulted in a selected patient population who demonstrated good tolerability and good response to AMLAI. Therefore, generalizability to clinical setting where patient may require adjunct medications is limited. Furthermore, strict inclusion and exclusion criteria were used including requiring a manic episode at study entry, which may limit the generalizability to patients who either are exhibiting depressive and mixed episodes of bipolar disorder or predominately have depressive and mixed episodes and rare manias.

Conclusions

With this said, having another approved medication for bipolar I disorder is an advance in our potential regimens for these patients. While much attention has been given to the need for stabilization and relapse prevention in schizophrenia, the consequences of non-adherence in bipolar I disorder are well documented and the potential risks significant.

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