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Aripiprazole long-acting injectable (ABILIFY MAINTENA) for treatment of schizophrenia

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ABSTRACT

Introduction: Patients with schizophrenia often relapse as a result of medication nonadherence.

Methods: Long-acting injectable antipsychotics have been developed to improve medication adherence rates in this patient population.

Results: Aripiprazole long-acting injection (LAI), branded Abilify Maintena®, received Food and Drug Administration approval for the treatment of schizophrenia in February of 2013. Aripiprazole LAI is the fourth intramuscular second-generation antipsychotic indicated for the treatment of schizophrenia.

Discussion: This manuscript reviews important clinical information regarding its use as well as efficacy and tolerability data.

Keywords: antipsychotic agents, treatment outcome, pharmacokinetics, delayed-action preparations, schizophrenia

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Introduction

Schizophrenia is a chronic, debilitating psychiatric condition that affects 24 million people worldwide and has been shown to decrease life expectancy by 12 to 15 years compared with the average population.[1-3] Antipsychotics are the mainstay of treatment for schizophrenia, with individuals requiring lifelong therapy. While medication nonadherence is a common barrier to pharmacotherapy, it is a particularly prevalent issue in patients with schizophrenia. Nonadherence rates are difficult to quantify given the varying definitions and methods used to assess adherence. Lacro and colleagues have estimated that 20% to 56% of patients with schizophrenia are nonadherent to their medication regimen.[4]

Consequences of medication nonadherence include an increased risk of relapse, hospitalization, and suicide attempts.[5,6] Numerous studies have been conducted to identify factors associated with nonadherence and discontinuation, with inconsistent findings. The variety of characteristics associated with nonadherence in this patient population include the duration of untreated psychosis, use of first-generation versus second-generation antipsychotic agents, poor insight into the effect of medication, lack of an established patient-physician relationship or therapeutic alliance, younger age of illness onset, severity of symptoms, illicit drug or alcohol use, and lower education level.[7]

Long-acting injectable (LAI) antipsychotics have been developed to improve adherence to antipsychotics, though studies have demonstrated mixed results. LAIs may potentially enhance adherence by providing more predictable and stable plasma levels of active drug compared with oral antipsychotic agents.[8] Additionally,

since injections are typically administered during a health care provider office visit, LAIs permit clinicians to immediately identify patients who become at risk of relapse by missing a scheduled injection and to intervene in a timely manner.[9] Thus, clinicians are better able to distinguish between patients who relapse as a result of therapeutic inefficacy and those who relapse secondary to medication nonadherence and discontinuation.[9]

Currently 6 LAI agents are available in the United States for the treatment of schizophrenia. There are 2 first-generation antipsychotic injections (haloperidol decanoate and fluphenazine decanoate) and 4 second-generation antipsychotic injections (aripiprazole extended-release injectable suspension, olanzapine pamoate extended-release injectable suspension, paliperidone palmitate extended-release injectable suspension, and risperidone long-acting injection). The first-generation LAIs are fatty acid esters dissolved in purified sesame oil. The second-generation LAI products are aqueous suspensions. The aqueous suspensions avoid the local reactions associated with the sesame oil formulations. Abilify Maintena is an extended-release suspension of aripiprazole approved by the Food and Drug Administration (FDA) in February 2013 for maintenance treatment of schizophrenia.[10]

Oral aripiprazole was originally approved in 2002 and is indicated for a variety of psychiatric conditions including schizophrenia, bipolar disorder, major depressive disorder, and autistic disorders.[10] A short-acting intramuscular formulation is also approved for acute agitation in schizophrenia or bipolar disorder.[10] Since an indication for schizophrenia was previously established, only one additional efficacy and safety study evaluating the new LAI formulation of aripiprazole was required for approval.

Pharmacology

Mechanism of Action

Aripiprazole is the first antipsychotic agent with D2 partial agonist properties.[11] Similar to other antipsychotics, the exact mechanism of action of aripiprazole for the treatment of schizophrenia is unknown but is believed to involve D2 and 5HT1A receptor partial agonism and 5HT2A receptor antagonism.[10] Aripiprazole is hypothesized to act as a partial agonist at both D2 autoreceptors and postsynaptic receptors.[12] Effects at D2 autoreceptors may result in reduced dopamine synthesis and release, ultimately leading to a reduction in dopaminergic neurotransmission.[12] In regions of the brain with hyperdopaminergic activity, such as the mesolimbic system, aripiprazole reduces dopamine transmission, thereby treating positive symptoms of schizophrenia.[12] Partial agonism at postsynaptic D2 receptors may reduce the risk of extrapyramidal side effects (EPS) and hyperprolactinemia, which are a result of full D2 receptor antagonism.[12] Additionally, 5HT2A antagonism yields an increase in dopaminergic release in the mesocortical and nigrostriatal dopaminergic pathways, which may lead to improvement in the negative symptoms of schizophrenia and a reduction in the risk of EPS, respectively.[12] Partial 5HT1A agonism has also been associated with a reduction in EPS and has been shown to enhance dopaminergic neurotransmission in frontocortical regions of the brain, which are often deficient in dopamine in patients with schizophrenia, thereby improving both negative and cognitive symptoms of schizophrenia.[13] In addition, partial 5HT1A agonism produces anxiolytic effects as well.[13]

Pharmacodynamics

Aripiprazole displays high binding affinity for D2, D3, 5HT1A, and 5HT2A receptors and moderate binding affinity for D4, 5HT2C, 5HT7, α-1, H1 receptors, and serotonin reuptake. Aripiprazole is considered to have no "appreciable affinity" to cholinergic receptors.[10]

Pharmacokinetics

Aripiprazole absorption from the aqueous intramuscular injection (15-400 mg) into the systemic circulation is slow and prolonged owing to low solubility of aripiprazole monohydrate. No evidence of dose dumping was observed in the aripiprazole LAI clinical trials.[14]

The median time to peak plasma concentrations (T_{max}) following a single 200-mg, 300-mg, and 400-mg intramuscular (IM) injection is 7, 7, and 22 days, respectively, while the median T_{max} after multiple IM injections administered every 4 weeks is 5 to 7 days. A single dose of 200 mg, 300 mg, and 400 mg aripiprazole LAI yields a half-life of 18.9, 24.9, and 10.5 days, respectively, with multiple doses of 300 mg or 400 mg administered every 4 weeks resulting in a mean half-life of 29.9 and 46.5 days, respectively. Dehydro-aripiprazole, the active metabolite of aripiprazole, displays a median T_{max} of 5.5 to 12.5 days after multiple doses of 200 to 400 mg administered every 4 weeks. Steady-state concentrations (Css) of aripiprazole are obtained by the fourth dose (16 weeks). After the fifth injection, more than dose-proportional increases in Css_{max}, area under the curve (AUC), and Css_{min} were noted to occur when comparing 300-mg and 400-mg injections of aripiprazole every 4 weeks.[14]

Aripiprazole is extensively metabolized, primarily by CYP3A4 and CYP2D6. Dehydro-aripiprazole circulates at a level ~30% of the parent drug at steady state. In contrast, the oral tablet steady state is ~ 40%. The ratios of dehydro-aripiprazole to aripiprazole for mean maximum concentration (C_{max}) and $AUC_{0-\tau}$ after the fifth

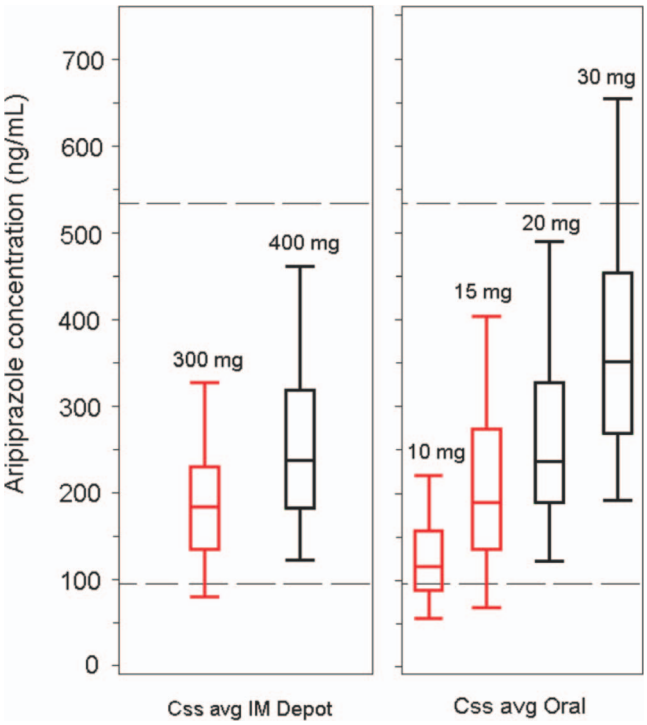

FIGURE: Steady-state long-acting injectable aripiprazole concentrations compared with oral aripiprazole concentrations[a]

[a]Simulated average steady-state aripiprazole concentrations for long-acting injection (LAI) (left) and oral (right). The dashed lines represent the apparent therapeutic window for aripiprazole.[14(p. 10)]

monthly injection of aripiprazole LAI in the range of 200 to 400 mg were 29.1% to 33.2%. This metabolite-parent ratio is comparable with the oral dosing ratio.[14]

Aripiprazole is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1 enzymes. Aripiprazole does not undergo direct glucuronidation.[14]

Dosing

Initial Dosing

Prior to initiating aripiprazole LAI, as with all long-acting antipsychotic injections, tolerability to the oral formulation must first be established.[10] The recommended starting and maintenance dose is 400 mg administered once monthly (no sooner than 26 days after the previous injection); however, a dosage reduction to 300 mg once monthly should be considered if adverse reactions occur.[10] Oral aripiprazole (10-20 mg/d) or another antipsychotic must be continued for the first 14 days following the initial aripiprazole LAI.[10] As displayed in the Figure, steady-state concentrations achieved by the 300- and 400-mg LAI formulations were within apparent therapeutic range observed with oral aripiprazole doses of 10 and 20 mg. Steady-state concentrations achieved with the 200-mg LAI formulation were found to be below the C_{min} levels observed with 10-mg oral daily dosing.[14] Recommendations for management of missed doses are provided in Table 1.

Dosing in Special Populations

Pregnancy and Lactation

Aripiprazole LAI has been placed in Pregnancy Category C owing to a lack of adequate studies in this patient population.[10] However, antipsychotic exposure during the third trimester of pregnancy has been associated with an increased risk of EPS and/or withdrawal symptoms in the neonate.[10] Additionally, possible teratogenic effects have been observed in rats and rabbits at 1 to 10 times the human oral maximum recommended dose of aripiprazole at 30 mg/d based on body surface area.[10] Use of aripiprazole LAI during pregnancy should occur only if the possible benefits outweigh the possible risks to the fetus.[10]

Aripiprazole is excreted into human breast milk but has not been studied in breast-fed children. A decision should be made with input from all involved parties to discontinue either aripiprazole or nursing, taking into consideration the need for the medication by the mother.[10]

Pediatrics

The safety and effectiveness of aripiprazole LAI has not been evaluated in those under 18 years of age.

Geriatrics

No published reports are yet available on the safety and effectiveness of aripiprazole LAI in patients over 60 years of age; however, there are clinical trials in progress

TABLE 1: Recommendations for management of missed doses[a]

Dose Missed	Weeks Since Last Injection	Oral Overlap 14 days	Administer LAI
2nd or 3rd	≥ 4 and < 5	No	Yes
	≥ 5	Yes	Yes
4th or later	> 4 and ≤ 6	No	Yes
	> 6	Yes	Yes

LAI = long-acting injection.

[a]Adapted from ABILIFY MAINTENA product label (section 2.2).[10]

TABLE 2: Recommended dose adjustments for CYP2D6 poor metabolizers and patients taking concomitant interacting medications for over 14 days[a]

Aripiprazole LAI Regimen	CYP2D6 PM	CYP2D6	CYP3A4	Adjusted Dose
New Start	Yes	—	—	300 mg
	Yes	—	Inhibitor	200 mg
400 mg	No	Strong inhibitor	—	300 mg
	No	—	Strong inhibitor	300 mg
	No	Inhibitor	Inhibitor	200 mg
	No	—	Inducer	Avoid use
300 mg	No	Strong inhibitor	—	200 mg
	No	—	Strong inhibitor	200 mg
	No	Inhibitor	Inhibitor	160 mg
	No	—	Inducer	Avoid use

LAI = long-acting injection; PM = poor metabolizer.

[a]Adapted from ABILIFY MAINTENA product label, Table 1.[10]

evaluating the use of aripiprazole in those up to 66 years of age. These can be found at the ClinicalTrials.gov Web site (in the public domain at http://clinicaltrials.gov/ct2/results?term=aripiprazole&Search=Search). Additionally, oral single-dose (15 mg) aripiprazole pharmacokinetic studies revealed that clearance was 20% lower in the elderly (65 years of age and over) compared with the younger adult (18 to 64 years of age) population.[10] However, no detectable effect of age on the population pharmacokinetic analysis of oral doses of aripiprazole for schizophrenia was observed.[10]

Dose Adjustments

Dose adjustments are recommended for patients who are CYP2D6 poor metabolizers and in patients taking concomitant CYP3A4 and/or CYP2D6 inhibitors for more than 14 days.[10] A 2-fold difference in steady-state aripiprazole exposure has been observed in patients who are CYP2D6 poor metabolizers compared with extensive metabolizers.[14] Aripiprazole LAI is not recommended for use in patients receiving concomitant treatment with CYP3A4 inducers for more than 14 days because of the potential for subtherapeutic plasma levels and diminished effectiveness.[14] Short-term use ($<$ 14 days) of a CYP3A4 or CYP2D inhibitor or both has not resulted in the achievement of plasma concentrations outside the therapeutic range.[14] Table 2 provides specific dosage adjustment recommendations.

Efficacy Data

A 52-week randomized, double-blind, placebo-controlled, multicenter study was conducted to evaluate the efficacy and safety of aripiprazole LAI formulation. Subjects meeting inclusion criteria had to be between 18 and 60 years of age, meet DSM-IV-TR diagnostic criteria for schizophrenia for a minimum duration of 3 years, and have a history of symptom exacerbation or relapse when not on antipsychotic treatment. Subjects with psychiatric comorbidities or medical conditions were excluded, as well as those with a history of being treatment refractory to antipsychotics or responsive to clozapine. Antidepressants, mood stabilizers, and other antipsychotics were prohibited during the study period; however, anticholinergics (up to 4 mg/d of benztropine or equivalent) and benzodiazepines (up to 6 mg/d of lorazepam or its equivalent) were permitted, but not within 8 or 12 hours, respectively, of rating-scale assessment.[15]

The primary outcome measure was time to exacerbation of psychotic symptoms/impending relapse in subjects stabilized on aripiprazole LAI for at least 12 weeks and randomized to treatment with aripiprazole LAI or placebo. A psychotic exacerbation or impending relapse was defined by meeting any or all of the 4 criteria at any time during phase 4. These included (1) clinical worsening defined by Clinical Global Impression improvement (CGI-I) score of ≥ 5 and an increase in score on any of the following 4 Positive and Negative Syndrome Scale (PANSS) items (conceptual disorganization, hallucinatory behavior, suspiciousness, or unusual thought content) to a score > 4 with an absolute increase ≥ 2 on that specific item or an increase > 4 on these PANSS items and an absolute increase ≥ 4 on the combined score; (2) hospitalization as a result of worsening of psychotic symptoms; (3) risk of suicide (Clinical Global Impression-Severity Scale (CGI-SS) score of 4 [severely suicidal] or 5 [attempted suicide] on part 1 or a score of 6 [much worse] or 7 [very much worse] on part 2); or (4) violent behavior causing clinically significant self-injury, injury to another person, or property damage.[15]

TABLE 3: Phase 4 impending relapse rates[a]

Group	Relapse Rate	NNTB[b] (95% CI)	HR[c] (95% CI)
Interim Analysis (N = 64)			
Placebo	36.8%	3.67 (2.70-5.57)	4.75 (2.81-7.94)
Aripiprazole	9.6%		
Final Analysis (N = 80)			
Placebo	39.6%	3.39 (2.59-4.83)	5.03 (3.15-8.02)
Aripiprazole	10.0%		

CI = confidence interval.

[a]Data from Kane et al.[15]

[b]NNTB = number needed to treat to benefit. This represents the number of patients that would need to be treated with aripiprazole long-acting injection (LAI) or placebo to see one less impending relapse.

[c]HR = hazard ratio. This represents the rate of impending relapse (events per unit time) for placebo compared with active drug.

The study comprised a screening phase, used to assess eligibility, followed by 4 treatment phases. In phase 1 (oral conversion phase), patients not currently treated with oral aripiprazole were cross-titrated to aripiprazole monotherapy over a 4 to 6 week period. Phase 2, known as the oral stabilization phase (4-12 weeks in duration), consisted of biweekly assessments to stabilize subjects on oral aripiprazole (10-30 mg/d). Stability was defined by meeting the following 5 criteria for a 4-week period: (1) outpatient status; (2) PANSS total score $\leq$ 80; (3) lack of specific psychotic symptoms on the PANSS (score $\leq$ 4 on each of the following items: conceptual disorganization, suspiciousness, hallucinatory behavior, unusual thought content); (4) CGI-Severity of Illness score $\leq$ 4 (moderately ill); and (5) CGI for Severity of Suicidality score $\leq$ 2 (mildly suicidal) on part 1 and $\leq$ 5 (minimally worsened) on part 2. Subjects entering phase 3 (stabilization phase) were assigned to receive single-blind aripiprazole LAI at a dose of 400 mg. For the first 2 weeks post injection, oral aripiprazole 10 to 20 mg/d was continued to maintain therapeutic concentration. If issues with tolerability arose, a single decrease to 300 mg aripiprazole LAI was permitted, followed by a subsequent increase back to 400 mg if the patient became symptomatic at the lower dose. Subjects meeting stability criteria for 12 consecutive weeks were then randomized in a 2:1 ratio to receive double blind aripiprazole LAI at the current dose (300 or 400 mg) or placebo for up to 52 weeks in phase 4.[15]

Of the 1025 subjects screened, a total of 843 subjects met inclusion criteria. Of these subjects, 710 proceeded to phase 2 (aripiprazole oral stabilization) followed by 576 to phase 3 (aripiprazole LAI stabilization). Reasons for dropout during these phases are detailed in the completed study and include sponsor discontinuation of the study, loss to follow-up, withdrawal of consent, adverse effects, lack of efficacy, and other. A total of 403 subjects entered phase 4 (aripiprazole LAI, n = 269; placebo, n = 134) of the study. Based on a prespecified interim analysis performed after 64 relapse events, the primary endpoint was achieved, and the efficacy of aripiprazole LAI was demonstrated. Therefore, the study was terminated early to prevent further exposure to placebo. Kaplan-Meyer analysis showed a statistically significant longer time to impending relapse (hazard ratio, 5.03; 95% confidence interval [CI], 3.15-8.02) and lower relapse rates (number needed to treat to benefit, 3.33; Table 3) with aripiprazole LAI compared with placebo in both the interim (64 events) and final (80 events) analyses. Relapse (aripiprazole LAI vs placebo) in the final analysis was attributed to (1) clinical worsening according to the CGI/PANSS (74.1%, n = 20/27 vs 86.8%, n = 46/53); (2) hospitalization (25.9%, n = 7/27 vs 9.4%, n = 5/53); (3) suicide risk (3.7%, n = 1/27 vs 1.9%, n = 1/53); and (4) violent behavior (3.7%, n = 1/27 vs 7.5%, n = 4/53). Statistically significant differences in mean PANSS total score from double-blind baseline in favor of aripiprazole LAI versus placebo were observed starting at week 2 of phase 4 and were maintained at all subsequent time points (PANSS administered every 4 weeks) up to study endpoint at 52 weeks. Similarly, statistically significant mean change in CGI-S score was demonstrated in favor of aripiprazole LAI (0.1 vs 0.7; $P < .0001$) starting at week 4 of phase 4 and was maintained to week 52.

The investigators concluded that aripiprazole LAI delayed time to relapse compared with placebo and was a well-tolerated treatment option. Additionally, aripiprazole LAI was noted to have a different benefit-to-risk profile compared with existing options. Limitations of this study include the requirement that all subjects be stabilized on oral aripiprazole monotherapy in phase 2 followed by a 12-week minimum aripiprazole LAI stabilization phase. In the real-world setting, LAI antipsychotics are commonly initiated in patients displaying medication adherence issues, who often spend little time stabilized on an oral antipsychotic regimen prior to receiving a LAI antipsychotic. Additionally, a selection bias may have occurred since inclusion criteria required that subjects not be considered treatment refractory to antipsychotics; furthermore, to proceed to phase 4, subjects had to have responded to both the oral and depot aripiprazole formulation. An additional limitation was failure to report the time since the most recent exacerbation, causing uncertainty with regard to the optimal time to initiate an LAI antipsychotic. It should also be noted that, because the study was terminated early as a result of the prespecified interim analysis demonstrating that aripiprazole LAI was efficacious, few patients received aripiprazole LAI for the planned 12-month period; thus additional relapse events that may have occurred were not captured.

In addition to the 52-week maintenance trial, a multicenter, open-label, mirror-image study was conducted to

evaluate hospitalization rates in adults aged 18 to 65 years with schizophrenia. A retrospective analysis of hospitalization rates in patients treated with oral standard-of-care antipsychotics for a minimum of 6 months was compared with prospective treatment with aripiprazole LAI for 6 months. Patients with a history of schizophrenia for more than 1 year and one inpatient hospitalization within 4 years prior to screening, who were adequately maintained as outpatients for the 4 weeks immediately preceding the prospective phase, were eligible for inclusion. Additionally, subjects had to have been prescribed oral antipsychotic therapy for 7 months prior to screening and had to be currently warranting a change in antipsychotic treatment for any reason.[16]

The study comprised a retrospective phase using standard-of-care antipsychotic treatment following by a prospective screening phase and 3 subsequent treatment phases. Upon completion of the screening phase, phase A consisted of patients who had never received treatment with oral aripiprazole or who had been previously treated with aripiprazole but were currently receiving treatment with a different oral antipsychotic and in need of cross-titration and conversion to oral aripiprazole (10-30 mg/d) over a 1 to 4 week period. Patients unable to tolerate oral aripiprazole or requiring inpatient hospitalization were withdrawn from the study. Patients completing phase A, in addition to those who were already receiving treatment with aripiprazole or those with a history of being treated with aripiprazole not requiring cross-titration or conversion to aripiprazole, entered phase B, which consisted of 6 months open-label treatment with aripiprazole 400 mg IM once monthly (patients could be decreased to 300 mg IM once monthly if issues with tolerability existed). Oral aripiprazole overlap (10-20 mg/d) was provided for the first 14 days following the initial injection. After completion of phase B, patients whom the investigator believed would continue to benefit from the LAI could enter phase C, where patients continued to receive aripiprazole injections (400 or 300 mg IM every 28 days).[16]

Only the results of the patients who completed or discontinued phase B ($n = 183$ comprised of 104 patients from phase A and 79 patients who entered directly into phase B) were reported in this publication. Of note, 115 patients were still undergoing phase-B treatment at the data cutoff point for the preliminary analysis and were not included in this preliminary analysis. Patients in phase B were considered to be of moderate disease severity (CGI-S, 3.9 ± 0.8). Of the 121 patients (66%, $n = 121$ of 183 patients) who had received ≥ 3 months of treatment in phase B, psychiatric hospitalization rates were significantly lower in phase-B prospective treatment (months 4 to 6) compared with the 3-month retrospective treatment phase (months -4 to -1) (6.6% vs 28.1%, $P < .0001$). Additionally, hospitalization rates were significantly lower in all patients who entered phase B during the 6 months after switching to aripiprazole once monthly compared with the 6 months prior to the prospective phases during the retrospective treatment phase (14.2% vs 41.5%, $P < .0001$). Results from sensitivity analysis also showed significant reductions in hospitalization rates prospectively compared with retrospectively.[16]

Though these results are from a preliminary analysis, study investigators concluded that switching from standard-of-care oral antipsychotic therapy to aripiprazole once monthly reduced total psychiatric hospitalization rates. Furthermore, it was suggested that use of aripiprazole once monthly could result in a reduction in costs to health care systems.[16]

Limitations of this study include the lack of a parallel active control arm, making it difficult to determine if other treatments would have produced similar outcomes. Additionally, the open-label design of this study may have influenced the decision of whether or not to hospitalize a patient. Independent factors such as admission patterns, insurance coverage, availability of hospital beds, and community support may also have affected study results. Also, the use of concomitant psychotropic medications was not reported.

Adverse Events

The most common treatment-emergent adverse events in phase 4 (double-blind maintenance treatment phase) of the 52-week maintenance and tolerability trial, which occurred in at least 5% of aripiprazole LAI-treated patients and at a rate greater than placebo, included insomnia, tremor, and headache (Table 4).[15,17] This trial was designed to evaluate relapse prevention; patients not stabilized on oral aripiprazole did not progress to phase 3 (LAI stabilization) and phase 4 (maintenance treatment phase) of the trial, which should be noted when evaluating Table 5, which displays discontinuation owing to adverse events by study phase. Since patients were required to be stabilized on oral aripiprazole prior to receiving aripiprazole LAI, a sampling bias may have occurred.[15]

Aside from the treatment-emergent adverse events previously mentioned, data on adverse events specific to aripiprazole LAI, including injection-site reactions, originate from the maintenance trial as well as the supplemental New Drug Application (sNDA 202971).[14,15] Treatment discontinuation owing to a potential lack of efficacy occurred in 15 of 576 patients (2.6%), while akathisia occurred in 2 of 576 patients (0.3%), with various single events such as dry mouth, chest pain, hyperkalemia, ovarian cancer, and allergic dermatitis occurring in the open-label aripiprazole LAI stabilization phase.[14] The total discontinuation rate during this phase was 4.9% (28

TABLE 4: Treatment-emergent adverse events occurring in >5% of patients receiving aripiprazole LAI during any phase, treatment phase safety sample[a]

	Phase 3 (Stabilization)	Phase 4 (Double-Blind Treatment)		
	Aripiprazole LAI (n = 576)	Aripiprazole LAI (n = 269)	Placebo (n = 134)	
Adverse Event	n (%)	n (%)	n (%)	NNTH[b]
Any AE	345 (59.9)	170 (63.2)	83 (61.9)	77
Akathisia	36 (6.3)	15 (5.6)	8 (6.0)	−250
Anxiety	38 (6.6)	16 (5.9)	10 (7.5)	−62.5
Headache	34 (5.9)	16 (5.9)	7 (5.2)	143
Injection-Site Pain	34 (5.9)	8 (3.0)	5 (3.7)	−143
Insomnia	46 (8.0)	27 (10.0)	12 (9.0)	100
Tremor	21 (3.6)	16 (5.9)	2 (1.5)	23
Weight Increase	40 (6.9)	26 (9.7)	13 (9.7)	−2773

AE = adverse event; LAI = long-acting injection.

[a]Based on Kane et al.[15] Table 3, p. 622, and NDA No. 202971 Medical Review,[14] section 7.4.1, p. 48.

[b]NNTH = Number needed to treat to harm. This represents the number of patients that would need to be treated with aripiprazole LAI or placebo to see one more adverse event. (Negative values mean that placebo group had higher rate of AEs.)

of 576 patients).[14] In the double-blind aripiprazole LAI maintenance phase, the most common cause of dropout was also related to lack of efficacy, with 3.3% and 10.4% of aripiprazole LAI-treated versus placebo-treated patients dropping out, respectively (number needed to harm of 15).[14] Overall, 7.1% and 13.4% of aripiprazole LAI-treated and placebo-treated patients, respectively, discontinued treatment owing to adverse events (number needed to harm of 16).[14] Tables 6 through 9 display injection-site reactions from subjective and objective ratings.[14] Patients' subjective rating of pain was assessed using a visual analog scale where 0 mm indicated no pain and 100 mm was unbearable pain, while investigators' assessment of swelling, redness, and induration was completed using a 4-point scale ranging from absent to severe.[14] A "current" injection-site reaction was evaluated 1 hour after the injection and a "follow-up" injection-site reaction of a previous injection was evaluated 30 minutes prior to the next injection.

Recently, 4 studies have been published that report on the safety and tolerability of aripiprazole LAI.[14,15,19] One study was a 24-week, open-label, parallel-arm, multiple-dose trial to assess the pharmacokinetics, safety, and tolerability of aripiprazole LAI 200 mg (n = 11), 300 mg (n = 16), and 400 mg (n = 14) in adult patients with schizophrenia.[18] Patients were randomized to receive 5 consecutive monthly injections of the 3 doses of aripiprazole LAI.[18] Four of 41 patients (10%) patients withdrew from the study owing to treatment-emergent adverse effects; 3 of 8 withdrawn patients (37%) in the 300-mg group withdrew because of drug dependence, worsening of psychosis, or worsening of schizophrenia, while one of 11 (9%) patients in the 200-mg group withdrew because of worsening of psychosis.[18] Four of 14 (29%) patients reported injection-site pain with the 400 mg dose, though no patients reported this adverse effect at any other doses.[18] Additional adverse effects that occurred in at least 5% of randomized patients include tremor, upper respiratory tract infection, vomiting, nasopharyngitis, muscle strain, musculoskeletal stiffness, sedation, rash, headache, akathisia, insomnia, cough, back pain, anxiety, auditory hallucination, fatigue, prolonged QTc interval, somnolence, psychotic disorder, and nausea.[18] Mean changes in the Abnormal Involuntary Movement Scale, Simpson-Angus Rating Scale, and Barnes Akathisia Rating Scale were not noted to be clinically significant at any dose from baseline to the last visit.[18] Mean weight changes from baseline to the last visit were +2.1 kg for 200-mg doses, +1.2 kg for 300-mg doses, and +2.2 kg for 400-mg doses. Since standard deviations were not reported, it is not possible to determine if the observed changes in weight were significantly different between doses.[18] Clinically significant weight gain (at least 7% increase from baseline) was reported in 11.1%, 14.3%, and 25.0% of patients at 200-mg, 300-mg, and 400-mg doses, respectively.[18] Two patients experienced clinically significant weight loss.[18] There were no clinically relevant changes observed for

TABLE 5: Discontinuation due to adverse events by study phase[a]

Phase	Description	Discontinuations
1	Conversion to oral aripiprazole	11/633 (1.7%)
2	Aripiprazole oral stabilization	14/710 (2.0%)
3	Aripiprazole LAI stabilization	17/576 (3.0%)
4	Double-blind	9/269 (3.3%)

LAI = long-acting injection.

[a]Data from Kane, Figure 1, p. 620.[15]

TABLE 6: Injection site pain ratings in aripiprazole LAI stabilization phase 3 (safety sample)[a]

	Injection No. 1		Injection No. 2		
Assessment	Current	Follow-up	Current	Follow-up	Last Injection
VAS N (mm)	568 (6.1)	518 (1.1)	517 (4.7)	471 (1.1)	571 (4.9)
Absent N (%)	419/568 (73.8%)	515/518 (99.4%)	382/514 (74.3%)	463/469 (98.7%)	436/570 (76.5%)
Mild N (%)	140/568 (24.6%)	3/518 (0.6%)	126/514 (24.5%)	4/469 (0.8%)	120/570 (21.0%)
Moderate N (%)	9/568 (1.6%)	0/518 (0%)	6/514 (1.2%)	1/469 (0.2%)	13/570 (2.3%)
Severe N (%)	0/568 (0%)	0/518 (0%)	0/514 (0%)	1/469 (0.2%)	1/570 (0.2%)

LAI = long-acting injection; VAS = visual analog scale.

[a]Data from NDA 202971 Medical Review, Tables 15, 16, pp. 37-38.[14]

serum chemistry, hematology, urinalysis, prolactin, or vital signs.[18]

The other open-label study by Potkin et al[19] evaluated the safety and tolerability of aripiprazole LAI in 60 patients stabilized on an oral second-generation antipsychotic other than aripiprazole. A single dose of aripiprazole long-acting injection 400 mg was evaluated. The oral antipsychotic was continued following the aripiprazole LAI for an overlap period of 14 days ±1 day. The most common treatment-emergent adverse events occurring in at least 5% of patients included increased blood creatine phosphokinase, dystonia, fatigue, injection-site pain, insomnia, restlessness, and toothache. Of note, treatment-emergent adverse events were more likely to occur within the first 15 days (32 subjects; 53%) after administration of aripiprazole LAI compared with > 15 days (13 subjects; 22%) post injection. Additionally, a post hoc analysis demonstrated that treatment-emergent adverse events were more likely to occur during the first 8 days of oral overlap compared with days 9 to 12 and 13 to 15 of oral overlap. Injection-site pain, dystonia, and restlessness were considered to be potentially related to aripiprazole LAI therapy. One patient attempted suicide and required hospitalization; however, this event resolved on the same day and was determined to be unrelated to trial medication. Mean changes on the Barnes Akathisia Rating Scale, Simpson Angus Rating Scale, and Abnormal Involuntary Movement Scale from baseline to last visit (aripiprazole once monthly with up to 15 days of concurrent oral antipsychotic) were not considered clinically relevant.[19]

Fleischhacker et al[20] specifically evaluated adverse effects and tolerability over 4 phases, including an oral aripiprazole conversion phase, an oral aripiprazole stabilization phase, aripiprazole LAI stabilization phase, and aripiprazole LAI maintenance phase. The only adverse effect reported in at least 5% of patients across all phases was insomnia. Adverse effects reported in at least 5% of patients in the aripiprazole LAI phases included increase in weight, headache, tremor, anxiety, akathisia, and injection-site pain. Fleischhacker et al also reported no clinically relevant mean changes from baseline in metabolic parameters in any of the study phases, and clinically significant weight gain or loss (at least 7% change from baseline) was reported in less than 7% of patients in any phase.[20]

An additional study evaluating safety was a multicenter, open-label study with the primary purpose of assessing hospitalization rates in patients transitioned from oral antipsychotics to aripiprazole 400 mg (with the option to decrease to 300 mg) LAI for 6 months; however, only results of those who had already completed or who had discontinued aripiprazole LAI have been reported. Of

TABLE 7: Injection site swelling ratings in aripiprazole LAI stabilization phase 3 (safety sample)[a]

	Injection No. 1		Injection No. 2		
Assessment	Current	Follow-up	Current	Follow-up	Last Injection
Absent N (%)	536/568 (94.4%)	518/518 (100%)	493/514 (95.9%)	468/469 (99.8%)	543/570 (95.3%)
Mild N (%)	32/568 (5.6%)	0/518 (0%)	20/514 (3.9%)	1/469 (0.2%)	25/570 (4.4%)
Moderate N (%)	0/568 (0%)	0/518 (0%)	1/514 (0.2%)	0/469 (0%)	2/570 (0.4%)
Severe N (%)	0/568 (0%)	0/518 (0%)	0/514 (0%)	0/469 (0%)	1/570 (0.2%)

LAI = long-acting injection.

[a]Data from NDA 202971 Medical Review, Tables 15, 16, pp. 37-38.[14]

TABLE 8: Injection site redness ratings in aripiprazole LAI stabilization phase 3 (safety sample)[a]

	Injection No. 1		Injection No. 2		
Assessment	Current	Follow-up	Current	Follow-up	Last Injection
Absent N (%)	506/568 (89.1%)	516/518 (99.6%)	469/514 (91.2%)	469/469 (100%)	518/570 (90.9%)
Mild N (%)	61/568 (10.7%)	2/518 (0.4%)	45/514 (8.8%)	0/469 (0%)	52/570 (9.1%)
Moderate N (%)	1/568 (0.2%)	0/518 (0%)	0/514 (0%)	0/469 (0%)	0/570 (0%)
Severe N (%)	0/568 (0%)	0/518 (0%)	0/514 (0%)	0/469 (0%)	0/570 (0%)

LAI = long-acting injection.

[a]NDA 202971 Medical Review, Table 15, 16, pp. 37-38.[14]

note, some subjects were still receiving aripiprazole LAI treatment at the preliminary data cut-off point. During the aripiprazole LAI phase, 44.8% (82 of 183) of evaluable patients discontinued the medication for any reason; of these, 26 patients discontinued owing to adverse effects, with the most common adverse events being "psychiatric disorders" (n = 20). Treatment-emergent adverse effects that occurred in at least 5% of patients receiving at least 1 dose of aripiprazole LAI include psychotic disorder, akathisia, insomnia, paranoid schizophrenia, back pain, and schizophrenia. Adverse effects occurred at higher rates during the first month of treatment (38.1%) and decreased with subsequent treatment (18.3% in month 2 and 6.5% in month 6). Most adverse effects were considered mild or moderate in intensity; though 19.9% of patients were considered to have experienced serious treatment-emergent adverse events during therapy.[16]

Because the safety profile of aripiprazole LAI and oral aripiprazole are expected to be similar, safety data presented in the prescribing information for Abilify Maintena is from oral aripiprazole trials. This information is presented in Table 10. With regard to observed adverse effects occurring in at least 5% of oral aripiprazole–treated patients with schizophrenia and twice that for placebo, the only adverse effect was akathisia (aripiprazole vs placebo, 8% vs 4%, respectively).[21] EPS, aside from akathisia, was reported to occur in 13% and 12% of those treated with oral aripiprazole and placebo, respectively.[21] Somnolence, including sedation, was the only dose-related adverse reaction associated with oral aripiprazole use compared with placebo.[21]

Warnings and Precautions

Similar to all other antipsychotic medications, aripiprazole LAI is not FDA approved for the treatment of patients with dementia-related psychosis and has a boxed warning for increased mortality in elderly patients with dementia-related psychosis.[10] In a meta-analysis of 17 placebo-controlled trials with olanzapine, aripiprazole, risperidone, or quetiapine, 15 trials showed increases in mortality in the groups treated with active drug compared with placebo.[22] With a total of 5106 patients, the risk of death among drug-treated patients was found to be 1.6 to 1.7 times the risk of death among placebo-treated patients.[10,22] Over the course of approximately 10 weeks, the rate of death in patients treated with active drug compared with placebo was 4.5% and 2.6%, respectively.[10] Upon review, most of the causes of death were found to be cardiovascular (eg, sudden death, heart failure) or infectious (mostly pneumonia) in etiology.[10,22] Aripiprazole LAI also carries warnings and precautions for cerebrovascular adverse reactions in elderly patients with dementia-related psychosis, neuroleptic malignant syndrome, tardive dyskinesia, metabolic changes, orthostatic

TABLE 9: Injection site induration ratings in aripiprazole LAI stabilization phase 3 (safety sample)[a]

	Injection No. 1		Injection No. 2		
Assessment	Current	Follow-up	Current	Follow-up	Last Injection
Absent N (%)	544/568 (95.8%)	515/518 (99.4%)	493/514 (95.9%)	466/469 (99.4%)	549/570 (96.3%)
Mild N (%)	24/568 (4.2%)	3/518 (0.6%)	21/514 (4.1%)	3/469 (0.6%)	21/570 (3.7%)
Moderate N (%)	0/568 (0%)	0/518 (0%)	0/514 (0%)	0/469 (0%)	0/570 (0%)
Severe N (%)	0/568 (0%)	0/518 (0%)	0/514 (0%)	0/469 (0%)	0/570 (0%)

LAI = long-acting injection.

[a]NDA 202971 Medical Review, Table 15, 16, pp. 37-38.[14]

TABLE 10: Adverse reactions in short-term, placebo-controlled trials in adult patients with any indication treated with oral aripiprazole

System Organ Class Preferred Term	Oral Aripiprazole (n = 1843)	Placebo (n = 1166)	NNTH
Eye Disorders			
Blurred Vision	3	1	50
Gastrointestinal Disorders			
Nausea	15	11	25
Constipation	11	7	25
Vomiting	11	6	20
Dyspepsia	9	7	50
Dry Mouth	5	4	100
Toothache	4	3	100
Abdominal Discomfort	3	2	100
Stomach Discomfort	3	2	100
General Disorders and Administration Site Conditions			
Fatigue	6	4	50
Pain	3	2	100
Musculoskeletal and Connective Tissue Disorders			
Musculoskeletal Stiffness	4	3	100
Pain in Extremity	4	2	50
Myalgia	2	1	100
Muscle Spasms	2	1	100
Nervous System Disorders			
Headache	27	23	25
Dizziness	10	7	33
Akathisia	10	4	17
Sedation	7	4	33
Extrapyramidal Disorder	5	3	50
Tremor	5	3	50
Somnolence	5	3	50
Psychiatric Disorders			
Agitation	19	17	50
Insomnia	18	13	20
Anxiety	17	13	25
Restlessness	5	3	50
Respiratory, Thoracic, and Mediastinal Disorders			
Pharyngolaryngeal Pain	3	2	100
Cough	3	2	100

NNTH = number needed to treat to harm. This represents the number of patients that would need to be treated with aripiprazole oral or placebo to see one more adverse event.

[a]Data from ABILIFY MAINTENA Product Label, Table 7.[10]

hypotension, leukopenia, neutropenia and agranulocytosis, seizures, the potential for cognitive and motor impairment, impaired body temperature regulation, and dysphagia.[10] In 3 placebo-controlled trials of oral aripiprazole for dementia-related psychosis, an increased incidence of cerebrovascular adverse events (eg, transient ischemic attack, stroke), including deaths, in patients receiving drug treatment compared with placebo was observed.[10,23] In one fixed-dose trial, a statistically significant dose-response relationship was identified for cerebrovascular adverse reactions in patients on oral aripiprazole.[10] Cases of neuroleptic malignant syndrome (NMS), a potentially fatal group of symptoms that may occur after antipsychotic drug administration, have been reported.[10] The product label describes cases of NMS associated with aripiprazole use in the worldwide clinical database as "rare."[10] Because of the risk of tardive dyskinesia (TD) associated with long-term antipsychotic usage, aripiprazole LAI should be used in a way that minimizes the risk of TD, such as considering its use (at the smallest dose for the shortest duration possible) in patients with chronic psychiatric illness who respond to antipsychotic medication and for whom the equally effective, but less harmful therapies are not available.[10] Additionally, patients should be continually reassessed for continued treatment as well as alternative options should TD occur; it is noted that some patients may continue to benefit from treatment with aripiprazole LAI despite the development or presence of TD.[10]

Metabolic changes associated with second-generation antipsychotics include hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain. The data presented in the prescribing information for aripiprazole LAI were obtained from data collected from oral aripiprazole studies; however, the manufacturers state that these data apply to patients receiving aripiprazole LAI as well. Hyperglycemia (including some cases of diabetic ketoacidosis, hyperosmolar coma, or fatalities) has been reported in patients taking second-generation antipsychotics, including aripiprazole. The relationship between second-generation antipsychotic use and adverse effects associated with elevated glucose is not well understood. It is recommended that patients treated with second-generation antipsychotics who have established diabetes mellitus should be monitored for worsening glucose control and that patients with risk factors for the development of diabetes mellitus should have fasting blood glucose testing completed prior to initiation of therapy as well as throughout the duration of therapy. Patients should be monitored for symptoms of elevated blood glucose, such as polydipsia, polyuria, and polyphagia. Though hyperglycemia may resolve after discontinuation of antipsychotic therapy, elevated blood glucose levels may persist and require treatment with pharmacotherapy. An analysis of 13 placebo-controlled trials in adult patients mostly with schizophrenia or bipolar disorder showed that mean change in fasting glucose in patients treated with aripiprazole was not significantly different compared with patients treated with placebo (+4.4 mg/dL; median exposure 25 days vs +2.5 mg/dL;

TABLE 11: Glucose category change[a]

Category Change[b]	Aripiprazole (%)	Placebo (%)	NNTH[c]
Normal → High	31/822 (3.8)	22/605 (3.6)	741
Borderline → High	31/176 (17.6)	13/142 (9.2)	12

[a]Data from ABILIFY MAINTENA Product Label, Table 4.[10]

[b]At least once compared with baseline. Normal = Fasting Glucose < 100 mg/dL; Borderline = Fasting Glucose ≥ 100 to < 126 mg/dL; High = Fasting Glucose ≥ 126 mg/dL.

[c]NNTH = number needed to treat to harm. This represents the number of patients that would need to be treated with aripiprazole long-acting injection (LAI) or placebo to see one more adverse event.

median exposure 22 days, respectively). At 24 weeks, the mean change in fasting glucose between groups was also not significantly different (+2.2 mg/dL and +9.6 mg/dL for aripiprazole vs placebo, respectively). Table 11 displays the percentage of patients who had either normal or borderline fasting glucose levels that switched to high fasting glucose levels in each treatment group as well as the number needed to harm. Dyslipidemia has also been shown in patients treated with second-generation antipsychotics. The prescribing information reports that no statistically and clinically significant differences were found in patients treated with aripiprazole compared with placebo, with regard to fasting/nonfasting total cholesterol, fasting triglycerides, fasting low-density lipoproteins (LDLs), and fasting/nonfasting high-density lipoproteins (HDLs). Table 12 highlights the percentage of patients who had normal to high levels of total cholesterol, fasting triglycerides, fasting LDL cholesterol, and normal to low levels of HDL cholesterol in each treatment group as well as the number needed to harm. Monotherapy trials at 12 and 24 weeks showed the proportion of patients with changes from normal to high levels of fasting total cholesterol (also nonfasting), triglycerides, and LDL cholesterol to be similar between patients in the aripiprazole versus placebo treatment arms. Monitoring weight gain is recommended as increased weight has been observed with second-generation antipsychotic use.[10] An analysis of trials showed mean change in body weight for patients in the aripiprazole versus placebo arms to be +0.3 kg versus −0.1 kg (median exposure, 21 to 25 days), respectively, and −1.5 kg versus −0.2 kg (at 24 weeks), respectively. Table 13 displays the percentage of patients with weight gain of at least 7% in 13 pooled placebo-controlled monotherapy trials of patients with mostly schizophrenia or bipolar mania.[10]

Orthostasis may occur in patients taking aripiprazole, possibly due to α1-adrenergic receptor antagonism. Orthostasis occurred in 0.7% (4 of 576) of patients treated with aripiprazole LAI during stabilization. Significant orthostasis, considered at least a 20 mm Hg reduction in systolic blood pressure with an increase in heart rate of 25 beats per minute, rated upon comparing standing to supine values, occurred in 0.2% (1 of 575) of patients. Oral aripiprazole has been associated with leukopenia, neutropenia, and agranulocytosis in clinical trials and postmarketing reports. Should a patient have a history of drug-induced leukopenia or neutropenia or clinical significantly low WBC, monitoring of CBC for the first months of aripiprazole LAI use is recommended. Otsuka recommends providers consider discontinuation of aripiprazole LAI should a clinically significant reduction in WBC occur without other potential etiology and discontinue aripiprazole LAI in patients with an absolute neutrophil count $<1000/mm^3$ and monitoring of WBC until recovery.[10] Providers are cautioned toward using second-generation antipsychotics in patients with a history of seizure or conditions lowering the seizure threshold. Patients should also be warned against engaging in activities that involve judgment, thinking, or motor skills until they know how the medication will affect them, owing to the potential for second-generation antipsychotics to impair cognitive and

TABLE 12: Lipid category changes[a]

Category Change[b]	Aripiprazole (%)	Placebo (%)	NNTH[c]
Total Cholesterol Normal (< 200 mg/dL) → High (≥ 240 mg/dL)	34/1357 (2.5)	27/973 (2.8)	−372
Fasting Triglycerides Normal (< 150 mg/dL) → High (≥ 200 mg/dL)	40/539 (7.4)	30/431 (7.0)	218
Fasting LDL Cholesterol Normal (< 100 mg/dL) → High (≥ 160 mg/dL)	2/332 (0.6)	2/268 (0.7)	−696
HDL Cholesterol Normal (≥ 40 mg/dL) → Low (< 40 mg/dL)	121/1066 (11.4)	99/794 (12.5)	−90

[a]Data from ABILIFY MAINTENA Product Label, Table 5.[10]

[b]At least once compared with baseline.

[c]NNTH = number needed to treat to harm. This represents the number of patients that would need to be treated with aripiprazole long-acting injection (LAI) or placebo to see one more adverse event. (Negative values mean that placebo group had higher rate of adverse events.)

TABLE 13: Weight Changes[a]

Weight Gain ≥7%[b]	Aripiprazole (%)	Placebo (%)	NNTH[c]
Schizophrenia[d]	69/852 (8.1)	12/379 (3.2)	21
Bipolar Mania[e]	16/719 (2.2)	16/598 (2.7)	−223

[a]Data from ABILIFY MAINTENA Product Label, Table 6.[10]

[b]From baseline.

[c]NNTH = Number needed to treat to harm. This represents the number of patients that would need to be treated with Aripiprazole LAI or Placebo to see one more adverse event. (Negative values mean that placebo group had higher rate of adverse events.)

[d]Four to 6 weeks duration.

[e]Three weeks duration.

motor functioning. Patients should also be warned about activities or conditions that may elevate core body temperature, such as exercise or heat/sun exposure, as antipsychotic agents may impair the body's ability to regulate core body temperature. Last, patients using antipsychotic medications may be at risk for aspiration pneumonia secondary to esophageal dysmotility and aspiration that have been associated with their use.[10]

Contraindications

Aripiprazole LAI is contraindicated in patients with a known hypersensitivity to aripiprazole, with reactions ranging from pruritus to anaphylaxis.[10]

Monitoring Parameters

According to the FDA-approved prescribing information, no specific laboratory tests are recommended for monitoring.[10] The consensus statement from the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity states that patients initiated on second-generation antipsychotics should be routinely monitored for a number of parameters as shown in Table 14.[24] Revisions to the recommended time interval for monitoring parameters are based on information from Stahl et al.[25]

Overdose

Since aripiprazole LAI is an IM injection only administered by a health care professional, overdose is not expected to occur. Adverse events reported in at least 5% of patients experiencing oral aripiprazole overdose include vomiting, somnolence, and tremor.[21] Other symptoms that have been reported in oral aripiprazole overdose (alone or concurrent with other substances) include acidosis, aggression, aspartate aminotransferase elevation, atrial fibrillation, bradycardia, coma, confusion, seizures (including status epilepticus), creatinine phosphokinase elevation, reduced or loss of consciousness, hypertension, hypokalemia, hypotension, lethargy, abnormal electrocardiogram, aspiration pneumonia, respiratory arrest, and tachycardia.[21]

The Future of Aripiprazole LAI

Prior to the approval of aripiprazole LAI, 3 second-generation antipsychotic injections were available for the treatment of schizophrenia: risperidone microspheres, paliperidone palmitate, and olanzapine pamoate. Comparative studies between LAI antipsychotics are needed to further determine aripiprazole LAI's role in therapy, based on both acute and long-term efficacy and safety data. However, the large sample size needed to conduct a randomized controlled trial of sufficient power to detect differences between LAIs would most likely be too costly to obtain; therefore indirect comparisons or retrospective studies are more feasible studies to perform that will also provide additional information on the efficacy and safety of aripiprazole LAIs. Clinical trials evaluating aripiprazole LAI for acute treatment of schizophrenia, as well as maintenance treatment in bipolar 1 disorder, are currently underway. Additionally, a comparative trial assessing aripiprazole LAI versus paliperidone palmitate, examining quality of life, is being conducted.[26]

Based on results from studies evaluating the use of oral aripiprazole, aripiprazole LAI may have a more favorable adverse effect profile with a lower risk of inducing metabolic abnormalities, compared with the other sec-

TABLE 14: Routine monitoring for antipsychotics

Parameter	Baseline	4 Weeks	8 Weeks	12 Weeks	Quarterly	Annually
Personal/Family History	X					X
Weight (BMI)	X	X	X	X	X	
Waist Circumference	X			X		
Blood Pressure	X			X		X
Fasting Plasma Glucose	X			X		X
Fasting Lipid Profile	X			X		X

BMI = body mass index.

ond-generation LAIs available. The incidence of movement-related adverse effects appears to be low, though an adequate follow-up period may not have been studied to identify emergence of certain types of movement-related adverse effects. The need for a 2-week period of oral overlap after administration of the initial injection may limit its use. Based on the available evidence, the ideal candidate for aripiprazole LAI is a patient with schizophrenia who has been stable on the oral formulation of aripiprazole but has demonstrated difficulty with taking oral medication daily.

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