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Drug safety evaluation of aripiprazole in bipolar disorder

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Abstract

Introduction: Safety and tolerability of medications are key variables to inform treatment choice for patients with bipolar disorder (BD). This review focuses on the overall tolerability and safety profile of aripiprazole when used for its bipolar disorder indications, which include acute treatment of manic and mixed episodes and maintenance treatment of bipolar I disorder for the oral formulation, agitation associated with bipolar mania for the injectable immediate-release formulation, and maintenance treatment of bipolar I disorder for the long acting once-monthly (AOM) formulation.

Areas covered: The authors reviewed aripiprazole safety in bipolar disorder according to product labeling. English language reports located through PubMed and information available on the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) websites, with a focus on the safety and tolerability of aripiprazole, were reviewed.

Expert opinion: Compared to many other antipsychotics, aripiprazole has a relatively favorable tolerability profile, with a lower risk for weight gain, dyslipidemia, diabetes and hyperprolactinemia. Compared to first-generation antipsychotics, and similar to most second-generation antipsychotics, aripiprazole has a reduced propensity for extrapyramidal side effects and a better cardiovascular safety.

Key words: aripiprazole, tolerability, safety, bipolar, metabolic, prolactin, long acting, weight, pregnancy, dyskinesia

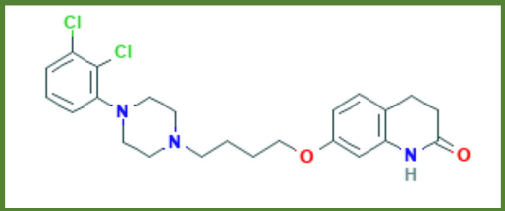
Box 1. Aripiprazole

Drug name

⇒ Aripiprazole

Chemical structure

⇒ 7-[4-[4-(2,3-dichlorophenyl)piperazin-1-yl]butoxy]-3,4-dihydro-1H-quinolin-2-one



Bipolar Disorder Indications (FDA)

- Manic and mixed episodes associated with Bipolar I Disorder
  - ⇒ monotherapy
  - ⇒ adjunctive to lithium or valproate
  - ⇒ children 10-17-year-old
  - ⇒ adults

- Maintenance treatment of bipolar I disorder
  - ⇒ oral formulation
  - ⇒ Long acting Aripiprazole Once-monthly (AOM) formulation

- Agitation associated with bipolar mania (or schizophrenia)
  - ⇒ intramuscular (immediate release) formulation

1. Introduction

Aripiprazole is a second-generation antipsychotic whose oral formulation is approved in the United States for the treatment of schizophrenia, manic and mixed episodes associated with bipolar I disorder in adults and children of age 10-17 (monotherapy or adjunct to lithium or valproate), irritability associated with autistic disorder, Tourette's disorder, and treatment of major depressive disorder (adjunctive to an antidepressant) [1]. The intramuscular immediate release formulation, is approved for agitation associated with schizophrenia or bipolar mania [1]. The long acting once-monthly (AOM) formulation, is approved for the treatment of schizophrenia and the maintenance monotherapy treatment of bipolar I disorder in adults [2].

The issue of safety and tolerability is particularly important for patients with BD for several reasons, including the frequent association of BD with physical comorbidities, such as migraine, pain disorders, cardiovascular disease, obesity, hyperglycemia, diabetes, hypertension, dyslipidemia, and metabolic syndrome, as well as the frequent association with smoking and alcohol or drugs abuse [3-7]. Indeed, several studies found all-cause mortality rate to be increased about 2 fold in BD [8-11].

Tolerability impacts on quality of life and medication effectiveness, as adverse side effects may add to the burden of the disease, precipitate non-adherence and result in treatment discontinuation. Hence, the balance of tolerability and efficacy should be a key informant for treatment selection [12]. A recent metanalysis suggested that aripiprazole is effective and safe in treating bipolar disorder [13].

The aim of this paper is to provide a summary of the safety of aripiprazole, using the medication label and the recent literature as a guide to translate the available data into clinically useful information pertaining to the treatment of bipolar disorder.

2. Methods

We reviewed the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) prescribing information for aripiprazole, with special reference

to its indications for BD, and conducted a literature search on the topic using PubMed. The selected time frame was 2002-2018. The search strings were the following: 1) Aripiprazole and [bipolar or mania or manic or maintenance or continuation]; 2) Aripiprazole and [tolerability or safety or side effect or warning or adverse or pharmacokinetic]. We selected the most representative papers based on the extent to which they reported relevant information about tolerability issues pertaining to the short and long-term use of aripiprazole in patients with bipolar disorder.

3. Results

3.1 Pharmacodynamics properties and implications for safety and tolerability

Aripiprazole (7-[4-[4-(2,3-dichlorophenyl)piperazin-1-yl]butoxy]-3,4-dihydro-1H-quinolin-2-one) is a second-generation anti-psychotic (SGA) that is pharmacologically and structurally different from the other SGAs [14].

Aripiprazole has *high affinity* for dopamine D2 and D3, serotonin 5-HT1A and 5-HT2A receptors, *moderate affinity* towards dopamine D4, alpha1-adrenergic, histamine H1 receptors, serotonin 5-HT2c and 5-HT7, and serotonin reuptake transporters, and *low affinity* for H1-histaminergic, muscarinic, cholinergic and adrenergic receptors. [15-17]. Aripiprazole is a partial agonist at the dopamine D2, D_3 and D_4 and serotonin 5-HT1A, $5\text{-}HT_{2C}$, $5\text{-}HT_7$ receptors, is an inverse agonist at $5\text{-}HT_{2B}$ receptors and is an antagonist at the other receptors [17-18].

At therapeutic doses, aripiprazole and its primary metabolite, dehydro-aripiprazole, occupy approximately 95% of D2 receptors in the striatum [16-19]. As a D2 partial agonist, aripiprazole behaves as a functional full antagonist at D2 receptor when the dopamine synaptic concentration is high and as a functional agonist when dopamine levels are low. As a result, aripiprazole may reduce psychotic symptoms by lowering the excess of dopamine activity in the mesolimbic region, while balancing dopamine activity in the mesocortical, nigrostriatal, and tubero-infundibular pathways. In fact, dopamine partial agonism in the mesocortical areas may result in functional dopamine stimulation and contribute to the improvement of negative symptoms in schizophrenia or depressive symptoms in bipolar disorder; dopamine partial agonism in the nigrostriatal pathways

may contribute to the relatively low incidence of extrapyramidal side effects (EPSE) [16-20]; dopamine partial agonism in the tubero-infundibular pathways may contribute to a tendency to decrease prolactin [21-23]. However partial agonism at the D2 receptor may contribute to anxiety, agitation, nausea, and insomnia [24].

Aripiprazole also shows high affinity partial agonist at dopamine D3 receptors. D3 receptors are widely distributed throughout the brain, are particularly concentrated within the limbic system, and are of interest for their implications in the pathogenesis of schizophrenia, mood disorders and drug abuse [25].

As mentioned above, aripiprazole has *low affinity* for H1-histaminergic, muscarinic, cholinergic and adrenergic receptors, which is correlated with its low tendency to cause weight gain, metabolic disruption, and sedation [15-16, 26].

3.2 Pharmacokinetics properties and implications for safety and tolerability

3.2.1. Oral aripirazole

Aripiprazole tablets are absorbed through the gastrointestinal tract, with a bioavailability of about 85%. The time to peak plasma concentration (Tmax) is about 3-5 hours. Food intake does not seem to significantly affect peak plasma concentration (Cmax), other than possibly delaying Tmax. Aripiprazole has a half-life of 48 – 75 hours and 94 hours for dehydro-aripiprazole. Hence, the steady state is achieved around the 14th day [1, 15-27]. The pharmacokinetics of aripiprazole are dose linear. Aripiprazole has an active metabolite, dehydroaripiprazole, which contributes to its effects and side effects. Monitoring drug plasma concentration of arpiprazole and its main metabolite is helpful to establish adherence and to understand if side effects are related to abnormal blood levels, for instance in slow metabolizers or in patients taking other medications which may interact with aripiprazole [28].

3.2.2 Intramuscular (immediate release) aripirazole

Tmax with aripiprazole injection is 1 – 3 hours with an absolute bioavailability of 100%. The mean Cmax reached with an intramuscular injection is higher than the Cmax of the oral tablet. The area under the curve (AUC) in the first 2 hours after the initial intramuscular injection is 90% greater than the AUC after a similar oral tablet dose.

However, over 24 h of dosing, the systemic exposure is similar between aripiprazole injection and oral tablet administration [1, 15-27].

Aripiprazole and its active principal metabolite dehydro-aripiprazole have a high plasma protein binding affinity (up to 99%) and only the fraction that is not bound to the plasma proteins is allowed to cross the blood brain barrier. Hence, the injectable formulation likely reaches higher concentrations in the brain, owing to its higher Cmax compared to the oral formulation [1, 15-27].

3.2.3 Long acting once-monthly (AOM) aripiprazole

Aripiprazole long acting once a month (AOM) [2, 29] absorption into the systemic circulation following intramuscular injection is slow and prolonged. Following a single-dose administration of AOM in the gluteal and deltoid muscle, the extent of absorption (AUCt_, AUC∞) was similar for both injection sites. However, the rate of absorption (C max) was 31% higher for the deltoid injection compared to the gluteal site. Yet, steady state, AUC and Cmax were similar for both sites of injection. After multiple intramuscular doses, plasma concentrations of aripiprazole rise to maximum plasma concentrations at a median Tmax of 5 - 7 days for the gluteal muscle and 4 days for the deltoid muscle. The differences in pharmacokinetics between gluteal and deltoid administration may be due to the differences in the intra-peri/muscular fat tissue or to the differences in muscle vascularization. After gluteal administration, the mean half-life was 29.9 days for AOM 300 mg and 46.5 for AOM 400 mg, respectively. Steady state concentrations were reached by the fourth dose for both deltoid and gluteus sites of administration [2, 29].

3.2.4 Aripiprazole metabolism and elimination

Aripiprazole elimination is primarily via the liver, via dehydrogenation, N-dealkylation, and hydroxylation, mainly through CYP3A4 and CYP2D6 enzyme systems. Therefore, dosage adjustment for aripiprazole is recommended when the medication is co-administered with CYP3A4 and CYP2D6 inhibitors or with inducers of CYP3A4 (Table 1) [1-2, 27,29].

For instance, aripiprazole dose should be doubled when the medication co-administered with CYP3A4 inducers, such as carbamazepine [30].

Conversely, the dose should be reduced to half of the usual dose if aripiprazole is co-administered with CYP3A4 inhibitors (such as ketoconazole) or CYP 2D6 inhibitors (such as fluoxetine or paroxetine) or to a quarter if it is administered with both CYP3A4 inhibitors and CYP 2D6 inhibitors or if a poor metabolizer receives either of these two [1, 15-16, 18, 27]. Aripiprazole does not undergo direct glucuronidation. Approximately 40% of aripiprazole AUC in plasma is comprised of dehydro-aripiprazole. Excretion is via the kidney and liver, with 25% and 55% of the dose recovered in the urine and feces, respectively [1, 15-16, 18, 28].

3.3 Overall safety and tolerability

In several trials, Aripiprazole has demonstrated a relatively favorable tolerability profile. For instance, the medication has a lower potential for weight gain or metabolic changes than other antipsychotics (e.g., olanzapine) as well as a usually lower liability for extrapyramidal symptoms (e.g., compared to many first generation antipsychotics) , sedation (e.g., compared to more anti histaminergic and/or anti alpha adrenergic antipsychotics), hyperprolactinemia (e.g. compared to those antipsychotics that are more likely to be associated with this side effects, such as risperidone, paliperidone or amisulpride), or QTc prolongation (e.g., compared to the older, first generation antipsychotics) [15-16, 31].

Regarding prolactin levels, Aripiprazole is known for reversing hyperprolactinemia commonly associated with other antipsychotic medications [32]. A risk of Aripiprazole-induced hypoprolactinemia has also been reported [33-35]. Hypo-prolactinemia may be related to sperm abnormalities and sexual dysfunction in men, and ovary dysfunction and failure to lactate in women.

3.3.1 Short term trials with oral aripiprazole

3.3.1.1 Discontinuation rate

Controlled bipolar disorder clinical trials data show that discontinuation rates of oral aripiprazole due to adverse events (AEs) in adult populations with bipolar disorder, manic episode, are 11% in monotherapy and 12% in combination with a mood stabilizer, compared to the 10% discontinuation rate observed in the groups receiving placebo and 6% in groups receiving placebo plus a mood stabilizer. In registrational

studies involving the paediatric population, the discontinuation rate for aripiprazole during a manic episode was 7% versus 2% observed in the placebo group [16]. In the trial of injectable aripiprazole for the treatment of agitation in bipolar disorder, only 2 patients discontinued due to adverse effects: stomach discomfort (aripiprazole 15 mg); and hypotension (placebo) [36].

3.3.1.2 Common adverse reaction

Common adverse reactions (incidence ≥5% and at least twice that for placebo) observed in bipolar disorder clinical trials [1] were the following:

• *Monotherapy in adult patients with mania*:

Akathisia (13% vs 4%), sedation (8% vs 3%), restlessness (6% vs 3%), tremor (6% vs 3%), and extrapyramidal disorder (5% vs 2%)

• *Adjunctive therapy (with lithium or valproate patients) in adults with mania*:

Akathisia (19% vs 5%), insomnia (8% vs 4%), and extrapyramidal disorder (5% vs 1%)

• *Pediatric patients (10 to 17 years) with mania*:

Somnolence (23% vs 3%), extrapyramidal disorder (20% vs 3%), fatigue (11% vs 4%), nausea (11% vs 4%), akathisia (10% vs 2%), blurred vision (8% vs 0%), salivary hypersecretion (6% vs 0%), and dizziness (5% vs 1%)

• *Adult patients with agitation associated with mania or schizophrenia (intramuscular immediate release formulation) [36]:*

Nausea was the only commonly (incidence of 5% or greater, and aripiprazole incidence at least twice that for placebo) observed adverse reaction associated with the use of aripiprazole injection in patients with agitation associated with bipolar mania or schizophrenia (15% vs 6%).

3.3.1.3 Dose-related adverse reactions

In the study of pediatric patients (10 to 17 years of age) with bipolar mania [1], 4 common adverse events showed a possible dose response relationship at 4 weeks; extrapyramidal disorder (aripiprazole 10 mg, 12.2%; 30 mg, 27.3%; placebo, 3.1%;); somnolence (aripiprazole 10 mg, 19.4%; 30 mg, 26.3%; placebo, 3.1%;); akathisia (aripiprazole 10 mg, 8.2%; 30 mg, 11.1%; placebo, 2.1%;); and salivary hypersecretion (aripiprazole 10 mg, 3.1%; 30 mg, 8.1%; placebo, 0%).

3.3.1.4 Metabolic issues

Aripiprazole unlikely causes diabetes and is associated with a relatively low risk of dyslipidemia and weight gain [15, 27, 31, 27-38]

Pooled data from 4 short-term (3 weeks) placebo-controlled trials, involving 977 patients with acute mania, showed no difference in mean weight change between aripiprazole (0 kg) and placebo (- 0.2 kg) [39]. Also, studies with patients switching to aripiprazole from other antipsychotic medications showed a reduction in both body weight and other metabolic effects [40].

3.3.1.5 Extrapyramidal symptoms (EPS)

In the placebo-controlled trials in bipolar mania in adults, the incidence of EPS-related events, excluding akathisia, was 16% for aripiprazole vs. 8% for placebo [1]. The incidence of akathisia was 13% for aripiprazole vs. 4% for placebo. In the trial for adjunctive therapy with lithium or valproate, the incidence of reported EPS-related events, excluding akathisia for was 15% for adjunctive aripiprazole vs. 8% for adjunctive placebo. The incidence of akathisia was 19% for aripiprazole vs. 5% for adjunctive placebo. In the pediatric (10 to 17 years) placebo-controlled trial for bipolar mania, the incidence of EPS-related events, excluding akathisia, was 26% for aripiprazole vs. 5% for placebo. The incidence of akathisia was 10% for aripiprazole vs. 2% for placebo [1].

In the trial of aripiprazole for agitation associated with bipolar mania [24], 9 patients (3.1%) experienced EPS (IM aripiprazole 9.75 mg, n = 3; IM aripiprazole 15 mg, n = 5; IM placebo, n = 1), and 3 patients (IM aripiprazole 9.75 mg, n = 1; IM aripiprazole 15 mg, n = 2) received concomitant benztropine for treatment of potential EPS. Akathisia scores, as measured via the Barnes Akathisia Rating Scale, were lower at 24 hours than at baseline and mean decreases in BARS scores from baseline were similar between study groups (IM placebo, IM aripiprazole 9.75%, IM aripiprazole 15 mg, IM lorazepam) [36].

Tardive dyskinesia (TD) is a potentially irreversible movement disorder consisting of repetitive, involuntary, body movements, which may include grimacing, smacking the lips, or sticking out the tongue [41]. First generation antipsychotics are the medications thought to have a higher risk of TD as compared to newer generation antipsychotics, possibly due to be due to the fact that the latter are associated with higher 5HT2A

receptor antagonist activity and-at least in some cases (i.e. quetiapine and clozapine), lower affinity for D2 receptors [42] .

Reports have been published of aripiprazole ability to reduce symptoms of TD [for instance, 43-45]. However, cases of TD possibly induced by aripiprazole have been reported as well [for instance, 43, 46-55]. Hence, clinician should remain vigilant about emergence of TD or other movement disorders when prescribing aripiprazole, especially in patients with risk factors for TD such as female gender, older age, affective disorders, and the presence of extrapyramidal side effects, diabetes mellitus, along with dose and duration of neuroleptic exposure [46]

The mechanism by which aripiprazole may increase TD risk remains unclear. However, the partial agonist action of aripiprazole and the high occupancy of dopamine receptor might enhance the dopamine receptors' hypersensitivity in the nigrostriatal dopaminergic system, especially when they are upregulated or hypersensitive following treatment with other antipsychotics [56-57]. Of interest, brexpiprazole has a stronger antagonism at 5-HT2A and a lower affinity at the D2 receptor than aripiprazole [58-60]. However, brexpiprazole has also a lower intrinsic activity at the D2 receptor, which makes it somewhat more similar to the D2 antagonists [58]. Hence, it remains to be established whether the risk of tardive dyskinesia of brexpiprazole is higher or lower than aripiprazole.

3.3.2 Longer term, maintenance trials with oral aripiprazole

3.3.2.1 Oral aripiprazole

A double-blind, randomized, parallel group, placebo-controlled study [61], evaluated the safety and efficacy of aripiprazole in preventing relapse in recently manic, or mixed episode patients with bipolar I disorder stabilized with aripiprazole [17-19]. The study started with an open-label stabilization phase, which was followed by a double-blind phase. At week 26 endpoint, the discontinuation rate, due to treatment emergent adverse events (TEAE), was more frequent for placebo (19%) than aripiprazole (10%). The five most commonly reported TEAEs (≥5%) for aripiprazole were anxiety (17%), insomnia (16%), depression (12%), nervousness (10%), and tremor (9%). The most commonly reported TEAEs in the placebo group were insomnia (19%), headache (17%), anxiety (15%), depression (15%), and manic reaction (13%). EPS rates were

higher in the aripiprazole group, with tremor being the most frequently reported EPS. The percentage of aripiprazole treated patients who had significant increase of Simpson Angus Scale (SAS) and Barnes Akathisia Rating Scale (BARS) scores was higher than in placebo. Mean weight change over the 26 weeks of treatment was +0.5+/−0.8 kg aripiprazole and −1.7+/−0.8 kg for placebo. A significant weight-gain was observed in 13% of the patients who received aripiprazole and 0% of those who received placebo. Aripiprazole was correlated with a decrease in mean serum prolactin but the difference from baseline did not reach statistical significance. No significant changes were observed in vital signs, corrected QT interval (QTc), high-density lipoprotein (HDL), low-density lipoprotein (LDL) or fasting glucose concentration [61]. A 74-week extension study [62] showed a higher rate of discontinuation due to lack of efficacy in the placebo group (26%) than the aripiprazole group (13%) whereas EPS adverse events were more frequent in the aripiprazole group (22% versus 15%). The most common EPS related adverse effects were tremor (9% versus 1%), akathisia (8% versus 1%), and hypertonia (4% versus 2%). No significant difference was observed for the mean change from baseline to endopoint on the score of EPS scales. The mean weight change in patients treated with aripiprazole was 0.4 ± 0.8 kg versus −1.9 ± 0.8 kg observed for placebo [62].

A randomized double-blind placebo- and lithium-controlled trial [63] evaluated aripiprazole for acute and maintenance treatment of bipolar I disorder. Patients with acute manic or mixed episodes were randomized to receive aripiprazole 15–30 mg/day, lithium 900–1500 mg or placebo for 3 weeks. At the end of 3 weeks of treatment, placebo treated patients were blindly switched to aripiprazole, whereas those that had been randomized to lithium and aripiprazole during the first 3 weeks, continued with their originally assigned treatment. All study subjects continued double-blind treatment to week 12, when they a 40-week double-blind extension phase began. The most commonly encountered adverse effects with aripiprazole and lithium were nausea (23% and 24% respectively), headache (23% and 22%), akathisia (15% and 5%), sedation (13% and 7%), constipation (10% and 13%), and tremor (8% and 12%). No significant differences were found between aripiprazole and lithium for total weight gain [63].

Woo and colleagues [64] conducted a double-blind, placebo-controlled, randomized, 6-month, multicenter study involving individuals with bipolar I disorder from 23 centers in Korea. During the first 6 weeks (acute phase), the most common (occurring in at least 5% of participants) adverse events were headache (14.9%), constipation (13.7%), akathisia (13.1%), diarrhea (8.0%), dyspepsia (8.0%), insomnia (8.0%), extrapyramidal symptom (5.7%), and back pain (5.1%). EPS adverse events including akathisia, extrapyramidal symptom, and tremor, were reported by 22% of patients, and mostly began before week 3 of treatment. The mean weight increased by 1.5 + 3.0 kg and 15% of participants showed clinically significant weight increase (≥7%). Fasting serum triglyceride significantly increased from 107.5 + 74.2mg/dL at baseline to 164.9 + 233.7mg/dL at week 6 ($p = 0.0013$). Vital signs and ECG did not show clinically significant change. During the 24-week double-blind maintenance phase treatment, adverse events reported at an incidence of ≥ 3% and at least twice that of the placebo were insomnia (10.0%), alopecia (10.0%), and tremor (5.0%). The incidence of EPS adverse events in aripiprazole group was not different from placebo (10.0% vs 12%, respectively; $p = 1.000$) and none of patients discontinued because of EPS. The mean weight gain of placebo treated patients was 1.0 + 3.8 kg whereas aripiprazole treated patients had mean gain of 1.2_+ 5.4 kg. Significant (≥7%) weight gain was observed for 19 % of placebo treated patients and 23% or aripiprazole patients. Significant (≥7%) weight loss was recorded in 5% of placebo group and in 3% of the aripiprazole group. Aripiprazole group experienced a mean increase in serum triglyceride (+41.0 + 90.9mg/dL) from randomization to endpoint. However, no study subject experienced clinically significant hypertriglyceridemia during the maintenance phase [64].

A 46-week open-label extension study [65] evaluated the BD maintenance efficacy of aripiprazole in combination with lithium or valproate, following a 6-week double-blind placebo-controlled phase [66]. During the 46-week open-label extension phase [32], the following adverse events (AE) were recorded in more than 5% of patients in either the aripiprazole-lithium or aripiprazole-valproate groups: tremor (17.0% vs. 12.1%), akathisia (6.6% vs. 8.6%), headache (6.6% vs. 4.0%), insomnia (9.4% vs. 10.3%), depression (7.5% vs. 9.2%) and weight increase (11.3% vs. 8.6%). Akathisia, tremor and insomnia events tended to occur early in the study, after treatment initiation. For

instance, out of 40 akathisia events that were registered over the 52-week study, 33 started before Week 6 and only two occurred after week 12. Also, by the end of the 52-week study, half of the akathisia cases had resolved and 80% of the cases that did not resolve were mild to moderate. Minimal changes were observed on the SAS, AIMS or BARS. Mean change in weight was 2.1 kg. Cholesterol and triglycerides did not change significantly. Fourteen per cent of participants dropped out because of AE, most frequently depression (3.2%), mania (1.4%) and depressive symptoms (1.1%) [65]. A 52-week trial compared aripiprazole to placebo, as an adjunct to lithium or valproate, for the maintenance treatment of bipolar I disorder [34]. In the randomized, placebo-controlled phase, 62.9% of patients assigned to aripiprazole (combined with lithium or valproate) and 63.3% of the placebo (combined with lithium or valproate) group experienced at least one AE. Adverse events that occurred in more than 5% of study subjects in either study group were headache (aripiprazole 13%, placebo 11%), insomnia (5% vs 10%), weight increase 11 (9% vs 7%), and tremor (6% vs 2%) [67].

3.3.2.2 Long acting injectable aripiprazole

The United States FDA has recently approved aripiprazole long acting injection once-monthly (AOM) for the maintenance monotherapy treatment of bipolar I disorder (BP-I) [2]. Overally, AOM has been deemed as a LAI is a safe and efficacious treatment option in the maintenance therapy of bipolar I disorder [68]

A large, double-blind, placebo-controlled, 52-week randomized withdrawal study was conducted to evaluate the safety, tolerability and efficacy of AOM once-monthly as maintenance treatment for BP-I [2, 69]. The most frequently AE (≥ 5%) occurring during the initial stabilization phase (single-blind AOM) were akathisia (17%), increased weight (11%), insomnia (10%), anxiety (7%), restlessness (6%), fatigue (5%), and nasopharyngitis (5%). Mean increase in weight from baseline to the last visit in AOM stabilization phase was 1.0 kg, with potentially clinically relevant weight gain at any time during the randomized phase observed 11% of patients. In the randomized phase (AOM vs Placebo), 18% of AOM subjects vs 13% or patients assigned to placebo had clinically significant (>7%) weight gain. Other AE occurring in more than 5% of either AOM or placebo group were akathisia (21% aripiprazole vs 13% placebo respectively), nasopharyngitis (8% vs 10%), insomnia (8% vs 8%), anxiety (7 % vs 5%), mania (2% vs

11%), and headache (3% vs 7%). No clinically meaningful changes in fasting glucose, lipids, or prolactin were observed within or between groups. Injection site pain was low and decreased with subsequent injections [69].

3.3.3 Pregnancy and lactation

No adequate and well controlled study of aripiprazole in pregnant women has ever been conducted [1, 27]. Intravenous and oral administration of aripiprazole during organogenesis in rats and/or rabbits at doses higher than the maximum recommended dose (MRD) in humans, lead to in fetal death, skeletal malformations or delayed ossification, undescended testicles, diaphragmatic hernia, and reduced fetal weight. Intravenous and oral administration of aripiprazole during the pre- and post-natal period in rats at doses higher than the MRD lead to prolonged gestation, stillbirths, decreased pup weight, and survival. We recently conducted a systematic literature search and review to inform clinical practice about aripiprazole use during pregnancy, peripartum and lactation [70] and concluded that definitive evidence on reproductive safety of aripiprazole is lacking. Yet, newer safety data are relatively reassuring and therefore we concluded that, in many cases, the potential benefits of aripiprazole use during pregnancy outweigh the potential risks. For instance, Bellet et al. [71] performed a prospective cohort study involving 81 women who were exposed to aripiprazole during embryogenesis. These 81 women were compared to pregnant women without exposure. Compared to unexposed women, exposure to aripiprazole was not associated with a significantly increased rate of major malformations, miscarriage, or gestational diabetes. However, exposure to aripiprazole was associated with a significantly increased risk of fetal growth retardation and prematurity.

A prospective follow-up study to evaluate pregnancy outcomes after exposure to aripiprazole was conducted by Paulus [72], who compared study subjects with a control group of pregnant women who were not exposed to teratogenic agents. The difference in the rate of spontaneous abortions was not significant. Three congenital anomalies were reported after intrauterine exposure to aripiprazole: hip dysplasia, anal atresia and motor developmental disorder. However, no significant difference was observed in the

rate of congenital anomalies between women exposed to aripiprazole (3/52 = 5.8% vs 6/174 = 3.4%, p = 0.43) and not exposed women.

3.3.3.1 Perinatal complications

The majority of published cases of aripiprazole use during pregnancy did not report perinatal complications [70]. However, extrapyramidal and/or withdrawal symptoms, including tremor, hypertonia, hypotonia, agitation, somnolence, and feeding disorder respiratory distress have been reported in neonates who were exposed to antipsychotic drugs (including aripiprazole) during the third trimester of pregnancy. Also, many antipsychotics have been associated with risk of respiratory distress, anomalies in muscle tone and perinatal cardiac rhythm disturbances, and transient respiratory distress, fetal tachycardia, reduced muscle tone have been rarely described in fetuses exposed to aripiprazole [70].

3.3.3.2 Lactation

The milk to-plasma ratio of aripiprazole and the risk of adverse events is relatively low [70]. However, caution is warranted as the treatment with aripiprazole may also be correlated with insufficient milk production due to reduced prolactin release.

3.3.4 Elderly patients

The tolerability and safety of aripiprazole in the elderly population with bipolar disorder is yet to be established and only few studies have addressed the issue of treatment decisions in older patients with bipolar disorder [73]. Indeed, the pharmacological treatment of late life bipolar disorder should be better evaluated with well-designed, adequately powered and controlled clinical trials. For instance, it is known that elderly patients are at increased risk of AE, because of their increased risk for drug interactions and because of age-related pharmacokinetic and pharmacodynamic changes, such as decreased hepatic metabolism, decreased kidney clearance, decreased gastric acid secretion, reduced cardiac output, decreased lean body mass and increased body fat, along with a change in receptors density and distribution.

Side effects from antipsychotics that are particularly bothersome for older adults include orthostatic hypotension, anticholinergic side effects (often resulting in urinary retention, fecaloma and bowel obstruction), sedation, extrapyramidal symptoms (i.e., tremor and rigidity), and tardive dyskinesia (e.g., lip smacking).

Based on the relatively low risk of aripiprazole for the symptoms above, this medication may be one of the first line antipsychotics for elderly patients.

3.3.5 Pathological gambling and other compulsive behaviors

Post-marketing case reports have described a relationship between the use of aripiprazole and the development of intense and incontrollable urges, particularly for gambling, while taking this medication. Although less frequently, other impulsive or compulsive behaviors and urges have been reported, such as sexual urges, shopping, eating or binge eating.

4. Conclusion

When used for its bipolar disorder indications, aripiprazole shows a favorable tolerability profile, with relatively low incidence of metabolic side effects, hyperprolactinemia, orthostatic hypotension, extrapyramidal symptoms, and sedation, both in its short term and in its long term, maintenance, use. The once-monthly injectable formulation, recently approved in the United States for the maintenance treatment of bipolar disorder, shares a generally benign tolerability profile with the injectable immediate release and with the oral formulation. Aripiprazole safety and tolerability profile is usually favorable but, of course, the medication is not completely free of risks or side effects. However, BD is a chronic, severe and debilitating disease and the balance between the potential risks and the potential benefits of aripiprazole use is largely favorable for many patients.

5. Expert opinion

Oral and injectable (immediate release or long acting once-monthly) aripiprazole, have proven efficacious and relatively well tolerated in different phases of BD treatment. Medication safety and tolerability are critical and of utmost importance for individuals with BD, given their need to stay on medications for the long-term. A medication that is poorly tolerated, dramatically impairs quality of life and jeopardizes treatment adherence. Hence, it is encouraging to note that the most of aripiprazole adverse events occur at a rate that is similar to the rate found in placebo or that is lower than the

rate observed for many of the other antipsychotics. For instance, a consistent finding across the many aripiprazole trials is the low change in metabolic parameters, with relatively low risk of diabetes, dyslipidemia, and weight gain. This issue is particularly important, given the high risk for metabolic illness in patients with BD. We previously demonstrated a very high prevalence of obesity and metabolic syndrome in patients with BD [74-75] and showed a strong correlation between obesity and an unfavorable psychiatric outcome. Specifically, we observed that obese patients with BD had a higher lifetime number, a higher degree of severity of bipolar episodes, along with a significantly shorter time to recurrence following remission of an acute episode [76], and a higher number of suicide attempt [77].

Aripiprazole is also associated with low risk of EPS (except akathisia) as well as with a low cardiovascular risk, owing to its low propensity to cause QTc interval prolongation or other arrhythmias and to the relatively low risk to induce a metabolic syndrome.

Aripiprazole has virtually no risk to induce hyperprolactinemia. If anything, aripiprazole may decrease hyperprolactinemia induced by other antipsychotics [21]. This is particularly important, in that hyperprolactinemia may be associated with a host of tolerability issues [79] including sexual dysfunction (reduced libido, erectile dysfunction, impotence, painful or retrograde ejaculation, orgasmic dysfunction), reproductive dysfunction (menstrual irregularity, sub-fertility, decreased estrogen and testosterone production, anovulation), breast pathology (galactorrhea, breast pain, breast enlargement, dysplasia and possibly increased risk for breast cancer), decreased bone mineral density and osteoporosis and even behavioral and mood alterations (depression, anxiety, memory deficit, psychosis) [80] or immunologic depression [81-82].

The development of new and/or intense gambling urges, compulsive sexual urges, compulsive shopping, binge or compulsive eating, or other urges while being treated with aripiprazole is uncommon but yet well worth of being considered [1, 27]. Many patients do not recognize these behaviors as abnormal. Hence, it is key that clinicians mention this risk before starting aripiprazole and then check with patients or caregivers about its presence once the medication has been started. In some cases, impulse-control symptoms may be more due to the underlying disorder than to aripiprazole.

However, an association with the medication has been observed and some patients, although not all of them, have been reported to have stopped their urges upon reduction of the dose or discontinuation of the medication. Hence, particular caution is warranted [1, 27].

Owing to its partial agonism at the D2 receptors, aripiprazole is unlikely to result in affective flattening or cognitive problems determined by dopamine antagonism in the mesocortical pathways. Indeed, it is our observation that this medication is unlikely to precipitate depression, despite the fact that it failed two studies in acute bipolar depression. Of interest, aripiprazole has instead proven effective for the adjunctive treatment of major depressive episodes in major depressive disorder. The negative results in the bipolar depression trials may be at least in part accounted for by some peculiarities in the study design, such as the medication administration in the evening, with the risk of insomnia and akathisia (well able to influence the score on the primary outcome measure), the inclusion of patients who were treated with benzodiazepines, followed by the mandatory discontinuation of those compounds, and a titration schedule and target dose of aripiprazole that was relatively high for the treatment of bipolar depression.

Aripiprazole has a low tendency to result in anticholinergic side effects, such as dry mouth, constipation or urinary retention, which makes this medication particularly useful for older patients or patients with medical conditions that make the conditions above more frequent or more clinically relevant. Similarly, aripiprazole is unlikely associated with anti alpha-adrenergic side effects, such as orthostatic hypotension, which is beneficial in general and particularly beneficial for populations such as the elderly patients. Aripiprazole is also associated with a low risk of sedation, owing to its low affinity for H1 and alpha 1 adrenergic receptors. Of interest, the rate of sedation reported in pediatric clinical trials is higher than the rate reported in adults, which is consistent with our clinical observations.

However, aripiprazole weak antihistamine, anti-alpha adrenergic and antimuscarinic properties may require adjunctive treatment with another medication, at least for the short term. For instance, if a patient with insomnia is treated with aripiprazole, it is usually necessary to associate a hypnotic or sedating medication. If a patient develops

akathisia, it is often necessary to add a beta antagonist, such as propranolol (provided that there are not contraindications, such as asthma or Chronic obstructive pulmonary disease), a GABAergic medication, such as a benzodiazepine, or an anticholinergic medication.

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Table 1

Aripiprazole Dose Adjustments in CYP2D6 Poor Metabolizers or in Patients Taking Concomitant CYP2D6 Inhibitors, 3A4 Inhibitors, and/or CYP3A4 Inducers [1-2, 20-21].

CYP2D6 Poor Metabolizers	Administer half of usual dose	300 mg (1.5 mL)
CYP3A4 inhibitors (e.g., clarithromycin itraconazole)	Administer half of usual dose	Reduce dose by 100 mg; e.g. from 400 mg (2 mL) to 300 mg (1.5 mL) or from 300 mg (1.5 mL) to 200 mg (1 mL)
CYP2D6 Poor Metabolizers taking CYP3A4 inhibitors (e.g., itraconazole, clarithromycin)	Administer a quarter of usual dose	200 mg (1 mL)
CYP2D6 (e.g., quinidine, fluoxetine,paroxetine) inhibitors	Administer half of usual dose	Reduce by 100 mg: from 400 mg (2 mL) to 300 mg (1.5 mL) or from 300 mg (1.5 mL) to 200 mg (1mL)
CYP2D6 and CYP3A4 inhibitors	Administer a quarter of usual dose	Reduce from 400 mg (2 mL) to 200 mg (1 mL) or from 300 mg (1.5 ml) to 160 mg (0.8mL)
CYP3A4 inducers (e.g., carbamazepine,	Double usual dose over 1 to 2	Avoid AOM use

rifampin)	weeks	