

This item is the archived peer-reviewed author-version of:

Pharmacokinetic evaluation of the aripiprazole (once-monthly) injection for the treatment of bipolar disorder

Reference:

Hebbrecht Kaat, Morrens Manuel, Neels Hugo, Roosens Laurence, Sabbe Bernard.- Pharmacokinetic evaluation of the aripiprazole (once-monthly) injection for the treatment of bipolar disorder
EXPERT OPINION ON DRUG METABOLISM & TOXICOLOGY - ISSN 1742-5255 - 14:10(2018), p. 999-1005
Full text (Publisher's DOI): <https://doi.org/10.1080/17425255.2018.1515911>
To cite this reference: <https://hdl.handle.net/10067/1548200151162165141>



Pharmacokinetic evaluation of the aripiprazole (once-monthly) injection for the treatment of bipolar disorder

Kaat Hebbrecht, Manuel Morrens, Hugo Neels, Laurence Roosens & Bernard G.C. Sabbe

To cite this article: Kaat Hebbrecht, Manuel Morrens, Hugo Neels, Laurence Roosens & Bernard G.C. Sabbe (2018): Pharmacokinetic evaluation of the aripiprazole (once-monthly) injection for the treatment of bipolar disorder, Expert Opinion on Drug Metabolism & Toxicology, DOI: [10.1080/17425255.2018.1515911](https://doi.org/10.1080/17425255.2018.1515911)

To link to this article: <https://doi.org/10.1080/17425255.2018.1515911>



Accepted author version posted online: 24 Aug 2018.



Submit your article to this journal [↗](#)



View Crossmark data [↗](#)

Publisher: Taylor & Francis

Journal: *Expert Opinion on Drug Metabolism & Toxicology*

DOI: 10.1080/17425255.2018.1515911

Pharmacokinetic evaluation of the aripiprazole (once-monthly) injection for the treatment of bipolar disorder

Kaat Hebbrecht^{1,2,*}, Manuel Morrens^{1,2}, Hugo Neels³, Laurence Roosens³, Bernard G.C. Sabbe^{1,2}

¹ Collaborative Antwerp Psychiatric Research Institute (CAPRI), Faculty of Medical and Health Sciences, University of Antwerp. Campus Drie Eiken - gebouw R, Universiteitsplein 1, 2610 Antwerpen, Belgium.

² University Department, Psychiatric Hospital Duffel, VZW Emmaüs. Stationsstraat 22c, 2570 Duffel, Belgium.

³ Toxicological Centre, Department of Pharmaceutical Sciences, University of Antwerp. Campus Drie Eiken - gebouw S, Universiteitsplein 1, 2610 Antwerpen, Belgium.

***Corresponding author:** Kaat Hebbrecht, University Department, Psychiatric Hospital Duffel, Stationsstraat 22c, 2570 Duffel, Belgium. E-mail: kaat.hebbrecht@uantwerpen.be

Abstract

Introduction

Bipolar disorder is a severe, chronic psychiatric disorder with a need for long-term treatment. Patient non-adherence is frequent and poses a major problem in maintenance therapy. Aripiprazole once-monthly long-acting injectable (AOM LAI) is a recently FDA approved treatment option for maintenance therapy that could be of great value.

Areas covered

This paper reviews the pharmacokinetic, efficacy and safety data for AOM LAI in bipolar disorder.

Expert opinion

AOM LAI is a safe and efficacious treatment option in the maintenance therapy of bipolar I disorder. However, further research is still needed to determine the position of AOM LAI relative to other available treatment options.

Keywords: antipsychotic; aripiprazole; bipolar disorder; long-acting injectable; LAI

1. Introduction

Bipolar disorder is a severe, chronic and relapsing psychiatric disorder present in 1-3% of the general population (1–3). It is characterized by episodes of (hypo)mania and major depression. A manic episode is marked by the presence of abnormally elevated or irritable mood and increased activity for at least one week. Hypomania shares the same features as mania, but these are present in a lesser degree and do not cause significant functional disruption. A major depressive episode is a period of persistent decreased mood and lack of interest or pleasure in nearly all activities (4,5). Inter-episodic periods in bipolar disorder are commonly characterized by residual (mostly depressed) symptoms, cognitive deficits and psychiatric and medical comorbidity. These features contribute to the significant burden of the disease (6,7). In 2013, bipolar disorder was ranked as the sixteenth leading cause of Years Lived with Disability (8).

Considering the chronic relapsing-remitting nature of the disease, life-long pharmacological treatment is necessary. The treatment of bipolar disorder consists of three phases: an acute phase targeted at rapid alleviation of depressed or manic symptoms, a continuation phase aiming at complete remission of the initial mood episode and a maintenance phase intended to prevent relapse, reduce residual symptoms and enhance social and occupational functioning (9,10). Effective maintenance treatment is of utmost importance in the management of bipolar disorder. However, despite pharmacological treatment, relapse rates are high. As an example, in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), nearly 50 % of patients (from a total of 858 patients who initially recovered from a mood episode) experienced relapse during a 2-year period (11).

An important obstacle in achieving the goals of maintenance therapy is treatment nonadherence. As many as 50 % of patients with bipolar disorder are not or partially adherent to pharmacological treatment (12–14). Apart from undermining the efficacy of treatment and thereby increasing the risk of relapse and illness recurrence, non-adherence also increases the risk of re-hospitalization and even suicide (15–17).

Clinical approaches to improve patient adherence include forming a genuinely collaborative clinician-patient therapeutic alliance and informing the patient and their caregivers about the nature of the illness and the importance of adherence. Other (medication-related) approaches are simplifying drug regimens, close monitoring of tolerability, addressing of side effects and considering the use of long-acting injectable (LAI) drugs (18–20). LAI drugs have the advantage of ensuring continuous drug exposure during a period of multiple weeks after one

single injection. The only LAI drugs approved for the maintenance treatment of BP-I are risperidone and aripiprazole LAI (Abilify Maintena[®]) (21).

The present paper provides an evaluation of the pharmacokinetic (PK) properties of the aripiprazole once-monthly injection and its efficacy in the treatment of bipolar disorder. We performed a systematic literature search of Web of Science and PubMed with the terms ‘aripiprazole once-monthly’ or ‘aripiprazole long-acting’ in combination with ‘pharmacokinetics’, ‘pharmacodynamics’, ‘bipolar disorder’, ‘mania’, ‘depression’ and ‘maintenance’.

ACCEPTED MANUSCRIPT

2. Overview of the market

For the treatment of an acute manic episode, the most recently updated guidelines recommend monotherapy of lithium, valproate or a second-generation antipsychotic (e.g., quetiapine, olanzapine, aripiprazole and risperidone) as first-line treatment. Combination treatment with lithium or valproate and a second-generation antipsychotic is also described as a first-line, especially in situations where fast response is needed (22–24). The described anti-manic agents are well studied and they show comparable efficacy (Cohen's d 0.32-0.66; small to medium effect size) (25). However, since head-to-head comparisons of the available drugs are scarce, a hierarchy on comparative efficacy is difficult to obtain. The efficacy and acceptability of all anti-manic drugs in acute mania were compared in the multiple-treatments meta-analysis by Cipriani et al. (26). The authors concluded that antipsychotics were a better overall option than mood stabilizers (26).

The evidence for the treatment of bipolar depression is far more limited than that for the treatment of manic symptoms, so, currently, there is no consensus on the treatment of acute bipolar depression (22–24). This is an important unmet need in the management of bipolar disorder since depressive symptoms occur three times more frequently than manic symptoms and cause more functional impairment (27). Monotherapy with quetiapine and the combination olanzapine-fluoxetine are considered as a first-line treatment option for bipolar depression (22–24). Lurasidone is a US FDA approved treatment option for bipolar depression in children and adults but it does not have a license for use in this indication in Europe. Based on current evidence, nor the use of lithium neither aripiprazole monotherapy is supported in treating bipolar depressed symptoms (28).

Selecting appropriate maintenance treatment remains a complex issue. Studies with a multi-year follow-up period are scarce and many factors need to be taken into account by the clinician when choosing treatment (e.g. tolerability and safety, polarity and cyclicity, psychiatric and somatic co-morbidities) (22,29). Currently recommended first-line treatments are lithium, valproate, lamotrigine, and the atypical antipsychotics quetiapine and aripiprazole (oral or once-monthly). Olanzapine, risperidone (oral or once-monthly) and carbamazepine are considered second line (22–24,29). Lithium, valproate and quetiapine have a bimodal efficacy in preventing both mania and depression (30–33). Aripiprazole and risperidone prevent mania, but not depression (34,35). Lamotrigine has been found more effective in preventing depression (36).

3. Introduction to the compound

Aripiprazole is an atypical antipsychotic that is available in different formulations: short-acting oral and injectable formulations and long-acting injectable (LAI) formulations. Two related

aripiprazole LAI formulations are currently available, Abilify Maintena[®] aripiprazole 400 once-monthly (AOM 400) LAI and Aristada[®] (aripiprazole lauroxil) but only AOM 400 LAI has a US Food and Drug Administration (FDA) approval for maintenance treatment in adult patients (age 18 and older) with bipolar disorder (21). Aripiprazole once-monthly (AOM) LAI is a depot formulation of aripiprazole consisting of a lyophilized powder that forms an injectable suspension when reconstituted with sterile water. AOM LAI is available in prefilled dual chamber syringes or single-use vials, both containing 300 or 400 mg of the anhydrous form of aripiprazole. The single-use vials are needed for injections of less than 300 mg (37). The recommended dose for maintenance treatment of bipolar I disorder is 400 mg once-monthly. Before starting AOM LAI, tolerability with oral aripiprazole has to be established for two weeks. The oral aripiprazole formulation needs to be continued for fourteen days after the initial administration of AOM LAI (37).

4. Chemistry

AOM LAI is the monohydrate polymorphic form of aripiprazole. Aripiprazole monohydrate is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyryl monohydrate. Its molecular formula is $C_{23}H_{27}Cl_2N_3O_2 \cdot H_2O$ and it has a molecular weight of 466.40. The chemical structure of aripiprazole monohydrate is shown in Figure 1 (38).

Box 1. Drug Summary

Drug name	Aripiprazole once-monthly long-acting injectable (AOM LAI)
Phase	Three
Indication	Maintenance treatment bipolar I disorder
Pharmacology	Partial agonism at D_2 and $5-HT_{1A}$, antagonism at $5-HT_{2A}$
Route of administration	Intramuscular (gluteal or deltoid)
Chemical structure	7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl] butoxy]-3,4 dihydrocarbostyryl monohydrate
Pivotal trial(s)	Maintenance treatment bipolar I disorder (36)

5. Pharmacodynamics

Aripiprazole is an atypical antipsychotic with a high affinity for dopamine D_2 and D_3 receptors and a moderate affinity for D_4 receptors. Functionally, aripiprazole has a unique

pharmacological profile, including partial D₂ agonism and functional selectivity at D₂ receptors. The concept of functional selectivity implies that aripiprazole may have effects as extreme as a full antagonist or a partial agonist depending on factors such as endogenous dopamine level and signaling status (39–41). Among serotonergic receptors, aripiprazole has a high affinity to 5-HT_{1A} and 5-HT_{2A} receptors (resulting in partial agonism and antagonism respectively) and a moderate affinity to 5-HT_{2C} and 5-HT₇ (both resulting in partial agonism). Aripiprazole also has a moderate affinity at alfa-adrenergic, muscarinic, cholinergic and histamine H₁ receptors. The modest H₁R affinity explains the minimal propensity of aripiprazole to induce weight gain or sedation (42-43).

The activity of aripiprazole LAI OM is primarily due to aripiprazole and, to a lesser extent, its metabolite dehydro-aripiprazole, which has similar pharmacodynamic effects at the D₂ receptors (37,44).

6. Pharmacokinetics and metabolism

The absorption and elimination characteristics of AOM LAI have been adequately studied. The available data on distribution and metabolism profile are mainly derived from studies with oral aripiprazole (37,44) (Table 1).

The systemic absorption of AOM LAI is slow and prolonged due to the low solubility of aripiprazole particles (44). In a study comparing the deltoid and gluteal administration, the aripiprazole exposure was similar, but the absorption rate was higher for deltoid administration (45). This can be explained by the smaller mass and higher perfusion of the deltoid muscle. The time to reach peak plasma values was four days for deltoid administration and five to seven days for gluteal administration (45). Steady-state concentrations are obtained after four once-monthly injections for both doses and both sites of administration (37,44,45). In comparison, the once-daily oral administration (doses of 15 to 30 mg) reaches peak plasma values after three to five hours and steady-state concentrations after fourteen days (46).

Aripiprazole is extensively serum protein bound (99%) and has a high distribution volume of 4.9 l/kg, indicating extensive extravascular distribution.

There is a minimal pre-systemic metabolism of aripiprazole at the site of injection. Systemic metabolism mostly occurs by the liver through three principal biotransformation pathways: dehydrogenation, hydroxylation (both mediated by 3A4 and CYP2D6) and CYP3A4-mediated N-dealkylation. Aripiprazole is the prevailing medicinal product moiety in systemic circulation. After multiple dose administration of Abilify Maintena, dehydro-aripiprazole, the

active metabolite, represents approximately 30 % of aripiprazole AUC in plasma. An overview of the main metabolites of aripiprazole is shown in Figure 2 (47).

Aripiprazole OM LAI has an elimination half-life of 29.9 days for 300 mg and 46.5 days for 400 mg. Excretion of aripiprazole occurs via the kidney (25%, less than 1 % unchanged) and the liver (55%, 18 % as unchanged drug) (37,44).

The influence of renal and hepatic impairment on the pharmacokinetics of (oral) aripiprazole has been investigated in two open-label, single-dose studies. No pharmacokinetic differences were observed between the group of patients with severe renal disease (creatinine clearance less than 30 mL/min; n=6) and the young healthy subjects (n=7). The hepatic impairment study also didn't reveal any significant effect of hepatic impairment on the pharmacokinetics of aripiprazole, however, the number of patients with severe hepatic impairment (Child-Pugh score C) was very small (n=3), thereby limiting the interpretation of the results (48).

The use of aripiprazole during pregnancy should be discouraged due to a lack of safety information (37,44).

Table 1. Summary of pharmacokinetic parameters of aripiprazole.

Property	Oral aripiprazole (Dose 20 – 30 mg)	Aripiprazole I.M. (Dose 400 mg)
Absorption		
- C _{max} (ng/ml)	393 – 452 ^a (46)	316 ^b (49)
- T _{max}	3 – 5 hours ^a (46)	4 days (gluteal administration); 5-7 days (deltoid administration) (45)
- T _{1/2}	75 h ^c	46.5 days (gluteal)
- Bioavailability (F)	87 %	N/A
- Food effect	A high fat meal does not affect the C _{max} but delays T _{max} by 3 hours	N/A
Distribution		
- V _d	4,9 l/kg	N/A
- % protein binding	> 99%	N/A
Metabolism	CYP3A4, CYP2D6	N/A

Excretion	1 % unchanged drug in urine 18 % unchanged drug in feces	N/A
-----------	---	-----

Abbreviations: C_{max} : maximum plasma concentration; T_{max} : time to maximum (peak) plasma concentration; C_{min} : minimum plasma concentration; $t_{1/2}$: elimination half-life;

F: bioavailability; V_d : distribution volume

^a following multiple oral dosing 14 days, n=5 (20 mg), n=5 (30 mg)

^b Following five injections of aripiprazole once-monthly

^c Caution is needed in case of CYP2D6 polymorphisms e.g. $T_{1/2}$ in CYP2D6 poor metabolizers: 146 h

N/A: no data available

7. Pharmacogenetics

CYP2D6 genetic variations can have an influence on serum concentrations of aripiprazole (50,51). For oral administration, a dose reduction of 30 to 50 % is recommended for CYP2D6 poor metabolizers. For ultra-rapid metabolizers, switch to an alternate antipsychotic may be necessary because of reduced drug levels (52).

Population PK evaluations revealed no effect of race or smoking behavior on the pharmacokinetics of aripiprazole. Similarly, there were no effects of gender and age on the pharmacokinetics of aripiprazole in oral formulations or AOM LAI (37,44).

8. Clinical efficacy

There is only one (phase three) study investigating the efficacy of AOM LAI in the treatment of bipolar disorder (53). In this randomized, placebo-controlled withdrawal study, Calabrese and colleagues (53) examined the effect of AOM LAI as maintenance monotherapy treatment for bipolar I disorder. The study sample consisted of 266 patients with bipolar I disorder, experiencing a manic episode (both according to DSM-4 criteria) at study entry. Bipolar patients with rapid cycling were excluded from the study.

The study consisted of four stages: conversion to oral aripiprazole (four to six weeks), stabilization on oral aripiprazole (target dose: 15-30 mg/day; two to eight weeks), single-blind AOM 400 stabilization (twelve to 28 weeks) and, for patients who fulfilled the stability criteria for \geq eight successive weeks, 1:1 randomization to 52 weeks of double-blind treatment with AOM 400 or placebo. The authors defined stability as fulfilling all the following criteria: outpatient status, Young Mania Rating Scale (YMRS) total score \leq 12,

Montgomery-Asberg Depression Rating Scale (MADRS) total score ≤ 12 , and no active suicidality (defined as score ≥ 4 on MADRS item 10 or “yes” on question 4 or 5 of the Columbia Suicide Severity Rating Scale (C-SSRS)).

The primary outcome measurement was time from randomization to recurrence of any mood episode. The main secondary outcome measurement was the number of patients who experienced recurrence of any mood episode. Time to recurrence and time to discontinuation were computed by the Kaplan-Meier method and analyzed using log-rank test statistics and Hazard ratios.

Of the 266 patients, 102 completed the study (48.1 % in the AOM 400 group and 28.6 % in the placebo group). In most cases, the discontinuation was due to recurrence of any mood episode with or without adverse events (AE). The AOM group had a significantly increased time to recurrence of any mood episode compared with placebo (log-rank test; $p < 0.0001$). Furthermore, the number of patients with recurrence of any mood episode was significantly lower (Fisher exact test $p < 0.0001$) in the treatment group compared to the placebo group (35/132 or 26.5 % vs. 68/133 or 51.1 %). When looking at the type of mood episode, there was a significant difference in recurrence of manic (52 episodes total; $p < 0.0001$) but no difference concerning the recurrence of depressive episodes (39 episodes total; $p = 0.864$). The proportion of patients with recurrence in mixed mood episode was comparable to that observed for manic recurrences (AOM 400, 1.5% vs placebo, 6.8%; Fisher exact test $P = .06$) but the total number was only 11 (53).

9. Safety and tolerability

The most common treatment-emergent adverse effects in the stabilization phase of the Calabrese study (53) were akathisia (17.4 %), weight increase (11.1 %) and insomnia (9.6 %). In treated patients, the mean (SD) increase in weight from baseline to week 52 was 1.3 kg (5.9) versus 1.5 kg (6.1 kg) for the placebo group. The proportion of patients experiencing clinically significant weight gain (increase $\geq 7\%$ from baseline) was higher in the treatment group compared to placebo (18.0 % vs 12.9 %)(53).

The safety of AOM LAI has also been investigated in multiple randomized controlled trials in schizophrenia patients. In the ASPIRE US Study ($n=269$), treatment-emergent adverse effects were weight gain (9.7%), akathisia (5.6%), headache (5.9%), tremor (5.9%), anxiety (5.9%) and insomnia (10.0%) (54). Mild injection site pain, induration and redness are other frequently reported adverse effects. We failed to find reports of AOM LAI-induced

lipodystrophy. The use of AOM LAI is contraindicated in patients with a history of hypersensitivity reactions to aripiprazole, ranging from pruritus to anaphylaxis (44).

10. Drug-drug interactions

Since aripiprazole is metabolized by CYP3A4 and CYP2D6 enzymes, drugs that induce or inhibit these enzymes can influence aripiprazole levels. For patients who are poor CYP2D6 metabolizers and who are also receiving a CYP3A4 inhibitor for \geq fourteen days, a 200 mg dose reduction is required. A 100 mg dose reduction is needed for patients taking a strong CYP2D6 or CYP3A4 inhibitor. A two-step reduction is proposed (i.e., 400 to 200 mg or 300 to 160 mg) in patients taking both 2D6 and 3A4 inhibitors. Concomitant use with CYP3A4 inducers with aripiprazole for more than fourteen days should be avoided. (37,44).

Due to its alpha-adrenergic antagonism, aripiprazole should be used with caution in co-administration with antihypertensive drugs. No dosage adjustments are required with lithium or valproate (55,56).

11. Dosing routes

The AOM LAI suspension should only be administered by intramuscular injection in the deltoid or gluteal muscle (37,44).

12. Regulatory affairs

Aripiprazole once-monthly injection was originally approved by the FDA in 2013 for the treatment of schizophrenia in adults. In July 2017, an FDA approval was achieved for the maintenance monotherapy in adult patients with bipolar I disorder, based on one phase three study (53).

13. Conclusion

Bipolar disorder is a severe psychiatric disorder marked by extreme shifts in mood. The efficacy of oral aripiprazole in both the treatment of acute (manic and mixed) episodes and in maintenance treatment is well established (34,57,58). Recently, also the depot form of aripiprazole, AOM LAI, has proven its value in the maintenance treatment of bipolar I disorder in one phase three placebo-controlled study, resulting in the FDA approval for this indication (53).

14. Expert opinion

Maintenance treatment forms a critically important mainstay in the management of bipolar disorder. Every relapse of mood episode negatively affects quality of life and psychosocial functioning (59) and can have an accumulating impairing effect on cognition (60). Unfortunately, current pharmacological options for maintenance treatment are limited and relapse is frequent (11). Medication non-adherence is a frequent complicating factor in the maintenance treatment. Up to half of patients with BD are not or partially compliant with prescribed medication (12–14). Long-acting injectable drugs are an attractive option for maintenance treatment of BD in that they improve adherence and consequently could lower relapse rates and preserve functionality. Currently, only two LAIs (risperidone LAI and aripiprazole LAI) are approved for this indication. The efficacy of risperidone LAI in maintenance treatment in BD, particularly in preventing manic/mixed episodes, has been shown in several studies (35,61,62). However, its long-term use is complicated by the occurrence of side effects such as extrapyramidal symptoms (especially akathisia), weight gain, sedation and prolactin elevation (63). There is only one placebo-controlled study that investigates the efficacy of AOM LAI in the maintenance treatment of bipolar I disorder (53). The authors demonstrated a significantly delayed time to recurrence of mood episodes, primarily manic episodes, in the patient group treated with AOM LAI. AOM LAI could be of particular interest in the maintenance treatment of bipolar I disorder since it combines the advantages of a long-acting formulation (in terms of treatment adherence) with a favorable pharmacokinetic and tolerability profile. Generally, aripiprazole has a mild interaction potential, but it should be used with caution in combination with CYP2D6-inhibitors (e.g. fluoxetine, paroxetine) and CYP3A4-inhibitors (e.g. diltiazem). The co-administration with the CYP3A4 inducer carbamazepine should be avoided. Aripiprazole's antipsychotic effect is not associated with over-sedation or with significant prolactin concentration increases. Furthermore, compared to other antipsychotics (including risperidone LAI), it has a lower propensity for weight gain and a lower risk of metabolic side effects. Like all antipsychotics, aripiprazole does carry the risk for EPS, which can be a possible reason for discontinuation, due to its disabling nature.

In conclusion, AOM LAI is a safe and efficacious treatment-option in the maintenance therapy of bipolar I disorder. However, future research is needed to address some remaining issues. Firstly, head-to-head comparisons, in terms of efficacy and tolerability, with other maintenance treatment options are needed to determine the precise placement of AOM LAI

within the existing therapeutic arsenal. Secondly, the finding that AOM LAI is not efficacious in preventing depressive episodes needs to be confirmed by other studies.

Funding

This paper was not funded.

Declaration of interest

M Morrens has received grants from Bristol-Myers, Janssen Pharmaceuticals and Lundbeck. B Sabbe has received consultancy fees from Takeda, Bristol-Myers, Janssen Pharmaceuticals, and Lundbeck. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

ACCEPTED MANUSCRIPT

References

Papers of special note have been highlighted as:

* of interest

** of considerable interest

1. Grande I, Berk M, Birmaher B et al. Bipolar disorder. *Lancet*. 2016 Apr;387(10027):1561–72
 2. Pedersen CB, Mors O, Bertelsen A et al. A comprehensive nationwide study of the incidence rate and lifetime risk for treated mental disorders. *JAMA psychiatry*. 2014 May 1;71(5):573–81
 3. Merikangas KR, Jin R, He J-P et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. *Arch Gen Psychiatry*. 2011 Mar 7 68(3):241–51
 4. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (5th ed.)*. Arlington: American Psychiatric Publishing; 2013
 5. Machado-Vieira R, Luckenbaugh DA, Ballard ED et al. Increased Activity or Energy as a Primary Criterion for the Diagnosis of Bipolar Mania in DSM-5: Findings From the STEP-BD Study. *Am J Psychiatry*. 2017 Jan 1;174(1):70–6
 6. Leboyer M, Kupfer DJ. Bipolar Disorder. *J Clin Psychiatry*. 2010 Dec 15;71(12):1689–95
 7. Bowie CR, Depp C, McGrath JA et al. Prediction of real-world functional disability in chronic mental disorders: a comparison of schizophrenia and bipolar disorder. *Am J Psychiatry*. 2010 Sep;167(9):1116–24
 8. Ferrari AJ, Stockings E, Khoo J-P et al. The prevalence and burden of bipolar disorder: findings from the Global Burden of Disease Study 2013. *Bipolar Disord*. 2016 Aug;18(5):440–50
 9. Swann AC. Long-term treatment in bipolar disorder. *J Clin Psychiatry*. 2005;66 Suppl 1:7–12
 10. Geddes JR, Miklowitz DJ. Treatment of bipolar disorder. *Lancet*. 2013 May 11;381(9878):1672–82
 11. Perlis RH, Ostacher MJ, Patel JK et al. Predictors of recurrence in bipolar disorder: primary outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Am J Psychiatry*. 2006 Feb;163(2):217–24
 12. Lingam R, Scott J. Treatment non-adherence in affective disorders. *Acta Psychiatr Scand*. 2002 Mar;105(3):164–72
 13. Keck PE, McElroy SL, Strakowski SM et al. Factors associated with pharmacologic noncompliance in patients with mania. *J Clin Psychiatry*. 1996 Jul;57(7):292–7
 14. Scott J, Pope M. Nonadherence with mood stabilizers: prevalence and predictors. *J Clin Psychiatry*. 2002 May;384–90
 15. Gonzalez-Pinto A, Mosquera F, Alonso M et al. Suicidal risk in bipolar I disorder patients and adherence to long-term lithium treatment. *Bipolar Disord*. 2006 Oct;8:618–24
 16. Keck PE, McElroy SL, Strakowski SM et al. 12-Month Outcome of Patients With Bipolar Disorder Following Hospitalization for a Manic or Mixed Episode. *Am J Psychiatry*. 1998 May;155(5):646–52
 17. Strakowski SM, Keck PE, McElroy SL et al. Twelve-month outcome after a first hospitalization for affective psychosis. *Arch Gen Psychiatry* 1998 Jan;55(1):49–55
 18. Chakrabarti S. Treatment-adherence in bipolar disorder: A patient-centred approach. *World J psychiatry*. 2016 Dec 22;6(4):399–409
- *Overview article on treatment non-adherence in bipolar disorder emphasizing**

the importance of a patient-centred approach

19. Colom F, Vieta E, Tacchi MJ et al. Identifying and improving non-adherence in bipolar disorders. *Bipolar Disord*. 2005 Dec;7 Suppl 5(s5):24–31
20. Thase ME. Strategies for Increasing Treatment Adherence in Bipolar Disorder. *J Clin Psychiatry*. 2012 Feb 15;73(02):e08
21. Drugs@FDA. FDA Approved Drug Products; U.S. Food and Drug Administration. Silver Spring, MD: U.S. Food and Drug Administration. 2017
22. Yatham LN, Kennedy SH, Parikh S V et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord*. 2018 Mar;20(2):97–17
****Most recent CANMAT guidelines for management of patients with bipolar disorder**
23. Goodwin GM, Haddad PM, Ferrier IN et al. Evidence-based guidelines for treating bipolar disorder: Revised third edition recommendations from the British Association for Psychopharmacology. *J Psychopharmacol*. 2016 Jun 15;30(6):495–553
****Most recent BAP guidelines**
24. Kendall T, Morriss R, Mayo-Wilson E et al. Assessment and management of bipolar disorder: summary of updated NICE guidance. *BMJ*. 2014 Sep 25;349(sep25 5):g5673–g5673
****Most recent NICE guidelines**
25. Yildiz A, Nikodem M, Vieta E et al. A network meta-analysis on comparative efficacy and all-cause discontinuation of antimanic treatments in acute bipolar mania. *Psychol Med*. 2015 Jan 18;45(2):299–317
26. Cipriani A, Barbui C, Salanti G et al. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. *Lancet*. 2011 Oct 8;378(9799):1306–1
****Multiple-treatments meta-analysis comparing efficacy and acceptability of all anti-manic drugs**
27. Calabrese JR, Hirschfeld RMA, Frye MA et al. Impact of depressive symptoms compared with manic symptoms in bipolar disorder: results of a U.S. community-based sample. *J Clin Psychiatry*. 2004 Nov;65(11):1499–504
28. Young AH, McElroy SL, Bauer M et al. A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN I). *J Clin Psychiatry*. 2010 Feb 15;71(2):150–62
29. Morsel AM, Morrens M, Sabbe B. An overview of pharmacotherapy for bipolar I disorder. *Expert Opin Pharmacother*. 2018 Feb 11;19(3):203–22
30. Geddes JR, Burgess S, Hawton K et al. Long-Term Lithium Therapy for Bipolar Disorder: Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Am J Psychiatry*. 2004 Feb;161(2):217–22
31. Bowden CL, Calabrese JR, McElroy SL et al. A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Divalproex Maintenance Study Group. *Arch Gen Psychiatry* 2000 May;57(5):481–9
32. Berk M, Daglas R, Dandash O et al. Quetiapine v. lithium in the maintenance phase following a first episode of mania: randomised controlled trial. *Br J Psychiatry*. 2017 Jun 2;210(6):413–21
33. Vieta E, Suppes T, Eggens I et al. Efficacy and safety of quetiapine in combination with lithium or divalproex for maintenance of patients with bipolar I disorder. *J Affect Disord* 2008 Aug;109(3):251–63
34. Keck PE, Calabrese JR, McIntyre RS et al. Aripiprazole monotherapy for maintenance

- therapy in bipolar I disorder: a 100-week, double-blind study versus placebo. *J Clin Psychiatry*. 2007 Oct;68(10):1480–91
35. Quiroz JA, Yatham LN, Palumbo JM et al. Risperidone Long-Acting Injectable Monotherapy in the Maintenance Treatment of Bipolar I Disorder. *Biol Psychiatry*. 2010 Jul 15;68(2):156–62
 36. Calabrese JR, Bowden CL, Sachs G et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *J Clin Psychiatry*. 2003 Sep;64(9):1013–24
 37. ABILIFY MAINTENA® (aripiprazole) for extended-release injectable suspension, for intramuscular use [package insert]. Tokyo (Japan): Otsuka Pharmaceuticals Co. Ltd.; 2015. Available from: <https://www.otsuka-us.com/media/static/Abilify-M-PI.pdf> [Last accessed: 13 August 2018]
- **Complete overview of clinical pharmacology, warnings and precautions for the prescribing physician**
38. Potkin SG, Preda A. Aripiprazole once-monthly long-acting injectable for the treatment of schizophrenia. *Expert Opin Pharmacother*. 2016;17(3):395–407
 39. Tuplin EW, Holahan MR. Aripiprazole, A Drug that Displays Partial Agonism and Functional Selectivity. *Curr Neuropharmacol*. 2017 Nov 14;15(8):1192–207
 40. Mailman RB, Murthy V. Third generation antipsychotic drugs; partial agonism or receptor functional selectivity? *Curr Pharm Des*. 2010;16(5):488–501
 41. de Bartolomeis A, Tomasetti C, Iasevoli F. Update on the Mechanism of Action of Aripiprazole: Translational Insights into Antipsychotic Strategies Beyond Dopamine Receptor Antagonism. *CNS Drugs*. 2015 Sep 7;29(9):773–99
 42. Davies MA, Sheffler DJ, Roth BL. Aripiprazole: a novel atypical antipsychotic drug with a uniquely robust pharmacology. *CNS Drug Rev*. 2004;10(4):317–36
 43. McIntyre RS, Konarski JZ. Tolerability profiles of atypical antipsychotics in the treatment of bipolar disorder. *J Clin Psychiatry*. 2005;66 Suppl 3:28–36
 44. Agency EM. Abilify Maintena (Aripiprazole); 2015. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002755/human_med_001711.jsp&mid=WC0b01ac058001d124 [Last accessed: 13 August 2018]
 45. Raoufinia A, Peters-Strickland T, Nylander A-G et al. Aripiprazole Once-Monthly 400 mg: Comparison of Pharmacokinetics, Tolerability, and Safety of Deltoid Versus Gluteal Administration. *Int J Neuropsychopharmacol*. 2017 Apr 1;20(4):295–304
 46. Mallikaarjun S, Salazar DE, Bramer SL. Pharmacokinetics, tolerability, and safety of aripiprazole following multiple oral dosing in normal healthy volunteers. *J Clin Pharmacol*. 2004 Feb;44(2):179–87
 47. Casey AB, Canal CE. Classics in Chemical Neuroscience: Aripiprazole. *ACS Chem Neurosci*. 2017;8(6):1135–1146
 48. Mallikaarjun S, Shoaf SE, Boulton DW et al. Effects of Hepatic or Renal Impairment on the Pharmacokinetics of Aripiprazole. *Clin Pharmacokinet*. 2008;47(8):533–42
 49. Mallikaarjun S, Kane JM, Bricmont P, et al. Pharmacokinetics, tolerability and safety of aripiprazole once-monthly in adult schizophrenia: an open-label, parallel-arm, multiple-dose study. *Schizophr Res*. 2013;150(1):281–8
 50. van der Weide K, van der Weide J. The Influence of the CYP3A4*22 Polymorphism and CYP2D6 Polymorphisms on Serum Concentrations of Aripiprazole, Haloperidol, Pimozide, and Risperidone in Psychiatric Patients. *J Clin Psychopharmacol*. 2015 Jun;35(3):228–36
 51. Hendset M, Molden E, Knappe M et al. Serum Concentrations of Risperidone and Aripiprazole in Subgroups Encoding CYP2D6 Intermediate Metabolizer Phenotype.

- Ther Drug Monit. 2013 Nov;36(1):1
52. Lisbeth P, Vincent H, Kristof M et al. Genotype and co-medication dependent CYP2D6 metabolic activity: effects on serum concentrations of aripiprazole, haloperidol, risperidone, paliperidone and zuclopenthixol. *Eur J Clin Pharmacol.* 2016 Feb;72(2):175–84
 53. Calabrese JR, Sanchez R, Jin N et al. Efficacy and Safety of Aripiprazole Once-Monthly in the Maintenance Treatment of Bipolar I Disorder. *J Clin Psychiatry.* 2017 Mar 29;78(3):324–31
****The only randomized, placebo- controlled trial of aripiprazole once-monthly in the maintenance treatment of bipolar 1 disorder.**
 54. Kane JM, Sanchez R, Perry PP et al. Aripiprazole intramuscular depot as maintenance treatment in patients with schizophrenia: a 52-week, multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry.* 2012 May 15;73(5):617–24
 55. Citrome L, Josiassen R, Bark N et al. Pharmacokinetics of Aripiprazole and Concomitant Lithium and Valproate. *J Clin Pharmacol.* 2005 Jan;45(1):89–93
 56. Boulton DW, Kollia GD, Mallikaarjun S, Kornhauser DM. Lack of a pharmacokinetic drug-drug interaction between lithium and valproate when co-administered with aripiprazole. *J Clin Pharm Ther.* 2012 Oct;37(5):565–70
 57. Keck PE, Marcus R, Tourkodimitris S et al. A Placebo-Controlled, Double-Blind Study of the Efficacy and Safety of Aripiprazole in Patients With Acute Bipolar Mania. *Am J Psychiatry.* 2003 Sep;160(9):1651–8
 58. Keck PE, Calabrese JR, McQuade RD et al. A randomized, double-blind, placebo-controlled 26-week trial of aripiprazole in recently manic patients with bipolar I disorder. *J Clin Psychiatry.* 2006 Apr;67(4):626–37
 59. Mansell W, Colom F, Scott J. The nature and treatment of depression in bipolar disorder: a review and implications for future psychological investigation. *Clin Psychol Rev.* 2005 Dec;25(8):1076–100
 60. Bellivier F. Cognitions and functioning in euthymic bipolar patients: screening and treatment. *Encephale.* 2012 Dec;38 Suppl 4:S151-4
 61. Yatham LN, Fallu A, Binder CE. A 6-month randomized open-label comparison of continuation of oral atypical antipsychotic therapy or switch to long acting injectable risperidone in patients with bipolar disorder. *Acta Psychiatr Scand Suppl.* 2007 Oct;116(434):50–6
 62. Macfadden W, Alphs L, Haskins JT et al. A randomized, double-blind, placebo-controlled study of maintenance treatment with adjunctive risperidone long-acting therapy in patients with bipolar I disorder who relapse frequently. *Bipolar Disord.* 2009 Dec;11(8):827–39
 63. Available from: <http://www.janssenprescriptionassistance.com/risperdal-consta-cost-assistance>.
[Last accessed: 13 August 2018]

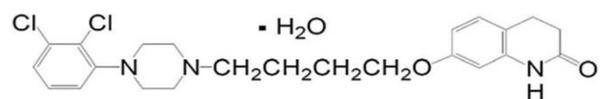
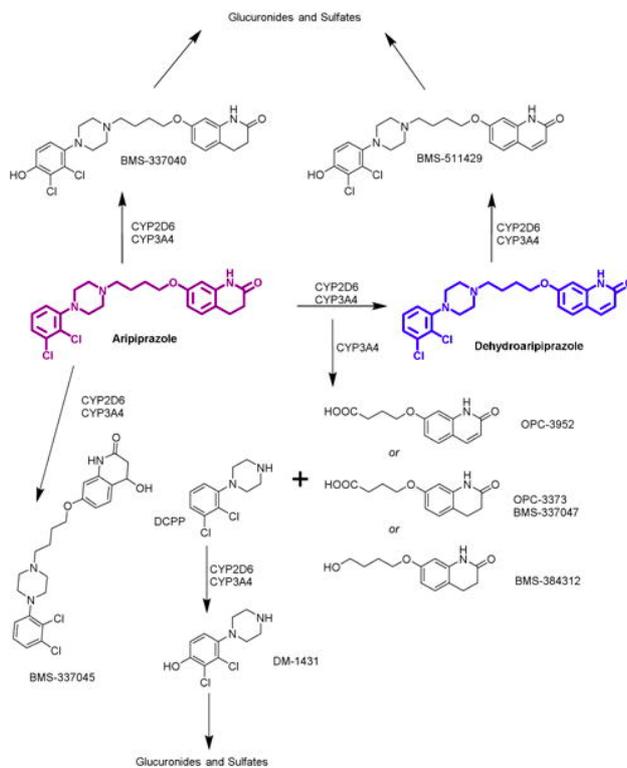


Figure 1: Chemical structure of aripiprazole (monohydrate polymorphic form) (38)



Structures of phase I metabolites of aripiprazole (adapted from FDA document NDA No. 21-436). Dehydroaripiprazole is the major metabolite after chronic dosing, and is pharmacologically active.

Figure 2: Structures of phase I metabolites of aripiprazole (47)