

TITLE: Aripiprazole for Patients with Bipolar Disorder: A Review of the Clinical Effectiveness, Cost-effectiveness and Guidelines

DATE: 25 May 2016

CONTEXT AND POLICY ISSUES

Bipolar disorder is a lifelong mental condition in which patients experience episodic mood swings between mania (elated, energized or irritable behaviour) and depression (sadness, despair, or hopelessness), that affects social activities, functioning, and relationships.¹ One percent (1%) of Canadians aged 15 years and over had symptoms that met the criteria for bipolar disorder in the previous 12 months.²

Symptoms of mania range from feelings of invincibility to irritability, increased activity and compulsive urges. Symptoms of depression can range from sadness to social withdrawal and suicidal thoughts.

The Diagnostic and Statistical Manual (5th edition; DSM-V) from the American Psychiatric Association³ differentiates between bipolar I and bipolar II disorders:

- Bipolar I Disorder: One or more manic episodes or mixed episodes. Individuals often have one or more major depressive episodes.
- Bipolar II disorder: One or more major episodes accompanied by at least one hypomanic episode.

The most common pharmacological treatments for bipolar disorders are lithium and valproic acid, but newer atypical antipsychotics, such as aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone are treatment options for patients with bipolar disorder, either as monotherapy or as adjunctive treatment.⁴ Aripiprazole is a third generation atypical antipsychotic which has a unique mode of action, acting as a partial agonist at dopamine D2 and D3, and serotonin 5-HT1A, and as an antagonist at the 5-HT2A and H1 receptors. It is frequently used in the treatment strategy for patients with bipolar disorders.⁵⁻⁸ In a recent Food and Drug Administration (FDA) safety communication, the FDA warns about impulse-control problems associated with an increase in activation symptoms such as compulsive or uncontrollable urges to gamble, binge eat, and shop in patients using aripiprazole.⁹

Disclaimer: The Rapid Response Service is an information service for those involved in planning and providing health care in Canada. Rapid responses are based on a limited literature search and are not comprehensive, systematic reviews. The intent is to provide a list of sources of the best evidence on the topic that CADTH could identify using all reasonable efforts within the time allowed. Rapid responses should be considered along with other types of information and health care considerations. The information included in this response is not intended to replace professional medical advice, nor should it be construed as a recommendation for or against the use of a particular health technology. Readers are also cautioned that a lack of good quality evidence does not necessarily mean a lack of effectiveness particularly in the case of new and emerging health technologies, for which little information can be found, but which may in future prove to be effective. While CADTH has taken care in the preparation of the report to ensure that its contents are accurate, complete and up to date, CADTH does not make any guarantee to that effect. CADTH is not liable for any loss or damages resulting from use of the information in the report.

Copyright: This report contains CADTH copyright material and may contain material in which a third party owns copyright. **This report may be used for the purposes of research or private study only.** It may not be copied, posted on a web site, redistributed by email or stored on an electronic system without the prior written permission of CADTH or applicable copyright owner.

Links: This report may contain links to other information available on the websites of third parties on the Internet. CADTH does not have control over the content of such sites. Use of third party sites is governed by the owners' own terms and conditions.

This Rapid Response report aims to review the clinical and cost-effectiveness of aripiprazole for patients with bipolar disorder. Guidelines associated with the use of aripiprazole for patients with bipolar disorder will also be examined.

RESEARCH QUESTIONS

1. What is the clinical efficacy of aripiprazole alone or as part of combination therapy for the treatment of bipolar disorder?
2. What is the cost-effectiveness of aripiprazole alone or as part of combination therapy for the treatment of bipolar disorder?
3. What are the evidence-based guidelines regarding the use of aripiprazole alone or as part of combination therapy for the treatment of bipolar disorder?

KEY FINDINGS

In both the acute and stabilization phases, the efficacy of aripiprazole was generally superior to placebo, and similar to traditional drugs in adult or pediatric populations with bipolar disorder. The safety profile of aripiprazole was similar to other drugs in both phases in general, with a higher risk of developing activation symptoms with aripiprazole during the acute phase and similar risk during the stabilization phase. Compared to placebo, the risk of sedation, akathisia, and extrapyramidal symptoms was higher with aripiprazole while the risk of developing activation symptoms was similar between the two. The risk of hyperprolactinemia was similar compared to placebo and lower than traditional drugs during the stabilization phase. Treatment with aripiprazole was associated with the lowest all-cause medical costs compared with olanzapine, quetiapine, risperidone, or ziprasidone. Treatment of adverse events due to aripiprazole was less costly than olanzapine. Aripiprazole as monotherapy or as an adjunct was recommended as first line therapy for pharmacological treatment of acute mania, or as maintenance therapy for recent manic or mixed episodes (mania and depression), but not recommended for acute bipolar depression. Aripiprazole was suggested as moderately safe in women with lactation but its risk on pregnancy cannot be ruled out.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, Ovid PsychINFO, Ovid Embase, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were used to limit retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2011 and April 27, 2016.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and examined the full-text publications for the final article selection. Selection criteria are outlined in Table 1.

Table 1: Selection Criteria

Population	Adults or children with bipolar disorder
Intervention	Aripiprazole alone or in combination with lithium or divalproex sodium
Comparator	Other antipsychotics and mood stabilizers, or placebo
Outcomes	Clinical effectiveness (e.g. improvement of bipolar disorder symptoms, mood stabilization, quality of life), harms, cost-effectiveness, guidelines
Study Designs	Health technology assessments (HTA), systematic reviews (SR), meta-analyses (MA), randomized controlled trials (RCTs), economic evaluations, guidelines.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria in Table 1, if they were published prior to January 2011, if they were duplicate publications of the same study, or if they were referenced in a selected systematic review.

Critical Appraisal of Individual Studies

The quality of the included systematic review, cost evaluation, and guidelines was assessed using the AMSTAR,¹⁰ Drummond,¹¹ and AGREE¹² checklists, respectively. Numeric scores were not calculated. Instead, the strengths and limitations of the study are summarized and presented narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 325 citations. After screening of abstracts from the literature search and from other sources, 20 potentially relevant studies were selected for full-text review. Six studies were included in the review.^{1,13-17} The PRISMA flowchart in Appendix 1 details the process of the study selection.

Summary of Study Characteristics

A detailed summary of the included studies is provided in Appendix 2.

Study design

One systematic review with meta-analysis of RCTs and non RCTs,¹³ two cost studies,^{14,15} and three guidelines^{1,16,17} were included. One cost study is a retrospective cohort study in the US looking at costs for an average length of therapy from 67 to 74 days,¹⁴ and one cost analysis performed Markov modeling with a time horizon of 12 months in Spain.¹⁵ The guidelines are evidence-based, one from Canada,¹⁶ one from Singapore,¹ and one from the UK.¹⁷

Population

The systematic review included a total of 2505 adult and pediatric patients with bipolar disorder type I and II.¹³ One cost study analyzed data from 19,176 adult patients with bipolar disorder type I and II,¹⁴ and one cost study included 1941 adult patients with bipolar type I disorder.¹⁵ Two guidelines were on patients with bipolar disorder,^{1,16} and one guideline was on adolescents with bipolar type I disorder.

Interventions and comparators

The systematic review compared aripiprazole to placebo or the anti-manic drugs haloperidol, lithium, and valproic acid.¹³ One cost study compared atypical antipsychotics aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone.¹⁴ One cost study compared aripiprazole and olanzapine.¹⁵

Outcomes

The systematic review evaluated efficacy, response rate, compliance (dropout rate), and adverse events of aripiprazole treatment during the acute phase (3-weeks evaluation) and during the stabilization phase (12-weeks evaluation) compared to placebo or traditional drugs.¹³ One cost study evaluated all cause medical costs (outpatient + inpatient + emergency department costs) and mental-health related costs,¹⁴ and one cost study assessed costs of adverse events related to the use of aripiprazole or olanzapine such as extrapyramidal symptoms, weight gain, and sexual dysfunction. This cost study considered that 41 to 47% of the patients did not adhere to treatments for any cause; the price of olanzapine was based on the generic price.¹⁵ The guidelines reported recommendations on the use of aripiprazole and other antipsychotic drugs.^{1,16,17}

Summary of Critical Appraisal

The included systematic review¹³ provided an a priori design and performed a comprehensive literature search. Procedures for the independent duplicate selection and data extraction of studies were in place, a list of included studies and characteristics were provided, and quality assessment was used in formulating conclusions. The review assessed publication bias. The review did not include a list of excluded studies and heterogeneity was present in a number of pooled analyses. The majority of the included RCTs were sponsored by the pharmaceutical industry.

The included cost studies^{14,15} had an economic evaluation that is likely to be usable, and outcomes and costs were assessed and compared appropriately. Both studies considered all relevant costs. The presentation and discussion of study results include issues of concern to users. One study did not perform a cost-effectiveness analysis.¹⁴ One study performed an economic evaluation with Markov modeling but did not perform an incremental analysis of the outcomes; adverse events were limited to extrapyramidal symptoms, weight gain and sexual dysfunction.¹⁵ The generalizability of the results in one study is limited due to the short average length of therapy with antipsychotic drugs,¹⁴ and was limited to a Spanish context in another study.¹⁵

The included guideline had specific and unambiguous recommendations, with a systematic and clearly described method of searching for and selecting the evidence. Clearly described methods were used to formulate the recommendations.^{1,16,17} Health benefits and risks were stated, and procedures to update the guidelines were provided. It is unclear whether the guideline was piloted among target users, or whether patients' views and preferences were sought. Potential cost implications of applying the recommendations were not included in two studies.^{1,16} The included guidelines did not discuss the recent warnings from FDA about impulse-control problems.

Details of the strengths and limitations of the included studies are summarized in Appendix 3.

Summary of Findings

Main findings of included studies are summarized in detail in Appendix 4.

1. What is the clinical efficacy of aripiprazole alone or as part of combination therapy for the treatment of bipolar disorder?

A 2016 meta-analysis on the efficacy and safety of aripiprazole for bipolar disorder in adults and children systematically searched the literature until June 2015, and included sixteen RCTs and six non-RCTs.¹³ The primary outcome was aripiprazole efficacy (used alone or as an adjunct to lithium or valproic acid) compared to placebo or traditional drugs such as haloperidol, lithium or valproic acid, and secondary outcomes were compliance (dropout rate) and safety (adverse events rate) of aripiprazole. Outcomes were assessed during the acute phase (3-weeks evaluation) and the stabilization phase (12-weeks evaluation). For the stabilization phase, some outcomes such as efficacy, response rate and dropout rate were reported in 3 subgroups: adults with aripiprazole alone, adults with aripiprazole as an adjunct to lithium or valproic acid, and the pediatric population. Outcomes during the acute phase were not subgrouped. Results are reported as superior when the difference to the comparators was statistically significantly better, and as similar (or comparable) when the difference was not statistically significant.

In both the acute and stabilization phases, the overall pooled estimates showed that efficacy of aripiprazole (mean change from baseline in Young Mania Rating Scale or YMRS) and response rate to aripiprazole (decrease in score on the YMRS or Montgomery-Asberg Depression Rating Scale or MADRS of $\geq 50\%$ from baseline) were superior to placebo, and similar to traditional drugs (as a group; alternative drugs were not considered individually). While the trend is generally consistent in all three subgroups, the response rate in adults with aripiprazole as adjunct was superior to placebo but aripiprazole alone was similar to placebo.

Aripiprazole had a lower dropout rate compared to placebo, and similar dropout rate compared to traditional drugs in the acute phase. In the stabilization phase, compared to placebo, subgroup analyses showed that adults with aripiprazole alone had a higher dropout rate, and a comparable rate was found in the other two subgroup populations. Aripiprazole led to a similar dropout rate compared to traditional drugs in all three subgroups populations.

The risk of sedation, akathisia, and extrapyramidal symptoms with aripiprazole was higher compared to placebo and similar to traditional drugs. Compared to placebo, the risk of developing activation symptoms was similar with aripiprazole. Compared to traditional drugs, the risk of developing activation symptoms was higher with aripiprazole during the acute phase and was similar during the stabilization phase. The risk of hyperprolactinemia was lower with

aripiprazole than placebo during the acute phase and similar during the stabilization phase. The risk of hyperprolactinemia was lower with aripiprazole than traditional drugs during the stabilization phase (no data available for the acute phase). The risk of weight gain was similar with aripiprazole compared to placebo and other drugs in both phases.

The authors concluded that aripiprazole is an effective treatment in children and adults with bipolar disorder at 3- and 12-weeks both in a controlled experimental setting and in the real world clinical practice.

2. What is the cost-effectiveness of aripiprazole alone or as part of combination therapy for the treatment of bipolar disorder?

A retrospective cohort cost study conducted in the US, published in 2012, compared the medical costs in patients from 18 to 64 years old diagnosed with bipolar disorder type 1 or 2.¹⁴ Costs were reported as costs per treated patient per month (mean \$ ± standard deviation [SD]) in 2008 US dollars.

Aripiprazole had the lowest inpatient and emergency department all-cause costs (\$804 ± 2523) as compared to other antipsychotic drugs olanzapine (\$1038 ± 3771), quetiapine (\$1089 ± 3450), risperidone (\$1032 ± 3103), or ziprasidone (\$1151 ± 2928). The difference was statistically significant between aripiprazole costs and other atypical antipsychotics ($P < 0.05$). The mental health-related costs for aripiprazole (\$475 ± 2145) were significantly lower only when compared to ziprasidone (\$711 ± 2263). The authors concluded that treatment with aripiprazole was associated with the lowest all-cause medical costs compared with olanzapine, quetiapine, risperidone, or ziprasidone.

A cost analysis conducted in Spain, published in 2014, evaluated the costs for the adverse reactions associated with the use of two atypical antipsychotic drugs aripiprazole and olanzapine in the treatment of adult patients diagnosed with bipolar disorder type 1.¹⁵ Costs were reported as annual average costs savings per patient due to adverse events in 2013 Euros. Treatment with aripiprazole led to an annual average costs savings of €289 per patient (95% confidence interval [CI] €271 to €308) per patient as compared to olanzapine (€3,344 vs €3,633).

3. What are the evidence-based guidelines regarding the use of aripiprazole alone or as part of combination therapy for the treatment of bipolar disorder?

The Canadian Network for Mood and Anxiety Treatments (CANMAT) issued guidelines for the management of bipolar disorders in 2013.¹⁶ Aripiprazole was recommended as first line therapy as monotherapy or as adjunctive therapy with lithium or valproic acid for the treatment of acute mania as well as for the maintenance therapy of bipolar disorders. Aripiprazole was not recommended for acute bipolar 1 depression. Aripiprazole was suggested as moderately safe in lactating women but its risk in pregnancy cannot be ruled out.

Recommendations for pharmacological treatment of acute mania

“First line

Monotherapy: lithium, divalproex, divalproex ER, olanzapineb, risperidone, quetiapine, quetiapine XR, aripiprazole, ziprasidone, asenapine, paliperidone ER

Adjunctive therapy with lithium or divalproex: risperidone, quetiapine, olanzapine, aripiprazole, asenapine” (p 5)

Recommendations for pharmacological treatment of acute bipolar 1 depression

“Not recommended

Monotherapy: gabapentin, aripiprazole, ziprasidone

Combination therapy: adjunctive ziprasidone, adjunctive levetiracetam” (p 9)

Recommendations for maintenance pharmacotherapy of bipolar disorder

“First line

Monotherapy: lithium, lamotrigine (limited efficacy in preventing mania), divalproex, olanzapine, quetiapine, risperidone LAI, aripiprazole

Adjunctive therapy with lithium or divalproex: quetiapine, risperidone LAI, aripiprazole, ziprasidone” (p 14)

Psychiatric medications in pregnancy and lactation

“Aripiprazole:

Pregnancy risk category: C

American Academy of Pediatrics rating: N/A (not available)

Lactation risk category: L3

C: risk cannot be ruled out

L3: moderately safe” (p 19)

The Singapore Ministry of Health issued published guidelines for the treatment of bipolar disorders in 2011.¹ Aripiprazole was recommended for acute mania, in acute treatment of agitation in mania, and as maintenance therapy in bipolar patients with recent manic or mixed periods. The recommendations were based on well-conducted systematic reviews or RCTs with consistent results.

“Aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone maybe used for the treatment of acute mania. (Grade A, Level 1+)” (p 17)

Haloperidol (IM or oral), olanzapine (IM or oral), quetiapine (oral) or aripiprazole (IM) may be used in the acute treatment of agitation in mania. (Grade A, Level 1+) (p 19)

Aripiprazole may be used as maintenance therapy in bipolar patients with recent manic or mixed episode (Grade A, Level 1+) (p 25)

“Levels of Evidence

1+: Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

Grades of recommendations

Grade A: At least one meta-analysis, systematic review of RCTs, or RCT rated as 1++ and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results” (page number not available)

The National Institute for Health and Care Excellence (NICE) published guidelines on aripiprazole for the treatment of moderate to severe episodes in adolescents with bipolar 1 disorder in 2013.¹⁷ The Appraisal Committee considered evidence submitted by the manufacturer of aripiprazole.

“Aripiprazole is recommended as an option for treating moderate to severe manic episodes in adolescents with bipolar I disorder, within its marketing authorisation (that is, up to 12 weeks of treatment for moderate to severe manic episodes in bipolar I disorder in adolescents aged 13 and older)” (p 3)

Limitations

The efficacy of aripiprazole was derived from the conclusion of a systematic review in which the majority of the included RCTs were sponsored by the pharmaceutical industry. The generalizability of the cost evaluations is limited due to the short average length of therapy or was limited to the costs of some adverse events in a Spanish context. Data from a mixed population of bipolar disorder type I and II needs to be interpreted with caution when applied to a single type. It was unclear whether the guidelines were piloted among target users and whether patients' views and preferences were sought.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

In both the acute and stabilization phases, the efficacy of aripiprazole was generally superior to placebo, and similar to traditional drugs in adult or pediatric populations with bipolar disorder. The safety profile of aripiprazole was similar to other drugs in both phases in general, with a higher risk of developing activation symptoms with aripiprazole during the acute phase and similar risk during the stabilization phase. Compared to placebo, the risk of sedation, akathisia, and extrapyramidal symptoms was higher with aripiprazole while the risk of developing activation symptoms was similar between the two. The risk of hyperprolactinemia was similar compared to placebo and lower than traditional drugs during the stabilization phase.

Treatment with aripiprazole was associated with the lowest all-cause medical costs compared with olanzapine, quetiapine, risperidone, or ziprasidone. Treatment of adverse events due to aripiprazole was less costly than olanzapine.

Aripiprazole as monotherapy or as an adjunct was recommended as first line therapy for pharmacological treatment of acute mania, or as maintenance therapy for recent manic or mixed episodes (mania and depression), but not recommended for acute bipolar depression. Aripiprazole was suggested to be moderately safe in women with lactation but its risk in pregnancy cannot be ruled out.

Evidence was derived from a systematic review in which the majority of the included RCTs were sponsored by the pharmaceutical industry and needs to be interpreted with caution. The generalizability of the cost evaluations to a Canadian context is limited due to the short average length of therapy or was limited to the Spanish health care system. More evidence is needed to evaluate the efficacy and safety of aripiprazole in the long-term maintenance therapy of bipolar disorder.

PREPARED BY:

Canadian Agency for Drugs and Technologies in Health

Tel: 1-866-898-8439

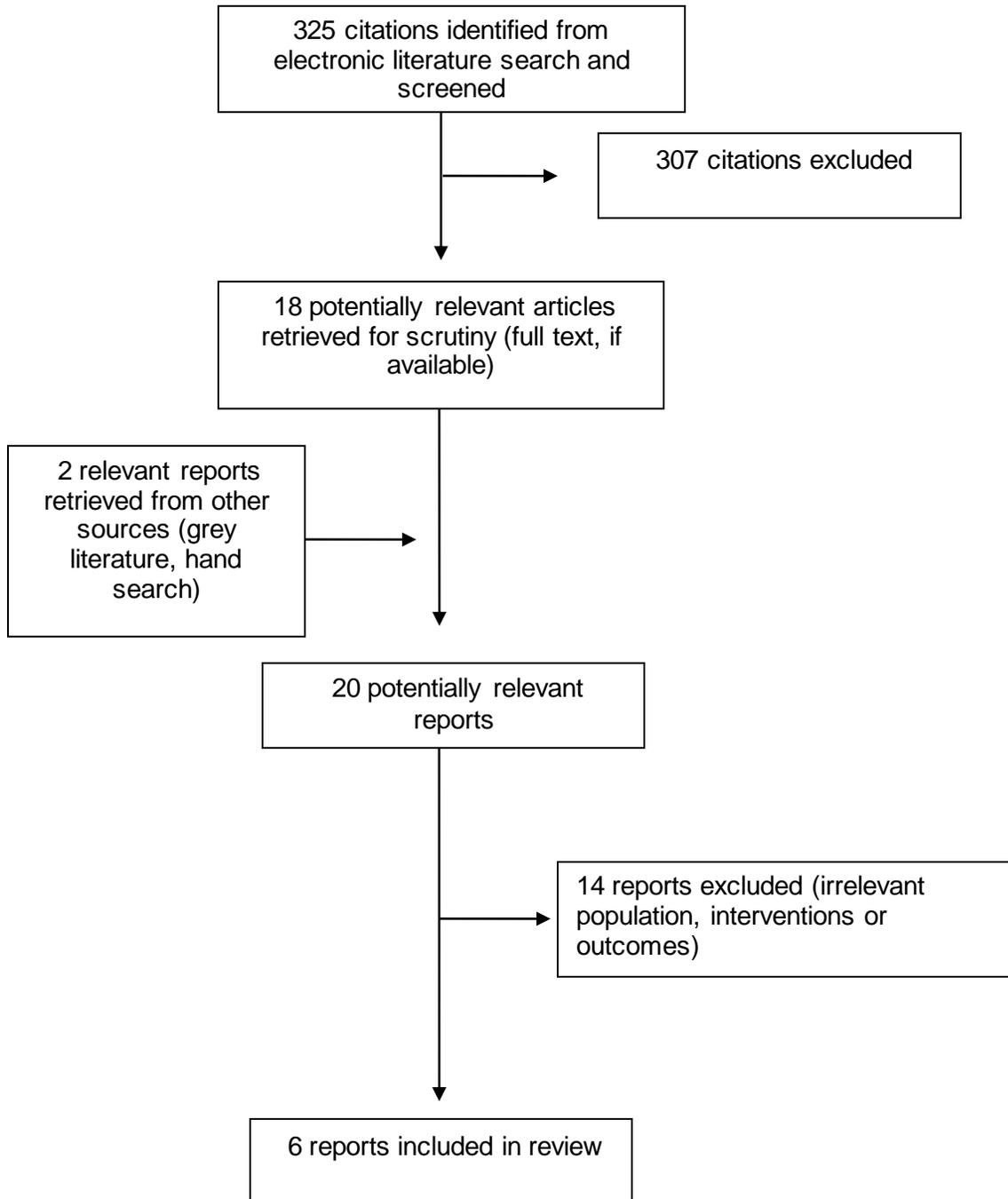
www.cadth.ca

REFERENCES

1. Bipolar disorder [Internet]. Singapore: Ministry of Health, Singapore; 2011 May. [cited 2016 May 24]. (MOH clinical practice guidelines). Available from: https://www.moh.gov.sg/content/dam/moh_web/HPP/Doctors/cpg_medical/current/2011/MOHcpg_Bipolar%20Disorder_Booklet.pdf
2. What should I know about bipolar disorder (manic-depression)? [Internet]. Ottawa: Public Health Agency of Canada; 2009 Apr 23. [cited 2016 May 12]. Available from: <http://www.phac-aspc.gc.ca/cd-mc/mi-mm/bipolar-bipolaire-eng.php>
3. Diagnostic and statistical manual of mental disorders: DSM-V. 5th. Arlington (VA): American Psychiatric Association; 2013.
4. Severus E, Schaaff N, Moller HJ. State of the art: treatment of bipolar disorders. *CNS Neurosci Ther*. 2012 Mar;18(3):214-8.
5. Sayyaparaju KK, Grunze H, Fountoulakis KN. When to start aripiprazole therapy in patients with bipolar mania. *Neuropsychiatr Dis Treat* [Internet]. 2014 [cited 2016 Apr 28];10:459-70. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3958500>
6. Moro MF, Carta MG. Evaluating aripiprazole as a potential bipolar disorder therapy for adults. *Expert Opin Invest Drugs*. 2014 Dec;23(12):1713-30.
7. Kirino E. Profile of aripiprazole in the treatment of bipolar disorder in children and adolescents. *Adolesc Health Med Ther* [Internet]. 2014 [cited 2016 May 24];5:211-21. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4250023>
8. de Bartolomeis A, Perugi G. Combination of aripiprazole with mood stabilizers for the treatment of bipolar disorder: from acute mania to long-term maintenance. *Expert Opin Pharmacother*. 2012 Oct;13(14):2027-36.
9. FDA Drug Safety Communication: FDA warns about new impulse-control problems associated with mental health drug aripiprazole (Abilify, Abilify Maintena, Aristada) [Internet]. Silver Spring (MD): U.S. Food and Drug Administration; 2016 May 3. [cited 2016 May 4]. Available from: <http://www.fda.gov/Drugs/DrugSafety/ucm498662.htm>
10. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol* [Internet]. 2007 [cited 2016 May 24];7:10. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810543/>
11. Higgins JPT, editors. *Cochrane handbook for systematic reviews of interventions* [Internet]. Version 5.0.2. Oxford (U.K.): The Cochrane Collaboration; 2009. Figure 15.5.a: Drummond checklist (Drummond 1996). [cited 2016 May 24]. Available from: http://handbook.cochrane.org/chapter_15/figure_15_5_a_drummond_checklist_drummond_1996.htm

12. Brouwers M, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in healthcare. CMAJ [Internet]. 2010 Dec [cited 2016 May 24];182(18):E839-E842. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3001530/>
13. Meduri M, Gregoraci G, Baglivo V, Balestrieri M, Isola M, Brambilla P. A meta-analysis of efficacy and safety of aripiprazole in adult and pediatric bipolar disorder in randomized controlled trials and observational studies. J Affect Disord. 2016 Feb;191:187-208.
14. Bergeson JG, Kalsekar I, Jing Y, You M, Forbes RA, Hebden T. Medical care costs and hospitalization in patients with bipolar disorder treated with atypical antipsychotics. Am Health Drug Benefits [Internet]. 2012 Sep [cited 2016 Apr 28];5(6):379-86. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4031693>
15. Rubio-Terrés C, Rubio-Rodríguez D, Baca-Baldomero E. Cost analysis of the adverse reactions of bipolar disorder treatment with aripiprazole and olanzapine in Spain. Actas Esp Psiquiatr [Internet]. 2014 Sep [cited 2016 Apr 28];42(5):242-9. Available from: <http://www.actaspsiquiatria.es/repositorio//16/91/ENG/16-91-ENG-242-249-261060.pdf>
16. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Beaulieu S, Alda M, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. Bipolar Disord. 2013 Feb;15(1):1-44.
17. Aripiprazole for treating moderate to severe manic episodes in adolescents with bipolar I disorder [Internet]. London (GB): National Institute for Health and Care Excellence (NICE); 2013 Jul 24. 43 p. [cited 2016 Apr 29]. (Technology appraisal guidance; no. 292). Available from: <https://www.nice.org.uk/guidance/ta292/resources/aripiprazole-for-treating-moderate-to-severe-manic-episodes-in-adolescents-with-bipolar-i-disorder-82600730031301>

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Studies

Table A1: Characteristics of Included studies				
First Author, Year, Country	Literature Search Strategy	Inclusion Criteria	Exclusion Criteria	Studies included Main outcomes
Systematic reviews				
Meduri, ¹³ 2016, Italy, US	<i>"We systematically searched electronic sources till June 30th, 2015, using EMBASE, MEDLINE, CINHAIL, PsychINFO, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, ClinicalTrials.gov, then used hand-search through references of other systematic reviews and meta-analyses" (p 188)</i>	<i>"We included randomized controlled trials (RCTs), retrospective and prospective observational studies that compared ARP with PCB or other active treatments" (p 188)</i>	<i>"Studies of acute treatment with ARP that recruited patients with diagnoses other than bipolar disorder or schizoaffective disorder or that did not stratify according to diagnosis were not included in this review" (p 188)</i>	<p>22 studies were included (16 RCTs, 6 non-RCTs)</p> <p><i>Primary outcomes</i></p> <p>Efficacy of ARP treatment (mean change from baseline in manic symptom rating using YMRS) during the acute phase (3-weeks evaluation) compared to placebo or traditional drugs</p> <p>Efficacy of ARP treatment (mean change from baseline in manic symptom rating using YMRS) during the stabilization phase (12-weeks evaluation) compared to placebo or traditional drugs</p> <p><i>Secondary outcomes</i></p> <p>Response rate (decrease in score on the YMRS or MADRS of ≥50% from baseline)</p> <p>Compliance (dropout rate)</p> <p>Adverse events</p>

Table A1: Characteristics of Included studies

First author, Year, Country	Study Objectives	Interventions/Comparators	Patients	Main Study Outcomes
Cost studies				
Bergeson, ¹⁴ 2012, US	<i>“To investigate medical care costs and hospitalization rates among patients with bipolar disorder who were managed with aripiprazole compared with olanzapine, quetiapine, risperidone, or ziprasidone”</i> (p 379)	Aripiprazole Olanzapine Quetiapine Risperidone Ziprasidone	19176 patients from 18 to 64 years old diagnosed with bipolar disorder type 1 or 2	All cause medical costs (outpatient + inpatient + emergency department costs) Mental-health related costs (costs adjusted to 2008 US\$)
Rubio-Teres, ¹⁵ 2014, Spain	<i>“This study investigates the healthcare costs of adverse events (AE) associated with treatment of bipolar disorder with two atypical oral antipsychotics (AOA): aripiprazole (ARI) and olanzapine (OLA).”</i> (p 242)	Aripiprazole Olanzapine	1941 adult patients diagnosed with bipolar disorder type 1	Costs of adverse events related to the use of aripiprazole or olanzapine Cost evaluation (using Markov modelling with time horizon of 12 months) (costs adjusted to 2013 €)

ARP : aripiprazole; MADRS : Montgomery-Asberg Depression Rating Scale; PCB : placebo; RCTs: randomized controlled trials; YMRS : Young Mania Rating Scale

Appendix 3: Summary of Critical Appraisal of Included Study

Table A2: Summary of Critical Appraisal of Included Study		
First Author, Publication Year	Strengths	Limitations
Critical appraisal of included systematic reviews (AMSTAR¹⁰)		
Meduri, ¹³ 2016	<ul style="list-style-type: none"> • a priori design provided • independent studies selection and data extraction procedure in place • comprehensive literature search performed • list of included studies, studies characteristics provided • quality assessment of included studies provided and used in formulating conclusions • assessment of publication bias performed • conflict of interest stated 	<ul style="list-style-type: none"> • heterogeneity across trials present in a number of pooled analyses • list of excluded studies not provided
Critical appraisal of included cost study (Drummond¹¹)		
Bergeson, ¹⁴ 2012	<ul style="list-style-type: none"> • outcomes and costs assessed and compared appropriately (all the important and relevant outcomes and costs for each alternative identified; outcomes and costs measured accurately in appropriate units prior to evaluation; outcomes and costs valued credibly; outcomes and costs adjusted for different times at which they occurred) • the presentation and discussion of study results include all issues of concern to users 	<ul style="list-style-type: none"> • There is no economic evaluation, no incremental or sensitivity analyses • Retrospective database design may lead to selection bias • Baseline characteristics varied across the cohorts • The generalizability of the results is limited due to the short average length of therapy (67 to 74 days)
Rubio-Teres, ¹⁵ 2014	<ul style="list-style-type: none"> • the economic evaluation is likely to be usable (a well-defined question posed in an answerable form; a comprehensive description of the competing alternatives given; evidence for the programme's effectiveness established) • outcomes and costs assessed and compared appropriately (all the important and relevant outcomes and costs for each alternative identified; outcomes and costs measured accurately in appropriate units prior to evaluation; outcomes and costs valued credibly; outcomes and costs adjusted for different times at which they occurred) • a sensitivity analysis performed • the presentation and discussion of study results include all issues of concern to users 	<ul style="list-style-type: none"> • An incremental analysis of the outcomes and costs of alternatives not performed • The generalizability of the results is limited to the Spanish National Health System
Critical appraisal of included guidelines (AGREE¹²)		
Canadian Network for Mood and Anxiety	<ul style="list-style-type: none"> • scope and purpose of the guidelines are clear • the recommendations are specific and 	<ul style="list-style-type: none"> • unclear whether the guideline was piloted among target users • unclear whether patients' views and

Table A2: Summary of Critical Appraisal of Included Study

First Author, Publication Year	Strengths	Limitations
Treatments (CANMAT) guidelines, ¹⁶ 2013	<ul style="list-style-type: none"> • unambiguous • the method for searching for and selecting the evidence are clear • methods used for formulating the recommendations are clearly described • health benefits, side effects and risks were stated in the recommendations • procedure for updating the guidelines provided • target users of the guideline are clearly defined 	<ul style="list-style-type: none"> • preferences were sought • potential cost implications of applying the recommendation not included
Singapore Ministry of Health guidelines, ¹ 2011	<ul style="list-style-type: none"> • scope and purpose of the guidelines are clear • the recommendations are specific and unambiguous • the method for searching for and selecting the evidence are clear • methods used for formulating the recommendations are clearly described • health benefits, side effects and risks were stated in the recommendations • procedure for updating the guidelines provided • target users of the guideline are clearly defined 	<ul style="list-style-type: none"> • unclear whether the guideline was piloted among target users • unclear whether patients' views and preferences were sought • potential cost implications of applying the recommendation not included
National Institute for Health and Care Excellence (NICE) guidelines, ¹⁷ 2013	<ul style="list-style-type: none"> • scope and purpose of the guidelines are clear • the recommendations are specific and unambiguous • the method for searching for and selecting the evidence are clear • methods used for formulating the recommendations are clearly described • health benefits, side effects and risks were stated in the recommendations • procedure for updating the guidelines provided • target users of the guideline are clearly defined • potential cost implications of applying the recommendation were included 	<ul style="list-style-type: none"> • unclear whether the guideline was piloted among target users • unclear whether patients' views and preferences were sought

Appendix 4: Main Study Findings and Authors' Conclusions

Table A3: Main Study Findings and Authors' Conclusions		
First Author, Publication Year	Main Study Findings	Authors' Conclusions
Research question 1 (clinical efficacy of aripiprazole alone or as part of combination therapy for the treatment of bipolar disorder)		
Meduri, ¹³ 2016	<p><u>Efficacy of ARP treatment during the acute phase (3-weeks evaluation)</u></p> <p>Mean change from baseline (using YMRS)</p> <p>ARP superior to placebo: SMD -0.31; 95% CI -0.46 to -0.16</p> <p>ARP similar to traditional drugs (haloperidol, lithium or valproic acid): SMD 0.01; 95% CI -0.12 to 0.13</p> <p>Response rate (decrease in score on the YMRS or MADRS of ≥50% from baseline)</p> <p>ARP superior to placebo: RR 1.41; 95% CI 1.25 to 1.58</p> <p>ARP similar to traditional drugs: RR 1.16; 95% CI 0.84 to 1.61</p> <p><u>Efficacy of ARP treatment during the stabilization phase (12-weeks evaluation)</u></p> <p>Mean change from baseline (using YMRS)</p> <p>ARP superior to placebo: SMD -0.48; 95% CI -0.78 to -0.18</p> <p>ARP similar to traditional drugs: SMD -0.14; 95% CI -0.29 to 0.01</p> <p>Response rate (decrease in score on the YMRS or MADRS of ≥50% from baseline)</p> <p>ARP superior to placebo: RR 1.28; 95% CI 1.09 to 1.50)</p> <p>ARP similar to traditional drugs: RR 1.13; 95% CI 0.92 to 1.39</p> <p><u>Compliance during the acute phase (3-weeks evaluation)</u></p> <p>The dropout rate with aripiprazole was approximately 45%</p> <p>ARP led to lower dropout rate compared to placebo: RR 0.90; 95% CI 0.82 to 0.98</p> <p>ARP led to similar dropout rate compared to traditional drugs: RR 0.80; 95% CI 0.52 to 1.23</p> <p><u>Compliance during the stabilization phase (12-weeks evaluation)</u></p> <p>The dropout rate with aripiprazole was 37%</p> <p>ARP led to higher dropout rate compared to placebo: RR</p>	<p><i>"ARP resulted to be an effective treatment in children and adults with BD at 3- and 12-weeks both in a controlled experimental setting and in the real world clinical practice, being poorly associated with hyperprolactinemia. Larger studies are needed to confirm our results related to the maintenance phases and to the pediatric bipolar population."</i> (p 187)</p>

Table A3: Main Study Findings and Authors' Conclusions

First Author, Publication Year	Main Study Findings	Authors' Conclusions
	<p>1.23; 95% CI 1.06 to 1.41</p> <p>ARP led to similar dropout rate compared to traditional drugs: RR 0.92; 95% CI 0.70 to 1.21</p> <p><u>Adverse events</u></p> <p><u>Compared to placebo</u></p> <p><i>During the acute phase (3-weeks evaluation)</i></p> <p>Sedation: RR 2.55; 95% CI 1.69 to 3.87 Extrapramidal symptoms: RR 2.43; 95% CI 1.85 to 3.19 Akathisia: RR 3.70; 95% CI 2.52 to 5.44 Activation symptoms: RR 1.08; 95% CI 0.85 to 1.38 Hyperprolactinemia: RR 0.54; 95% CI 0.32 to 0.91 Weight gain: RR 0.63; 95% CI 0.34 to 1.15</p> <p><i>During the stabilization phase (12-weeks evaluation)</i></p> <p>Sedation: RR 2.69; 95% CI 1.09 to 6.68 Extrapramidal symptoms: RR 3.35; 95% CI 2.52 to 4.45 Akathisia: RR 4.66; 95% CI 3.06 to 7.09 Activation symptoms: RR 1.59; 95% CI 0.99 to 2.53 Hyperprolactinemia: RR 1.02; 95% CI 0.58 to 1.78 Weight gain: RR 1.59; 95% CI 0.99 to 2.53</p> <p><u>Compared to traditional drugs</u></p> <p><i>During the acute phase (3-weeks evaluation)</i></p> <p>Sedation: RR 1.69; 95% CI 0.83 to 3.46 Extrapramidal symptoms: RR 0.82; 95% CI 0.24 to 2.76 Akathisia: RR 0.95; 95% CI 0.20 to 4.63 Activation symptoms: RR 2.29; 95% CI 1.12 to 4.65 Hyperprolactinemia: no studies available Weight gain: RR 0.65; 95% CI 0.18 to 2.29</p> <p><i>During the stabilization phase (12-weeks evaluation)</i></p> <p>Sedation: RR 1.22; 95% CI 0.68 to 1.22 Extrapramidal symptoms: RR 0.99; 95% CI 0.44 to 2.24 Akathisia: RR 1.20; 95% CI 0.55 to 2.65 Activation symptoms: RR 1.54; 95% CI 0.64 to 3.73 Hyperprolactinemia: RR 0.27; 95% CI 0.18 to 0.41 Weight gain: RR 1.74; 95% CI 0.76 to 3.98</p>	
<p>Research question 2 (cost effectiveness of aripiprazole alone or as part of combination therapy for the treatment of bipolar disorder)</p>		
<p>Bergeson,¹⁴ 2012</p>	<p>Costs reported as costs per treated patient per month</p> <p>Aripiprazole Total medical costs - mean \$ (± SD) 804 (± 2523) Mental-health related costs \$ (± SD) 475 (± 2145)</p> <p>Olanzapine Total medical costs - mean \$ (± SD) 1038 (± 3771) Mental-health related costs \$ (± SD) 621 (± 2382)</p>	<p><i>“Treatment with aripiprazole was associated with... the lowest all-cause and mental health-related medical costs compared with olanzapine, quetiapine, risperidone, or ziprasidone. Therefore, aripiprazole may offer an economic advantage over other atypical antipsychotics in patients</i></p>

Table A3: Main Study Findings and Authors' Conclusions

First Author, Publication Year	Main Study Findings	Authors' Conclusions
	<p>Quetiapine Total medical costs - mean \$ (± SD) 1089 (± 3450) Mental-health related costs \$ (± SD) 655 (± 2479)</p> <p>Risperidone Total medical costs - mean \$ (± SD) 1032 (± 3103) Mental-health related costs \$ (± SD) 674 (± 2453)</p> <p>Ziprasidone Total medical costs - mean \$ (± SD) 1151 (± 2928) Mental-health related costs \$ (± SD) 711 (± 2263)</p>	<p><i>with bipolar disorder.” (p 379)</i></p>
<p>Rubio-Teres,¹⁰ 2014</p>	<p>Costs reported as annual average costs savings per patient due to adverse events (extrapyramidal symptoms, weight gain, sexual dysfunction)</p> <p>Aripiprazole €3,344</p> <p>Olanzapine €3,633</p> <p>Savings: €289</p>	<p><i>“The results of this analysis show that patients treated with aripiprazole demonstrate lower adverse events costs in comparison to olanzapine. This difference may generate significant cost savings in the Spanish health system in the treatment of patients affected by bipolar disorders” (p 242)</i></p>
<p>Research question 3 (evidence-based guidelines regarding the use of aripiprazole alone or as part of combination therapy for the treatment of bipolar disorder)</p>		
<p>Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines,¹⁶ 2013</p>	<p><u>Recommendations for pharmacological treatment of acute mania</u> “First line <i>Monotherapy: lithium, divalproex, divalproex ER, olanzapineb, risperidone, quetiapine, quetiapine XR, aripiprazole, ziprasidone, asenapine, paliperidone ER</i> <i>Adjunctive therapy with lithium or divalproex: risperidone, quetiapine, olanzapine, aripiprazole, asenapine” (p 5)</i></p> <p><u>Recommendations for pharmacological treatment of acute bipolar I depression</u> “Not recommended <i>Monotherapy: gabapentin, aripiprazole, ziprasidone</i> <i>Combination therapy: adjunctive ziprasidonec, adjunctive levetiracetam” (p 9)</i></p> <p><u>Recommendations for maintenance pharmacotherapy of bipolar disorder</u> “First line <i>Monotherapy: lithium, lamotrigine (limited efficacy in preventing mania), divalproex, olanzapine, quetiapine, risperidone LAI, aripiprazole</i> <i>Adjunctive therapy with lithium or divalproex: quetiapine, risperidone LAI, aripiprazole, ziprasidone” (p 14)</i></p> <p><u>Psychiatric medications in pregnancy and lactation</u> “Aripiprazole: <i>Pregnancy risk category: C</i> <i>American Academy of Pediatrics rating: N/A (not available)</i> <i>Lactation risk category: L3</i> <i>C: risk cannot be ruled out</i></p>	<p>Not applicable</p>

Table A3: Main Study Findings and Authors' Conclusions

First Author, Publication Year	Main Study Findings	Authors' Conclusions
	<i>L3: moderately safe</i> " (p 19)	
Singapore Ministry of Health guidelines, ¹¹ 2011	<p><i>"Aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone maybe used for the treatment of acute mania. (Grade A, Level 1+)"</i> (p 17)</p> <p><i>Haloperidol (IMor oral), olanzapine (IMor oral), quetiapine (oral) or aripiprazole (IM) may be used in the acute treatment of agitation in mania. (Grade A, Level 1+)</i> (p 19)</p> <p><i>Aripiprazole may be used as maintenance therapy in bipolar patients with recent manic or mixed episode (Grade A, Level 1+)</i> (p 25)</p> <p><i>"Levels of Evidence 1+: Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias</i></p> <p><i>Grades of recommendations Grade A: At least one meta-analysis, systematic review of RCTs, or RCT rated as 1++ and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results"</i> (page number not available)</p>	Not applicable
National Institute for Health and Care Excellence (NICE) guidelines, ¹⁰ 2013	<p><i>"The Appraisal Committee considered evidence submitted by the manufacturer of aripiprazole and a review of this submission by the Evidence Review Group"</i> (p 6)</p> <p><i>"Aripiprazole is recommended as an option for treating moderate to severe manic episodes in adolescents with bipolar I disorder, within its marketing authorisation (that is, up to 12 weeks of treatment for moderate to severe manic episodes in bipolar I disorder in adolescents aged 13 and older)"</i> (p 3)</p>	<p><i>"The Committee concluded that based on the evidence available, aripiprazole was as effective as other antipsychotics for treating acute mania and had a comparable and acceptable adverse reaction profile"</i> (p 25)</p> <p><i>"The Committee agreed that the base-case results suggested that a treatment strategy that includes aripiprazole is a cost-effective option when compared with a treatment strategy without aripiprazole. Given that each of the strategies was dominated by every other strategy in at least some of the probabilistic iterations, the Committee agreed that the results were not sufficiently robust to make a recommendation on the position of aripiprazole in the treatment pathway. The Committee concluded that aripiprazole should be recommended as an option for the treatment of moderate to severe manic episodes in bipolar I disorder in adolescents"</i> (p 25)</p>

ARP: aripiprazole; SMD: standard mean difference; RR: relative risk