CADTH

CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Atypical Injectable Antipsychotics for Schizophrenia or Bipolar Disorder: A Review of Clinical Effectiveness and Cost-Effectiveness

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	January 3, 2019
Report Length:	20 Pages

CADTH

Authors: Tasha Narain, Caitlyn Ford

Cite As: Atypical Injectable Antipsychotics for Schizophrenia or Bipolar Disorder: A Review of Clinical Effectiveness and Cost-Effectiveness. Ottawa: CADTH; 2019 Jan. (CADTH rapid response report: summary with critical appraisal).

ISSN: 1922-8147 (online)

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Abbreviations

AE	Adverse event
EPS	extrapyramidal side effects
FDA	Food and drug administration
HR	hazard ratio
LAI	long-acting injectable
PANSS	Positive and negative syndrome scale
QALY	quality-adjusted life year
RCT	randomized controlled trial
RR	relative risk
SR	systematic review
SMD	Standardized mean difference
TEAE	treatment emergent adverse event
US	United States

Context and Policy Issues

Atypical injectable antipsychotics are second-generation therapeutics that can be used as an alternative to first-generation antipsychotics to treat patients with schizophrenia or bipolar disorder.[1] In Canada, both schizophrenia and bipolar disorder each affect approximately 1% of Canadians.[2,3]

Atypical injectable antipsychotics were developed with the goal of increased tolerability/increased adherence and as a formation that would allow for more reliable administration.[4] First-generation antipsychotics were based on the blockade of dopamine receptors, and while this effected positive symptoms (e.g., delusions and hallucinations), it resulted in extrapyramidal symptoms (e.g., tremor, slurred speech, akathisia, dystonia, and tardive dyskinesia).[5] Conversely, atypical injectable antipsychotics were developed to block both dopamine and serotonin receptors with the goal of affecting both positive and negative symptoms (e.g., passive or apathetic social withdrawal and blunted affect).[5] In Canada, atypical long-acting injectable (LAI) antipsychotics available for the treatment of schizophrenia or bipolar disorder include the following: risperidone, aripiprazole, paliperidone palmitate, and paliperidone extended-release.

The purpose of this report is to evaluate the clinical effectiveness and cost-effectiveness, for the use of atypical injectable antipsychotics for patients with schizophrenia or bipolar disorder.

Research Questions

1. What is the clinical effectiveness of atypical long-acting injectable antipsychotics for the treatment of patients with schizophrenia or bipolar disorder?
2. What is the cost-effectiveness of atypical long-acting injectable antipsychotics for the treatment of patients with schizophrenia or bipolar disorder?

Key Findings

The results of four systematic reviews[6-9] (including one overview of systematic reviews[8], and one indirect comparison[9]) were used to inform the clinical effectiveness of atypical long-acting injectable (LAI) antipsychotics for the treatment of patients with schizophrenia or bipolar disorder. Three systematic reviews (SRs) provided some evidence to suggest that

aripiprazole LAI is clinically effective compared to placebo based on time to recurrence, any relapse, manic relapse, and the positive and negative syndrome scale (PANSS) outcomes.[6,8,9] One SR provided evidence to suggest clinical effectiveness of paliperidone palmitate LAI compared to placebo based on PANSS outcomes.[9] Generally, LAI formulations were not found to differ in clinical effectiveness compared to oral formations based on evidence for aripiprazole and risperidone.[7,8]

Two economic evaluations provided evidence to suggest cost-effectiveness of aripiprazole LAI over placebo,[10] and an increase in market shares and increase in budget impact per member per month after 5 years.[11]

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, Medline, Embase and PsycINFO via Ovid, 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. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, and economic studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2017 and November 28, 2018.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients with schizophrenia and/or bipolar disorder
Intervention	Long-acting injectable atypical antipsychotics (i.e., risperidone, aripiprazole, paliperidone palmitate, and paliperidone extended-release injection)
Comparator	Oral atypical antipsychotic agents (i.e., risperidone, aripiprazole, paliperidone palmitate, and paliperidone extended-release injection) Placebo
Outcomes	Q1: Clinical effectiveness (e.g., rates of relapse or hospitalization, length of hospital stay, functional decline) and safety (e.g., rates of adverse events) Q2: Cost-effectiveness outcomes (e.g., reduction in costs associated with hospitalization, patient-level economic outcomes)
Study Designs	Health technology assessments, systematic reviews, meta-analyses, economic evaluations

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2017.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised by one reviewer using AMSTAR II,[12] indirect treatment comparisons were assessed using the ISPOR checklist,[13] and economic studies were assessed using the Drummond checklist.[14] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 670 citations were identified in the literature search. Following screening of titles and abstracts, 630 citations were excluded and 40 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 36 publications were excluded for various reasons, and 6 publications met the inclusion criteria and were included in this report. These comprised 4 systematic reviews and 2 economic evaluations. Appendix 1 presents the PRISMA[15] flowchart of the study selection.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

Four systematic reviews[6,7] including one overview of systematic reviews,[8] and one indirect comparison[9] were identified. A systematic review of patients with bipolar disorder from 2018 included 157 studies (randomized controlled trials [RCTs] and prospective cohort studies).[6] A systematic review from 2017 included 21 RCTs and examined adults with schizophrenia or bipolar disorder.[7] An overview of reviews included 14 meta-analyses of RCTs[8] and an indirect comparison included four RCTs.[9]

Two economic evaluations were identified.[10,11] One evaluation used a de novo Markov state transition model with a yearly cycle length using the US payer perspective. The goal of this evaluation was to assess the cost–effectiveness of long-acting injectable aripiprazole once-monthly 400 mg in maintenance monotherapy treatment of bipolar I disorder.[10] A second economic evaluation used a budget impact model with a 5-year time horizon and a healthcare payer perspective. The goal of this budget impact evaluation was to assess the incremental impact of LAI aripiprazole once-monthly 400 mg as a maintenance monotherapy treatment of bipolar I disorder in a hypothetical cohort.[11] Both economic evaluations used RCT[16] and systematic review[17] data to inform clinical input, and used Truven MarketScan Medicaid and Medicare/Commercial Database and RED BOOK to inform the cost data. The cost-effectiveness model included the following assumptions: all oral comparators had the same probabilities of relapse, and the euthymic, manic, mixed and depressive health states costs were applied as a constant cost. The budget impact model assumed the following: market share data remained stable through the 5-year time horizon, patients not treated with one of the included drugs but with another treatment on the market were assumed to be receiving best supportive care, and all the patients with bipolar I disorder were eligible for maintenance treatment with the chosen comparators.

Country of Origin

The systematic reviews were conducted in the US[6] and Italy.[7] The overview of reviews was conducted in Brazil[8] and the indirect comparison was conducted in Canada.[9]

The economic evaluations were both written by the same author from the US.[10,11]

Patient Population

The systematic review from the US included adults with bipolar disorder while the systematic review from Italy included adults with bipolar disorder or schizophrenia.[67] The overview of reviews and the indirect comparison were based on adults with schizophrenia.[8,9]

The base case for the cost-effectiveness economic evaluation[10] used a Markov state transition model based on six states: euthymia while on first-line treatment, euthymia while on subsequent treatment, acute mania, mixed episode, acute depression and death. Using this model, patients entered the model with a diagnosis of bipolar I disorder in the euthymia health state. The base case for the budget impact economic evaluation[11] used a model with a hypothetical cohort of 1,000,000 health plan members with 6,000 patients would be eligible for maintenance treatment for bipolar I disorder.

Interventions and Comparators

One systematic review for adults with bipolar disorder included all drug and non-drug therapies for bipolar disorder including those not approved by the FDA; this extensive list did not specify doses and included but was not limited to the following: aripiprazole, risperidone, paliperidone and placebo.[6] A systematic review evaluated drugs with a LAI and oral formulation that were within therapeutic doses, this included but was not limited to the following: paliperidone palmitate, aripiprazole monohydrate, risperidone microsphere.[7] The overview of reviews included aripiprazole at an unspecified dose compared to placebo or other antipsychotic drug therapies including but not limited to the following: aripiprazole, clozapine, risperidone, and olanzapine.[8] The indirect comparison included aripiprazole lauroxil (441 mg and 882 mg), paliperidone palmitate (156 mg and 234 mg) and placebo.[9]

Both economic evaluations compared the cost-effectiveness/budget impact of aripiprazole once-monthly 400 mg to risperidone LAI, paliperidone palmitate, cariprazine, asenapine, and placebo/best supportive care.[10,11]

Outcomes

The SRs assessed clinical effectiveness using a number of outcomes including response, recurrence, and relapse.[67] The positive and negative syndrome scale (PANSS), a widely used symptom severity rating scale for patients with schizophrenia, was used in two SRs.[89] A number of symptoms and side-effects were assessed across SRs; these included extrapyramidal side effects (EPS), akathisia, dystonia and weight gain.[789]

The economic evaluations reported quality-adjusted life year (QALY)[10] and incremental impact of aripiprazole once-monthly 400 mg as a maintenance monotherapy.[11]

Summary of Critical Appraisal

Details regarding the strengths and limitations of the included systematic reviews[6-9] and economic evaluations[10,11] are provided in Appendix 3.

The four SRs (including the overview of reviews and indirect comparison) included detailed research questions and inclusion criteria.[6-9] Three SRs included detailed protocols that were published in advance of the reviews.[6-8] Comprehensive literature search strategies were used across all SRs, however only the SR by Butler et al. included a grey literature search and list of excluded studies. Study selection was performed in duplicate in the SRs by Butler et al. and the overview of reviews, while data extraction was performed in duplicate across the three SRs. Not including grey literature and duplicate screening can increase the likelihood of missing relevant studies. All SRs included adequate detail about the individual studies included, however the SR by Ostuzzi et al. did not include the study specific funding sources. The meta-analysis in the Ostuzzi et al. study was performed using appropriate techniques to combine data and explore sensitivity. In the meta-analysis, only comparisons employing antipsychotics within therapeutic doses were included, however the actual doses used in the individual studies were not provided. Risk of bias was assessed across all SRs using appropriate methods. In the Ostuzzi et al. SR and meta-analysis, individual studies were generally not removed from the analysis based on their level of bias, thereby decreasing the overall quality of the meta-analysis. The indirect comparison was based on data from four RCTs that were determined to be very similar in design and population.

The research objectives, time horizons, and perspectives of each economic study were clearly stated.[10,11] Both studies clearly described the various sources of data including drug acquisition costs, treatment initiation costs, drug administration costs, adverse event costs, and hospitalization costs. Discount rates in the cost-effectiveness trial were applied following recommendations from the US Public Health Service Panel. One limitation of both studies was that authors are affiliated with PAREXEL International and Otsuka Pharmaceutical Development & Commercialization, Inc and the study was funded by Otsuka Pharmaceutical Development & Commercialization.

Summary of Findings

Appendix 4 presents a table of the main study findings and authors' conclusions.

Clinical Effectiveness of Atypical Injectable Antipsychotics for Schizophrenia or Bipolar Disorder

Four SRs (including one overview of reviews and one indirect comparison) assessed the clinical effectiveness of atypical injectable antipsychotics in patients with schizophrenia or bipolar disorder.[6-9]

Response

The response rate (a decrease of 25% or more at the PANSS score) for risperidone LAI compared to oral risperidone showed no differences (relative risk [RR] = 1.02; 95% CI, 0.97 to 1.07) for patients with schizophrenia or bipolar disorder.[7] Similar findings were observed for aripiprazole LAI compared to oral aripiprazole (RR = 0.98; 95% CI, 0.93 to 1.04).

Recurrence and Relapse

The time to recurrence of any mood state (e.g., bipolar episode, mania, depression) over a period of 52 weeks favoured aripiprazole LAI compared to placebo (hazard ratio [HR] = 0.45; 95% CI, 0.30 to 0.68) for patients with bipolar disorder.[6]

The risk of relapse did not differ for both risperidone LAI and aripiprazole LAI compared to the oral formulations for patients with schizophrenia or bipolar disorder.[7]

Symptoms

Compared to treatment with placebo, treatment with LAI aripiprazole once a month showed statistically significant improvements in symptoms as measured by PANSS, where PANSS total (standardized mean difference [SMD] = − 0.65, 95% CI, − 0.90 to − 0.41, p < 0.00001), PANSS positive (SMD = − 0.85, 95% CI, − 1.01 to − 0.69, p < 0.00001), and PANSS negative (SMD = − 0.44, 95% CI, − 0.59 to − 0.28, p < 0.00001) were reduced for patients with schizophrenia.[8] These findings were echoed in the indirect comparison of patients with schizophrenia evaluating aripiprazole lauroxil 441 mg and 882 mg compared to placebo and for paliperidone palmitate 156 mg and 234 mg compared to placebo.[9] For aripiprazole lauroxil 441 mg the PANSS total mean difference was -11.08 (95% CI, -17.69 to -4.39), for aripiprazole lauroxil 882 mg the PANSS total mean difference was -12.03 (95% CI, -18.59 to -5.31). For paliperidone palmitate 156 mg the PANSS total mean difference was -9.11 (95% CI, 13.24 to -4.94), for paliperidone palmitate 234 mg PANSS total mean difference was -9.10 (95% CI, -13.98 to -3.21).[9]

The experience of EPS for patients with schizophrenia or bipolar disorder did not differ between any of the comparisons: risperidone LAI compared to oral risperidone; aripiprazole LAI compared to oral aripiprazole; aripiprazole lauroxil 441 mg and 882 mg compared to placebo; paliperidone palmitate 156 mg and 234 compared to placebo.[79]

In the overview of reviews, aripiprazole LAI compared to the oral formulation showed no statistical difference in the occurrence of akathisia and dystonia.[8] This study also determined that aripiprazole LAI compared to placebo showed statistical difference in the occurrence of akathisia and dystonia, although this finding was based on low quality evidence. In the indirect comparison, a statistically significant increase in the occurrence of akathisia was associated with aripiprazole LAI at both 441 mg and 882 mg compared to placebo.[9] Conversely, for paliperidone palmitate 156 mg and 234 mg compared to placebo, there was no statistical difference in the occurrence of akathisia.

LAI drugs were associated with a numerically greater increase in weight when compared to placebo, however differences in weight gain were not statistically significant for any of the comparisons studied including the following: both risperidone LAI and aripiprazole LAI compared to the oral formulations, as well as for aripiprazole LAI compared to placebo.[78]

Adverse Events

Dropouts due to adverse events (AEs) did not differ for both risperidone LAI and aripiprazole LAI compared to the oral formulations for patients with schizophrenia or bipolar disorder.[7] Treatment-emergent adverse events (TEAEs) did not differ statistically for aripiprazole lauroxil 441 mg and 882 mg compared to placebo and paliperidone palmitate 156 mg and 234 mg compared to placebo.[9]

Cost-Effectiveness of Aripiprazole once-monthly 400 mg versus placebo

The included economic evaluation for cost-effectiveness analyzed QALY gain and total cost compared to best supportive care (using placebo as a proxy) and determined that treatment with aripiprazole once-monthly 400 mg was dominant over treatment with best supportive care.[10] The incremental costs associated with aripiprazole once-monthly 400 mg versus best supportive care was US$-19,594 and the incremental QALY was 1.966.

The included economic evaluation for budget impact for the introduction aripiprazole once-monthly 400 mg predicted a market share increase from 0.6% in Year 1 (current scenario) to 1.3% in Year 5 (predicted scenario).[11] Market share was predicted to decrease for best

supportive care (placebo) from 95.37% in Year 1 (current scenario) to 91.73% in Year 5 (predicted scenario).The per member per month incremental cost specific to aripiprazole once-monthly 400 mg increase from US$0.02 in Year 1 to US$0.09 in Year 5, and decreased for best supportive care (US$-0.01 in Year 1 to US$-0.06 in Year 5).

Limitations

The authors in the SR by Butler et al. did not extract data in duplicate, thereby increasing the possibility of error. The SR by Ostuzzi et al. and the overview of reviews by Ribeiro et al. did not include a grey literature search; this increases the likelihood of missing relevant studies. The SR by Ostuzzi et al. did not include information on funding sources of individual studies, and pooled data in a meta-analysis without specifying doses of drugs. The overview of review also did not specify the dose of aripiprazole.

The cost-effectiveness studies were based on the US and do not directly apply to Canadian costing. Additionally, several oral comparators of interest (e.g., risperidone, aripiprazole, paliperidone palmitate) were not included in the analysis.

This review was limited by a literature search spanning articles published from 2017 to 2018 due to the high amount of literature retrieved in the initial search. Additionally, primary studies (RCTs and non-RCTs) were excluded from this review thereby increasing the possibility of missing relevant information.

Conclusions and Implications for Decision or Policy Making

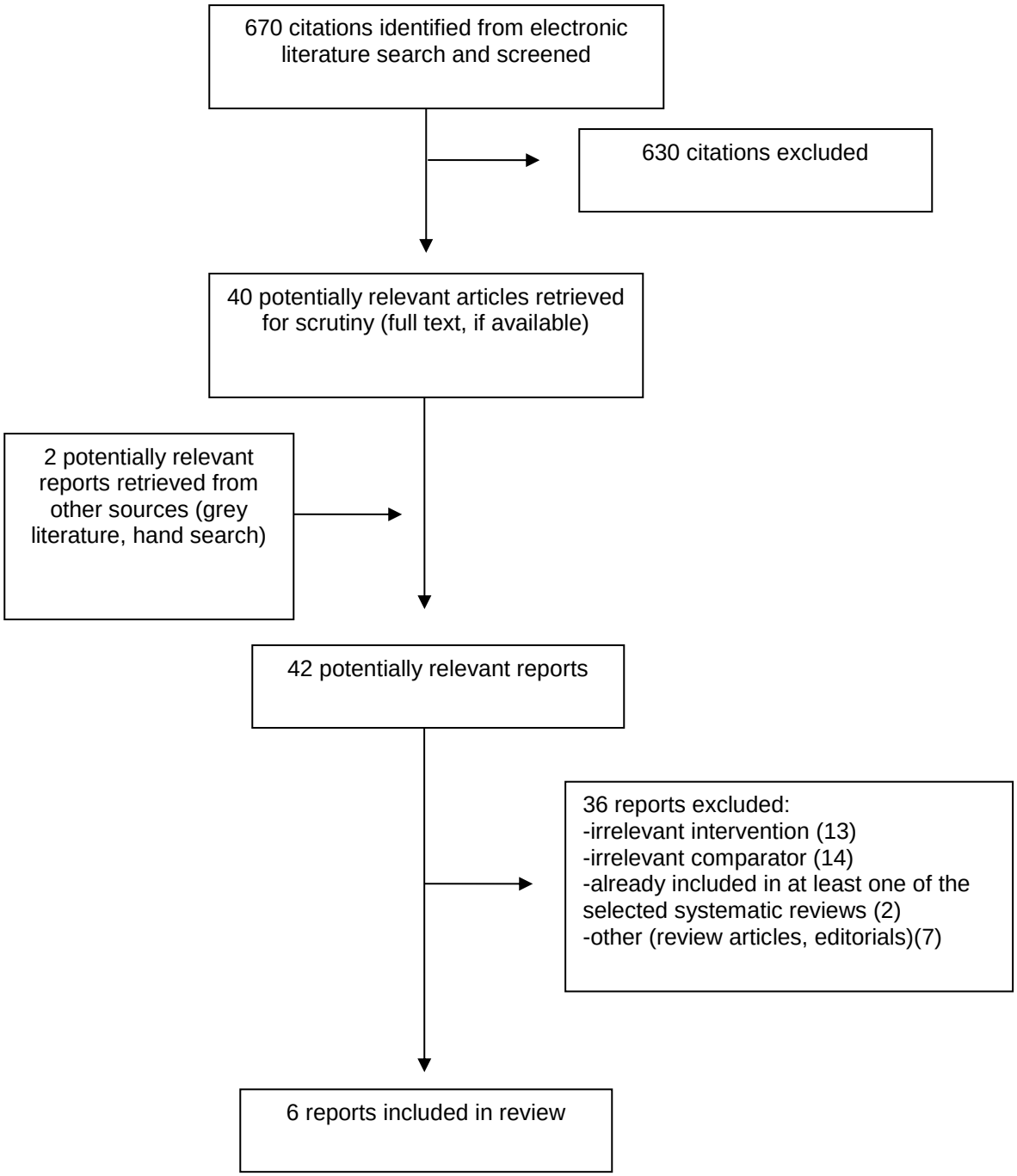
This review was comprised of four systematic reviews[6-9] (including one overview of systematic reviews[8], and one indirect comparison[9]) and two economic evaluations[10,11] that assessed the clinical effectiveness and cost-effectiveness of atypical LAI antipsychotics for the treatment of patients with schizophrenia or bipolar disorder compared with their oral counterparts or placebo.

Three SRs provided some evidence to suggest clinical effectiveness of aripiprazole LAI compared to placebo based on longer time to recurrence, reduced occurrence of any relapse, reduced occurrence of manic relapse, and improvement in symptoms as assessed by PANSS outcomes.[6,8,9] One SR provided evidence to suggest clinical effectiveness of paliperidone palmitate LAI compared to placebo based on improvement in symptoms as assessed by PANSS outcomes.[9] Generally, LAI formulations were not found to differ in clinical effectiveness compared to oral formations based on evidence from aripiprazole and risperidone.[7,8] Two economic evaluations provided evidence to suggest cost-effectiveness of aripiprazole over placebo,[10] and an increase in market shares and increase in budget impact per member per month after 5 years.[11] Collectively, the evidence supports the clinical and economic effectiveness for LAI antipsychotics compared to placebo, however more information is needed for the comparison of LAI antipsychotics and the oral formulations of the drugs.

References

1. Remington G, Addington D, Honer WG, Ismail Z, Raedler T, Teehan M. Guidelines for the pharmacotherapy of schizophrenia in adults. *Can J Psychiatry.*62(9):604-616.
2. Pearson C, Janz T, Ali J. Mental and substance use disorders in Canada. Ottawa (ON): Statistics Canada: https://www150.statcan.gc.ca/n1/pub/82-624-x/2013001/article/11855-eng.htm. Accessed 2018 Dec 11.
3. Canadian Mental Health Association. Fast facts about mental illness. Toronto (ON): CMHA National; 2018: https://cmha.ca/about-cmha/fast-facts-about-mental-illness. Accessed 2018 Dec 11.
4. Sacchetti E, Grunze H, Leucht S, Vita A. Long-acting injection antipsychotic medications in the management of Schizophrenia. *E-bPC.* 2015;1:27-36.
5. Abou-Setta AM, Mousavi SS, Spooner C, Schouten JR, Pasichnyk D, Armijo-Olivio S, et al. First-generation versus second-generation antipsychotics in adults: Comparative effectiveness *(Comparative effectiveness review no. 63)*. Rockville (MD): Agency for Healthcare Research and Quality; 2012: https://www.ncbi.nlm.nih.gov/books/NBK107237/. Accessed 2018 Dec 11.
6. Butler M, Urosevic S, Desai P, Sponheim SR, Popp J, Nelson VA, et al. Treatment for bipolar disorder in adults: A systematic review. *(Comparative effectiveness review no. 208)*. Rockville (MD): Agency for Healthcare Research and Quality; 2018: https://www.ncbi.nlm.nih.gov/books/NBK532183/. Accessed 2018 Dec 11.
7. Ostuzzi G, Bighelli I, So R, Furukawa TA, Barbui C. Does formulation matter? A systematic review and meta-analysis of oral versus long-acting antipsychotic studies. *Schizophr Res.* 2017;183:10-21.
8. Ribeiro ELA, de Mendonca Lima T, Vieira MEB, Storpirtis S, Aguiar PM. Efficacy and safety of aripiprazole for the treatment of schizophrenia: an overview of systematic reviews. *Eur J Clin Pharmacol.* 2018;74(10):1215-1233.
9. Cameron C, Zummo J, Desai DN, Drake C, Hutton B, Kotb A, et al. Aripiprazole lauroxil compared with paliperidone palmitate in patients with schizophrenia: An indirect treatment comparison. *Value Health.* 2017;20(7):876-885.
10. Augusto M, Greene M, Touya M, Sweeney SM, Waters H. Cost-effectiveness of long-acting injectable aripiprazole once-monthly 400 mg in bipolar I disorder in the USA. *J Comp Eff Res.* 2018;7(7):637-650.
11. Augusto M, Greene M, Touya M, Sweeney SM, Waters H. Budget impact analysis of long-acting injectable aripiprazole once-monthly 400 mg in bipolar I disorder in the USA. *J Comp Eff Res.* 2018;7(7):627-636.
12. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017;358:j4008. http://www.bmj.com/content/bmj/358/bmj.j4008.full.pdf. Accessed 2018 Dec 12.
13. Jansen JP, Fleurence R, Devine B, Itzler R, Barrett A, Hawkins N, et al. Interpreting indirect treatment comparisons and network meta-snalysis for health-care decision making: Report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: Part 1. *Value Health.* 2011;14(4):417-428.
14. Higgins JPT, Green S, editors. Figure 15.5.a: Drummond checklist (Drummond 1996). *Cochrane handbook for systematic reviews of interventions*. London (GB): The Cochrane Collaboration; 2011: http://handbook-5-1.cochrane.org/chapter_15/figure_15_5_a_drummond_checklist_drummond_1996.htm. Accessed 2018 Dec 12.
15. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34.
16. Calabrese JR, Sanchez R, Jin N, Amatniek J, Cox K, Johnson B, et al. Efficacy and safety of aripiprazole once-monthly in the maintenance treatment of bipolar I disorder: A double-blind, placebo-controlled, 52-week randomized withdrawal study. *J Clin Psychiatry.* 2017;78(3):324-331.
17. Miura T, Noma H, Furukawa TA, Mitsuyasu H, Tanaka S, Stockton S, et al. Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. *Lancet Psychiatry.* 2014;1(5):351-359.
18. Oya K, Kishi T, Iwata N. Efficacy and tolerability of aripiprazole once monthly for schizophrenia: a systematic review and meta-analysis of randomized controlled trials. *Neuropsychiatr Dis Treat.* 2015;11:2299-2307.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Butler et al. 2018, US[6]	157 RCT and prospective cohorts included, 108 studies for 28 drugs, 49 studies for nondrug interventions.	Adults with bipolar disorder of any type	All drug and non- drug therapies not limited to the following: Aripiprazole, Valproic Acid, Lithium/Valproate, Cariprazine, Haloperidol, Olanzapine, Lithium, carbamazepine, Divalproex, Quetiapine, Divalproex, Risperidone, Ziprasidone, placebo	Not limited to the following: Reduction of episodes outcomes Remission/Prevention of episodes Increased time between episodes/Time to remission Reduced hospitalization Reduction in self-harm Reduction in suicide Reduction in suicidal thoughts or self-harming behaviors Improved function Improved social and occupational functioning Change in disability Health related quality of life Severity reduction Remission of co-occurring substance use disorder Worsening of condition Adverse events
Ostuzzi et al. 2017, Italy[7]	21 RCTs (18 RCTs contributed to meta-analysis)	Adults with schizophrenia or bipolar disorder	Long-acting injectable formulation with oral formulation of the same drug, not limited to the following: paliperidone palmitate, aripiprazole monohydrate, risperidone microsphere,	Drop outs, drop outs due to adverse events, extrapyramidal symptoms, weight gain, relapse
Overview of Reviews				
Ribeiro et al. 2018, Brazil[8]	14 systematic reviews with meta-analyses of randomized controlled trials	Patients with schizophrenia	Drug therapies not limited to the following: Aripiprazole, Clozapine, Risperidone, Olanzapine, Placebo	PANSS, adverse events (e.g., weight gain, change in glucose and cholesterol, extrapyramidal side effects)

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Indirect Comparison				
Cameron et al. 2017, Canada[9]	4 RCTs (indirect comparison)	Adults with schizophrenia	Aripiprazole lauroxil, paliperidone palmitate, placebo	PANSS, weight gain, treatment emergent adverse events, akathisia, extrapyramidal symptom related adverse events

PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; US = United States.

Table 3: Characteristics of Included Economic Evaluations

First Author, Publication Year, Country	Type of Analysis, Time Horizon, Perspective	Decision Problem	Population Characteristics	Intervention and Comparators	Approach	Clinical and Cost Data Used in Analysis	Main Assumptions
Augusto et al. 2018, US[10]	*De novo* lifetime Markov model US payer perspective	Cost–effectiveness of long-acting injectable aripiprazole once-monthly 400 mg in maintenance monotherapy treatment of BP-I	US patients with a diagnosis of BP-I by DSM-5 criteria with use of aripiprazole once-monthly 400 mg for at least 8 weeks	aripiprazole once-monthly 400 risperidone LAI paliperidone palmitate cariprazine asenapine placebo/best supportive care	Markov state transition model	Clinical data: Relapse rates[16] Relative risks of transition from the first euthymic health state[17] Cost data: Truven MarketScan Medicaid and Medicare/Commercial Database RED BOOK	All oral comparators are assumed to have the same probabilities of relapse. It is assumed that the euthymic, manic, mixed and depressive health states costs are applied as a constant cost.
Augusto et al. 2018, US[11]	Budget impact model 5-year time horizon Healthcare payer perspective	Budget impact of long-acting injectable aripiprazole once-monthly 400 mg in maintenance monotherapy treatment of BP-I in a hypothetical cohort	Based on a 12-month BP-I prevalence of 0.6%, 6000 patients would be eligible for maintenance treatment in a hypothetical cohort of 1,000,000 health plan members	aripiprazole once-monthly 400 risperidone LAI paliperidone palmitate cariprazine asenapine placebo/best supportive care	Budget impact model	Clinical data: Mood episode[16] Hospitalization[17] Cost data: Truven MarketScan Medicaid and Medicare/Commercial Database RED BOOK	Market share data assumed to remain stable through the 5-year time horizon. The patients not treated with one of the included drugs but with another treatment on the market were assumed to be receiving best supportive care. All the patients with BP-I were eligible for maintenance treatment with the chosen comparators.

BP-I = bipolar I disorder; DSM-5 = diagnostic and statistical manual of mental Disorders, 5th Edition; LAI = long acting injectable.

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR2[12]

Strengths	Limitations
Butler et al., 2018[6]	
• The research question and inclusion criteria included a defined population, intervention, comparator groups, outcomes and follow-up times • The protocol for the SR was published in advance of the study. The protocol was detailed and included the review questions, search strategy, inclusion/exclusion criteria, and risk of bias assessment • Quality of studies was a factor in inclusion in the SR • A comprehensive literature search strategy of multiple sources including a grey literature search was preformed • Two investigators independently performed full-text screening to assess study eligibility with differences in screening resolved between investigators or with a third investigator • A second investigator reviewed and verified the data extracted by another investigator • A list of excluded studies and basic information for each study was provided • Individual studies were described in adequate detail including but not limited to the following: population, interventions, comparators, outcomes, research design and funding source • Risk of bias was assessed and discussed in the context of the results. RCTs were assessed using the Cochrane Risk of Bias tool, and observational studies were assessed using a tool based on the RTI Observational Studies Risk of Bias and Precision Item Bank. • The authors reported no competing interests	• Percent agreement between investigators assessing study inclusion was not reported • One investigator abstracted data from studies
Ostuzzi et al., 2017[7]	
• The research question and inclusion criteria included a defined population, intervention, comparator groups, and outcomes • The protocol for the SR was registered and published in advance of the study. The protocol was detailed and included the review questions, search strategy, inclusion/exclusion criteria, and risk of bias assessment • Data extraction was performed in duplicate • A comprehensive literature search strategy of multiple sources was preformed • Individual studies were described in adequate detail including but not limited to the following: population, interventions, comparators, outcomes, and research design • Risk of bias assessment was performed by two authors for the individual studies using the using the Cochrane Risk of Bias tool. Publication bias was assessed. • Quality of evidence was assessed using the GRADE approach • Meta-analysis using appropriate techniques to combine data were performed; including sensitivity analyses excluding	• A grey literature search was not completed • It is unclear if study selection was performed in duplicate • A list of excluded studies was not provided • Sources of funding for individual studies was not provided • The risk of bias due to factors besides sponsorship did not influence the decision to include studies in the meta-analysis • Doses of drugs were not provided

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR2[12]

Strengths	Limitations
studies with high risk of sponsorship bias • Only comparisons employing antipsychotics within therapeutic doses were included • Sources of heterogeneity were discussed • The authors reported no competing interests	
Overview of Reviews	
Ribeiro et al., 2018[8]	
• The research question and inclusion criteria included a defined population, intervention, comparator groups, and outcomes • The protocol for the SR was registered and published in advance of the study. The protocol was detailed and included the review questions, search strategy, inclusion/exclusion criteria, and risk of bias assessment • A comprehensive literature search strategy of multiple sources was preformed • Study selection and data extraction were performed in duplicate with differences resolved with a third investigator • Individual studies were described in adequate detail including but not limited to the following: population, interventions, comparators, outcomes, research design and funding source • Risk of bias assessment was performed by two authors for the individual studies using the using ROBIS tool • Quality of evidence was assessed using the GRADE approach • Heterogeneity was discussed • The authors reported no competing interests	• A grey literature search was not completed • A list of excluded studies was not provided • Dose for aripiprazole once a month not provided
Indirect Comparison[a]	
Cameron et al., 2017[9]	
• The rationale and study objectives were stated clearly • The methods section describes the description of eligibility criteria, information sources, search strategy, study selection process, outcome measures and data extraction • The analysis methods (including sensitivity analyses) were described • The network of evidence is presented for the overall study • The discussion includes a description of the main findings, internal and external validity	• Estimated study drop-out was not presented

[a]Indirect comparison assessed using ISPOR checklist[13]

GRADE = Grading of Recommendations, Assessment, Development and Evaluation; RCT = randomized control trial; ROBIS = Risk of Bias in Systematic Review; SR = systematic review.

Table 5: Strengths and Limitations of Economic Studies using the Drummond Checklist[14]

Strengths	Limitations
Augusto et al., 2018[10]	
• The research question and objective of the cost-analysis were stated • The perspective and time horizon were clearly stated • The rationale for comparators was stated • Comparators were clearly described • The sources of the clinical and economic data were stated • The primary outcome measure was clearly stated • Currency and price data were recorded • Discount rate applied in sensitivity analyses and justified • The answer to the study question was provided and conclusions based on the data reported were clearly stated	• Generalizability limited to the US • Conflict of interest stated, but authors are affiliated with PAREXEL International and Otsuka Pharmaceutical Development & Commercialization, Inc. The study was funded by Otsuka Pharmaceutical Development & Commercialization
Augusto et al., 2018[11]	
• The research question and objective of the cost-analysis were stated • The perspective and time horizon were clearly stated • The rationale for comparators was stated • Comparators were clearly described • The sources of the clinical and economic data were stated • The primary outcome measure was clearly stated • Currency and price data were recorded • The answer to the study question was provided and conclusions based on the data reported were clearly stated	• Generalizability limited to the US • Conflict of interest stated, but authors are affiliated with PAREXEL International and Otsuka Pharmaceutical Development & Commercialization, Inc. The study was funded by Otsuka Pharmaceutical Development & Commercialization

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Butler et al., 2018[6]	
• 157 studies included (RCTs and prospective cohorts) • 108 studies for 28 drugs (all drug therapies for bipolar disorder) • 1 individual relevant study[16], one comparison of interest: • Aripiprazole LAI vs. placebo ○ Time to any recurrence**:** 52 weeks**,** HR = 0.45 (95% CI 0.30 to 0.68) Favors Aripiprazole ○ Any relapse**:** 52 weeks**,** Aripiprazole 35/132**,** Placebo 68/133 Favors Aripiprazole, p<0.0001 ○ Manic relapse**:** 52 weeks**,** Favors Aripiprazole, p<0.0001 ○ Weight gain > 7%**:** Aripiprazole 23/132, Placebo 17/133 ○ SAE >1 patient: Aripiprazole 0.8%, Placebo 2.3% ○ EPS: Aripiprazole 36/132, Placebo 22/133	"We found no high- or moderate-strength evidence for any intervention to effectively treat any phase of any type of BD versus placebo or an active comparator. All antipsychotics approved by the Food and Drug Administration, except aripiprazole, had low strength evidence for benefit for acute mania in adults with BD-I… Information on harms was limited across all studies." p. ix "Evidence was insufficient for all outcomes to address whether ten drugs were better than placebo for maintenance in adults with BD: long-acting aripiprazole (n=226)…" p. 93.
Ostuzzi et al., 2017[7]	
• 21 RCTs included, 18 contributed to meta-analysis, 2 comparisons of interest: • Risperidone (6 RCTs) LAI vs. oral ○ Dropouts for any reason: RR = 1.17 (95%CI, 0.95 to 1.44) ○ Dropouts due to AEs: RR = 1.01 (95% CI, 0.67 to 1.53) ○ EPS: RR = 0.66 (95% CI, 0.37 to 1.18) ○ Weight gain RR = 1.01 (95% CI, 0.73 to 1.41) ○ Response rate: RR = 1.02 (95% CI, 0.97 to 1.07) ○ Risk of relapse: RR = 0.45 (95% CI, 0.05 to 3.82) ○ Dropouts due to inefficacy: RR = 1.08 (95% CI, 0.43 to 2.71) ○ **Hyperprolactinemia: RR = 0.81 (95% CI, 0.68 to 0.98)** • Aripiprazole (2 RCTs) LAI vs. oral ○ **Dropouts for any reason: RR = 0.78 (95% CI, 0.64 to 0.95)** ○ Dropouts due to AEs: RR = 0.93 (95% CI, 0.42 to 2.02) ○ EPS: RR = 1.11 (95% CI 0.85 to 1.46) ○ Prolactin increase: RR = 6.25 (95% CI, 0.33 to 120.01) ○ Weight gain: RR = 0.85 (95% CI, 0.64 to 1.14) ○ Response rate: RR = 0.98 (95% CI, 0.93 to 1.04) ○ Risk of relapse: RR = 1.03 (95% CI, 0.66 to 1.60) ○ Dropouts due to inefficacy: RR = 0.93 (95% CI, 0.61 to 1.42)	"Despite a theoretical pharmacokinetic basis suggesting potential advantages of LAI over oral antipsychotic formulations, meta-analysis of data from almost 5000 participants found no robust evidence in support of better tolerability or efficacy of LAIs, with the possible exception of aripiprazole." p. 17.
Overview of Reviews	
Ribeiro et al., 2018[8]	
• 14 SRs included • 1 individual relevant SR[18], 2 comparisons of interest: • Aripiprazole LAI vs. aripiprazole oral: ○ Akathisia: SMD = 0.25 (95% CI, − 0.24 to 0.74, p = 0.31) ○ Dystonia: SMD = − 0.06 (95% CI,− 0.38 to 0.26, p = 0.73)	"Aripiprazole-based therapy presented significant reduction in total PANSS (very low quality), positive PANSS (moderate quality), and negative PANSS (low quality) upon direct comparison to placebo." p. 1218

Table 6: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
○ PANSS total: SMD = − 0.08 (95% CI, − 0.31 to 0.14, p = 0.46) ○ Weight gain: RR = 0.97 (95% CI, 0.46 to 2.06, p = 0.94) • Aripiprazole LAI vs. placebo: ○ Akathisia: SMD= 0.22 (95% CI,− 0.24 to 0.68, p = 0.34) ○ Dystonia: SMD = 0.00 (95% CI, − 0.17 to 0.17, p = 1.00) ○ Anxiety: RR = 0.87 (95% CI, 0.51 to 1.47) ○ EPS: RR = 1.63 (95% CI, 0.64 to 4.15) ○ **PANSS total: SMD = − 0.65 (95%CI, − 0.90 to − 0.41, p < 0.00001)** ○ **PANSS positive: SMD = − 0.85 (95% CI, − 1.01 to − 0.69, p < 0.00001)** ○ **PANSS negative: − 0.44 (95% CI, − 0.59 to − 0.28, p < 0.00001)** ○ Weight gain: RR = 1.58 (95% CI, 0.92 to 2.73, p = 0.10)	"The findings of this overview showed that aripiprazole is effective for the reduction in the total PANSS and has efficacy similar to that of typical and atypical (with the exception of olanzapine and amisulpride) antipsychotics." p. 1232
Indirect Comparison	
Cameron et al., 2017[9]	
• 4 RCTs included, N = 1,589 • 4 comparative arms of interest: • Aripiprazole lauroxil 441 mg vs. placebo ○ **PANSS total: mean difference = -11.08 (95% CI, -17.69 to -4.39)** ○ Weight gain > 7%: OR = 1.74 (95% CI, 0.19 to 16.11) ○ TEAEs: OR = 0.87 (95% CI, 0.26 to 2.92) ○ EPS: OR = 1.00 (95% CI, 0.48 to 2.08) ○ **Akathisia: OR = 2.96 (95% CI, 1.38 to 6.99)** • Aripiprazole lauroxil 882 mg vs. placebo ○ **PANSS total: mean difference = -12.03 (95% CI, -18.59 to -5.31)** ○ Weight gain > 7%: OR = 1.55 (95% CI, 0.17 to 14.4) ○ TEAEs: OR = 0.81 (95% CI, 0.24 to 2.71) ○ EPS: OR = 1.14 (95% CI, 0.56 to 2.32) ○ **Akathisia: OR = 2.95 (95% CI, 1.36 to 6.96)** • Paliperidone Palmitate 156 mg vs. placebo ○ **PANSS total: mean difference = -9.11 (95% CI, 13.24 to -4.94)** ○ Weight gain > 7%: OR = 3.47 (95% CI, 0.96 to 14.78) ○ TEAEs: OR = 0.89 (95% CI, 0.44 to 1.89) ○ EPS: OR = 1.67 (95% CI, 0.53 to 5.82) ○ Akathisia: OR = 0.99 (95% CI, 0.36 to 2.81) • Paliperidone Palmitate 234 mg vs. placebo ○ **PANSS total: mean difference = -9.10 (95% CI, -13.98 to -3.21)** ○ Weight gain > 7%: OR = 3.14 (95% CI, 0.49 to 14.32) ○ TEAEs: OR = 1.04 (95% CI, 0.45 to 2.73) ○ EPS: OR = 1.92 (95% CI, 0.63 to 6.56) ○ Akathisia: OR = 1.14 (95% CI, 0.42 to 3.15)	"We found that AL was associated with an increase in akathisia relative to placebo… PP was associated with a greater risk of weight gain compared with placebo." p. 882 "The present NMA suggests that AL is associated with similar reductions in PANSS total score compared with PP in patients with schizophrenia experiencing an acute exacerbation. No differences in TEAEs, EPS, akathisia, or weight gain were found between AL and PP. These results suggest that clinicians can consider either AL or PP when treating adults experiencing an acute exacerbation of schizophrenia." p. 884

AE = adverse events; AL = Aripiprazole lauroxil; BD = bipolar disorder; EPS = Extrapyramidal symptoms; HR = hazard ratio; LAI = long-acting injectable; OR = odds ratio; RCT = randomized control trial; RR = relative risk; SAE = severe adverse event; SR = systematic review; SMD = standardized mean difference; TEAE = treatment-emergent adverse event; NMA = network meta-analysis; PANSS = Positive and Negative Syndrome Scale; PP = Paliperidone Palmitate.

Table 7: Summary of Findings of Included Economic Evaluations

Main Study Findings	Authors' Conclusion
Augusto et al., 2018[10]	
Base Case Analysis AOM400 vs. BSC Total Cost ($US) 373,305 vs 392,899 Incremental cost = -19,594 QALY 18.32 vs. 16.35 Incremental QALY = 1.966 ICER (US$/QALY) Dominant	"This cost–effectiveness analysis from a US healthcare payer perspective with a lifetime horizon showed that AOM 400 may be a cost-effective treatment strategy for adults with BP-I. For all but one comparator, treatment with AOM400 was the dominant treatment strategy, with lower total cost and more QALY gain over comparators. When comparing AOM 400 versus asenapine, the ICER was US$2007 per QALY. Patients treated with AOM 400 were estimated to have fewer mood episodes and fewer hospitalizations per patient than the other comparators analyzed for a lifetime horizon. This reduction in mood episodes and hospitalizations results in clinical benefit and translates into less accumulation of estimated costs of hospitalization and mood event-specific treatments throughout a patient's life" p. 11
Augusto et al., 2018[11]	
• 6000 patients would be eligible for maintenance treatment in a cohort of 1,000,000 health plan members **Base Case Analysis AOM400 vs. BSC** Market shares (current scenario) • Year 1 = 0.59 vs. 95.37 Market shares (predicted scenario) • Year 5 = 1.33 vs. 91.73 Budget impact • Year 1 = $0.02 vs. -$0.01 per member per month • Year 5 = $0.09 vs. -$0.06 per member per month	"The analysis showed an increased uptake of AOM400, paliperidone palmitate, asenapine and cariprazine as maintenance treatments for BP-I in the predicted scenario. With this predicted shift in market shares, the overall PMPM cost for all such treatments would increase from US$ .06 in Year 1 to US$0.26 in Year 5. Increases in paliperidone palmitate accounted for the majority of the overall PMPM increase, followed by AOM 400 and asenapine, with a smaller increase resulting from cariprazine. An increase in treatment-related costs in the predicted scenario was partially offset by reductions in hospitalization costs and costs related to management of AE" p. 634

AE = adverse event; AOM400 = aripiprazole once-monthly 400 mg; BSC = best supportive care (placebo); ICER = incremental cost-effectiveness ratio; PMPM = per member per month; QALY = quality-adjusted life year.