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Lurasidone Hydrochloride for Bipolar Disorder: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

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Abbreviations

AEs	Adverse events
BD	Bipolar disorder
CANMAT	Canadian Network for Mood and Anxiety Treatments
CI	Confidence interval
CGI-BP-S	Clinical Global Impression Bipolar Scale
CrI	Credible interval
DB	Double-blind
ED	Emergency department
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HbA1c	Hemoglobin A1c
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IR	Immediate release
ITT	Intention-to-treat
JBI	Joanna Briggs Institute
MA	Meta-analysis
MADRS	Montgomery-Asberg-Depression Scale
MD	Mean difference
NHLBI	National Heart, Lung, and Blood Institute
NMA	Network meta-analysis
NR	Not reported
OR	Odds ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trial
XR	Extended release
WTP	Willingness-to-pay

Context and Policy Issues

Bipolar disorder (BD) is a psychiatric illness characterized by cyclical periods of mania (great excitement or euphoria) or hypomania (mild form of mania) and depression.[1] The onset of BD commonly occurs during late adolescence or early adulthood.[2] Both environmental and genetic factors are responsible for the development of the disease.[1] BD is highly inheritable; about 85% of the risk is attributed to genetics.[3] Environmental factors include history of childhood abuse or long-term stress.[1] Patients with BD type I condition have experienced at least one manic episode, with or without depressive episodes; those with BD type II condition have experienced at least one hypomanic episode and one major depressive episode.[1] The estimated prevalence of BD I and BD II in Canada in 2012 was 0.87% and 0.57%, respectively.[4]

Both acute and maintenance treatment are required for optimal management of BD. For decades, lithium salts have been used for long term mood stabilizers in the treatment of acute mania, preventing suicide, self-harm and death.[5,6] Most antipsychotics are effective for short-term treatment of BD mania, and have antimanic effects more rapidly than lithium.[7] The anticonvulsants valproate and carbamazepine have also been approved for acute maniac episodes.[7] Antidepressant monotherapy is not recommended for treatment of BD.[8] Some atypical antipsychotics including olanzapine/fluoxetine combination, quetiapine

(immediate release or extended release) and lurasidone (monotherapy or adjunctive to lithium or valproate) have been recently approved for treatment of acute bipolar depression.[9] In bipolar I depression, lurasidone monotherapy and lurasidone adjunctive to lithium or valproate were found to be efficacious in placebo-controlled trials.[10-12] However, head-to-head comparisons between lurasidone and other pharmacological agents in the treatment of adult patients with BD would provide stronger evidence regarding their comparative effectiveness and safety.

The aim of this report is to review the comparative clinical effectiveness and cost-effectiveness of lurasidone hydrochloride (as monotherapy or as adjunctive therapy with lithium or valproate) versus other treatments such as typical antipsychotics, other atypical antipsychotics, lithium, lamotrigine, antidepressants, valproate, or tryptophan, for the treatment of adults with BD. This report also aims to identify safety-related outcomes and evidence-based guidelines regarding the use of lurasidone hydrochloride for the treatment of adults with BD.

Research Question

1. What is the clinical effectiveness of lurasidone hydrochloride for the treatment of adults with bipolar disorder?
2. What is the clinical evidence regarding the safety of lurasidone hydrochloride for the treatment of adults with bipolar disorder?
3. What is the cost-effectiveness of lurasidone hydrochloride for the treatment of adults with bipolar disorder?
4. What are the evidence-based guidelines regarding the use of lurasidone hydrochloride for the treatment of adults with bipolar disorder?

Key Findings

This review included one systematic review, five primary studies, one economic study and two guidelines regarding the use of lurasidone hydrochloride for the treatment of adults with bipolar disorder.

Based on findings from a network meta-analysis, lurasidone monotherapy of acute bipolar depression (mostly type I) was more efficacious than aripiprazole and ziprasidone monotherapy. Lurasidone was associated with less weight gain than olanzapine and quetiapine, and lower somnolence incidence than quetiapine and ziprasidone.

Common adverse events of lurasidone therapy included nausea, somnolence, headache, dizziness, akathisia, fatigue, insomnia, tremor, Parkinsonism, nasopharyngitis, anxiety, depression, and extrapyramidal symptoms. Discontinuation of treatment due to adverse events was 9% or less. Metabolic related changes in weight, glucose and lipids were not clinically meaningful.

Based on the US third-party payer perspective, lurasidone monotherapy resulted in an incremental cost-effectiveness ratio of $3,474 per remission gained when compared with quetiapine extended release for the treatment of adults with bipolar I depression.

Both good quality guidelines recommend lurasidone (monotherapy or adjunctive to lithium or valproate) as first-line treatment for acute bipolar depression. For maintenance therapy,

lurasidone adjunctive may be appropriate as second line in patients who responded to lurasidone during a depressive episode.

Well-designed trials are needed that directly compare lurasidone monotherapy or lurasidone adjunctive therapy with other interventions. Cost-effectiveness studies of lurasidone that are conducted with respect to the Canadian health care perspective are also warranted. Current findings may not be generalizable to the Canadian context, and they should be interpreted with caution given their limitations.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, Medline, Embase and PsycINFO via Ovid, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were lurasidone and bipolar disorder. No filters were applied to limit the 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, 2015 and January 14, 2020.

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	Q1-4: Adults (≥ 18 years) with bipolar disorder, with or without comorbid conditions
Intervention	Q1-4: Lurasidone hydrochloride, as monotherapy or as adjunctive therapy with lithium or valproate, all formulations and all routes of administration
Comparator	Q1,3: • Typical antipsychotics (e.g., chlorpromazine, methotrimeprazine, loxapine, perphenazine, zuclopenthixol, flupentixol, fluphenazine, haloperidol, pimozide, trifluoperazine) • Atypical antipsychotics (e.g., aripiprazole, asenapine, brexpiprazole, clozapine, quetiapine, olanzapine, paliperidone, risperidone, ziprasidone) • Lithium • Lamotrigine • Antidepressants (e.g., monoamine oxidase inhibitors, norepinephrine and dopamine reuptake inhibitors, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, serotonin antagonist and reuptake inhibitors tricyclic antidepressants, and tetracyclic antidepressants) • Valproic acid, valproate • Tryptophan Q2: No comparator Q4: Not applicable

Outcomes	Q1: Clinical effectiveness (e.g., symptoms, mood stability, depression, remission, discontinuation of treatment) Q2: safety (e.g., misuse, abuse, nausea, weight gain, somnolence, restlessness, mortality) Q3: Cost-effectiveness (e.g., cost per quality adjusted life year, cost per patient adverse event avoided, cost per clinical outcome) Q4: Guidelines on appropriate use and place in therapy
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, economic evaluations, non-randomized studies, and evidence-based guidelines

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria in Table 1 or if they were published prior to 2015.

Critical Appraisal of Individual Studies

The systematic review (SR) with network meta-analysis (NMA) was critically appraised by one reviewer using a checklist[13] based on the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) criteria.[14] The critical appraisal checklists of the Joanna Briggs Institute were used to assess the quality of the included randomized controlled trial (RCT),[15] prevalence study[16] and economic study.[17] The quality of the before-after studies with no control group were assessed using the National Heart, Lung, and Blood Institute (NHLBI) checklist.[18] The quality of the evidence-based guidelines were assessed using the Appraisal of Guidelines for Research and Development (AGREE) II instrument.[19] Summary scores were not calculated for the included studies; rather, the strengths and limitations were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 132 citations were identified in the literature search. Following screening of titles and abstracts, 118 citations were excluded and 14 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search. Of the 16 potentially relevant articles, seven publications were excluded for various reasons, while nine publications met the inclusion criteria and were included in this report. These comprised one SR, five primary studies (one RCT, one prevalence study and three before-and-after studies) reporting utilization and safety, one economic study, and two guidelines. No primary studies reporting the comparative clinical effectiveness of lurasidone with other interventions were identified. Appendix 1 presents the PRISMA flowchart[20] of the study selection.

Summary of Study Characteristics

The detailed characteristics of the included SR,[21] (Table 2) primary studies,[22-26] (Table 3) economic study,[27] (Table 4) and two guidelines[28,29] (Table 5) are presented in Appendix 2.

Study Design

The included SR,[21] published in 2018, used NMA in a Bayesian framework to compare lurasidone with other atypical antipsychotic monotherapies for acute bipolar depression. RCTs were searched using multiple databases with search dates between 1999 and 2015. Assessment of the quality of the included RCTs was not conducted. NMA results and sensitivity analysis results were reported.

Five primary studies reporting the health care utilization and safety of lurasidone for treatment of adult patients with BD were included. One was a double-blind placebo controlled trial (parallel arm),[25] one was a prevalence study[22] using commercial claims data, and three were before-and-after studies[23,24,26] with no control group.

The cost-effectiveness study[27] used a decision analytic model comparing direct health care costs of lurasidone with quetiapine extended release (XR). The model was based on a US third-party payer perspective over a 3-month time horizon. The treatment effect used in the model was remission rates obtained from placebo-controlled trials. The comparison of the remission rates between interventions was made through adjusted indirect comparison. The costs input into the model included pharmacy and medical costs (which included numbers of emergency department visits, number of inpatient days and number of office visits). One-way deterministic sensitivity analysis and probabilistic sensitivity analysis were conducted.

Both included guidelines[28,29] did not describe the methods used to search for evidence, or to select and synthesize evidence. The British Association for Psychopharmacology (BAP) guideline[29] was an update of a previous guideline. Its recommendations were made through consensus of expert opinion, and were rated based on pre-defined levels of evidence, using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach. The Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) guideline[28] was also an updated one, and was developed by members from research, academic and clinical centres across Canada and internationally. Treatment options in this guideline were hierarchical ranked as “first line”, “second line”, “third line” or “not recommended” based on the level of evidence. Both guidelines[28,29] were peer-reviewed.

Country of Origin

The SR,[21] all additionally included primary studies,[22-26] and the included cost-effectiveness study[27] were conducted by authors from US. One included guideline was from Canada,[28] the other guideline was from the UK.[29]

Patient Population

All of the studies cited in the SR[21] included patients with bipolar I disorder, with the exception of studies in which quetiapine was the comparator, which included both patients with bipolar I and bipolar II disorder. The mean age ranged from 29.2 years to 42.2 years.

Of the five additional primary studies, two[22,24] included BD patients of any type, and three[23,25,26] included only BD patients of type I. The mean age varied between 38.6 years and 45.1 years.

The included cost-effectiveness study[27] assessed the cost-effectiveness of lurasidone and quetiapine XR in patients with bipolar I depression.

The target population for the identified guidelines[28,29] was patients with BD, and the intended users of the guidelines were psychiatrists, primary care providers, patients and their families.

Interventions and Comparators

The SR[21] used NMA to indirectly compare lurasidone monotherapy with other atypical antipsychotic monotherapies (i.e., aripiprazole, olanzapine, quetiapine, ziprasidone) using placebo as the common comparator.

The RCT[25] compared lurasidone (in combination with lithium or valproate) with placebo. The prevalence study[22] used a commercial database to compare lurasidone monotherapy with other atypical antipsychotic monotherapies (i.e., aripiprazole, olanzapine, quetiapine, ziprasidone). The intervention in the three before-and-after studies[23,24,26] was lurasidone as adjunctive therapy with lithium or valproate, and had no comparator group.

Treatment duration of the cited RCTs in the SR[21] ranged from 6 weeks to 8 weeks. The prevalence study[22] assessed the outcomes after one month of monotherapy treatment. Treatment duration of the remaining studies[23-26] ranged from 4 months to 6 months.

The interventions evaluated in the cost-effectiveness study[27] were lurasidone monotherapy and quetiapine XR monotherapy. The comparison was made over the 3-month time horizon.

The interventions considered in the guidelines were psychological[28] and pharmacological interventions[28,29] for management of bipolar mania and bipolar depression.

Outcomes

The primary efficacy outcome of the SR[21] was change from baseline in depressive symptoms assessed by Montgomery-Asberg-Depression Scale (MADRS). Other efficacy outcomes were change in Clinical Global Impression Bipolar Scale (CGI-BP-S), response (≥ 50% improvement in MADRS) and remission (MADRS ≤ 12 at study endpoint). Tolerability outcomes were weight change, somnolence, extrapyramidal symptoms, and all-cause discontinuation.

The outcomes in all identified primary studies[22-26] were mainly acceptability, tolerability and safety outcomes. They were all-cause discontinuation, discontinuation due to adverse events (AEs), discontinuation due to inadequate efficacy, AEs, and laboratory parameters. One study[22] also reported adherence and hospitalization as outcomes.

The primary outcome of the identified cost-effectiveness study[27] was expressed as incremental cost-effectiveness ratio (ICER) per remission gained of lurasidone compared with quetiapine XR.

Both identified guidelines[28,29] had recommendations on lurasidone treatment of bipolar depression. The guidelines considered clinical effectiveness and safety outcomes of the interventions, without considering patient preferences or potential resource (cost) implications, in their recommendations.

Summary of Critical Appraisal

The detailed quality assessments of the identified SR,[21] (Table 6) RCT,[25] (Table 7) prevalence study,[22] (Table 8) before-and-after studies with no control group,[23,24,26] (Table 9) economic study,[27] (Table 10) and guidelines[28,29] (Table 11) are presented in Appendix 3.

The identified SR[21] with NMA clearly stated the rationale for the study and the study objectives. The methods section included a description of eligibility criteria and sources of information and outcome measures, but did not report the process for study selection or data extraction, or the risk of bias in the included studies. The SR provided a description of analyses methods/models, analysis framework and sensitivity analyses. Methods of handling potential bias or inconsistency were not described. The SR provided data from individual studies and the network of studies. An assessment of model fit (Deviance Information Criterion) and competing models (fixed and random effects models) being compared were included. The SR clearly presented the results of the evidence synthesis, and conducted sensitivity analyses. The SR included in its discussion a summary of the main findings, internal, external validity, and implications of the results for the target audience. Also discussed was the need of an economic model to present the real impact of the intervention of interest. The study was funded by Sunovion Pharmaceuticals Inc.

The included RCT[25] was a two-phase study in which open-label treatment with adjunctive lurasidone in all patients was followed by double-blind placebo-controlled trial in those who were stable. Concealment to treatment allocation and blinding of outcomes assessors were not reported. Treatment groups had numerically similar baseline characteristics (not compared statistically), and were treated identically other than the intervention of interest. Analyses were conducted based on the intention-to-treat population. Outcomes were measured in a reliable way and appropriate statistical analysis was used. Trial design (i.e., parallel RCT) was appropriate. The study was funded by Sunovion Pharmaceuticals Inc.

The included prevalence study[22] used commercial claims data from a large, national health insurer in the US. Although sample size calculation was not conducted, the sample size (n = 11,132) might be adequate. Patient characteristics and setting were described in detail. Data analysis was probably not conducted with sufficient coverage of the identified sample as all subgroups might not respond at the same rate. For instance, overall response rate may be high, but response rate of certain subgroups may be quite low. Statistical analysis was appropriate. The study was funded by Sunovion Pharmaceuticals Inc.

All three included before-and-after studies[23,24,26] clearly described the study objectives and eligibility criteria for the study populations. It was unclear if the participants in these studies were representative of the general population of interest. A sample size calculation was not conducted in any of the three studies. The interventions were clearly described, and the outcomes were prespecified and clearly defined. Outcome assessors were not blinded to the intervention received. All-cause discontinuation was substantive (77%,[24] 27.6%,[23] and 43.4%[26]), and those lost to follow-up were not accounted for in the analysis. Statistical analysis used to examine the pre-post changes of outcome measures was appropriate in all three studies. It was unclear if the outcome measures were taken multiple times before and after the interventions. In cases when the intervention was conducted at a group level, it was unclear whether statistical analysis considered the use of individual-level data to determine effects at the group level. All studies were funded by Sunovion Pharmaceuticals Inc.

The included cost-effectiveness study used established clinical inputs, and conducted sensitivity analyses to investigate uncertainty in costs and consequences. It was unclear if the study accurately measured and credibly valued costs and outcomes, and had study results that included all issues of concern to users. It was also unclear if the results could be generalizable to the Canadian setting. The study was funded by Sunovion Pharmaceuticals Inc.

The two included guidelines[28,29] were explicit in terms of scope and purpose (i.e., objectives, health questions and population) and clarity of presentation (i.e., specific and unambiguous recommendations, different options for management of the condition or health issue, and easy to find key recommendations). In terms of stakeholder involvement, the guidelines clearly defined target users and the development groups included individuals from all relevant professional groups. However, it was unclear if the views and preferences of the target populations were sought. For rigour of development, although the systematic methods were used to search for the evidence, criteria for selecting the evidence were not reported. The guidelines were explicit in terms of strengths and limitations of the body of evidence, the methods of formulating the recommendations, and the link between the recommendations and the supporting evidence. Both guidelines were externally reviewed by experts prior to publication, and provided a procedure for future updating. For applicability, the facilitators and barriers to the guidelines' applications were unclear, and no advice and/or tools on how the recommendations can be put into practice were apparent. Cost was not considered in the recommendations, and monitoring and/or auditing criteria were not presented in both guidelines. For editorial independence, it was unclear if the funding bodies influenced the content of the guidelines. The Canadian guideline was funded by the Canadian Network for Mood and Anxiety Treatments, while the British guideline declared that the authors received no financial support from any organization. The competing interests of guideline development group members were reported in both guidelines.

Summary of Findings

The main findings and authors' conclusions of the SR,[21] (Table 12), primary studies,[22-26] (Table 13), economic study[27] (Table 14) and guidelines[28,29] (Table 15) are presented in Appendix 4.

Clinical Effectiveness of Lurasidone Hydrochloride

Depressive Symptoms (MADRS score)

NMA results[21] showed that lurasidone was associated with a statistically significant improvement in MADRS compared to aripiprazole (mean difference [MD] 95% confidence interval [CI] = -3.62 [-7.04 to -0.20]) and ziprasidone (MD [95% CI] = -3.38 [-6.68 to -0.11]). Lurasidone had no significant difference in improvement compared with olanzapine (MD [95% CI] = -0.15 [-3.12 to 2.74]) and quetiapine (MD [95% CI] = 0.10 [-2.68 to 2.84]).

Overall severity (CGI-BP-S score)

NMA findings[21] showed that lurasidone was associated with a statistically significant improvement in CGI-BP-S compared to aripiprazole (MD [95% CI] = -0.42 [-0.78 to -0.07) and ziprasidone (MD [95% CI] = -0.59 [-0.94 to -0.24]). Lurasidone had no significant difference in improvement compared with olanzapine (MD [95% CI] = -0.31 [-0.65 to 0.03]) and quetiapine (MD [95% CI] = -0.09 [-0.39 to 0.21]).

Response (≥ 50% improvement in MADRS)

NMA findings[21] showed that lurasidone was associated with a statistically significant improvement in response rate compared to aripiprazole (odds ratio [OR] [95% CI] = 2.40 [1.36 to 3.96) and ziprasidone (OR [95% CI] = 2.45 [1.38 to 4.05]). Lurasidone had no significant difference in improvement compared with olanzapine (OR [95% CI] = 1.68 [0.99 to 2.69]) and quetiapine (OR [95% CI] = 1.29 [0.78 to 2.01]).

Remission (MADRS ≤ 12 at study endpoint)

NMA findings[21] showed that lurasidone was associated with a statistically significant improvement in remission rate compared to aripiprazole (odds ratio [OR] [95% CI] = 2.28 [1.22 to 3.90) and ziprasidone (OR [95% CI] = 2.18 [1.21 to 3.65]). Lurasidone had no significant difference in improvement compared with olanzapine (OR [95% CI] = 1.54 [0.87 to 2.53]) and quetiapine (OR [95% CI] = 1.11 [0.66 to 1.77]).

Adherence

Results from a prevalence study showed that lurasidone was associated with significantly higher adherence rate compared with olanzapine, risperidone and quetiapine, but the adherence rate was not significantly different from that with aripiprazole and ziprasidone.[22]

Psychiatric hospitalization

Results from a prevalence study showed that lurasidone was associated with significantly lower hospitalization rate compared with olanzapine and quetiapine, but had no statistically significant difference in comparison with aripiprazole, risperidone and ziprasidone.[22]

All-cause hospitalization

Results from a prevalence study showed that lurasidone was associated with significantly lower all-cause hospitalization compared with olanzapine, risperidone and quetiapine, but had no statistically significant difference in comparison with aripiprazole and ziprasidone.[22]

All-cause discontinuation

NMA results[21] showed that differences between lurasidone and other atypical antipsychotics (i.e., aripiprazole, olanzapine, risperidone and quetiapine and ziprasidone) in terms of all-cause discontinuation were not statistically significant. In two before-and-after studies,[23,24] lurasidone was associated with all-cause discontinuation rates of 32.7%[23] in lurasidone monotherapy, and 24.4%[23] or 77.0%[24] in adjunctive lurasidone.

Discontinuation due to AEs

Discontinuation rate due to AEs in studies with open-label lurasidone was 6.1%[25] or 6.6%.[26] In a double-blind RCT,[25] discontinuation rate due to AEs was 3.3% in the lurasidone group and 2.0% in the placebo group.

Common AEs

Common AEs (incidence ≥ 5%) of lurasidone therapy[22-26] included nausea, somnolence, headache, dizziness, akathisia, fatigue, insomnia, tremor, Parkinsonism, nasopharyngitis, anxiety, depression, and extrapyramidal symptoms. NMA results[21] showed that lurasidone was associated with significantly less weight gained compared to olanzapine and quetiapine, but not significantly different compared to aripiprazole. One post-hoc analysis of a 6-month, open-label study[23] reported that mean change in weight with lurasidone monotherapy was -1.0 kg, and with adjunctive lurasidone therapy was -0.4 kg after six

months. Another study[26] showed that adjunctive lurasidone therapy was associated with a mean weight change of +1.8 kg at 12 months, and +0.8 kg at 24 months. Lurasidone was associated with significantly lower incidence of somnolence compared to quetiapine and ziprasidone, but not significantly different compared to aripiprazole and olanzapine.[21] Differences between lurasidone and aripiprazole, or between lurasidone and quetiapine in terms of extrapyramidal symptoms were not statistically significant.[21]

Severe AEs

The proportion of patients reporting at least one AEs rated as "severe" was 10.9% in monotherapy[23] and 4.9% to 10.5% in adjunctive lurasidone therapy.[23,25,26]

Metabolic parameters

The median changes in the levels of total cholesterol, triglyceride, glucose, and hemoglobin A1c, and prolactin compared to baseline after 6-month[23] or 18-month[26] lurasidone therapy were not clinically meaningful.

Cost-effectiveness of Lurasidone Hydrochloride

One cost-effectiveness study[27] evaluated the cost-effectiveness of lurasidone and quetiapine XR in patients with bipolar I depression over 3-month time period. Patients treated with lurasidone and quetiapine XR had numerically similar mean numbers of emergency department visits (0.48 versus 0.50), mean number of inpatient days (2.1 versus 2.2), and mean numbers of office visits (9.3 versus 9.6), however no statistical comparisons were conducted. Lurasidone patients achieved numerically higher remission rate than quetiapine XR patients (52.0% versus 43.2%), with numerically higher total costs ($4,982 versus $4,676), however no statistical comparisons were conducted. Compared to quetiapine XR, lurasidone treatment resulted in an ICER of $3,474 per remission gained. One-way sensitivity analysis showed that the results were most sensitive to remission rates and pharmacy costs. In probabilistic sensitivity analysis, lurasidone had 65% probability of being cost-effective compared with quetiapine XR at willingness-to-pay (WTP) threshold of $5,000 per remission gained; 86% at a WTP of $10,000 per remission gained; and over 90% at WTP thresholds of $15,000 and higher.

Guidelines Regarding Lurasidone Hydrochloride

Both included guidelines[28,29] recommend lurasidone as pharmacological treatment for acute bipolar depression. The Canadian guideline[28] recommends lurasidone monotherapy or lurasidone adjunctive (+ lithium or divalproex) therapy as a first line treatment option in a hierarchical manner following the order in this list: Quetiapine; Lurasidone + Lithium/divalproex; Lithium; Lamotrigine; Lurasidone; Lamotrigine (adjunctive). The Canadian guideline[28] also recommends lurasidone adjunctive as second line for maintenance treatment of bipolar depression in patients who responded to lurasidone during a depressive episode in a hierarchical manner following the order in this list: Olanzapine; Risperidone long-acting injectable; Risperidone long-acting injectable (adjunctive); Carbamazepine; Paliperidone (> 6 mg); Lurasidone (adjunctive); Ziprasidone (adjunctive). In the Canadian guideline,[28] "first line" recommendations were based on level 1 or level 2 evidence, while "second line" recommendations were based on level 3 or higher evidence. In the British guidelines,[29] the grade of recommendation for lurasidone was strong based on high level evidence.

Limitations

There was a lack of clinical efficacy evidence derived from direct comparison of lurasidone with active comparators. All of the identified primary studies were selected to address the tolerability and safety of lurasidone treatment without any comparator. The identified SR[21] used NMA to compare the efficacy and tolerability of lurasidone versus other atypical antipsychotics via placebo as common comparator. NMA results may have been affected by potential biases (e.g., choice of therapy dosage and duration) and heterogeneity (e.g., patient characteristics, mixed population of patients with BD I and BD II, response and remission criteria, level of BD severity, dosage and duration) and inconsistent outcomes across trials. The NMA findings were limited to atypical antipsychotic monotherapy for the treatment of bipolar depression, mainly in BD I patients. It was uncertain whether NMA findings could be applied to adjunctive therapy or to patients with other types of BD. The potential bias of financial sponsorship in all identified studies, including the SR, by a pharmaceutical company (Sunovion Pharmaceuticals Inc.) making lurasidone cannot be ruled out. Thus, the validity of the conclusions is limited, and the evidence should be cautiously interpreted.

In the cost-effectiveness study,[27] the clinical inputs (i.e., comparisons in clinical efficacy and tolerability between lurasidone and quetiapine XR) were indirect, due to the lack of head-to-head trials. AEs were not included in the models, as the authors suggested that AEs would develop when the drugs were taken for a longer duration. It was unclear whether the findings could be extrapolated to longer durations of treatment. Not all costs were incorporated in the models such as costs of monitoring tests and costs associated with work productivity losses. The study was sponsored by Sunovion Pharmaceuticals Inc.

It remains unclear whether the clinical findings and cost-effectiveness results in the included studies are generalizable to the Canadian context.

Conclusions and Implications for Decision or Policy Making

This review included one SR,[21] five primary studies,[22-26] one economic study[27] and two guidelines. [28,29]

Based on findings from a network meta-analysis,[21]lurasidone monotherapy in BD patients (mostly type I) was more efficacious than aripiprazole and ziprasidone for reducing depressive symptoms (MADRS), for improving overall severity (GCI-BO-S), and for increasing response and remission rates. Lurasidone was associated with less weight gain than olanzapine and quetiapine, and lower somnolence incidence than quetiapine and ziprasidone.

Common AEs (incidence ≥ 5 %)[23,25,26] of lurasidone therapy included nausea, somnolence, headache, dizziness, akathisia, fatigue, insomnia, tremor, Parkinsonism, nasopharyngitis, anxiety, depression, and extrapyramidal symptoms. Discontinuation of treatment due to AEs was 9% or less,[23,26] and there were non-clinically meaningful changes in values of metabolic parameters (weight, glucose, lipids) compared to baseline.

The cost-effectiveness study,[27] based on the US third-party payer perspective, showed that lurasidone monotherapy resulted in an ICER of $3,474 per remission gained when compared with quetiapine XR for the treatment of adults with bipolar I depression.

Both good quality guidelines recommend lurasidone monotherapy or lurasidone adjunctive to lithium or valproate as first-line pharmacological treatment for acute bipolar depression. For maintenance therapy, lurasidone adjunctive may be appropriate as second line in patients who responded to lurasidone during a depressive episode.

The evidence identified in the current review should be cautiously interpreted given the aforementioned limitations. Future trials are warranted for direct comparison of lurasidone monotherapy or lurasidone adjunctive therapy with other available interventions. There is also a need for cost-effectiveness studies of lurasidone that are conducted with respect to the Canadian health care perspective.

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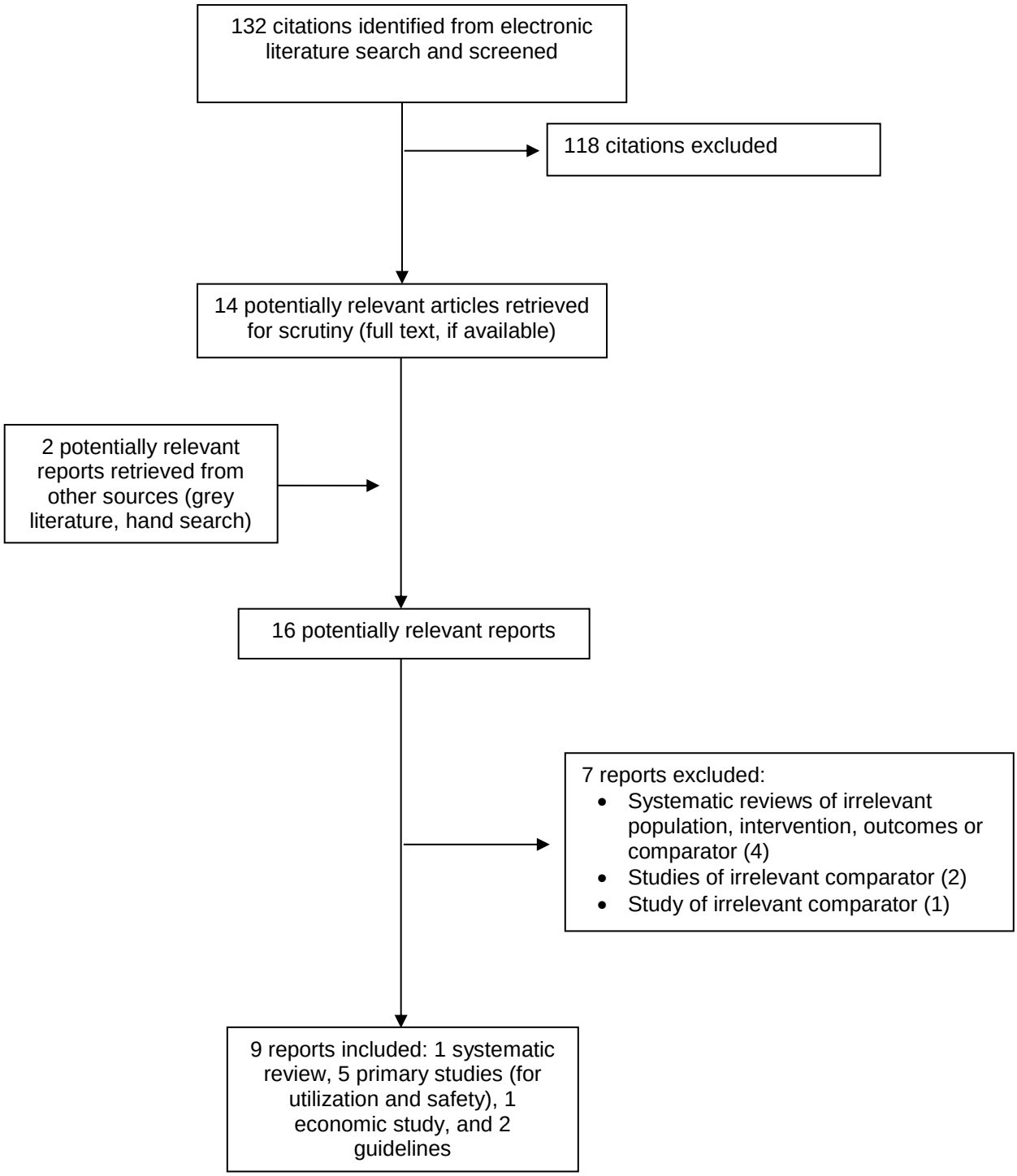
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Studies

Table 2: Characteristics of Included Systematic Review

First Author, Publication Year, Country, Funding	Objectives, Types and Numbers of Primary Studies Included, Quality Assessment Tool, Databases and Search Date	Patient Characteristics	Interventions and comparators	Outcomes
Ostacher et al., 201821 USA Funding: Sunovion Pharmaceuticals Inc.	Objective: To assess the efficacy and tolerability of lurasidone versus other atypical antipsychotic monotherapy agents in patients with depression, using Bayesian NMA. Total 14 RCTs (n = 6,221) Quality assessment tool: Not conducted Databases: EMBASE, MEDLINE, PsyINFO, Cochrane Library and Google Scholar search engines Search date: from 1999 to 2013 Data analysis: NMA (Bayesian framework); sensitivity analysis	Adult patients with diagnosis of BD I and BD II Mean age: Range from 29.2 to 42.2 years % Male: 35.5 to 44.3 % Bipolar I disorder: 50 to 100 MADRS: 28.2 to 32.0	Interventions: – Lurasidone Comparators (other atypical antipsychotics): – Aripiprazole – Olanzapine – Quetiapine IR or XR – Ziprasidone Treatment duration: Range from between 6 weeks and 8 weeks	– Change in MADSR score – Change in CGI-BP-S score – Response (≥ 50% improvement in MADRS at endpoint – Remission (MADRS score ≤ 12 at endpoint) – Tolerability (weight change, somnolence, extrapyramidal symptoms, all-cause discontinuation)

BD I = bipolar disorder type I; BD II = bipolar disorder type II; CGI-BP-S = Clinical Global Impression Bipolar Scale; IR = immediate release; MA = meta-analysis; MADRS = Montgomery-Asberg-Depression Scale; NMA = network meta-analysis; NR = not reported; RCTs = randomized controlled trials; XR = extended release.

Table 3: Characteristics of Included Primary Studies

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Outcomes
Ng-Mak et al., 2019[22] USA Funding: Sunovion Pharmaceuticals Inc.	Prevalence study US commercial claims analysis (Optum Research Database) 4 April 2010 through 24 September 2014 Statistical analysis: Appropriate Index date = first claim (pre-index = 180 days; post-index = 360 days)	Adult patients with BD treated with atypical antipsychotics (N = 11,132) – Mean age: 38.6 years – % Female: 63.6 – Bipolar diagnosis: 44.25 unspecified, 31.3% depression, 13.8% mixed, 10.7% mania	Lurasidone monotherapy	Other atypical antipsychotics: – Aripiprazole – Olanzapine – Quetiapine – Risperidone – Ziprasidone	– Adherence – Hospitalization
Forester et al., 2018[23] USA Funding: Sunovion Pharmaceuticals Inc.	Before-and-after study Post-hoc analysis of a multicenter, 6-month, open-label extension study	Outpatients with BD I (n = 141) Mean age: 60.2 years (ranging from 55 to 75 years) % Male: 42.4 Mean MADRS at open-label baseline: 17.2	Lurasidone monotherapy (n = 55) Lurasidone + lithium or valproate (n = 86) Mean dose: 65 mg/day	None	Efficacy outcomes were not relevant for this report, as the study had no active comparator(s) Safety outcomes: – AEs – Discontinued due to AEs – Laboratory parameters
Miller et al., 2019[24] USA Funding: Sunovion Pharmaceuticals Inc.	Before-and-after study Outpatients assessed with Systematic Treatment Enhancement Program for BD (STEP-BD) Affective Disorders Evaluation	Outpatients with BD treated at the Stanford University Bipolar Disorders Clinic (n = 61) Mean age: 45.1 years	Adjunctive open-label lurasidone Median duration: 126 days Dosing:	No comparator	– All-cause discontinuation – Discontinuation due to AEs – Discontinuation due to

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Outcomes
	Assessment period: February 11, 2011 through July 27, 2016	% Female: 63.9 % BP II: 42.6	– Initiation: 21.8 ± 6.2 mg/day – Month 1: 43.1 ± mg/d Final visit: 55.6 ± 30.8 mg/day		inadequate efficacy – AEs
Calabrese et al., 2017[25] USA Funding: Sunovion Pharmaceuticals Inc.	Open-label treatment with lurasidone + lithium or valproate (12 to 20 weeks) followed by double-blind placebo-controlled RCT (lurasidone + lithium or valproate versus placebo + lithium or valproate) (28 weeks).	Adult patients with BD I underwent maintenance treatment with lurasidone in combination with lithium or valproate (n = 496) Mean age: 44.4 years % Male: 43.8 Mean MADRS at baseline: 18.2	Lurasidone in open-label treatment (20 to 80 mg/d) + lithium or valproate In double-blind RCT, lurasidone (20 to 80 mg/d) + lithium or valproate	Placebo in double-blind RCT	Efficacy outcomes were not relevant for this report, as placebo was used as comparator Safety outcomes: – AEs – Discontinued due to AEs – Laboratory parameters
Pikalov et al., 2017[26] USA Funding: Sunovion Pharmaceuticals Inc.	Before-and-after study Open-label extension study of a placebo-controlled RCT Completers in RCT underwent 6-momth, open-label extension with lurasidone Completers in 6-momth, open-label extension underwent 18 months of continuation treatment	Adult patients with BD I depression Mean age: 41.3 years % Male: 52.5 Mean MADRS at 6-month extension baseline:13.8 Mean MADRS at 18-month extension baseline: 6.5	Lurasidone in 18-month continuation treatment (n = 122; 20 to 80 mg/day)	None	Efficacy outcomes were not relevant for this report, as the study had no active comparator(s) Safety outcomes: – AEs – Discontinued due to AEs – Laboratory parameters

AEs = adverse events; BD = bipolar disorder; MADRS = Montgomery-Asberg-Depression Scale; RCT = randomized controlled trial

Table 4: Characteristics of Included Economic Study

Study, Year, Country, Funding	Study design	Perspective, Time Horizon, Dollar, Discounting	Population, Inclusion criteria	Interventions, Model Assumption	Costs
Rajagopalan et al., 2015[27] US Funding: Sunovion Pharmaceuticals Inc.	Cost-effectiveness Decision analytic model comparing direct health care costs of lurasidone with quetiapine XR Primary outcome: ICER per remission Treatment effects: Remission rates were obtained from clinical trials. Comparison was made through adjusted indirect treatment comparison Sensitivity analyses: one-way deterministic sensitivity analysis and probabilistic sensitivity analysis	Perspective: US third-party payer perspective Time horizon: 3 months Currency: US dollars (2011 to 2012) Discount rate: not applicable Setting: Inpatient and outpatient care	Patients with BD I depression	– Lurasidone monotherapy – Quetiapine XR monotherapy Model assumption: Patients with acute state of bipolar I depression received treatment (lurasidone or quetiapine XR) for 6 weeks. After 6 weeks, patients either achieved remission or no remission (still remained in a state of acute depression)	Costs: – Pharmacy – Medical (inpatient, outpatient, physician's office, and emergency)

ED = emergency department; ICER = incremental cost-effectiveness ratio; XR = extended release; WTP = willingness-to-pay.

Table 5: Characteristics of Included Guidelines

First Author, Society/Group Name, Publication Year, Country, Funding	Intended Users and Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection and Synthesis	Recommendations Development and Evaluation	Guideline Validation
CANMAT and ISBD, Yatham et al., 2018[28] Canada Funding: CANMAT	Intended users: Psychiatrists and primary care providers. Target population: Patients with BD	Assessment, treatment of acute symptoms, prevention of episode recurrence, and management of comorbidities	All outcomes (clinical, non-clinical,) related to screening, diagnosis and treatment of BD	Systematic methods used to search for evidence, selection and synthesis were not reported in the published article	The guideline was developed by members from research, academic and clinical centers across Canada and internationally Each level of evidence was graded[a] (highest to lowest): 1, 2, 3, 4	The guideline was peer-reviewed

First Author, Society/Group Name, Publication Year, Country, Funding	Intended Users and Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection and Synthesis	Recommendations Development and Evaluation	Guideline Validation
					Treatment options were hierarchical ranked[b] as first line, second line, third line or not recommended based on the evidence level	
BAP, Goodwin et al., 2016[29] UK Funding: No financial support	Intended users: All doctors, psychiatrists, primary care providers, patients and their families. Target population: Patients with BD	Diagnosis of BD, clinical management and strategies for the use of drugs in short-term treatment, relapse prevention and stopping treatment	Evidence relating to medical management of BD	Expert participants were asked to review new available data. This is an updated guideline. Unclear if a systematic method was used for evidence collection, selection and synthesis.	The guideline was developed by experts in BD and recommendations were made through consensus. Recommendations were rated based on pre-defined level of evidence, using GRADE approach[c]	The guideline was peer-reviewed

BAP = British Association for Psychopharmacology; BD = bipolar disorder; CANMAT = Canadian Network for Mood and Anxiety Treatments; DB = double-blind; GRADE = Grading of Recommendations, Assessment, Development and Evaluations; ISBD = International Society for Bipolar Disorders; RCT = randomized controlled trial

[a] Level of evidence ratings

Level 1: Meta-analysis with narrow confidence interval or replicated double-blind (DB), randomized controlled trial (RCT) that includes a placebo or active control comparison (n ≥ 30 in each active treatment arm)

Level 2: Meta-analysis with wide confidence interval or one DB RCT with placebo or active control comparison (n ≥ 30 in each active treatment arm)

Level 3: At least one DB RCT with placebo or active control comparison condition (n = 10-29 in each active treatment arm) or health system administrative data

Level 4: Uncontrolled trial, anecdotal reports, or expert opinion

[b] Definitions for line of treatment ratings

First line: Level 1 or level 2 evidence for efficacy plus clinical support for safety/tolerability and no risk of treatment-emergent switch

Second line: Level 3 or higher evidence for efficacy plus clinical support for safety/tolerability and low risk of treatment-emergent switch

Third line: Level 4 evidence or higher for efficacy

[c] Grade of recommendations and their relationship with supporting levels of evidence

High: RCTs or double upgraded observational studies

Moderate: Downgraded RCTs or upgraded observational studies

Low: Double downgraded RCTs or observational studies

Very low: Triple downgraded RCTs or downgraded observational studies or case series/reports

Appendix 3: Quality Assessment of Included Studies

Table 6: Quality Assessment of Systematic Reviews

ISPOR checklist Items[13]	Ostacher et al., 208[21]
1. Are the rationale for the study and the study objectives stated clearly?	Yes
2. Does the methods section include the following?	
• Description of eligibility criteria	Yes
• Information sources	Yes
• Study selection process	No
• Data extraction	No
• Validity (risk of bias) of individual studies	No
3. Are the outcome measures described?	Yes
4. Is there a description of methods for analysis/synthesis of evidence?	—
• Description of analyses methods/models	Yes
• Handling of potential bias/inconsistency	No
• Analysis framework	Yes
5. Are sensitivity analyses presented?	Yes
6. Do the results include a summary of the studies included in the network of evidence?	—
• Individual study data?	Yes
• Network of studies?	Yes
7. Does the study describe an assessment of model fit? Are competing models being compared?	Yes
8. Are the results of the evidence synthesis presented clearly?	Yes
9. Are sensitivity/scenario analyses conducted?	Yes
10. Does the discussion include the following?	—
– Description/summary of main findings	Yes
– Internal validity of analysis	Yes
– External validity	Yes
– Implications of results for target audience	Yes

Table 7: Quality Assessment of Randomized Controlled Trial

JBI Critical Appraisal Checklist for RCT[15]	Calabrese et al., 2017[25]
1. Was true randomization used for assignment of participants to treatment groups?	Yes
2. Was allocation to treatment groups concealed?	NR
3. Were treatment groups similar at the baseline?	Yes
4. Were participants blind to treatment assignment?	Yes

JBI Critical Appraisal Checklist for RCT[15]	Calabrese et al., 2017[25]
5. Were those delivering treatment blind to treatment assignment?	Yes
6. Were outcomes assessors blind to treatment assignment?	Unclear
7. Were treatment groups treated identically other than the intervention of interest?	Yes
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	Yes (ITT)
9. Were participants analyzed in the groups to which they were randomized?	Yes
10. Were outcomes measured in the same way for treatment groups?	Yes
11. Were outcomes measured in a reliable way?	Yes
12. Was appropriate statistical analysis used?	Yes
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	Yes

ITT = intention-to-treat; JBI = Joanna Briggs Institute; NR = not reported; RCT = randomized controlled trial.

Table 8: Quality Assessment of Prevalence Study

JBI Critical Appraisal Checklist for Prevalence Study[16]	Ng-Mak et al., 2019[22]
1. Was the sample frame appropriate to address the target population?	Probably Yes
2. Were study participants sampled in an appropriate way?	Probably Yes
3. Was the sample size adequate?	Probably Yes
4. Were the study subjects and the setting described in detail?	Yes
5. Was the data analysis conducted with sufficient coverage of the identified sample?	Probably No
6. Were valid methods used for the identification of the condition?	Not applicable
7. Was the condition measured in a standard, reliable way for all participants?	Not applicable
8. Was there appropriate statistical analysis?	Yes
9. Was the response rate adequate, and if not, was the low response rate managed appropriately?	Not applicable

JBI = Joanna Briggs Institute.

Table 9: Quality Assessment of Before-and-After Studies with No Control Group

NHLBI Checklist for Studies With No Control Group[18]	Miller et al., 2018[24]	Forester et al., 2017[23]	Pikalov et al., 2017[26]
1. Was the study question or objective clearly stated?	Yes	Yes	Yes
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Yes	Yes
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Unclear	Unclear	Unclear
4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	Yes	Yes
5. Was the sample size sufficiently large to provide confidence in the findings?	Probably No	Probably No	Probably No

NHLBI Checklist for Studies With No Control Group[18]	Miller et al., 2018[24]	Forester et al., 2017[23]	Pikalov et al., 2017[26]
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	Yes	Yes
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Yes	Yes
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	No	No
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	77% discontinued No	27.6% discontinued No	43.4% discontinued No
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	Yes	Yes
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	Unclear	Unclear	Unclear
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	Unclear	Unclear	Unclear

NHLBI = National Heart, Lung, and Blood Institute.

Table 10: Quality Assessment of Economic Studies

JBI Checklist for Economic Evaluations[17]	Rajagopalan et al., 2015[27]
1. Is there a well-defined question?	Yes
2. Is there comprehensive description of alternatives?	Yes
3. Are all important and relevant costs and outcomes for each alternative identified?	Probably No
4. Has clinical effectiveness been established?	Yes
5. Are costs and outcomes measured accurately?	Unclear
6. Are costs and outcomes valued credibly?	Unclear
7. Are costs and outcomes adjusted for differential timing? (Discount rate)	Not applicable
8. Is there an incremental analysis of costs and consequences?	Yes
9. Were sensitivity analyses conducted to investigate uncertainty in estimates of cost or consequences?	Yes
10. Do study results include all issues of concern to users?	Unclear
11. Are the results generalizable to the setting of interest in the review?	Unclear

JBI = Joanna Briggs Institute.

Table 11: Quality Assessment of Guidelines

AGREE II checklist[19]	CANMAT and ISBD, Yatham et al., 2018[28]	BAP, Goodwin et al., 2016[29]
Scope and purpose		
1. Objectives and target patient population were explicit	Yes	Yes
2. The health question covered by the guidelines is specifically described	Yes	Yes
3. The population to whom the guideline is meant to apply is specifically described	Yes	Yes
Stakeholder involvement	—	—
4. The guideline development group includes individuals from all relevant professional groups	Yes	Yes
5. The views and preferences of the target population have been sought	Unclear	Unclear
6. The target users of the guideline are clearly defined	Yes	Yes
Rigour of development	—	—
7. Systematic methods were used to search for evidence	Unclear	Unclear
8. The criteria for selecting the evidence are clearly described	Unclear	Unclear
9. The strengths and limitations of the body of evidence are clearly described	Yes	Yes
10. The methods of formulating the recommendations are clearly described	Yes	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations	Yes	Yes
12. There is an explicit link between the recommendations and the supporting evidence	Yes	Yes
13. The guideline has been externally reviewed by experts prior to its publication	Yes	Yes
14. A procedure for updating the guideline is provided	Yes	Yes
Clarity of presentation	—	—
15. The recommendations are specific and unambiguous	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented	Yes	Yes
17. Key recommendations are easily identified	Yes	Yes
Applicability	—	—
18. The guideline describes facilitators and barriers to its application	Unclear	Unclear
19. The guidelines provides advice and/or tools on how the recommendations can be put into practice	Unclear	Unclear
20. The potential resource (cost) implications of applying the recommendations have been considered	No	No
21. The guideline presents monitoring and/or auditing criteria	No	No
Editorial independence	—	—
22. The views of the funding body have not influenced the content of the guideline	Unclear	Unclear
23. Competing interests of guideline development group members have been recorded and addressed	Yes	Yes

BAP = British Association for Psychopharmacology; CANMAT = Canadian Network for Mood and Anxiety Treatments; International Society for Bipolar Disorders (ISBD).

Appendix 4: Main Study Findings and Author's Conclusions

Table 12: Summary of Findings of Systematic Reviews

Main Study Findings	Author's Conclusions
Ostacher et al., 2018[21]	
Lurasidone versus other atypical antipsychotics (aripiprazole, olanzapine, ziprasidone, quetiapine) NMA base case analysis of efficacy outcomes Change in depressive symptoms (MADRS score) – Lurasidone versus placebo: MD (95% CrI) = -4.70 (-7.20 to -2.21) – Lurasidone versus aripiprazole: MD (95% CrI) = -3.62 (-7.04 to -0.20) – Lurasidone versus olanzapine: MD (95% CrI) = -0.15 (-3.12 to 2.74) – Lurasidone versus quetiapine: MD (95% CrI) = 0.10 (-2.68 to 2.84) – Lurasidone versus ziprasidone: MD (95% CrI) = -3.38 (-6.68 to -0.11) Change in overall disease severity (CGI-BP-S score) – Lurasidone versus placebo: MD (95% CrI) = -0.63 (-0.90 to -0.37) – Lurasidone versus aripiprazole: MD (95% CrI) = -0.42 (-0.78 to -0.07) – Lurasidone versus olanzapine: MD (95% CrI) = -0.31 (-0.65 to 0.03) – Lurasidone versus quetiapine: MD (95% CrI) = -0.09 (-0.39 to 0.21) – Lurasidone versus ziprasidone: MD (95% CrI) = -0.59 (-0.94 to -0.24) Response (≥ 50% improvement in MADRS) – Lurasidone versus placebo: OR (95% CrI) = 2.59 (1.65 to 3.89) – Lurasidone versus aripiprazole: OR (95% CrI) = 2.40 (1.36 to 3.96) – Lurasidone versus olanzapine: OR (95% CrI) = 1.68 (0.99 to 2.69) – Lurasidone versus quetiapine: OR (95% CrI) = 1.29 (0.78 to 2.01) – Lurasidone versus ziprasidone: OR (95% CrI) = 2.45 (1.38 to 4.05) Remission (MADRS ≤ 12 at study endpoint) – Lurasidone versus placebo: OR (95% CrI) = 2.19 (1.36 to 3.37) – Lurasidone versus aripiprazole: OR (95% CrI) = 2.28 (1.22 to 3.90) – Lurasidone versus olanzapine: OR (95% CrI) = 1.54 (0.87 to 2.53) – Lurasidone versus quetiapine: OR (95% CrI) = 1.11 (0.66 to 1.77) – Lurasidone versus ziprasidone: OR (95% CrI) = 2.18 (1.21 to 3.65) NMA base case analysis of tolerability outcomes Weight change from baseline (kg) – Lurasidone versus placebo: MD (95% CrI) = 0.34 (-0.33 to 1.00) – Lurasidone versus aripiprazole: MD (95% CrI) = 0.14 (-0.95 to 0.21) – Lurasidone versus olanzapine: MD (95% CrI) = -2.54 (-3.42 to -1.67) – Lurasidone versus quetiapine: MD (95% CrI) = -0.83 (-1.58 to -0.08) Somnolence – Lurasidone versus placebo: OR (95% CrI) = 1.57(0.55 to 3.77) – Lurasidone versus aripiprazole: OR (95% CrI) = 0.87 (0.23 to 2.42) – Lurasidone versus olanzapine: OR (95% CrI) = 0.56 (0.18 to 1.41) – Lurasidone versus quetiapine: OR (95% CrI) = 0.33 (0.11 to 0.82) – Lurasidone versus ziprasidone: OR (95% CrI) = 0.34 (0.09 to 0.93)	*"In this network meta-analysis, lurasidone was found to be more efficacious than aripiprazole and ziprasidone, and was associated with less weight gain than quetiapine and olanzapine and les somnolence than quetiapine and ziprasidone."*[21] p. 586

Main Study Findings	Author's Conclusions
Extrapyramidal symptoms – Lurasidone versus placebo: OR (95% CrI) = 4.15 (1.07 to 12.50) – Lurasidone versus aripiprazole: OR (95% CrI) = 2.36 (0.48 to 7.76) – Lurasidone versus quetiapine: OR (95% CrI) = 1.63 (0.36 to 5.18) All-cause discontinuation – Lurasidone versus placebo: OR (95% CrI) = 1.09 (0.64 to 1.75) – Lurasidone versus aripiprazole: OR (95% CrI) = 0.68 (0.35 to 1.21) – Lurasidone versus olanzapine: OR (95% CrI) = 1.60 (0.84 to 2.78) – Lurasidone versus quetiapine: OR (95% CrI) = 1.05 (0.59 to 1.75) – Lurasidone versus ziprasidone: OR (95% CrI) = 0.82 (0.42 to 1.44) NMA Sensitivity analyses – Dividing quetiapine IR and XR formulations into separate nodes in the network evidence: Similar results as in base case analysis across all outcomes – Excluding one study that caused between-study heterogeneity: Similar results as in base case analysis across all outcomes – Fixed effects models versus random effects models: Similar results as in base case analysis across all outcomes	

CGI-BP-S = clinical global impression bipolar scale; CrI = credible interval; IR = immediate release; MADRS = Montgomery-Asberg-Depression Scale; MD = mean difference; NMA = network meta-analysis; OR = odds ratio; XR = extended release.

Table 13: Summary of Findings of Included Primary Studies

Main Study Findings	Author's Conclusions
Ng-Mak et al., 2019[22]	
Lurasidone monotherapy versus other atypical antipsychotics (aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone) (n = 11,132 BD patients) Adherence rates[a] (mean weighted adherence across all antipsychotics was 0.27): – Lurasidone versus olanzapine: 0.32 versus 0.21; *P* < 0.001 – Lurasidone versus risperidone: 0.32 versus 0.23; *P* < 0.001 – Lurasidone versus quetiapine: 0.32 versus 0.26; *P* = 0.002 – Lurasidone versus aripiprazole: 0.32 versus 0.29; *P* = 0.224 – Lurasidone versus ziprasidone: 0.32 versus 0.30; *P* = 0.432 Hospitalization rates (per 100 Patient-Months) during the 12-month follow-up period (Psychiatric hospitalization rates per 100 patients-months): – Lurasidone versus olanzapine: 1.12 versus 2.18; *P* = 0.045 – Lurasidone versus risperidone: 1.12 versus 2.06; *P* = 0.063 – Lurasidone versus quetiapine: 1.12 versus 2.36; P = 0.019 – Lurasidone versus aripiprazole: 1.12 versus 1.41; *P* = 0.472 – Lurasidone versus ziprasidone: 1.12 versus 1.99; *P* = 0.085 All-cause hospitalization rates (per 100 Patient-Months) – Lurasidone versus olanzapine: 1.12 versus 2.56 ; *P* = 0.017 – Lurasidone versus risperidone: 1.12 versus 2.25 ; *P* = 0.033 – Lurasidone versus quetiapine: 1.12 versus 2.61 ; *P* = 0.007 – Lurasidone versus aripiprazole: 1.12 versus 1.65 ; *P* = 0.223 – Lurasidone versus ziprasidone: 1.12 versus 2.15 ; *P* = 0.052	*"In this claims database analysis, lurasidone-treated patients with bipolar disorder had a significantly lower risk of psychiatric hospitalization compared to quetiapine, olanzapine and risperidone, but not aripiprazole or ziprasidone. Lurasidone-treated patients had a significantly lower risk of all-cause hospitalization compared to quetiapine, olanzapine, risperidone and aripiprazole, but not ziprasidone."*[22] p. 211

Main Study Findings	Author's Conclusions
Marginal structural model (using inverse probability weights and statistically controlling for pre-index covariates) – Lurasidone had statistically significantly lower odds of a psychiatric hospitalization than olanzapine, quetiapine and risperidone. – Lurasidone had statistically significantly lower odds of all-cause hospitalization than aripiprazole, olanzapine, quetiapine and risperidone. – Comorbidities increasing the odds of psychiatric hospitalization and all-cause hospitalization regardless of treatment: hypertension, obesity, type 2 diabetes, anxiety, alcohol abuse and drug abuse. [a] *"Adherence was conceptualized as possessing the monotherapy antipsychotic treatment for at least 122 days of a treatment month (i.e., ≥ 75%). Each treatment-month with ≥ 22 days of monotherapy antipsychotic treatment was coded as adherent and assigned a value of 1, and each treatment-month of no/minimal or other treatment was coded as non-adherent and assigned a value of 0."*[22] p. 212 to 213	
Forester et al., 2018[23]	
Post-hoc analysis of a 6-month open-label lurasidone (older adults with BD I; n = 55 in monotherapy; n = 86 in adjunctive therapy) Discontinuation (in monotherapy; in adjunctive therapy) – All-cause: 32.7%; 24.4% – Due to AEs: 5.5%; 9.3% – Due to insufficient response: 7.3%; 7.0% – Other reasons: 20.0%; 8.1% AEs (in monotherapy; in adjunctive therapy) – Headache: 14.5%; 10.5% – Nasopharyngitis: 32.7%; 4.7% – Fatigue: 9.1%; 3.5% – Insomnia: 7.3%; 11.6% – Anxiety: 7.7%; 7.0% – Depression: 7.3%; 4.7% – Nausea: 5.5%; 8.1% – Urinary tract infection: 5.5%; 4.7% – Dizziness: 5.5%; 4.7% – Somnolence: 5.5%; 3.5% – Akathisia: 3.6%; 11.6% – Tremor: 1.8%; 8.1% – Parkinsonism: 3.6%; 7.0% Severe adverse events: 10.9% in monotherapy; 10.5% in adjunctive therapy Mean change in weight: -1.0 kg in monotherapy; -0.4 kg in adjunctive therapy Proportion with weight increase 7% or more: 3.8% in monotherapy; 6.0% in adjunctive therapy Proportion with weight reduction 7% or more: 11.3% in monotherapy; 4.8% in adjunctive therapy Metabolic parameters (in monotherapy; in adjunctive therapy) – Total cholesterol: +1.3; +5.4 mg/dL – Triglyceride: +1.8; -3.8 mg/dL – Glucose: -1.8; -0.4 mg/dL – HbA1c: -0.1%; -0.1%	*"Results of these post-hoc analyses found that up to 7.5 months of lurasidone treatment for bipolar depression in older adults was associated with minimal effects on weight and metabolic parameters, with low rates of switching to hypomania or mania, and was well tolerated."*[23] p. 150

Main Study Findings	Author's Conclusions
Miller et al., 2018[24]	
Before-after adjunctive open-label lurasidone (n = 61; 32 type I BD, 26 type II BD, and 3 type not specified) Discontinuation – All-cause: 77.0% after median 103 days with final dose of 49.5 ± 24.4 mg/day – Due to AEs: 54.1% – Due to inadequate efficacy: 16.4% – Other reasons: 6.6% AEs – Central nervous: 14.8% akathisia; 13.1% sedation/somnolence – Gastrointestinal/metabolic: 8.2% nausea; 8.2% weight gain Predictors of early discontinuation of lurasidone – Baseline syndromal depression: 51.4% – Baseline subsyndromal depression: 50.0% Baseline euthymia: 66.7%	*"In American specialty clinic BD outpatients, adjunctive longer-term lurasidone commonly relieved syndromal depression and maintained euthymia, suggesting possible effectiveness/efficacy. However, lurasidone was discontinued in 54.1% because of adverse events, suggesting tolerability limitations in these challenging patients, nearly 90% of whom were already taking at least 2 other nonanxiolytic/hypnotic prescription psychotropics."*[24] p. 207
Calabrese et al., 2017[25]	
Lurasidone in open-label treatment + lithium or valproate (12 to 20 weeks; n = 962), followed by double-blind placebo RCT, lurasidone + lithium or valproate (28 weeks; n = 246 in lurasidone; n = 250 in placebo) At least one AE: Open label (66.0%); RCT (62.2% in lurasidone; 60.4% in placebo) At least one severe AEs: Open label (7.3%); RCT (5.3% in lurasidone; 4.0% in placebo) At least one serious AEs: Open label (4.3%); RCT (5.3% in lurasidone; 4.4% in placebo); no death Discontinuation due to AEs: Open label (6.1%); RCT (3.3% in lurasidone; 2.0% in placebo) Treatment-emergent suicidal ideation: RCT (4.5% in lurasidone; 6.4% in placebo) Extrapyramidal symptom-related events: Open label (2.6%); RCT (2.0% in lurasidone; 1.6% in placebo) Mean weight increase: Open label (+ 1.1 kg); RCT (+2.0 kg in lurasidone; +0.0 kg in placebo) Metabolic parameters: No clinically meaningful differences in change from open-label baseline to double-blind endpoint in laboratory measures in lipids, glycemic indices, and prolactin. AEs (in monotherapy) – Nausea: 11.5% – Somnolence: 11.0% – Headache: 9.1% – Akathisia: 8.3% – Insomnia: 8.0% – Parkinsonism: 6.8% – Vomiting: 6.1%	*"Long-term treatment with lurasidone combined with lithium or valproate was found to be safe and well-tolerated, with minimal effects on weight or metabolic parameters."*[25] p. 865

Main Study Findings	Author's Conclusions
– Diarrhea: 5.5% AEs in RCT (lurasidone; placebo) – Weight increase: 9.8%; 5.2% – Headache: 8.5%; 7.2% – Parkinsonism: 8.1%; 5.6% – Nasopharyngitis: 6.1%; 4.8% – Insomnia: 3.7%; 6.4%	
Pikalov et al., 2017[26]	
Lurasidone in 18-month continuation treatment (BD I; n = 122); 76.2% received adjunctive with lithium or valproate AEs: 42.6% – Headache: 7.4% – Diarrhea, influenza, nasopharyngitis: 4.9% each – Increase in hepatic enzymes, mania, nausea, viral upper respiratory infection: 3.3% each – Parkinsonian symptoms: 2.5% – Sedation/somnolence: 0.8% – Extrapyramidal symptoms: 4.1% Severe AEs: 4.9% Discontinuation due to AEs: 6.6% Mean weight change: +1.8 kg at 12 months (n = 118); +0.8 kg at 24 months (n = 55) Metabolic parameters: No clinically meaningful changes in median values compared to baseline	*"Up to 2 years of treatment with lurasidone was safe and well tolerated in this bipolar disorder population presenting with an index episode of depression. Improvement in depressive symptoms was maintained in the majority of patients treated with lurasidone, with relatively low rates of relapse, and with minimal effects on weight and metabolic prameters."*[26] p.1

AEs = adverse events; BD = bipolar disorder; CI = confidence interval; HbA1c = hemoglobin A1c; RCT = randomized controlled trial

Table 14: Summary of Findings of Economic Study

Main Study Findings	Author's Conclusions
Rajagopalan et al., 2015[27]	
Cost-effectiveness of lurasidone monotherapy versus quetiapine XR monotherapy in patients with BD depression Remission after 3 months (No statistical comparison conducted): – Lurasidone: 52.0%; quetiapine XR = 43.2% Mean numbers of ED visits: – Lurasidone: 0.48; quetiapine XR = 0.50 Mean number of inpatient days: – Lurasidone: 2.1; quetiapine XR = 2.2 Mean numbers of office visits: – Lurasidone: 9.3; quetiapine XR = 9.6 Mean pharmacy costs	*"Lurasidone may be a cost-effective option when compared to quetiapine XR for the treatment of adults with bipolar depression."*[27] p. 821

Main Study Findings	Author's Conclusions
– Lurasidone: $1,899 (95% CI 1,573 to 2,241); quetiapine XR = $1,455 (95% CI 1,260 to 3,469) Mean medical costs – Lurasidone: $3,083 (95% CI 2,101 to 4,195); quetiapine XR = $3,222 (95% CI 2,207 to 4,359) Mean total costs – Lurasidone: $4,982 (95% CI 3,965 to 6,135); quetiapine XR = $4,676 (95% CI 3,632 to 5,835) ICER – Lurasidone treatment resulted in an ICER of $3,474 per remission gained compared to quetiapine XR Sensitivity analysis – One way: The results were most sensitive to remission rates and pharmacy costs – Probabilistic: Lurasidone had 65% probability of being cost-effective compared with quetiapine XR at WTP threshold of $5,000 per remission gained; 86% at a WTP of $10,000 per remission gained; and over 90% at WTP thresholds of ≥ $15,000 and higher.	

CI = confidence interval; ICER = incremental cost-effectiveness ratio; XR = extended release; WTP = willingness-to-pay.

Table 15: Summary of Findings of Included Guidelines

Recommendations
CANMAT and ISBD, Yatham et al., 2018[28]
Pharmacological treatment for acute bipolar depression "Quetiapine (level 1), lithium (level 2), lamotrigine (level 2) and lurasidone (level 2) are all recommended as first line treatment options with evidence for efficacy as monotherapy."[28] p.117 "Lurasidone (level 1) and lamotrigine (level 2) are also recommended as first-line adjunctive treatments"[28] p.117 "Recommendations as to which first-line treatment should be considered first are outlined in our hierarchy. We recommended that the agents listed first in the hierarchy be tried first, in the order listed, unless there are patient-specific reasons for choosing an agent lower down in the order, such as previous history of response/ non-response or clinical features."[28] p.117 Hierarchy of first line treatments: Quetiapine; Lurasidone + Lithium/divalproex; Lithium; Lamotrigine; Lurasidone; Lamotrigine (adjunctive) **Maintenance therapy for bipolar disorder** Second line "Lurasidone adjunctive may be appropriate for those who responded to this medication during an index depressive episode." [28] p.125 Hierarchy of second line treatments: Olanzapine; Risperidone long acting injectable; Risperidone long acting injectable (adjunctive); Carbamazepine; Paliperidone (> 6 mg); Lurasidone + Lithium/divalproex; Ziprasidone + Lithium/divalproex

Recommendations
BAP, Goodwin et al., 2016[29]
Acute depressive episode *"For patients not already taking long-term treatment for bipolar disorder. Consider quetiapine (*** [moderate]), lurasidone (**** [high]) or olanzapine (*** [moderate])"*[29] p. 503

BAP = British Association for Psychopharmacology; CANMAT = Canadian Network for Mood and Anxiety Treatments; International Society for Bipolar Disorders (ISBD).

Levels of evidence

Level 1	Meta-analysis with narrow confidence interval or replicated double-blind (DB), randomized controlled trial (RCT) that includes a placebo or active comparison (n ≥ 30 in each active treatment arm)
Level 2	Meta-analysis with wide confidence interval or one DB RCT with placebo or active control comparison condition (n ≥ 30 in each active treatment arm)
Level 3	At least one DB RCT with placebo or active control comparison condition (n = 10-29 in each active treatment arm) or health system administrative data
Level 4	Uncontrolled trial, anecdotal reports, or expert opinion

Definitions for line of treatment ratings

First	Level 1 or level 2 evidence for efficacy plus clinical support for safety/tolerability and no risk of treatment-emergent switch
Second	Level 3 or higher evidence for efficacy plus clinical support for safety/tolerability and low risk of treatment-emergent switch
Third	Level 4 or higher evidence for efficacy plus clinical support for safety/tolerability
Not recommended	Level 1 evidence for lack of efficacy, or level 2 evidence for lack of efficacy plus expert opinion

Grades of recommendation and level of evidence

High	RCTs or double upgraded observational studies	****
Moderate	Downgraded RCTs or upgraded observational studies	***
Low	Double downgraded RCTs or observational studies	**
Very low	Triple downgraded RCTs or downgraded observational studies or case series/reports	*