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Reimbursement Review

Aripiprazole

Requester: Public drug programs
Therapeutic area: Major depressive disorder

Summary

What Is Major Depressive Disorder?

- Major depressive disorder (MDD) is a serious mental health condition. MDD is a heterogeneous disorder that can be disabling and negatively impact an individual's daily functioning and health-related quality of life (HRQoL).
- MDD is a common disorder, with an annual prevalence in Canada ranging from 5.4% to 11.7% in adults. The economic impact of MDD is substantial, affecting productivity through presenteeism (the practice of being present at one's place of work for more hours than is required as a performative measure, despite impaired function and having reduced productivity levels or negative consequences) and absenteeism, as well as increased health care use related directly to MDD or comorbidities.

What Are the Treatment Goals and Current Treatment Options for MDD?

- Treatment goals for MDD are the alleviation of symptoms, improved HRQoL, and restoration of functional capacity and engagement in daily activities.
- Current treatment options include antidepressant medications and psychotherapy (e.g., cognitive behavioural therapy, interpersonal therapy, and behaviour therapy), or a combination of these 2 types of treatment. Other treatments include transcranial magnetic stimulation, electroconvulsive therapy, IV ketamine, and intranasal esketamine.

What Is Aripiprazole and Why Did Canada's Drug Agency Conduct This Review?

- Aripiprazole is a drug that is available as an oral tablet. Health Canada has approved aripiprazole for use as an adjunct to antidepressants for the treatment of MDD in adult patients who had an inadequate response to prior antidepressant treatments during the current episode.
- At the request of the participating public drug programs, Canada's Drug Agency (CDA-AMC) reviewed aripiprazole to inform a recommendation on whether it should be reimbursed as adjunct treatment for MDD in adult patients who have had an inadequate response to at least 1 antidepressant.
    - CDA-AMC previously reviewed aripiprazole for this indication in 2014. The Canadian Drug Expert Committee (CDEC) issued a recommendation not to reimburse due to a lack of evidence regarding the comparative clinical benefit of adjunctive treatment

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with aripiprazole versus other available treatment strategies for the management of MDD. Since then, new relevant evidence has become available.

How Did CDA-AMC Evaluate Aripiprazole?

- CDA-AMC reviewed the clinical evidence on the beneficial and harmful effects and compared costs of aripiprazole versus other atypical antipsychotics reimbursed by the provincial drug plans in Canada for MDD. Risperidone, quetiapine, olanzapine, and brexpiprazole were considered relevant treatments to compare with aripiprazole.
- The clinical evidence was identified through systematic searches for available studies.
- The review was also informed by 1 patient group submission in response to our call for input and by input from the participating public drug programs around issues that may impact their ability to implement a recommendation.
- Two psychiatrists with expertise in the diagnosis and management of MDD participated as part of the review team, with representation from Ontario and the Prairies.

What Were the Findings?

Clinical Evidence

- CDA-AMC reviewed the following clinical evidence:
  - 1 randomized controlled trial (RCT) comparing aripiprazole with olanzapine in 20 patients with MDD who did not experience a treatment response with paroxetine
  - 1 indirect treatment comparison (ITC) of aripiprazole versus risperidone, quetiapine, olanzapine, and brexpiprazole
  - 1 ITC of aripiprazole versus brexpiprazole
  - 1 ITC of aripiprazole versus risperidone, quetiapine, and olanzapine.
- The evidence suggests the following:
  - compared to risperidone, aripiprazole may have similar efficacy, specifically in terms of response rate, remission rate, symptom severity, and social function or HRQoL
  - compared to quetiapine, aripiprazole may have similar effects on response rate, remission rate, symptom severity, and social function or HRQoL
  - aripiprazole may result in a higher response rate compared to olanzapine, but this finding is very uncertain

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    - compared to olanzapine, aripiprazole may have similar effects on remission rate, symptom severity, and social function or HRQoL
    - aripiprazole may result in a higher remission rate compared to brexpiprazole, but this finding is very uncertain
    - compared to brexpiprazole, aripiprazole may have similar effects on response rate, symptom severity, and social function or HRQoL.
- The overall safety of aripiprazole for MDD appeared to be comparable to that of risperidone, quetiapine, olanzapine, and brexpiprazole.
- The findings of this report apply to short-term to medium-term treatment (e.g., 4 to 24 weeks). The evidence on long-term treatment with aripiprazole compared to other atypical antipsychotics remains unknown.

Economic Evidence

- Reimbursing aripiprazole as adjunctive treatment for MDD in adult patients who have had an inadequate response to antidepressant treatment is expected to increase costs to the public drug programs.

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Abbreviations

AE	adverse event
CANMAT	Canadian Network for Mood and Anxiety Treatments
CDA-AMC	Canada's Drug Agency
CDEC	Canadian Drug Expert Committee
CI	confidence interval
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
HRSD-17	17-item Hamilton Rating Scale for Depression
HRQoL	health-related quality of life
ITC	indirect treatment comparison
MADRS	Montgomery-Asberg Depression Rating Scale
MDD	major depressive disorder
MDSC	Mood Disorders Society of Canada
NMA	network meta-analysis
OR	odds ratio
RCT	randomized controlled trial
SMD	standardized mean difference
SR	systematic review
TRD	treatment-resistant depression
XR	extended release

Background

Introduction

The objective of the Clinical Review is to review and critically appraise the evidence on the beneficial and harmful effects of aripiprazole 2 mg to 15 mg per day administered orally as adjunctive treatment for major depressive disorder (MDD) in adult patients who have had an inadequate response to at least 1 antidepressant treatment. The focus will be placed on comparing aripiprazole to relevant comparators in clinical practice in Canada and identifying gaps in the current evidence. The Economic Review consists of a cost comparison for aripiprazole compared with relevant comparators for the same population. The comparators considered relevant to the reviews were risperidone, quetiapine, olanzapine, and brexpiprazole.

Table 1: Information on the Drug Under Review and the CDA-AMC Review

Item	Description
Information on the drug under review	
Drug	Aripiprazole, 2 mg to 15 mg per day administered orally
Relevant Health Canada indication	Adjunct to antidepressants for the treatment of major depressive disorder in adult patients who had an inadequate response to prior antidepressant treatments during the current episode
Mechanism of action	Unknown; proposed that efficacy may be mediated through a combination of partial agonist activity at D_2 and 5-HT_{1A} receptors and antagonist activity at $5HT_{2A}$
Data protection status	The data protection end date for aripiprazole is January 9, 2018
Status of generic drugs or biosimilars	Thirteen approved and marketed generics identified with 4 generic submissions listed as under review with Health Canada
Information on the CDA-AMC review	
Requester	Formulary Working Group
Indication under consideration for reimbursement	Adjunct to antidepressants for the treatment of major depressive disorder in adult patients who had an inadequate response to at least 1 prior antidepressant treatment

CDA-AMC = Canada's Drug Agency.

Submission History for the Drug Under Review

Aripiprazole has previously been reviewed by Canada's Drug Agency (CDA-AMC) as an adjunct to antidepressants for the treatment of MDD. In 2014, the Canadian Drug Expert Committee (CDEC) issued a negative recommendation. Three double-blind randomized controlled trials (RCTs) demonstrated that aripiprazole was statistically superior to placebo in response rate, remission, and symptom severity. However, the magnitude of improvement was limited and failed to clearly and consistently exceed the minimal clinically important differences for these end points. In addition, clinical benefit was not consistently observed in patient-reported outcomes. The safety and efficacy of aripiprazole as an adjunctive treatment in MDD had not been evaluated in RCTs longer than 6 weeks, a relatively short duration for evaluating clinical benefit. Therefore, the committee considered the clinical benefit of treatment with aripiprazole to be uncertain. Finally, there were no RCTs evaluating the comparative clinical benefit of adjunctive treatment

with aripiprazole against other available treatment strategies (i.e., other antipsychotics, add-on therapy with different antidepressants, or neurostimulation therapies) for the management of MDD.

Context for the Review

A review of the evidence for aripiprazole for MDD was requested by the Formulary Working Group. Specifically, the public drug programs requested a review of the efficacy and safety of aripiprazole compared to other antipsychotics currently reimbursed for adjunctive treatment of MDD in adult patients who have had an inadequate response to at least 1 antidepressant treatment. While risperidone and olanzapine have not been approved by Health Canada for adjunct treatment of MDD, they are included in this review to assess the effect and harms for off-label use.

Sources of Information

The contents of the Clinical Review were informed by studies identified through systematic literature searches, input received from interested parties (a patient group and drug programs), and input from 2 clinical experts consulted for this review.

Calls for patient group, clinician group, and industry input are issued for each Non-Sponsored Reimbursement Review. One patient group submission was received for this review, from Mood Disorders Society of Canada (MDSC). MDSC conducted extensive direct discussions with patients (including focus groups, meetings, online discussions); obtained input from family members and caregivers; distributed a national online survey between March 3, 2018, and March 22, 2018, with 119 respondents; and engaged with its community over a variety of multimedia channels. Through outreach conducted via networks, volunteers, and partners, MDSC gathered insights from a patient currently undergoing treatment for MDD with aripiprazole. There were no submissions from clinician groups or industry. The full submission received is available on the project landing page in the consolidated input document.

Input from the patient group and from clinical experts was considered throughout the review, including in the selection of outcomes to include in the Clinical Review and in the interpretation of the clinical evidence. Relevant patient group input is summarized in the Disease Background, Current Management, and Unmet Needs and Existing Challenges sections.

The drug programs provide input on each drug being reviewed through the Reimbursement Review process by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted for this review were summarized and provided to the expert committee in a separate document.

Each review team includes at least 1 clinical expert with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process. Two psychiatrists with expertise in the diagnosis and management of MDD participated as part of the review team, with representation from Ontario and the Prairies.

Disease Background

MDD is characterized by the occurrence of 1 or more major depressive episodes, which include depressed mood or anhedonia (markedly diminished interest or pleasure in previously enjoyed activities) and 4 or more of the following symptoms for at least 2 weeks: psychomotor retardation or agitation, fatigue or low energy, poor concentration or memory, changes in appetite or weight, changes in sleep, suicidal thoughts or ideation, and feelings of worthlessness or guilt.[1,2] Although the definition is not standardized, *treatment-resistant depression* (TRD) is commonly defined as the occurrence of major depressive episodes that do not respond satisfactorily after 2 trials of antidepressant monotherapy at recommended doses for adequate duration.[1,3]

MDD is a common, chronic mental health condition, with an annual prevalence in Canada of 5.4% among adults who are employed and 11.7% among adults who are unemployed, as determined by the Canadian Community Health Survey.[4] According to the Canadian Community Health Survey, the mean duration of major depressive episodes ranged from 7.6 to 11.4 weeks.[4] The estimated lifetime prevalence of MDD in Canada is 14.0%, as determined by the 2022 Mental Health and Access to Care Survey.[5] The prevalence of MDD is twice as high for females as it is for males, but this difference declines with age.[6] MDD is a major cause of disability worldwide.[7] Because of its early age of onset and frequent recurrences, MDD is also among the leading causes of disability-adjusted life-years. Both presenteeism and high levels of absenteeism have been shown to contribute to economic loss.[8]

Patient Group Input

As noted in the patient group submission by MDSC, MDD has a profound and often devastating impact on day-to-day functioning and overall quality of life, for both individuals and their families or caregivers (e.g., emotional distress, stigma, and financial strain). The impacts extend to the community and society at large (e.g., economic burden). Patients report that the mental, emotional, and physical toll of depression can be relentless, especially in cases of TRD or difficult-to-treat depression, which is now recognized by clinicians as a chronic illness.

Current Management

Treatment Goals

According to the clinical experts consulted for this review, the goals of treatment in MDD are to alleviate symptoms, improve health-related quality of life (HRQoL), restore functional capacity, and engage in daily activities (with a presumption that adverse effects need to be tolerable and/or acceptable). Symptoms of MDD include those that are used in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) to making a diagnosis, but may also include other concerns not explicitly included as DSM-5 diagnostic criteria, such as anxiety, self-criticism, pessimism, and somatic symptoms such as headache and muscle aches. Regulatory approval of antidepressant drugs has typically focused more narrowly on symptom relief, as reflected by standard observed-rated scales such as the Montgomery-Asberg Depression Rating Scale (MADRS) or the 17-item Hamilton Rating Scale for Depression (HRSD-17). Some — but not all — clinical trials for MDD have included measures of HRQoL or functional status, typically for secondary analyses.

Current Treatment Options

The typical first-line (and second-line) treatments for MDD include evidence-based psychotherapy (e.g., cognitive behavioural therapy, interpersonal therapy, and behaviour therapy), antidepressant medications with various pharmacologic mechanisms of action, or a combination of these 2 modalities. In many jurisdictions, there are challenges with access to psychotherapeutic treatments. According to the clinical experts, the more severe that a patient's illness or functional impairment is, the more likely that an antidepressant medication may be necessary. Beyond these typical first-line and second-line therapies, there are other evidence-based treatments for MDD, including transcranial magnetic stimulation, electroconvulsive therapy, IV ketamine, and intranasal esketamine (which are all out of scope for this review). There are several treatment guidelines available for MDD, including the Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical Guidelines for Management of Major Depressive Disorder In Adults (latest version published in 2023).[9]

Key characteristics of aripiprazole are summarized with other antipsychotics available for MDD in the Supplemental Material document, in the Key Characteristics table in Appendix 1.

Unmet Needs and Existing Challenges

According to the clinical experts, current treatments for MDD have many limitations. There is a very substantial group of patients whose condition does not respond well to current treatments, even when they are given in combination and/or sequentially. The STAR*D trial found that 50% of patients with MDD did not experience a response to first-line treatment and 70% did not achieve full remission after initial treatment.[10-12] A significant group (approximately 20% to 25% of people with MDD) go on to have chronic symptoms (for 2 years or more). Even when appropriate maintenance treatments are utilized to prevent relapse, many patients have a relapse or recurrence of MDD symptoms. Current treatments do not alleviate the underlying mechanism of MDD. While there are some generally well-tolerated treatments that benefit most MDD patients at least to some degree, there are drawbacks. Some patients find it challenging to adhere to the multiple therapy sessions and/or the required homework or practice required with psychotherapy. Medication side effects are also common, and are variable according to the class of antidepressant drug that is chosen. Nonadherence to medication treatment is common, due to factors such as medication acceptability, inadequate relief of the condition, motivational factors, and the desire to feel better without drugs.

Patient Group Input

According to MDSC, antidepressants — especially second-generation medications such as bupropion hydrochloride, venlafaxine, citalopram, fluoxetine, escitalopram, and paroxetine — enable many individuals to function and maintain wellness, although their efficacy often diminishes over time and varies widely across patients. While a substantial number of people reported to MDSC that they felt symptom relief and improved daily functioning, other patients reported experiencing a wide range of side effects, including blurred vision, weight gain, emotional blunting, sedation, restlessness, sexual dysfunction, cognitive difficulties, gastrointestinal issues, and dizziness. As a result, many patients discontinue treatment or undergo a long, exhausting trial-and-error process to find a tolerable and effective regimen. Treatment gaps remain a serious concern.

According to MDSC, access and delivery of treatment also present challenges. Although most antidepressants are covered by provincial drug plans and employer-based benefits, others often face delays and inequities across the country in public coverage. In addition, although private insurers do tend to have superior coverage, they vary in how quickly they reimburse drugs. Individuals reported to MDSC that coverage of new treatments significantly improves their outcomes by accelerating recovery, enabling return to work, and reducing burden on families. However, patients frequently reported additional barriers, such as long wait times, difficulty accessing knowledgeable prescribers, and financial constraints.

Considerations for Using the Drug Under Review

Contents within this section have been informed by input from 2 clinical experts consulted for the purpose of this review. The following has been summarized by the review team.

Place in Therapy

Patients who do not benefit from the first antidepressant medication prescribed are commonly prescribed a different antidepressant drug. Patients who have some positive effect but do not sufficiently benefit from an initial antidepressant medication are frequently prescribed a second medication in combination with the initial antidepressant (variably referred to as *adjunctive* or *combination* therapy). Just as there are multiple mechanisms of action of antidepressant drugs, there are also different mechanisms of action of these adjunctive strategies. For example, in the CANMAT 2023 guidelines,[9] several different atypical antipsychotics are suggested with varying levels of evidence (e.g., aripiprazole and brexpiprazole as first-line adjunctive medication; olanzapine, quetiapine extended release (XR), and risperidone as second-line adjunctive medication), as are other agents with diverse mechanisms of action (e.g., bupropion, ketamine, lithium, and mirtazapine as third-line adjunctive medication; stimulants and lamotrigine as third-line adjunctive medication).

There is no specific adjunctive treatment that addresses the underlying disease process. According to the clinical experts, aripiprazole is not a drug that fundamentally shifts the current treatment paradigm. When selecting adjunctive treatments, clinicians typically try to match the add-on treatment in terms of anticipated benefits (e.g., with a more activating treatment [such as bupropion or a stimulant], versus a more anxiety-relieving drug [such as aripiprazole, brexpiprazole, or quetiapine], versus a more sleep-promoting drug [such as mirtazapine or quetiapine]). Alternatively, the add-on treatment may also be selected based on specific side effects that are expected to be acceptable to the patient. Several different side effects that are commonly seen as being problematic by patients include sexual side effects, weight gain, other metabolic effects, and gastrointestinal side effects. Aripiprazole, like all options, has a significant list of potential side effects. Some of the more concerning side effects are restlessness, weight gain, tardive dyskinesia, and impulse control problems (the latter 2 are uncommon but potentially very problematic).

Patient Group Input

According to MDSC, individuals living with depression, along with their families, consistently express a desire for meaningful symptom relief and a return to full functioning, which are clear indicators that a treatment is truly effective. They emphasized the importance of being seen and treated as whole individuals, recognizing

that depression is not a uniform experience, and that recovery looks different for everyone. For those facing TRD, there is a troubling tendency to feel blamed or dismissed when progress is slow, compounding the emotional toll of the illness. Above all, patients and families seek compassion, patience, and understanding — not judgment or frustration — from care providers and systems. Currently, patients often find themselves forced to adapt their lives around the limitations of available treatments, rather than receiving care that adapts to their individual needs and goals.

The patient who was interviewed by MDSC, with direct experience with aripiprazole for MDD, expressed that success with a new depression treatment would mean having more day-to-day stability in their mental health. They did not expect the treatment to completely eliminate depression but hoped it could reduce the intensity and frequency of severe low periods, allowing for more moments of clarity, hope, and motivation. Small improvements, such as having more days where getting dressed does not feel overwhelming, were seen as meaningful signs of progress.

When considering new treatments and trade-offs they would make, the patient indicated that they would be willing to tolerate mild sadness, low energy, poor concentration, sleep issues, and even loss of interest if the medication helped them function better during the day. However, they were not willing to tolerate side effects that could cause possible permanent damage to the thyroid, such as those associated with lithium. Ideally, they hoped for a treatment that could provide these benefits without significant side effects or long-term health risks.

Patient Population

Patients with an inadequate response to a conventional monoamine antidepressant (e.g., selective serotonin reuptake inhibitor) for MDD would be best suited for adjunctive treatment with aripiprazole, according to the clinical experts. Any patient who is taking an antidepressant but still has MDD symptoms that are distressing or causing interference with function would be a candidate for a change of therapy, including the option of using an add-on therapy for depression. It is not clearly established which patients are the most likely to respond to the addition of aripiprazole. Similarly, there is no definitive evidence to preferentially select other add-on options. Instead, clinicians have a list of multiple options, some of which have more accumulated evidence and are therefore ranked in treatment guidelines as first-line, second-line, or third line options. Aripiprazole is listed as first-line adjunctive treatment in the CANMAT guidelines.[9] Clinical observation suggests that aripiprazole is frequently helpful, and patients with prominent anxiety seem to benefit from this approach. Aripiprazole is relatively more “metabolically friendly” than some of the other add-on options like quetiapine, mirtazapine, and olanzapine. However, monitoring for metabolic effects (e.g., blood tests for fasting glucose, hemoglobin A1C, and lipids, and measurement of weight, body mass index, and blood pressure) is still appropriate. It is generally considered “best practice” to incorporate measurement of depression symptoms into routine follow-up care for MDD, but in practice, many clinicians do not do this.

Assessing the Response to Treatment

MDD is commonly considered to respond to treatment when there is a 50% reduction of symptoms on a standardized scale. MDD is commonly considered to remit with treatment when minimal or no symptoms continue after treatment (e.g., a score of < 8 on the HRSD-17). Of course, if measurement is not

incorporated into clinical practice, these outcomes (response and remission) would be determined through routine clinical enquiry. Improvement in symptoms would be based on clinical impression, augmented with measurement-based care. Functional recovery is very important. Function can also be measured with a standardized scale, but it is commonly assessed through clinical enquiry about household tasks, work and school function, and return to normal activity.

Discontinuing Treatment

If an add-on treatment is effective and well tolerated, it is generally continued for as long as “maintenance medication” is recommended. This is usually 6 to 12 months beyond the end of acute treatment. However, most of the evidence for maintenance treatment duration is typically based on trials of monotherapy (e.g., an antidepressant alone). For patients who have had multiple recurrences, very prolonged depressive episodes, or very high levels of functional impairment when depressed, longer periods of maintenance therapy (sometimes even indefinite) may be recommended. Very long-term maintenance treatment studies are rare and difficult to undertake. When deciding to discontinue treatment with aripiprazole, the following factors should also be considered: patient experience, well-being, satisfaction, symptom control, and course of illness.

Prescribing Considerations

Aripiprazole can be used in clinical, community, or hospital settings. It can be prescribed by specialists or primary care providers. Sometimes, primary care providers are reluctant to prescribe combined therapies without the recommendation of a psychiatrist. However, no particular specialty is required. According to 1 clinical expert, more than 75% of prescriptions for aripiprazole are made by nurse practitioners or in outpatient primary care.

Additional Considerations

There is a significant overarching limitation of the current knowledge base for adjunctive treatments. There is evidence for the efficacy of multiple different add-on therapies for MDD. Much more comparative evidence for various different pharmacologic strategies and alternatives is needed. There is also an urgent need in Canada for patients with an inadequate response to antidepressant therapy for MDD to have access to treatments like aripiprazole that have been shown to be safe and effective for augmenting antidepressants.

Patient Group Input

MDSC also highlighted the following considerations in the patient group input.

Heterogeneity and Mental Illness

Because mental illnesses vary widely and individuals respond differently to treatment, it is crucial to offer a broad spectrum of therapeutic options for managing depression. The ability of patients to access aripiprazole is paramount, should that be the treatment they need.

Addressing Inequities in Access to Care

An issue in depression and all mental illness treatment is the disparity in access to effective care, particularly for those with lower incomes or those in underserved regions. Many individuals face significant barriers

due to the cost of treatment or lack of public funding for therapies such as aripiprazole, perpetuating health inequities. Ethical considerations demand a focus on making effective treatment widely available and affordable.

Stigma

While public awareness of mental health has improved, stigma remains a significant barrier that prevents many people from seeking the treatment they need. Moreover, an added layer of stigma surrounds prescription medications, driven by the misconception (even among those who are struggling) that mental illness, including depression, is not “serious enough” to warrant medical treatment; however, for many individuals, these medications are essential and life-changing.

Generic Standards

Quality control in generic medications is critical, particularly in mental health, where even minor variations in formulation can significantly affect treatment outcomes. Physicians have reported notable inconsistencies between generic products to MDSC, yet there is no robust oversight mechanism to ensure uniform quality, posing serious risks to patient stability and recovery.

Beyond Medication

Psychotherapy is recommended in combination with medication for maximized outcomes, but it is very rarely covered through public funding, despite the fact that a full circle of care (including psychosocial supports such as therapy, peer support, housing, and vocational services) is essential for sustained recovery and long-term stability.

Clinical Review

Methods

The review team conducted a systematic review (SR) to identify evidence for aripiprazole as adjunctive treatment for MDD in adults who have had an inadequate response to at least 1 antidepressant treatment. Studies were selected according to the eligibility criteria in Table 2.

Relevant comparators included treatments used in clinical practice in Canada in the patient population under review. Input from the clinical experts and patient group were considered when selecting outcomes for review. Selected outcomes are those considered relevant to expert committee deliberations for reimbursement. Detailed methods for the literature searches, study selection, data extraction, and risk of bias appraisal are in the Supplemental Material document, in Appendix 2.

Table 2: Systematic Review Eligibility Criteria

Criteria	Description
Population	Adults (aged ≥ 18 years) diagnosed with MDD who have had an inadequate response[a] to at least 1 prior antidepressant treatment and who are candidates for adjunctive treatment[b]
Intervention	Adjunctive aripiprazole 2 mg to 15 mg per day administered orally[c]

Comparator	Adjunctive treatment with:
	• antipsychotics
	  ◦ risperidone
	  ◦ quetiapine IR or quetiapine XR
	  ◦ olanzapine
	  ◦ brexpiprazole

Outcomes	**Efficacy outcomes:**
	• response rate (e.g., ≥ 50% decrease in MADRS total score from baseline)
	• remission rate (e.g., MADRS total score of ≤ 10)
	• symptom severity (e.g., HRSD-17 score)
	• function or disability (e.g., SDS score)
	• HRQoL
	Harms outcomes:
	• TEAEs, SAEs (including AEs grade ≥ 3), discontinuation due to AEs, deaths due to AEs
	• AEs of special interest:
	  ◦ weight gain
	  ◦ extrapyramidal symptoms
	  ◦ metabolic parameters (e.g., blood sugar levels, lipid levels, blood pressure, and waist circumference)
	  ◦ sexual dysfunction

Study design	• Published RCTs[d] • Systematic reviews of RCTs[d,e]

AE = adverse event; CANMAT = Canadian Network for Mood and Anxiety Treatments; HRSD-17 = 17-item Hamilton Rating Scale for Depression; HRQoL = health-related quality of life; IR = immediate release; MADRS = Montgomery-Asberg Depression Rating Scale; MDD = major depressive disorder; RCT = randomized controlled trial; SAE = serious adverse event; SDS = Sheehan Disability Scale; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse event; XR = extended release.

[a]According to the 2016 CANMAT MDD guidelines, a partial inadequate response to an initial antidepressant may be defined as a 25% to 49% reduction in symptom scores. No response to initial treatment may be defined as less than a 25% reduction in symptom scores.[13]

[b]We used criteria similar to the summary algorithm for managing inadequate response to an antidepressant in the 2016 CANMAT MDD guidelines.[13]

[c]Dosage based on Abilify product monograph[14] and 2016 CANMAT MDD guidelines.[13]

[d]We took a hierarchical approach to identifying published evidence for each comparator-outcome: First, we looked for RCTs with direct evidence or systematic reviews of RCTs with direct evidence. Next, if no relevant RCTs or systematic reviews were identified, we proceeded to identify published indirect treatment comparisons. Then, if no relevant indirect treatment comparisons were identified, we proceeded to identify published nonrandomized comparative studies of direct evidence.

[e]Systematic reviews needed to include a research question, a list of the sources searched and a reproducible search strategy, clear inclusion and exclusion criteria, a description of methods for study selection, information about how the data were synthesized, and an appraisal of the quality of the included studies.[15]

Clinical Evidence

An information specialist conducted a literature search of key bibliographic databases, trial registries, and grey literature sources, using a peer-reviewed search strategy. The initial search was completed on May 28, 2025. A total of 1,507 unique records were identified. Following title and abstract screening, 1,468 were excluded. The review team screened 40 records by full text and included 1 report from 1 RCT,[16] which is included in the review.

In the absence of a single multiarm RCT or multiple eligible RCTs for each comparator, we proceeded to identify 9 reports of indirect treatment comparisons (ITCs) that met our inclusion criteria. All 9 reports had a relevant population and comparison of aripiprazole with at least 1 comparator of interest, and included an outcome of interest. The characteristics of these studies, including number of studies included, treatment comparisons, and outcomes, were extracted. Due to the overlap and redundancy in primary studies and outcome data across the ITCs, ITC selection and inclusion were based on methodological quality, recency, comprehensiveness, and relevance to the populations, interventions, comparators, and outcomes (PICOs) in Table 2.[17] In total, 3 reports of 3 ITCs[18-20] were included in this report.

A list of excluded studies (including reasons for exclusion) is in the Supplemental Material document, in Appendix 2.

Randomized Controlled Trial

Description of Study

Study Characteristics

Characteristics of the included RCT are summarized in Table 3.

Table 3: Characteristics of the Included RCT

Study name, design, sample size, country, funding source	Key inclusion criteria	Key exclusion criteria	Relevant intervention and comparator	Relevant end points
Yoshimura et al. (2014)[16] RCT N = 30 (n = 20 relevant for this review) Japan **Funding**: One of the coauthors received support from Astellas Pharma, Janssen Pharmaceutical, Eli Lily, Glaxo Smith Kline, Pfizer, Dainippon Sumitomo Pharma, Otsuka Pharmaceutical, and Chugai Pharmaceutical.	• Patients who met the DSM-5 Text Revision criteria for MDD • No response to treatment (defined as < 50% reduction in HRSD-17 score) with paroxetine within 8 weeks	• Current alcohol or drug use or dependency, comorbid anxiety, or personality disorders	**Intervention:** Adjunctive treatment with aripiprazole, mean dose per day: 9 mg (SD = 6)[a] for 4 weeks **Comparator:** Adjunctive treatment with olanzapine, mean dose per day: 7 mg (SD = 5)[a] for 4 weeks	• Response[b] • Remission[c] • Disease severity (HRSD-17 score)

DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; HRSD-17 = 17-item Hamilton Rating Scale for Depression; MDD = major depressive disorder; RCT = randomized controlled trial; SD = standard deviation.

[a]Dosages varied among patients and were not standardized for ethical reasons, according to study authors.

[b]Response was defined as ≥ 50% decrease in score on the HRSD-17.

[c]Remission was defined as HRSD-17 score below 7.

Source: Yoshimura et al. (2014).[16]

Statistical Testing and Analysis Populations

There was no formal sample size calculation. The analysis populations were not defined. The repeated measures analysis of variance with Bonferroni correction was used for comparison of disease severity (as measured by the HRSD-17 total score) between aripiprazole and olanzapine. The level of significance was set with P values less than 0.05.

Patient Disposition

Of 89 patients with MDD, 30 patients (34%) did not experience a response to treatment with paroxetine within 8 weeks. Patients categorized as "nonresponders" were those who did not show a treatment response (defined as a decrease of 50% or more on the HRSD-17) or treatment remission (defined as HRSD-17 total score below 7). Twenty of the 30 patients in the nonresponder group were randomized to either aripiprazole (n = 10) or olanzapine (n = 10). The other 10 patients were randomized to lithium, which is not relevant for this report.

Patient disposition for the included study is summarized in Appendix 4 of the Supplemental Material document.

Baseline Characteristics

Patients' baseline characteristics from the included study are summarized in Table 4.

Table 4: Summary of Baseline Characteristics From Included RCT

Characteristic	Yoshimura et al. (2014)	
	Aripiprazole (N = 10)	Olanzapine (N = 10)
Age in years, mean (SD)	40 (10)	42 (7)
Age in years, range	29 to 71	
Female sex, n (%)	7 (70)	5 (50)
Male sex, n (%)	3 (30)	5 (50)

SD = standard deviation.

Source: Yoshimura et al. (2014).[16]

Treatment Exposure and Concomitant Medications

Patients' treatment exposure and adherence were not reported for the included study.

All patients continued to take paroxetine concomitantly with the intervention (i.e., aripiprazole or olanzapine). Benzodiazepines were allowed and their dosages were kept constant throughout the study period (proportions not reported). No other hypnotics were permitted during the study.

Critical Appraisal

Internal Validity

Details regarding the randomization process (e.g., sequence generation and allocation concealment) were not reported. Additionally, data regarding the baseline characteristics of randomized patients were limited to age and sex, making it impossible to assess potential baseline imbalances in other prognostic factors. This raises concerns about risks of bias arising from the randomization process (e.g., selection bias), especially given the relatively small sample size (N = 10 per group).

There was no information on whether the trial was blinded or if there were deviations from intended interventions. It was reported that 2 patients withdrew from the study due to adverse events (AEs) (1 of these 2 patients was in the lithium group, which is not a comparator of interest), but no information was reported

about how these or other missing outcome data were handled. The omissions contribute to a high risk for performance due to the possibility of an open-label design and a lack of clarity about the analysis population (e.g., intention to treat).

The HRSD-17 is a validated, clinician-reported scale and is frequently used as an end point in clinical trials of MDD to evaluate outcomes of response, remission, and changes in severity with treatment.[21] The thresholds for response (i.e., ≥ 50% decrease in HRSD-17 score) and remission (HRSD-17 score < 7) were the established thresholds based on the HRSD-17.[22] As mentioned previously, the study did not report blinding or whether assessors were aware of treatment allocation. There is a potential risk of detection bias on response, remission, and depression severity, which were based on HRSD-17 scores. Similarly, reporting of AEs may have been influenced by awareness of treatment assignment.

Effect estimates with confidence intervals (CIs) were not reported for treatment response and remission rates; however, the small sample size (N = 10 per group) limits the precision of effect estimates, including those presented graphically for the depressive severity score. No hypothesis was reported, yet the authors claimed that the antipsychotics had equivalent efficacy. The study protocol was unavailable, making it uncertain whether selective reporting occurred. Given the serious limitations and the high risk of misinterpretation of the results, no attempt was made to extract data that were presented graphically.

Overall, the risk of bias for the trial by Yoshimura et al. was judged to be high. This high risk of bias limits the utility of the study for informing reimbursement decisions.

External Validity

The small sample size (N = 10 per group) limits the generalizability and transportability of the results to the broader population of adults with MDD. While the study was conducted in Japan, the clinical experts indicated that the findings from the study were applicable to the population in Canada. The setting in which participants were recruited and treated was not reported. Given that the reporting of baseline characteristics was restricted to sex and age, it is uncertain if the included participants would represent patients encountered in Canadian clinical practice. Aripiprazole and olanzapine were administered for 4 weeks, which may not be long enough to evaluate the efficacy and harms of adjunctive antipsychotics in MDD. According to the clinical experts, the HRSD-17 is accepted as a robust observer-rated measure of depression and is occasionally used in clinical practice in Canada. The instrument could be used more frequently in clinical practice; however, many clinicians are not doing measurement-based care.

Results

Efficacy

Results for outcomes important to this review are presented in Table 5.

Key results include the following:

- The response rates and remission rates were reported for each treatment group, but no formal analyses were performed.

- There was an improvement in HRSD-17 scores from baseline to 4 weeks in both treatment groups, and the evidence was insufficient to suggest a difference in disease severity between aripiprazole and olanzapine.

Table 5: Summary of Key Efficacy Results

Variable	Yoshimura et al. (2014)	
	Aripiprazole (N = 10)	Olanzapine (N = 10)
Response (≥ 50% decrease in HRSD-17 total score from baseline)		
Response, n (%)	4 (40)	3 (30)
Remission (HRSD-17 total score of ≤ 7)		
Remission, mean (SD)	2 (20)	1 (10)
Disease severity (HRSD-17 total score)		
Baseline score, mean (SD)	22 (4)	24 (6)
Change from baseline at 4 weeks	NR[a]	NR[a]
Treatment group difference vs. control (95% CI)	NR	
P value	NR	

CI = confidence interval; HRSD-17 = 17-item Hamilton Rating Scale for Depression; NR = not reported; SD = standard deviation; vs. = versus.

[a]Changes in scores were depicted graphically, but not numerically (i.e., Figure 2 in the publication).

Source: Yoshimura et al. (2014).[16]

Harms

Detailed results for harms for each included study are in the Supplemental Material document, in Appendix 4. Key results include the following:

- Three treatment-emergent AEs were reported. Two patients (20%) in the aripiprazole group reported akathisia (inability to remain still) and 1 patient (10%) in the olanzapine group reported drowsiness.
- One patient in the aripiprazole group discontinued treatment due to akathisia. There were no discontinuations due to AEs in the olanzapine group.
- Severe AEs, deaths, and AEs of special interest were not reported.

Indirect Evidence

Published evidence on ITCs was included, given the lack of head-to-head RCTs directly comparing aripiprazole with risperidone, quetiapine (immediate release [IR] or XR), or brexpiprazole, as well as the methodological limitations of the included RCT comparing aripiprazole with olanzapine.

We identified 9 overlapping ITCs that met our inclusion criteria. Because the inclusion of overlapping ITCs can introduce bias, especially if outcome data from primary studies are included multiple times, we selected 1 ITC per comparator-outcome pair based on a balance of methodological quality, recency, comprehensiveness, and relevance.[17] Therefore, we included 3 ITCs[18-20] in this report. The 6 ITCs that met our inclusion criteria but were not included are presented in Appendix 2 of the Supplemental Material document.

Description of Indirect Comparisons

Saelens et al. (2025)[18] reported response rate and remission rate for aripiprazole compared to risperidone, quetiapine IR, olanzapine, and brexpiprazole; discontinuations due to AEs for aripiprazole compared to quetiapine XR, olanzapine, and brexpiprazole; and disease severity for aripiprazole compared to quetiapine.

Kishi et al. (2024)[19] reported disease severity, social function, AEs, and SAEs for aripiprazole versus brexpiprazole.

Zhou et al. (2015)[20] reported disease severity and function or HRQoL for aripiprazole versus risperidone, quetiapine, and olanzapine as well as discontinuations due to AEs for aripiprazole compared to risperidone.

Study Selection and Review Methods

The objectives, selection criteria, and SR methods of the 3 included ITCs are presented in Table 6.

Descriptions of the relevant outcome measures in the 3 included ITCs are presented in Appendix 5 of the Supplemental Material.

Table 6: Study Selection Criteria and Review Methods for ITCs

Characteristic	Saelens et al. (2025)	Kishi et al. (2024)	Zhou et al. (2015)
Population	Adults (aged ≥ 18 years) with MDD whose condition did not respond to ≥ 2 antidepressant treatments (TRD definition endorsed by FDA and EMA)	Patients in Japan (at least 70% of patients were ethnically Japanese) with antidepressant-resistant MDD (definition NR)	Adult patients (aged > 18 years) diagnosed with a current episode of MDD according to standard diagnostic interviews and an inadequate response to ≥ 1 antidepressant treatment
Intervention	Adjunctive treatment with: • aripiprazole (dosing NR)	Adjunctive treatment with: • aripiprazole, 3 mg per day • aripiprazole, mean 8 mg per day (flexible dose)	Adjunctive treatment with: • aripiprazole, standard dose[a] • aripiprazole, low dose[b]
Relevant comparators	Adjunctive treatment with: • risperidone • quetiapine IR • quetiapine XR • olanzapine • olanzapine + fluoxetine • brexpiprazole (dosing for each comparator NR)	Adjunctive treatment with: • brexpiprazole, 1 mg daily • brexpiprazole, 2 mg daily	Adjunctive treatment with: • risperidone, standard dose[a] • quetiapine, mean 150 mg to 250 mg daily • quetiapine, mean 250 mg to 400 mg daily • olanzapine + fluoxetine, standard dose[a]
Outcomes presented	• Response rate (≥ 50% reduction in depressive symptoms measured by standardized depression scale) • Remission rate (MADRS score of ≤ 10 or HRSD score of ≤ 7) • Symptom severity (MADRS	• Symptom severity (MADRS score) • Social function (SDS or SASS score) • AEs • SAEs • Discontinuations due to AEs	• Symptom severity (score on MADRS, HRSD, or other scale) • Function or HRQoL (Q-LES-Q, SDS, or SF-36 score) • Discontinuations due to AEs

Characteristic	Saelens et al. (2025)	Kishi et al. (2024)	Zhou et al. (2015)
	score) • Discontinuations due to AE		
Study designs	RCTs with ≥ 10 participants per study arm	Published and unpublished, double-blind, randomized, placebo-controlled trials	RCTs, including crossover trials and cluster-randomized trials
Publication restrictions	English language	NR	No restrictions
Exclusion criteria	• Participants with bipolar depression or depression with psychotic features	• Open-label studies • High risk of selection bias according to RoB 2 tool • Child or adolescent participants • Individuals with a dual diagnosis of MDD and another disorder such as substance use disorder • Use of antipsychotics as a rescue medication during the trial • Studies terminated early with no efficacy analysis	• Patients with bipolar depression • Coadministered a psychotherapeutic intervention • Trials for relapse prevention or maintenance treatment
Databases searched	• Embase • PubMed • CENTRAL	• Embase • PubMed • Cochrane Library	• Embase • PubMed • Web of Science • Cochrane Library • CINAHL • LiLACS • PsycINFO • Clinical trial registries (not specified) • Pharmaceutical company websites (not specified) • FDA reports (not specified)
Last search date	April 13, 2023	November 16, 2023	January 31, 2014
Selection process	Two investigators independently screened abstracts and selected relevant studies, and resolved discrepancies via discussion (or consensus).	Two investigators independently checked the literature search.	Two investigators independently screened abstracts and selected relevant studies, and resolved discrepancies via discussion (or consensus).
Data extraction process	Data were collected by 1 reviewer and checked by another. Handling of disagreements was NR.	Two investigators independently checked data transfer accuracy and calculations.	Two independent reviewers independently extracted study parameters using a standardized data extraction form. Disagreements between reviewers were resolved by consensus.

Characteristic	Saelens et al. (2025)	Kishi et al. (2024)	Zhou et al. (2015)
Assessment of risk of bias	One researcher assessed risk of bias using the RoB 2 tool; this rating was then compared to the ratings of 2 other researchers.	Overall risk of bias for all trials was classified using the RoB 2 tool (number of evaluators NR).	Two reviewers independently assessed risk of bias according to the Cochrane Handbook (tool NR).
Assessment of publication bias	Publication bias was checked using comparison-adjusted funnel plots to visually evaluate asymmetry and Egger's test to statistically evaluate asymmetry.	As the number of studies and patients included in the NMA was small, publication bias was not analyzed.	Publication bias was checked using the funnel plot method to visually evaluate asymmetry.
Assessment of certainty of evidence	NR	The results were incorporated into the CINeMA application to assess the credibility of the findings of each NMA.	NR
Source(s) of funding	Intramural Research Program at the National Institute of Mental Health, National Institutes of Health	Grant-in-Aid for Scientific Research	National Basic Research Program of China

AE = adverse event; CENTRAL = Cochrane Central Register of Controlled Trials; CINeMA = Confidence in Network Meta-Analysis; DSM = Diagnostic and Statistical Manual of Mental Disorders; EMA = European Medicines Agency; HRSD-17 = 17 item Hamilton Rating Scale for Depression; IR = immediate release; ITC = indirect treatment comparison; MADRS = Montgomery-Asberg Depression Rating Scale; MDD = major depressive disorder; NMA = network meta-analysis; NR = not reported; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire; RCT = randomized controlled trial; RoB 2 = Cochrane Risk of Bias tool, version 2; SASS = Social Adaptation Self-Evaluation Scale; SDS = Sheehan Disability Scale; SF-36 = Short Form (36) Health Survey; TRD = treatment-resistant depression.

[a]Standard dose was defined as equal to or more than the defined daily dose by the FDA-approved indications.

[b]Low dose was defined as less than half the defined dose by the FDA-approved indications.

Sources: Saelens et al. (2025);[18] Kishi et al. (2024);[19] Zhou et al. (2015).[20]

Statistical Analysis Methods

The analysis methods of the 3 included ITCs are presented in Table 7.

Table 7: ITC Analysis Methods

Methods	Saelens et al. (2025)	Kishi et al. (2024)	Zhou et al. (2015)
Analysis methods	Frequentist NMA using random-effects model or fixed-effects model depending on the analysis (based on heterogeneity and funnel plot asymmetry); Bayesian NMA for validating the findings on the primary outcome	Frequentist NMA and pairwise meta-analyses using a random-effect model	Bayesian NMA with random-effects models for multiarm trials
Statistical software	R (version 4.0.5) using the Netmeta package (version 2.0 to 1); gemtc package (Bayesian)	NR	WinBUGS software package (version 1.4.3, MRC Biostatistics Unit)
Construction of nodes	Treatments were grouped by their primary clinical use or mechanism of action.	The primary NMA compared the outcomes of BRE and ARI. For studies with 2 or more treatment arms of the same drug at different doses, data from the treatment arms were pooled for analysis	To compare the relative outcomes of different types and dosages of atypical antipsychotic agents, the pooled estimates were used. The pooled estimates were obtained

Methods	Saelens et al. (2025)	Kishi et al. (2024)	Zhou et al. (2015)
		so there were 3 treatment arms: BRE, ARI, and placebo. In the secondary NMA, the drugs were divided by dose so there were 5 treatment arms: BRE 1 mg per day, BRE 2 mg per day, ARI 3 mg per day, ARI flexible dose, and placebo.	using the MCMC method. Two Markov chains were run simultaneously with different arbitrarily-chosen initial values. There were 8 nodes and 10 comparisons of symptom severity (primary outcome) in the network plot of different types (and dosages) of atypical antipsychotic drugs.
Priors	Noninformative priors used in the Bayesian analysis	NA	Minimally informative priors
Posterior distribution	Estimated using MCMC: 500,000 iterations, 5,000 burn-in	NA	After running 50,000 samples for 2 Markov chains simultaneously with different arbitrarily-chosen initial values, these samples were then discarded as "burn-in" and posterior summaries were based on 100,000 subsequent simulations.
Assessment of heterogeneity	The heterogeneity of treatment effects was assessed using I^2 statistics.	Global and local heterogeneity were evaluated with the common tau^2 and design by treatment interaction model.	Network metaregression analyses were used to investigate whether potential heterogeneity could be explained by differences in publication year and placebo response rate.
Assessment of transitivity	The distribution of several variables was examined to check for potential violations of the transitivity assumption; these included severity of baseline symptoms, duration of the current depressive episode, comorbidities, concurrent medications, age, and sex.	The assumption of transitivity was evaluated by extracting potential effect modifiers (sample size, proportion of males, proportion of participants with recurrent episodes, and baseline MADRS score). The distributions of these were compared across the comparisons in the network.	NR
Assessment of consistency	No direct comparisons were available for pairwise contrasts (i.e., no closed loops). Therefore, assessment of consistency was not relevant.	No direct comparisons were available for pairwise contrasts (i.e., no closed loops). Therefore, assessment of consistency was not relevant.	No direct comparisons were available for pairwise contrasts (i.e., no closed loops). Therefore, assessment of consistency was not relevant.
Assessment of convergence	Bayesian model convergence assessed via MCMC diagnostics	NA	Trace plots and the Brooks-Gelman-Rubin statistics were assessed. Convergence was found to be adequate after running 50,000 samples for 2 Markov chains with different arbitrarily-chosen initial values.

Methods	Saelens et al. (2025)	Kishi et al. (2024)	Zhou et al. (2015)
Follow-up time points	If more than 1 time point was measured, the nearest time point after the last treatment dose given to participants was used. Follow-up time ranged from 6 weeks to 24 weeks (mean = NR).	6 weeks	For trials with multiple durations of acute treatment, the 8-week outcomes were used. Follow-up time ranged from 4 weeks to 12 weeks (mean = 7 weeks).
Relevant sensitivity analyses	The robustness of the analyses was examined via several sensitivity analyses that included the following data subsets: nonsponsored trials, studies with low and moderate risk of bias, placebo-controlled trials, trials where participants were blinded to treatment, and trials where response rate was provided.	NR	The first sensitivity analysis was performed on a network excluding trials with low-dose drugs for symptom severity (primary outcome) and discontinuations due to AEs. The second sensitivity analysis was performed by omitting trials with small sample sizes (each study arm < 10 patients) for symptom severity (primary outcome) and discontinuations due to AEs.
Relevant subgroup analyses	NR	NR	NR

AE = adverse event; ARI = aripiprazole; BRE = brexpiprazole; ITC = indirect treatment comparison; MADRS = Montgomery-Asberg Depression Rating Scale; MCMC = Markov chain Monte Carlo; NMA = network meta-analysis; NA = not applicable; NR = not reported.

Sources: Saelens et al. (2025);[18] Kishi et al. (2024);[19] Zhou et al. (2015).[20]

Summary of Included Studies

Saelens et al. (2025)

The frequentist NMA by Saelens et al. (2025)[18] had broader inclusion criteria for the interventions and comparators than the present review. The NMA included studies of antipsychotics, mood stabilizers, N-methyl-D-aspartate receptor-targeting agents, serotonergic psychedelics, neuromodulators, and other pharmacological treatments. Only the characteristics and results of the subset of relevant studies meeting our selection criteria are described in this report. This included 15 relevant blinded, placebo-controlled RCTs published between 2005 and 2018. Of these 15 trials, 6 assessed aripiprazole compared to placebo, 1 trial assessed quetiapine XR compared to placebo, 1 trial assessed olanzapine versus placebo, 2 trials assessed olanzapine plus fluoxetine versus olanzapine versus fluoxetine versus placebo, 4 trials assessed brexpiprazole versus placebo, and 1 trial assessed brexpiprazole versus quetiapine XR versus placebo.

The sample sizes in the relevant RCTs ranged from 14 to 444 patients per treatment arm. Eligible patients had not experienced a response to 2 or more antidepressant trials. Patients with bipolar depression or depression with psychotic features were excluded from the NMA. Across RCTs, the mean age ranged from 37 years to 47 years. The proportion of patients that were female ranged from 36% to 78%, and the proportion of males was 22% to 64%. The mean duration of the current MDD episode ranged from 8 weeks to 49 weeks. The mean baseline MADRS score of participants ranged from 20 (indicating moderate depression) to 47 (indicating severe depression). Patients in at least 1 treatment arm of each study received

additional antidepressant treatments. Treatment doses were not reported. The treatment duration was 6 weeks in 11 RCTs (73%), 8 weeks in 2 RCTs (13%), 12 weeks in 1 trial (0.7%), and 24 weeks in 1 RCT (0.7%). The 15 trials were all commercially funded.

The study authors judged 5 of the 15 RCTs (33%) to be at a low overall risk of bias and 9 trials (60%) to have some concerns due to randomization, selection of reported results, and/or adherence to the intervention. The study authors judged 1 RCT (7%) to be at a high risk of bias due to missing outcome data.

Kishi et al. (2024)

The frequentist NMAs by Kishi et al. (2024)[19] included 3 double-blind, placebo-controlled RCTs with 1,736 participants. Two trials assessed aripiprazole compared to placebo and 1 trial compared brexpiprazole to placebo. The trials were published in 2013, 2018, and 2023. The sample sizes in the 3 RCTs ranged from 194 patients to 250 patients per treatment arm. Eligible patients had not experienced a response to 1 to 3 antidepressant treatments. The mean age ranged from 39 years to 40 years. The proportion of patients that were female ranged from 56% to 63% and the proportion that were male ranged from 37% to 44%. The mean baseline MADRS score was 26 (indicating severe depression). Forty-three percent to 53% of participants had experienced recurrent episodes of MDD. The treatment duration was 6 weeks in the 3 trials.

The 3 trials were evaluated by the study authors as having a low overall risk of bias.

Zhou et al. (2015)

The Bayesian NMA by Zhou et al. (2015)[20] included 18 placebo-controlled RCTs with 4,422 participants. Of these 18 trials, 5 assessed aripiprazole compared to placebo, 3 trials assessed risperidone versus placebo, 5 trials assessed quetiapine compared to placebo, and 5 trials assessed olanzapine plus fluoxetine versus fluoxetine. The trials were published between 2001 and 2013. The sample sizes across RCTs ranged from 15 patients to 586 patients per treatment arm. Eleven trials (61%) recruited patients that previously experienced treatment failure with at least 2 conventional antidepressant treatment trials. Fifteen trials (83%) included adjunctive treatment with selective serotonin reuptake inhibitors or selective noradrenalin reuptake inhibitors. Patients with bipolar depression or who were coadministered psychotherapeutic interventions were excluded from the NMA. The mean age was 44 years (range, 18 to 65 years); 41.5% were female and 58.5% were male. The mean treatment duration was 7 weeks (range, 4 to 12 weeks).

The study authors judged 17 of the 18 RCTs (94%) as having an unclear risk of bias due to missing details in at least 1 domain, mostly regarding allocation sequence generation (94%), allocation concealment (88%), other biases 29%), and/or selective reporting (12%). The authors judged 1 RCT (0.06%) to be at a low risk of bias.

Critical Appraisal of ITCs

The 3 SRs with NMAs aimed to synthesize comparative evidence across multiple interventions for MDD. Each specified their research questions using a structured PICO framework. Saelens et al. (2025) aimed to compare the relative effectiveness of diverse interventions — including pharmacological, neuromodulatory, and psychedelic treatments — in adults with TRD. Zhou et al. (2014) assessed the comparative efficacy, tolerability, and HRQoL impact of 7 atypical antipsychotics used as adjunctive strategies in TRD. Kishi et al.

(2024) had a much narrower scope, focusing on comparing aripiprazole and brexpiprazole in patients in Japan with MDD. The variation in PICOs and scope has implications for the generalizability of the results to comparisons between antipsychotics as adjunctive therapies for MDD in practice in Canada.

Each NMA provided rationale for using this methodology for comparative evidence (i.e., limited head-to-head trials of relevant interventions and comparators as adjunctive therapies in MDD).

All 3 reviews registered protocols in advance. However, none explained deviations from their protocols or provided clear rationales for key methodological decisions, such as model selection. For instance, Saelens et al. (2025) referenced model selection criteria based on heterogeneity in their PROSPERO protocol but did not specify the model used in the published article.

The search strategies in the 3 reviews primarily relied on bibliographic databases. Only the review by Zhou et al. (2014) searched grey literature, such as clinical trial registries and industry websites, reducing the risk that eligible studies were missed. In the reviews by Saelens et al. (2025) and Zhou et al. (2024), the methods for study selection and data extraction were aligned with recommended approaches and likely minimized the risk of error; however, this information was not provided in the review by Kishi et al. (2024).

All 3 NMAs assessed risk of bias using validated tools (the Cochrane Risk of Bias tools [RoB or RoB 2]) for each included study, but not for each outcome. Two or more reviewers independently conducted these assessments. Saelens et al. (2025) provided risk of bias figures, with sensitivity analyses excluding studies at high risk of bias, and discussed the implications of commercial sponsorship on bias. Zhou et al. (2014) also provided trial-level risk of bias assessment, and although they stated that none of the studies were assessed as having a high risk of bias, several studies were rated as having an unclear risk of bias. It was not transparent how the risk of bias findings were incorporated into the network syntheses, making it difficult to determine the potential effects on results. Kishi et al. (2024) visually summarized risk of bias assessments using node colour on the trial-level network plot, declaring the studies had a low risk of bias, but the evidence base was small. The limited reporting on risk of bias assessments by Kishi et al. (2024) weakens confidence in their findings.

Network geometry diagrams for outcomes were presented in each NMA. Saelens et al. (2025) constructed a network of 25 treatments plus placebo. The network presented by Zhou et al. (2014) was smaller, with 7 treatment nodes and placebo. Both networks were primarily connected through placebo as the common comparator. Closed loops (representing direct comparisons between active treatments) were identified in the Saelens et al. (2025) networks, including 1 of relevance between brexpiprazole, quetiapine XR, and placebo; none were presented for aripiprazole. Zhou et al. (2014) also identified closed loops in their network; however, these represented comparisons between different doses of the same medication, not between different drugs. The network by Kishi et al. (2024) was sparse, with only 2 active treatment nodes and 1 placebo node. The generally sparse nature of the networks for comparisons between antipsychotics reduces the reliability of indirect comparisons, limiting the ability to formally check for inconsistency or transitivity.

The 3 NMAs prespecified random-effects models for all analyses. This is a conservative and generally appropriate approach, especially when there is potential for differences in patient characteristics and study

designs across the included trials. However, the smaller and more sparse networks — particularly in the review by Kishi et al. (2024) — are more vulnerable to model instability and potentially biased estimates when random effects are applied. None of the reviews reported whether model fit was formally evaluated (e.g., deviance information criterion or residual deviance), nor did they consistently address model assumptions across frequentist versus Bayesian frameworks, the handling of multiarm trials, or missing data. Saelens et al. (2025) and Zhou et al. (2014) did conduct several sensitivity analyses to test assumptions and the robustness of their base-case results. These included examining sponsor type, imputation status, and trial blinding (Saelens et al.) and excluding studies with unusually low drug doses or with fewer than 10 patients per arm (Zhou et al.). All sensitivity analyses were generally consistent with the base-case findings. By contrast, Kishi et al. (2024) presented both pairwise and NMA results but, because of the small number of treatments (nodes) and absence of multiarm trials, were unable to conduct meaningful sensitivity analyses to support their findings.

Heterogeneity parameters such as I^2 and tau^2 were reported by Saelens et al. (2025) and Kishi et al. (2024). Zhou et al. (2014) did not quantify heterogeneity but conducted sensitivity analyses that removed studies expected to contribute greater variability, such as those with low-dose drugs or very small sample sizes. In the review by Saelens et al. (2025), heterogeneity was moderate (I^2 = 47.3%; 95% CI, 26.8% to 62%). Kishi et al. (2014) reported both global and local tau^2 estimates; however, the small number of studies (particularly single-study nodes) limits the interpretability of these statistics, meaning heterogeneity could be either overestimated or underestimated.

None of the 3 NMAs included direct comparisons between interventions relevant to our review. This absence of direct comparison restricts the ability to verify the consistency assumption and weakens the robustness of the conclusions.

To assess the transitivity assumption, Saelens et al. (2025) compared study populations with respect to potential treatment effect modifiers such as baseline symptom severity, duration of depressive episode, comorbidities, concurrent medications, age, and sex. They also conducted a metaregression, which evaluated baseline depression score, year of publication, age, and sex, and found no significant impact of these factors on the primary outcome. Kishi et al. (2024) assessed potential modifiers including baseline depression severity (MADRS scores), recurrence of depressive episodes, and sex distribution, but did not perform metaregression analyses. Zhou et al. (2014) reported the use of network metaregression to explore whether heterogeneity was explained by publication year or placebo response rate; these analyses did not identify statistically significant associations, including no evidence of bias related to publication year.

Across the 3 reviews, and with input from clinical experts, we did not identify major violations of the transitivity assumption based on the available evidence. However, reporting on patient-level factors was incomplete. Several known effect modifiers (e.g., socioeconomic status and comorbidities) were not consistently described, limiting assessment of transitivity across studies.

Beyond patient characteristics, differences in outcome definitions (e.g., variation in depression rating scales and thresholds for treatment response) and trial design features (e.g., inclusion criteria, methods used to confirm prior antidepressant exposure or nonresponse, duration of follow-up, and management of

concomitant therapies) were not systematically examined. As a result, while the available analyses did not detect significant modifiers, gaps in reporting and inconsistent evaluation across reviews reduce certainty that the evidence base fully met the transitivity assumption. It is also unclear how well the evidence base drawn from clinical trials included in the 3 reviews reflects real-world practice for aripiprazole or other atypical antipsychotics as adjunctive treatments in MDD. According to the clinical experts, the inclusion and exclusion criteria of each review resulted in more homogeneous groups that do not fully represent the population to whom aripiprazole and the other 4 antipsychotic drugs may be prescribed in clinical practice.

In the review by Kishi et al. (2024), the authors did not clearly describe how they calculated social functioning, including which scales were used and how they were applied. Similarly, in the review by Zhou et al. (2015), the authors did not clearly describe how they calculated the "function or health-related quality of life" outcome.

Geographic information (i.e., countries in which the included studies were conducted) was absent in the reviews by Saelens et al. (2025) and Zhou et al. (2015). Although the review by Kishi et al. (2024) focused exclusively on patients in Japan, the clinical experts indicated that the findings from the review were applicable to the population in Canada.

Efficacy Results of ITCs

The network diagram for each included NMA is presented in Appendix 5 of the Supplemental Material document.

Results for outcomes important to this review are presented in Table 8, Table 9, Table 10, Table 11, and Table 12.

Key results include the following:

- Treatment with aripiprazole may result in a higher response rate compared to olanzapine.
- There were no differences in response rate for aripiprazole compared to risperidone, quetiapine IR, olanzapine plus fluoxetine, and brexpiprazole.
- Aripiprazole may result in a higher remission rate compared to brexpiprazole.
- Aripiprazole may result in a higher remission rate compared to quetiapine XR, but the effect estimate was imprecise due to very wide 95% CIs.
- There were no differences in remission rate for aripiprazole compared to risperidone, olanzapine, and olanzapine plus fluoxetine.
- There were no differences in depressive symptom severity for aripiprazole compared to risperidone, quetiapine XR, olanzapine, olanzapine plus fluoxetine, and brexpiprazole.
- There were no differences in social function or HRQoL for aripiprazole compared to risperidone, quetiapine IR, olanzapine and brexpiprazole.

Table 8: Summary of ITC Results for Response Rate, Remission Rate, and Symptom Severity; Aripiprazole vs. Comparators

Comparator	Response rate,[a,b] OR (95% CI)	Remission rate,[b,c] OR (95% CI)	Symptom severity,[b,d] SMD (95% CI)
Risperidone	2.67 (0.38 to 18.90)	4.75 (0.63 to 35.78)	NR
Quetiapine IR	1.92 (0.82 to 4.49)	NR	NR
Quetiapine XR	NR	5.20 (1.18 to 22.97)	−0.48 (−2.66 to 1.69)
Olanzapine	2.58 (1.24 to 5.35)	1.51 (0.97 to 2.33)	NR
Olanzapine + fluoxetine	1.83 (0.84 to 3.99)	1.18 (0.73 to 1.91)	NR
Brexpiprazole	1.24 (0.65 to 2.37)	1.74 (1.28 to 2.36)	NR

CI = confidence interval; HRSD-17 = 17-item Hamilton Rating Scale for Depression; IR = immediate release; ITC = indirect treatment comparison; MADRS = Montgomery-Asberg Depression Rating Scale; NR = not reported; RevMan = Cochrane Review Manager; SD = standard deviation; SMD = standardized mean difference; XR = extended release; vs. = versus.

[a]Response rate was defined as ≥ 50% reduction in depressive symptoms measured by standardized depression scales that varied across studies.

[b]If SDs were not provided, the RevMan Calculator was used to impute them based on the provided data.

[c]Remission rate was defined as MADRS score of ≤ 10 or HRSD-17 score of ≤ 7.

[d]To compare the severity of depressive symptoms, a mapping formula was used to convert HRSD-17 scores and respective SDs to MADRS scores (MADRS = 1.04 × HRSD-17 + 10.13).

Source: Saelens et al. (2025).[18]

Table 9: Summary of ITC Results for Symptom Severity and Social Function, Aripiprazole vs. Brexpiprazole, Based on Primary NMA[a]

Comparator	Symptom severity,[b] SMD (95% CI)	Social function,[c] SMD (95% CI)
Brexpiprazole	−0.081 (−0.282 to 0.120)	−0.157 (−0.393 to 0.079)

CI = confidence interval; ITC = indirect treatment comparison; NMA = network meta-analysis; NR = not reported; SMD = standardized mean difference; vs. = versus.

[a]The primary NMA compared the outcomes of aripiprazole and brexpiprazole. For studies with 2 or more treatment arms of the same drug at different doses, data from the treatment arms were pooled for analysis so there were 3 treatment arms: aripiprazole, brexpiprazole, placebo.

[b]Depressive symptom severity was measured using the Montgomery-Asberg Depression Rating Scale total score.

[c]Social function was measured using the Sheehan Disability Scale and Social Adaptation Self-Evaluation Scale.

Source: Kishi et al. (2024).[19]

Table 10: Summary of ITC Results for Symptom Severity and Social Function, Aripiprazole vs. Brexpiprazole, Based on Secondary NMA[a]

Comparator	Aripiprazole, 3 mg per day		Aripiprazole, flexible dose[b]	
	Symptom severity,[c] SMD (95% CI)	Social function,[d] SMD (95% CI)	Symptom severity,[c] SMD (95% CI)	Social function,[d] SMD (95% CI)
Brexpiprazole, 1 mg per day	−0.132 (−0.389 to 0.125)	−0.126 (−0.404 to 0.151)	−0.033 (−0.258 to 0.193)	−0.165 (−0.410 to 0.080)
Brexpiprazole, 2 mg per day	−0.173 (−0.430 to 0.085)	−0.132 (−0.410 to 0.146)	−0.074 (−0.299 to 0.152)	−0.171 (−0.416 to 0.075)

CI = confidence interval; ITC = indirect treatment comparison; NMA = network meta-analysis; NR = not reported; SMD = standardized mean difference; vs. = versus.

[a]In the secondary NMA, the drugs were divided by dose so there were 5 treatment arms: brexpiprazole 1 mg/day, brexpiprazole 2 mg/day, aripiprazole 3 mg/day, aripiprazole flexible dose, and placebo.

[b]The final mean doses in this treatment group were 9.8 mg per day and 6.3 mg per day (mean dose = 8.0 mg per day).

[c]Depressive symptom severity was measured using the Montgomery-Asberg Depression Rating Scale total score.

[d]Social function was measured using the Sheehan Disability Scale and Social Adaptation Self-Evaluation Scale.

Source: Kishi et al. (2024).[19]

Table 11: Summary of ITC Results for Symptom Severity and Function or HRQoL, Standard-Dose[a] Aripiprazole vs. Comparators

Comparator	Symptom severity, SMD[a,b,c] (95% CrI)	Function or HRQoL, SMD[b,c,d] (95% CrI)
Risperidone, standard dose[e]	0.10 (−0.29 to 0.51)[f]	0.13 (−0.17 to 0.43)[f]
Quetiapine IR, mean 150 to 250 mg daily	0.06 (−0.22 to 0.40)[f]	−0.16 (−0.42 to 0.11)
Quetiapine IR, mean 250 to 400 mg daily	0.12 (−0.16 to 0.48)[f]	−0.23 (−0.49 to 0.04)
Olanzapine + fluoxetine, standard dose[e]	−0.04 (−0.30 to 0.25)	−0.07 (−0.39 to 0.25)
Olanzapine + fluoxetine, low dose[g]	−0.28 (−0.72 to 0.18)	NR

CrI = credible interval; IR = immediate release; ITC = indirect treatment comparison; NA = not applicable; NR = not reported; SMD = standardized mean difference; HRQoL = health-related quality of life; vs. = versus.

[a]When a study reported multiple depression rating scales, the Montgomery-Asberg Depression Rating Scale was used as the primary measure, followed by the Hamilton Rating Scale for Depression, or other rating scales.

[b]The SMD is the difference of means between the 2 groups divided by the pooled standard deviation of the measurements.

[c]A negative SMD value indicates greater symptomatic relief.

[d]When data were reported on more than 1 measure in 1 study, data from the Quality of Life Enjoyment and Satisfaction Questionnaire were chosen first, then the Sheehan Disability Scale, and finally the Short Form (36) Health Survey.

[e]*Standard dose* was defined as equal to or more than the defined daily dose by the FDA-approved indications.

[f]In the study publication, the SMDs were presented for risperidone vs. aripiprazole and quetiapine vs. aripiprazole. To present SMDs for aripiprazole vs. the comparator (risperidone or quetiapine), we reversed the direction of the SMD and inverted the signs of both bounds of the CrI and reversed their order.

[g]*Low dose* was defined as less than half the defined dose by the FDA-approved indications.

Source: Zhou et al. (2015).[20]

Table 12: Summary of ITC Results for Symptom Severity and Function or HRQoL, Low-Dose[a] Aripiprazole vs. Comparators

Comparator	Symptom severity, SMD[a,b,c] (95% CrI)	Function or HRQoL, SMD[b,c,d] (95% CrI)
Risperidone, standard dose[e]	0.14 (−0.29 to 0.60)[f]	0.15 (−0.21 to 0.52)
Quetiapine IR, mean 150 to 250 mg daily	0.10 (−0.24 to 0.51)[f]	−0.14 (−0.47 to 0.20)
Quetiapine IR, mean 250 to 400 mg daily	0.16 (−0.17 to 0.59)[f]	−0.20 (−0.54 to 0.14)
Olanzapine + fluoxetine, standard dose[e]	0.00 (−0.32 to 0.36)	−0.05 (−0.43 to 0.34)
Olanzapine + fluoxetine, low dose[g]	−0.24 (−0.72 to 0.27)	NR

CrI = credible interval; HRQoL = health-related quality of life; IR = immediate release; ITC = indirect treatment comparison; NA = not applicable; NR = not reported; SMD = standardized mean difference; vs. = versus.

[a]When a study reported multiple depression rating scales, the Montgomery-Asberg Depression Rating Scale was used as the primary measure, followed by the Hamilton Rating Scale for Depression, or other rating scales.

[b]The SMD is the difference of means between the 2 groups divided by the pooled standard deviation of the measurements.

[c]A negative SMD value indicates greater symptomatic relief.

[d]When data were reported on more than 1 measure in 1 study, data from the Quality of Life Enjoyment and Satisfaction Questionnaire were chosen first, then the Sheehan Disability Scale, and finally the Short Form (36) Health Survey.

[e]*Standard dose* was defined as equal to or more than the defined daily dose by the FDA-approved indications.

[f]In the study publication, the SMDs were presented for risperidone vs. aripiprazole and quetiapine vs. aripiprazole. To present SMDs for aripiprazole vs. the comparator (risperidone or quetiapine), we reversed the direction of the SMD and inverted the signs of both bounds of the CrI and reversed their order.

[9]*Low dose* was defined as less than half the defined dose by the FDA-approved indications.
Source: Zhou et al. (2015).[20]

Harms Results of ITCs

Detailed results for harms are presented in Appendix 5 in the Supplemental Material document. Key results include the following:

- There was no difference between aripiprazole and brexpiprazole with respect to the number of people experiencing at least 1 treatment-emergent AE, severe AE, or AE of special interest (i.e., akathisia, tremor, weight gain).
- There were no differences in treatment discontinuations due to AEs with aripiprazole compared to risperidone, quetiapine XR, and olanzapine.
- AEs, severe AEs, and AEs of special interest were not reported for aripiprazole compared to risperidone, quetiapine IR, and olanzapine.
- Deaths and sexual dysfunction were not reported for any comparisons.

Discussion

Efficacy

Patients living with MDD reported challenges with their condition, including limited ability to participate in activities of daily living, a devasting effect on overall quality of life, the need for meaningful symptom relief, stigma, financial burden, and the need to adapt to available treatments rather than receiving individualized care. Clinicians noted that treatment goals for MDD are to alleviate symptoms, improve HRQoL, and restore functional status. Clinicians expressed that a substantial proportion of patients do not experience an adequate response to current treatment for MDD. These patients may benefit with adjunctive therapy with an atypical or second-generation antipsychotic, such as aripiprazole.

In 2014, CDEC concluded that although adjunctive aripiprazole consistently demonstrated statistically significant benefits over placebo, including improvements in response rate, remission rate, and depressive symptom severity, the magnitude and clinical significance of these effects were inconsistent. Key limitations included the lack of evidence for meaningful improvements in HRQoL, the short duration of the trials (less than 7 weeks), and the absence of head-to-head RCTs comparing aripiprazole with other adjunctive treatment strategies for MDD. In this report, we assessed the comparative efficacy and safety of aripiprazole against 4 antipsychotics currently reimbursed by the drugs plans for the adjunctive treatment of MDD: risperidone, quetiapine (IR and XR), olanzapine, and brexpiprazole.

Due to the small sample size (n = 20) and high risk of bias, the findings from the included RCT comparing aripiprazole with olanzapine in patients with MDD who did have a response to treatment with paroxetine were inconclusive. In the absence of direct evidence comparing aripiprazole with risperidone, quetiapine (IR or XR), or brexpiprazole, as well as the methodological limitations of the included RCT comparing aripiprazole versus olanzapine, we included 3 SRs with ITCs.

All 3 reviews reported either odds ratios (ORs) or standardized mean differences (SMDs) to quantify comparative effect estimates. However, interpreting ORs in terms of clinical significance is inappropriate. ORs are relative measures of effect, which cannot be directly translated into the absolute changes required to judge minimally important differences on validated clinician-rated instruments (e.g., MADRS, HRSD-17) or patient-rated instruments (e.g., Sheehan Disability Scale, Short Form [36] Health Survey). In addition, published guidance on minimally important differences is based on absolute mean differences and not relative effect measures,[23-25] further limiting the interpretability of ORs for clinical relevance. For SMDs, a commonly-used "rule of thumb" categorizes an SMD of 0.2 as a small effect, 0.5 as a moderate effect, and 0.8 or higher as a large effect.[26] These thresholds serve as general benchmarks for effect size magnitude but are not definitive indicators of clinical importance.

In the review by Saelens et al. (2025),[18] response rate and remission rate for aripiprazole were compared to risperidone, quetiapine IR, olanzapine, and brexpiprazole within a larger network of 25 different interventions, using placebo as a common comparator. The results indicated that aripiprazole may result in a statistically significant higher response rate compared to olanzapine (OR = 2.58; 95% CI, 1.24 to 5.35) and a higher remission rate compared to brexpiprazole (OR = 1.74; 95% CI, 1.28 to 2.36). While these ORs suggest substantial relative differences, their clinical significance remains uncertain. The clinical experts consulted for the review indicated that, based on experience from practice, they would not expect the odds of response or remission would realistically be doubled or greater in favour of aripiprazole. For example, aripiprazole and brexpiprazole have similar pharmacological profiles and Health Canada approvals as adjunctive treatments for MDD, and are expected to have similar efficacy. The results may be influenced by unaccounted-for effect modifiers in patient characteristics or differences between studies, such as whether patients had not experienced a response to antidepressants and how this was determined, which was not clearly reported across trials. Other limitations of the evidence base, as well as concerns about incomplete reporting, further weaken confidence in the magnitude of these observed relative effects. Notably, the OR for remission rate with aripiprazole compared to quetiapine XR was very high (5.20) but the estimate was imprecise, with a 95% CI from 1.18 to 22.97, indicating low certainty.

The remaining findings in all 3 reviews were consistent with the expectations of the clinical experts.

Saelens et al. (2025) reported no statistically significant differences in response rate for aripiprazole compared to risperidone, quetiapine XR, olanzapine plus fluoxetine, and brexpiprazole. There were no statistically significant differences in remission rate for aripiprazole compared to risperidone, olanzapine, and olanzapine plus fluoxetine. For symptom severity, the SMD (−0.48) for aripiprazole compared to quetiapine XR suggested a low to moderate clinical improvement in depressive symptoms; however, the 95% CI crossed unity, indicating no statistically significant difference between interventions.

The review by Kishi et al. (2024)[19] reported no differences between depressive symptom severity and social function for aripiprazole versus brexpiprazole. These findings were comparable in the secondary analyses by treatment dose.

The review by Zhou et al. (2015)[20] assessed disease severity and function or HRQoL for aripiprazole versus risperidone, quetiapine IR, and olanzapine. According to the SMDs, aripiprazole appeared to improve

symptom severity compared to a low dose of olanzapine plus fluoxetine (SMD = −0.28) and to improve function or HRQL compared to quetiapine (SMD = −0.23); however, the 95% credible interval (CrI) crossed unity in both cases.

Treatment duration in the included studies in the 3 SRs with NMAs ranged from 4 weeks to 24 weeks, with most studies assessing a 6-week treatment period. However, MDD is a chronic disorder and the efficacy and safety of aripiprazole for long-term treatment remains uncertain.

Harms

The overall findings from the 3 SRs with NMAs suggested there were no clear differences between aripiprazole and the other active treatment comparators with respect to adverse effects, although the estimates were imprecise with very wide 95% CIs or CrIs. The clinical experts shared that, in practice, clinicians will prescribe aripiprazole or brexpiprazole for MDD adjunctive treatment due to the increased AE profiles of the other atypical antipsychotics. The direction of effect estimates (although statistically nonsignificant) for treatment discontinuations due to AEs were as expected, favouring aripiprazole compared to risperidone, quetiapine XR, and olanzapine. Other harms (AEs, SAEs, SAEs of special interest, and deaths due to AEs) were not reported for aripiprazole compared to risperidone, quetiapine IR, and olanzapine. While the OR (2.46) indicated a clinical meaningfully increase in weight gain with aripiprazole compared to brexpiprazole in the Kishi et al. (2024) review, the 95% CI crossed the line of significance (indicating no statistically significant effect) and was wide (indicating imprecision). The OR (3.33) in the Zhou et al. (2015) review indicated a clinical meaningful increase in discontinuations due to AEs with standard-dose aripiprazole compared to risperidone, but the 95% CrI crossed unity and was wide. According to the clinical experts, both clinical experience and studies comparing the extent of weight gain and metabolic effects of antipsychotic drugs show very large differences among them. These large differences have clinically important implications for treatment selection, especially the less favourable metabolic profile of olanzapine and quetiapine.

Conclusion

Overall, the direct and indirect clinical evidence on the beneficial and harmful effects of short-term to medium-term treatment with adjunctive aripiprazole compared to risperidone, quetiapine IR or XR, olanzapine, and brexpiprazole is of very low to low quality. Overall, it appears that aripiprazole, risperidone, quetiapine IR and XR, olanzapine, and brexpiprazole have at least similar efficacy and safety in patients with MDD. There is no clear signal that aripiprazole worsens response, remission, disease severity, function, or HRQoL, or that it increases tolerability compared to other antipsychotics currently being reimbursed by the public drug plans as adjunctive treatment for MDD. While evidence from 1 ITC suggests aripiprazole is superior in response rate compared to olanzapine and in achieving remission compared to brexpiprazole and quetiapine XR, the absence of direct comparisons, limited evidence base, methodological limitations, and unclear reporting weaken the confidence of these conclusions. Current evidence suggests that aripiprazole would provide a suitable alternative to existing reimbursed antipsychotics for the adjunctive treatment of patients with MDD.

Economic Review

Methods

The Economic Review consisted of a cost comparison for aripiprazole compared with risperidone, quetiapine IR, quetiapine XR, olanzapine, and brexpiprazole. These comparators comprise other drugs recommended for adult patients who had an inadequate response to early-line antidepressant therapies.

Based on public list prices, aripiprazole is expected to have a per-patient cost of $464 per year (refer to Supplemental Material document, Appendix 4). The costs per patient of the comparators vary between $141 (quetiapine IR) and $1,278 (brexpiprazole) per year. Therefore, aripiprazole is $815 less costly than brexpiprazole and more costly than the other comparators, costing up to $322 more (relative to quetiapine IR) per patient per year. As such, the reimbursement of aripiprazole as adjunctive treatment for MDD in adult patients who have had an inadequate response to at least 1 prior antidepressant treatment is expected to increase overall drug acquisition costs, unless it displaces more costly treatments for MDD. Additional items for consideration are as follows:

- According to the Clinical Review, direct and indirect evidence suggests that aripiprazole, risperidone, quetiapine, olanzapine, and brexpiprazole have at least similar efficacy and safety in patients with MDD, and that aripiprazole would provide an alternative to existing reimbursed antipsychotics for the adjunctive treatment of patients with MDD.
- As of September 2025, there are multiple versions of generic aripiprazole currently marketed in Canada.
- All comparators are available in Canada as generics with the exception of brexpiprazole, which is only available as a brand name product (Rexulti).
- No health care resource use outcomes were reported in the studies included in this review.
- According to the clinical experts consulted for this review, aripiprazole is expected to have similar treatment-related health care resource use to its comparators. They noted that among these drugs there is a variable risk of metabolic changes and aripiprazole may reduce the frequency of metabolic testing (weight, body mass index, waist circumference, blood glucose, hemoglobin A1C, lipids) relative to some of its comparators.
- Aripiprazole was previously reviewed by CDA-AMC for this indication in 2014, with a recommendation not to reimburse it. As of September 2025, there are no drugs under review for MDD at CDA-AMC.
- No cost-effectiveness studies conducted in Canada were identified based on a literature search conducted on May 28, 2025, with alerts maintained until the Formulary Management Expert Committee (FMEC) meeting on November 20, 2025.

Conclusion

The reimbursement of aripiprazole as adjunctive treatment for MDD in adult patients who have had an inadequate response to at least 1 prior antidepressant treatment is expected to increase overall drug

acquisition costs, depending on what treatments are displaced. Based on the Clinical Review conclusions, aripiprazole seems to have a similar efficacy and safety profile to its comparators in patients with MDD.

Given that aripiprazole is associated with increased drug acquisition costs relative to most of its comparators and similar effectiveness, there is no evidence to support a price premium for aripiprazole over other treatments for adult patients with MDD who have had inadequate response to at least 1 prior antidepressant treatment.

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