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Quetiapine for Major Depressive Disorder: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

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Abbreviations

AEs	Adverse events
BDI	Beck Depression Inventory
CI	Confidence interval
CrI	Credible interval
ECT	Electroconvulsive therapy
ED	Emergency department
GDS	Geriatric Depression Scale
HAM-D	Hamilton Depression Scale
HDL	High density lipoprotein
HR	Hazard ratio
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
JBI	Joanna Briggs Institute
LDL	Low density lipoprotein
LMS	Least means squares
MADRS	Montgomery-Asberg-Depression Scale
MD	Mean difference
MDD	Major depressive disorder
NMA	Network meta-analysis
NA	Not applicable
NR	Not reported
NS	Not statistically significant
OR	Odds ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QoL	Quality of life
QALYs	Quality-adjusted life-years
RCT	Randomized controlled trial
RR	Risk ratio
rTMS	Repetitive Transcranial magnetic stimulation
SD	Standard deviation
SMD	Standardized mean difference
TL	Turkish lira
TRD	Treatment-resistant depression
VAS	Visual analog scale
XR	Extended release
WTP	Willingness-to-pay

Context and Policy Issues

Major depressive disorder (MDD) is a debilitating mental health condition that affects people of all ages, leading to significant negative impact on functional status, quality of life, productivity, risk of suicide and health care costs.[1] Based on data from a 2012 survey of the Canadian Community Health Study-Mental Health, the prevalence of MDD in Canada was 3.9%, with two-thirds of which sought treatment.[2] Patients with MDD are first treated with various antidepressants.[3] However, less than 50% of patients with MDD do not achieve adequate response or remission under first line antidepressant therapy.[4]

Second-generation antipsychotics or atypical antipsychotics, including quetiapine, aripiprazole, brexpiprazole and olanzapine have been approved as add-on treatment to antidepressant therapy.[5] In Canada, quetiapine extended release (XR) under the brand name of Seroquel XR by AstraZeneca received the approval for treatment of MDD in patients who have failed previous antidepressant treatment due to a lack of efficacy and/or lack of tolerability.[6] Adverse events associated with quetiapine use includes somnolence, sedation, weight gain, extrapyramidal symptoms, and abnormal laboratory results related to glucose, thyroid and cholesterol metabolism.[7] It remains uncertain whether the benefits outweigh the risks of adjunctive treatment with quetiapine for MDD.

The aim of this report is to review the comparative clinical effectiveness and cost-effectiveness of quetiapine versus other competing interventions such as typical antipsychotics, other atypical antipsychotics, lithium, lamotrigine, and antidepressants for the treatment of adults with MDD. This report also aims to identify evidence-based guidelines regarding the use of quetiapine for MDD.

Research Question

1. What is the clinical effectiveness of quetiapine for the treatment of adults with major depressive disorder?
2. What is the cost-effectiveness of quetiapine for the treatment of adults with major depressive disorder?
3. What are the evidence-based guidelines regarding the use of quetiapine with major depressive disorder?

Key Findings

This review included four systematic reviews, one randomized controlled trial, and six economic studies. Two evidence-based guidelines on the use of quetiapine for treatment of patients with major depressive disorder were identified.

Based on findings from a network meta-analysis, quetiapine monotherapy in older adults with major depressive disorder was found to be more efficacious compared to several antidepressants; however, However there remain uncertainty regarding the robustness of these findings, given the lack of available comparative data.

The efficacy of quetiapine add-on therapy in patients with treatment-resistant depression, characterized by response rate, remission rate, or depressive symptoms was not significantly different compared to competing interventions including other atypical antipsychotics, antidepressants, and lithium. Quetiapine add-on therapy and quetiapine

monotherapy were associated with higher withdrawals due to adverse events compared to placebo, thyroid hormone and lithium. Common adverse events of quetiapine add-on therapy and quetiapine monotherapy included somnolence, fatigue, dry mouth, sedation, headache, dizziness and weight gain.

Quetiapine add-on therapy was associated with significantly higher in total medical costs, and outpatient services costs, but lower in pharmacy costs compared with brexpiprazole. Compared with aripiprazole, quetiapine and olanzapine were associated with higher all-cause hospitalization, all-cause emergency department visits, and total medical costs. In cost-effective analyses, quetiapine add-on therapy was found to be less cost-effective than aripiprazole.

Both guidelines recommend quetiapine as add-on therapy in patients who were insufficiently treated with antidepressants. Evidence on quetiapine misuse and abuse by patients with major depressive disorder were not identified.

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

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were quetiapine and major depressive disorder. No filters were applied to limit the retrieval by study type. The search was also limited to English language documents published between January 1, 2009 and January 2, 2020.

Selection Criteria and Methods

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

Table 1: Selection Criteria

Population	Adults with major depressive disorder, with or without comorbid conditions
Intervention	Quetiapine, as a primary or adjunct therapy, all formulations and all routes of administration
Comparator	Q1-2: • Typical antipsychotics (e.g., chlorpromazine, methotrimeprazine, loxapine, perphenazine, zuclopenthixol, flupentixol, fluphenazine, haloperidol, pimozide, trifluoperazine). • Atipical antipsychotics (e.g., aripiprazole, asenapine, brexpiprazole, clozapine, lurasidone, olanzapine, paliperidone, risperidone, ziprasidone),

	• Lithium, • Lamotrigine, • Antidepressants (e.g., monoamine oxidase inhibitors, norepinephrine and dopamine reuptake inhibitors, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, serotonin antagonist and reuptake inhibitors, tricyclic antidepressants, and tetracyclic antidepressants), Q3: not applicable
Outcomes	Q1: Clinical effectiveness (e.g., symptoms, mood stability, quality of life, cognitive function) and safety (e.g., misuse, abuse, side effects, adverse events, morbidity, mortality) Q2: Cost-effectiveness (e.g., cost per quality adjusted life year, cost per patient adverse event avoided, cost per clinical outcome) Q3: Recommendations related to the appropriate use and place in therapy of quetiapine
Study Designs	Health technology assessments (HTAs), systematic reviews (SRs), randomized controlled trials (RCTs), economic evaluations, non-randomized studies, and evidence-based guidelines

Exclusion Criteria

Clinical and economic studies were excluded if they did not meet the selection criteria in Table 1 and if they were published prior to 2009. Non-randomized studies that did not measure and provide findings on safety were excluded. Guidelines were excluded if they were published prior to 2015.

Critical Appraisal of Individual Studies

The systematic reviews (SRs) which included an indirect comparison or network meta-analysis (NMA) were critically appraised using a checklist[8] based on the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) criteria.[9] The critical appraisal checklists of the Joanna Briggs Institute were used to assess the quality of the included RCT[10] and economic studies.[11] The quality of the evidence-based guidelines was assessed using the Appraisal of Guidelines for Research and Development (AGREE) II instrument.[12] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 231 citations were identified in the literature search. Following screening of titles and abstracts, 211 citations were excluded and 20 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search. Of the 22 potentially relevant articles, 9 publications were excluded for various reasons, while 13 publications including four SRs with an NMA or indirect comparison, one RCT, six economic studies and two guidelines met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA flowchart[13] of the study selection.

Summary of Study Characteristics

The characteristics of the included SRs,[14-17] (Table 2) RCT,[18] (Table 3) and economic studies[19-24] (Table 4) and guidelines[25,26] (Table 5) are presented in Appendix 2.

Study Design

The identified SRs[14-17] used NMA in a frequentist[14] or Bayesian[15,16] framework, or indirect comparison of Butcher method[17] to compare quetiapine with other pharmacological or non-pharmacological agents. All identified SRs searched for RCTs using multiple databases with indicated search dates. The authors of all identified SRs assessed the quality of the included RCTs using the Cochrane Risk-of-Bias tool. Three SRs[14,16,17] reported both pairwise and NMA results.

The included RCT[18] was an international, multicentre, open-label, rater-blinded and parallel trial. Sample size calculation with 80% power was used to determine the required number of patients enrolled. Three populations were employed in the analyses: 1) the modified intention-to-treat population, 2) the per-protocol population, and 3) the safety population.

Four included cost analysis studies[19-21,24] compared healthcare utilization and costs in patients with MDD treated with atypical antipsychotics as add-on therapy to antidepressants. Clinical and cost data were obtained from private insurance databases or from databases of Medicaid and Medicare in USA. These studies were funded by pharmaceutical companies.

Two cost-effectiveness studies[22,23] were also included. Both compared cost-effectiveness of atypical antipsychotics (i.e., aripiprazole, quetiapine and olanzapine) as add-on therapy in patients with MDD who had insufficient response to antidepressants. Both studies were funded by pharmaceutical companies.

One cost-effectiveness study[22] used a lifetime economic patient-level simulation model with depressive episode as the initial health state, while remission, between episodes and death as transition states. The treatment effects were remission rates obtained from Phase 3 clinical trials. Comparative clinical effectiveness of atypical antipsychotics was estimated by using indirect comparison. Resource utilization and costs and were obtained from Turkish studies. Costs were expressed in 2010 Turkish lira and were estimated from the Turkish healthcare system. Cost data included drug prices, health care resource cost (hospitalization, psychiatric visit), cost during the between episode states, and cost of suicide attempts. The utility was expressed as quality-adjusted life-years (QALYs) derived from health-related quality of life. Both costs and QALYs were discounted with 3.5% per year.

Other cost-effectiveness study[23] used decision-analytic model, with time horizon of six weeks, to estimate expected clinical outcomes and economic costs. The treatment effects were clinical response, discontinuation, and adverse events were obtained from Phase 3 clinical trials. Cost of study medication, cost of adverse events, cost of treatment discontinuation and total cost of MDD-related care were estimated using secondary data sources. Costs were expressed in 2011 US dollars and were estimated from the perspective of the US health care system.

Both identified guidelines[25,26] described methods used for search of evidence, selection and synthesis. The recommendations of the French guideline[25] were made through consensus survey of expert opinion. The Canadian guideline[26] was developed by members from research, academic and clinical centers across Canada. Treatment options were hierarchical ranked based on the level of evidence.[26] Both guidelines[25,26] were peer-reviewed.

Country of Origin

The SRs were conducted by authors from Germany,[14,15] China,[16] and UK.[17]

The included RCT was conducted by authors from Germany.[18]

Four included cost analysis studies were conducted authors from USA, [19-21,24] one cost-effectiveness study was conducted in Turkey,[22] and the other cost-effectiveness study was in USA.[23]

One identified guideline was from France,[25] the other guideline was from Canada.[26]

Patient Population

One SR[14] included elderly patients (mean age 73.7 years) with diagnosis of MDD, while three other SRs[15-17] included adult patients (age range from 18 to 75 years) with MDD, who were resistant to antidepressant treatments. The identified RCT included adult patients (age range from 18 to 65 years) with MDD, who had inadequate response to antidepressant treatment.

All identified economic studies[19-24] included adult patients with MDD, who were refractory to antidepressant therapy.

The target population for the identified guidelines[25,26] was patients with MDD. The French guideline[25] specifically targeted to patients who were treatment-resistant to antidepressants.

Interventions and Comparators

One SR[14] had placebo, quetiapine and 25 antidepressant agents as monotherapy or add-on in its NMA network for the treatment of older patients with MDD. One SR[15] had 13 pharmacologic and non-pharmacologic agents in its NMA network including atypical antipsychotics, antidepressants, anticonvulsant, lithium, ketamine, olanzapine/fluoxetine, and somatic interventions as add-on treatment for patients with treatment-resistant depression. One SR[16] had 11 add-on pharmacological agents in its NMA network including atypical antipsychotics, antidepressants, anxiolytic agents, anticonvulsant, lithium, beta-blocker, and thyroid hormone interventions. One SR[17] indirectly compared five add-on agents including quetiapine, antidepressants, lithium and S-adenosyl methionine; these agents were compared with placebo.

The identified RCT[18] compared quetiapine 300 mg/day as add-on and quetiapine 300 mg/day as monotherapy with add-on lithium (0.6 to 1.2 mmol/L) in patients with treatment-resistant MDD.

Treatment duration of the interventions varied among studies. One SR[14] included studies with treatment duration varying from four weeks to 26 weeks. The other SRs had studies with treatment durations of two weeks and six weeks,[15] one week to 12 weeks,[16] and three weeks to six weeks.[17] Treatment duration in the identified RCT[18] was six weeks.

The interventions evaluated in the each of the cost analysis studies were brexpiprazole, quetiapine and lurasidone,[19] brexpiprazole and quetiapine,[20] aripiprazole, olanzapine and quetiapine,[21] and aripiprazole, quetiapine and olanzapine.[24] The interventions evaluated in both cost-effectiveness studies[22,23] were aripiprazole, quetiapine and olanzapine.

Outcomes

The primary outcomes in all four identified SRs[14-17] was response rate defined as a reduction of at least 50% of depressive symptoms. The secondary outcome was remission, [14-17] which is a state of relative absence of symptoms. Other outcomes included change in depressive symptoms at endpoint,[14,15] quality of life,[14] discontinuation due to inefficacy,[14] all-cause discontinuation (acceptability outcome),[14-16] discontinuation due to side effects (tolerability outcome),[14-16] and adverse events.[14-16]

The primary outcome of the identified RCT[18] was change in depressive symptom score measured using the Montgomery-Asberg-Depression Scale (MADRS). The secondary outcomes were response and remission. The study also evaluated patient-reported outcomes, safety and tolerability outcomes.

The identified cost analysis studies[19-21,24] reported health care utilization and costs as outcomes. The utilization outcomes included discontinuation of treatment, all-cause hospitalization or emergency department (ED) visits, all-cause physician visits, and mental health-related ED visits. Cost outcomes were total health care costs (medical and pharmacy costs), medical costs, pharmacy costs, hospitalization costs, cost-associated with ED visits and other outpatient services, and cost of physician office visits. One cost-effectiveness study[22] estimated whether or not an add-on treatment was cost-effective among treatment strategies by determining the probability for willingness-to-pay values per QALY gained using probabilistic sensitivity analysis. The other cost-effectiveness study[23] expressed the cost-effectiveness of each adjunctive intervention in terms of cost per additional responder versus antidepressant therapy alone.

Both identified guidelines[25,26] considered all clinical and non-clinical outcomes related to the treatment of MDD.

Summary of Critical Appraisal

The quality assessments of the identified SRs,[14-17] (Table 6) RCT,[18] (Table 7) economic studies[19-24] (Table 8) and guidelines[25,26] (Table 9) are presented in Appendix 3.

All SRs with NMA,[14-16] or indirect comparison[17] clearly stated the rationale for the study and the study objectives. The methods section in all SRs included a description of eligibility criteria, sources of information, study selection process data, extraction, risk of bias of included studies, and outcome measures. All SRs[14-17] provided a description of analyses methods/models, analysis framework and sensitivity analyses. Methods of handling of potential bias or inconsistency was described in two SRs,[14,16] but not in the others.[15,17] Two SRs[14,16] provided individual study data and the network of studies, while the other SRs either did not include individual study data[15] or a network of the study[17] in the results. An assessment of model fit and competing models being compared were described in three SRs with NMA.[14-16] All SRs[14-17] clearly presented the results of the evidence synthesis, and conducted sensitivity analyses. All SRs[14-17] included in their discussion summary of the main findings, internal and external validity. Implication of the results for target audience and its impact were discussed in two SRs,[14,16] but not in the other two. [15,17] Overall, the included SRs were of high methodological quality.

The included RCT[18] was an open-label trial, which may be subjected to performance bias. However, there was low risk of detection bias as the rater was blinded. All three treatment groups had similar baseline characteristics, and were treated identically other than the intervention of interest. Analyses were conducted based on the modified intention-to-treat

population, per-protocol population and safety population. Outcomes were measured in a reliable way and appropriate statistical analysis was used. Trial design (i.e., parallel RCT) was appropriate. The duration of treatment was relatively short (six weeks). This study was funded by pharmaceutical company.

All identified economic studies[19-24] provided appropriate research questions and comprehensive descriptions of alternatives, identified all important and relevant costs and outcomes for each alternative. Many of the criteria in the checklist (i.e., established clinical effectiveness, costs and outcomes measured, costs and outcomes valued, discount rate, incremental analysis of costs and consequences, and sensitivity analyses), which were designed for cost-effectiveness studies, were not applicable to the identified cost analysis studies.[19-21,24] Both cost-effectiveness studies[22,23] used established clinical effectiveness data, and conducted sensitivity analyses to investigate uncertainty in costs and consequences. It was unclear if both studies[22,23] accurately measured and credibly valued costs and outcomes. It was also unclear if the study results included all issues of concern to users, and if the results and costs could be generalizable to the Canadian setting.

An important limitation of the two cost-effectiveness studies[22,23] is the relatively short treatment duration (i.e., 6 weeks). The adverse events were not included in the models, as the authors suggested that the adverse events would develop when the drugs were taken for a longer duration. One cost-effectiveness study[23] did not incorporate utility values in the analysis, while the other study[22] used Swedish-specific utility values for the analysis under Turkish health care perspective. Not all costs were incorporated in the models such as costs of monitoring tests and costs associated with work productivity losses. These studies[22,23] were sponsored by drug manufacturers.

The four cost analysis studies[19-21,24] had a major limitation in their design and data source (i.e., retrospective database studies). Heterogeneity in baseline characteristics occurred across cohorts and likely to impact the results, although some adjustments for differences were attempted in the analyses. Reasons for treatment discontinuation or decision to switch to other drugs were not captured. It was assumed that prescription filled is equivalent to prescription used, and patient adherence to medication was not measured. The choice of add-on therapy was unclear. Indirect costs associated with productivity loss were not available. As the studies included commercially insured populations, Medicare or Medicaid populations, these could not represent the general population of all patients with treatment-resistant depression. All these four cost-analysis studies were sponsored by drug manufacturers, and therefore the results should be interpreted with caution.

The two identified guidelines[25,26] were explicit in terms of scope and purpose (i.e., objectives, health questions and population) and clarity of presentation (i.e., specific and unambiguous recommendations, different options for management of the condition or health issue, and easy to find key recommendations). In terms of stakeholder involvement, the guidelines clearly defined target users and the development groups included individuals form all relevant professional groups. However, it was unclear if the views and preferences of the target populations were sought. For rigour of development, the guidelines were explicit in terms of systematic methods to search for the evidence, criteria for selecting the evidence, strengths and limitations of the body of evidence, methods of formulating the recommendations, and the link between the recommendations and the supporting evidence. Both guidelines were externally reviewed by experts prior to publication. One guideline[26] provided a procedure for future updating. For applicability, the facilitators and barriers to the guidelines' applications were unclear, and no advice and/or tools on how the

recommendations can be put into practice were apparent. Cost was not considered in the recommendations, and monitoring and/or auditing criteria were not presented in both guidelines. For editorial independence, it was unclear if the funding body influenced the content of the guidelines. The competing interests of guideline development group members were reported in both guidelines.

Summary of Findings

The main findings and authors' conclusions of the SRs,[14-17] (Table 10), RCT,[18] (Table 11), and economic studies[19-24](Table 12) and guidelines[25,26] (Table 13) are presented in Appendix 4

Clinical Effectiveness of Quetiapine for the Treatment of Adults with Major Depressive Disorder

Response

In older patients with MDD,[14] the results of NMA showed that quetiapine monotherapy had a significantly greater response rate compared several antidepressants (i.e., escitalopram, venlafaxine, citalopram, clomipramine, mianserin, trazodone, fluoxetine, tianeptine, nortriptyline, maprotiline). However, significant overall inconsistency was observed for the outcome response (Chi^2 = 32.96; *P* = 0.003), as some drugs were more efficacious than placebo in pairwise MA and not in NMA.

In adult patients with treatment-resistant depression, the results of two NMAs[15,16] and one indirect comparison[17] showed that add-on therapy of quetiapine at 150 mg or 300 mg daily had no significant difference in response rate compared to other atypical antipsychotics (i.e., risperidone, olanzapine, aripiprazole), antidepressants (i.e., fluoxetine, venlafaxine, nortriptyline, bupropion, methylphenidate, mianserin, mirtazapine), anticonvulsant (i.e., lamotrigine), lithium, ketamine, olanzapine/fluoxetine, anxiolytic agent (i.e., buspirone), beta-blocker (i.e., pindolol), thyroid hormone, and S-adenosyl methionine. Add-on quetiapine at 800 mg daily had a point estimate higher than competing interventions.[15] However, their credible intervals were overlapped showing no significant difference.[15]

The results of the identified RCT[18] also showed that add-on quetiapine 300 mg per day and quetiapine monotherapy 300 mg per day had no significant difference in response rate compared with add-on lithium in the management of patients with treatment-resistant MDD.

Remission

In older patients with MDD,[14] the results of the NMA showed that quetiapine monotherapy had significantly higher remission rate compared to several antidepressants (i.e., duloxetine, vortioxetine, sertraline, citalopram, amitriptyline, bupropion, escitalopram, nortriptyline, venlafaxine, fluoxetine, tianeptine).

In adult patients with treatment-resistant depression, the results of two NMAs[15,16] and one indirect comparison[17] showed that add-on therapy of quetiapine at 150 mg or 300 mg daily achieved similar response rate compared to all competing interventions. Add-on quetiapine at 800 mg daily showed no significant difference compared to competing interventions due to overlapping credible intervals.[15]

The results of the identified RCT[18] also showed that add-on quetiapine 300 mg per day and quetiapine monotherapy 300 mg per day had no significant difference in remission rate compared with add-on lithium.

Depressive symptoms

In older patients with MDD,[14] the results of NMA showed that quetiapine monotherapy had no significant difference in the reduction of depressive symptoms compared to any of the antidepressants. The results showed significant overall inconsistency for this outcome (Chi^2 = 61.02; *P* = 0.0000).

In adult patients with treatment-resistant depression, the results of one NMA[15] showed that add-on therapy of quetiapine at 150 mg or 300 mg daily had no significant difference in disease severity change from baseline compared to all competing interventions.

The results of the identified RCT[18] also showed that add-on quetiapine 300 mg per day and quetiapine monotherapy 300 mg per day had no significant difference in change of depressive symptoms compared with add-on lithium.

Patient reported outcomes

In older patients with MDD,[14] the results of NMA showed that quetiapine monotherapy was associated with a significant increase in quality of life compared to several antidepressants (i.e., citalopram, duloxetine, bupropion).

The results of the identified RCT[18] showed no significant differences between add-on quetiapine 300 mg per day and add-on lithium or between quetiapine monotherapy 300 mg per day and add-on lithium for all-patients reported outcomes including pain, anxiety and quality of life.

All-cause discontinuation

In older patients with MDD,[14] the results of the NMA showed no difference in the total dropouts with quetiapine monotherapy compared to any of the antidepressants.

In adult patients with treatment-resistant depression, the results of one NMA[16] showed that quetiapine had no significant difference in all-cause discontinuation compared with all other investigated agents.

Discontinuation due to adverse events

In older patients with MDD,[14] the results of NMA showed that quetiapine monotherapy was associated with a significant higher rate of dropout due to adverse events compared to bupropion.

In adult patients with treatment-resistant depression, the results of two NMAs[15,16] showed that add-on therapy of quetiapine at 150 mg or 300 mg daily was associated with higher withdrawals due to adverse events compared to thyroid hormone.

The results of the identified RCT[18] showed that add-on quetiapine 300 mg per day and quetiapine monotherapy 300 mg per day had higher proportion of patients discontinued treatment due to adverse events compared to add-on lithium.

Common adverse events

Common adverse events of add-on quetiapine and quetiapine monotherapy were somnolence, fatigue, dry mouth, sedation, headache, dizziness and weight gain.[18]

In older patients with MDD,[14] the results of NMA showed that quetiapine monotherapy was associated with significant higher incidence of sedation compared to several antidepressants (i.e., reboxetine, paroxetine, milnacipran, mirtazapine, imipramine).

Cost-effectiveness of Quetiapine for the Treatment of Adults with Major Depressive Disorder

Two cost analysis studies[19,20] compared medication adherence (discontinuation), health care utilization and costs in patients with MDD treated with quetiapine or brexpiprazole as add-on treatment to antidepressant therapy. One study[19] reported that, after adjustment for baseline differences, quetiapine was associated with higher risk of discontinuation, risk of hospital care and all-cause medical costs compared to brexpiprazole. The other study,[20] using matched cohorts, found no significant difference in all-cause hospitalization, ED visits, and total health care costs between quetiapine and brexpiprazole. Quetiapine was associated with significantly higher medical costs, and outpatient services costs, but lower in pharmacy costs compared with brexpiprazole.[20]

Two cost analysis studies[21,24] compared health care utilization and costs in patients with MDD treated with quetiapine, olanzapine, or aripiprazole as add-on treatment to antidepressant therapy. Comparisons were made between quetiapine and aripiprazole and between olanzapine and aripiprazole. Compared with aripiprazole, quetiapine and olanzapine were associated with higher all-cause hospitalization, all-cause ED visits, and total medical costs.

One cost-effectiveness study[22] evaluated the cost-effectiveness of add-on aripiprazole compared with that of add-on quetiapine and add-on olanzapine for treatment of MDD from a Turkish payer perspective. Patients treated with aripiprazole spent less time in major depressive episodes compared with quetiapine and olanzapine over a lifetime horizon. Patients treated with aripiprazole had better quality of life compared those treated with quetiapine or olanzapine, characterized by increase in QALYs. Probabilistic sensitivity analysis showed that the improvement of quality of life and lower costs of aripiprazole occurred in 85% and 86% of the cases compared with quetiapine and olanzapine, respectively. The probability that aripiprazole would be cost-effective among three strategies ranged from 74% to 75% for the willingness-to-pay values between 0 and 100,000 Turkish lira per QALY gained.

One cost-effectiveness study examined the cost-effectiveness of aripiprazole, quetiapine, and olanzapine/fluoxetine as add-on therapy in patients with MDD who are resistant to antidepressants. Add-on therapy with aripiprazole, quetiapine or olanzapine/fluoxetine was associated with increase response rate at 6 weeks and increase in costs of MDD-related care compared with antidepressant alone. Evaluation of cost-effectiveness, expressed as cost per additional responder versus antidepressant therapy alone, revealed that aripiprazole was more cost-effective than quetiapine or olanzapine/fluoxetine.

Evidence-based Guidelines Regarding the Use of Quetiapine with Major Depressive Disorder

The French guideline[25] recommends quetiapine as add-on therapy to patients with MDD were treated with antidepressants and resistant to antidepressants. The Canadian guideline[26] recommends quetiapine as second-line treatment after antidepressants. Overall, both guidelines recommend quetiapine as add-on therapy in patients who were insufficiently treated with antidepressants.

Limitations

The NMA results had several limitations. The evidence was limited by few studies available per comparison and the missing of direct evidence, especially for quetiapine, which was mostly compared with placebo. NMA results were likely affected by potential biases (e.g., choice of therapy dosage and duration) and heterogeneity (e.g., patient characteristics, response and remission criteria, level of MDD severity, dosage and duration) and inconsistent outcomes across trials. The potential bias of financial sponsorship in the original publications by pharmaceutical companies cannot be ruled out. Thus, the validity of the conclusion is limited, and the evidence should be cautiously interpreted.

It remains unclear whether the findings and costs in the included studies are generalizable to the Canadian context.

Conclusions and Implications for Decision or Policy Making

This review included four SRs,[14-17] one RCT,[18] six economic studies,[19-24] and two guidelines.[25,26]

Based on findings from a network meta-analysis, quetiapine monotherapy in older adults with MDD was found to be more efficacious compared to several antidepressants; however, there remain uncertainty regarding the robustness of these findings, given the lack of available comparative data. Quetiapine monotherapy was associated with higher rates of dropout due to adverse events compared bupropion.

In adult patients with treatment-resistant depression, the efficacy of quetiapine add-on therapy, characterized by response rate, remission rate, or depressive symptoms change was not significantly different compared with competing interventions including other atypical antipsychotics, antidepressants, and lithium. Quetiapine add-on therapy was associated with higher withdrawals due to adverse events compared to thyroid hormone and lithium. Common adverse events of quetiapine add-on therapy and quetiapine monotherapy included somnolence, fatigue, dry mouth, sedation, headache, dizziness and weight gain.

Cost analysis studies revealed that quetiapine add-on therapy was associated with significantly in higher total medical costs, and outpatient services costs, but lower in pharmacy costs compared with brexpiprazole. Compared with aripiprazole, quetiapine and olanzapine were associated with higher all-cause hospitalization, all-cause ED visits, and total medical costs. Cost-effectiveness studies showed that quetiapine add-on therapy was less cost-effective than aripiprazole.

Both guidelines recommend quetiapine as add-on therapy in patients who were insufficiently treated with antidepressants.

This report did not identify outcomes of misuse and abuse of quetiapine by MDD patients.

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

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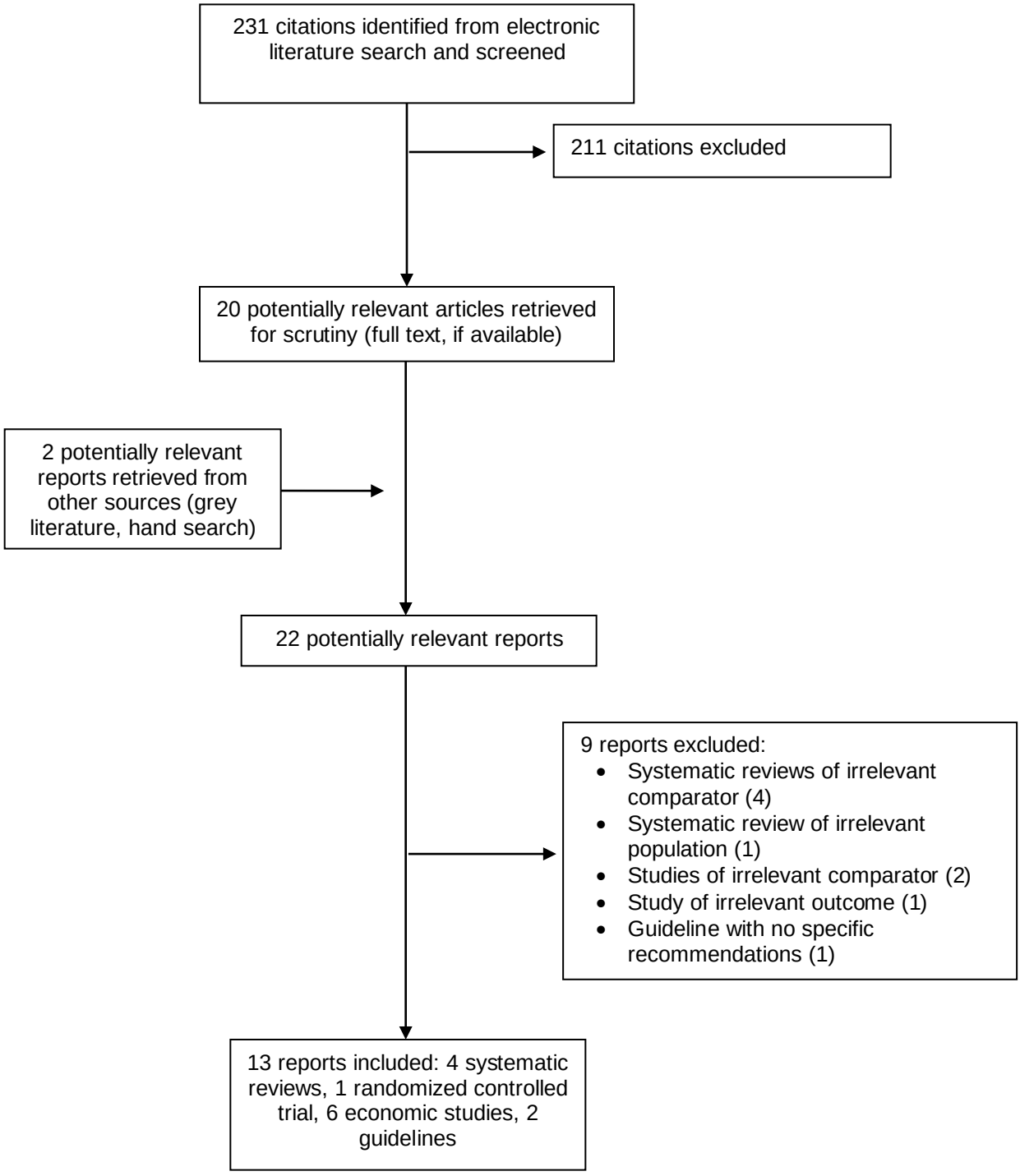
27.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Studies

Table 2: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country, Funding	Objectives, Types and Numbers of Primary Studies Included, Quality Assessment Tool, Databases and Search Date	Patient Characteristics	Interventions and comparators	Outcomes
Krause et al., 2019[14] Germany Funding: German Federal Ministry of Education and Research	Objective: To evaluate the efficacy and safety of pharmacological and non-pharmacological interventions in elderly patients with MDD Total 53 RCTs (n = 9,274) Quality assessment tool: Cochrane risk-of-bias tool Databases: Cochrane group "common mental disorders", EMBASE, MEDLINE, PsycINFO, and the clinical trials registers Cochrane Central Register of controlled trials (CENTRAL), CliicalTrials.gov and WHO International Clinical Trials Registry Platform (ICTRP) Search date: No restriction for publication period Data analysis: Pairwise and network meta-analysis (frequentist framework)	Elderly patients with diagnosis of MDD Mean age: 73.7 years (range 68.9 to 83.2)	Interventions: – Antidepressants (43 trials [23 interventions]), non-pharmacological interventions (8 trials), and one placebo-controlled quetiapine study. Total 24 pharmacological interventions, excluding placebo Comparators: – Active and inactive controls Treatment duration: 4 weeks to 26 weeks	Primary outcomes: – Response (defined as a reduction of at least 50% in depressive symptoms) Secondary outcomes: – Remission (a state of relative absence of symptoms) – Depressive symptoms at endpoint (measured by Geriatric Depression Scale [GDS], Hamilton Depression Scale [HAM-D], Montgomery-Asberg-Depression Scale [MADRS], Beck Depression Inventory [BDI], or any other validated depression scale) – Total dropout (all-cause discontinuation) – Dropout due to inefficacy – Quality of life and social functioning – All reported side effects
Papadimitropoulou et al., 2017[15] Germany Funding: Mapi Group on behalf of Janssen Pharmaceutica NV	Objective: To compare the relative efficacy and tolerability of pharmacological and somatic TRD interventions Total 31 RCTs: 19 RCTs investigating 13 pharmacological interventions and 12 RCTs of electroconvulsive therapy	Adult patients with TRD (defined as failure respond to ≥ 2 antidepressant treatment regimens prescribed at adequate dose and duration, with at least one failure in the current episode)	Interventions (add-on): – 13 pharmacological interventions – 2 somatic interventions Comparators:	– Disease severity change from baseline (measured on HAM-D, MADRS or other depression rating scales) – Response – Remission – Withdrawals due to adverse events

First Author, Publication Year, Country, Funding	Objectives, Types and Numbers of Primary Studies Included, Quality Assessment Tool, Databases and Search Date	Patient Characteristics	Interventions and comparators	Outcomes
	(ECT) and repetitive transcranial magnetic stimulation (rTMS) Quality assessment tool: Cochrane risk-of-bias tool Databases: MEDLINE, MEDLINE In-Process, EMBASE, PsycInfo, Econlit (through OVID) and Cochrane Library databases (including CETRAL, CDSR, CMR, DARE, HTAD, and NHS EED) Search date: From 2003 to September 2014 Data analysis: Bayesian network meta-analysis	Mean age: – Pharmacological: 41 to 52 years – Somatic: 38 to 58 years MADRS score: – Pharmacological: 29.8 (range 25.2 to 33.7) – Somatic: 34.1 (range 18.9 to 43.5)	– Active and inactive controls Treatment duration: 2 weeks, 6 weeks	
Zhou et al., 2015[16] China Funding: National Basic Research Program of China	Objective: To comparatively analyze the efficacy, acceptability, and tolerability of various augmentation agents in adult patients with treatment-resistant depression. Total 48 RCTs investigating 11 augmentation agents Quality assessment tool: Cochrane risk-of-bias tool Databases: MEDLINE, Pubmed, EMBASE, the Cochrane Library, Web of Science, PsycINFO, and EBSCO, the European Association for Gray Literature Exploitation (EAGLE), the National Technical Information Service (NTIS), and the ProQuest For RCTs Search date: From 1970 to December 2013 Data analysis: Pairwise and network meta-analysis (Bayesian framework);	Adult patients with TRD, who had one historical treatment failure and failed to respond to at least one first-line antidepressant during the current MDD episode. Age range: 18 to 75 years	Interventions (add-on): – Aripiprazole, bupropion, buspirone, lamotrigine, lithium, methylphenidate, olanzapine, pindolol, quetiapine, risperidone, and thyroid hormone Comparators: – Active and placebo Treatment duration: one week to 12 weeks	Primary efficacy outcome – Response (a reduction of 50% or more in scores from baseline to post-treatment on the depression scale used in the respective studies Secondary efficacy outcome – Remission (defined as an HAM-D score of ≤ 7, a MADRS score of ≤ 10, or other comparable criteria for various scales used Acceptability outcome – All-cause discontinuation Tolerability outcome – Side-effects discontinuation

First Author, Publication Year, Country, Funding	Objectives, Types and Numbers of Primary Studies Included, Quality Assessment Tool, Databases and Search Date	Patient Characteristics	Interventions and comparators	Outcomes
	sensitivity analysis and meta-regression			
Turner et al., 2014[17] United Kingdom Funding: AstraZeneca UKMC	Objective: To assess the clinical efficacy of add-on therapies for patients with MDD who had not responded to antidepressant treatment, and to compare the efficacy between add-on therapies Total 7 RCTs – Add-on lithium versus placebo (2 trials) – Add-on mianserin versus placebo (1 trial) – Add-on mirtazapine versus placebo (1 trial) – Add-on quetiapine XR versus placebo (2 trials) – Add-on S-adenosyl methionine versus placebo (1 trial) Quality assessment tool: Cochrane risk-of-bias tool Databases: CENTRAL, EMBASE, MEDLINE Search date: From inception to November 2011 Data analysis: Pairwise and adjusted indirect comparisons (Butcher method)	Adult patients with MDD who had not responded to antidepressant treatment Mean age: 37 to 47 years	Interventions (add-on): – Add-on lithium (2 trials) – Add-on mianserin (1 trial) – Add-on mirtazapine (1 trial) – Add-on quetiapine XR (2 trials) – Add-on S-adenosyl methionine (1 trial) Comparator: – Placebo Treatment duration: Three weeks to six weeks	– Response – Remission

BDI = Beck Depression Inventory; GDS = Geriatric Depression Scale; HAM-D = Hamilton Depression Scale; MADRS = Montgomery-Asberg-Depression Scale; MDD = major depressive disorder; RCTs = randomized controlled trials; TRD = treatment-resistant depression.

Table 3: Characteristics of Included Primary Study

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Outcomes
Bauer et al., 2013[18] Germany Funding: AstraZeneca	Open-label, rater-blinded, parallel RCT International, multicentre ITT analysis: Yes Sample size calculation: Yes Statistical analysis: Appropriate	Adults in- or out-patients with MDD who had inadequate response to antidepressant treatment – Age: 18 to 65 years – MADRS total score ≥ 25 (Inadequate response was defined as not achieving remission from depressive symptoms after receiving at least a minimum effective dose of an antidepressant with ≥ 1 dose increase for ≥ 28 days prior to the study)	Add-on quetiapine XR (target dose: 300 mg/day) (n = 231) Quetiapine XR monotherapy (target dose: 300 mg/day) (n = 228) Treatment duration: 6 weeks	Add-on lithium (target plasma level: 0.6 to 1.2 mmol/L) (n = 229) Treatment duration: 6 weeks	Efficacy Primary outcome: – MADRS total score Secondary outcomes – MADRS response – MADRS remission (defined as a MADRS total score ≤ 10, with additional cut-offs of ≤ 8 and ≤ 12 also analyzed) Patient-reported outcomes – BDI – Pain (VAS) – Anxiety (VAS and State-Trait Anxiety Inventory) – QoL (Short-Form Health Questionnaire, SF-36 an EuroQoL Health Utility Index, EQ-5D) – Work Productivity and Activity Impairment: General Health (WPAI:GH) scales Safety and tolerability – Adverse events – Laboratory measurements – Vital signs – Body weight

BDI = Beck Depression Inventory; ITT = intention-to-treat; MADRS = Montgomery-Asberg-Depression Scale; MDD = major depressive disorder; QoL = quality of life; RCT = randomized controlled trial; VAS = visual analog scale; XR = extended release.

Table 4: Characteristics of Included Economic Studies

Study, Year, Country, Funding	Study design	Perspective, Time Horizon, Dollar, Discounting	Population, Inclusion criteria	Interventions	Utilization, Costs
Broder et al., 2019[19] USA Funding: Otsuka Pharmaceutical Development and Commercialization Inc and Lundbeck, USA	Cost analysis Retrospective cohort study using MarketScan Commercial, Medicaid, and Medicare Supplemental Databases Outcome: Utilization and medical costs over 6-month post-index period	Perspective: Not applicable Time horizon: Not applicable Currency: US dollars Discount rate: Not applicable Setting: Real-world (inpatient and outpatient) claims	Adult patients (n = 879,540) with MDD had at least one fill of brexpiprazole, quetiapine, or lurasidone from July 1, 2015 to June 30, 2016 for Medicaid data and from July 1, 2015 to March 31, 2016 for Commercial and Medicare Supplemental data. Mean age (SD): 47.4 (16.2) years – Brexpiprazole: 47.8 (13.2) years – Quetiapine: 48.0 (17.1) years – Lurasidone: 44.2 (14.0) years The index date was the start date of the prescription fill of the adjunctive antipsychotic.	Atypical antipsychotics (Brexpiprazole, quetiapine and lurasidone) as adjunctive therapy to antidepressants	Utilization: – Discontinuation of index atypical antipsychotics – All-cause hospitalization or ED visit in the 6-month post-index period – All-cause psychiatric hospital care Medical costs: – All-cause costs – All-cause psychiatric medical costs
Seetasith et al., 2019[20] USA Funding: Otsuka Pharmaceutical Development and Commercialization Inc and Lundbeck, USA	Cost analysis Retrospective cohort study using adjudicated health plan claims data between July 2014 and September 2016 Outcomes: Utilization and costs over 6-month post-index period	Perspective: Not applicable Time horizon: Not applicable Currency: US dollars Discount rate: Not applicable Setting: Real-world (inpatient and outpatient) claims	Adult patients with MDD starting adjunctive treatment with brexpiprazole (n = 844) or quetiapine XR (n = 688)	Atypical antipsychotics (brexpiprazole, quetiapine XR) as adjunctive therapy to antidepressants	Utilization: – All-cause hospital stay ED visit for any reason during the 6-month post-index period – Mean numbers of all-cause hospitalizations and ED visits per patient during follow-up – All-cause physician office visits – Pharmacy fills Costs:

Study, Year, Country, Funding	Study design	Perspective, Time Horizon, Dollar, Discounting	Population, Inclusion criteria	Interventions	Utilization, Costs
					– Total healthcare costs (medical and pharmacy costs) – Medical costs – Pharmacy costs – Hospitalization costs – Costs associated with ED visits and other outpatient services – Costs associated with ED visits – Costs associated other outpatient services – Costs of physician office visits
Nadkarni et al., 2013[21] USA Funding: Bristol-Myers Squibb and Otsuka Pharmaceutical Development and Commercialization	Cost analysis Retrospective cohort study using PharMetrics data (commercial health plan) from 2005 to 2010 Outcomes: Utilization and costs over 12-month post-index period	Perspective: Not applicable Time horizon: Not applicable Currency: US dollars Discount rate: Not applicable Setting: Real-world (inpatient and outpatient) claims	Adults patients with MDD who filled a prescription for aripiprazole, olanzapine, or quetiapine from July 1, 2005 to July 1, 2009. Mean age (SD): – Aripiprazole: 45.1 (11.9) years – Olanzapine: 46.9 (11.7) – Quetiapine: 44.8 (11.8)	Atypical antipsychotics (aripiprazole, olanzapine, or quetiapine) as adjunctive therapy to antidepressants	Utilization: – Hospitalization – ED visits Costs: – Total medical costs
Saylan et al., 2013[22] Turkey Funding: Bristol-Myers Squibb pharmaceuticals	Cost-effectiveness Primary outcome: Cost-effective among three augmentation strategies (aripiprazole, quetiapine and olanzapine) for WTP values per QALY gained	Perspective: Turkish health care system; payer perspective Time horizon: Lifetime Currency: Turkish Lira Discount rate: 3.5% per annum	Patients with MDD who had insufficient response to antidepressants, and were treated with adjunctive atypical antipsychotics (aripiprazole, quetiapine or olanzapine)	Atypical antipsychotics (aripiprazole, olanzapine, or quetiapine) as adjunctive therapy to antidepressants	Costs: – Drug prices – Health care resource cost (hospitalization, psychiatric visit) – Cost during the between episode states (only antidepressant use)

Study, Year, Country, Funding	Study design	Perspective, Time Horizon, Dollar, Discounting	Population, Inclusion criteria	Interventions	Utilization, Costs
	Utility: QALY Patient-level simulation model with depressive episode as the initial health state of a patient. Transition states included remission, between episodes and death. Treatment effects: Remission rates were obtained from Phase 3 clinical trials Sensitivity analyses: Probabilistic sensitivity analysis showing the incremental costs as a function of incremental QALY gained	Setting: Inpatient and outpatient care			– Cost of suicide attempts
Taneja et al., 2012[23] USA Funding: Bristol-Myers Squibb and Otsuka Pharmaceutical Development and Commercialization	Cost-effectiveness analysis Primary outcome: Cost per additional responder versus antidepressant therapy alone (defined as ratio of the difference between the cost of MDD-related care over 6 weeks in patients receiving aripiprazole, quetiapine, and olanzapine/fluoxetine, respectively, versus antidepressant therapy alone, to the difference in the number of patients achieving clinical response by 6 weeks with these therapies in comparison with	Perspective: US health care system Time horizon: 6 weeks Currency: 2011 US dollars Discount rate: Not applicable Setting: Inpatient and outpatient care	Adults patients with MDD from Phase 3 clinical trials (age not specified)	Atypical antipsychotics (aripiprazole, quetiapine, or olanzapine/fluoxetine) as adjunctive therapy to antidepressants	Costs: – Cost of study medication – Cost of adverse events – Cost of therapy discontinuation – Total cost of MDD-related care

Study, Year, Country, Funding	Study design	Perspective, Time Horizon, Dollar, Discounting	Population, Inclusion criteria	Interventions	Utilization, Costs
	antidepressant therapy alone). Decision-analytic model to estimate expected clinical outcomes and economic costs in adults with MDD treated with aripiprazole 2 to 20 mg/day, quetiapine 150 mg/day or 300 mg/day, or olanzapine/fluoxetine as adjunctive therapy to antidepressants. Treatment effects: Clinical response, discontinuation, and adverse events were obtained from Phase 3 clinical trials. Sensitivity analyses: 1-way deterministic				
Jing et al., 2011[24] USA Funding: Bristol-Myers Squibb and Otsuka Pharmaceutical Co, Ltd	Cost analysis Retrospective cohort study using MarketScan Commercial Claims and Encounters Database from January 1, 2001 to June 30, 2009 Outcomes: Utilization and costs over 6-month post-index period		Adult patients (n = 3,932) with MDD who were treated with antidepressants and adjunctive second-generation antipsychotics (aripiprazole, quetiapine, or olanzapine) Mean age (SD): – Aripiprazole: 37.2 (16.2) years – Olanzapine: 41.6 (12.6) – Quetiapine: 39.7 (12.6)	Atypical antipsychotics (aripiprazole, quetiapine, or olanzapine) as adjunctive therapy to antidepressants	Utilization: – All-cause hospitalization – Mental health-related ED visits Costs: – All-cause medical care costs – All-cause prescription drug costs – Mental health-related medical care cost – Mental health-related prescription drug costs – Total mental health-related costs

ED = emergency department; MDD = major depressive disorder; QALY = quality-adjusted life-years; SD = standard deviation; XR = extended release; WTP = willingness-to-pay.

Table 5: Characteristics of Included Guidelines

First Author, Society/Group Name, Publication Year, Country, Funding	Intended Users/ Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection and Synthesis	Recommendations Development and Evaluation	Guideline Validation
Bennabi et al., 2019[25] France Funding: No specific funding	Intended users: Psychiatrists and primary care providers. Target population: Adult patients with treatment-resistant depression	Assessment and pharmacological strategies in treatment-resistant depression	All outcomes (clinical, non-clinical) related to treatment of resistant depression	Methods used to search for evidence, selection and synthesis were briefly reported	Recommendations were made through consensus survey of expert opinion	The guideline was peer-reviewed
CANMAT, Kennedy et al., 2018[26] Canada Funding: CANMAT fund	Intended users: Psychiatrists and primary care providers. Target population: Adult patients with MDD	Pharmacological treatments of MDD	All outcomes (clinical, non-clinical) related to treatment of MDD	Systematic methods used to search for evidence, selection and synthesis were reported	The guideline was developed by members from research, academic and clinical centres across Canada Each level of evidence was graded[a] (highest to lowest): 1, 2, 3, 4 Treatment options were hierarchical ranked[b] as first line, second line, or third line based on the evidence level	The guideline was peer-reviewed

MDD = major depressive disorder; CANMAT = Canadian Network for Mood and Anxiety Treatments
a Level of evidence ratings
Level 1: Meta-analysis with narrow confidence interval and/or 2 or more RCTs with adequate sample size, preferably placebo controlled
Level 2: Meta-analysis with wide confidence interval and/or 1 or more RCTs with adequate sample size
Level 3: Small sample RCTs or nonrandomized, controlled prospective studies or case series or high-quality retrospective studies
Level 4: Expert opinion/consensus
b Definitions for line of treatment ratings
First line: Level 1 or level 2 Evidence, plus clinical support
Second line: Level 3 Evidence or higher, plus clinical support
Third line: Level 4 evidence or higher, plus clinical support

Appendix 3: Quality Assessment of Included Studies

Table 6: Critical Appraisal of Network Meta-Analysis Studies Using ISPOR Criteria[9]

ISPOR checklist Items[8]	Krause et al., 2019[14]	Papadimitropoulou et al., 2017[15]	Zhou et al., 2015[16]	Turner et al., 2014[17]
1. Are the rationale for the study and the study objectives stated clearly?	Yes	Yes	Yes	Yes
2. Does the methods section include the following?				
• Description of eligibility criteria	Yes	Yes	Yes	Yes
• Information sources	Yes	Yes	Yes	Yes
• Study selection process	Yes	Yes	Yes	Yes
• Data extraction	Yes	Yes	Yes	Yes
• Validity (risk of bias) of individual studies	Yes	Yes	Yes	Yes
3. Are the outcome measures described?	Yes	Yes	Yes	Yes
4. Is there a description of methods for analysis/synthesis of evidence?				
• Description of analyses methods/models	Yes	Yes	Yes	Yes
• Handling of potential bias/inconsistency	Yes	No	Yes	No
• Analysis framework	Yes	Yes	Yes	Yes
5. Are sensitivity analyses presented?	Yes	Yes	Yes	Yes
6. Do the results include a summary of the studies included in the network of evidence?				
• Individual study data?	Yes	No	Yes	Yes
• Network of studies?	Yes	Yes	Yes	No
7. Does the study describe an assessment of model fit? Are competing models being compared?	Yes	Yes	Yes	No

ISPOR checklist Items[8]	Krause et al., 2019[14]	Papadimitropoulou et al., 2017[15]	Zhou et al., 2015[16]	Turner et al., 2014[17]
8. Are the results of the evidence synthesis presented clearly?	Yes	Yes	Yes	Yes
9. Are sensitivity/scenario analyses conducted?	Yes	Yes	Yes	Yes
10. Does the discussion include the following?				
– Description/summary of main findings	Yes	Yes	Yes	Yes
– Internal validity of analysis	Yes	Yes	Yes	Yes
– External validity	Yes	Yes	Yes	Yes
– Implications of results for target audience	Yes	No	Yes	No

Table 7: Quality Assessment of Randomized Controlled Trial

JBI Critical Appraisal Checklist for RCT[10]	Bauer et al., 2013[18]
1. Was true randomization used for assignment of participants to treatment groups?	Yes
2. Was allocation to treatment groups concealed?	NA (open-label)
3. Were treatment groups similar at the baseline?	Yes
4. Were participants blind to treatment assignment?	No
5. Were those delivering treatment blind to treatment assignment?	No
6. Were outcomes assessors blind to treatment assignment?	Yes
7. Were treatment groups treated identically other than the intervention of interest?	Yes
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	Yes
9. Were participants analyzed in the groups to which they were randomized?	Yes
10. Were outcomes measured in the same way for treatment groups?	Yes
11. Were outcomes measured in a reliable way?	Yes
12. Was appropriate statistical analysis used?	Yes
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	Yes

JBI = Joanna Briggs Institute; RCT = randomized controlled trial.

Table 8: Quality Assessment of Economic Studies

JBI Checklist for Economic Evaluations[11]	Broder et al., 2019[19]	Seetasith et al., 2019[20]	Nadkarni et al., 2013[21]	Saylan et al., 2013[22]	Taneja et al., 2012[23]	Jing et al., 2011[24]
1. Is there a well-defined question?	Yes	Yes	Yes	Yes	Yes	Yes
2. Is there comprehensive description of alternatives?	Yes	Yes	Yes	Yes	Yes	Yes
3. Are all important and relevant costs and outcomes for each alternative identified?	Yes	Yes	Yes	Yes	Yes	Yes
4. Has clinical effectiveness been established?	NA	NA	NA	Yes	Yes	NA
5. Are costs and outcomes measured accurately?	NA	NA	NA	Unclear	Unclear	NA
6. Are costs and outcomes valued credibly?	NA	NA	NA	Unclear	Unclear	NA
7. Are costs and outcomes adjusted for differential timing? (Discount rate)	NA	NA	NA	Yes	NA	NA
8. Is there an incremental analysis of costs and consequences?	NA	NA	NA	Yes	No	NA
9. Were sensitivity analyses conducted to investigate uncertainty in estimates of cost or consequences?	NA	NA	NA	Yes	Yes	NA
10. Do study results include all issues of concern to users?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
11. Are the results generalizable to the setting of interest in the review?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

JBI = Joanna Briggs Institute; NA = not applicable.

Table 9: Quality Assessment of Guidelines

AGREE II checklist[12]	Bennabi et al., 2019[25]	CANMAT, Kennedy et al., 2018[26]
Scope and purpose		
1. Objectives and target patient population were explicit	Yes	Yes
2. The health question covered by the guidelines is specifically described	Yes	Yes
3. The population to whom the guidelines is meant to apply is specifically described	Yes	Yes
Stakeholder involvement		
4. The guideline development group includes individuals from all relevant professional groups	Yes	Yes
5. The views and preferences of the target population have been sought	Unclear	Unclear

AGREE II checklist[12]	Bennabi et al., 2019[25]	CANMAT, Kennedy et al., 2018[26]
6. The target users of the guideline are clearly defined	Yes	Yes
Rigour of development		
7. Systematic methods were used to search for evidence	Yes	Yes
8. The criteria for selecting the evidence are clearly described	Yes	Yes
9. The strengths and limitations of the body of evidence are clearly described	Yes	Yes
10. The methods of formulating the recommendations are clearly described	Yes	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations	Yes	Yes
12. There is an explicit link between the recommendations and the supporting evidence	Yes	Yes
13. The guideline has been externally reviewed by experts prior to its publication	Yes	Yes
14. A procedure for updating the guideline is provided	Unclear	Yes
Clarity of presentation		
15. The recommendations are specific and unambiguous	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented	Yes	Yes
17. Key recommendations are easily identified	Yes	Yes
Applicability		
18. The guideline describes facilitators and barriers to its application	Unclear	Unclear
19. The guidelines provides advice and/or tools on how the recommendations can be put into practice	Unclear	Unclear
20. The potential resource (cost) implications of applying the recommendations have been considered	No	No
21. The guideline presents monitoring and/or auditing criteria	No	No
Editorial independence		

AGREE II checklist[12]	Bennabi et al., 2019[25]	CANMAT, Kennedy et al., 2018[26]
22. The views of the funding body have not influenced the content of the guideline	Unclear	Unclear
23. Competing interests of guideline development group members have been recorded and addressed	Yes	Yes

CANMAT = Canadian Network for Mood and Anxiety Treatments

Appendix 4: Main Study Findings and Author's Conclusions

Table 10: Summary of Findings of Systematic Reviews

Main Study Findings	Author's Conclusions
Krause et al., 2019[14]	
Pairwise and NMA of quetiapine and 25 antidepressants in older patients with MDD **Response rates (a reduction of at least 50% in depressive symptoms)** Pairwise – Quetiapine versus placebo: RR (95% CI) = 2.09 (1.62 to 2.70) NMA – Quetiapine versus escitalopram: RR (95% CI) = 2.00 (1.09 to 3.67) – Quetiapine versus venlafaxine: RR (95% CI) = 2.03 (1.14 to 3.63) – Quetiapine versus citalopram: RR (95% CI) = 2.07 (1.17 to 3.64) – Quetiapine versus placebo: RR (95% CI) = 2.09 (1.33 to 3.28) – Quetiapine versus clomipramine: RR (95% CI) = 2.20 (1.06 to 4.54) – Quetiapine versus mianserin: RR (95% CI) = 2.43 (1.30 to 4.54) – Quetiapine versus trazodone: RR (95% CI) = 2.62 (1.25 to 5.48) – Quetiapine versus fluoxetine: RR (95% CI) = 2.48 (1.44 to 4.25) – Quetiapine versus tianeptine: RR (95% CI) = 2.63 (1.41 to 4.91) – Quetiapine versus nortriptyline: RR (95% CI) = 3.59 (1.36 to 9.47) – Quetiapine versus maprotiline: RR (95% CI) = 3.84 (1.36 to 10.82) Overall inconsistency : chi^2 = 32.96; *P* = 0.0003 **Remission** Pairwise – Quetiapine versus placebo: RR (95% CI) = 2.38 (1.90 to 1.52) NMA – Quetiapine versus duloxitine: RR (95% CI) = 1.57 (1.07 to 2.32) – Quetiapine versus vortioxetine: RR (95% CI) = 1.76 (1.11 to 2.80) – Quetiapine versus sertraline: RR (95% CI) = 2.00 (1.21 to 2.30) – Quetiapine versus citalopram: RR (95% CI) = 2.01 (1.31 to 3.11) – Quetiapine versus amitryptiline: RR (95% CI) = 2.03 (1.28 to 3.23) – Quetiapine versus bupropion: RR (95% CI) = 2.09 (1.41 to 3.12) – Quetiapine versus placebo: RR (95% CI) = 2.38 (1.76 to 3.23) – Quetiapine versus escitalopram: RR (95% CI) = 2.50 (1.69 to 3.69) – Quetiapine versus nortriptyline: RR (95% CI) = 2.84 (1.13 to 7.15) – Quetiapine versus venlafaxine: RR (95% CI) = 2.91 (1.85 to 4.56) – Quetiapine versus fluoxetine: RR (95% CI) = 3.27 (2.22 to 4.83) – Quetiapine versus tianeptine: RR (95% CI) = 5.68 (3.35 to 9.62) Overall inconsistency : chi^2 = 5.58; *P* = 0.4720 **Depressive symptoms** Pairwise – Quetiapine versus placebo: SMD (95% CI) = -0.88 (-1.11 to -0.66) NMA – Quetiapine showed no significant difference in the reduction of depressive symptoms compared to placebo or any of the antidepressants. Overall inconsistency : chi^2 = 61.02; *P* = 0.0000 **Quality of life** Pairwise – Quetiapine versus placebo: SMD (95% CI) = 0.47 (0.26 to 0.69) NMA	*"Several antidepressants and quetiapine have been shown to be efficacious in elderly patients with major depressive disorder, but due to the comparably few available data, the results are not robust. Differences in the multiple side-effects analyzed should also be considered in drug choice."*[14] (*p1004*)

Main Study Findings	Author's Conclusions
– Quetiapine versus citalopram: SMD (95% CI) = 0.54 (0.16 to 0.91) – Quetiapine versus placebo: SMD (95% CI) = 0.47 (0.26 to 0.69) – Quetiapine versus duloxitine: SMD (95% CI) = 0.33 (0.04 to 0.62) – Quetiapine versus bupropion: SMD (95% CI) = 0.31 (0.02 to 0.60) **Total dropouts** Pairwise – Quetiapine showed no significant difference in the total dropouts compared to placebo. NMA – Quetiapine showed no significant difference in the total dropouts compared to placebo or any of the antidepressants. **Dropouts due to inefficacy** Pairwise – Quetiapine versus placebo: RR (95% CI) = 0.09 (0.01 to 0.66) NMA – Quetiapine versus placebo: RR (95% CI) = 0.09 (0.01 to 0.66) – Quetiapine versus bupropion: RR (95% CI) = 0.08 (0.01 to 0.72) **Dropouts due to AEs** Pairwise – Quetiapine versus placebo: RR (95% CI) = 2.76 (1.11 to 6.89) NMA – Quetiapine versus placebo: RR (95% CI) = 2.76 (1.07 to 7.11) – Quetiapine versus bupropion: RR (95% CI) = 3.64 (1.16 to 11.49) **Anticholinergic side effects** Pairwise – Quetiapine versus placebo: RR (95% CI) = 1.96 (1.15 to 3.33) NMA Quetiapine versus tianeptine: RR (95% CI) = 4.93 (1.16 to 21.01) Quetiapine versus fluoxetine: RR (95% CI) = 2.31 (1.06 to 5.04) Quetiapine versus placebo: RR (95% CI) = 1.96 (1.15 to 3.33) **Constipation** Pairwise – Quetiapine showed no significant difference in constipation compared to placebo. NMA – Quetiapine versus escitalopram: RR (95% CI) = 8.55 (1.30 to 56.40) **Diarrhea** Pairwise – Quetiapine showed no significant difference in diarrhea compared to placebo. NMA – Quetiapine showed no significant difference in diarrhea compared to placebo or any of the antidepressants. **Dizziness** Pairwise – Quetiapine showed no significant difference in dizziness compared to placebo. NMA – Quetiapine versus tianeptine: RR (95% CI) = 4.69 (1.27 to 17.34)	

Main Study Findings	Author's Conclusions
Dry mouth Pairwise – Quetiapine showed no significant difference in dry mouth compared to placebo. NMA – Quetiapine showed no significant difference in dry mouth compared to placebo or any of the antidepressants. **Insomnia** Pairwise – Quetiapine showed no significant difference in insomnia compared to placebo. NMA – Quetiapine showed no significant difference in insomnia compared to placebo or any of the antidepressants. **Nausea** Pairwise – Quetiapine showed no significant difference in nausea compared to placebo. NMA – Quetiapine showed no significant difference in nausea compared to placebo or any of the antidepressants. **Sedation** Pairwise – Quetiapine versus placebo: RR (95% CI) = 4.07 (2.36 to 7.03) NMA – Quetiapine versus reboxetine: RR (95% CI) = 7.48 (1.50 to 37.43) – Quetiapine versus paroxetine: RR (95% CI) = 6.75 (1.32 to 34.54) – Quetiapine versus milnacipran: RR (95% CI) = 6.56 (1.39 to 30.95) – Quetiapine versus mirtazapine: RR (95% CI) = 6.51 (1.22 to 34.74) – Quetiapine versus placebo: RR (95% CI) = 4.07 (2.36 to 7.03) – Quetiapine versus imipramine: RR (95% CI) = 2.69 (1.20 to 6.01) **Tremor** Pairwise – Quetiapine showed no significant difference in tremor compared to placebo. NMA – Quetiapine showed no significant difference in tremor compared to placebo or any of the antidepressants. **Weight gain** Pairwise – Quetiapine versus placebo: SMD (95% CI) = 0.39 (0.17 to 0.60) NMA – No placebo-controlled trials of antidepressants reporting data about the mean change of weight gain. **Headache** Pairwise – Quetiapine showed no significant difference in headache compared to placebo. NMA – Quetiapine showed no significant difference in headache compared to placebo or any of the antidepressants.	

Main Study Findings	Author's Conclusions
Papadimitropoulou et al., 2017[15]	
NMA of 13 agents: **Atypical antipsychotics (quetiapine, risperidone, olanzapine, aripiprazole), antidepressants (fluoxetine, venlafaxine, nortriptyline), anticonvulsant (lamotrigine), lithium, ketamine, olanzapine/fluoxetine, somatic interventions (rTMS, ECT) as add-on treatment for patients with treatment-resistant depression** **NMA** Disease severity (MADRS) change from baseline at 2 weeks of treatment (16 interventions) – Quetiapine 800 mg (add-on) were ranked lower than intravenous ketamine and add-on risperidone, but higher than quetiapine 150 mg (add-on), quetiapine 300 mg (add-on), lamotrigine (add-on), lithium (add-on), venlafaxine (mono), aripiprazole (add-on), olanzapine/fluoxetine, olanzapine (mono), fluoxetine (mono), nortriptyline, rTMS, ECT. Disease severity (MADRS) change from baseline at 6 weeks of treatment (16 interventions) – Quetiapine 150 mg (add-on) and quetiapine 300 mg (add-on) showed no difference compared with other treatments – Quetiapine 800 mg (add-on) better compared to all competing interventions, despite overlapping CrI (*NS*) Response rate 6 weeks (17 interventions) – Quetiapine 150 mg (add-on) and quetiapine 300 mg (add-on) showed no difference compared with other treatments – Quetiapine 800 mg (add-on) was better compared to all competing interventions, despite overlapping CrI (*NS*) Remission rate at 6 weeks (16 interventions) – Quetiapine 150 mg (add-on) and quetiapine 300 mg (add-on) showed no difference compared with other treatments – Quetiapine 800 mg (add-on) was better compared to all competing interventions, despite overlapping CrI (*NS*) Withdrawals due to AEs at 6 weeks compared with placebo/sham (5 interventions) – Quetiapine 150 mg (add-on): four-fold higher – Quetiapine 300 mg (add-on): two-fold higher – rTMS: four-fold higher – Lamotrigine (add-on): no difference – Aripiprazole (add-on): three-fold	*"This analysis revealed scarcity of long-term data on sustained remission that would allow a comparative long-term efficacy assessment. Key limitations of the analysis can be considered the search timeframe and the use of mapping formula for the depression scores"*[15] (*p701*)
Zhou et al., 2015[16]	
NMA of 11 add-on agents: Atypical antipsychotics (aripiprazole, olanzapine, quetiapine, risperidone), antidepressants (bupropion, methylphenidate), anxiolytic agent (buspirone), anticonvulsant agent (lamotrigine), lithium, beta-blocker (pindolol), and thyroid hormone as add-on treatment for patients with treatment-resistant depression **Pairwise** – Quetiapine versus lithium: No significant difference in response, remission, all-cause discontinuation, or discontinuation due to side-effects – Quetiapine versus placebo: Response: OR (95% CI) = 1.63 (1.26 to 2.11) Remission: OR (95% CI) = 1.90 (1.42 to 2.54) All-cause discontinuation: OR (95% CI) = 1.40 (1.00 to 1.96)	*"Quetiapine and aripiprazole appear to be the most robust evidence-based options for augmentation therapy in patients with treatment-resistant depression, but clinicians should interpret these findings cautiously in light of the evidence of potential treatment-related side effects."*[16] (*pe487*)

Main Study Findings	Author's Conclusions
Discontinuation due to side-effects: OR (95% CI) = 6.34 (2.99 to 13.45) **NMA** Response – Quetiapine showed no significant difference compared with all other investigated agents – Quetiapine versus placebo: OR (95% CI) = 1.92 (1.39 to 3.13) Remission – Quetiapine showed no significant difference compared with all other investigated agents – Quetiapine versus placebo: OR (95% CI) = 2.08 (1.45 to 3.45) All-cause discontinuation: – Quetiapine showed no significant difference compared with all other investigated agents or with placebo Discontinuation due to side-effects: – Quetiapine versus thyroid hormone: OR (95% CI) = 5.64 (1.28 to 16.72) – Quetiapine versus placebo: OR (95% CI) = 3.85 (1.92 to 8.33) **Sensitivity analyses** Most sensitivity analyses showed stronger primary efficacy estimates (response) for aripiprazole and quetiapine than for thyroid hormone and lithium.	
Turner et al., 2014[17]	
Indirect comparisons of five agents: quetiapine, lithium, antidepressants (mianserin, mirtazapine), and S-adenosyl methionine as add-on treatment for patients with treatment-resistant depression Response – Quetiapine XR (150 mg or 300 mg) achieved similar response rate compared to antidepressants (mirtazapine, mianserin), lithium or S-adenosyl methionine. Remission – Quetiapine XR (150 mg or 300 mg) achieved similar response rate compared to antidepressants (mirtazapine, mianserin), or S-adenosyl methionine.	*"Current data indicate that add-on therapies analysed in this study have equivalent efficacy for the treatment of patients with MDD and an inadequate response to their index antidepressant."*[17] (*p96*)

AEs = adverse events; CI = confidence interval; CrI = credible interval; ECT = electroconvulsive therapy; MADRS = Montgomery-Asberg-Depression Scale; NMA = network meta-analysis; NS = not statistically significant; RR = risk ratio; rTMS = repetitive Transcranial magnetic stimulation; SMD = standardized mean difference; XR = extended release.

Table 11: Summary of Findings of Included Primary Study

Main Study Findings	Author's Conclusions
Bauer et al., 2013[18]	
MADRS total score at week 6 – Quetiapine XR (add-on) versus lithium (add-on): LSM differences (97.5%) = -1.64 (-3.5 to 0.23; *P* = 0.0489) – Quetiapine XR (monotherapy) versus lithium (add-on): LSM differences (97.5%) = -0.67 (-2.6 to 1.27; *P* = 0.4368) **Response rate at week 6 (≥ 50 % reduction on MADRS total score from randomization to week 6)** – Quetiapine XR (add-on): 54.2% – Quetiapine XR (monotherapy): 50.7% – Lithium (add-on): 46.2% – No significant differences between groups **Remission rate at week 6 (MADRS total score of ≤ 10 at week 6)** – Quetiapine XR (add-on): 31.9% – Quetiapine XR (monotherapy): 23.6% – Lithium (add-on): 27.1% – No significant differences between groups **Patient-reported outcomes** – No significant differences between quetiapine XR (add-on) and lithium (add-on) or between quetiapine XR (monotherapy) and lithium (add-on) for all patient-reported outcomes evaluated. **Total AEs** – Quetiapine XR (add-on): 67.1% – Quetiapine XR (monotherapy): 66.7% – Lithium (add-on): 51.5% **Common AEs (> 5% in any group) for quetiapine XR (add-on), quetiapine XR (monotherapy) and lithium (add-on)** – Quetiapine XR (add-on): Somnolence (17.7%); Fatigue (16.9%); Dry mouth (18.2%); Sedation (11.3%); Headache (6.1%); Dizziness (10.0%); Weight increased (6.1%) – Quetiapine XR (monotherapy): Somnolence (20.2%); Fatigue (16.2%); Dry mouth (11.8%); Sedation (10.5%); Headache (9.2%); Vertigo (8.3%); Dizziness (7.9%); Weight increased (5.7%) – Lithium (add-on): Fatigue (6.1%); Headache (10.5%); Nausea (9.6%); Diarrhea (7.0%); Tremor (12.2%) **Most common AEs (≥ 1% of patients) leading to treatment discontinuation** – Quetiapine XR (add-on): Somnolence (2.2%); fatigue (1.7%) ; Sedation (1.3%); Depression (1.3%) – Quetiapine XR (monotherapy): Somnolence (2.6%); Sedation (2.6%); Vertigo (1.8%); Fatigue (1.3%); dizziness (1.3% ; Nausea (1.3%) – Lithium (add-on): Vomiting (2.6%) ; Nausea (1.3%); Diarrhea (1.3%) **Proportion of patients discontinued treatment due to AEs** – Quetiapine XR (add-on): 10.0% – Quetiapine XR (monotherapy): 12.3% – Lithium (add-on): 7.9%	*"Add-on quetiapine XR (300 mg/day) and quetiapine XR monotherapy (300 mg/day) are non-inferior to add-on lithium in the management of patients with treatment-resistant MDD."*[18] (*p209*)

Main Study Findings	Author's Conclusions
AEs potentially related to suicidality – Quetiapine XR (add-on): 2.2% – Quetiapine XR (monotherapy): 2.6% – Lithium (add-on): 2.6% **Mean change in body weight from randomization** – Quetiapine XR (add-on): +1.3 kg – Quetiapine XR (monotherapy): +1.0 kg – Lithium (add-on): +0.4 kg **Proportion of patients experienced ≥ 7% increase in body weight from randomization** – Quetiapine XR (add-on): 8.7% – Quetiapine XR (monotherapy): 7.6% – Lithium (add-on): 3.2% **Proportion of patients with potentially clinically relevant shift to elevated fasting glucose level (≥ 126 mg/dL)** – Quetiapine XR (add-on): 1.6% – Quetiapine XR (monotherapy): 3.4% – Lithium (add-on): 5.9% **Proportion of patients with potentially clinically relevant shift to elevated triglycerides (≥ 200 mg/dL)** – Quetiapine XR (add-on): 9.0% – Quetiapine XR (monotherapy): 9.3% – Lithium (add-on): 5.9% **Proportion of patients with potentially clinically relevant shift to elevated total cholesterol (≥ 240 mg/dL)** – Quetiapine XR (add-on): 13.1% – Quetiapine XR (monotherapy): 11.9% – Lithium (add-on): 4.2% **Proportion of patients with potentially clinically relevant shift to LDL-cholesterol (≥ 160 mg/dL)** – Quetiapine XR (add-on): 11.5% – Quetiapine XR (monotherapy): 6.8% – Lithium (add-on): 5.1% **Proportion of patients with potentially clinically relevant shift to lowered HDL-cholesterol (≤ 40 mg/dL)** – Quetiapine XR (add-on): 8.2% – Quetiapine XR (monotherapy): 11.0% – Lithium (add-on): 7.6%	

AEs = adverse events; CI = confidence interval; HDL = high density lipoprotein; LDL = low density lipoprotein; LMS = least means squares; MDD = major depressive disorder; XR = extended release.

Table 12: Summary of Findings of Economic Studies

Main Study Findings	Author's Conclusions
Broder et al., 2019[19]	
Quetiapine versus atypical antipsychotics (brexpiprazole, lurasidone) during 6-month postindex period **Medication adherence** • Risk of discontinuation of index atypical antipsychotics (adjusted) – Quetiapine versus brexpiprazole: HR (95% CI) = 1.13 (1.02 to 1.25) ; *P* = 0.023 – Brexpiprazole versus lurasidone: HR (95% CI) = 1.14 (1.00 to 1.29) ; *P* = 0.054 **Health care utilization** • Rate of all-cause hospitalization or ED visit (adjusted) – Quetiapine: 35.5% (95% CI 33.5% to 37.1%) – Brexpiprazole: 27.4% (95% CI 27.3% to 35.2%) – Lurasidone: 31.1% (95% CI 33.5% to 37.1%) – *P* < 0.001 for all comparisons • Risk of all-cause hospital care (adjusted) – Quetiapine versus brexpiprazole: OR (95% CI) = 1.45 (1.19 to 1.76) ; *P* < 0.001 – Brexpiprazole versus lurasidone: OR (95% CI) = 1.20 (0.03 to 1.54) ; *P* = 0.153 **Costs** • All-cause costs (adjusted) – Quetiapine versus brexpiprazole : Estimate (95% CI) = $2,309 ($31 to $4,587) ; *P* = 0.047 – Brexpiprazole versus lurasidone: Estimate (95% CI) = $913 (-$2033 to $3,859) ; *P* = 0.543 • There were no differences among groups for adjusted psychiatric care, psychiatric costs, and adherence using proportion of days covered.	*"In patients with MDD and a variety insurance types, use of brexpiprazole was associated with lower risk of discontinuation, risk of hospital care (hospitalization and ED visits), and all-cause medical costs compared to adjunctive quetiapine. Brexpiprazole also had the lowest hospital care rates compared with quetiapine and lurasidone. Even though this is a retrospective, observational study and no causal relationship should be drawn, our study findings suggest drug choice may affect subsequent health care utilization and costs."*[19] (*p231*)
Seetasith et al., 2019[20]	
Quetiapine XR (add-on) versus brexpiprazole (add-on) in matched cohorts (both are atypical antipsychotics) **Healthcare resource use during 6-month postindex period** • Rate of all-cause hospitalization: Quetiapine (9.8%) versus brexpiprazole (6.5%); *P* = 0.0924 • Mean number of all-cause hospitalizations per patient during follow-up: Quetiapine (0.14) versus brexpiprazole (0.10); *P* = 0.1562 • Rate of all-cause ED visits: Quetiapine (21.9%) versus brexpiprazole (18.6%); *P* = 0.2512 • Mean number of all-cause ED visits per patient during follow-up: Quetiapine (0.38) versus brexpiprazole (0.33); *P* = 0.4920 • Rate of all-case physician office visits: Quetiapine (98.0%) versus brexpiprazole (97.7%); *P* = 0.8063 • Mean number of all-cause physician office visits per patient during follow-up: Quetiapine (13.28) versus brexpiprazole (13.47); *P* = 0.8341 • Pharmacy fills per patient during follow-up: Quetiapine (34.06) versus brexpiprazole (34.20); *P* = 0.9277 **Healthcare costs during 6-month postindex period** • Mean total healthcare costs (medical and pharmacy costs) per patients	*"Significantly lower medical costs were observed in patients with MDD treated with brexpiprazole vs quetiapine XR."*[20] (*p741*)

Main Study Findings	Author's Conclusions
– Quetiapine: mean (SD) = $13,693 (22,845) – Brexpiprazole: mean (SD) = $12,810 (12,760); *P* = 0.5016 – Quetiapine versus brexpiprazole: *NS* • Mean medical costs per patients – Quetiapine: mean (SD) = $8,602 (19,378) – Brexpiprazole: mean (SD) = $5,719 (10,440); *P* = 0.0092 – Quetiapine versus brexpiprazole: MD (95% CI) = + $2,884 (721 to 5,046) • Mean pharmacy costs per patients – Quetiapine: mean (SD) = $5,091 (9,944) – Brexpiprazole: mean (SD) = $7,491 (6,278); *P* = 0.0007 – Quetiapine versus brexpiprazole: MD (95% CI) = - $2,001 (-3,156 to -845) • Mean hospitalization costs per patients – Quetiapine: mean (SD) = $2,349 (10,634) – Brexpiprazole: mean (SD) = $1,166 (6,759); *P* = 0.0619 – Quetiapine versus brexpiprazole: MD (95% CI) = + $1,182 (-56 to 2,420) ; *NS* • Mean ED visit costs per patients – Quetiapine: mean (SD) = $435 (1,713) – Brexpiprazole: mean (SD) = $279 (984); *P* = 0.1161 – Quetiapine versus brexpiprazole: *NS* • Mean other outpatient services costs per patients – Quetiapine: mean (SD) = $3,966 (12,079) – Brexpiprazole: mean (SD) = $2,471 (5,927); *P* = 0.0271 – Quetiapine versus brexpiprazole: MD (95% CI) = + $1,701 (159 to 3,244) • Mean costs of physician office visits per patient – Quetiapine: mean (SD) = $1,618 (2,408) – Brexpiprazole: mean (SD) = $1,599 (1,784); *P* = 0.8996 – Quetiapine versus brexpiprazole: *NS*	
Nadkarni et al., 2013[21]	
Quetiapine (add-on) or olanzapine (add-on) versus aripiprazole (add-on) in adjusted cohorts (all three are atypical antipsychotic) after 12-month treatment **Total medical costs** – Quetiapine: $12,998 – Olanzapine: $14,275 – Aripiprazole: $9,801; *P* < 0.05 for all comparisons with aripiprazole **All-cause hospitalization** – Quetiapine: 26.0% – Olanzapine: 30.3% – Aripiprazole: 20.1%; *P* < 0.001 for all comparisons with aripiprazole – Quetiapine versus aripiprazole: OR (95% CI) = 1.40 (1.21 to 1.60) – Olanzapine versus aripiprazole: OR (95% CI) = 1.73 (1.42 to 2.10)	*"In commercially insured major depressive disorder patients, olanzapine and quetiapine were associated with higher total medical costs, the difference being primarily attributable to higher inpatient costs. Additionally, olanzapine and quetiapine were associated with significantly higher odds of hospitalization and ER visits compared to aripiprazole."*[21] (*p49*)

Main Study Findings	Author's Conclusions
All-cause ED visits – Quetiapine: 32.8% – Olanzapine: 29.6% – Aripiprazole: 23.1%; *P* < 0.001 for all comparisons with aripiprazole – Quetiapine versus aripiprazole: OR (95% CI) = 1.62 (1.44 to 1.81) – Olanzapine versus aripiprazole: OR (95% CI) = 1.40 (1.18 to 1.65)	
Saylan et al., 2013[22]	
Cost-effectiveness of aripiprazole (add-on) versus quetiapine (add-on) or olanzapine (add-on) **Base case** • Time spent in major depressive episodes – Aripiprazole versus quetiapine: -11 weeks – Aripiprazole versus olanzapine: -7 weeks • QALYs gained – Aripiprazole versus quetiapine: MD (95% CI) = 0.054 (-0.038 to 0.213) – Aripiprazole versus olanzapine: MD (95% CI) = 0.039 (-0.048 to 0.171) • Cost saving – Aripiprazole versus quetiapine: MD (95% CI) = -593 TL (-3,780 to 619) – Aripiprazole versus olanzapine: MD (95% CI) = -485 TL (-3,132 to 757) **Probabilistic sensitivity analysis** Aripiprazole (add-on) would be cost-effective among three strategies ranged from 74% to 75% for willingness-to-pay values between 0 TL and 100,000 TL per QALY gained.	*"This is the first lifetime health economic model in Turkey that takes patient heterogeneity into account when assessing QOL and costs of different adjunctive strategies in MDD. The results indicate that adjunctive treatment with aripiprazole provides health benefits at lower costs in patients with MDD when compared with quetiapine and olanzapine augmentation."*[22] (*p171*)
Taneja et al., 2012[23]	
Cost-effectiveness of aripiprazole (add-on), quetiapine (add-on) or olanzapine/fluoxetine (add-on) – 6 weeks **Base case** • Clinical response 6 weeks – Antidepressant alone: 30% – Aripiprazole: 49%; difference: 19% – Quetiapine 150 mg/day: 34%; difference: 4% – Quetiapine 300 mg/day: 38%; difference: 8% – Olanzapine/fluoxetine: 45%; difference: 15% • Expected cost per person – Antidepressant alone: $192 – Aripiprazole: $847; difference: $655 – Quetiapine 150 mg/day: $541; difference: $349 – Quetiapine 300 mg/day: $672; difference: $480 – Olanzapine/fluoxetine: $791; difference: $599 **Cost-effectiveness (cost per additional responder versus antidepressant therapy alone)** – Aripiprazole: $3,447 – Quetiapine 150 mg/day: $8,725 – Quetiapine 300 mg/day: $6,000 – Olanzapine/fluoxetine: $3,993	*"Atypical antipsychotics substantially increase clinical response at 6 weeks. Cost per additional responder is lower for aripiprazole than for quetiapine or olanzapine/fluoxetine."*[23] (*p642*)

Main Study Findings	Author's Conclusions
One-way sensitivity analysis: cost-effectiveness was most sensitive to response rate – Aripiprazole: range from $2,179 to $5,949 – Quetiapine 150 mg/day: Dominated by antidepressant therapy alone using lower bound of the 95% CI; the ratio at upper bound of the 95% CI was $3,439 – Quetiapine 300 mg/day: range from $3,450 to $20,266 – Olanzapine/fluoxetine: range from $1,734 to $22,351	
Jing et al., 2011[24]	
Quetiapine (add-on) or olanzapine (add-on) versus aripiprazole (add-on) in adjusted cohorts (all three are atypical antipsychotic) after 6-month treatment **All-cause Hospitalization** – Quetiapine: 15.6%; *P* = 0.02 compared with aripiprazole – Olanzapine: 14.1%; *P* = 0.21 with aripiprazole – Aripiprazole: 11.8% – Quetiapine versus aripiprazole: RR (95% CI) = 1.42 (1.07 to 1.89) – Olanzapine versus aripiprazole: RR (95% CI) = 0.30 (0.95 to 1.78) **All-cause ED visits** – Quetiapine: 19.7%; *P* = 0.06 compared with aripiprazole – Olanzapine: 18.0%; *P* = 0.37 compared with aripiprazole – Aripiprazole: 16.1% – Quetiapine versus aripiprazole: OR (95% CI) = 1.35 (1.06 to 1.72) – Olanzapine versus aripiprazole: OR (95% CI) = 1.28 (0.98 to 1.68) **All-cause expenditures** – Quetiapine: $8,788; *P* < 0.01 compared with aripiprazole – Olanzapine: $8,009; *P* = 0.04 compared with aripiprazole – Aripiprazole: $5,952 **All-cause medical care expenditures** – Quetiapine: $7,298; *P* < 0.01 compared with aripiprazole – Olanzapine: $6,062; *P* = 0.02 compared with aripiprazole – Aripiprazole: $3,986 **Mental health-related expenditures** – Quetiapine: $3,325; *P* = 0.06 compared with aripiprazole – Olanzapine: $2,514; *P* < 0.01 compared with aripiprazole – Aripiprazole: $3,986 **Mental health-related medical care expenditures** – Quetiapine: $2,344; *P* < 0.01 compared with aripiprazole – Olanzapine: $2,278; *P* = 0.01 compared with aripiprazole – Aripiprazole: $1,176	*"Compared with patients treated with antidepressants and aripiprazole, those treated with antidepressants and olanzapine or quetiapine had greater utilization and higher expenditures."*[24] (*p1246*)

CI = confidence interval; ED = emergency department; HR = hazard ratio; MD = mean difference; MDD = major depressive disorder; *NS* = not statistically significant; OR = odds ratio; QALY = quality-adjusted life-year; RR =relative risk; SD = standard deviation; TL = Turkish lira; XR = extended release.

Table 13: Summary of Findings of Included Guidelines

Recommendations
Bennabi et al., 2019[25]
"Adding lithium or quetiapine to the ongoing ADT is recommended to enhance ADT efficacy"[25] (*p6*)
CANMAT, Kennedy et al., 2018[26]
Quetiapine (Seroquel) at 150 to 300 mg per day is recommended as second line treatment

ADT = antidepressant therapy; CANMAT = Canadian Network for Mood and Anxiety Treatments

Level of evidence ratings

Level 1: Meta-analysis with narrow confidence interval and/or 2 or more RCTs with adequate sample size, preferably placebo controlled

Level 2: Meta-analysis with wide confidence interval and/or 1 or more RCTs with adequate sample size

Level 3: Small sample RCTs or nonrandomized, controlled prospective studies or case series or high-quality retrospective studies

Level 4: Expert opinion/consensus

Definitions for line of treatment ratings

First line: Level 1 or level 2 Evidence, plus clinical support

Second line: Level 3 Evidence or higher, plus clinical support

Third line: Level 4 evidence or higher, plus clinical support

Appendix 5: Additional References of Potential Interest

1. Vento AE, Kotzalidis GD, Cacciotti M, et al. Quetiapine abuse fourteen years later: where are we now? A systematic review. *Subst Use Misuse.* 2019:1-10.