

Health Technology Review

Quetiapine for Schizophrenia

Summary

Main Take-Aways

- Evidence-based guidelines recommend second-generation antipsychotics over first-generation antipsychotics for the management of first-episode schizophrenia.
- Clinical evidence did not clearly indicate which antipsychotics, including quetiapine, are the better choice for treatment of schizophrenia.

Key Messages

What Is the Issue?

- Antipsychotic medications are the mainstay of treatment and the most prescribed drugs for the treatment of schizophrenia. There are 2 classes of antipsychotics — first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs). Quetiapine is an SGA drug. Decision-makers are interested in understanding the clinical efficacy, safety, and place in therapy of quetiapine compared to other medications for the treatment of schizophrenia in adults.

What Did We Do?

- We searched key resources, including journal citation databases, and conducted a focused internet search for relevant evidence published since 2020.

What Did We Find?

- The clinical evidence did not clearly indicate which antipsychotics, including quetiapine, are the better choice for the treatment of schizophrenia.
- Evidence-based guidelines recommend SGAs over FGAs for the management of first-episode psychosis and schizophrenia, as well as for maintenance treatment of schizophrenia. For the treatment of recurrent or relapsing schizophrenia, the guidelines provided diverging recommendations.

What Does This Mean?

- Prescribing antipsychotics for the treatment of schizophrenia should be based on patient characteristics, patient tolerability, patient values, side effect profiles of different antipsychotic medications, and clinician expertise.

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Abbreviations

AE	adverse event
BPRS	Brief Psychiatric Rating Scale
CDSS	Calgary Depression Scale for Schizophrenia
CGI	Clinical Global Impression
CI	confidence interval
FGA	first-generation antipsychotic
JSNPP	Japanese Society of Neuropsychopharmacology
LAI	long-acting injection
LS	least squares
MA	meta-analysis
MD	mean difference
NMA	network meta-analysis
PANSS	Positive and Negative Symptom Scale
RCT	randomized controlled trial
RR	relative risk
SANS	Scale for Assessment of Negative Symptoms
SAPS	Scale for Assessment of Positive Symptoms
SE	standard error
SGA	second-generation antipsychotic
SMD	standardized mean difference
SR	systematic review
VA/DoD	Veterans Affairs/Department of Defense
XR	extended release
YMRS	Young Mania Rating Scale

Context and Policy Issues

What Is Schizophrenia?

Schizophrenia is a mental health condition that involves cognitive, behavioural, and emotional dysfunctions and mood-related symptoms.^{1,2} The symptoms are usually classified into positive symptoms (e.g., hallucination and delusion), negative symptoms (e.g., social withdrawal, appearing emotionless, and self-neglect), disorganized speech and/or behaviour, and cognitive symptoms (e.g., difficulties with attention, processing speed, and executive function).^{1,3} It affects approximately 1% of people living in Canada, with a slightly higher proportion in males than females (56% males and 44% females).⁴

What Are the Medications for the Treatment of Schizophrenia?

There is no cure for schizophrenia. However, the symptoms associated with schizophrenia can be managed by medication. Other modes of management include brain stimulation therapies, psychosocial therapies and supports, physical activity, and diet.³

Antipsychotic medications are the most commonly prescribed drugs for the treatment of schizophrenia.⁵ Antipsychotics are broadly classified into 2 classes — first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) — based on the time of their development.⁵ FGAs, which are also called conventional or typical antipsychotics, are associated with extrapyramidal side effects that include Parkinson-like symptoms (e.g., stiffness, dry mouth, sedation), akathisia (inability to remain still), and dyskinesia (e.g., involuntary, erratic, writhing movements of the face, arms, legs, or trunk).⁶ SGAs, which are also called atypical antipsychotics, appear to be associated with a lower risk of the extrapyramidal side effects associated with FGAs. However, overall, SGAs have more metabolic side effects (e.g., weight gain, risk of diabetes, high cholesterol) than FGAs.⁶

Examples of FGAs include chlorpromazine, levomepromazine, fluphenazine, haloperidol, thioridazine, perphenazine, pipotiazine, thiothixene, and trifluoperazine. Examples of SGAs include quetiapine, sertindole, zotepine, aripiprazole, asenapine, clozapine, lurasidone, olanzapine, risperidone, amisulpride, sulpiride, and ziprasidone. Immediate-release quetiapine is available as 25 mg, 100 mg, 200 mg, and 300 mg quetiapine fumarate tablets, whereas extended-release quetiapine (quetiapine XR) is available as 50 mg, 150 mg, 200 mg, 300 mg, and 400 mg quetiapine fumarate tablets.

Why Is It Important to Do This Review?

Quetiapine is approved for the treatment of schizophrenia based on short-term (6 weeks) efficacy trials.⁷ Data on the long-term efficacy of quetiapine in clinical trials are still limited.⁷ In addition, there have not been systematic evaluations of the clinical efficacy and safety of quetiapine with other relevant comparators for the treatment of schizophrenia.

Objective

To support decision-making on quetiapine for the treatment of schizophrenia, we prepared this Rapid Review report to summarize and critically appraise the available studies on the clinical effectiveness and safety of quetiapine compared with other drug interventions for the treatment of adults with schizophrenia. We also sought to summarize recommendations from evidence-based guidelines on the use of quetiapine for the treatment of adults with schizophrenia.

Research Questions

1. What is the clinical effectiveness and safety of quetiapine versus other drug interventions for adults with schizophrenia?
2. What are the evidence-based guidelines regarding the use and administration of quetiapine for adults with schizophrenia?

Methods

Literature Search Methods

An information specialist conducted a literature search of key resources, including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevancy. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the research questions and selection criteria. The main search concepts were quetiapine and schizophrenia. Search filters were applied to limit retrieval to health technology assessments, systematic reviews (SRs), meta-analyses (MAs), or indirect treatment comparisons, randomized controlled trials (RCTs), controlled clinical trials, or guidelines. The search was completed on March 20, 2025, and was limited to English-language documents published since January 1, 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

Criteria	Description
Population	Adults aged 18 years or older with schizophrenia
Intervention	Quetiapine fumarate immediate-release tablets, quetiapine fumarate extended-release tablets
Comparator	Other drug interventions (e.g., other first- or second-generation antipsychotics, placebo)
Outcomes	• Clinical effectiveness (including long-term effectiveness [> 6 to 8 weeks]) • Safety outcomes (including potential for misuse or diversion) • Guideline recommendations • Patient-reported outcomes
Study designs	RCTs, SRs (including NMAs and MAs), evidence-based guidelines, ^a published HTAs

HTA = health technology assessment; MA = meta-analysis; NMA = network meta-analysis; RCT = randomized controlled trial; SR = systematic review.

^aA guideline is defined as a systematically developed statement or set of statements to help practitioners and patients make decisions about appropriate health care for specific clinical circumstances. A guideline is considered evidence-based if a systematic search of the literature was undertaken to inform the recommendations.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in [Table 1](#) or if they were published before 2020. SRs in which all relevant studies were captured in other more recent or more comprehensive SRs were excluded. Primary studies retrieved by the search were excluded if they were captured in 1 or more included SRs. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)⁸ for SRs, the “Questionnaire to assess the relevance and credibility of a network meta-analysis”⁹ for network meta-analyses (NMA), the Downs and Black checklist¹⁰ for RCTs, and the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument¹¹ for guidelines. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 223 citations were identified in the literature search. Following screening of titles and abstracts, 211 citations were excluded and 12 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 8 publications were excluded for various reasons, and 6 publications met the inclusion criteria and were included in this report. These comprised 3 SRs, 1 RCT, and 2 evidence-based guidelines. [Appendix 1](#) presents the PRISMA¹² flow chart of the study selection.

Summary of Study Characteristics

[Appendix 2](#) provides details regarding the characteristics of the included SRs¹³⁻¹⁵ ([Table 2](#)), the included RCT¹⁶ ([Table 3](#)), and the included evidence-based guidelines^{17,18} ([Table 4](#)).

Included Studies for Research Question 1: What Is the Clinical Effectiveness and Safety of Quetiapine Versus Other Drug Interventions for Adults With Schizophrenia?

Study Design

Three SRs¹³⁻¹⁵ and 1 RCT¹⁶ were included to answer research question 1.

The SR by Dong et al. (2024)¹³ included 60 RCTs and used an NMA to examine the efficacy and adverse events (AEs) of different antipsychotics in the treatment-resistant schizophrenia. The literature search was conducted on April 27, 2020, and updated 3 times, with the last update on January 20, 2023. The median duration of the included trials was 12 weeks (range: 4 weeks to 52 weeks).

The SR by Leucht et al. (2023)¹⁴ included 45 RCTs and used NMA to assess the long-term efficacy and tolerability of antipsychotics in patients with an acute episode of schizophrenia. The literature search was conducted on June 14, 2021, and updated twice, with the last update on March 6, 2022. The included RCTs had at least a 24-week duration (range: 24 weeks to 156 weeks).

The authors of both SRs^{13,14} conducted a random-effects pairwise MA and NMA in a frequentist framework. In the primary outcome (i.e., change in overall symptoms), there were 12 network comparators included in the NMA by Dong et al. (2024)¹³ and 13 network comparators included in the NMA by Leucht et al. (2023).¹⁴ Both NMAs^{13,14} included comparisons of different types of antipsychotics (both FGAs and SGAs) and placebo. Only the relevant comparisons of quetiapine with other antipsychotics are described throughout this report.

The SR by Sherzad Qadir et al. (2023)¹⁵ included 21 RCTs and used an MA to compare the efficacy and tolerability of oral antipsychotics used for the treatment of patients newly diagnosed with schizophrenia. The literature search was restricted to the period from 2000 to 2021. The pooled effect size with a 95% confidence interval (CI) was obtained using a random-effects model or fixed-effects model based the I^2 value, which describes the percentage of total variation across trials that is due to heterogeneity rather than chance or sampling errors. When the I^2 value was 30% or less, the fixed-effects model was used for reporting, and when it was more than 30%, the random-effects model was used for more precise findings. The follow-up period of the included RCTs ranged from 8 weeks to 9 years.

The included RCT by Kim et al. (2024)¹⁶ compared the efficacy and safety of lurasidone, an SGA, with quetiapine XR in acutely psychotic patients with schizophrenia. The study was a randomized, parallel (1:1 ratio), double-blind, active-controlled trial over a 6-week period. The follow-up (week 7) visit took place 1 week after patients' last dose of the study medication. The trial was published in 2024.

Country of Origin

The 3 SRs were conducted by authors in Germany;¹³ in Germany, Switzerland, and the US;¹⁴ and in Australia.¹⁵

The included RCT was conducted by authors in the Republic of Korea.¹⁶

Patient Population

The patient population included in the SR by Dong et al. (2024)¹³ were those with treatment-resistant schizophrenia and a mean age of 38 years, and there were more male (71.5%) than female (28.5%) participants. The mean duration of illness was 14.5 years.

The patient population in the SR by Leucht et al. (2023)¹⁴ consisted of acutely ill adults with schizophrenia and a mean age of 37 years, and there were more male (60%) than female (40%) participants. The mean study duration of the studies included in the SR was 42 weeks.

The SR by Sherzad Qadir et al. (2023)¹⁵ included studies with patients aged 15 years or older (mostly adults) who were newly diagnosed with schizophrenia. Details of the study characteristics and patient characteristics of each primary study were not summarized in the SR but were presented in its supplementary appendix.

The RCT by Kim et al. (2024)¹⁶ recruited adult patients with a diagnosis of schizophrenia who were in a state of acute exacerbation of psychosis symptoms lasting 2 months or less. The mean age of participants was 41.7 years, with more female (63%) than male (37%) participants. The duration of illness ranged from 1 year to ≥ 10 years.

Interventions and Comparators

Both SRs — Dong et al. (2024)¹³ and Leucht et al. (2023)¹⁴ — included all SGAs available in Europe or the US, and a selection of FGAs informed by a survey of international schizophrenia experts.¹⁹

The interventions included in the SR by Sherzad Qadir et al. (2023)¹⁵ were quetiapine, aripiprazole, ziprasidone, risperidone, olanzapine, and haloperidol.

The RCT by Kim et al. (2024)¹⁶ compared the efficacy and safety of lurasidone versus quetiapine XR.

Outcomes

The primary outcome in all included studies (i.e., 3 SRs¹³⁻¹⁵ and 1 RCT¹⁶) was the overall symptoms of schizophrenia as measured by various rating scales such as the Positive and Negative Syndrome Scale (PANSS), the Brief Psychiatric Rating Scale (BPRS), or any other validated scales. Brief Descriptions of the scales used in the included SRs and RCT are as follows:

- PANSS: A 30-item clinician-rated instrument to assess schizophrenia psychopathology, including positive (e.g., hallucinations, delusions) and negative (e.g., blunted affect, social withdrawal) symptoms, as well as general psychopathology (range: 30 to 210 points, lower score is favourable).
- BPRS: Measures psychiatric symptoms such as depression, anxiety, hallucinations, psychosis, and unusual behaviour (range: 18 to 126 points, lower score is favourable).
- Scale for the Assessment of Negative Symptoms (SANS): Measures the levels of negative symptoms of schizophrenia (affective flattening or blunting, alogia [speaking with fewer words], avolition-apathy [lack of motivation and/or lack of interest], anhedonia-asociality [diminished ability to experience pleasure or enjoyment and/or lack of interest in social interaction, attention]) (range: 0 to 125, lower score is favourable).

- Scale for the Assessment of Positive Symptoms (SAPS): Measures levels of positive symptoms of schizophrenia (delusions, hallucinations, and thought disorder) (range: 0 to 170, lower score is favourable).
- Calgary Depression Scale for Schizophrenia (CDSS): Measures the level of depression in people with schizophrenia (range: 0 to 27, lower score is favourable).
- Young Mania Rating Scale (YMRS): Measures manic symptoms (elevated mood, increased motor activity and/or energy, sexual interest, sleep, irritability, speech, language-thought disorder, content, disruptive-aggressive behaviour, appearance, insight) (range: 0 to 60, lower score is favourable).

The secondary outcomes reported in the included studies were positive symptoms; negative symptoms; response to treatment; social functioning; study discontinuation; use of antiparkinsonian medication; and AEs such as sedation, akathisia, increased prolactin level, weight gain, corrected QT interval (QTc) prolongation (longer-than-normal time for the heart's electrical system to recharge between beats), depressive symptoms, and other metabolic parameters. The authors of 2 SRs^{13,14} reported health-related quality of life (HRQoL) as a patient-reported outcome.

Included Studies for Research Question 2: What Are the Evidence-Based Guidelines Regarding the Use and Administration of Quetiapine for Adults With Schizophrenia?

Study Design

The Veterans Affairs/Department of Defense (VA/DoD) clinical practice guideline¹⁷ was developed by a panel of multidisciplinary experts in psychiatry, psychology, internal medicine, nursing, primary care, pharmacy, mental health counselling, and social work. The working group determined the scope of the guideline, crafted key questions to guide the systematic evidence review, identified discussion topics, provided direction on inclusion and exclusion criteria, developed evidence-based recommendations, and determined the strength and category of each recommendation. The working group used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to craft each recommendation and determined its strength (i.e., strong or weak) based on 4 domains:

- confidence in the quality of the evidence
- balance of desirable and undesirable outcomes
- patient values and preferences
- other considerations (e.g., resource use, equity, acceptability, feasibility, subgroup considerations).

The strength of recommendation was described with the general corresponding text as follows:

- Strong for (We recommend...)
- Weak for (We suggest...)
- Neither for nor against (There is insufficient evidence to recommend for or against...)
- Weak against (We suggest against...).

The Japanese Society of Neuropsychopharmacology (JSNPP) clinical practice guideline¹⁸ was developed by a panel of multidisciplinary experts in the treatment and management of schizophrenia. The society's task

force determined the scope of the guideline and determined clinical questions based on the scope. Each working group of the task force conducted an SR for each question, evaluated the body of evidence, and crafted the recommendation drafts for each clinical question. The level of evidence was assessed as strong, moderate, weak, and very weak, based on the degree of certainty of the true effect:

- Strong (A): It is almost certain that the true effect is close to the estimated effect.
- Moderate (B): The true effect is thought to be close to the estimated effect, but the possibility that results may be different remains.
- Weak (C): The true effect is thought to be close to the estimated effect, but the results may be different.
- Very weak (D): The estimated effect is very unclear and is often very different from the true effect.

The strength of recommendation was described with the general corresponding text as follows:

- Action is recommended (labelled as 1)
- Action is not recommended (1)
- Action is suggested or desirable (labelled as 2)
- Action is not suggested or desirable (2).

Country of Origin

The authors of the VA/DoD guideline and of the JSNPP guideline were from the US¹⁷ and Japan,¹⁸ respectively.

Patient Population

The patient population for the VA/DoD guideline¹⁷ consists of adults with schizophrenia, schizophrenia spectrum disorders, schizoaffective disorder, schizophreniform disorder, or first-episode of psychosis being treated in any setting. The intended users of this guideline include primary care providers, mental health providers, and others involved in the health care team for this patient population.

The patient population of the JSNPP guideline¹⁸ is patients with first-episode psychosis and schizophrenia. The intended users of this guideline include specialists in the treatment of schizophrenia and patients, their families, and their supporters.

Interventions and Practice Considered

The VA/DoD guideline¹⁷ provides clinical practice recommendations for the care of patients with schizophrenia using various treatments (e.g., drugs, surgery, lifestyle changes) and approaches (e.g., doses, frequency, methods of administering treatments).

The JSNPP guideline¹⁸ provides recommendations on comprehensive treatments such as pharmacological therapy and psychosocial therapy in collaboration with medical welfare.

Outcomes

Both included guidelines^{17,18} considered all relevant outcomes related to the clinical questions outlined in the guidelines, including short, intermediate, and long-term outcomes.

Summary of Critical Appraisal

The SRs with NMA by Dong et al. (2024)¹³ and by Leucht et al. (2023)¹⁴ included relevant populations, interventions, and outcomes. Both SRs^{13,14} used the same NMA method and approach. This NMA had several strengths contributing to its credibility related to the quality and comprehensiveness of the evidence base, appropriate analysis methods, and reporting and interpretation of results. Specifically, the rationale for the study and the study objectives were clearly stated. The authors of both SRs^{13,14} clearly presented the literature search methods, search terms, search dates, search strategy, and criteria for the SRs, with an attempt to identify and include all relevant RCTs. All included RCTs were assessed for risk of bias using the Cochrane Risk of Bias tool, the results of which were presented and discussed in terms of risk of bias and heterogeneity. The authors of both SRs^{13,14} conducted sensitivity analyses to exclude studies that were not double-blind, studies that presented completer analyses only, studies that did not use operationalized criteria to diagnose schizophrenia, studies with a high risk of bias, and studies that only included children and/or adolescents. Based on the results of the sensitivity analyses, the authors found that the results of the primary analyses were not altered. Study selection, appraisal, and data extraction were performed in duplicate. The primary outcome (i.e., overall symptoms of schizophrenia) was clearly defined. The authors provided a description of analysis methods and models, a description of statistics used, and justification for the statistics. The analysis in the primary model was well-conducted using appropriate methodology. The authors initially performed a pairwise MA using a random-effects model. The statistical heterogeneity among trials was assessed using a visual inspection of forest plots, I^2 statistics, and the Chi-square test. The authors then evaluated the feasibility of conducting an NMA by checking the availability of evidence, transitivity assumption (assessing transitivity involves evaluating the similarity of study characteristics across different comparisons), connectivity (all treatments in the network must be linked together, either directly or indirectly through a shared comparator), and coherence or consistency (level of statistical agreement between direct and indirect evidence) in the network. The authors performed a frequentist random-effects NMA using a multivariate MA. The relative effect estimates were described as standardized mean differences (SMDs) for efficacy-related continuous outcomes and odds ratios for binary outcomes, with their 95% CIs. The presence of incoherence between direct and indirect estimates of the effect was investigated on possible sources of incoherence (e.g., mistakes in data entry, clear differences in study characteristics) and used analytical approaches. The confidence in the relative treatment effects for the primary outcome was evaluated using the Confidence in Network Meta-Analysis framework, which evaluated the credibility of the findings across the domains of within-study bias, across-study bias, indirectness, imprecision, heterogeneity, and incoherence. The authors performed subgroup or subset analysis, and explored the potential sources of heterogeneity or inconsistency using a priori planned subgroup analyses. Network diagrams of connected interventions were presented. Study characteristics and patient characteristics of the included RCTs were presented in an appendix to the SRs. Forest plots were provided summarizing the results for each intervention. Heterogeneity observed in the results was discussed. The authors noted that the robustness of the analysis may be limited due to a high risk of bias from the individual studies and heterogeneity. Thus, the effect estimates may not be driven solely by the assessed interventions.

The SR with MA by Sherzad Qadir et al. (2023)¹⁵ was explicit in its objective, inclusion criteria for the review, and selection of the study designs for inclusion. A study protocol had been published before conducting the review, preventing bias in modifying the methods after the review had been conducted. The literature search strategy was comprehensive and clearly described. The review authors performed study selection in duplicate. This reduced the risk of missing relevant studies and making errors in data extraction. The characteristics of the included studies were described in adequate detail, including objective, design, setting, population, follow-up time, interventions, outcomes, and the source of funding. However, a list of excluded studies and the reasons for exclusion were not provided. Therefore, it was not possible to assess whether any relevant articles were excluded and, if so, for what reasons. The methodological quality of the included studies was assessed using the Cochrane Risk of Bias tool. A MA was conducted for both continuous and dichotomous outcomes, which were reported as a mean difference (MD) and relative risk (RR), respectively, with a 95% CI. A subgroup analysis was performed to explore diverse outcomes or to address particular inquiries concerning specific categories of interventions. The review authors provided a discussion of the heterogeneity observed in the results. The review authors declared that this research received no external funding and that there were no potential conflicts of interest.

For reporting, the authors of the included RCT by Kim et al. (2024)¹⁶ clearly described the objective of the study, the intervention of interest, the main outcomes, and the main findings of the study. The authors clearly described the patient characteristics at baseline, and there were no group differences in the demographics of the randomized participants. The existence of potential confounders was low. Actual P values and AEs of the intervention were reported. In terms of external validity, the patients included in the RCT may represent the entire eligible population, given that they were recruited from multiple centres. The treatment settings (i.e., hospitals) appeared to be representative of the treatment received by most of the patients in Korea. However, the generalizability of the patient population and treatment settings to the context in Canada remains questionable. For internal validity related to bias, the study was a randomized, double-blind, active-controlled study that took place over a 6-week period in which all patients were followed up for the same period of time, which took place 1 week after the patients' last dose of the study medication. Statistical tests were used appropriately, and the main outcome measures were accurate and reliable. Compliance with the intervention was reliable, given that 95% of the patients completed the study. The primary end point, which was the overall symptoms of schizophrenia, was accurately measured using PANNS. For internal validity related to confounding, patients in both intervention groups appeared to be recruited from the same population and over the same period of time, and methods of randomization and allocation concealment were described. However, about one-third of the intention-to-treat population was excluded, and the reasons for exclusion were not reported. Those patients were not taken into account in the analysis, and the primary analysis was based on the per-protocol set, leading to a potentially high risk of reporting bias. Because a sample size calculation was not performed, real effects may not be detected due to a lack of power.

For reporting, both included guidelines^{17,18} were explicit in terms of scope and purpose (i.e., objectives, health questions and populations) and had a clear presentation of recommendations (i.e., specific, unambiguous, and easy to find key recommendations, with options for managing the different conditions or health issues). In terms of the involvement of interested parties, the authors of both guidelines^{17,18} clearly defined target

users and the development groups, and reported that the views and preferences of the patients were sought. The methodology for the development of the guidelines was robust. The authors of both guidelines^{17,18} clearly reported methods for evidence collection, criteria for selection, and methods for evidence synthesis. There were explicit links between recommendations and the supporting evidence and the methods for formulating the recommendations. Also, the authors of both guidelines^{17,18} considered health benefits and risks of side effects when formulating the recommendations. Both guidelines^{17,18} will be updated when new important information and appropriate comments are received, though specific dates were not indicated. Both guidelines^{17,18} were reviewed independently by relevant professional experts, professional colleges, and societies and through public consultation. However, there were some limitations related to guideline implementation and applicability. Specifically, facilitators and barriers to application and monitoring or auditing criteria were unclear. Both guidelines^{17,18} provide advice and/or tools on how the recommendations can be put into practice. For editorial independence, the authors of the guidelines^{17,18} declared the competing interests of all guideline development group members and disclosed that the views of the funding body had no influence on the content of the guidelines. Overall, the included guidelines^{17,18} were robust in terms of scope and purpose, involvement of interested parties, rigour of development, clarity of presentation, and editorial independence.

Additional details regarding the strengths and limitations of the included SRs¹³⁻¹⁵ are provided in [Table 5](#), the RCT¹⁶ in [Table 6](#), and the guidelines^{17,18} in [Table 7](#) of [Appendix 3](#).

Summary of Findings

[Appendix 4](#) presents the main study findings, which are summarized by outcome. Only comparisons of quetiapine with other antipsychotics are presented.

Clinical Effectiveness and Safety of Quetiapine Versus Other Drug Interventions for Adults With Schizophrenia

Overall Symptoms of Schizophrenia

The authors of 3 included SRs¹³⁻¹⁵ and 1 RCT¹⁶ reported on overall symptoms of schizophrenia ([Table 8](#)). In the SRs, the results were reported as an SMD with a 95% CI of the changes from baseline. In the included RCT, the changes from baseline were presented as least squares (LS) mean plus or minus the standard error (SE) of the mean.

Efficacy and safety of antipsychotics in treatment-resistant schizophrenia: In the SR with NMA by Dong et al. (2024),¹³ clozapine (SMD = -0.44; 95% CI, -0.66 to -0.22) and olanzapine (SMD = -0.40; 95% CI, -0.67 to -0.13) were more effective than quetiapine. There were no clear differences between quetiapine and other antipsychotics (i.e., levomepromazine, amisulpride, zotepine, risperidone, ziprasidone, haloperidol, fluphenazine, chlorpromazine, and sertindole) according to the 95% CI. The results were based on 45 studies with 12 interventions involving 5,303 patients.

Long-term efficacy and safety of antipsychotics in acutely ill adults with schizophrenia: In the SR with NMA by Leucht et al. (2023),¹⁴ lurasidone (SMD = -0.42; 95% CI, -0.71 to -0.13) and olanzapine (SMD = -0.25; 95% CI, -0.38 to -0.12) appeared to be more effective than quetiapine. The differences between

quetiapine and other antipsychotics (i.e., amisulpride, perphenazine, clozapine, risperidone, aripiprazole, zotepine, haloperidol, paliperidone, iloperidone, asenapine, and ziprasidone) were uncertain. The results were based on 23 studies with 9,814 patients.

Efficacy and safety of antipsychotics for treatment of newly diagnosed patients with schizophrenia:

The SR with MA by Sherzad Qadir et al. (2023)¹⁵ presented 2 sets of comparisons using different rating scales to measure symptoms of schizophrenia:

- Aripiprazole versus quetiapine (3 studies): Aripiprazole appeared to be more effective than quetiapine under BPRS (MD = -4.77; 95% CI, -7.83 to -1.71), but the differences between quetiapine and aripiprazole were not statistically significant according to other rating scales (i.e., Clinical Global Impression [CGI], SANS, SAPS, CDSS, and YMRS).
- Ziprasidone versus quetiapine (3 studies): There were no statistically significant differences between quetiapine and ziprasidone assessed by various rating scales (i.e., CGI, BPRS, SANS, SAPS, CDSS, and YMRS).

The RCT by Kim et al. (2024)¹⁶ verified the noninferiority of lurasidone to quetiapine XR, given that the lower limit of the 95% 2-sided CI for the difference in score change did not exceed the predefined noninferiority margin of -8.99. The difference in PANSS total score between groups was -0.91 (95% CI, -6.31 to 4.53). Thus, the noninferiority of lurasidone compared to quetiapine XR was verified, given that the lower limit of the CI did not exceed the noninferiority margin. Under CGI scores, the results showed statistically significant differences between groups, which were observed at 4 weeks and 6 weeks of treatment, favouring lurasidone.

Positive Symptoms

The authors of 1 included SR¹³ and 1 RCT¹⁶ reported on positive symptoms ([Table 9](#)). In the SR, the results were reported as SMD with 95% CI of the changes from baseline. In the included RCT, the changes from baseline were presented as LS means plus or minus the SE of the mean.

Efficacy of antipsychotics in treatment-resistant schizophrenia: In the SR with NMA by Dong et al. (2024),¹³ amisulpride (SMD = -1.48; 95% CI, -0.16 to -0.22), clozapine (SMD = -0.61; 95% CI, -0.90 to -0.32), risperidone (SMD = -0.51; 95% CI, -0.82 to -0.20), and olanzapine (SMD = -0.49; 95% CI, -0.78 to -0.19) were found to be more effective than quetiapine for treatment of positive symptoms. Quetiapine showed no clear difference from levomepromazine, ziprasidone, haloperidol, sertindole, chlorpromazine, and fluphenazine. The results were based on 39 studies with 4,649 patients.

Efficacy and safety of antipsychotics for the treatment of newly diagnosed patients with schizophrenia: The results from the RCT by Kim et al. (2024)¹⁶ showed no statistically significant difference between lurasidone and quetiapine in terms of PANSS positive subscale scores.

Negative Symptoms

The authors of 1 included SR¹³ and 1 RCT¹⁶ reported on negative symptoms ([Table 10](#)). In the SR, the results were reported as SMD with 95% CI of the changes from baseline. In the included RCT, the changes from baseline were presented as LS mean plus or minus the SE of the mean.

Efficacy and safety of antipsychotics in treatment-resistant schizophrenia: In the SR with NMA by Dong et al. (2024),¹³ the differences in negative symptoms between quetiapine and most antipsychotics (i.e., amisulpride, clozapine, zotepine, olanzapine, fluphenazine, levomepromazine, ziprasidone, risperidone, haloperidol, and sertindole) were uncertain, except that chlorpromazine was less effective than quetiapine (SMD = -0.66; 95% CI, -1.28 to -0.05). The results were based on 42 studies with 4,863 patients.

Efficacy and safety of antipsychotics for the treatment of newly diagnosed patients with schizophrenia: The results from the RCT by Kim et al. (2024)¹⁶ showed no statistically significant difference between lurasidone and quetiapine in terms of PANSS negative subscale scores. The study included 210 patients.

Response to Treatment

The authors of 1 included SR¹³ reported on response to treatment ([Table 11](#)). The results were reported as RR with 95% CI.

Efficacy and safety of antipsychotics in treatment-resistant schizophrenia: The differences in response to treatment between quetiapine and all other antipsychotics under investigation (i.e., sulpiride, levomepromazine, aripiprazole, trifluoperazine, perphenazine, clozapine, thioridazine, olanzapine, ziprasidone, amisulpride, risperidone, chlorpromazine, haloperidol, fluphenazine, sertindole, thiothixene, fluphenazine long-acting injection [LAI], and pipotiazine LAI) were uncertain. The results were based on 46 studies with 6,043 patients.

Social Functioning

The authors of 1 included SR¹⁴ reported on social functioning ([Table 12](#)). The results were reported as SMD with 95% CI of the changes from baseline.

Long-term efficacy and safety of antipsychotics in initially acutely ill adults with schizophrenia: In 5 studies with 1,390 patients, there were no clear differences in social functioning between quetiapine and other antipsychotics (i.e., olanzapine, amisulpride, risperidone, and paliperidone).

Quality of Life

The authors of 2 SRs^{13,14} reported on quality of life ([Table 13](#)). The results were reported as SMD with 95% CI of the changes from baseline.

Efficacy and safety of antipsychotics in treatment-resistant schizophrenia: In the SR by Dong et al. (2024),¹³ 8 studies with 1,159 patients provided data on QoL. Because conducting an NMA was not feasible given that there were no closed loops in the network, pairwise MA results were presented instead. The results showed no statistically significant differences between quetiapine and fluphenazine, between quetiapine and risperidone, and between quetiapine and chlorpromazine.

Long-term efficacy and safety of antipsychotics in initially acutely ill adults with schizophrenia: In the SR by Leucht et al. (2023), there were no clear differences in QoL between quetiapine and other antipsychotics (i.e., zotepine, amisulpride, olanzapine, asenapine, ziprasidone, perphenazine, haloperidol, and risperidone). The results were based on 8 studies with 2,949 patients.

All-Cause Discontinuation

The authors of 2 SRs^{13,14} reported on all-cause discontinuation ([Table 14](#)). The results were reported as RR with 95% CI.

Efficacy and safety of antipsychotics in treatment-resistant schizophrenia: In the SR by Dong et al. (2024),¹³ quetiapine showed no clear difference in all-cause discontinuation compared to other antipsychotics (i.e., sulpiride, levomepromazine, olanzapine, clozapine, ziprasidone, risperidone, sertindole, chlorpromazine, zotepine, haloperidol, fluphenazine LAI, pipotiazine LAI). The results were based on 54 studies with 6,228 patients.

Long-term efficacy and safety of antipsychotics in initially acutely ill adults with schizophrenia: In the SR by Leucht et al. (2023),¹⁴ long-term treatment with quetiapine resulted in a higher frequency of all-cause discontinuation compared with amisulpride (RR = 0.70; 95% CI, 0.54 to 0.88), aripiprazole (RR = 0.73; 95% CI, 0.57 to 0.89), risperidone (RR = 0.82; 95% CI, 0.68 to 0.95), and perphenazine (RR = 0.82; 95% CI, 0.67 to 0.97). The differences in all-cause discontinuation between quetiapine and other antipsychotics (i.e., lurasidone, zotepine, haloperidol, ziprasidone, asenapine, paliperidone, thiothixene, fluspirilene, pimozide, fluphenazine, olanzapine) were uncertain. The results were based on 41 studies with 8,882 patients.

Discontinuation Due to Lack of Efficacy

The authors of 2 included SRs^{13,15} reported on discontinuation due to lack of efficacy ([Table 15](#)). The results were reported as RR with 95% CI.

Efficacy and safety of antipsychotics in treatment-resistant schizophrenia: In the SR by Dong et al. (2024),¹³ treatment with quetiapine resulted in no clear differences in discontinuation due to lack of efficacy compared to other antipsychotics (i.e., fluphenazine LAI, ziprasidone, pipotiazine LAI, sulpiride, amisulpride, chlorpromazine, risperidone, sertindole, haloperidol, zotepine, trifluoperazine, thioridazine, and fluphenazine), with the exception of clozapine (RR = 0.28; 95% CI, 0.14 to 0.53) and olanzapine (RR = 0.52; 95% CI, 0.27 to 0.95), which were superior than quetiapine. The results were based on 48 studies with 5,142 patients.

Efficacy and safety of antipsychotics for treatment of newly diagnosed patients with schizophrenia:

The SR by Sherzad Qadir et al. (2023)¹⁵ with pairwise MA showed that discontinuation due to lack of efficacy was statistically significantly more frequent with quetiapine compared to olanzapine (RR = 3.48; 95% CI, 3.05 to 5.91), ziprasidone (RR = 2.05; 95% CI, 1.57 to 2.68), and aripiprazole (RR = 3.69; 95% CI, 2.56 to 5.32). Discontinuation due to lack of efficacy was not statistically significant between quetiapine and risperidone.

Discontinuation Due to AEs

The authors of 2 included SRs^{13,15} reported on discontinuation due to AEs ([Table 16](#)). The results were reported as RR with 95% CI.

Efficacy and safety of antipsychotics in treatment-resistant schizophrenia: In the SR by Dong et al. (2024),¹³ there were no clear differences in treatment discontinuation due to AEs between quetiapine and most antipsychotics (i.e., fluphenazine, olanzapine, risperidone, haloperidol, clozapine, sertindole, zotepine,

ziprasidone, thioridazine, sulpiride, levomepromazine, trifluoperazine, thiothixene, amisulpride, pipotiazine LAI, and fluphenazine LAI), with the exception being that chlorpromazine (RR = 0.51; 95% CI, 0.26 to 0.95) was less tolerable than quetiapine. The results were based on 50 studies with 5,103 patients.

Efficacy and safety of antipsychotics for treatment of newly diagnosed patients with schizophrenia:

The SR by Sherzad Qadir et al. (2023)¹⁵ with pairwise MA showed that discontinuation due to AEs was statistically significantly less frequent with quetiapine compared with risperidone (RR = 0.44; 95% CI, 0.21 to 0.89), ziprasidone (RR = 0.34; 95% CI, 0.22 to 0.51), and haloperidol (RR = 0.43; 95% CI, 0.22 to 0.84).

Use of Antiparkinsonian Medication

The authors of 2 SRs^{13,14} reported on use of antiparkinsonian medication ([Table 17](#)). The results were reported as RR with 95% CI.

Efficacy and safety of antipsychotics in treatment-resistant schizophrenia: In the SR by Dong et al. (2024),¹³ quetiapine showed no clear difference in the use of antiparkinsonian medication compared to most antipsychotics (i.e., levomepromazine, thioridazine, sulpiride, clozapine, amisulpride, olanzapine, ziprasidone, pipotiazine LAI, chlorpromazine, fluphenazine LAI, risperidone, and trifluoperazine), with the exception that quetiapine was associated with less use of antiparkinsonian medication compared with fluphenazine (RR = 0.37; 95% CI, 0.11 to 0.99) and haloperidol (RR = 0.34; 95% CI, 0.13 to 0.77). The results were based on 24 studies with 2,061 patients.

Long-term efficacy and safety of antipsychotics in initially acutely ill adults with schizophrenia:

In the SR by Leucht et al. (2023),¹⁴ long-term treatment with quetiapine was associated with less use of antiparkinsonian medication compared with a number of antipsychotics, including amisulpride (RR = 0.43; 95% CI, 0.20 to 0.86), risperidone (RR = 0.35; 95% CI, 0.19 to 0.65), paliperidone (RR = 0.35; 95% CI, 0.18 to 0.69), ziprasidone (RR = 0.35; 95% CI, 0.183 to 0.68), perphenazine (RR = 0.34; 95% CI, 0.17 to 0.67), haloperidol (RR = 0.24; 95% CI, 0.12 to 0.46), and asenapine (RR = 0.18; 95% CI, 0.06 to 0.51). The differences between quetiapine and other antipsychotics such as aripiprazole, zotepine, and olanzapine were uncertain. The results were based on 14 studies with 7,794 patients.

Sedation

The authors of 2 SRs^{13,14} reported sedation ([Table 18](#)). The results were reported as RR with 95% CI.

Efficacy and safety of antipsychotics in treatment-resistant schizophrenia: In the SR by Dong et al. (2024),¹³ quetiapine showed no clear differences in sedation compared with other antipsychotics (i.e., thiothixene, ziprasidone, sertindole, sulpiride, olanzapine, fluphenazine, haloperidol, risperidone, trifluoperazine, chlorpromazine, thioridazine, and levomepromazine), with the exception that quetiapine was associated with higher risk of sedation than amisulpride (RR = 1.72; 95% CI, 1.01 to 3.85) and lower risk of sedation than clozapine (RR = 0.82; 95% CI, 0.65 to 0.96). The results were based on 30 studies with 4,079 patients.

Long-term efficacy and safety of antipsychotics in initially acutely ill adults with schizophrenia: In the SR by Leucht et al. (2023),¹⁴ there were no clear differences in sedation between quetiapine and other

antipsychotics (i.e., lurasidone, ziprasidone, haloperidol, amisulpride, asenapine, perphenazine, risperidone, paliperidone, zotepine, and olanzapine), with the exception that quetiapine had a higher risk of sedation compared to aripiprazole (RR = 1.89; 95% CI, 1.08 to 3.03). The results were based on 16 studies with 8,096 patients.

Akathisia (Inability to Remain Still)

The authors of 1 SR¹⁴ reported on akathisia ([Table 19](#)). The results were reported as RR with 95% CI.

Long-term efficacy and safety of antipsychotics in initially acutely ill adults with schizophrenia: In the SR by Leucht et al. (2023),¹⁴ there were no clear differences in the risk of akathisia between quetiapine and other antipsychotics such as paliperidone, amisulpride, aripiprazole, risperidone, perphenazine, ziprasidone, and olanzapine. Quetiapine had a lower risk of akathisia compared with haloperidol (RR = 0.43; 95% CI, 0.23 to 0.81), asenapine (RR = 0.40; 95% CI, 0.17 to 0.86), and lurasidone (RR = 0.22; 95% CI, 0.05 to 0.80). The results were based on 16 studies with 7,916 patients.

Increased Prolactin Levels

The authors of 2 SRs^{13,14} reported on increased prolactin levels ([Table 20](#)). The results were reported as an MD with 95% CI.

Efficacy and safety of antipsychotics in treatment-resistant schizophrenia: In the SR by Dong et al. (2024),¹³ quetiapine was associated with less of an effect on prolactin levels than olanzapine (MD = -13.19; 95% CI, -21.95 to -4.43), chlorpromazine (MD = -20.57; 95% CI, -32.74 to -8.39), haloperidol (MD = -23.96; 95% CI, -35.92 to -12.00), and risperidone (MD = -34.24; 95% CI, -43.51 to -24.96). The differences in increased prolactin levels between quetiapine and other antipsychotics such as ziprasidone, clozapine, and fluphenazine were uncertain. The results were based on 18 studies with 1,533 patients.

Long-term efficacy and safety of antipsychotics in initially acutely ill adults with schizophrenia: In the SR by Leucht et al. (2023),¹⁴ the data of direct and indirect evidence for this outcome were inconsistent. The results were therefore focused on pairwise MA. Quetiapine was associated with higher average prolactin levels than risperidone (MD = -24.70; 95% CI, -37.41 to -11.99), but there were no statistically significant differences between quetiapine and other antipsychotics such as olanzapine, lurasidone, ziprasidone, and perphenazine.

Weight Gain

The authors of 2 SRs^{13,14} reported on weight gain ([Table 21](#)). The results were reported as a MD with 95% CI.

Efficacy and safety of antipsychotics in treatment-resistant schizophrenia: In the SR by Dong et al. (2024),¹³ quetiapine was associated with less weight gain compared to olanzapine (MD = -2.86; 95% CI, -4.14 to -1.21) and clozapine (MD = -2.70; 95% CI, -4.17 to -1.23). There were no clear differences in weight gain between quetiapine and other antipsychotics (i.e., haloperidol, fluphenazine, chlorpromazine, levomepromazine, amisulpride, risperidone, and sertindole). The results were based on 20 studies with 3,393 patients.

Long-term efficacy and safety of antipsychotics in initially acutely ill adults with schizophrenia: In the SR by Leucht et al. (2023),¹⁴ the network for this outcome was inconsistent. The results of the pairwise MA showed that quetiapine was associated with less weight gain compared to olanzapine (MD = -3.76; 95% CI, -6.10 to -1.42). There were no statistically significant differences in weight gain between quetiapine and other antipsychotics such as ziprasidone, perphenazine, lurasidone, and risperidone.

QTc Prolongation

The authors of 2 SRs^{13,14} reported on QTc prolongation ([Table 22](#)). The results were reported as MD with 95% CI.

Efficacy and safety of antipsychotics in treatment-resistant schizophrenia: In the SR by Dong et al. (2024),¹³ data on QTc prolongation were scarce and the network was disconnected. Pairwise MA showed that chlorpromazine was associated with more QTc prolongation than quetiapine (MD = 19.80; 95% CI, 12.10 to 27.50).

Long-term efficacy and safety of antipsychotics in initially acutely ill adults with schizophrenia: In the SR by Leucht et al. (2023),¹⁴ quetiapine was associated with larger average QTc prolongation than paliperidone (MD = -7.40; 95% CI, -13.19 to -1.62), risperidone (MD = -5.30; 95% CI, -10.21 to -0.40), and olanzapine (MD = -5.18; 95% CI, -9.81 to -0.55). The differences in QTc prolongation between quetiapine and other antipsychotics (i.e., asenapine, perphenazine, ziprasidone, amisulpride, and lurasidone) were uncertain. The results were based on 7 studies with 4,060 patients.

Depressive Symptoms

The authors of 1 SR¹⁴ reported on depressive symptoms ([Table 23](#)). The results were reported as SMD with 95% CI.

Long-term efficacy and safety of antipsychotics in initially acutely ill adults with schizophrenia: In the SR by Leucht et al. (2023),¹⁴ most results of quetiapine compared with other antipsychotics (i.e., lurasidone, olanzapine, perphenazine, aripiprazole, risperidone, amisulpride, ziprasidone, asenapine, haloperidol, and paliperidone) were uncertain. The results were based on 11 studies with 6,686 patients.

Other Side Effects

One included SR¹⁵ and 1 RCT¹⁶ presented the results of different AEs in the comparisons of aripiprazole versus quetiapine, quetiapine versus ziprasidone, olanzapine versus quetiapine, risperidone versus quetiapine, and lurasidone versus quetiapine ([Table 24](#)).

Aripiprazole versus quetiapine:

- Sleepiness (RR = 0.58; 95% CI, 0.45 to 0.75), increased duration of sleep (RR = 0.53; 95% CI, 0.36 to 0.78), galactorrhea (milk production from the breast unrelated to pregnancy or lactation) (RR = 0.10; 95% CI, 0.01 to 0.78), and erectile dysfunction (RR = 0.20; 95% CI, 0.07 to 0.56) occurred less frequently with aripiprazole than with quetiapine.
- Aripiprazole was associated with a higher incidence of tremors compared to quetiapine (RR = 3.07; 95% CI, 1.07 to 8.77).

- There were no clear differences between quetiapine and aripiprazole for other AEs such as concentration difficulties, increased fatigability, depression, restlessness, rigidity, increased salivation, constipation, vertigo, amenorrhea, diminished sexual desire, orgasmic dysfunction, ejaculatory dysfunction, weight gain, and memory impairment.

Quetiapine versus ziprasidone:

- There were no clear differences in most AEs (i.e., concentration difficulties, increased fatigability, sleepiness, memory impairment, depression, restlessness, increased duration of sleep, rigidity, tremors, increased salivation, constipation, diminished sexual desire, orgasmic dysfunction, ejaculatory dysfunction, and weight gain) between quetiapine and ziprasidone.
- Vertigo (RR = 0.13; 95% CI, 0.02 to 0.99) and amenorrhea (RR = 0.11; 95% CI, 0.02 to 0.50) occurred more frequently with ziprasidone than with quetiapine.

Olanzapine versus quetiapine:

- There were no clear differences in most AEs (i.e., sleepiness, increased duration of sleep, akinesia, constipation, galactorrhea, diminished sexual desire, and orgasmic dysfunction) between olanzapine and quetiapine.
- Weight gain (RR = 1.34; 95% CI, 1.15 to 1.56) occurred more frequently with olanzapine than with quetiapine.

Risperidone versus quetiapine:

- There were no clear differences between risperidone and quetiapine in weight gain, sleepiness, akinesia, constipation, galactorrhea, and orgasmic dysfunction.
- Quetiapine was associated with a higher incidence of increased duration of sleep (RR = 0.54; 95% CI, 0.32 to 0.91) compared to risperidone.

Lurasidone versus quetiapine:

- Quetiapine was associated with higher risk of weight gain (1.65 kg versus -0.24 kg), elevation of serum glucose levels (2.77 mg/dL versus 1.69 mg/dL), increased total cholesterol levels (11.13 mg/dL versus -3.92 mg/dL), increased LDL-cholesterol levels (5.32 mg/dL versus -4.84 mg/dL), and increased triglyceride levels (24.21 mg/dL versus 0.63 mg/dL) compared with lurasidone.
- Lurasidone was associated with a higher incidence of nausea (16.7% versus 2.9%) and increased blood prolactin (7.8% versus 1.9%) compared with quetiapine.
- There were no clear differences between lurasidone and quetiapine in akathisia, dizziness, somnolence, tremor, constipation, anxiety, muscle rigidity, HDL-cholesterol, electrocardiography, extrapyramidal side effects (involuntary movements induced by medications), and suicidal ideation and behaviour.

Evidence-Based Guidelines Regarding the Use and Administration of Quetiapine for Adults With Schizophrenia

A summary of recommendations from the included guidelines is presented in [Table 25](#) of [Appendix 4](#).

Management of First-Episode Psychosis and Schizophrenia

- The VA/DoD guideline¹⁷ recommends the use of an antipsychotic medication other than clozapine (strong recommendation, categorized as reviewed, newly added).
- Similarly, the JSNPP guideline¹⁸ recommends SGAs over FGAs (degree 2 recommendation based on strong-quality evidence).
- The JSNPP guideline¹⁸ presents optimal doses of various antipsychotics, including quetiapine, which has been reported to be effective at 311.4 mg/day to 506 mg/day. However, the guideline noted that treatment discontinuation rates of quetiapine were higher than other antipsychotics in long-term trials (recommendation with no reported degree based on moderate- to weak-quality evidence).
- The JSNPP guideline¹⁸ suggests an optimal period of 2 to 4 weeks of treatment for determining the therapeutic response of antipsychotics in first-episode psychosis (degree 2 recommendation based on very weak-quality evidence).
- Both guidelines^{17,18} indicated that the choice of antipsychotic medication should be based on patient characteristics and side effect profiles of different antipsychotic medications.

Maintenance Treatment of Schizophrenia

- The VA/DoD guideline¹⁷ recommends the use of antipsychotic medication for the maintenance treatment of schizophrenia to prevent relapse and hospitalization (strong recommendation, categorized as reviewed, newly added).
- The JSNPP guideline¹⁸ recommends SGAs over FGAs for reducing the relapse rate (recurrence of a psychotic episode after a period of response to treatment) or for continuing treatment in the maintenance phase (degree 2 recommendation based on moderate-quality evidence).
- The JSNPP guideline¹⁸ recommends continuing the administration of antipsychotics for at least 1 year to prevent the recurrence of first-episode psychosis (degree 1 recommendation based on strong-quality evidence).
- Both guidelines^{17,18} indicated that the choice of antipsychotic medication should be based on patient characteristics and side effect profiles of different antipsychotic medications.

Treatment of Recurrence or Relapse of Schizophrenia

- The VA/DoD guideline¹⁷ suggests switching to another antipsychotic medication for patients who do not respond to (or tolerate) the current medication (weak recommendation, categorized as reviewed, newly added).
- In contrast, the JSNPP guideline¹⁸ suggests increasing the dose rather than switching the antipsychotic (Degree 2 recommendation based on weak-quality evidence).
- The JSNPP guideline¹⁸ noted that, among antipsychotics, quetiapine is effective at doses of more than 150 mg/day, or of more than 250 mg/day at the time of recurrence or relapse of schizophrenia (recommendation with no reported degree based on moderate- to weak-quality evidence).

Limitations

Evidence Gaps

The included clinical studies (i.e., 2 SRs^{13,14} with NMA, 1 SR¹⁵ with MA, and 1 RCT¹⁶) on antipsychotic drugs covered different areas of treatment of adults with schizophrenia, including treatment of patients newly diagnosed with schizophrenia, long-term maintenance treatment, and treatment-resistant schizophrenia. Most of the outcomes assessed by the included studies focused mainly on clinical efficacy and safety outcomes. However, the evidence on HRQoL and social functioning, which are outcomes important to patients, is too scarce to make any conclusions.

Generalizability

The findings of the included clinical studies and the recommendations of the guidelines could be generalizable to the adult population with schizophrenia living in Canada.

Certainty of Evidence

The 2 SRs^{13,14} with NMA had several limitations. First, there were some inconsistencies in the analyses of certain outcomes, which was mainly due to disagreement between direct and indirect evidence. To find the reason for inconsistency, the authors of the SRs^{13,14} performed a sensitivity analysis by excluding some studies. Second, there was substantial heterogeneity in patient characteristics and in the definition of treatment-resistant schizophrenia, which varied from partial to substantial treatment resistance. However, subgroup analyses performed across different criteria of definitions did not reveal significant differences from the main analysis. Third, although the search was comprehensive, there was potential publication bias as indicated by the pairwise MA funnel plot. Fourth, the scarcity of available evidence with several comparisons lay outside the networks, resulting in thinly connected networks and low statistical power to detect possible differences. Finally, the confidence in the evidence was generally moderate to low, meaning the results could potentially change if more evidence becomes available.

The SR¹⁵ with MA had several limitations. First, heterogeneity existed among studies with respect to patient characteristics, reported numerical data, number of outcome measures, and rating scales used to measure the outcomes. Second, the scarcity of evidence in some subgroups meant that it was not possible to generalize the findings to a wider population. Third, the SR did not consider confounding factors such as age, gender, or ethnicity, which may impact the outcome measures such as response to treatment and side effects. Fourth, the findings are not applicable to patients with chronic psychosis, because the included patients were either antipsychotic-naïve or exposed to short-term antipsychotic use (0 to 16 weeks).

The included RCT¹⁶ had several limitations. First, treatment duration was short (i.e., 6 weeks), so the findings could not be extrapolated to a longer time period. Second, the study had a mixed population that may have included patients with treatment-resistant schizophrenia. Patients included in the study had an illness duration of at least 1 year, and more than one-third had the disease for more than 10 years.

Although the guidelines^{17,18} included in this report were generally of high methodological quality, the strength of some relevant recommendations was weak due to low-quality evidence.

Taken together, despite several limitations of the included SRs¹³⁻¹⁵ and RCT,¹⁶ the findings were derived from a collective large body of evidence that aligned with the included guidelines,^{17,18} which provided comprehensive recommendations and supporting evidence.

Conclusions and Implications for Decision- or Policy-Making

This review included 3 SRs,¹³⁻¹⁵ 1 RCT,¹⁶ and 2 evidence-based guidelines,^{17,18} all of which were relevant to the research questions.

Clinical Efficacy and Safety of Treatment With Quetiapine

Quetiapine demonstrated moderate efficacy for schizophrenia symptoms, showing that it was less effective than olanzapine and lurasidone (in acutely ill adults with schizophrenia) and less effective than clozapine and olanzapine (in patients with treatment-resistant schizophrenia) for overall symptoms, but comparable to most other antipsychotics (e.g., risperidone, ziprasidone). It showed no clear benefit for negative symptoms, social functioning, or quality of life compared to other antipsychotics. Among newly diagnosed patients with schizophrenia, quetiapine had higher discontinuation rates due to lack of efficacy compared to olanzapine, aripiprazole, and ziprasidone, but lower discontinuation due to AEs compared to risperidone, ziprasidone, and haloperidol. Quetiapine was associated with less use of antiparkinsonian medication and lower prolactin increases than several antipsychotics; comparable sedation risk to other antipsychotics (with the exception of amisulpride and aripiprazole); comparable weight gain to other antipsychotics; and more QTc prolongation than paliperidone, risperidone, and olanzapine.

In newly diagnosed patients with schizophrenia (evidence from 1 SR with MA¹⁵ and 1 RCT¹⁶):

- There were no clear differences in overall symptoms (including positive and negative symptoms) assessed by various rating scales between quetiapine and other antipsychotics such as aripiprazole, ziprasidone, and lurasidone.
- Treatment with quetiapine was associated with higher rates of discontinuation due to lack of efficacy compared to olanzapine, ziprasidone, and aripiprazole.
- Discontinuation due to AEs was less frequent with quetiapine than with risperidone, ziprasidone, and haloperidol.
- For AEs, quetiapine was associated with high rates of sleepiness compared with aripiprazole and risperidone, and higher rates of weight gain and metabolic outcomes compared to lurasidone. Quetiapine was associated with a lower incidence of tremors compared to aripiprazole, less frequent incidence of vertigo and amenorrhea compared to ziprasidone, and lower rates of nausea and blood prolactin increases compared to lurasidone.

In long-term treatment (at least 6-month duration) (evidence from 1 SR with NMA¹⁴):

- Quetiapine was less effective than lurasidone and olanzapine in overall symptoms, but the differences between quetiapine and other antipsychotics were uncertain.

- There were no clear differences in social functioning and QoL between quetiapine and other antipsychotics.
- Long-term treatment with quetiapine resulted in higher rates of all-cause discontinuation compared with amisulpride, aripiprazole, risperidone, and perphenazine. Discontinuation due to lack of efficacy and due to AEs was not reported.
- Long-term treatment with quetiapine was associated with less use of antiparkinsonian medication compared with a number of antipsychotics.
- For AEs, long-term treatment of quetiapine was associated with a higher risk of sedation compared to aripiprazole, higher average prolactin levels than risperidone, and higher average QTc prolongation than paliperidone, risperidone, and olanzapine. In contrast, long-term treatment with quetiapine was associated with less weight gain compared with olanzapine and clozapine. There were no clear differences in depressive symptoms between quetiapine and other antipsychotics.

In treatment-resistant schizophrenia (evidence from 1 SR with NMA¹³):

- Quetiapine was less effective than clozapine and olanzapine in terms of managing overall symptoms. For positive symptoms, quetiapine was less effective than amisulpride, clozapine, risperidone, and olanzapine. For negative symptoms, quetiapine was less effective than chlorpromazine. The differences in response to treatment between quetiapine and all other antipsychotics investigated were uncertain.
- Studies on QoL were scarce and not feasible for NMA. The pairwise MA results showed no statistically significant differences between quetiapine and other antipsychotics such as fluphenazine, risperidone, and chlorpromazine.
- There were no clear differences in all-cause discontinuation and discontinuation due to lack of efficacy for treatment-resistant schizophrenia between quetiapine and other antipsychotics. Similarly, there were no clear differences in treatment discontinuation due to AEs between quetiapine and most antipsychotics, except that chlorpromazine was less tolerable than quetiapine.
- Treatment with quetiapine in treatment-resistant schizophrenia was associated with less use of antiparkinsonian medication compared with fluphenazine and haloperidol. There were no clear differences between quetiapine and other antipsychotics.
- For AEs, quetiapine was associated with a higher risk of sedation than amisulpride, and a lower risk of sedation than clozapine. Quetiapine was associated with less prolactin increase than olanzapine, chlorpromazine, haloperidol, and risperidone. Quetiapine was also associated with less weight gain compared with olanzapine and clozapine, and shorter QTc prolongation than chlorpromazine. There were no clear differences for the reported AEs between quetiapine and other antipsychotics.

Recommendations From Included Evidence-Based Guidelines

- For the management of first-episode psychosis and schizophrenia, both guidelines^{17,18} recommend the use of antipsychotic medication, particularly SGAs over FGAs, except clozapine. The JSNPP guideline¹⁸ suggests an optimal period of 2 to 4 weeks of treatment for determining the therapeutic

response of antipsychotics. The choice of antipsychotic medication should be based on patient characteristics and side effect profiles of different antipsychotic medications.^{17,18}

- For maintenance treatment of schizophrenia, both guidelines^{17,18} recommend the use of antipsychotic medication, particularly SGAs over FGAs, to prevent relapse and hospitalization. The JSNPP guideline¹⁸ recommends continuing the administration of antipsychotics for at least 1 year. The choice of antipsychotic medication should be based on patient characteristics and side effect profiles of different antipsychotic medications.^{17,18}
- For the treatment of recurring or relapsing schizophrenia, the VA/DoD guideline¹⁷ suggests switching to another antipsychotic medication, while the JSNPP guideline¹⁸ suggests increasing the dose rather than switching the antipsychotic.

Considerations for Future Research

The guideline recommendations included in this review that were based on a low level of evidence, particularly in the treatment of recurrent or relapsing schizophrenia, indicate areas for which future clinical research is needed. More research investigating the effect of antipsychotics on patient-reported outcomes such as QoL is also warranted.

Implications for Clinical Practice

The findings of this review suggest that antipsychotics have different efficacy and safety profiles in the treatment of schizophrenia. The evidence was insufficient for an accurate comparison of antipsychotics, which cannot be ranked relative to each other. Prescribing antipsychotics for the treatment of newly diagnosed patients, for maintenance treatment, and for the treatment of recurring or relapsing schizophrenia should be based on patient characteristics, patient tolerability, patient values and preferences, the side effect profiles of different antipsychotic medications, and clinician expertise.

Acknowledgement

Clinical Expert

This individual has kindly provided comments on the report:

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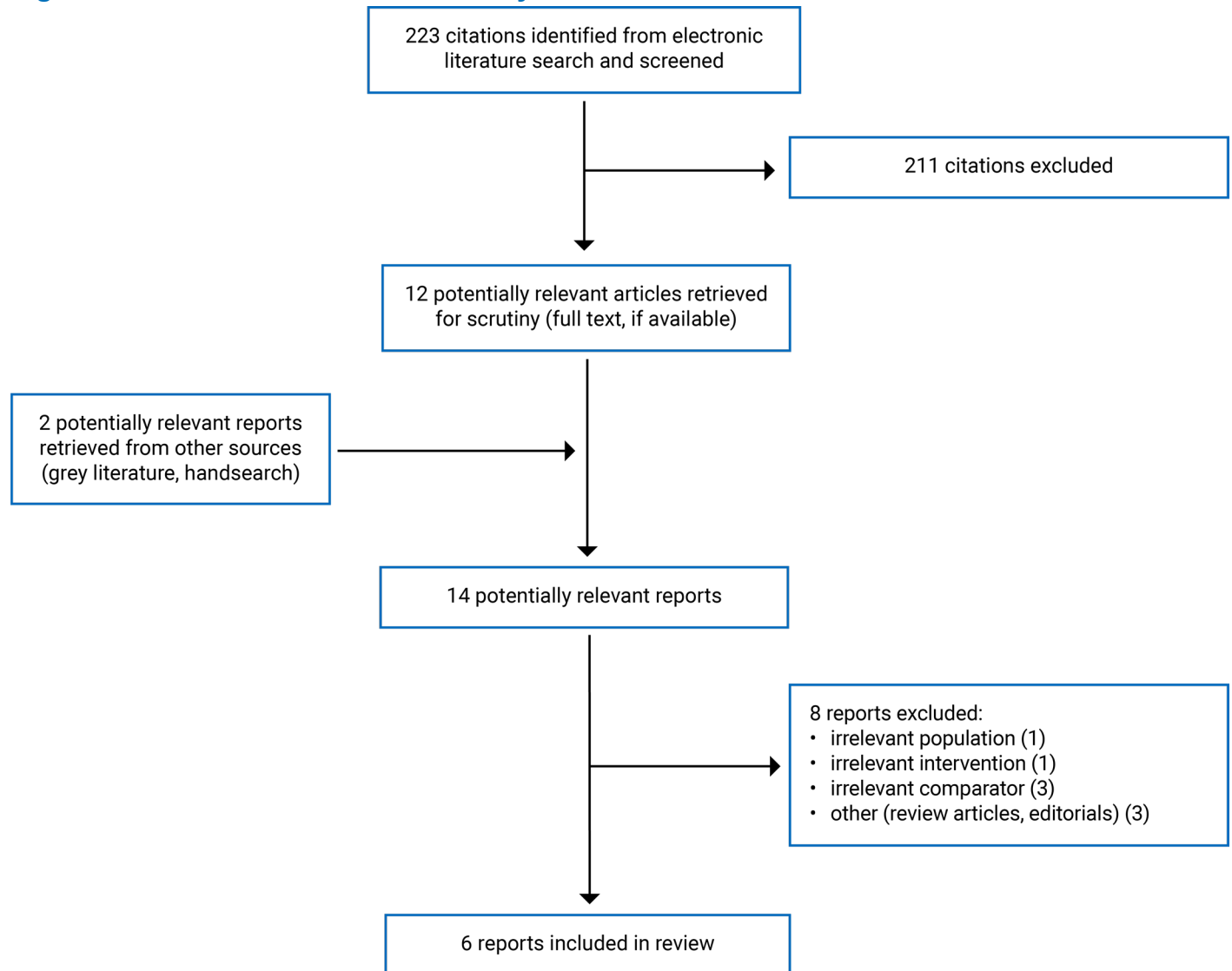
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Appendix 1: Selection of Included Studies

Figure 1: PRISMA¹² Flow Chart of Study Selection



Appendix 2: Characteristics of Included Publications

Please note that this appendix has not been copy-edited.

Table 2: Characteristics of Included Systematic Reviews

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Interventions	Clinical outcomes, length of follow-up
Dong et al. (2024) ¹³ Germany Funding source: Projekt DEAL and China Scholarship Council	SR with NMA 60 RCTs	Patients with treatment-resistant schizophrenia (N = 6,838 patients) Sex: Female: 28.5% Male: 71.5% Mean (SD) age: 38.07 (6.98) years Mean (SD) duration of illness: 14.53 (5.56) years Mean (SD) number of previous episodes: 6.97 (3.41)	SGAs available in Europe or the US, and a selection of FGAs based on a survey of international schizophrenia experts. (i.e., sulpiride, levomepromazine, aripiprazole, trifluoperazine, perphenazine, clozapine, thioridazine, olanzapine, ziprasidone, quetiapine, amisulpride, risperidone, chlorpromazine, haloperidol, fluphenazine, sertindole, thiothixene, fluphenazine LAI, pipotiazine LAI, and placebo)	Outcomes: Primary: - Overall symptoms of schizophrenia (measured by the PANSS,^a the BPRS,^b or any other validated scale) Secondary: - Positive symptoms - Negative symptoms - Response to treatment - Study discontinuation - AEs Follow-up: Median trial duration: 12 weeks (range, 4 to 52)
Leucht et al. (2023) ¹⁴ Germany, Switzerland, US Funding source: German Ministry of Education and Research	SR with NMA 45 RCTs	Acutely ill adult patients with schizophrenia Sex: Female: 40% Male: 60% Mean (IQR) age: 37.2 (IQR: 35.2 to 39.1) years Mean (IQR) study duration: 42 (IQR: 26 to 52) weeks	SGAs available in Europe or the US, and a selection of FGAs based on a survey of international schizophrenia experts. (i.e., amisulpride, aripiprazole, asenapine, chlorpromazine, clozapine, fluphenazine, fluspirilene, haloperidol, iloperidone, loxapine, lurasidone, olanzapine, paliperidone, penfluridol, perphenazine, pimozide, quetiapine, risperidone, thioridazine, tiotixene, trifluoperazine, ziprasidone, zotepine, and placebo)	Outcomes: Primary: - Overall symptoms of schizophrenia (measured by PANSS, BPRS, or any other validated scale) Secondary: - Positive symptoms - Negative symptoms - Response to treatment - Study discontinuation - AEs Follow-up: Trial duration: at least 24 weeks (range, 24 to 156)

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Interventions	Clinical outcomes, length of follow-up
Sherzad Qadir et al. (2023) ¹⁵ Australia Funding source: The authors declared that the study received no external funding	SR with MA 21 RCTs	Patients newly diagnosed with schizophrenia (N = 3,911 reported in 19 studies) Details of study characteristics and patient characteristics of individual studies were presented in the supplementary appendix of the study.	Quetiapine Aripiprazole Ziprasidone Risperidone Olanzapine Haloperidol	Outcomes: - Overall symptoms of schizophrenia (measured by BPRS,^b SANS,^c SAPS,^d CDSS,^e and YMRS^f) - AEs - Treatment discontinuation Follow-up: 8 weeks to 9 years

AE = adverse event; BPRS = Brief Psychiatric Rating Scale; CDSS = Calgary Depression Scale for Schizophrenia; FGA = first-generation antipsychotic; IQR = interquartile range; LAI = long-acting injectable; MA = meta-analysis; NMA = network meta-analysis; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; SD = standard deviation; SGA = second-generation antipsychotic; SR = systematic review; YMRS = Young Mania Rating Scale.

^aPANSS is a 30-item clinician-rated instrument to assess schizophrenia psychopathology, including positive (e.g., hallucinations, delusions) and negative (e.g., blunted effect, social withdrawal) symptoms, as well as general psychopathology. Of the 30 items, each is rated on a 7-point scale (1 = absent to 7 = extreme). The items are divided into 3 subscales: positive symptoms — 7 items focusing on hallucinations, delusions, and other positive symptoms; negative symptoms — 7 items assessing negative symptoms such as blunted affect and social withdrawal; general psychopathology — 16 items covering a broader range of symptoms, including somatic concern, anxiety, and depression.

^bBPRS is a rating scale used to measure psychiatric symptoms such as depression, anxiety, hallucinations, psychosis, and unusual behaviour. Total scores range from 18 to 126, whereas higher scores indicate stronger psychotic symptoms.

^cSANS: Measures the levels of negative symptoms of schizophrenia (affective flattening or blunting, alogia, avolition-apathy, anhedonia-asociality, attention). 0 to 125, a lower score is favourable.

^dSAPS: Measures levels of positive symptoms of schizophrenia (delusions, hallucination, and thought disorder). 0 to 170, lower score is favourable.

^eCDSS: Measures the level of depression in people with schizophrenia. 0 to 27, lower score is favourable.

^fYMRS: Measures manic symptoms (elevated mood, increased motor activity/energy, sexual interest, sleep, irritability, speech, language-thought disorder, content, disruptive-aggressive behaviour, appearance, insight). 0 to 60, lower score is favourable.

Table 3: Characteristics of Included Primary Clinical Study

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Kim et al. (2024) ¹⁶ Republic of Korea Funding source: Bukwang Pharmaceuticals	Parallel, 1:1 ratio, double-blind, active-controlled trial (RCT) Predefined noninferiority margin: -8.99	Adult patients with a diagnosis of schizophrenia, being at a state of acute exacerbation of psychosis symptoms, lasting ≤ 2 months. Mean (SD) age: 41.74 (14.81) years Sex, %: Female: 63% Male: 37% Duration of illness: 1 year to ≥ 10 years	Intervention: Lurasidone (N = 102) Comparator: Quetiapine XR (N = 104)	Outcomes: Primary: • Overall symptoms of schizophrenia (measured by PANSS) ^a Secondary: • Positive symptoms • Negative symptoms • General psychopathology • CGI-S ^b • AEs • Metabolic parameters Treatment duration: 6 weeks Follow-up: 1 week after last dose of study medication

AE = adverse event; CGI-S = Clinical Global Impression–Severity of Illness; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; SD = standard deviation; XR = extended release.

^aPANSS is a 30-item clinician-rated instrument to assess schizophrenia psychopathology, including positive (e.g., hallucinations, delusions) and negative (e.g., blunted effect, social withdrawal) symptoms, as well as general psychopathology. 30 to 210, lower score is favourable.

^bCGI-S is a 7-point scale ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill patients) used by clinicians to rate the current severity of a patient's mental illness.

Table 4: Characteristics of Included Guidelines

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
VA/DoD (2023)¹⁷						
Intended users: Primary care providers, mental health providers, and others involved in the health care team Target population: Patients with schizophrenia and their caregivers	Treatment (e.g., drug, surgery, lifestyle changes), approach (e.g., doses, frequency, methods of administering treatments), or diagnostic or screening test or both used with the patient or population Management of first-episode psychosis and schizophrenia	Outcomes of interest (e.g., mortality, morbidity, QoL, complications). Outcomes can include short, intermediate, and long-term outcomes.	Systematic search for evidence, study selection, data extraction, and data synthesis were performed.	The WG used the GRADE approach to craft each recommendation and determined its strength ^a (strong, weak) based on 4 domains: 1. Confidence in the quality of the evidence 2. Balance of desirable and undesirable outcomes 3. Patient values and preferences 4. Other considerations (e.g., resource use, equity, acceptability, feasibility, subgroup considerations)	The CPG WG comprised experts in psychiatry, psychology, internal medicine, nursing, primary care, pharmacy, mental health counselling, and social work. Tasks of the WG: • Determine the scope • Craft key questions • Identify discussion topics • Provide direction on inclusion and exclusion criteria • Develop evidence-based recommendations • Determine the strength and category of each recommendation	The CPG was reviewed by experts outside the organization.
JSNPP (2021)¹⁸						
Intended users: Specialists in the treatment of schizophrenia, patients, and their families and supporters	Pharmacological therapy and psychosocial therapy in collaboration with medical welfare	All relevant outcomes	Systematic search for evidence, study selection, data extraction, and data synthesis were performed.	Level of evidence was assessed as strong, moderate, weak, and very weak. ^b The strength of recommendation was	The Task Force determined the scope of the guideline and determined clinical questions based on scope.	The guideline was reviewed by internal and external experts.

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
Target population: Patients with first-episode psychosis and schizophrenia	Management of schizophrenia			described with the general corresponding text. ^c	Each WG conducted a systematic review and evaluated the body of evidence. Each WG crafted the recommendation drafts for each clinical question.	

CPG = clinical practice guideline; GRADE = Grading of Recommendations Assessment, Development and Evaluation; JSNPP = Japanese Society of Neuropsychopharmacology; QoL = quality of life; VA/DoD = Veterans Affairs/Department of Defense; WG = working group.

^aRecommendation strength (General corresponding text): Strong for (We recommend...), Weak for (We suggest...), Neither for nor against (There is insufficient evidence to recommend for or against...), Weak against (We suggest against...), Strong against (We recommend against...).

^bLevel of evidence: Strong (A): It is almost certain that the true effect is close to the estimated effect; Moderate (B): The true effect is thought to be close to the estimated effect, but the possibility that results may be different remains; Weak (C): The true effect is thought to be close to the estimated effect, but the results may be different; Very weak (D): The estimated effect is very unclear and is often very different from the true effect.

^cStrength of recommendation: Action is recommended (1), Action is not recommended (1), Action is suggested/desirable (2), Action is not suggested/desirable (2).

Appendix 3: Critical Appraisal of Included Publications

Please note that this appendix has not been copy-edited.

Table 5: Strengths and Limitations of the SRs and NMAs Using AMSTAR 2⁸ and the ISPOR Questionnaire⁹

Strengths	Limitations
Dong et al. (2024)¹³	
Objectives: - Research questions and inclusion criteria for the review included the components of population, intervention, comparison, and outcomes. Search strategies: - Literature search methods, search terms, search dates, search strategy, and criteria for the systematic review were presented. - The review authors explained their selection of RCTs for inclusion in the review. - The review authors attempted to include all relevant RCTs based on a comprehensive search of multiple databases, and the grey literature search included trial registries and conference proceedings. Data collection: - Study selection and data extraction were performed in duplicate by 2 reviewers. - Included studies were described in adequate detail. - The authors used a satisfactory technique, the Cochrane Risk of Bias tool, RoB 2.0, for assessing the risk of bias of included individual studies. - Primary and secondary outcome measures were described. Methods for analysis/synthesis of evidence: - The authors initially performed pairwise MA using a random-effects model. The statistical heterogeneity among trials was assessed using visual inspection of forest plots, I^2 statistics, and the Chi-square test. - The authors evaluated the feasibility of conducting NMA by checking the availability of evidence, transitivity assumption, connectivity, and coherence in the network. - The authors performed frequentist random-effects NMA using multivariate meta-analysis. - The relative effect estimates were described as SMDs for efficacy-related continuous outcomes and ORs for binary outcomes, with their 95% CIs. - The presence of incoherence between direct and indirect estimates of the effect was investigated on possible sources of it (mistakes in data entry, clear differences in study characteristics) and used analytical approaches. - The confidence in the relative treatment effects for the primary outcome was evaluated using the Confidence in Network	Search strategies: - A published protocol was not established before the conduct of the review. Methods for analysis/synthesis of evidence: - The authors provided no justification of why the analyses were performed with a frequentist instead of a Bayesian approach. - The authors did not provide raw data by study and treatment as used in the analysis or model. Reporting: - A list of excluded studies was not published; therefore, reasons for exclusion cannot be verified. - Sources of funding for the included studies were not reported.

Strengths	Limitations
Meta-Analysis framework, which evaluated the credibility of the findings across the domains of within-study bias, across-study bias, indirectness, imprecision, heterogeneity, and incoherence. • The authors performed subgroup or subset analysis. • The authors explored the potential sources of heterogeneity or inconsistency using a priori planned subgroup analyses. • Sensitivity analyses were conducted. Reporting: • Network diagrams were presented. • Study characteristics and patient characteristics were presented in an appendix. • Satisfactory explanation and discussion were provided for the heterogeneity observed in the results of the review. • The authors presented direct estimates, indirect estimates, and network estimates with 95% CI. Discussion: • The authors provided a clear summary of the main findings. • The authors discussed the strengths and limitations at the study and outcome level. Internal validity and external validity were discussed. • The authors provided a general interpretation of the results in the context of other evidence, and implications for future research, and considered the relevance of the findings to health care providers, patients, and clinical practice guidelines. • Potential sources of conflict of interest and funding were disclosed.	
Leucht et al. (2023) ¹⁴	
Objectives: • Research questions and inclusion criteria for the review included the components of population, intervention, comparison, and outcomes. Search strategies: • Literature search methods, search terms, search dates, search strategy, and criteria for the systematic review were presented. • The review authors explained their selection of RCTs for inclusion in the review. • The review authors attempted to include all relevant RCTs based on a comprehensive search of multiple databases, and the grey literature search included trial registries and conference proceedings. Data collection: • Study selection and data extraction were performed in duplicate by 2 reviewers. • Included studies were described in adequate detail. • The authors used a satisfactory technique, the Cochrane Risk of Bias tool, RoB 2.0, for assessing the risk of bias of included individual studies.	Search strategies: • A published protocol was not established before the conduct of the review. Methods for analysis/synthesis of evidence: • The authors provided no justification of why the analyses were performed with a frequentist instead of a Bayesian approach. • The authors did not provide raw data by study and treatment as used in the analysis or model. Reporting: • A list of excluded studies was not published; therefore, reasons for exclusion cannot be verified. • Sources of funding for the included studies were not reported.

Strengths	Limitations
• Primary and secondary outcome measures were described. Methods for analysis/synthesis of evidence: • The authors initially performed pairwise MA using a random-effects model. The statistical heterogeneity among trials was assessed using visual inspection of forest plots, I^2 statistics, and the Chi-square test. • The authors evaluated the feasibility of conducting NMA by checking the availability of evidence, transitivity assumption, connectivity, and coherence in the network. • The authors performed frequentist random-effects NMA using multivariate meta-analysis. • The relative effect estimates were described as SMDs for efficacy-related continuous outcomes and ORs for binary outcomes, with their 95% CIs. • The presence of incoherence between direct and indirect estimates of the effect was investigated on possible sources of it (mistakes in data entry, clear differences in study characteristics) and used analytical approaches. • The confidence in the relative treatment effects for the primary outcome was evaluated using the Confidence in Network Meta-Analysis framework, which evaluated the credibility of the findings across the domains of within-study bias, across-study bias, indirectness, imprecision, heterogeneity, and incoherence. • The authors performed subgroup or subset analysis. • The authors explored the potential sources of heterogeneity or inconsistency using a priori planned subgroup analyses. • Sensitivity analyses were conducted. Reporting: • Network diagrams were presented. • Study characteristics and patient characteristics were presented in an appendix. • Satisfactory explanation and discussion were provided for the heterogeneity observed in the results of the review. • The authors presented direct estimates, indirect estimates, and network estimates with 95% CI. Discussion: • The authors provided a clear summary of the main findings. • The authors discussed the strengths and limitations at the study and outcome level. Internal validity and external validity were discussed. • The authors provided a general interpretation of the results in the context of other evidence, and implications for future research, and considered the relevance of the findings to health care providers, patients, and clinical practice guidelines. • Potential sources of conflict of interest and funding were disclosed.	

Strengths	Limitations
Sherzad Qadir et al. (2023)¹⁵	
• The research question or objective and the inclusion criteria for the review clearly include the components of PICO. • A study protocol was published before conducting the review. A meta-analysis was initially planned. • The review authors explained their selection of study designs, which were published, and unpublished RCTs. • The literature search strategy was comprehensive and clearly described, increasing reproducibility. • The review authors performed study selection in duplicate. This reduced the risk of missing relevant studies and making errors in data extraction. • The characteristics of the included studies were described in adequate detail, including objective, design, setting, population, follow-up time, interventions, outcomes, and the source of funding. • The methodological quality of the included studies was assessed using the Cochrane Risk of Bias tool. • The review authors provided a discussion of the heterogeneity observed in the results, which was the main limitation of the review. • Subgroup analyses were performed. • The review authors declared that this research received no external funding. The authors also declared no potential conflicts of interest.	• A list of excluded studies and the reasons for exclusion were not provided. Therefore, it was not possible to assess whether any relevant articles were excluded and if so, for what reasons.

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2; CI = confidence interval; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; MA = meta-analysis; NMA = network meta-analysis; OR = odds ratio; PICO = population, intervention, comparator, and outcome; RCT = randomized controlled trial; SMD = standardized mean difference.

Table 6: Strengths and Limitations of Clinical Studies Using the Downs and Black Checklist¹⁰

Strengths	Limitations
Kim et al. (2024)¹⁶	
Reporting: • The objective of the study, the main outcomes to be measured, the characteristics of the participants included in the study, the interventions of interest, and the main findings were clearly described. • There were no group differences in the demographics of the randomized participants. • Actual P values were reported for the main outcomes. • Adverse events of the intervention were reported. External validity: • Patients were recruited from multiple centres (35 sites). In total, 210 patients who agreed to participate in the study were included. It was likely that the patients who participated were representative of the entire population from which they were recruited.	Internal validity — confounding: • A sample size calculation was not performed. • Although efficacy evaluation was conducted for both the PP set and the ITT set population, the primary analysis was based on the PP set. This would have some risk in reporting bias. • About 1/3 of the ITT population were excluded, and the reasons for exclusion were not reported. These patients were not taken account in the analysis.

Strengths	Limitations
- The staff, places, and facilities where the patients were treated, were representative of the treatment the majority of the patients receive. The study was conducted in hospital setting. Internal validity — bias: - The study was a randomized, double-blind, active-controlled study over a 6-week period. - All patients were followed up for the same period of time, which took place 1 week after the patients' last dose of study medication. - Statistical tests were used appropriately, and the main outcome measures were accurate and reliable. - Compliance with the intervention was reliable, as 95% of the patients completed the study. - The primary end point, which was the overall symptoms of schizophrenia, was accurately measured using PANSS. Internal validity — confounding: - Patients in both intervention groups appeared to be recruited from the same population and over the same period of time. - Methods of randomization and allocation concealment were described. This minimizes selection bias.	

ITT = intention-to-treat; PANSS = Positive and Negative Syndrome Scale; PP = per-protocol.

Table 7: Strengths and Limitations of Guidelines Using AGREE II¹¹

Item	VA/DoD (2023) ¹⁷	JSNPP (2021) ¹⁸
Domain 1: Scope and purpose		
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	Yes
3. The population (patients, public, and so forth) to whom the guideline is meant to apply is specifically described.	Yes	Yes
Domain 2: Stakeholder involvement [wording from original source]		
4. The guideline development group includes individuals from all relevant professional groups.	Yes	Yes
5. The views and preferences of the target population (patients, public, and so forth) have been sought.	Yes	Yes
6. The target users of the guideline are clearly defined.	Yes	Yes
Domain 3: 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 for 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

Item	VA/DoD (2023) ¹⁷	JSNPP (2021) ¹⁸
12. There is an explicit link between the recommendations and the supporting evidence.	Yes	Yes
13. The guideline has been externally reviewed by experts before its publication.	Yes	Yes
14. A procedure for updating the guideline is provided.	Yes	Yes
Domain 4: 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 identifiable.	Yes	Yes
Domain 5: Applicability		
18. The guideline describes facilitators and barriers to its application.	Unclear	Unclear
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Yes	Yes
20. The potential resource implications of applying the recommendations have been considered.	Yes	Yes
21. The guideline presents monitoring and/or auditing criteria.	Unclear	Unclear
Domain 6: Editorial independence		
22. The views of the funding body have not influenced the content of the guideline.	Yes	Yes
23. Competing interests of guideline development group members have been recorded and addressed.	Yes	Yes

AGREE II = Appraisal of Guidelines for Research and Evaluation II; JSNPP = Japanese Society of Neuropsychopharmacology; VA/DoD = Veterans Affairs/Department of Defense.

Appendix 4: Main Study Findings

Please note that this appendix has not been copy-edited.

Table 8: Summary of Findings by Outcome — Overall Symptoms of Schizophrenia

Study citation and study design	Interventions vs. comparators	Results SMD or MD (95% CI)	Notes
Dong et al. (2024) ¹³ SR with NMA	Levomepromazine vs. quetiapine	-0.71 (-1.49 to 0.07)	Uncertain
	Amisulpride vs. quetiapine	-0.64 (-1.28 to 0.01)	Uncertain
	Clozapine vs. quetiapine	-0.44 (-0.66 to -0.22)	Favours clozapine
	Olanzapine vs. quetiapine	-0.40 (-0.67 to -0.13)	Favours olanzapine
	Zotepine vs. quetiapine	-0.37 (-1.08 to 0.33)	Uncertain
	Risperidone vs. quetiapine	-0.29 (-0.57 to 0.00)	Uncertain
	Ziprasidone vs. quetiapine	-0.25 (-0.64 to 0.14)	Uncertain
	Haloperidol vs. quetiapine	-0.14 (-0.40 to 0.13)	Uncertain
	Fluphenazine vs. quetiapine	-0.04 (-0.51 to 0.42)	Uncertain
	Chlorpromazine vs. quetiapine	-0.01 (-0.25 to 0.24)	Uncertain
	Quetiapine vs. sertindole	-0.03 (-0.55 to 0.48)	Uncertain
Leucht et al. (2023) ¹⁴ SR with NMA	Lurasidone vs. quetiapine	-0.42 (-0.71 to -0.13)	Favours lurasidone
	Olanzapine vs. quetiapine	-0.25 (-0.38 to -0.12)	Favours olanzapine
	Amisulpride vs. quetiapine	-0.19 (-0.38 to 0.01)	Uncertain
	Perphenazine vs. quetiapine	-0.16 (-0.32 to 0.00)	Uncertain
	Clozapine vs. quetiapine	-0.14 (-0.55 to 0.27)	Uncertain
	Risperidone vs. quetiapine	-0.13 (-0.27 to 0.01)	Uncertain
	Aripiprazole vs. quetiapine	-0.09 (-0.27 to 0.08)	Uncertain
	Zotepine vs. quetiapine	-0.09 (-0.49 to 0.31)	Uncertain
	Quetiapine vs. haloperidol	-0.02 (-0.19 to 0.16)	Uncertain
	Quetiapine vs. paliperidone	-0.03 (-0.22 to 0.17)	Uncertain
	Quetiapine vs. lloperidone	-0.07 (-0.28 to 0.14)	Uncertain
	Quetiapine vs. asenapine	-0.08 (-0.26 to 0.10)	Uncertain
	Quetiapine vs. ziprasidone	-0.12 (-0.28 to 0.03)	Uncertain
Sherzad Qadir et al. (2023) ¹⁵ SR with MA	Aripiprazole vs. quetiapine	CGI: -0.32 (-0.71 to 0.07)	NS
		BPRS: -4.77 (-7.83 to -1.71)	P = 0.002; favours aripiprazole

Study citation and study design	Interventions vs. comparators	Results SMD or MD (95% CI)	Notes
		SANS: -1.06 (-2.43 to 0.32)	NS
		SAPS: -0.32 (-0.93 to 0.30)	NS
		CDSS: 0.25 (-0.56 to 1.06)	NS
		YMRS: -0.43 (-1.78 to 0.91)	NS
	Ziprasidone vs. quetiapine	CGI: -0.21 (-0.60 to 0.17)	NS
		BPRS: 1.07 (-2.60 to 4.93)	NS
		SANS: -0.20 (-1.55 to 1.14)	NS
		SAPS: -0.33 (-1.49 to 0.82)	NS
		CDSS: 0.73 (-0.04 to 1.49)	NS
		YMRS: 0.27 (-1.10 to 1.63)	NS
Kim et al. (2024) ¹⁶ RCT	Lurasidone vs. quetiapine	MD (95% CI) PANNS: -0.91 (-6.35 to 4.53)	NS
		CGI: Results were presented in a graphical manner.	Statistically significant differences observed at 4-week and 6-week treatments, favouring lurasidone

BPRS = Brief Psychiatric Rating Scale; CDSS = Calgary Depression Scale for Schizophrenia; CGI = Clinical Global Impression; CI = confidence interval; MA = meta-analysis; MD = mean difference; NMA = network meta-analysis; NS = not statistically significant; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; SMD = standardized mean difference; SR = systematic review; vs. = versus; YMRS = Young Mania Rating Scale.

Table 9: Summary of Findings by Outcome — Positive Symptoms

Study citation and study design	Interventions vs. comparators	Results SMD (95% CI)	Notes
Dong et al. (2024) ¹³ SR with NMA	Amisulpride vs. quetiapine	-0.82 (-1.48 to -0.16)	Favours amisulpride
	Levomepromazine vs. quetiapine	-0.81 (-1.62 to 0.00)	Uncertain
	Clozapine vs. quetiapine	-0.61 (-0.90 to -0.32)	Favours clozapine
	Risperidone vs. quetiapine	-0.51 (-0.82 to -0.20)	Favours risperidone
	Olanzapine vs. quetiapine	-0.49 (-0.78 to -0.19)	Favours olanzapine
	Ziprasidone vs. quetiapine	-0.33 (-0.75 to 0.10)	Uncertain
	Haloperidol vs. quetiapine	-0.26 (-0.55 to 0.03)	Uncertain
	Sertindole vs. quetiapine	-0.13 (-0.67 to 0.40)	Uncertain
	Chlorpromazine vs. quetiapine	-0.12 (-0.43 to 0.19)	Uncertain
	Fluphenazine vs. quetiapine	0.02 (-0.74 to 0.78)	Uncertain
Leucht et al. (2023) ¹⁴ SR with NMA	Quetiapine was not part of the NMA	—	—

Study citation and study design	Interventions vs. comparators	Results SMD (95% CI)	Notes
Kim et al. (2024) ¹⁶ RCT	Lurasidone vs. quetiapine	PANSS positive subscores: Results were presented in a graphical manner.	No statistically significant difference was found between groups in terms of PANSS positive subscale scores.

CI = confidence interval; NMA = network meta-analysis; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; SMD = standardized mean difference; SR = systematic review; vs. = versus.

Table 10: Summary of Findings by Outcome — Negative Symptoms

Study citation and study design	Interventions vs. comparators	Results SMD (95% CI)	Notes
Dong et al. (2024) ¹³ SR with NMA	Amisulpride vs. quetiapine	−0.46 (−1.68 to 0.75)	Uncertain
	Clozapine vs. quetiapine	−0.22 (−0.76 to 0.31)	Uncertain
	Zotepine vs. quetiapine	−0.36 (−1.61 to 0.89)	Uncertain
	Olanzapine vs. quetiapine	−0.14 (−0.68 to 0.40)	Uncertain
	Fluphenazine vs. quetiapine	−0.10 (−0.98 to 0.78)	Uncertain
	Levomepromazine vs. quetiapine	−0.11 (−1.44 to 1.22)	Uncertain
	Ziprasidone vs. quetiapine	−0.01 (−0.90 to 0.89)	Uncertain
	Quetiapine vs. risperidone	0.02 (−0.54 to 0.57)	Uncertain
	Quetiapine vs. haloperidol	0.01 (−0.54 to 0.56)	Uncertain
	quetiapine vs. sertindole	−0.17 (−1.33 to 0.98)	Uncertain
	Quetiapine vs. chlorpromazine	−0.66 (−1.28 to −0.05)	Favours quetiapine
Leucht et al. (2023) ¹⁴ SR with NMA	Quetiapine was not part of the NMA	—	—
Kim et al. (2024) ¹⁶ RCT	Lurasidone vs. quetiapine	PANSS negative subscores: Results were presented in a graphical manner.	No statistically significant difference was found between groups in terms of PANSS negative subscale scores.

CI = confidence interval; NMA = network meta-analysis; PANSS = Positive and Negative Syndrome Scale; SMD = standardized mean difference; SR = systematic review; vs. = versus.

Table 11: Summary of Findings by Outcome — Response to Treatment

Study citation and study design	Interventions vs. comparators	Results RR (95% CI)	Notes
Dong et al. (2024) ¹³ SR with NMA	Sulpiride vs. quetiapine	1.67 (0.75 to 2.24)	Uncertain
	Levomepromazine vs. quetiapine	1.43 (0.72 to 2.02)	Uncertain
	Aripiprazole vs. quetiapine	1.33 (0.41 to 2.15)	Uncertain
	Trifluoperazine vs. quetiapine	1.32 (0.45 to 0.11)	Uncertain

Study citation and study design	Interventions vs. comparators	Results RR (95% CI)	Notes
	Perphenazine vs. quetiapine	1.29 (0.48 to 2.05)	Uncertain
	Clozapine vs. quetiapine	1.16 (0.79 to 1.55)	Uncertain
	Thioridazine vs. quetiapine	1.15 (0.37 to 1.99)	Uncertain
	Olanzapine vs. quetiapine	1.11 (0.73 to 1.51)	Uncertain
	Ziprasidone vs. quetiapine	1.10 (0.63 to 1.61)	Uncertain
	Quetiapine vs. amisulpride	1.03 (0.39 to 1.82)	Uncertain
	Quetiapine vs. Risperidone	1.13 (0.73 to 1.58)	Uncertain
	Quetiapine vs. Chlorpromazine	1.30 (0.87 to 1.77)	Uncertain
	Quetiapine vs. Haloperidol	1.33 (0.89 to 1.82)	Uncertain
	Quetiapine vs. Fluphenazine	1.36 (0.61 to 2.28)	Uncertain
	Quetiapine vs. Sertindole	1.56 (0.71 to 2.59)	Uncertain
	Quetiapine vs. Thiothixene	2.96 (0.87 to 5.64)	Uncertain
	Quetiapine vs. Fluphenazine LAI	3.52 (0.59 to 7.50)	Uncertain
	Quetiapine vs. Pipotiazine LAI	3.52 (0.59 to 7.50)	Uncertain
Leucht et al. (2023) ¹⁴ SR with NMA	No NMA for this outcome	—	—

CI = confidence interval; LAI = long-acting injectable; NMA = network meta-analysis; RR = relative risk; SR = systematic review; vs. = versus.

Table 12: Summary of Findings by Outcome — Social Functioning

Study citation and study design	Interventions vs. comparators	Results SMD (95% CI)	Notes
Dong et al. (2024) ¹³ SR with NMA	No NMA for this outcome	—	—
Leucht et al. (2023) ¹⁴ SR with NMA	Quetiapine vs. olanzapine	−0.17 (−0.60 to 0.25)	Uncertain
	Quetiapine vs. amisulpride	−0.18 (−0.65 to 0.29)	Uncertain
	Quetiapine vs. risperidone	−0.37 (−0.88 to 0.13)	Uncertain
	Quetiapine vs. paliperidone	−0.47 (−1.00 to 0.06)	Uncertain

CI = confidence interval; NMA = network meta-analysis; SMD = standardized mean difference; SR = systematic review; vs. = versus.

Table 13: Summary of Findings by Outcome — Quality of Life

Study citation and study design	Interventions vs. comparators	Results SMD (95% CI)	Notes
Dong et al. (2024) ¹³ SR with NMA	Fluphenazine vs. quetiapine	0.18 (−0.68 to 1.03)	Pairwise MA; NS
	Quetiapine vs. risperidone	0.03 (−0.81 to 0.86)	Pairwise MA; NS
	Chlorpromazine vs. quetiapine	−0.21 (−0.46 to 0.04)	Pairwise MA; NS

Study citation and study design	Interventions vs. comparators	Results SMD (95% CI)	Notes
Leucht et al. (2023) ¹⁴ SR with NMA	Zotepine vs. quetiapine	-0.44 (-1.12 to 0.23)	Uncertain
	Amisulpride vs. quetiapine	-0.33 (-0.83 to 0.16)	Uncertain
	Olanzapine vs. quetiapine	-0.33 (-0.69 to 0.03)	Uncertain
	Asenapine vs. quetiapine	-0.30 (-0.76 to 0.17)	Uncertain
	Ziprasidone vs. quetiapine	-0.26 (-0.67 to 0.14)	Uncertain
	Perphenazine vs. quetiapine	-0.19 (-0.60 to 0.23)	Uncertain
	Haloperidol vs. quetiapine	-0.17 (-0.69 to 0.34)	Uncertain
	Risperidone vs. quetiapine	-0.16 (-0.53 to 0.22)	Uncertain

CI = confidence interval; MA = meta-analysis; NMA = network meta-analysis; NS = not statistically significant; SMD = standardized mean difference; SR = systematic review; vs. = versus.

Table 14: Summary of Findings by Outcome — All-Cause Discontinuation

Study citation and study design	Interventions vs. comparators	Results RR (95% CI)	Notes
Dong et al. (2024) ¹³ SR with NMA	Sulpiride vs. quetiapine	0.42 (0.02 to 2.21)	Uncertain
	Levomepromazine vs. quetiapine	0.43 (0.08 to 1.51)	Uncertain
	Olanzapine vs. quetiapine	0.75 (0.52 to 1.05)	Uncertain
	Clozapine vs. quetiapine	0.77 (0.53 to 1.05)	Uncertain
	Ziprasidone vs. quetiapine	0.81 (0.46 to 1.17)	Uncertain
	Risperidone vs. quetiapine	0.83 (0.57 to 1.16)	Uncertain
	Sertindole vs. quetiapine	0.99 (0.52 to 1.57)	Uncertain
	Chlorpromazine vs. quetiapine	0.99 (0.73 to 1.27)	Uncertain
	Quetiapine vs. zotepine	0.93 (0.32 to 1.72)	Uncertain
	Quetiapine vs. haloperidol	0.90 (0.64 to 1.18)	Uncertain
	Quetiapine vs. fluphenazine LAI	0.87 (0.08 to 2.09)	Uncertain
	Quetiapine vs. pipotiazine LAI	0.87 (0.08 to 2.09)	Uncertain
	Quetiapine vs. amisulpride	0.78 (0.31 to 1.40)	Uncertain
	Quetiapine vs. Fluphenazine	0.69 (0.30 to 1.18)	Uncertain
	Quetiapine vs. thioridazine	0.52 (0.07 to 1.25)	Uncertain
	Quetiapine vs. trifluoperazine	0.49 (0.09 to 1.11)	Uncertain
Leucht et al. (2023) ¹⁴ SR with NMA	Amisulpride vs. quetiapine	0.70 (0.54 to 0.88)	Favours amisulpride
	Aripiprazole vs. quetiapine	0.73 (0.57 to 0.89)	Favours aripiprazole
	Lurasidone vs. quetiapine	0.80 (0.60 to 1.01)	Uncertain

Study citation and study design	Interventions vs. comparators	Results RR (95% CI)	Notes
	Risperidone vs. quetiapine	0.82 (0.68 to 0.95)	Favours risperidone
	Perphenazine vs. quetiapine	0.82 (0.67 to 0.97)	Favours perphenazine
	Zotepine vs. quetiapine	0.91 (0.60 to 1.20)	Uncertain
	Haloperidol vs. quetiapine	0.93 (0.78 to 1.08)	Uncertain
	Ziprasidone vs. quetiapine	0.93 (0.78 to 1.07)	Uncertain
	Asenapine vs. quetiapine	0.94 (0.78 to 1.09)	Uncertain
	Paliperidone vs. quetiapine	0.95 (0.79 to 1.10)	Uncertain
	Thiothixene vs. quetiapine	0.98 (0.66 to 1.24)	Uncertain
	Fluspirilene vs. quetiapine	0.99 (0.23 to 1.49)	Uncertain
	Quetiapine vs. pimozide	0.80 (0.30 to 1.14)	Uncertain
	Quetiapine vs. fluphenazine	0.77 (0.41 to 1.04)	Uncertain
	Quetiapine vs. olanzapine	1.55 (1.35 to 1.72)	Favours olanzapine

CI = confidence interval; LAI = long-acting injectable; NMA = network meta-analysis; RR = relative risk; SR = systematic review; vs. = versus.

Table 15: Summary of Findings by Outcome — Discontinuation Due to Lack of Efficacy

Study citation and study design	Interventions vs. comparators	Results RR (95% CI)	Notes
Dong et al. (2024) ¹³ SR with NMA	Clozapine vs. quetiapine	0.28 (0.14 to 0.53)	Favours clozapine
	Fluphenazine LAI vs. quetiapine	0.32 (0.03 to 2.27)	Uncertain
	Ziprasidone vs. quetiapine	0.43 (0.08 to 1.73)	Uncertain
	Pipotiazine LAI vs. quetiapine	0.48 (0.04 to 2.71)	Uncertain
	Sulpiride vs. quetiapine	0.51 (0.01 to 3.78)	Uncertain
	Amisulpride vs. quetiapine	0.51 (0.03 to 3.02)	Uncertain
	Chlorpromazine vs. quetiapine	0.52 (0.19 to 1.25)	Uncertain
	Olanzapine vs. quetiapine	0.52 (0.27 to 0.95)	Favours olanzapine
	Risperidone vs. quetiapine	0.63 (0.32 to 1.17)	Uncertain
	Sertindole vs. quetiapine	0.81 (0.33 to 1.69)	Uncertain
	Quetiapine vs. haloperidol	0.98 (0.56 to 1.57)	Uncertain
	Quetiapine vs. zotepine	0.86 (0.04 to 3.21)	Uncertain
	Quetiapine vs. trifluoperazine	0.73 (0.06 to 2.60)	Uncertain
	Quetiapine vs. thioridazine	0.54 (0.03 to 1.91)	Uncertain
	Quetiapine vs. fluphenazine	0.51 (0.17 to 1.12)	Uncertain
Leucht et al. (2023) ¹⁴ SR with NMA	No NMA for this outcome	—	—

Study citation and study design	Interventions vs. comparators	Results RR (95% CI)	Notes
Sherzad Qadir et al. (2023) ¹⁵ SR with MA	Quetiapine vs. olanzapine	3.48 (3.05 to 5.91)	P < 0.001; more frequent with quetiapine
	Quetiapine vs. risperidone	0.68 (0.01 to 33.70)	NS
	Quetiapine vs. ziprasidone	2.05 (1.57 to 2.68)	P < 0.001; more frequent with quetiapine
	Quetiapine vs. haloperidol	1.14 (0.41 to 3.16)	NS
	Quetiapine vs. aripiprazole	3.69 (2.56 to 5.32)	P < 0.001; more frequent with quetiapine

CI = confidence interval; LAI = long-acting injectable; MA = meta-analysis; NMA = network meta-analysis; NS = not statistically significant; RR = relative risk; SR = systematic review; vs. = versus.

Table 16: Summary of Findings by Outcome — Discontinuation Due to AEs

Study citation and study design	Interventions vs. comparators	Results RR (95% CI)	Notes
Dong et al. (2024) ¹³ SR with NMA	Fluphenazine vs. quetiapine	0.36 (0.04 to 2.65)	Uncertain
	Olanzapine vs. quetiapine	0.47 (0.22 to 1.00)	Uncertain
	Risperidone vs. quetiapine	0.52 (0.24 to 1.11)	Uncertain
	Haloperidol vs. quetiapine	0.57 (0.29 to 1.12)	Uncertain
	Clozapine vs. quetiapine	0.74 (0.38 to 1.40)	Uncertain
	Sertindole vs. quetiapine	0.89 (0.25 to 2.86)	Uncertain
	Zotepine vs. quetiapine	0.92 (0.21 to 3.55)	Uncertain
	Quetiapine vs. ziprasidone	0.99 (0.42 to 2.23)	Uncertain
	Quetiapine vs. thioridazine	0.55 (0.01 to 7.15)	Uncertain
	Quetiapine vs. sulpiride	0.52 (0.01 to 7.56)	Uncertain
	Quetiapine vs. chlorpromazine	0.51 (0.26 to 0.95)	Favours quetiapine
	Quetiapine vs. levomepromazine	0.51 (0.03 to 4.94)	Uncertain
	Quetiapine vs. trifluoperazine	0.45 (0.03 to 4.17)	Uncertain
	Quetiapine vs. thiothixene	0.41 (0.03 to 3.29)	Uncertain
	Quetiapine vs. amisulpride	0.37 (0.03 to 2.45)	Uncertain
	Quetiapine vs. pipotiazine LAI	0.30 (0.02 to 2.69)	Uncertain
	Quetiapine vs. fluphenazine LAI	0.22 (0.01 to 1.85)	Uncertain
Leucht et al. (2023) ¹⁴ SR with NMA	No NMA for this outcome	—	—
Qadir et al. (2023) SR with MA	Quetiapine vs. olanzapine	0.81 (0.49 to 1.37)	NS

Study citation and study design	Interventions vs. comparators	Results RR (95% CI)	Notes
	Quetiapine vs. risperidone	0.44 (0.21 to 0.89)	P = 0.02; more frequent with risperidone
	Quetiapine vs. ziprasidone	0.34 (0.22 to 0.51)	P < 0.001; more frequent with ziprasidone
	Quetiapine vs. haloperidol	0.43 (0.22 to 0.84)	P = 0.01; more frequent with haloperidol
	Quetiapine vs. aripiprazole	1.03 (0.62 to 1.73)	NS

AE = adverse event; CI = confidence interval; LAI = long-acting injectable; MA = meta-analysis; NMA = network meta-analysis; NS = not statistically significant; RR = relative risk; SR = systematic review; vs. = versus.

Table 17: Summary of Findings by Outcome — Use of Antiparkinsonian Medication

Study citation and study design	Interventions vs. comparators	Results RR (95% CI)	Notes
Dong et al. (2024) ¹³ SR with NMA	Levomepromazine vs. quetiapine	0.30 (0.01 to 3.92)	Uncertain
	Thioridazine vs. quetiapine	0.38 (0.01 to 4.70)	Uncertain
	Sulpiride vs. quetiapine	0.57 (0.03 to 4.84)	Uncertain
	Clozapine vs. quetiapine	0.68 (0.23 to 1.81)	Uncertain
	Amisulpride vs. quetiapine	0.77 (0.15 to 3.01)	Uncertain
	Olanzapine vs. quetiapine	0.79 (0.29 to 1.94)	Uncertain
	Ziprasidone vs. quetiapine	0.92 (0.23 to 2.87)	Uncertain
	Pipotiazine LAI vs. quetiapine	0.97 (0.01 to 7.53)	Uncertain
	Quetiapine vs. chlorpromazine	0.96 (0.07 to 5.37)	Uncertain
	Quetiapine vs. fluphenazine LAI	0.80 (0.01 to 6.08)	Uncertain
	Quetiapine vs. risperidone	0.59 (0.22 to 1.36)	Uncertain
	Quetiapine vs. trifluoperazine	0.41 (0.03 to 2.57)	Uncertain
	Quetiapine vs. fluphenazine	0.37 (0.11 to 0.99)	Favours quetiapine
	Quetiapine vs. haloperidol	0.34 (0.13 to 0.77)	Favours quetiapine
Leucht et al. (2023) ¹⁴ SR with NMA	Quetiapine vs. aripiprazole	0.78 (0.73 to 1.53)	Uncertain
	Quetiapine vs. zotepine	0.62 (0.22 to 1.57)	Uncertain
	Quetiapine vs. amisulpride	0.43 (0.20 to 0.86)	Favours quetiapine
	Quetiapine vs. risperidone	0.35 (0.19 to 0.65)	Favours quetiapine
	Quetiapine vs. paliperidone	0.35 (0.18 to 0.69)	Favours quetiapine
	Quetiapine vs. ziprasidone	0.35 (0.18 to 0.68)	Favours quetiapine
	Quetiapine vs. perphenazine	0.34 (0.17 to 0.67)	Favours quetiapine
	Quetiapine vs. haloperidol	0.24 (0.12 to 0.46)	Favours quetiapine

Study citation and study design	Interventions vs. comparators	Results RR (95% CI)	Notes
	Quetiapine vs. asenapine	0.18 (0.06 to 0.51)	Favours quetiapine
	Quetiapine vs. olanzapine	0.56 (0.29 to 1.04)	Uncertain

CI = confidence interval; LAI = long-acting injectable; NMA = network meta-analysis; RR = relative risk; SR = systematic review; vs. = versus.

Table 18: Summary of Findings by Outcome — Sedation

Study citation and study design	Interventions vs. comparators	Results RR (95% CI)	Notes
Dong et al. (2024) ¹³ SR with NMA	Thiothixene vs. quetiapine	0.37 (0.03 to 1.29)	Uncertain
	Amisulpride vs. quetiapine	0.58 (0.26 to 0.99)	Favours amisulpride
	Ziprasidone vs. quetiapine	0.89 (0.63 to 1.12)	Uncertain
	Sertindole vs. quetiapine	0.96 (0.62 to 1.22)	Uncertain
	Sulpiride vs. quetiapine	0.99 (0.56 to 1.28)	Uncertain
	Olanzapine vs. quetiapine	0.99 (0.77 to 1.17)	Uncertain
	Fluphenazine vs. quetiapine	1.00 (0.47 to 1.33)	Uncertain
	Quetiapine vs. haloperidol	0.98 (0.73 to 1.18)	Uncertain
	Quetiapine vs. risperidone	0.97 (0.74 to 1.14)	Uncertain
	Quetiapine vs. trifluoperazine	0.95 (0.44 to 1.27)	Uncertain
	Quetiapine vs. chlorpromazine	0.92 (0.74 to 1.06)	Uncertain
	Quetiapine vs. thioridazine	0.89 (0.41 to 1.18)	Uncertain
	Quetiapine vs. clozapine	0.82 (0.65 to 0.96)	Favours quetiapine
	Quetiapine vs. levomepromazine	0.81 (0.33 to 1.09)	Uncertain
Leucht et al. (2023) ¹⁴ SR with NMA	Aripiprazole vs. quetiapine	0.53 (0.33 to 0.93)	Favours aripiprazole
	Lurasidone vs. quetiapine	0.73 (0.21 to 2.09)	Uncertain
	Ziprasidone vs. quetiapine	0.78 (0.54 to 1.12)	Uncertain
	Haloperidol vs. quetiapine	0.78 (0.47 to 1.27)	Uncertain
	Amisulpride vs. quetiapine	0.82 (0.43 to 1.48)	Uncertain
	Asenapine vs. quetiapine	0.85 (0.50 to 1.37)	Uncertain
	Perphenazine vs. quetiapine	0.92 (0.64 to 1.29)	Uncertain
	Risperidone vs. quetiapine	0.93 (0.67 to 1.26)	Uncertain
	Quetiapine vs. paliperidone	0.88 (0.33 to 1.99)	Uncertain
	Quetiapine vs. zotepine	0.69 (0.24 to 1.61)	Uncertain
	Quetiapine vs. olanzapine	1.02 (0.75 to 1.36)	Uncertain

CI = confidence interval; NMA = network meta-analysis; RR = relative risk; SR = systematic review; vs. = versus.

Table 19: Summary of Findings by Outcome — Akathisia

Study citation and study design	Interventions vs. comparators	Results RR (95% CI)	Notes
Dong et al. (2024) ¹³ SR with NMA	No NMA for this outcome	—	—
Leucht et al. (2023) ¹⁴ SR with NMA	Paliperidone vs. quetiapine	0.85 (0.40 to 1.75)	Uncertain
	Amisulpride vs. quetiapine	0.93 (0.44 to 1.94)	Uncertain
	Quetiapine vs. aripiprazole	0.93 (0.49 to 1.75)	Uncertain
	Quetiapine vs. risperidone	0.77 (0.43 to 1.37)	Uncertain
	Quetiapine vs. perphenazine	0.77 (0.39 to 1.46)	Uncertain
	Quetiapine vs. ziprasidone	0.72 (0.38 to 1.31)	Uncertain
	Quetiapine vs. haloperidol	0.43 (0.23 to 0.81)	Favours quetiapine
	Quetiapine vs. asenapine	0.40 (0.17 to 0.86)	Favours quetiapine
	Quetiapine vs. lurasidone	0.22 (0.05 to 0.80)	Favours quetiapine
	Quetiapine vs. olanzapine	1.03 (0.58 to 1.79)	Uncertain

CI = confidence interval; NMA = network meta-analysis; RR = relative risk; SR = systematic review; vs. = versus.

Table 20: Summary of Findings by Outcome — Increased Prolactin Levels

Study citation and study design	Interventions vs. comparators	Results MD (95% CI)	Notes
Dong et al. (2024) ¹³ SR with NMA	Quetiapine vs. ziprasidone	-5.90 (-20.63 to 8.83)	Uncertain
	Quetiapine vs. clozapine	-6.82 (-15.48 to 1.83)	Uncertain
	Quetiapine vs. fluphenazine	-10.76 (-29.29 to 7.78)	Uncertain
	Quetiapine vs. olanzapine	-13.19 (-21.95 to -4.43)	Favours quetiapine
	Quetiapine vs. chlorpromazine	-20.57 (-32.74 to -8.39)	Favours quetiapine
	Quetiapine vs. haloperidol	-23.96 (-35.92 to -12.00)	Favours quetiapine
	Quetiapine vs. risperidone	-34.24 (-43.51 to -24.96)	Favours quetiapine
Leucht et al. (2023) ¹⁴ SR with NMA	Olanzapine vs. quetiapine	3.20 (-9.39 to 15.79)	Pairwise MA; NS
	Quetiapine vs. lurasidone	-1.30 (-19.41 to 16.81)	Pairwise MA; NS
	Quetiapine vs. ziprasidone	-4.80 (-17.56 to 7.96)	Pairwise MA; NS
	Quetiapine vs. perphenazine	-9.70 (-22.51 to 3.11)	Pairwise MA; NS
	Quetiapine vs. risperidone	-24.70 (-37.41 to -11.99)	Pairwise MA; favours quetiapine

CI = confidence interval; MA = meta-analysis; MD = mean difference; NMA = network meta-analysis; NS = not statistically significant; QTc = QT interval; SR = systematic review; vs. = versus.

Table 21: Summary of Findings by Outcome — Weight Gain

Study citation and study design	Interventions vs. comparators	Results MD (95% CI)	Notes
Dong et al. (2024) ¹³ SR with NMA	Ziprasidone vs. quetiapine	-1.21 (-3.05 to 0.63)	Uncertain
	Haloperidol vs. quetiapine	-0.93 (-2.33 to 0.46)	Uncertain
	Fluphenazine vs. quetiapine	-0.71 (-4.57 to 3.15)	Uncertain
	Chlorpromazine vs. quetiapine	-0.50 (-2.13 to 1.13)	Uncertain
	Quetiapine vs. levomepromazine	0.30 (-11.96 to 12.56)	Uncertain
	Quetiapine vs. amisulpride	-1.18 (-3.64 to 1.29)	Uncertain
	Quetiapine vs. risperidone	-1.28 (-2.79 to 0.23)	Uncertain
	Quetiapine vs. sertindole	-1.88 (-4.10 to 0.34)	Uncertain
	Quetiapine vs. olanzapine	-2.68 (-4.14 to -1.21)	Favours quetiapine
	Quetiapine vs. clozapine	-2.70 (-4.17 to -1.23)	Favours quetiapine
Leucht et al. (2023) ¹⁴ SR with pairwise NMA	Ziprasidone vs. quetiapine	-1.23 (-3.64 to 1.18)	Pairwise MA; NS
	Perphenazine vs. quetiapine	-1.41 (-3.82 to 1.00)	Pairwise MA; NS
	Lurasidone vs. quetiapine	-0.50 (-3.19 to 2.19)	Pairwise MA; NS
	Quetiapine vs. risperidone	0.14 (-2.20 to 2.48)	Pairwise MA; NS
	Quetiapine vs. olanzapine	-3.76 (-6.10 to -1.42)	Pairwise MA; favours quetiapine

CI = confidence interval; MA = meta-analysis; MD = mean difference; NMA = network meta-analysis; NS = not statistically significant; SR = systematic review; vs. = versus.

Table 22: Summary of Findings by Outcome — QTc Prolongation

Study citation and study design	Interventions vs. comparators	Results MD (95% CI)	Notes
Dong et al. (2024) ¹³ SR with NMA	Chlorpromazine vs. quetiapine (1 RCT)	19.80 (12.10 to 27.50)	Pairwise MA; More frequent with chlorpromazine
Leucht et al. (2023) ¹⁴ SR with NMA	Paliperidone vs. quetiapine	-7.40 (-13.19 to -1.62)	More frequent with quetiapine
	Risperidone vs. quetiapine	-5.30 (-10.21 to -0.40)	More frequent with quetiapine
	Olanzapine vs. quetiapine	-5.18 (-9.81 to -0.55)	More frequent with quetiapine
	Asenapine vs. quetiapine	-4.78 (-9.92 to 0.36)	Uncertain
	Perphenazine vs. quetiapine	-4.50 (-9.90 to 0.90)	Uncertain
	Ziprasidone vs. quetiapine	-4.47 (-9.32 to 0.37)	Uncertain
	Amisulpride vs. quetiapine	-0.18 (-8.41 to 8.05)	Uncertain
	Quetiapine vs. lurasidone	-3.20 (-10.22 to 3.82)	Uncertain

CI = confidence interval; MA = meta-analysis; NMA = network meta-analysis; RCT = randomized controlled trial; RR = relative risk; SR = systematic review; vs. = versus.

Table 23: Summary of Findings by Outcome — Depressive Symptoms

Study citation and study design	Interventions vs. comparators	Results SMD (95% CI)	Notes
Dong et al. (2024) ¹³ SR with NMA	No NMA for this outcome	—	—
Leucht et al. (2023) ¹⁴ SR with NMA	Lurasidone vs. quetiapine	-0.31 (-0.61 to 0.00)	Uncertain
	Olanzapine vs. quetiapine	-0.01 (-0.18 to 0.16)	Uncertain
	Quetiapine vs. perphenazine	-0.03 (-0.22 to 0.17)	Uncertain
	Quetiapine vs. aripiprazole	-0.03 (-0.28 to 0.22)	Uncertain
	Quetiapine vs. risperidone	-0.09 (-0.26 to 0.09)	Uncertain
	Quetiapine vs. amisulpride	-0.10 (-0.34 to 0.13)	Uncertain
	Quetiapine vs. ziprasidone	-0.13 (-0.32 to 0.06)	Uncertain
	Quetiapine vs. asenapine	-0.15 (-0.38 to 0.08)	Uncertain
	Quetiapine vs. haloperidol	-0.15 (-0.40 to 0.10)	Uncertain
	Quetiapine vs. paliperidone	-0.24 (-0.49 to 0.01)	Uncertain

CI = confidence interval; NMA = network meta-analysis; SMD = standardized mean difference; SR = systematic review; vs. = versus.

Table 24: Summary of Findings by Outcome — Other Side Effects

Study citation and study design	Interventions vs. comparators	Results RR (95% CI) or % or mean change from baseline	Notes
Sherzad Qadir et al. (2023) ¹⁵ SR with MA	Aripiprazole vs. quetiapine	Concentration difficulties: 1.10 (0.49 to 2.48)	NS
		Increased fatigability: 0.76 (0.58 to 1.01)	NS
		Sleepiness: 0.58 (0.45 to 0.75)	P < 0.001; more frequent with quetiapine
		Depression: 2.11 (0.58 to 7.66)	NS
		Restlessness: 2.05 (0.42 to 9.91)	NS
		Increased duration of sleep: 0.53 (0.36 to 0.78)	P = 0.001; more frequent with quetiapine
		Rigidity: 1.36 (0.60 to 7.29)	NS
		Tremors: 3.07 (1.07 to 8.77)	P = 0.04; more frequent with aripiprazole
		Increased salivation: 0.72 (0.35 to 1.47)	NS
		Constipation: 0.60 (0.31 to 1.17)	NS
		Vertigo: 4.81 (0.60 to 38.41)	NS
		Amenorrhea: 5.33 (0.96 to 29.48)	NS

Study citation and study design	Interventions vs. comparators	Results RR (95% CI) or % or mean change from baseline	Notes
		Galactorrhea: 0.10 (0.01 to 0.78)	P = 0.03; more frequent with quetiapine
		Diminished sexual desire: 0.62 (0.30 to 1.26)	NS
		Orgasmic dysfunction: 0.34 (0.06 to 1.82)	NS
		Erectile dysfunction: 0.20 (0.07 to 0.56)	P = 0.002; more frequent with quetiapine
		Ejaculatory dysfunction: 0.52 (0.10 to 2.58)	NS
		Weight gain: 1.10 (0.84 to 1.44)	NS
		Memory impairment: 2.05 (0.42 to 9.91)	NS
	Quetiapine vs. ziprasidone	Concentration difficulties: 0.62 (0.35 to 1.11)	NS
		Increased fatigability: 1.14 (0.86 to 1.50)	NS
		Sleepiness: 1.22 (0.98 to 1.52)	NS
		Memory impairment: 0.39 (0.81 to 1.86)	NS
		Depression: 0.38 (0.10 to 1.37)	NS
		Restlessness: 0.39 (0.08 to 1.86)	NS
		Increased duration of sleep: 1.05 (0.71 to 1.56)	NS
		Rigidity: 0.19 (0.04 to 0.84)	NS
		Tremors: 0.77 (0.22 to 2.64)	NS
		Increased salivation: 2.21 (0.29 to 16.63)	NS
		Constipation: 1.81 (0.58 to 3.70)	NS
		Vertigo: 0.13 (0.02 to 0.99)	P = 0.05; more frequent with ziprasidone
		Amenorrhea: 0.11 (0.02 to 0.50)	P = 0.006; more frequent with ziprasidone
		Galactorrhea: 1.16 (0.34 to 4.02)	NS
		Diminished sexual desire: 1.56 (0.74 to 3.29)	NS
		Orgasmic dysfunction: 0.77 (0.22 to 2.64)	NS
		Erectile dysfunction: 1.17 (0.45 to 3.00)	NS
		Ejaculatory dysfunction: 0.91 (0.35 to 2.35)	NS
		Weight gain: 1.49 (1.15 to 1.94)	NS

Study citation and study design	Interventions vs. comparators	Results RR (95% CI) or % or mean change from baseline	Notes
	Olanzapine vs. quetiapine	Weight gain: 1.34 (1.15 to 1.56)	P < 0.001; more frequent with olanzapine
		Sleepiness: 0.90 (0.75 to 1.08)	NS
		Increased duration of sleep: 0.80 (0.61 to 1.05)	NS
		Akinesia: 0.62 (0.18 to 2.14)	NS
		Constipation: 0.71 (0.39 to 1.30)	NS
		Galactorrhea: 4.84 (0.56 to 42.07)	NS
		Diminished sexual desire: 1.02 (0.70 to 1.49)	NS
		Orgasmic dysfunction: 1.05 (0.62 to 1.79)	NS
	Risperidone vs. quetiapine	Weight gain: 1.11 (0.88 to 1.41)	NS
		Sleepiness: 0.76 (0.55 to 1.05)	NS
		Increased duration of sleep: 0.54 (0.32 to 0.91)	P = 0.02; more frequent with quetiapine
		Akinesia: 1.06 (0.73 to 1.54)	NS
		Constipation: 0.86 (0.50 to 1.46)	NS
		Galactorrhea: 5.96 (0.72 to 49.02)	NS
		Orgasmic dysfunction: 1.22 (0.74 to 2.03)	NS
Kim et al. (2024) ¹⁶ RCT	Lurasidone vs. quetiapine	Akathisia: 22.6% vs. 15.4%	NS
		Dizziness: 2.9% vs. 8.7%	NS
		Somnolence: 2.0% vs. 7.7%	NS
		Tremor: 6.9% vs. 2.9%	NS
		Nausea: 16.7% vs. 2.9%	P = 0.001; more frequent with lurasidone
		Constipation: 4.9% vs. 9.6%	NS
		Anxiety: 6.9% vs. 2.9%	NS
		Blood prolactin increased: 7.8% vs. 1.9%	P = 0.048; more frequent with lurasidone
		Muscle rigidity: 5.9% vs. 1%	NS
		Weight: -0.24 kg vs. 1.65 kg	P < 0.001; significant increase with quetiapine
		Serum glucose levels: 1.69 mg/dL vs. 2.77 mg/dL	P < 0.001; significant higher with quetiapine
		Total cholesterol: -3.92 mg/dL vs. 11.13 mg/dL	P = 0.040; significant higher with quetiapine

Study citation and study design	Interventions vs. comparators	Results RR (95% CI) or % or mean change from baseline	Notes
		HDL-C: 0.06 mg/dL vs. -0.68 mg/dL	NS
		LDL-C: -4.84 mg/dL vs. 5.32 mg/dL	P = 0.032; significant higher with quetiapine
		Triglyceride: 0.63 mg/dL vs. 24.21 mg/dL	P = 0.033; significant higher with quetiapine
		ECG; EPS; Suicidal ideation and behaviour	NS

CI = confidence interval; ECG = electrocardiography; EPS = extrapyramidal side effects; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein; MA = meta-analysis; NS = not statistically significant; RR = relative risk; SMD = standardized mean difference; RCT = randomized controlled trial; SR = systematic review; vs. = versus.

Table 25: Summary of Recommendations in Included Guidelines for Schizophrenia

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
VA/DoD (2023)¹⁷	
Management of first-episode psychosis and schizophrenia — Pharmacological interventions for psychosis	
<i>“We recommend the use of an antipsychotic medication other than clozapine for the treatment of an acute episode in individuals with schizophrenia or first-episode psychosis who have previously responded to antipsychotic medications. The choice of antipsychotic medication should be based on an individualized evaluation that considers patient characteristics and side effect profiles of the different antipsychotic medications.”</i> p. 35 Supporting evidence: 3 RCTs, 14 SRs and MAs, and a review of guidelines. The Working Group considered antipsychotic medications as a class rather than individually when formulating the recommendation. FGAs are more prone to produce persistent EPS, while SGAs are less likely than FGAs to cause EPS but might be associated with increased risk of weight gain and other metabolic abnormalities, including hyperlipidemias and type 2 diabetes mellitus. Therefore, the choice of antipsychotic medication should be based on an individualized evaluation that considers patient-specific characteristics and preferences and the side effect profiles of the medications.	Strength: Strong for Category: Reviewed, newly added
<i>“We recommend the use of an antipsychotic medication for the maintenance treatment of schizophrenia to prevent relapse and hospitalization in individuals with schizophrenia who have responded to treatment. Choice of antipsychotic medication should be based on an individualized evaluation that considers patient-specific characteristics and side effect profiles of the different antipsychotic medications.”</i> p. 35 Supporting evidence: 8 SRs, 3 RCTs The Working Group considered antipsychotic medications as a class, rather than considering each medication individually. The choice of antipsychotic medication should be based on an individualized evaluation that considers individual characteristics, including culturally influenced beliefs about mental illness and medication, and preferences and the side effect profiles of the different antipsychotic medications.	Strength: Strong for Category: Reviewed, newly added

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
<i>"We suggest a trial of another antipsychotic medication for individuals with schizophrenia who do not respond to (or tolerate) an adequate trial of an antipsychotic medication. Choice of antipsychotic medication should be based on an individualized evaluation that considers patient-specific characteristics and side effect profiles of the different antipsychotic medications."</i> p. 36 Supporting evidence: 13 SRs, 2 RCTs, 1 case-control study, and 1 cohort study The Working Group's confidence in the quality of the evidence was very low. However, the benefits of monotherapy outweighed the potential harm of no medication, polypharmacy, or continuing a medication with significant adverse events. Choice of antipsychotic medication should be based on an individualized evaluation that considers patient-specific characteristics and side effect profiles of the different antipsychotic medications.	Strength: Weak for Category: Reviewed, newly added
JSNPP (2021)¹⁸	
Which antipsychotics are recommended for the treatment of first-episode psychosis?	
<i>"SGAs are recommended over FGAs."</i> p. 276 <i>"SGAs are the better choice for treatment of first-episode psychosis."</i> p. 277 Supporting evidence: 2 SRs, 10 RCTs, 1 guideline, 1 cohort study Both short-term and long-term studies showed that SGAs had a low discontinuation rate due to side effects and tended to have a lower all-cause of discontinuation.	Degree of recommendation: 2 Strength of evidence: A
<i>"No specific drugs are recommended when selecting SGAs."</i> p. 276 <i>"It is recommended to choose the specific SGA after considering the individual factors in each case."</i> p. 277 Supporting evidence: 2 SRs, 9 RCTs, and 1 cohort study There are no MAs that directly compare SGAs, and it was not possible to strictly define a drug's relative superiority or inferiority. There are RCTs and open-label trials of SGAs for first-episode psychosis, but it is difficult to establish a ranking among drugs because there are no RCTs or network meta-analyses which directly compared all SGAs. However, meta-analyses which examine the efficacy and safety of SGAs and FGAs suggest that SGAs should be prioritized for first-episode psychosis.	Degree of recommendation: 2 Strength of evidence: D
What is the optimal dose of antipsychotics for first-episode psychosis?	
<i>"Quetiapine has been shown to be effective at 311.4-506 mg/d."</i> p. 278 Supporting evidence: 5 RCTs The average dose in 2 trials, which showed efficacy with short-term (6 to 12 weeks) administration, was 358.3 to 413.8 mg/d. The average dose in 3 trials, which showed efficacy with long-term (1 year) administration, was 311.4 to 506 mg/d.	Degree of recommendation: NR Strength of evidence: C
<i>"Treatment discontinuation rates (of quetiapine) tended to be higher than with other antipsychotics in long-term administration trials."</i> p. 278 Supporting evidence: 3 RCTs The all-cause of treatment discontinuation rate of quetiapine in long-term trials was 53% to 82.3% and tended to be higher than for other antipsychotics.	Degree of recommendation: NR Strength of evidence: B

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
What is the optimal period for determining the therapeutic response of antipsychotics in first-episode psychosis?	
<i>"Approximately 60%-70% of patients may respond to treatment by 2-4 weeks after starting treatment with antipsychotics for first-episode psychosis, but patients may respond after this period as well. Therefore, it is desirable to wait at least 2-4 weeks after the start of treatment to determine the response to treatment.</i> <i>However, increasing the dose while paying attention to side effects may be considered before the 2 to 4-week period if the response to treatment is insufficient at low doses."</i> p. 280 Supporting evidence: 2 guidelines, 1 review, 4 observational studies Many treatment guidelines for acute schizophrenia with multiple episodes recommend an effect decision period of 4 to 6 weeks. However, treatment response by 2 to 4 weeks after starting treatment has been suggested in different studies, which showed that about 60% to 70% of patients with first-episode psychosis may have a treatment response by 2 to 4 weeks.	Degree of recommendation: 2 Strength of evidence: D
What is the optimal treatment duration for antipsychotics for preventing the recurrence of first-episode psychosis?	
<i>"Continuing the administration of antipsychotics for at least one year is recommended for preventing the recurrence of first-episode psychosis."</i> p. 281 Supporting evidence: SR, 3 RCTs The SR reported that antipsychotics had a significant recurrence prevention effect relative to placebos over a half-year to 1-year timespan. Evidence from additional RCTs also supported continued antipsychotic treatment for as long as possible when remission of symptoms is first seen in first-episode psychosis.	Degree of recommendation: 1 Strength of evidence: A
Which is more appropriate, increasing the dose of the current antipsychotic or switching to another one?	
<i>"It is desirable to attempt to increase the dose rather than switching the antipsychotic during at the time of the recurrence/relapse of schizophrenia."</i> p. 282 Supporting evidence: 4 guidelines Many guidelines recommend increasing doses to the maximum level while confirming adherence and side effects and observing for a sufficient period before switching.	Degree of recommendation: 2 Strength of evidence: D
Which antipsychotics have evidence of usefulness and recommended dose at the time of recurrence/relapse of schizophrenia?	
<i>"Quetiapine is effective at over 250 mg/d and may be effective even at over 150 mg/d. Certainty of evidence for efficacy is weak to moderate, but tolerability is high"</i> p. 284 Supporting evidence: 4 RCTs One RCT showed a higher efficacy than placebo at doses of more than 150 mg/d, and 1 RCT showed a higher efficacy than placebo at doses of more than 250 mg/d. However, the remaining 2 RCTs did not show any differences from placebo at doses of 300 mg/d to 800 mg/d.	Degree of recommendation: NR Strength of evidence: B, C, A
Which antipsychotics are favourable for reducing the relapse rate or for continuing treatment in the maintenance phase?	
<i>"It is desirable to select SGAs over FGAs. There is insufficient evidence regarding comparisons between SGAs. No recommendations are made for drug selection since factors of each case need to be considered."</i> P. 289 Supporting evidence: 1 SR, 2 RCTs A meta-analysis that compared the relapse prevention effects of FGAs and SGAs. There were no significant differences between the 2 groups for discontinuation due to all	Degree of recommendation: 2 Strength of evidence: B

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
reasons, discontinuation due to side effects, and adherence. However, SGAs tended to show superior values for discontinuation due to all reasons and discontinuations due to side effects. There are only a few RCTs that directly compared individual SGAs, and there is little evidence on which drug is superior.	

EPS = extrapyramidal symptoms; FGA = first-generation antipsychotics; JSNPP = Japanese Society of Neuropsychopharmacology; MA = meta-analysis; NR = not reported; RCT = randomized controlled trial; SGAs = second-generation antipsychotics; SR = systematic review; VA/DoD = Veterans Affairs/Department of Defense.



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