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Draft Comparative Effectiveness Review

Number XX

**Antipsychotics in Adults: Comparative Effectiveness
of First-Generation versus Second-Generation
Medications**

Prepared for:

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see <http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm>

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (<http://www.effectivehealthcare.ahrq.gov>) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly. We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

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Structured Abstract

Objectives: To compare individual first-generation antipsychotics (FGAs) with individual second-generation antipsychotics (SGAs) in adults (18 to 64 years) with schizophrenia or schizophrenia-related psychoses or bipolar disorder.

Data Sources: We conducted comprehensive searches in 10 electronic databases up to July 2010. We hand searched conference proceedings, clinical trials registers, and reference lists of relevant studies. We contacted experts in the field and authors of relevant studies.

Methods: Two reviewers independently conducted study selection, assessed methodological quality, extracted data, and graded the strength of evidence. We conducted a descriptive analysis and performed meta-analyses when appropriate.

Results: A total of 20 comparisons were made across 112 studies of schizophrenia or schizophrenia-related psychoses. A total of six comparisons were made across 11 studies of bipolar disorder. The trials (n=120) had an unclear (65 percent) or high (35 percent) risk of bias. Cohort studies (n=2) were methodologically good.

Core illness symptoms: For schizophrenia, clozapine was favored over chlorpromazine for general symptoms; however, results were discordant for total psychosis score. Olanzapine was favored over fluphenazine for positive symptoms, general symptoms, and total psychosis score. Findings for haloperidol versus clozapine were discordant for total psychosis score depending on the scale. Results for haloperidol versus olanzapine were discordant for positive symptoms depending on the scale; olanzapine was favored for negative symptoms, general symptoms, and total psychosis score. Differences favored haloperidol over quetiapine for total psychosis score based on one scale. Risperidone was favored over haloperidol for positive symptoms and total psychosis score. Olanzapine was favored over perphenazine for positive symptoms and general symptoms; perphenazine was favored for total psychosis score.

For bipolar disorder, haloperidol was favored over ziprasidone for total mania score. No other differences were observed across comparisons.

Functional outcomes and health care system utilization: Evidence came primarily from single studies. The variety of measures assessed across studies precludes firm conclusions regarding the overall comparative effectiveness of individual drugs for patient functioning. No differences were observed across comparisons for health care system utilization.

Adverse effects: No differences found in mortality for chlorpromazine versus clozapine. Haloperidol showed fewer cases of metabolic syndrome compared with clozapine but no difference compared with olanzapine. For diabetes mellitus, haloperidol was more favorable than olanzapine.

Other outcomes: For schizophrenia, few significant differences were found across comparisons and outcomes. For all significant findings, the SGA was preferred. No differences were observed in health-related quality of life. For bipolar disorder, there were few comparisons or significant differences.

Subgroups: The most common subgroups were race and treatment resistance. No notable differences were found compared with the overall results.

Conclusion: This is a comprehensive synthesis of the evidence on the comparative effectiveness and safety of individual FGAs compared with individual SGAs. Few significant differences of clinical importance for outcomes of effectiveness were found. Patient-important outcomes were rarely assessed. Data were sparse for the four key adverse effects deemed a priori to be most clinically important.

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Executive Summary

Introduction

Antipsychotic medications are used to treat and manage symptoms for several psychiatric disorders and are commonly categorized into two classes. First-generation antipsychotics (FGAs), also known as “typical antipsychotics,” were developed in the 1950s. Second-generation antipsychotics (SGAs), also known as “atypical antipsychotics,” emerged in the 1980s. Excluding the unique neurochemistry of clozapine (a SGA), differences in the affinities of FGAs and SGAs mainly on dopamine, cholinergic and 5-HT receptors appear to contribute to the development of abnormal involuntary movement side-effects. It appears that this particular “typical” side-effect clinically distinguishes FGAs from SGAs. There is ongoing research testing these proposed mechanisms of action within each class with respect to the neurobiology of different psychiatric disorders.^{1,2} In 2003, 3.2 million patients in the United States were prescribed an antipsychotic medication; of these patients, almost 2.3 million were taking a SGA.³ An estimated \$2.82 billion was spent in the country on these medications, with SGAs accounting for 93 percent of this expenditure.³

Both FGAs and SGAs are associated with a range of side effects. FGAs are commonly associated with various side effects including extrapyramidal symptoms (EPS), dry mouth, sedation, and, in severe cases, tardive dyskinesia and neuroleptic malignant syndrome. SGAs are generally thought to have a lower risk of motor side effects, but are associated with a higher risk of weight gain, elevated lipid and prolactin levels, and development of type 2 diabetes mellitus.

Individuals taking antipsychotics may stop taking their medication for a number of reasons, including adverse effects and a lack of improvement in their symptoms;⁴ therefore, ongoing evaluations of drug effectiveness and models of patient consumerism are essential.

This comparative effectiveness review provides a comprehensive synthesis of the evidence examining the benefits and harms associated with the use of FGAs and SGAs that are approved by the U.S. Food and Drug Administration (FDA). The focus of this report is adults aged 18 to 64 years with schizophrenia, schizophrenia-related psychoses, or bipolar disorder.

Key Questions

The following key questions were investigated in the report:

1. For adults (aged 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what is the comparative efficacy and effectiveness of FGAs versus SGAs for improving core illness symptoms? The following core symptoms were considered:
 - a. Schizophrenia or related psychoses: positive (i.e., delusions and hallucinations) and negative (i.e., passive or apathetic social withdrawal and blunted affect) symptoms, and general psychopathology (i.e., preoccupation, lack of insight, and motor retardation).
 - b. Core illness symptoms for bipolar disorder: mood, motor activity or energy, sleep, speech, behavior, and mood stability.

2. For adults (aged 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what is the comparative effectiveness of FGAs versus SGAs for improving functional outcomes and decreasing health care system utilization?
 - a. Functional outcomes include any of the following: employment or personal earnings, social relatedness or functioning, encounters with the legal system, sexual function or dysfunction, functional capacity, and living situation.
 - b. Health care system utilization include: time to hospitalization or re-hospitalization because of mental illness and all other causes; rates of hospitalization or re-hospitalization; mean hospital bed days; length of hospitalization stay; rates of emergency department visits; attendance in day care programs; and use of ancillary caseworkers.

3. For adults (aged 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, do FGAs and SGAs differ in medication-associated adverse events and safety? Adverse events included:
 - a. Overall adverse events.
 - b. Specific adverse events:
 - i. *Major*: mortality, cerebrovascular disease-related events, development of diabetes mellitus, diabetic ketoacidosis, neuroleptic malignant syndrome, seizures, tardive dyskinesia, cardiomyopathies and cardiac arrhythmias, agranulocytosis, suicide-related behaviors, and death by suicide.
 - ii. *General*: EPS, weight gain, agitation, constipation, sedation, elevated cholesterol, adverse events related to prolactin elevations, galactorrhea or bloody galactorrhea, weight gain, hypotension, and metabolic changes (including changes in glucose levels, triglycerides, lipids, and the risk of developing diabetes).
 - c. Study withdrawals and time to withdrawal because of adverse events.
 - d. Persistence and reversibility of adverse events.

4. For adults (aged 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what is the comparative effectiveness of FGAs versus SGAs for the following other outcomes:
 - a. Relapse and remission rates.
 - b. Medication adherence and persistent use (and associated dosing and time to discontinuation of treatment).
 - c. Patient insight into illness.
 - d. Health-related quality of life.
 - e. Patient satisfaction.
 - f. Comorbidity: end points of victimization, homelessness, and substance abuse.
 - g. Patient-reported outcomes.
 - h. Ability to obtain and retain employment and succeed in job duties.
 - i. Concomitant use of other medications, especially those used to treat EPS.
 - j. Patient preferences.

5. For adults (aged 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what is the comparative effectiveness and risks of FGAs versus SGAs in subgroups defined by the following variables?
 - a. Disorder subtypes.
 - b. Gender.
 - c. Age group (18–35 years, 36–54 years, 55–64 years).
 - d. Race.
 - e. Comorbidities.
 - f. Drug dosage.
 - g. Followup period.
 - h. Previous exposure to antipsychotics.
 - i. Treatment of a first episode versus treatment in the context of previous episodes.
 - j. Treatment resistance.

Methods

Literature Search

We conducted comprehensive searches in the following electronic databases: MEDLINE®, EMBASE, PsycINFO, International Pharmaceutical Abstracts, CINAHL, ProQuest® Dissertations and Theses–Full Text, Cochrane Central Register of Controlled Trials (CENTRAL), and Scopus™. The searches are up to date to July 2010. For the questions on adverse effects, we also searched U.S. National Library of Medicine’s TOXLINE® and the MedEffect™ Canada Adverse Drug Reaction Database.

We hand searched proceedings for the Annual Convention of the American Psychiatric Association (2009–2011), the International College of Neuropsychopharmacology (2009–2011), and the International Society for Bipolar Disorders (2009–2011). We searched clinical trials registers, contacted experts in the field, and contacted authors of relevant studies. In addition, we reviewed the reference lists of reviews and guidelines and searched for articles citing the studies that met our inclusion criteria using Scopus™ Citation Tracker.

Study Selection

Two reviewers independently screened titles and abstracts to determine if an article met the broad inclusion criteria. We independently rated each article as: “include,” “exclude,” or “unclear.” We retrieved the full text of studies identified as “include” or “unclear.” Two reviewers independently reviewed each article using a priori eligibility criteria and a standardized form. We resolved discrepancies through discussion and consensus or by third-party adjudication.

We included studies if they: were randomized (RCTs) or nonrandomized controlled trials (nRCTs), or prospective or retrospective cohort studies with a followup of two years or greater; included adults aged 18 to 64 years with schizophrenia or related psychoses or bipolar disorder; and compared an FDA-approved FGA to an FDA-approved SGA.

Quality Assessment and Rating the Body of Evidence

Two reviewers independently assessed the methodological quality of included studies and resolved disagreements through discussion or third party adjudication. We assessed RCTs and nRCTs using the Cochrane Collaboration’s Risk of Bias (RoB) tool. We assessed cohort studies

using the Newcastle-Ottawa Scale (NOS). A priori, the research team developed decision rules regarding application of the tools.

Two reviewers independently evaluated the overall strength of the evidence using the EPC GRADE approach and resolved discrepancies through discussion. We examined the following four major domains: risk of bias (low, medium, or high), consistency (inconsistency not present, inconsistency present, unknown, or not applicable), directness (direct or indirect), and precision (precise or imprecise). We assigned an overall evidence grade of high, moderate, low, or insufficient. We graded core illness symptoms in the categories of positive symptoms, negative symptoms, general symptoms, and total score. We provided a grade for each different scale that was used. We graded the following adverse effects that were deemed to be most clinically important a priori: diabetes mellitus, mortality, tardive dyskinesia, and major metabolic syndrome.

Data Extraction

Two reviewers independently extracted data using standardized data extraction forms and resolved discrepancies through consensus. We extracted information on study characteristics, population, interventions and dosing regimens, outcomes assessed, results, and funding source. When there were multiple reports of the same study, we referenced the primary or most relevant study and extracted only additional data from companion reports.

Data Analysis

We presented evidence tables for all studies and a qualitative description of results. We conducted meta-analyses using random effects models to answer the key questions when studies were sufficiently similar in terms of design, population, interventions, and outcomes. We presented results separately for the conditions of interest (schizophrenia or schizophrenia-related psychoses and bipolar disorder). Within each condition, we presented results separately for each individual FGA versus SGA comparison. We quantified statistical heterogeneity using the I-squared (I^2) statistic.

Applicability

We assessed the applicability of the body of evidence using the PICOTS format (population, intervention, comparator, outcomes, timing of outcome measurement, and setting). We reported factors that may potentially limit applicability in the results.

Results

Description of Included Studies

The searches identified 8,798 unique study reports. A total of 122 primary publications and 139 companion publications were included. The studies included 118 RCTs, 2 NRCTs, and 2 retrospective cohorts. The studies were published between 1974 and 2010. The majority of studies were multicenter ($n = 67$, 56 percent), involved inpatients ($n = 60$, 50 percent), and were most often conducted in North America ($n=50$, 42 percent). The number of participants in the studies ranged from 10 to 15,767 (median = 86 [interquartile range (IQR), 36 to 298]). The average age of study participants ranged from 21 to 51 years (median = 38 years [IQR, 33 to 41]). The length of followup ranged from 1 day to 22 years (median = 8 weeks [IQR, 6 to 26

weeks]). Seventy percent of studies (n = 85) had some form of support from the pharmaceutical industry.

Overall, 111 studies examined schizophrenia or schizophrenia-related psychoses, 10 studies examined bipolar disorder, and one study included both. A total of 20 and 6 drug comparisons were made for schizophrenia and bipolar disorder, respectively (Table ES–1).

Table ES–1. Comparisons examined in the included studies (n = 122)

Schizophrenia or Schizophrenia-Related Psychoses		Bipolar disorder	
Comparison	Number of studies	Comparison	Number of studies
Chlorpromazine vs. clozapine	10	Chlorpromazine vs. clozapine	1
Chlorpromazine vs. olanzapine	1	Haloperidol vs. aripiprazole	2
Chlorpromazine vs. quetiapine	1	Haloperidol vs. olanzapine	2
Chlorpromazine vs. ziprasidone	1	Haloperidol vs. quetiapine	1
Fluphenazine vs. olanzapine	2	Haloperidol vs. risperidone	4
Fluphenazine vs. quetiapine	1	Haloperidol vs. ziprasidone	1
Fluphenazine vs. risperidone	1		
Haloperidol vs. aripiprazole	7		
Haloperidol vs. asenapine	1		
Haloperidol vs. clozapine	10*		
Haloperidol vs. olanzapine	37*		
Haloperidol vs. quetiapine	12*		
Haloperidol vs. risperidone	41 [†]		
Haloperidol vs. ziprasidone	9 [‡]		
Perphenazine vs. aripiprazole	1		
Perphenazine vs. olanzapine	1		
Perphenazine vs. quetiapine	1		
Perphenazine vs. risperidone	1		
Perphenazine vs. ziprasidone	1		
Trifluoperazine vs. clozapine	1		

* includes 1 cohort study; † includes one cohort study and one NRCT; ‡ includes one NRCT

Methodological Quality of Included Studies

None of the 120 RCTs and nRCTs was rated as having a low risk of bias. The majority of the trials (n = 78, 65 percent) had an unclear risk of bias; the remaining trials (n = 42, 35 percent) had a high risk of bias. In the majority of cases, trials were assessed at unclear risk of bias due to unclear reporting with respect to sequence generation, concealment of allocation, and methods of blinding. The most common reasons for trials to be assessed as high risk of bias were lack of blinding and inadequate handling or reporting of outcome data.

Data were collected retrospectively in both cohort studies. The methodological quality of the cohort studies was good.

Results of Included Studies

The results are presented by the key question they address. Within each key question, we present results by condition and comparison. Tables with summary of findings for efficacy and safety are presented below.

Key Question 1: Core illness symptoms. The findings for core illness symptoms are presented for each condition in Table ES–2. Comparisons and outcomes for which there was insufficient evidence to draw a conclusion are not displayed in the tables. The evidence comparing individual

FGAs and SGAs was insufficient to draw conclusions for the following comparisons: fluphenazine versus quetiapine, fluphenazine versus risperidone, haloperidol versus asenapine, and chlorpromazine versus olanzapine.

For schizophrenia or schizophrenia-related psychoses, seven studies provided data on core illness symptoms for chlorpromazine versus clozapine. No differences were found for positive symptoms. Moderate evidence showed benefits for clozapine for general symptoms. Moderate evidence also suggested benefits for clozapine in terms of total score; however, low evidence suggested benefits for chlorpromazine for total score.

One study provided data on core illness symptoms for fluphenazine versus olanzapine. The results showed significant differences in favor of olanzapine for positive symptoms, general symptoms, and total score. The strength of evidence was considered low for each outcome. No studies provided data for negative symptoms.

Five studies provided data on core illness symptoms for haloperidol versus aripiprazole. No differences were found for positive symptoms, negative symptoms, or total score. The strength of evidence was low for each outcome. No studies provided data for general symptoms.

Ten studies provided data on core illness symptoms for haloperidol versus clozapine. No significant differences were found for positive symptoms, negative symptoms, or general symptoms. The strength of evidence was low for these three outcomes. The findings were discordant for total score: low levels of evidence showed benefits for haloperidol in terms of the CGI-EI scale, whereas moderate levels of evidence favored clozapine in terms of the CGI-I and CGI-S scales.

Thirty-four studies provided data on core illness symptoms for haloperidol versus olanzapine. Results were discordant for positive symptoms: a significant difference favoring haloperidol was observed based on the Prepulse Inhibition test, whereas a significant benefit for olanzapine was found based on the Young Mania rating scale (YMRS). No differences were observed for the other five scales assessed. The strength of evidence was low for all outcomes. Olanzapine was favored for negative symptoms, general symptoms, and total score. The strength of evidence for these outcomes was low to moderate.

Ten studies provided data on core illness symptoms for haloperidol versus quetiapine. No significant differences were found for positive symptoms, negative symptoms, or general symptoms. A significant difference favoring haloperidol was found for total score. The strength of evidence for each of these outcomes was low.

Thirty-one studies provided data on core illness symptoms for haloperidol versus risperidone. The results showed significant benefits for risperidone in terms of positive symptoms and total score. The strength of evidence was low for positive symptoms, and low to moderate for total score depending on the scale used. There was no significant difference for negative symptoms and no studies provided data for general symptoms.

Seven studies provided data on core illness symptoms for haloperidol versus ziprasidone. There were no significant differences in terms of negative symptoms or total score. The strength of evidence was considered low. No studies provided data on positive symptoms or general symptoms.

One study provided data on core illness symptoms for perphenazine versus olanzapine. There were significant benefits for olanzapine in terms of positive symptoms and general symptoms. The results showed significant benefits for perphenazine for total score. The strength of evidence for each of these outcomes was low.

A total of 11 studies included patients with bipolar disorder. The most frequent comparison was haloperidol versus risperidone (four RCTs). No significant differences were found in total symptom score. Two studies compared haloperidol versus olanzapine and found no significant differences in total symptom score. One study compared haloperidol with ziprasidone and found a significant difference favoring haloperidol for total symptom score. The strength of evidence was considered low for all comparisons.

Table ES–2. Summary of the strength of evidence for core illness symptoms (Key Question 1)

Outcome	Comparison (number of studies)	Strength of evidence	Summary
Schizophrenia and schizophrenia-related psychoses			
Positive symptoms	Chlorpromazine vs. clozapine (2 RCTs)	Low	No significant difference.
	Fluphenazine vs. olanzapine (1 RCT)	Low	Significant difference favoring olanzapine for HAM–A and PANSS.
	Haloperidol vs. aripiprazole (3 RCTs)	Low	No significant difference.
	Haloperidol vs. clozapine (4 RCTs)	Low	No significant difference.
	Haloperidol vs. olanzapine (20 RCTs)	Low	Significant difference favoring haloperidol for PPI. Significant difference favoring olanzapine for YMRS. No differences in ACES, BPRS, PANSS, or SAPS.
	Haloperidol vs. quetiapine (5 RCTs)	Low	No significant difference.
	Haloperidol vs. risperidone (24 RCTs)	Low	Significant difference favoring risperidone for PPI. No difference for PANSS or SAPS.
	Perphenazine vs. olanzapine (1 RCT)	Low	Significant difference favoring olanzapine for PANSS.
Negative symptoms	Haloperidol vs. aripiprazole (3 RCTs)	Low	No significant difference.
	Haloperidol vs. clozapine (5 RCTs)	Low	No significant difference.
	Haloperidol vs. olanzapine (18 RCTs)	Low to moderate	Significant difference favoring olanzapine for BPRS, HAM–D, PANSS, and SANS (moderate). No difference for CDS–S (low).
	Haloperidol vs. quetiapine (6 RCTs)	Low	No significant difference.
	Haloperidol vs. risperidone (25 RCTs)	Low	No significant difference.
	Haloperidol vs. ziprasidone (2 RCTs + 1 cohort)	Low	No significant difference.
	Perphenazine vs. olanzapine (1 RCT)	Low	Significant difference favoring olanzapine for PANSS.
General symptoms	Chlorpromazine vs. clozapine (2 RCTs)	Moderate	Significant difference favoring clozapine.
	Fluphenazine vs. olanzapine (1 RCT)	Low	Significant difference favoring olanzapine.
	Haloperidol vs. clozapine (3 RCTs)	Low	No significant difference.

ACES = Agitation–Calmness Evaluation Scale; BPRS = Brief Psychiatric Rating Scale; CDS–S = Calgary Depression Scale for Schizophrenia; CGI–EI = Clinical Global Impressions–Efficacy Index; CGI–I = Clinical Global Impressions–Improvement; CGI–S = Clinical Global Impression–Severity; HAM–A = Hamilton Rating Scale for Anxiety; HAM–D = Hamilton Rating Scale for Depression; MADRS = Montgomery–Asberg Depression Rating Scale; PANSS = Positive and Negative Syndrome Scale; PPI = Prepulse inhibition; pts = patients; RCT = randomized controlled trial; SAPS = Scale for the Assessment of Positive Symptoms; SCL = Symptom Check List; YMRS = Young Mania Rating Scale

Table ES–2. Summary of the strength of evidence for core illness symptoms (KQ1) (continued)

Outcome	Comparison (number of studies)	Strength of evidence	Summary
Schizophrenia and schizophrenia-related psychoses			
General symptoms	Haloperidol vs. olanzapine (11 RCTs)	Low	Significant difference favoring olanzapine for BPRS. No difference for PANSS.
	Haloperidol vs. quetiapine (4 RCTs)	Low	No significant difference.
Total score	Chlorpromazine vs. clozapine (6 RCTs)	Low to moderate	Significant difference favoring chlorpromazine based on CGI–EI scale (low). Significant difference favoring clozapine for CGI–S (moderate).
	Fluphenazine vs. olanzapine (1 RCT)	Low	Significant difference favoring olanzapine.
	Haloperidol vs. aripiprazole (4 RCTs)	Low	No significant difference.
	Haloperidol vs. clozapine (7 RCTs)	Low to moderate	Significant difference favoring haloperidol for CGI–EI (low). Significant differences favoring clozapine for CGI–I (moderate), and CGI–S (moderate). No differences for BPRS (low) and PANSS (low).
	Haloperidol vs. olanzapine (23 RCTs)	Low to moderate	Significant difference favoring olanzapine for MADRS (moderate) and PANSS (moderate). No difference for BPRS (low) or CGI–I (low).
	Haloperidol vs. quetiapine (10 RCTs)	Low	Significant difference favoring haloperidol for CGI–S. No differences for BPRS, CGI–I, or PANSS.
	Haloperidol vs. risperidone (23 RCTs)	Low to moderate	Significant difference favoring risperidone for SCL–90–R (low). No difference for BPRS (low), CGI–I (low), CGI–S (moderate), or YMRS (low).
	Haloperidol vs. ziprasidone (6 RCTs + 1 cohort)	Low	No significant difference.
	Perphenazine vs. olanzapine (1 RCT)	Low	Significant difference favoring perphenazine for PANSS.
Bipolar Disorder			
Total score	Haloperidol vs. olanzapine (2 RCT)	Low	No significant difference.
	Haloperidol vs. risperidone (4 RCTs)	Low	No significant difference.
	Haloperidol vs. ziprasidone (1 RCT)	Low	Significant difference favoring haloperidol for YMRS.

Key Question 2: Functional outcomes and health care system utilization. The findings for functional outcomes and health care system utilization are presented for each condition and comparison in Table ES–3. We did not assess the strength of evidence for outcomes in KQ2.

Results for functional outcomes were available from 13 head-to-head comparisons in studies of patients with schizophrenia or schizophrenia-related psychoses. No significant differences in functional outcomes were observed between groups for: fluphenazine versus olanzapine,

quetiapine or risperidone; and perphenazine versus olanzapine, quetiapine, risperidone, and ziprasidone. However, in most cases evidence came from single studies.

Significant differences in functional outcomes were found in studies comparing haloperidol with SGAs (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone); however, the drug favored was not always consistent. Further, in several cases the proportion of significant findings was small compared to the number of outcomes assessed. For example, 16 trials provided data on 79 different functional capacity measures for haloperidol versus olanzapine. In most cases, there were only single studies contributing to each measure. Overall, significant results were found for 24 of the measures; however, in some cases haloperidol was favored whereas in other cases olanzapine was favored. The variety of functional measures assessed across the studies precludes firm conclusions regarding the overall comparative effectiveness of individual drugs in terms of patient functioning.

Only one trial comparing haloperidol with olanzapine provided data on functional outcomes in patients with bipolar disorder. Significant differences were found favoring olanzapine in terms of the number of individuals actively working for pay. No differences were found for household or work activities impairment.

Table ES–3. Summary of evidence for functional outcomes, healthcare system utilization, and other outcomes (KQ2)

Outcome	Comparison (number of studies)	Summary
Schizophrenia and schizophrenia-related psychoses		
Functional outcomes	Fluphenazine vs. olanzapine (2 RCTs)	No significant difference in functional capacity.
	Fluphenazine vs. quetiapine (1 RCT)	No significant difference in sexual function/dysfunction.
	Fluphenazine vs. risperidone (1 RCT)	No significant difference in sexual function/dysfunction.
	Haloperidol vs. aripiprazole (1 RCT)	Significant difference favoring haloperidol for Fagerstrom Tolerance Questionnaire.
	Haloperidol vs. clozapine (4 RCTs)	Significant difference favoring clozapine for three functional capacity outcomes. No differences for remaining 27 functional capacity outcomes.
	Haloperidol vs. olanzapine (17 RCTs)	Significant difference favoring haloperidol for three functional capacity outcomes. Significant difference favoring olanzapine for 23 outcomes. No significant differences for remaining 53 reported functional capacity outcomes, social relatedness or functioning, sexual function or dysfunction, or encounters with the legal system.
	Haloperidol vs. quetiapine (3 RCTs)	Significant difference favoring haloperidol for one functional capacity outcome. Significant difference favoring quetiapine for three functional capacity measures. No significant differences for other 29 functional capacity outcomes or sexual function/dysfunction.

* For all comparisons reported, data were available on rates of hospitalization/rehospitalization; for haloperidol vs. olanzapine, data also available for mean hospital bed days. RCT = Randomized Controlled Trial

Table ES–3. Summary of evidence for functional outcomes, healthcare system utilization, and other outcomes (KQ2)

Outcome	Comparison (number of studies)	Summary
Schizophrenia and schizophrenia-related psychoses		
Functional outcomes (continued)	Haloperidol vs. risperidone (13 RCTs)	Significant difference favoring risperidone for 15 functional capacity measures and for one measure of social relatedness/ functioning. Significant difference favoring haloperidol for two functional capacity measures and one measure of social relatedness/ functioning. No significant differences for other 58 functional capacity outcomes, other 10 social relatedness/ functioning outcomes, economic independence, or attitude regarding drugs.
	Haloperidol vs. ziprasidone (1 RCT)	Significant difference favoring ziprasidone for one functional capacity measure. No differences for five other functional capacity measures or sexual function/ dysfunction.
	Perphenazine vs. olanzapine (1 RCT)	No significant difference in the number of patients with paid employment.
	Perphenazine vs. quetiapine (1 RCT)	No significant difference in the number of patients with paid employment.
	Perphenazine vs. risperidone (1 RCT)	No significant difference in the number of patients with paid employment.
	Perphenazine vs. ziprasidone (1 RCT)	No significant difference in the number of patients with paid employment.
Health care system use*	Chlorpromazine vs. clozapine (1 RCT)	No significant difference.
	Haloperidol vs. olanzapine (2 RCTs)	No significant difference.
	Haloperidol vs. quetiapine (1 RCT)	No significant difference.
	Haloperidol vs. risperidone (3 RCTs)	No significant difference.
	Haloperidol vs. ziprasidone (2 RCTs)	No significant difference.
	Perphenazine vs. olanzapine (1 RCT)	No significant difference.
	Perphenazine vs. quetiapine (1 RCT)	No significant difference.
	Perphenazine vs. risperidone (1 RCT)	No significant difference.
Perphenazine vs. ziprasidone (1 RCT)	No significant difference.	
Bipolar Disorder		
Functional outcomes	Haloperidol vs. olanzapine (1 RCT)	Significant difference favoring olanzapine for number of active workers (i.e., working for pay). No difference in household or work activities impairment.

Key Question 3: Medication-associated adverse events and safety. The findings for the adverse events that were deemed most clinically important are summarized in Table ES–4. The evidence comparing individual FGAs and SGAs was insufficient to draw conclusions for the following outcomes and comparisons: tardive dyskinesia (chlorpromazine versus clozapine, chlorpromazine versus ziprasidone, haloperidol versus clozapine, haloperidol versus quetiapine, haloperidol versus ziprasidone), mortality (chlorpromazine versus ziprasidone, haloperidol versus aripiprazole, haloperidol versus olanzapine), diabetes mellitus (haloperidol versus olanzapine, haloperidol versus quetiapine, haloperidol versus risperidone, perphenazine versus olanzapine, perphenazine versus quetiapine, perphenazine versus risperidone, perphenazine versus ziprasidone), and metabolic syndrome (perphenazine versus quetiapine, perphenazine versus risperidone, perphenazine versus ziprasidone).

Two trials provided data on mortality for chlorpromazine versus clozapine and no significant difference was found. For metabolic syndrome, one trial provided data for haloperidol versus clozapine and showed significantly fewer cases for haloperidol. Two trials provided data for haloperidol versus olanzapine and no differences were found. The strength of evidence for these comparisons was low suggesting that further research may change the results and change our confidence in the results.

Data were also recorded for general measures of adverse events (AEs) and specific AEs by physiological system (e.g., cardiovascular, endocrine). For general measures of AEs, significant differences were found in the incidence of patients with AEs and withdrawals due to AEs for several comparisons. Most often the comparison included haloperidol, and the risk was consistently higher for the FGA. The most frequently reported AEs with significant differences were in the category of EPS and most often involved a comparison with haloperidol. In the vast majority of cases, the SGA had the preferred AE profile for EPS.

Table ES–4. Summary of the strength of evidence for medication-associated adverse events and safety (KQ3)

Adverse event	Comparison (number of studies)	Strength of evidence	Summary
Schizophrenia and schizophrenia-related psychoses			
Mortality	Chlorpromazine vs. clozapine (2 RCTs)	Low	No significant difference.
Metabolic syndrome	Haloperidol vs. clozapine (1 RCTs)	Low	Significantly less frequent with haloperidol.
	Haloperidol vs. olanzapine (2 RCTs)	Low	No significant difference.

RCT = Randomized Controlled Trial

Key Question 4: Other outcomes. The findings for other outcomes are presented for each condition and comparison in Table ES–5. We did not assess the strength of evidence for outcomes in KQ2.

Results for other outcomes were available for 14 head-to-head comparisons in studies of patients with schizophrenia or schizophrenia-related psychoses. Few significant differences were found across the comparisons and outcomes examined. For all significant findings, the SGA was preferred. The most commonly reported other outcome was response rate. A significant difference in response rates based on three studies was found favoring clozapine versus chlorpromazine. Olanzapine was favored over haloperidol for response rates based on 15 studies. Significant differences were found favoring aripiprazole over haloperidol for caregiver satisfaction (n = 1 RCT) and patient satisfaction (n = 1 RCT). Risperidone was favored over haloperidol for relapse rates (n = 6 RCT). Health-related quality of life was evaluated for the following comparisons and no significant differences were found: haloperidol versus olanzapine (4 RCTs), quetiapine (1 RCT), risperidone (3 RCTs) and ziprasidone (1 RCT); perphenazine versus olanzapine, quetiapine, risperidone and ziprasidone (1 RCT each).

Results for other outcomes were available for three head-to-head comparisons in studies of patients with bipolar disorder. Significant differences were found for health-related quality of life in one study comparing haloperidol versus olanzapine: haloperidol was favored for the mental summary score and olanzapine was favored for the physical summary score. One study showed a significant difference favoring haloperidol compared with ziprasidone for response rates.

Table ES–5. Summary of the evidence for other outcomes (KQ4)

Comparison (number of studies)	Summary
Schizophrenia and schizophrenia-related psychoses	
Chlorpromazine vs. clozapine (5 RCTs)	Significant difference in response rates favoring clozapine. No difference in remission rates.
Chlorpromazine vs. olanzapine (1 RCT)	No significant difference in response rates.
Chlorpromazine vs. quetiapine (1 RCT)	No significant difference in response rates.
Chlorpromazine vs. ziprasidone (1 RCT)	No significant difference in response rates.
Fluphenazine vs. olanzapine (1 RCT)	No significant difference in response rates.
Fluphenazine vs. quetiapine (1 RCT)	No significant difference in response rates.
Fluphenazine vs. risperidone (1 RCT)	No significant difference in response rates.
Haloperidol vs. aripiprazole (4 RCTs)	No significant difference in response rates or medication adherence. Significant difference favoring aripiprazole for caregiver satisfaction and patient satisfaction.
Haloperidol vs. asenapine (1 RCT)	No significant difference in response rates.
Haloperidol vs. clozapine (4 RCTs)	No significant differences in relapse rates, response rates, remission rates, or patient satisfaction.
Haloperidol vs. olanzapine (15 RCTs)	Significant difference favoring olanzapine for response rates. No significant difference for remission rates, medication adherence, patient insight into illness, or HRQoL.
Haloperidol vs. quetiapine (6 RCTs)	No significant difference in response rates, remission rates, or HRQoL.
Haloperidol vs. risperidone (22 RCTs)	Significant difference favoring risperidone for relapse rates. No significant difference for remission rates, medication adherence, patient satisfaction, or HRQoL.
Haloperidol vs. ziprasidone (7 RCTs)	No significant difference in response rates, remission rates, or HRQoL.
Perphenazine vs. olanzapine (1 RCT)	No significant difference in HRQoL.
Perphenazine vs. quetiapine (1 RCT)	No significant difference in HRQoL.
Perphenazine vs. risperidone (1 RCT)	No significant difference in HRQoL.
Perphenazine vs. ziprasidone (1 RCT)	No significant difference in HRQoL.
Bipolar Disorder	
Haloperidol vs. olanzapine (1 RCT)	No difference for relapse, response, or remission rates. Significant difference favoring haloperidol for HRQoL mental summary score. Significant difference favoring olanzapine for HRQoL physical summary score.
Haloperidol vs. quetiapine (1 RCT)	No significant difference in response or remission rates.
Haloperidol vs. ziprasidone (1 RCT)	Significant difference favoring haloperidol for response rates. No difference for remission rates.

RCT = Randomized Controlled Trial; HRQoL = health-related quality of life

Key Question 5: Subgroups. A total of 38 studies compared outcomes for predefined subgroups. Among the studies of patients with schizophrenia and schizophrenia-related psychoses, data were most often available for race and treatment resistance. The race most often examined was Asian. No notable differences were observed for the subgroups compared to the overall findings.

The only subgroup available for analysis in studies of patients with bipolar disorder was disorder subtype, specifically bipolar 1 and bipolar 2. The results were consistent with the overall findings. A significant difference favoring haloperidol compared with ziprasidone in terms of core illness symptoms (YMRS and total score) was found for patients with bipolar 1 disorder.

Applicability

This report included studies that compared an individual FGA to an individual SGA. Placebo-controlled studies or studies comparing a FGA versus another FGA, or a SGA versus another SGA, were not included. Therefore, the evidence is focused on the comparative effectiveness of FGAs versus SGAs, but not on their effectiveness compared to placebo or other active agents. Overall, there were 20 head-to-head comparisons across the relevant studies; however, within most comparisons there were few studies. The focus of FGA/SGA comparisons was in adults, aged 18 to 64 years, with schizophrenia or schizophrenia-related psychoses and bipolar disorder. The average age across studies ranged from 21 to 51 years (median = 38 years [IQR, 33 to 41]). Most studies were highly selective in patient enrolment and included patients who (1) met strict diagnostic criteria for case definition, (2) had few comorbidities, and (3) used few or no concomitant medications. Older adults, minorities, and the most seriously ill patients were also underrepresented. Such highly selective criteria may increase the likelihood of drug benefit and decrease the likelihood of AE occurrence. Almost half the studies involved hospitalized patients (inpatient treatment) (60 of 122 studies) or mixed inpatient and outpatient treatment populations (25 studies); relatively few studies examined only outpatient treatment populations (19 studies). As such we judge the results of this report to be applicable to patients in outpatient and inpatient treatment settings. Another factor that restricts the applicability is the limited duration of followup. Despite our efforts to identify long-term safety data from observational studies, only two retrospective cohort studies provided data for a minimum 2-year followup period.

Future Research

More longitudinal research is needed on the long-term comparative effectiveness of FGAs versus SGAs. Only two cohort studies were identified for this review that examined serious AEs with long-term antipsychotic use; however, these studies only examined two serious events and the strength of evidence was insufficient to draw conclusions: new-onset diabetes mellitus and tardive dyskinesia. Studies examining the naturalistic and long-term efficacy and, particularly, the safety of antipsychotics over the course of several years and across a number of important AEs are urgently required. Further, consensus is needed on the most important FGA/SGA comparisons for future studies; the most frequent FGA in the studies to date was haloperidol.

Short- and long-term evaluations of the effectiveness of FGAs and SGAs with patient subpopulations including patients with medical and neurological comorbidities are needed. Further, there is a need for studies investigating how drug dose, age, and other factors such as comorbidities influence the occurrence of serious AEs, which would help estimate possible risks in specific patient populations.

Future studies should examine functional naturalistic outcomes that are important to patients. These outcomes include health-related quality of life and other patient-reported outcomes, relationships, academic and occupational performance, and legal interactions.

Conclusions

Numerous studies provided data on core illness symptoms; however, many different scales were used to assess outcomes, which limited the quantitative pooling of data. Few notable differences of clinical importance were identified. The strength of evidence was low for most

comparisons suggesting that future research may change the results and change our confidence in the results.

Data on the relative effectiveness for functional outcomes, health care system utilization, and other outcomes were generally sparse. The variety of functional measures assessed across studies precluded firm conclusions regarding the overall effectiveness of individual drugs in terms of function. Few studies reported on health care system utilization or patient-important outcomes. Where health-related quality of life was assessed, no differences were found.

We included cohort studies with a minimum followup of two years in order to identify AEs of most clinical importance, including diabetes mellitus, mortality, tardive dyskinesia, and major metabolic syndrome. Only two studies with long-term followup were identified; hence, evidence on these important AEs is limited and urgently needed. A variety of AEs associated with numerous physiological systems were reported. The AEs most often reported involved EPS, which occurred more frequently for FGAs, particularly haloperidol, than for SGAs. Long-term longitudinal studies of at least 2-year duration are needed to detect important differences in the relative safety profile of individual FGAs and SGAs.

The evidence for important subgroups was limited. The most frequently examined subgroups were race and treatment resistance. There were no notable differences in outcomes for these subgroups compared to the overall results.

In summary, data on the comparative effectiveness of individual FGAs and SGAs precluded drawing firm conclusions for outcomes that are directly relevant to front-line clinical decisions. Overall, there were few significant differences of clinical importance. Outcomes potentially important to patients were rarely assessed. Data on long-term safety are lacking and urgently needed.

Comparative Effectiveness Review

Introduction

Antipsychotic medications are used to treat and manage symptoms for several psychiatric disorders and are commonly categorized into two classes. First-generation antipsychotics (FGAs), also known as “typical antipsychotics,” were developed in the 1950s. Second-generation antipsychotics (SGAs), also known as “atypical antipsychotics,” emerged in the 1980s. To date, FGAs have been classified according to their chemical structure which includes serotonin-dopamine antagonists and multi-acting receptor-targeted antipsychotics, whereas SGAs have been categorized according to their pharmacological properties as dopamine partial agonists. There is ongoing research testing these proposed mechanisms of action within each class with respect to the neurobiology of different psychiatric disorders.^{1,2}

In 2003, 3.2 million patients in the United States were prescribed an antipsychotic medication; of these patients, almost 2.3 million were taking a SGA.³ An estimated \$2.82 billion was spent in the country on these medications with SGAs accounting for 93 percent of this expenditure.³

FGAs were first developed in the 1950s for the treatment of psychosis (e.g., schizophrenia). Since then they have also been proven effective in the treatment of other conditions including acute mania, agitation, and bipolar disorder. Most FGAs are phenothiazine derivatives and are confounded by their varying degrees of dopamine (e.g., D1–D5), histamine, and cholinergic receptor antagonism. Today, there are 11 U.S. Food and Drug Administration (FDA)-approved and commercially available FGAs in the U.S., with chlorpromazine, perphenazine, and haloperidol being the most often prescribed (Table 1). The major differences between these three FGAs are their potency (low to high, respectively) and side-effect profiles.

The mechanisms of action and side-effects profiles of SGAs differ markedly from drug to drug. They have been proven effective for treating conditions similar to the FGAs by blocking the cerebral dopamine pathways. Currently, nine SGAs are FDA-approved and commercially available in the U.S., with clozapine, risperidone, and olanzapine being the most frequently prescribed (Table 1).

Both FGAs and SGAs are associated with a range of side effects. FGAs are commonly associated with extrapyramidal symptoms, dry mouth, sedation, and, in severe cases, tardive dyskinesia, and neuroleptic malignant syndrome (NMS). SGAs are generally thought to have a lower risk of motor side effects, but are associated with a higher risk of weight gain, elevated lipid and prolactin levels, and the development of type 2 diabetes mellitus.

Individuals taking an antipsychotic may stop taking their medication for a number of reasons including adverse side effects and lack of improvement in their symptoms.⁴ As a result, ongoing evaluations of drug efficacy and models of patient consumerism are essential.

This comparative effectiveness review (CER) provides a comprehensive synthesis of the evidence examining the benefits and harms associated with the use of FDA-approved FGAs and SGAs. The focus of this report is on adults aged 18 to 64 years with schizophrenia, schizophrenia-related psychoses, and bipolar disorder. These illnesses are discussed in more detail in the sections that follow.

Table 1. List of antipsychotics included in the comparative effectiveness review

First-Generation Antipsychotics	Second-Generation Antipsychotics
Chlorpromazine	<u>Monotherapy</u>
Droperidol	Aripiprazole
Fluphenazine	Asenapine
Haloperidol	Clozapine
Loxapine	Iloperidone
Perphenazine	Lurasidone
Pimozide	Olanzapine
Prochlorperazine	Paliperidone
Thioridazine	Quetiapine
Thiothixene	Risperidone
Trifluoperazine	Ziprasidone
	<u>Combination therapy</u>
	Olanzapine plus fluoxetine

Schizophrenia and Related Psychoses

Schizophrenia is a heterogeneous syndrome that includes disturbances in language, perception, cognition, social relatedness, and volition.⁵ Symptoms include positive (i.e., delusions and hallucinations) and negative (i.e., passive or apathetic social withdrawal and blunted affect) symptoms and general psychopathology (i.e., preoccupation, lack of insight, and motor retardation). Onset of symptoms typically occurs in late adolescence or early adulthood, with approximately 0.4 to 0.6 percent of the population affected worldwide.⁶ Antipsychotic medications represent the first-line treatment for patients with schizophrenia and have been the mainstay treatment since the 1950s. The American Psychiatric Association (APA) currently recommends that selection of an antipsychotic medication should be based on a patient's previous responses to the drug and its side-effect profile.⁷

In the treatment of schizophrenia, FGAs act on the dopaminergic system by blocking the dopamine type 2 (D2) receptors.⁸ This mechanism, however, leads to a variety of extrapyramidal side effects (e.g., tremor, slurred speech, akathisia, and dystonia), some of which appear after long-term exposure (e.g., tardive dyskinesia).^{9,10} Although these antipsychotics are effective against the positive symptoms of schizophrenia, they have been considered to be ineffective in treating negative symptoms.¹¹ Such symptoms particularly play a critical role in producing the severe social and vocational disabilities experienced by many patients with schizophrenia.¹²

The search for antipsychotic medications that manage both the positive and negative symptoms of schizophrenia lead to the emergence of a second generation of antipsychotic drugs. SGAs have shown greater benefits in many outcome domains compared with FGAs⁹ and have been replacing FGAs as the treatments of choice. Although SGAs were developed to improve on the shortcomings of FGAs, they also have significant limitations in terms of side effects. As a class, they have a more favorable profile in terms of extrapyramidal side effects and tardive dyskinesia, but produce other side effects, including sedation, hypotension, weight gain, and sexual dysfunction.¹³ SGAs have also been associated with metabolic side effects (e.g., elevated lipids and development of type 2 diabetes mellitus),¹³ but it is unclear whether these are secondary to, independent of, or causative of weight gain. The long-term consequences of SGAs largely remain unknown.¹⁴

There is debate surrounding the efficacy of SGAs on negative symptoms, with several published reports indicating no clear advantage over FGAs.^{12,15} Trials in which SGAs have been evaluated are criticized for 1) including patients with positive and negative symptoms, making it unclear whether a drug had direct effects, indirect effects, or both, on primary negative

symptoms¹⁵ and 2) deriving data on negative symptoms from short-term trials that focused on patients selected on the basis of positive symptoms (or, for longer-term trials, on the basis of clinical stability).¹² Recent findings from the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CutLASS 1)^{16,17} and the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study^{18,19} found few differences in the effectiveness of SGAs and FGAs in patients with nonrefractory schizophrenia. Subsequent meta-analyses have generally confirmed these results²⁰ and have helped to provide a clearer picture of the comparative effectiveness of the two classes of antipsychotic medications.

The disconnect between the research findings of CutLASS 1, CATIE, and meta-analyses (showing no difference between FGAs and SGAs), individual efficacy trials (pharmaceutical industry trials favoring SGAs), and the prescribing patterns of clinicians (favoring SGAs) make this review an important step toward bringing together rigorous evidence for making clinical decisions and shaping health care policy.

Scales for Assessing the Core Symptoms of Schizophrenia

The most frequently used scales for measuring core symptoms in patients with schizophrenia are the Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression (CGI), and Positive and Negative Syndrome Scale (PANSS). Additionally, the Calgary Depression Scale for Schizophrenia (CDS-S), Montgomery-Åsberg Depression Rating Scale (MADRS), Scale for the Assessment of Negative Symptoms (SANS), and Scale for the Assessment of Positive Symptoms (SAPS) are often used to gauge positive and negative symptoms in this patient population.

The BPRS is a 7-point scale for measuring psychiatric symptoms (e.g., depression, anxiety, hallucinations, and unusual behavior). Depending on the version, a total score of 18 to 24 points can be accumulated, with a higher score reflecting worse symptoms. The items on the scale are: somatic concern, anxiety, depression, suicidality, guilt, hostility, elated mood, grandiosity, suspiciousness, hallucinations, unusual thought content, bizarre behavior, self-neglect, disorientation, conceptual disorganization, blunted affect, emotional withdrawal, motor retardation, tension, uncooperativeness, excitement, distractibility, motor hyperactivity, mannerisms, and posturing.

The CGI scale was developed for use in National Institute of Mental Health (NIMH)-sponsored clinical trials to provide a clinician-oriented assessment of the patient's global function before and after study medication is given. CGI scales are commonly used for measuring symptom severity (CGI-S), treatment response or improvement (CGI-I), and the efficacy of treatments (CGI-Efficacy Index). The former two scales are measured on a 7-point scale and the latter is measured on a 4 x 4-point scale.

The PANSS is used for measuring symptom severity following a 45-minute clinical interview with patient and reviewing relevant reports from family members and primary care hospital workers. Each of 30 symptoms is rated from 1 (absent) to 7 (extreme). Symptoms are grouped into three subscales: positive symptoms (i.e., delusions, conceptual disorganization, hallucinations, hyperactivity, grandiosity, suspiciousness or persecution, and hostility), negative symptoms (i.e., blunted affect, emotional withdrawal, poor rapport, passive or apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking), and general psychopathology symptoms (i.e., somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and

insight, disturbance of volition, poor impulse control, preoccupation, and active social avoidance).

The CDS–S consists of nine items that are rated 0 to 3 following a structured interview. The MADRS is a generic depression diagnostic questionnaire used by psychiatrists to measure the severity of depressive episodes. This scale consists of 10 items (i.e., apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts). The SANS and SAPS are designed to assess negative (i.e., affective blunting, alogia (impoverished thinking), avolition or apathy, anhedonia or asociality, and disturbance of attention) and positive (i.e., hallucinations, delusions, bizarre behavior, and positive formal thought disorder) symptoms, respectively, on 6-point scales from 0 (not at all) to 5 (severe).

Bipolar Disorder

Bipolar disorder is characterized by severe fluctuations in mood, activity, thought, and behavior.⁵ The disorder involves one or more episodes of mania or mixed mood, which are associated with increased psychomotor activity, excessive social extroversion, decreased need for sleep, impulsivity, impairment in judgment, and grandiose mood. Patients may experience delusions, paranoid thinking, and extreme agitation. Bipolar 2 disorder is characterized by at least one hypomanic episode and at least one major depressive episode. Prevalence of bipolar disorder is 0.4 to 1.6 percent in community samples and has an average age of onset of 20 years.⁵ The APA (2002) recommends the following treatment plan: 1) polytherapy (lithium or valproate in conjunction with an antipsychotic) for severe manic or mixed episodes; and 2) monotherapy (lithium, valproate, or an antipsychotic) for less ill patients. The APA states that SGAs are preferred over FGAs because of their side-effect profile.²¹

Commonly used scales for measuring core symptoms in bipolar disorder are the Clinical Global Impression–bipolar version (CGI–BP), Global Assessment Scale (GAS), and Young Mania Rating Scale (YMRS). CGI–BP was developed for rating the severity of manic and depressive episodes and the degree of change from the immediately preceding phase and from the worst phase of illness. GAS is a single-item scale for evaluating overall patient functioning (i.e., 1 (sickest person) to 100 (healthiest person) divided into 10 equal intervals). The YMRS scale is an 11-item multiple-choice diagnostic questionnaire for psychiatrists to measure the severity of manic episodes. Items include elevated mood, increased motor activity, sexual interest, sleep, irritability, speech (rate and amount), thought disorder, thought content, aggressive behavior, appearance, and insight.

The Key Questions

From mid-December 2009 to mid-January 2010, the draft Key Questions (KQs) for this report were posted for public comment on the AHRQ Effective Health Care Program Web site. The Technical Expert Panel, Evidence-based Practice Center, and AHRQ reviewed the comments that we received. We made the following changes based on this feedback:

1. The terminology of “typical” and “atypical” antipsychotics was changed to “first-generation” and “second-generation” antipsychotics in the title and throughout the KQs, protocol, and report.
2. KQ 1 will focus on the core symptoms, and KQ 2 will focus on functional outcomes.

3. Study inclusion in the CER was not limited by drug dosage.
4. Individual antipsychotic medications, rather than a particular class, were set as the interventions and comparators for this review.
5. Relapse and remission rates were included as key outcomes.
6. The search strategy was expanded to include studies from 1950 onward to capture all studies that compared FGAs with SGAs.
7. The search strategy was expanded to include randomized trials, cohort studies (for serious adverse events; see point 8 below), and systematic reviews that may answer the KQs.
8. To capture data on long-term serious adverse events, the inclusion criteria were modified to include cohort studies that compare FGAs with SGAs, have a followup period of at least 2 years and present data on at least one serious adverse event as determined by the Technical Expert Panel (i.e., type 2 diabetes mellitus, mortality, tardive dyskinesia, and major metabolic syndromes).
9. We added the following outcomes of interest:
 - Key symptoms:
 - Core symptoms, including and maintenance of mood stability (particularly for bipolar disorder).
 - Measures of neurocognition for schizophrenia: YMRS, MADRS, and CGI-BP.
 - Adverse effects:
 - Weight gain, hypotension, and metabolic changes (including changes in glucose levels, triglycerides, and lipids and the risk of developing diabetes).
 - Other outcomes:
 - Comorbidity: end points of victimization, homelessness, and substance abuse.
 - Patient-reported outcomes.
 - Ability to obtain and retain employment and succeed in job duties.
 - Concomitant use of other medications, especially those used to treat extrapyramidal symptoms.
 - Patient preferences.
10. Proposed subgroup analyses were revised to include dosage, length of followup, previous exposure to antipsychotics, treatment of a first episode versus treatment in the context of previous episodes, and treatment resistance.

The final revised key questions are as follows:

KQ 1: For adults (aged 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what is the comparative efficacy and effectiveness of FGAs versus SGAs for improving core illness symptoms?

Population: Adults (aged 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder.

Interventions: Any commercially available FDA-approved FGA.

Comparators: Any commercially available FDA-approved SGA.

Outcomes: Improvement or change in disorder-specific and nonspecific symptoms.

The following symptoms are included for each disorder:

- 1) Core illness symptoms for schizophrenia or related psychoses: positive (i.e., delusions and hallucinations) and negative (i.e., passive or apathetic social withdrawal and blunted affect) symptoms, and general psychopathology (i.e., preoccupation, lack of insight, and motor retardation).
- 2) Core illness symptoms for bipolar disorder: mood, motor activity or energy, sleep, speech, behavior, and mood stability.

Timing: All time points; the last time point will be assessed if data on multiple time points are provided.

Settings: All settings, including treatment in hospital and outpatient settings.

KQ 2: For adults (aged 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what is the comparative effectiveness of FGAs versus SGAs for improving functional outcomes and decreasing health care system utilization?

Population: See KQ 1 above.

Interventions: See KQ 1 above.

Comparators: See KQ 1 above.

Outcomes:

- 1) Functional outcomes include any of the following: employment or personal earnings, social relatedness or functioning, encounters with legal system, sexual function or dysfunction, functional capacity, and living situation.
- 2) Health care system utilization include: time to hospitalization or re-hospitalization because of mental illness and all other causes; rates of hospitalization or re-hospitalization; mean hospital bed days; length of hospitalization stay; rates of emergency department visits; attendance in day care programs; and use of ancillary caseworkers.

Timing: See KQ 1 above.

Settings: See KQ 1 above.

KQ 3: For adults (aged 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, do FGAs and SGAs differ in medication-associated adverse events and safety?

Population: See KQ 1 above.

Interventions: See KQ 1 above.

Comparators: See KQ 1 above.

Outcomes: Disorder-specific and -nonspecific adverse events:

- 1) Overall adverse events.
- 2) Specific adverse events:
 - a. *Major:* mortality, cerebrovascular disease-related events, development of diabetes mellitus, diabetic ketoacidosis, neuroleptic malignant syndrome, seizures,

tardive dyskinesia, cardiomyopathies and cardiac arrhythmias, agranulocytosis, suicide-related behaviors, and death by suicide.

b. *General*: extrapyramidal side effects, weight gain, agitation, constipation, sedation, elevated cholesterol, adverse events related to prolactin elevations, galactorrhea or bloody galactorrhea, weight gain, hypotension, and metabolic changes (including changes in glucose levels, triglycerides, lipids, and the risk of developing diabetes).

3) Study withdrawals and time to withdrawal because of adverse events.

4) Persistence and reversibility of adverse events.

Timing: See KQ 1 above.

Settings: See KQ 1 above.

KQ 4: For adults (aged 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what is the comparative effectiveness of FGAs versus SGAs for other outcomes?

Population: See KQ 1 above.

Interventions: See KQ 1 above.

Comparators: See KQ 1 above.

Outcomes:

1) Relapse and remission rates.

2) Medication adherence and persistent use (and associated dosing and time to discontinuation of treatment).

3) Patient insight into illness.

4) Health-related quality of life.

5) Patient satisfaction.

6) Comorbidity: end points of victimization, homelessness, and substance abuse.

7) Patient-reported outcomes.

8) Ability to obtain and retain employment and succeed in job duties.

9) Concomitant use of other medications, especially those used to treat extrapyramidal symptoms.

10) Patient preferences.

Timing: See KQ 1 above.

Settings: See KQ 1 above.

KQ 5: For adults (aged 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what is the comparative effectiveness and risks of FGAs versus SGAs in subgroups defined by the following variables?

1) Disorder subtypes.

2) Gender.

3) Age group (18–35 years, 36–54 years, 55–64 years).

- 4) Race.
- 5) Comorbidities.
- 6) Drug dosage.
- 7) Followup period.
- 8) Previous exposure to antipsychotics.
- 9) Treatment of a first episode versus treatment in the context of previous episodes.
- 10) Treatment resistance.

Population: See KQ 1 above.

Interventions: See KQ 1 above.

Comparators: See KQ 1 above.

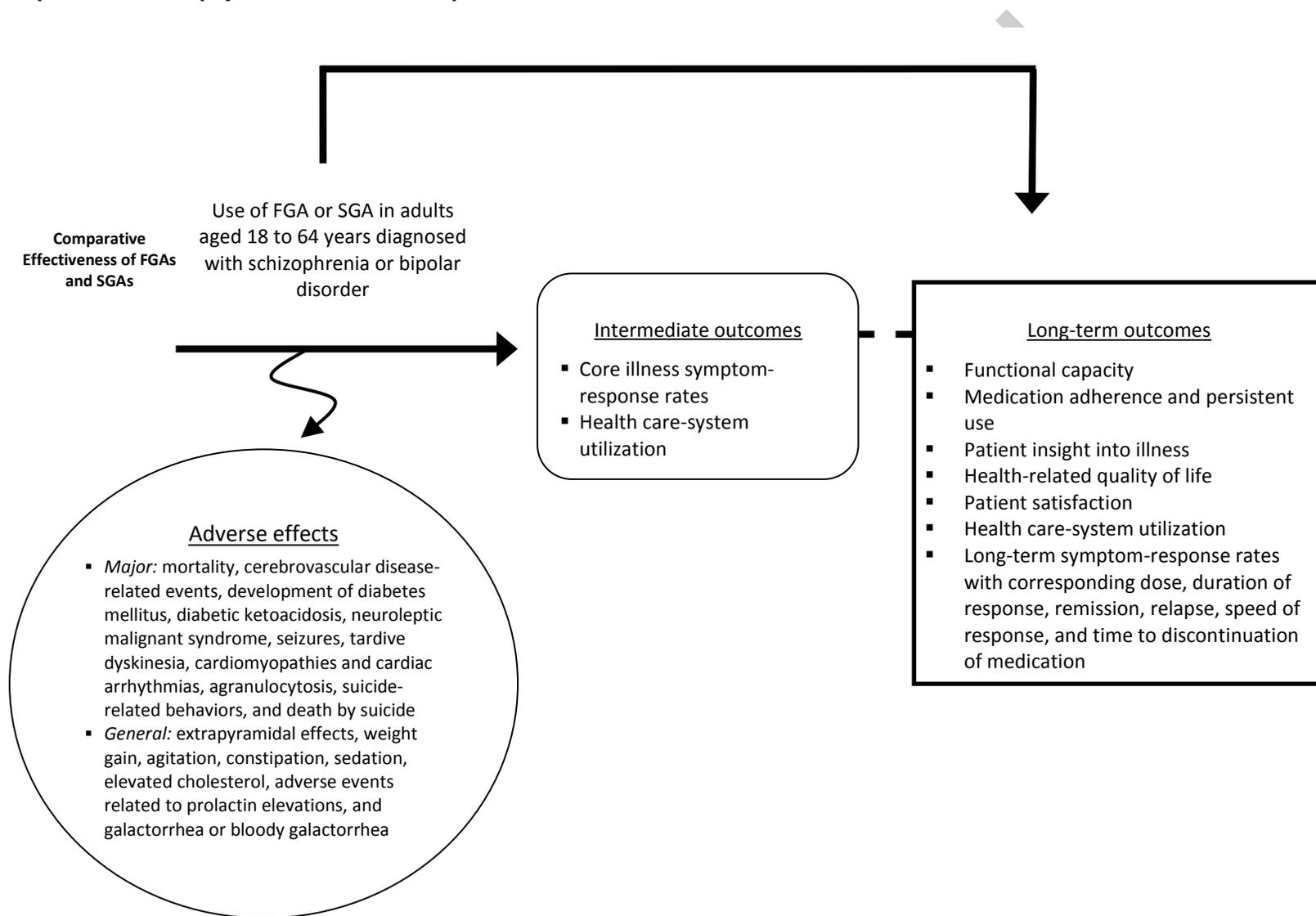
Outcomes: Core illness symptoms (see KQ 1), functional capacity and decreasing health care-system utilization (see KQ 2), adverse events (see KQ 3), or other outcomes (KQ 4).

Timing: See KQ 1 above.

Settings: See KQ 1 above.

Figure 1 depicts the key questions within the context of the framework described in the previous section. We will compare the efficacy and effectiveness of commercially available FDA-approved FGAs and SGAs in a population of adults (18–64 years of age) who have been diagnosed with schizophrenia, schizophrenia-related psychoses, or bipolar disorder by using 1) intermediate outcomes such as core illness symptom-response rates, health care-system utilization (KQ 1, KQ 2, and KQ 5); 2) long-term outcomes such as functional capacity, medication adherence and persistent use, patient insight into illness, health-related quality of life, patient satisfaction, health care-system utilization, and long-term symptom-response rates with corresponding dose, duration of response, remission, relapse, speed of response time, time to discontinuation of medication (KQ 1, KQ 2, KQ 4, and KQ 5); or 3) both intermediate and long-term outcomes. We will compare medication-associated AEs in FGAs and SGAs (KQ 3). We will compare the benefits and harms of FGAs and SGAs in different subpopulations (KQ 5), including but not limited to disorder subtypes, gender, age group (18–35 years, 36–54 years, 55–64 years), race, and comorbidities.

Figure 1. Analytic framework for evaluating the comparative effectiveness of FGAs and SGAs for treating adults with schizophrenia or schizophrenia-related psychotic illnesses or bipolar disorder.



FGA = first-generation antipsychotic; SGA = second-generation antipsychotic

Methods

This chapter describes the a priori methods we used to synthesize the evidence on the comparative effectiveness of first-generation (FGAs) and second-generation antipsychotics (SGAs) in the adult population. We describe the topic refinement process for developing the key questions. We outline the literature search strategy, the selection process for identifying relevant articles, the process for extracting data from eligible studies, the methods for assessing the methodological quality of individual studies and for grading the overall body of evidence, and our approach to data analysis and synthesis.

Topic Refinement and Technical Expert Panel

Our Evidence-based Practice Center (EPC) was commissioned to conduct a preliminary literature review to gauge the availability of evidence and to draft the key research questions for a full comparative effectiveness review (CER). Investigators from our EPC developed the key questions in consultation with the Agency for Healthcare Research and Quality (AHRQ), the Scientific Resource Center, and a Technical Expert Panel. AHRQ posted the initial questions on their website for public comment for a period of 1 month. After reviewing the public comments, we revised the key questions, and AHRQ approved the final questions.

We invited the Technical Expert Panel to provide high-level content and methodological expertise throughout the development of the CER.

Literature Search Strategy

Our research librarian conducted comprehensive searches in the following electronic databases: Ovid's MEDLINE[®] (1950 to July 2010), EMBASE (1950 to July 2010), PsycINFO (1950 to July 2010), International Pharmaceutical Abstracts (1950 to July 2010), Ebscohost CINAHL (1950 to July 2010), ProQuest[®] Dissertations and Theses—Full Text (1950 to July 2010), Cochrane Central Register of Controlled Trials (CENTRAL) (1950 to July 2010), and Scopus[™] (1950 to July 2010) (Appendix A–1 to A–5). We also searched the U.S. National Library of Medicine's TOXLINE[®] database (1950 to July 2010) and the MedEffect[™] Canada Adverse Drug Reaction Database (1950 to July 2010) to identify additional data on adverse events. The search was restricted to English language randomized controlled trials, nonrandomized controlled trials, cohort studies and review articles published, from 1950 to present, in adults.

We selected search terms by scanning search strategies of systematic reviews on similar topics and by examining index terms of potentially relevant studies. The detailed search strategies for each database are presented in Appendix A. We conducted the original searches between July 15 and July 22, 2010.

We hand searched conference proceedings of the American Psychiatric Association (2008–2010), the International College of Neuropsychopharmacology (2008–2010), and the International Society for Bipolar Disorders (2008–2010). To identify unpublished studies and studies in progress, we searched clinical trials registers, contacted experts in the field, and contacted authors of relevant studies. We reviewed the reference lists of reviews and guidelines to identify potential studies for inclusion. We searched for articles citing the studies that met the inclusion criteria for this review using Scopus[™] Citation Tracker. We searched grey literature

including the available data on the Food and Drug Administration website for relevant documents, and “Scientific Information Packets” were solicited from manufacturers of the FGAs and SGAs through the Scientific Resource Center. These materials were collected by asking the manufacturers for any material (published or unpublished) related to the key questions of the review. Manufacturers were also made aware of the fact that any materials submitted may become public due to the freedom of information act.

We used a Reference Manager[®] 11.0.1 (Thomson Reuters, Carlsbad, CA) bibliographic database to manage the results of our literature searches.

Criteria for Study Selection

Study selection was based on an a priori set of inclusion and exclusion criteria for study design, patient population, interventions, comparators, and outcome measures (Table 2). We screened the results of our searches using a two-step process. First, two reviewers independently screened the titles and abstracts (level 1 screening) to determine if an article met the broad inclusion or exclusion criteria for study design, population, and intervention. We rated each article as: “include,” “exclude,” or “unclear.” Records rated as “include” or “unclear” by both reviewers were advanced to level 2 screening.

Once potentially relevant articles were retrieved, two reviewers independently reviewed each study using a standardized screening form (Appendix B) that was developed and piloted by the review team. We resolved discrepancies through discussion and consensus or by third-party adjudication. Reviewers were not masked to the study authors, institution, or journal.²² We included studies that included at least 80 percent of patients from the adult population (18–64 years). Polypharmacy is common in clinical practice; therefore, studies including patients taking other medications were not excluded in the CER. Studies that included both patients with schizophrenia and patients with bipolar disorder, but did not provide separate results for these two conditions, were included only for the adverse events section (KQ 3).

Table 2. Inclusion and exclusion criteria

Inclusion criteria	
Publication type	English-language, full-text publications from 1950 to present
Study design	Randomized controlled trials Nonrandomized controlled trials Prospective and retrospective cohort studies
Participants	Adults (aged 18 to 64 years) with schizophrenia or related psychoses Adults (aged 18 to 64 years) with bipolar disorder
Interventions	Any currently available FDA-approved first-generation antipsychotic (Table 1)
Comparators	Any currently available FDA-approved second-generation antipsychotic (Table 1)
Outcomes	Outcomes presented in the key questions
Timing	All followup periods for trials; cohort studies must have a minimum followup period of 2 years
Setting	All settings

Exclusion criteria	
Publication type	Non-English language publications Conference abstracts
Study design	Observational study designs with no comparison group (e.g., case reports, case series, and cross-sectional studies) Case-controlled studies Prospective cohorts with followup <2 years Retrospective cohorts with followup <2 years
Participants	Pediatric population (aged <18 years) Geriatric population (aged >64 years)
Interventions and Comparators	Currently unavailable or non-FDA-approved FGA Currently unavailable or non-FDA-approved SGA Placebo Other interventions
Outcomes	None of the a priori identified outcomes were available from the trial report or through communication with the study's corresponding author

FDA = U.S. Food and Drug Administration; FGA = first-generation antipsychotic; SGA = second-generation antipsychotic

Assessment of Methodological Quality

We assessed the risk of bias of randomized controlled trials (RCTs) and nonrandomized controlled trials (nRCTs) using the Cochrane Collaboration's Risk of Bias (RoB) tool.²³ We assessed the methodological quality of cohort studies using the Newcastle-Ottawa Scale (NOS).²⁴ A priori, the research team developed decision rules regarding application of the tools.

For RCTs and nRCTs, we performed a domain-based risk of bias assessment according to the principles of the RoB tool. The domains were: (1) sequence generation (i.e., was the allocation sequence adequately generated?); (2) allocation concealment (i.e., was allocation adequately concealed?); (3) blinding of participants, personnel, and outcome assessors (i.e., was knowledge of the allocated intervention adequately prevented during the study?); (4) incomplete outcome data (i.e., were incomplete outcome data adequately addressed?); (5) selective outcome reporting (i.e., were reports of the study free of suggestion of selective outcome reporting?); and (6) other sources of bias (i.e., was the study apparently free of other problems that could put it at a high risk of bias?). Other sources of bias included baseline imbalances and appropriateness of crossover design. Each domain was rated as having "low," "unclear," or "high" risk of bias.

The overall assessment was based on the responses to individual domains. If one or more of the individual domains had a high risk of bias, we rated the overall score as high risk of bias. We rated the overall risk of bias as low only if all components were assessed as having a low risk of bias. The overall risk of bias was unclear for all other studies.

The NOS used to assess the quality of cohort studies is comprised of eight items that evaluate three broad domains: (1) the selection of the study groups; (2) the comparability of the groups; and (3) the assessment of study outcomes. Each item that is adequately addressed is awarded one star, except for the "comparability of cohorts" item, for which a maximum of two stars can be given. The overall score is calculated by tallying the stars. We considered a total score of 7 to 9 stars to indicate high quality, 4 to 6 stars to indicate moderate quality, and 3 or fewer stars to indicate poor quality.

Two reviewers independently performed quality assessment of the included studies and resolved disagreements through discussion or third party adjudication, as needed.

Data Extraction

Two reviewers independently extracted published data using standardized data extraction forms in Microsoft Word and Excel (Microsoft Corporation, Redmond, WA; Appendix B) forms. We resolved discrepancies through discussion and consensus or by third-party adjudication. We piloted the data extraction forms with three studies²⁵⁻²⁷ and resolved any identified issues. We extracted data on the following: general study characteristics (e.g., study design); population characteristics (e.g., age and sex); interventions and dosing regimens; numbers of patients allocated into relevant treatment groups; outcomes measured, and the results of each outcome, including measures of variability by relevant intervention arm. We also recorded the funding source, if reported.

When there were multiple reports of the same study we referenced the primary or most relevant study and extracted only additional data from companion reports. We contacted corresponding authors for data clarification and missing data. We imported all data into Microsoft Excel (Microsoft Corporation, Redmond, WA) for data management.

For dichotomous data, we extracted the number of participants with events and the total number of participants. For continuous outcomes, we extracted the mean with the accompanying measure of variance for each treatment group or the mean difference (MD) between treatments. We analyzed continuous data as post-treatment score or absolute difference (or change score) from baseline.²⁸ Multiple scales and scoring systems were used to measure the outcomes. Therefore, in addition to summary data and measure of variance, we extracted the scale and the type of analysis used in the study. For all outcomes, we used the definitions as reported by the authors of individual studies.

When data were available only in a graphical format, we extracted data from the available graphs using the distance measurement tool in Adobe Acrobat 8 Professional (Adobe Systems Inc., San Jose, CA). When data were not available for the measure of variability for continuous outcomes, we calculated the variability from the computed p-value; if not available, we imputed the variability from other studies in the same analysis. When relevant data for multiple followup or observation periods were reported, we extracted only the longest followup data. When studies incorporated multiple relevant treatment arms, we extracted data from all groups. We noted the specific intervention, dosage, and intervals of each intervention to determine if arms were clinically appropriate for pooling.

Applicability

Applicability of evidence distinguishes between effectiveness studies conducted in primary care or office-based settings that use less stringent eligibility criteria, assess health outcomes, and have longer followup periods than most efficacy studies.²⁹ The results of effectiveness studies are more applicable to the spectrum of patients in the community than efficacy studies, which usually involve highly selected populations. The applicability of the body of evidence was assessed following the PICOTS (population, intervention, comparator, outcomes, timing of outcome measurement, and setting) format used to assess study characteristics. Clinically important outcomes and participant characteristics are reported in the results.

Grading the Strength of a Body of Evidence

We evaluated the overall strength of the evidence for key outcomes. We used the EPC GRADE³⁰ approach, which is based on the standard GRADE approach developed by the Grading

of Recommendation Assessment, Development and Evaluation (GRADE) Working Group.³¹ We assessed the strength of evidence for the key core symptom scales (Table 3). The following four major domains were examined: risk of bias (low, medium, or high), consistency (inconsistency not present, inconsistency present, unknown, or not applicable), directness (direct or indirect), and precision (precise or imprecise).

For each key outcome for each comparison of interest, we assigned an overall evidence grade based on the ratings for the individual domains. The overall strength of evidence was graded as “high” (i.e., high confidence that the evidence reflects the true effect, and further research is very unlikely to change our confidence in the estimate of effect); “moderate” (i.e., moderate confidence that the evidence reflects the true effect, and further research may change our confidence in the estimate of effect and may change the estimate); “low” (i.e., low confidence that the evidence reflects the true effect, and further research is likely to change our confidence in the estimate of effect and is likely to change the estimate); or “insufficient” (i.e., evidence is either unavailable or does not permit estimation of an effect). When no studies were available for an outcome or comparison of interest, the evidence was graded as insufficient. A detailed explanation of the parameters used to grade the evidence and their operationalization are summarized in Appendix C. We used the GRADEprofiler software (GRADE Working Group) and modified the results in accordance with the EPC GRADE. Two reviewers independently graded the body of evidence and resolved disagreements through discussion.

Data Analysis

We present evidence tables for all included studies and a qualitative description of results. Where appropriate, we conducted meta-analyses to answer the key questions using Review Manager 5.01 (The Cochrane Collaboration, Copenhagen, Denmark).

We pooled binary data using the Mantel-Haenszel (MH) method and a random-effects model (DerSimonian and Laird).³² For continuous outcomes, we used the inverse variance (IV) method and a random-effects model (DerSimonian and Laird).³² We used Chi-square to test for significant heterogeneity reduction in partitioned subgroups. A Chi-square test of $p < 0.1$ was considered to be significant. We generated forest plots for KQ 1 when at least two trials could be pooled. For all other outcomes, we presented forest plots only if there were at least five included studies.

We combined RCTs and nRCTs in the meta-analyses. We synthesized cohort studies separately, as meta-analysis including both trials and cohort studies is controversial.³³ For continuous summary estimates where the same measure of analysis was used, we calculated the MD with 95 percent confidence intervals (CI). We reported dichotomous summary estimates as relative risk (RR) with accompanying 95 percent CI.

We tested for heterogeneity using an I^2 statistic and accompanying 95 percent uncertainty intervals.³⁴ Heterogeneity could not be estimated when only one study provided evidence for an outcome. We did not calculate uncertainty intervals around the I^2 statistic when less than three studies were pooled. If the lower uncertainty boundary for the I^2 had a value of 75 percent or greater, we considered this to represent substantial heterogeneity, thereby precluding pooling of studies. When there was substantial statistical heterogeneity in a meta-analysis, we explored heterogeneity in subgroup and sensitivity analyses, and removal of outliers.

Effect modifiers that we considered important to explain heterogeneity included specific intervention details (e.g., type and quantity), study design, and risk of bias. In addition, we conducted sensitivity analyses on studies with imputed data to determine if the imputations had

any effect on the effect estimate or heterogeneity. A priori subgroup analyses included disorder subtypes, gender, age group (18–35 years, 36–54 years, and 55–64 years), race, comorbidities, drug dosage, followup period, previous exposure to antipsychotics, treatment of a first episode versus treatment in the context of prior episodes, and treatment resistance.

When appropriate, we combined data across the available dosing arms before conducting the meta-analysis. We combined dichotomous arms by simple addition and combined continuous arms by calculating the pooled mean and standard deviation.

We did not include dichotomous data with zero values (i.e., no participant experienced an event) in meta-analyses because summary trial results were not estimable. However, we reported the results from these studies in the narrative synthesis for the relevant intervention.

We explored potential publication bias graphically through funnel plots for comparisons for which meta-analyses were conducted and when there were at least 10 studies in the analysis. Additionally, if bias was suspected, we quantitatively assessed publication bias using the Begg adjusted rank correlation test and Egger regression asymmetry test.³⁵

Table 3. Outcomes assessed by GRADE

KQ 1 – Key core symptoms			
Bipolar Disorder			
Sleep		Total score	
Number of Awakenings	Total REM Activity	CGI–BP	
Sleep efficiency (%)	Total sleep time (min)	HAM–D	
Stage REM (min)		YMRS	
Schizophrenia			
Positive symptoms	Negative symptoms	Total score	
ACES	BPRS	BPRS	
BPRS	CDS–S	CARS–M	
Covi Anxiety Scale	HAM–D	CGI–Efficacy Index	
HAM–A	PANSS	CGI–Improvement	
MOAS	SANS	CGI–Severity	
PANSS		GAF	
Prepulse inhibition	General symptoms	MADRS	
SAPS–C	BDI	NOSIE–30	
Startle Reactivity	BPRS	PANSS	
YMRS	PANSS	SADS	
		SCL–90–R	
		SWBUN	
		YMRS	
KQ 3 – Serious adverse events			
Diabetes Miletus	Major metabolic syndrome	Mortality	Tardive dyskinesia

ABS = Agitated Behavior Scale; ACES = Agitation–Calmness Evaluation Scale; BDI = Beck Depression Inventory; BPRS = Brief Psychiatric Rating Scale; CARS–M = Clinician–Administered Rating Scale for Mania; CDS–S = Calgary Depression Scale for Schizophrenia; CGI = Clinical Global Impressions; GAF = Global Assessment of Functioning; GRADE = Grading of Recommendations Assessment, Development and Evaluation; HAM–D = Hamilton Rating Scale for Depression; MADRS = Montgomery–Asberg Depression Rating Scale; MOAS = Modified Overt Aggression Scale; NOSIE = Nurses’ Observation Scale for Inpatient Evaluation; PANSS = Positive and Negative Syndrome Scale; SADS = Schedule for Affective Disorders and Schizophrenia; SANS = Scale for the Assessment of Negative Symptoms; SAPS–C = Scale for the Assessment of Positive Symptoms–change; SCL = Symptom Check List; SWBUN = Subjective Well-Being Under Neuroleptics scale; YMRS = Young Mania Rating Scale

Results

This chapter reports on the results of our literature review and synthesis. First, we describe the results of our literature search and selection process. Description of the characteristics and methodological quality of the studies follow. For Key Questions 1, 2, 4, and 5, we present the results of our analysis separately for schizophrenia and bipolar disorder and then by comparison. The findings for Key Question 3 are presented at the end of this section and are organized by comparison across both conditions. The results of all meta-analyses, including sample sizes, effect estimates, 95 percent confidence intervals (CI), and I^2 statistics, are available in tables for each comparison.

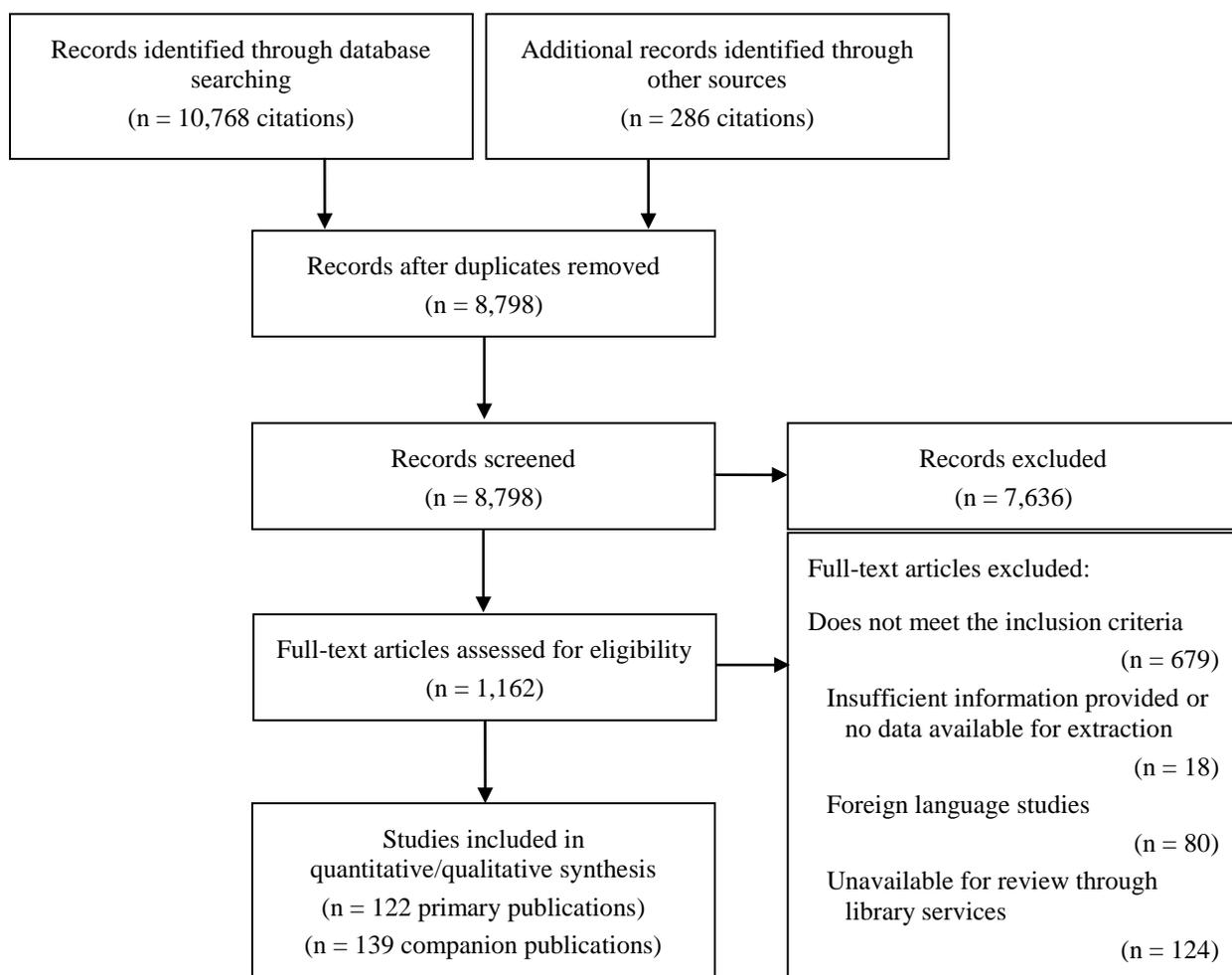
Several appendixes provide supporting information to the findings presented in this section. Appendix D provides a list of citations for the excluded and unobtained studies. Risk of bias assessments for trials are available in Appendix E and F, and quality assessments for cohort studies are available in Appendix G. A description of the included studies and the characteristics of interventions, characteristics of the patient populations, and patient flow through the trial are provided in Appendix H through J, respectively. Forest plots for the outcomes and funnel plots for comparisons and outcomes for which there were 10 or more studies are available in Appendix K and L. Appendixes are available at the Agency for Healthcare Research and Quality (AHRQ) website at <http://ahrq.gov/>.

Literature Search

All citations from electronic or hand searching and expert-nominated studies were pooled into a single database (Figure 2).³⁶ Of the 11,054 citations identified, 2,256 were duplicates, and 8,798 were unique study reports.

Following level 1 screening, 7,636 were excluded, and 1,162 were further evaluated for inclusion. Of these, 122 primary publications^{25-27,37-155} passed level 2 screening and were included in this comparative effectiveness review (CER). An additional 139 companion publications¹⁵⁶⁻²⁸⁶ passed level 2 screening and are also included. The characteristics of the publications excluded at level 2 screening are presented in Figure 2. The main exclusion criteria were publication type (e.g., case-control study, observational study with followup <2 years, or review article), population characteristics (e.g., patient age and other psychiatric condition), use of antipsychotic medications that are not Food and Drug Administration (FDA)-approved or medications no longer available in the U.S., and no extractable data related to the outcomes of interest (e.g., ongoing studies).

Figure 2. Flow diagram for study retrieval and selection.



Description of Included Studies

The 122 unique studies included in this review are described in detail in the evidence tables found in Appendixes H through J, and an overview is provided in Tables 4–6. We also found 139 companion articles that met our inclusion criteria. These companion articles were used for data that were not provided in the primary report. The studies were published between 1974 and 2010 (median = 2002 [interquartile range (IQR), 1999 to 2006]). Most of the studies were RCTs (98 percent) and were conducted in multicenter settings (56 percent). Studies were most frequently conducted in North America (42 percent). The number of enrolled participants ranged from 10 to 15,767 (median = 86 [IQR, 36 to 298]). The mean age of study participants ranged from 21 to 51 years (median = 38 years [IQR, 33 to 41]). The length of followup ranged from 1 day to 22 years (median = 8 weeks [IQR, 6 to 26 weeks]). Seventy percent of studies (n = 85) had some form of support from the pharmaceutical industry.

Table 4. Characteristics of included studies

Study design	RCT	118
	nRCT	2
	Retrospective cohort study	2
Number of centers	Multicenter	69
	Single center	50
	Two-center	3
Setting	Inpatient	61
	Outpatient	19
	Mixed	25
	Unclear/not reported	17
Country	Africa	2
	Asia	16
	Australia	1
	Europe	22
	Middle East	1
	North America	51
	South America	5
	International (including North America)	6
	International (not including North America)	18

nRCT = nonrandomized controlled trial; RCT = randomized controlled trial

111 studies examined adults with schizophrenia or schizophrenia-related psychoses, 10 studies examined adults with bipolar disorder, and one study examined adults with either diagnosis. Twenty comparisons of individual first-generation antipsychotics (FGAs) versus individual second-generation antipsychotics (SGAs) were made (Table 5 and 6).

Table 5. Drug comparisons available and number of studies for each comparison

	Aripiprazole	Asenapine	Clozapine	Olanzapine	Quetiapine	Risperidone	Ziprasidone
Chlorpromazine			11	1	1		1
Fluphenazine				2	1	1	
Haloperidol	9	1	10	39	13	46	10
Perphenazine	1			1	1	1	1
Trifluoperazine			1				

Table 6. Comparisons in included studies

Comparison	Schizophrenia (n)	Bipolar disorder (n)
1. Chlorpromazine vs. Clozapine	10	1
2. Chlorpromazine vs. Olanzapine	1	0
3. Chlorpromazine vs. Quetiapine	1	0
4. Chlorpromazine vs. Ziprasidone	1	0
5. Fluphenazine vs. Olanzapine	2	0
6. Fluphenazine vs. Quetiapine	1	0
7. Fluphenazine vs. Risperidone	1	0
8. Haloperidol vs. Aripiprazole	7	2
9. Haloperidol vs. Asenapine	1	0
10. Haloperidol vs. Clozapine	10	0
11. Haloperidol vs. Olanzapine	37	2
12. Haloperidol vs. Quetiapine	12	1
13. Haloperidol vs. Risperidone	42	4
14. Haloperidol vs. Ziprasidone	9	1
15. Perphenazine vs. Aripiprazole	1	0
16. Perphenazine vs. Olanzapine	1	0
17. Perphenazine vs. Quetiapine	1	0
18. Perphenazine vs. Risperidone	1	0
19. Perphenazine vs. Ziprasidone	1	0
20. Trifluoperazine vs. Clozapine	1	0

n = number; vs. = versus

Methodological Quality of Included Studies

Two independent reviewers assessed the risk of bias (RoB) of RCTs and nonrandomized trials (nRCTs) using the RoB tool and the methodological quality of cohort studies using the Newcastle Ottawa Scale (NOS). Consensus ratings are presented in Appendix E, Appendix F, and Appendix G, respectively. A summary of the overall quality trends by study design is presented below.

Randomized and Nonrandomized Controlled Trials

None of the 120 trials were rated as having a low risk of bias. The majority of the trials (n = 78)^{25-27,37,38,40,41,43-50,53-55,58,60,61,64,66,68,72-75,79,80,82-84,88,89,91-94,96-101,103-107,109,110,112,114-125,129-131,135,140,142-144,147,150-152,155} were rated as having an unclear risk of bias due to under-reporting in the trial reports. The key potential biases in these studies were related to selection bias (random sequence generation and allocation concealment) and performance bias (proper blinding of participants, personnel and outcome assessors) (Appendix F). The remaining trials (n = 42)^{39,42,51,52,56,57,59,62,63,65,67,69-71,76,78,81,85-87,90,95,108,111,113,126-128,132-134,136-139,141,145,146,148,149,153,154} were considered to have a high risk of bias. The key potential biases in these studies were related to attrition bias (incomplete outcome data) and performance bias (proper blinding of participants,

personnel and outcome assessors) (Appendix F). A summary of the distribution of scores across the risk of bias domains is presented in Table 7.

Table 7. Distribution of risk of bias scores by domain for trials

Domain	High	Unclear	Low
Adequate sequence generation	3 (2.50%)	103 (85.83%)	14 (11.67%)
Allocation concealment	1 (0.83%)	113 (94.17%)	6 (5.00%)
Blinding	19 (15.83%)	81 (67.50%)	20 (16.67%)
Incomplete outcome data addressed	24 (20.00%)	31 (25.83%)	65 (54.17%)
Free of selective reporting	1 (0.83%)	3 (2.50%)	116 (96.67%)
Free of other bias	0 (0.00%)	17 (14.17%)	103 (85.83%)

Cohort Studies

Two cohort studies^{77,102} met the inclusion criteria of follow-up ≥ 2 years and presented data on at least one serious adverse event (i.e., type 2 diabetes mellitus,¹⁰² mortality, tardive dyskinesia,⁷⁷ and major metabolic syndromes) The methodological quality of the cohort studies was good (8/9 stars for both studies). Both of the studies received only 1 of a possible 2 points for measures taken to ensure the comparability of cohorts.

Schizophrenia

For schizophrenia, we included 112 studies that enrolled a total of 78,171 patients. The individual studies are described in Appendix H through J. The results from the studies and pooled analyses, where appropriate, are presented in Tables 8 – 47. The following sections provide an overview of results according to key question: 1) core illness symptoms; 2) functional outcomes and health care system utilization; 4) other outcomes; and 5) subgroup analyses. For key question 1, the outcomes are grouped as follows: positive symptoms, negative symptoms, general psychopathology, and total score. Additionally, overall scores for scales are presented prior to scores on subscales or composite scores. Key questions 2 and 4 were grouped and are reported together throughout the results section. Within all key questions, comparisons are presented in alphabetic order by drug name.

Chlorpromazine versus Clozapine

Ten studies, including 859 adults with schizophrenia, compared chlorpromazine versus clozapine. The results from the studies and pooled analyses, where appropriate, for key questions 1, 2, and 4 are presented in Table 8.

Key Question 1. Improving core illness symptoms.

Positive symptoms. Two trials^{82,287} (n=260) reported positive symptoms based on the Positive and Negative Syndrome Scale (PANSS) and found no significant difference between groups. Four trials^{89,106,151,155} examined subscales or composite outcomes. One study⁸⁹ examined a cluster of four key items of the Brief Psychiatric Rating Scale (BPRS) and found a significant benefit for

clozapine. Three trials^{106,151,155} reported results for the hostility subscale of the BPRS; pooled results showed no significant difference between groups.

Negative symptoms. One study¹⁰⁶ (n=164) reported results separately for five subscales of the Scale for the Assessment of Negative Symptoms (SANS) and found no significant differences between groups.

General symptoms. Two trials^{82,287} (n=260) reported PANSS (general psychopathology) and found a significant difference favoring clozapine. Two studies^{106,151} reported results and found no significant differences between groups for the following subscales or composite outcomes of the BPRS: agitation or activation (n=164), anergy (n=179), and thought disorder (n=179).

Total score. Five trials^{82,89,106,151,154} (n=508) reported total scores based on the BPRS. Pooled results are not reported due to marked heterogeneity among the included trials ($I^2 = 93$ percent). Heterogeneity was not explained by mode of administration or dosage of the intervention. However, the patient population (drug-naïve versus on-medication patients) could explain the heterogeneity: removal of one trial of drug-naïve patients¹⁰⁶ from the analysis reduced the heterogeneity to 0 percent. Pooling of the remaining four trials showed a significant difference favoring clozapine (MD = 9.88, 95% CI: 7.40 to 12.36; $I^2 = 0$ percent).

One trial¹⁵⁴ (n=220) reported Clinical Global Impressions–Efficacy Index and found a significant difference favoring chlorpromazine. Two trials^{89,287} (n=488) reported Clinical Global Impressions–Severity (CGI–S) and found a significant difference favoring clozapine. Results based on four other scales showed no significant differences between groups: Clinical Global Impressions–Improvement (CGI–I) (n=384), Global Assessment of Functioning (GAF) (n=164), PANSS (n=40), and SANS (n=164).

Key Question 2 and 4. Improvement in functional outcomes, decreasing health care system utilization, and other outcomes.

Health care system utilization. One trial¹⁰⁶ (n=164) reported rates of hospitalization or rehospitalization and found no significant differences.

Other outcomes. Three trials^{82,89,151} (n=323) reported response rates and showed a significant difference favoring clozapine. Two trials^{106,155} (n=189) reported remission rates and found no significant difference between groups.

Key Question 5. Subgroups.

Race. One trial⁸² was performed exclusively in 31 Asian patients and reported no significant difference for the PANSS (positive) score, PANSS (general psychopathology) score, or PANSS (total) score. However, a significant difference was found in BPRS score favoring clozapine (MD = 7.00, 95% CI: 0.18 to 13.82).

Treatment naïve and treatment of first episode. One trial¹⁰⁶ was performed in 164 treatment naïve patients experiencing their first episode of schizophrenia and reported no significant difference for the BPRS, CGI–I, and SANS.

Treatment resistance. One trial⁸⁹ was performed in 268 patients with treatment resistance and reported a significant difference favoring clozapine for the BPRS (MD = 11.00, 95% CI: 7.99 to 14.01) and CGI–S scales (MD = 0.90, 95% CI: 0.67 to 1.13).

Table 8. Evidence summary table: chlorpromazine versus clozapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Positive symptoms					
Scales					
PANSS scale ^{82,287}	2	260	0.60 (-1.37, 2.56)	42%	NA
Subscales/ composite outcomes					
BPRS: cluster of four key items ⁸⁹	1	268	3.00 (1.91, 4.09)	NE	clozapine
BPRS: hostility subscale ^{106,151,155}	3	204	0.16 (-0.84, 1.17)	39%	NA
Negative symptoms					
Subscales/ composite outcomes					
SANS: affective blunting subscale ¹⁰⁶	1	164	1.20 (0.00, 2.40)	NE	NA
SANS: alogia subscale ¹⁰⁶	1	164	0.30 (-0.46, 1.06)	NE	NA
SANS: avolition subscale ¹⁰⁶	1	164	0.50 (-0.66, 1.66)	NE	NA
SANS: apathy subscale ¹⁰⁶	1	164	-0.10 (-0.87, 0.67)	NE	NA
SANS: disturbance of attention subscale ¹⁰⁶	1	164	0.10 (-0.22, 0.42)	NE	NA
General symptoms					
Scales					
PANSS scale ^{82,287}	2	260	4.24 (1.84, 6.64)	0%	clozapine
Subscales/ composite outcomes					
BPRS: Agitation/ Activation ¹⁰⁶	1	164	0.10 (-0.26, 0.46)	NE	NA
BPRS: Anergy ^{106,151}	2	179	0.26 (-1.10, 1.63)	0%	NA
BPRS: Thought Disorder ^{106,151}	2	179	0.53 (-1.13, 2.19)	65%	NA
Total score					
Scales					
BPRS scale ^{82,89,106,151,154}	5	508	NR	93%	NA
BPRS scale excluding outlier ¹⁰⁶	4	344	9.88 (7.40 to 12.36)	0%	chlorpromazine
CGI-EI scale ¹⁵⁴	1	220	-2.41 (-2.55, -2.27)	NE	chlorpromazine
CGI-I scale ^{106,287}	2	384	0.37 (-0.71, 1.46)	95%	NA
CGI-S scale ^{89,287}	2	488	0.66 (0.19, 1.13)	86%	clozapine
GAF scale ¹⁰⁶	1	164	-1.00(-12.11, 10.11)	NE	NA
PANSS scale ⁸²	1	40	12.00 (-4.48, 28.48)	NE	NA
SANS scale ¹⁰⁶	1	164	2.00 (-2.66, 6.66)	NE	NA
Healthcare system utilization					
Rates of hospitalization/ rehospitalization ¹⁰⁶	1	164	0.70 (0.23, 2.11)*	NE	NA
Other outcomes					
Response rates ^{82,89,151}	3	323	0.13 (0.06, 0.28)*	0%	clozapine
Remission rates ^{106,155}	2	189	0.66 (0.25, 1.74)*	72%	NA

Note: bolded results are statistically significant; * = binary outcome; BPRS = Brief Psychiatric Rating Scale; CGI-EI = Clinical Global Impression-Efficacy Index; CGI-I = Clinical Global Impressions-Improvement; CGI-S = Clinical Global Impression-Severity; CI = confidence intervals; GAF = Global Assessment of Functioning; I² = I-squared; NA = not applicable; NE = not estimable; NR = not reported; PANSS = Positive and Negative Syndrome Scale; SANS = Scale for the Assessment of Negative Symptoms

Chlorpromazine versus Olanzapine

Only one trial⁶⁰ involving 84 adults compared chlorpromazine with olanzapine. The results from the included trial for key questions 1, 2 and 4 are presented in Table 9.

Key Question 1. Improving core illness symptoms.

No significant differences were found between groups for any of the core illness symptom assessments, including positive symptoms, negative symptoms, general symptoms, and total scores.

Key Question 2 and 4. Improvement in functional outcomes, decreasing health care system utilization, and other outcomes.

Other outcomes. The same trial⁶⁰ examined response rates and found no significant differences between groups.

Key Question 5. Subgroups.

The only included trial⁶⁰ was preformed exclusively in patients with treatment resistance. No other subgroups were examined.

Table 9. Evidence summary table: chlorpromazine versus olanzapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
General symptoms					
Subscales/ composite outcomes					
BPRS: anxiety/ depression ⁶⁰	1	84	1.30 (-0.37, 2.97)	NE	NA
BPRS: activation ⁶⁰	1	84	0.40 (-1.10, 1.90)	NE	NA
BPRS: anergia ⁶⁰	1	84	0.60 (-1.05, 2.25)	NE	NA
Total score					
Scales					
BPRS scale ⁶⁰	1	84	2.80 (-2.74, 8.34)	NE	NA
CGI-S scale ⁶⁰	1	84	0.10 (-0.29, 0.49)	NE	NA
Other outcomes					
Response rates ⁶⁰	1	84	0.14 (0.01, 2.68)*	NE	NA

* = binary outcome; BPRS = Brief Psychiatric Rating Scale; CGI-S = Clinical Global Impression-Severity; CI = confidence intervals; I² = I-squared; NA = not applicable; NE = not estimable; SANS = Scale for the Assessment of Negative Symptoms

Chlorpromazine versus Quetiapine

Only one trial¹¹⁸ involving 201 adults with schizophrenia compared chlorpromazine with quetiapine. The results from the trial for key questions 2 and 4 are presented in Table 10.

Key Question 1. Improving core illness symptoms.

The trial¹¹⁸ did not report on core illness symptoms.

Key Question 2 and 4. Improvement in functional outcomes, decreasing health care system utilization, and other outcomes.

Other outcomes. The trial¹¹⁸ found no significant difference between groups in response rates.

Key Question 5. Subgroups.

None of the subgroups of interest were reported.

Table 10. Evidence summary table: chlorpromazine versus quetiapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Other outcomes					
Response rates ¹¹⁸	1	201	0.81 (0.64, 1.02)*	NE	NA

* = binary outcome; CI = confidence intervals; I² = I-squared; NA = not applicable; NE = not estimable

Chlorpromazine versus Ziprasidone

Only one trial⁹¹ involving 306 adults compared chlorpromazine with ziprasidone. The results from the trial for key questions 2 and 4 are presented in Table 11.

Key Question 1. Improving core illness symptoms.

The trial⁹¹ did not report results for core illness symptoms.

Key Question 2 and 4. Improvement in functional outcomes, decreasing health care system utilization, and other outcomes.

Other outcomes. The trial⁹¹ found no significant difference between groups in response rates.

Key Question 5. Subgroups.

Race and treatment resistance. The only included trial⁹¹ was preformed exclusively in Asian patients with treatment resistance. No other subgroups were examined.

Table 11. Evidence summary table: chlorpromazine versus ziprasidone

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Other outcomes					
Response rates ⁹¹	1	306	0.95 (0.78, 1.16)*	NE	NA

* = binary outcome; CI = confidence intervals; I² = I-squared; NA = not applicable; NE = not estimable

Fluphenazine versus Olanzapine

Two trials,^{84,109} including 78 adults with schizophrenia, compared fluphenazine versus olanzapine. The results from the studies and pooled analyses, where appropriate, for key questions 1, 2, and 4 are presented in Table 12.

Key Question 1. Improving core illness symptoms.

One trial⁸⁴ reported core illness symptoms. Significant differences favoring olanzapine were found for positive symptoms based on the Hamilton Rating Scale for Anxiety (HAM-A) and

PANSS, but not for BPRS. No differences were found between groups for negative symptoms based on BPRS or PANSS. In terms of general symptoms, there was a significant difference favoring olanzapine based on the overall PANSS score; however, there were no significant difference for the mood subscale. Olanzapine also showed significant benefits for total scores using three other scales (BPRS, CGI-S, and PANSS).

Key Question 2 and 4. Improvement in functional outcomes, decreasing health care system utilization, and other outcomes.

Functional outcomes. One trial⁸⁴ found no significant differences between groups for four domains assessed by the Leeds Sleep Evaluation Questionnaire (awakening, behavior following wakefulness, getting to sleep, and quality of sleep). A second small trial¹⁰⁹ found no significant differences between groups for intelligence or for a variety of functional tasks, including auditory verbal learning, finger tapping tests, serial digital learning, various tasks within the Stroop Neuropsychological Screening Test, and the Wisconsin Card Sorting Test.

Other outcomes. One trial⁸⁴ found no significant differences in response rates between groups.

Key Question 5. Subgroups.

Race. One trial⁸⁴ involved only Caucasian participants. Results for core illness symptoms are reported above showing some benefits for olanzapine in terms of positive symptoms, general symptoms, and total scores. As above, no differences were found for domains within the Leeds Sleep Evaluation Questionnaire or in response rates.

Table 12. Evidence summary table: fluphenazine versus olanzapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Core symptoms					
Positive symptoms					
Scales					
BPRS scale ⁸⁴	1	60	2.90 (-0.16, 5.96)	NE	NA
HAM-A scale ⁸⁴	1	60	4.00 (0.28, 7.72)	NE	olanzapine
PANSS scale ⁸⁴	1	60	5.10 (0.57, 9.63)	NE	olanzapine
Negative symptoms					
Scales					
BPRS scale ⁸⁴	1	60	1.70 (-0.23, 3.63)	NE	NA
PANSS scale ⁸⁴	1	60	3.00 (-1.00, 7.00)	NE	NA
General symptoms					
Scales					
PANSS scale ⁸⁴	1	60	8.20 (0.83, 15.57)	NE	olanzapine
Subscales/ composite outcomes					
PANSS: mood ⁸⁴	1	60	1.60 (-0.32, 3.52)	NE	NA
Total score					
BPRS scale ⁸⁴	1	60	9.30 (0.57, 18.03)	NE	olanzapine
CGI-S scale ⁸⁴	1	60	0.90 (0.17, 1.63)	NE	olanzapine
PANSS scale ⁸⁴	1	60	16.20 (1.22, 31.18)	NE	olanzapine
Functional capacity					
Auditory verbal learning (# words recalled) ¹⁰⁹	1	18	2.30 (-1.73, 6.33)	NE	NA
Finger tapping test dominant hand ¹⁰⁹	1	18	34.70 (-38.87, 108.27)	NE	NA
Finger tapping test non-dominant hand ¹⁰⁹	1	18	47.10 (-13.64, 107.84)	NE	NA
LSEQ awakening score ⁸⁴	1	60	-2.70 (-9.76, 4.36)	NE	NA
LSEQ behavior following wakefulness ⁸⁴	1	60	-6.60 (-13.50, 0.30)	NE	NA
LSEQ getting to sleep ⁸⁴	1	60	-6.10 (-15.37, 3.17)	NE	NA
LSEQ quality of sleep ⁸⁴	1	60	-4.40 (-13.59, 4.79)	NE	NA
Serial digital learning ¹⁰⁹	1	18	-2.30 (-9.72, 5.12)	NE	NA
SNST color task (# of errors) ¹⁰⁹	1	18	-0.40 (-2.83, 2.03)	NE	NA
SNST color task (# of words) ¹⁰⁹	1	18	-4.50 (-50.60, 41.60)	NE	NA
SNST word task (# of errors) ¹⁰⁹	1	18	-1.80 (-4.97, 1.37)	NE	NA
SNST word task (# of words) ¹⁰⁹	1	18	6.80 (-24.02, 37.62)	NE	NA
WAIS overall function ¹⁰⁹	1	18	0.70 (-16.08, 17.48)	NE	NA
WCST total correct ¹⁰⁹	1	18	-0.50 (-27.56, 26.56)	NE	NA
Other outcomes					
Response rates ⁸⁴	1	60	0.74 (0.51, 1.07)*	NE	NA

Note: bolded outcomes are statistically significant; * = binary outcome; BPRS = Brief Psychiatric Rating Scale; CGI-S = Clinical Global Impression-Severity; CI = confidence intervals; HAM-A = Hamilton Rating Scale for Anxiety; I² = I-squared; LSEQ = Leeds Sleep Evaluation Questionnaire; NA = not applicable; NE = not estimable; PANSS = Positive and Negative Syndrome Scale; SNST = Stroop Neuropsychological Screening Test; WAIS = Weschler Adult Intelligence Scale; WCST = Wisconsin Card Sorting Test

Fluphenazine versus Quetiapine

One trial,⁶¹ including 25 adults with schizophrenia, compared fluphenazine versus quetiapine. The results for key questions 1, 2, and 4 are presented in Table 13.

Key Question 1. Improving core illness symptoms.

The one small trial⁶¹ found no significant differences in core illness symptoms between groups.

Key Question 2 and 4. Improvement in functional outcomes, decreasing health care system utilization, and other outcomes.

Functional outcomes. The same small trial⁶¹ assessed sexual function or dysfunction and found no differences.

Other outcomes. There were no differences in response rates.

Key Question 5. Subgroups.

The only included trial⁶¹ was preformed exclusively in patients with treatment resistance. No other subgroups were examined.

Table 13. Evidence summary table: fluphenazine versus quetiapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Core symptoms					
Positive symptoms					
Scales					
BPRS scale ⁶¹	1	25	-1.02 (-4.92, 2.88)	NE	NA
Subscales/ composite outcomes					
BPRS - hostility subscale ⁶¹	1	25	0.79 (-2.37, 3.95)	NE	NA
Negative symptoms					
Scales					
BPRS scale ⁶¹	1	25	-0.11 (-2.23, 2.01)	NE	NA
General symptoms					
Subscales/ composite outcomes					
BPRS: activation ⁶¹	1	25	-0.33 (-2.89, 2.23)	NE	NA
BPRS: anxiety/ depression ⁶¹	1	25	0.13 (-3.39, 3.65)	NE	NA
Total score					
Scales					
BPRS scale ⁶¹	1	25	-1.98 (-12.96, 9.00)	NE	NA
CGI-S scale ⁶¹	1	25	-0.03 (-0.92, 0.86)	NE	NA
Functional outcomes					
Sexual function/ dysfunction					
Dysfunction ⁶¹	1	25	2.15 (0.72, 6.48)*	NE	NA
Improvement on treatment ⁶¹	1	25	0.46 (0.05, 4.46)*	NE	NA
Other outcomes					
Response rates ⁶¹	1	25	0.62 (0.12, 3.07)*	NE	NA

* = binary outcome; BPRS = Brief Psychiatric Rating Scale; CGI-S = Clinical Global Impression-Severity; CI = confidence intervals; I² = I-squared; NA = not applicable; NE = not estimable

Fluphenazine versus Risperidone

One trial,⁶¹ including 26 adults with schizophrenia, compared fluphenazine versus risperidone. The results for key questions 1, 2, and 4 are presented in Table 14.

Key Question 1. Improving core illness symptoms.

One small trial⁶¹ found no significant differences between groups for core illness symptoms.

Key Question 2 and 4. Improvement in functional outcomes, decreasing health care system utilization, and other outcomes.

Functional outcomes. The same trial⁶¹ found no differences for sexual function or dysfunction.

Other outcomes. No difference was found in response rates.

Key Question 5. Subgroups.

The only included trial⁶¹ was preformed exclusively in patients with treatment resistance. No other subgroups were examined.

Table 14. Evidence summary table: fluphenazine versus risperidone

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Core symptoms					
Positive symptoms					
Scales					
BPRS scale ⁶¹	1	26	-0.15 (-4.11, 3.81)	NE	NA
Subscales/ composite outcomes					
BPRS: hostility subscale ⁶¹	1	26	0.92 (-2.12, 3.96)	NE	NA
Negative symptoms					
Scales					
BPRS scale ⁶¹	1	26	-1.54 (-3.91, 0.83)	NE	NA
General symptoms					
Subscales/ composite outcomes					
BPRS: activation ⁶¹	1	26	0.00 (-2.62, 2.62)	NE	NA
BPRS: anxiety/ depression ⁶¹	1	26	1.07 (-3.21, 5.35)	NE	NA
Total score					
Scales					
BPRS scale ⁶¹	1	26	-0.30 (-10.80, 10.20)	NE	NA
CGI-S scale ⁶¹	1	26	0.07 (-0.77, 0.91)	NE	NA
Sexual function/ dysfunction					
Dysfunction ⁶¹	1	26	1.40 (0.60, 3.28)*	NE	NA
Improvement on treatment ⁶¹	1	26	0.17 (0.02, 1.20)*	NE	NA
Other outcomes					
Response rates ⁶¹	1	26	0.67 (0.13, 3.35)*	NE	NA

* = binary outcome; BPRS = Brief Psychiatric Rating Scale; CGI-S = Clinical Global Impression–Severity; CI = confidence intervals; I² = I-squared; NA = not applicable; NE = not estimable

Haloperidol versus Aripiprazole

Seven trials,^{25-27,38,67,68,70,87,97} including 1,959 adults with schizophrenia, compared haloperidol versus aripiprazole. The results for key questions 1, 2, and 4 are presented in Table 15.

Key Question 1. Improving core illness symptoms.

Positive symptoms. Two trials^{70,87} (n=407) assessed positive symptoms using PANSS and one trial⁹⁷ (n=66) used the Scale for the Assessment of Positive Symptoms (SAPS); no significant differences were observed.

Negative symptoms. Two trials^{70,87} (n=407) assessed negative symptoms using PANSS while one trial⁹⁷ (n=66) used SAPS; no significant differences were observed.

General symptoms. One trial⁷⁰ (n=99) found no differences based on PANSS.

Total score. Two trials^{38,288} (n=484) reported no differences on BPRS (total score). Three trials^{38,70,87} (n=767) reported no differences on CGI-S.

Key Question 2 and 4. Improvement in functional outcomes, decreasing health care system utilization, and other outcomes.

Functional outcomes. One trial⁹⁷ (n=66) reported results of the Fagerstrom Tolerance Questionnaire and found a significant difference favoring haloperidol.

Other outcomes. Four trials^{38,70,87,288} (n = 891) reported on response rates and found no significant difference between groups. One trial⁷⁰ (n=99) reported on medication adherence rates and found no significant difference between groups. The same trial reported on caregiver satisfaction and patient satisfaction and found a significant difference for both outcomes favoring aripiprazole.

Key Question 5. Subgroups.

Race. One trial⁹⁷ involving 66 Chinese participants compared haloperidol with aripiprazole and reported no significant difference for positive or negative core illness symptoms.

Table 15. Evidence summary table: haloperidol versus aripiprazole

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Core symptoms					
Positive symptoms					
Scales					
PANSS scale ^{70,87}	2	407	-0.99 (-2.64, 0.67)	32%	NA
SAPS scale ⁹⁷	1	66	-3.10 (-11.08, 4.88)	NE	NA
Negative symptoms					
Scales					
PANSS scale ^{70,87}	2	407	0.18 (-1.16, 1.53)	0%	NA
SANS scale ⁹⁷	1	66	-1.10 (-5.24, 3.04)	NE	NA
General symptoms					
Scales					
PANSS scale ⁷⁰	1	99	-1.60 (-5.28, 2.08)	NE	NA
Total score					
Scales					
BPRS scale ^{38,288}	2	484	1.23 (-2.35, 4.82)	56%	NA
CGI-S scale ^{38,70,87}	3	767	-0.04 (-0.27, 0.20)	0%	NA
Functional capacity					
Fagerstrom Tolerance Questionnaire ⁹⁷	1	66	3.40 (2.56, 4.24)	NE	haloperidol
Other outcomes					
Response rates ^{38,70,87,288}	4	891	1.06 (0.72, 1.57)	79%	NA
Low medication adherence ⁷⁰	1	99	0.66 (0.03, 15.70)	NE	NA
Caregiver satisfaction ⁷⁰	1	99	0.32 (0.15, 0.67)*	NE	aripiprazole
Patient satisfaction ⁷⁰	1	99	0.33 (0.17, 0.66)*	NE	aripiprazole

Note: bolded results are statistically significant; * = binary outcome; BPRS = Brief Psychiatric Rating Scale; CGI-S = Clinical Global Impression-Severity; CI = confidence intervals; I² = I-squared; NA = not applicable; NE = not estimable; Positive and Negative Syndrome Scale; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms

Haloperidol versus Asenapine

Only one trial,⁹² involving 335 adults with schizophrenia, compared haloperidol with asenapine. The results for key questions 1, 2, and 4 are presented in Table 16.

Key Question 1. Improving core illness symptoms.

The included trial⁹² found no significant differences between groups for positive, negative, or general symptoms or total scores.

Key Question 2 and 4. Improvement in functional outcomes, decreasing health care system utilization, and other outcomes.

Other outcomes. The same trial⁹² examined response rates and found no significant differences.

Key Question 5. Subgroups.

None of the subgroups of interest were reported.

Table 16. Evidence summary table: haloperidol versus asenapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Core symptoms					
Positive symptoms					
Scales					
PANSS scale ⁹²	1	335	0.16 (-1.22, 1.54)	NE	NA
Subscales/ composite outcomes					
PANSS: hostility/ excitement ⁹²	1	335	-0.70 (-1.54, 0.14)	NE	NA
Negative symptoms					
Scales					
CDS-S scale ⁹²	1	335	0.56 (-0.20, 1.32)	NE	NA
PANSS scale ⁹²	1	335	0.39 (-0.72, 1.51)	NE	NA
General symptoms					
PANSS scale ⁹²	1	335	0.26 (-1.59, 2.10)	NE	NA
Subscales/ composite outcomes					
PANSS: anxiety/ depression ⁹²	1	335	0.26 (-0.51, 1.04)	NE	NA
PANSS-disorganized thought ⁹²	1	335	0.01 (-0.95, 0.97)	NE	NA
Total score					
Scales					
CGI-S scale ⁹²	1	335	0.01 (-0.24, 0.25)	NE	NA
PANSS scale ⁹²	1	335	0.23 (-2.50, 2.95)	NE	NA
Other outcomes					
Response rates ⁹²	1	335	0.82 (0.64, 1.04)*	NE	NA

* = binary outcome; CDS-S = Calgary Depression Scale for Schizophrenia; CGI-S = Clinical Global Impression-Severity; CI = confidence intervals; I² = I-squared; NA = not applicable; NE = not estimable; PANSS = Positive and Negative Syndrome Scale

Haloperidol versus Clozapine

Nine trials^{49,56,64,90,98,100,124,142,152} and one cohort study,⁷⁷ involving 1,260 adults with schizophrenia, compared haloperidol with clozapine. The results for key questions 1, 2, and 4 are presented in Table 17.

Key Question 1. Improving core illness symptoms.

Positive symptoms. Five trials found no significant differences in positive symptoms based on BPRS⁴⁹ (n=75), the Modified Overt Aggression Scale¹⁰⁰ (n=73), and PANSS^{100,142,287} (n=367). A variety of subscales or composite outcomes were assessed in individual trials with no significant differences between groups.

Negative symptoms. Three trials^{100,142,287} (n=370) reported PANSS and found no significant difference between groups. Two trials^{49,64} (n=157) reported SANS and found no significant differences. A variety of subscales or composite outcomes were examined in individual trials with no significant difference observed between groups.

General symptoms. Three trials^{100,142,287} (n=370) reported PANSS and found no significant difference between group. A variety of subscales or composite outcomes were examined in individual trials and no significant differences were found.

Total score. Four trials^{50,90,98,152} (n=268) reported BPRS (total score) and showed no significant difference between groups. Likewise, three trials^{100,142,287} (n=573) reported PANSS (total score) and found no difference. One trial²⁸⁷ (n=220) showed benefits in favor of haloperidol based on CGI-Efficacy Index, whereas two trials^{90,287} (n=291 participants) showed benefits favoring clozapine based on CGI-I and CGI-S.

Key Question 2 and 4. Improvement in functional outcomes, decreasing health care system utilization, and other outcomes.

Functional outcomes. A large number of functional tasks were assessed, primarily in single trials, and no differences were found between groups in any of the outcomes assessed with the exception of categorical fluency,⁴⁹ general intelligence,⁹⁸ Syndrome Short Test,⁹⁸ and Neurocognitive testing (simple motor functioning),¹⁴² all in favor of clozapine.

Other outcomes. A small number of studies reported relapse, response, and remission rates and patient satisfaction; no statistically significant differences were found.

Key Question 5. Subgroups.

Race. One trial¹²⁴ in 88 Asian patients with schizophrenia reported no significant difference on the BPRS (total) score.

Disorder subtypes and treatment naïve. One trial⁹⁸ in 34 treatment naïve patients with paranoid schizophrenia reported no significant difference on the BPRS (total) score.

Table 17. Evidence summary table: haloperidol versus clozapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Core symptoms					
Positive symptoms					
Scales					
BPRS scale ⁴⁹	1	75	0.80 (-1.46, 3.06)	NE	NA
MOAS scale ¹⁰⁰	1	73	17.60 (-2.25, 37.45)	NE	NA
PANSS scale ^{100,142,287}	3	367	-0.37 (-2.35, 1.60)	56%	NA
Subscales/ composite outcomes					
BPRS: hostile/ suspiciousness subscale ⁹⁰	1	71	1.40 (0.29, 2.51)	NE	NA
BPRS: psychosis cluster subscale ⁹⁰	1	71	2.70 (0.48, 4.92)	NE	NA
PANSS: hostility subscale ⁵⁶	1	77	0.71 (0.07, 1.35)	NE	NA
PANSS: excitement factor ¹⁴²	1	77	-0.60 (-1.20, 0.00)	NE	NA
PANSS: positive factor ¹⁴²	1	77	0.06 (-0.38, 0.50)	NE	NA
Negative symptoms					
Scales					
PANSS scale ^{100,142,287}	3	370	0.85 (-0.53, 2.23)	43%	NA
SANS scale ^{49,64}	2	157	0.94 (-2.60, 4.48)	0%	NA
Subscales/ composite outcomes					
PANSS: negative factor ¹⁴²	1	77	-0.41 (-0.80, -0.02)	NE	NA
SANS: affective flattening subscale ⁹⁰	1	71	-0.30 (-0.84, 0.24)	NE	NA
SANS: alogia subscale ⁹⁰	1	71	0.10 (-0.44, 0.64)	NE	NA
SANS: anhedonia/ asociality subscale ⁹⁰	1	71	-0.30 (-0.89, 0.29)	NE	NA
SANS: avolition/ apathy subscale ⁹⁰	1	71	0.20 (-0.36, 0.76)	NE	NA
General symptoms					
Scales					
PANSS scale ^{100,142,287}	3	370	1.91 (-3.32, 7.15)	88%	NA
Subscales/ composite outcomes					
BPRS: activation ⁹⁰	1	71	0.60 (-0.26, 1.46)	NE	NA
BPRS: anergia ⁹⁰	1	71	-0.70 (-2.55, 1.15)	NE	NA
BPRS: anxiety/ depression ⁹⁰	1	71	1.10 (-0.65, 2.85)	NE	NA
BPRS: thought disorder ⁹⁰	1	71	0.30 (-1.68, 2.28)	NE	NA
PANSS: cognitive factor ¹⁴²	1	77	-0.03 (-0.36, 0.30)	NE	NA
PANSS: depression/ anxiety factor ¹⁴²	1	77	-0.05 (-0.46, 0.36)	NE	NA
Subscales/ composite outcomes					
Total score					
Scales					
BPRS scale ^{50,90,98,152}	4	268	2.16 (-0.56, 4.87)	0%	NA

Note: bolded results are statistically significant; * = binary outcome; BPRS = Brief Psychiatric Rating Scale; CGI-EI = Clinical Global Impression-Efficacy Index; CGI-I = Clinical Global Impressions-Improvement; CGI-S = Clinical Global Impression-Severity; CI = confidence intervals; GCI = General Cognitive Index; I² = I-squared; MMSE = Mini-mental State Examination; MOAS = Modified Overt Aggression Scale; NA = not applicable; NE = not estimable; NR = not reported; SANS = Scale for the Assessment of Negative Symptoms; SNST = Stroop Neuropsychological Screening Test; WCST = Wisconsin Card Sorting Test

Table 17. Evidence summary table: haloperidol versus clozapine (continued)

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
CGI-EI scale ²⁸⁷	1	220	-2.31 (-2.45, -2.17)	NE	haloperidol
CGI-I scale ^{90,287}	2	291	0.82 (0.65, 0.99)	0%	clozapine
CGI-S scale ^{90,287}	2	291	0.52 (0.28, 0.75)	0%	clozapine
PANSS scale ^{100,142,287}	3	573	1.04 (-3.91, 5.98)	58%	NA
Functional capacity					
Block Design ⁴⁹	2	148	-0.89 (-2.44, 0.67)	80%	NA
Cat. Fluency ⁴⁹	1	75	-11.50 (-17.71, -5.29)	NE	clozapine
Disorientation ¹⁰⁰	1	73	0.19 (-0.28, 0.66)	NE	NA
Executive function ¹⁰⁰	1	73	0.15 (-0.12, 0.42)	NE	NA
General intelligence ⁹⁸	1	34	-9.00 (-17.87, -0.13)	NE	clozapine
GCJ ¹⁰⁰	1	73	-0.07 (-0.35, 0.21)	NE	NA
Judgment of Lines ⁴⁹	1	75	-5.00 (-11.96, 1.96)	NE	NA
Memory: Figural ⁴⁹	1	75	0.17 (-0.67, 1.01)	NE	NA
Memory: Logical ⁴⁹	1	75	5.80 (-2.67, 14.27)	NE	NA
Memory: Verbal pairs ⁴⁹	1	75	-0.60 (-2.94, 1.74)	NE	NA
Memory: Visual pairs ⁴⁹	1	75	-0.90 (-3.09, 1.29)	NE	NA
Memory: Visual Reproduction ⁴⁹	1	75	-0.80 (-4.70, 3.10)	NE	NA
Motor function ¹⁰⁰	1	73	-0.29 (-0.60, 0.02)	NE	NA
Neurocognitive testing: Global Score ¹⁴²	1	77	-0.19 (-0.43, 0.05)	NE	NA
Neurocognitive testing: Declarative verbal learning and memory ¹⁴²	1	77	0.06 (-0.40, 0.52)	NE	NA
Neurocognitive testing: General executive and perceptual organization ¹⁴²	1	77	-0.19 (-0.46, 0.08)	NE	NA
Neurocognitive testing: Processing speed and attention ¹⁴²	1	77	-0.29 (-0.74, 0.16)	NE	NA
Neurocognitive testing: Simple motor Functioning ¹⁴²	1	77	-0.55 (-1.00, -0.10)	NE	clozapine
Mooney Faces ⁴⁹	1	75	-0.80 (-1.70, 0.10)	NE	NA
MMSE ⁴⁹	1	73	-1.14 (-3.59, 1.31)	NE	NA
Poor attention ¹⁰⁰	1	73	0.21 (-0.26, 0.68)	NE	NA
SNST ⁴⁹	1	75	-1.00 (-5.08, 3.08)	NE	NA
Syndrome short test ⁹⁸	1	34	-28.70(-31.51, -25.89)	NE	clozapine
Trail Making Test: A ¹⁰⁰	1	73	-0.27 (-0.78, 0.24)	NE	NA
Trail Making Test: B ⁴⁹	1	75	0.00 (-0.10, 0.10)	NE	NA
Verbal fluency ⁴⁹	1	75	-1.50 (-7.42, 4.42)	NE	NA
Verbal Memory ¹⁰⁰	1	73	0.01 (-0.44, 0.46)	NE	NA
Visual Memory ¹⁰⁰	1	73	0.23 (-0.36, 0.82)	NE	NA
WCST ⁴⁹	1	75	0.40 (-8.02, 8.82)	NE	NA
Relapse rates ⁴⁹	1	75	0.68 (0.12, 3.87)*	NE	NA
Response rates ^{90,100}	2	144	0.64 (0.28, 1.47)*	72%	NA
Other outcomes					
Remission rates ⁹⁰	1	71	0.16 (0.02, 1.20)*	NE	NA
Patient satisfaction ⁹⁸	1	34	0.82 (0.46, 1.45)*	NE	NA

Haloperidol versus Olanzapine

Thirty-six trials^{37,43-45,48,50,52,56,65,67,69,72,79,83,86,93,95-97,99-101,105,107,121,125,127,128,131,133,134,138,139,142,144,145} and one cohort study,¹⁰² involving 15,521 adults with schizophrenia, compared haloperidol with olanzapine. The results for key questions 1, 2, and 4 are presented in Table 18.

Key Question 1. Improving core illness symptoms.

Positive symptoms. Twenty trials assessed positive symptoms using nine different scales. The majority (13 trials,^{44,45,48,83,96,99,100,105,107,121,133,138,142} 3,715 participants) reported symptoms based on the PANSS; pooled results showed no significant difference between groups. Two trials individually showed significant results based on the Prepulse Inhibition Scale and the Young Mania Rating Scale (YMRS); however, the results were discordant, with one trial¹⁴⁵ favoring haloperidol and the other⁶⁵ favoring olanzapine. A variety of subscale or composite outcomes were examined in small numbers of trials. Only one⁸³ (n=182) showed a significant difference (hostility subscale of BPRS) favoring olanzapine.

Negative symptoms. Eighteen trials assessed negative symptoms using five different scales. The majority (13 trials,^{44,45,48,83,96,99,100,105,107,121,133,138,142} 3,715 participants) reported symptoms based on the PANSS; pooled results showed a significant difference favoring olanzapine. Significant results were also observed for three of the other four scales examined; all favored olanzapine. Single trials examined a variety of subscales or composite outcomes, but no significant differences were found.

General symptoms. Two scales were used across 10 studies to assess general symptoms: 9 studies^{44,48,83,100,105,107,121,133,142} (n=1160) showed no difference based on PANSS, whereas 1 trial¹³⁸ (n=1996) showed a significant difference favoring olanzapine on the BPRS. Single trials examined a variety of subscales or composite outcomes, with only one of eight outcomes (self-control) showing a significant difference in favor of olanzapine.

Total score. Twenty-three trials assessed total scores using seven different scales. PANSS was most often used (14 studies, 4,181 participants) and showed a significant difference favoring olanzapine. BPRS was used in 13 studies (n=4014) and showed no significant difference between groups. The next most commonly used scale was CGI-S; however, results were not pooled due to substantial heterogeneity. The heterogeneity was not explained by mode of administration or dosage; however, removal of one trial⁶⁵ of drug-naïve patients markedly reduced the heterogeneity. With this trial removed, the remaining trials showed a significant difference favoring olanzapine. The trial of drug-naïve patients (n=111) was significant in favor of haloperidol. Four studies reported the total score using the Montgomery-Asberg Depression Rating Scale (MADRS) and found a significant difference in favor of olanzapine. No significant differences were found based on the CGI-I, GAF, or the Subjective Well-Being under Neuroleptics Scale; however, these were used in only one or two studies each.

Key Question 2 and 4. Improvement in functional outcomes, decreasing health care system utilization, and other outcomes.

Functional outcomes. *Encounters with legal system:* One trial¹³³ (n=31) reported on positive urine toxicology for cocaine and found no difference between the groups.

Functional capacity: Many functional tasks were assessed. Approximately one-third of the 79 outcomes and analyses presented showed significant differences between groups. Significant differences were found for 3 outcomes favoring haloperidol and for 23 outcomes favoring olanzapine (see Table 18 for specific outcomes).

Social relatedness or function: Single studies evaluated five different aspects of social relatedness or functioning and found no differences between groups.

Sexual function or dysfunction: One trial⁸⁶ (n=208) reported on sexual dysfunction and found no significant difference between groups.

Health care system utilization. One trial⁸⁶ (n=208) reported on rates of hospitalization or rehospitalization and showed no difference between the groups. One trial¹²⁴ (n=309) reported mean hospital bed days and found no significant difference between groups.

Other outcomes. Fourteen trials^{43,65,83,86,96,99-101,105,107,128,138,144,288} (n=4099) reported on response rates and showed a significant difference favoring olanzapine. Two trials^{86,105} (n=471) reported remission rates and found no significant difference. One trial each examined medication adherence⁹⁶ (n=256) and patient insight into illness¹⁰⁵ (n=263) and found no differences between groups. Three trials examined health-related quality of life using different scales; no differences were found between groups.

Key Question 5. Subgroups.

Treatment of a first episode. Five trials^{65,69,105,127,139} reported on 928 patients undergoing treatment for their first schizophrenic episode. There was no significant difference on PANSS (positive), SAPS, PANSS (general psychopathology), and Calgary Depression Scale for Schizophrenia (CDS-S). However, there was a significant difference in favor of olanzapine on the YMRS (MD = 0.40, 95% CI: 0.21 to 0.59), PANSS (negative) (MD = 1.49, 95% CI: 0.05 to 2.93), SANS (MD = 1.80, 95% CI: 1.58 to 2.02), Hamilton Rating Scale for Depression (HAM-D) (MD = 1.70, 95% CI: 1.42 to 1.98), and BPRS (total) (MD = 1.10, 95% CI: 0.58 to 1.62). On the other hand, there was a significant difference favoring haloperidol on the CGI-S scale (MD = 0.80, 95% CI: 0.69 to 0.91).

Treatment naïve. Three trials^{65,127,139} in 271 treatment naïve patients reported no significant difference on the SAPS, but a significant difference in favor of olanzapine on the YMRS (MD = 0.40, 95% CI: 0.21 to 0.59), SANS (MD = 1.80, 95% CI: 1.58 to 2.02), HAM-D (MD = 1.70, 95% CI: 1.42 to 1.98), BPRS (total) (MD = 1.10, 95% CI: 0.58 to 1.62), and the CDS-S scales (MD = 0.80, 95% CI: 0.69 to 0.91). On the other hand, there was a significant difference favoring haloperidol on the CGI-S scale (MD = 0.80, 95% CI: 0.69 to 0.91).

Treatment resistance. One trial¹³³ in 31 patients with comorbid cocaine use reported no significant difference on the PANSS (positive) scale, but a significant difference in favor of

haloperidol on the PANSS (negative) scale (MD = -3.20, 95% CI: -6.03 to -0.37) and the PANSS (general psychopathology) scale (MD = -6.10, 95% -10.90 to -1.30).

Disease subgroup. One trial³⁷ in 28 patients with paranoid schizophrenia reported no significant difference on the BPRS (total) scale.

Race. Three trials^{83,97,99} in 597 Asian patients reported no significant difference on the BPRS (positive) scale, PANSS (positive), SAPS, PANSS (negative), SANS, or PANSS (general psychopathology), but a significant difference in favor of olanzapine on the BPRS (total) (MD = 3.36, 95% CI: 0.63 to 6.09) and PANSS (total) scales (MD = 5.53, 95% CI: 1.10 to 9.96).

One trial⁶⁵ in 111 Caucasian patients compared haloperidol with olanzapine and reported no significant difference on the SAPS scale, but a significant difference in favor of olanzapine on the YMRS scale (MD = 0.40, 95% CI: 0.21 to 0.59), SANS (MD = 1.80, 95% CI: 1.58 to 2.02), HAM-D (MD = 1.70, 95% CI: 1.42 to 1.98), BPRS (total) (MD = 1.10, 95% CI: 0.58 to 1.62), and the CDS-S (MD = 0.80, 95% CI: 0.69 to 0.91). On the other hand, there was a significant difference favoring haloperidol on the CGI-S scale (MD = 0.80, 95% CI: 0.69 to 0.91).

Comorbidities. Two trials^{128,133} in patients with comorbid cocaine use and reported no significant difference on the PANSS (positive) scale, but a significant difference in favor of haloperidol on the PANSS (negative) scale (MD = -3.20, 95% CI: -6.03 to -0.37) and the PANSS (general psychopathology) scale (MD = -6.10, 95% -10.90 to -1.30).

Table 18. Evidence summary table: haloperidol versus olanzapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Core symptoms					
Positive symptoms					
Scales					
ABS scale ^{50,144}	2	482	0.80 (-1.22, 2.83)	74%	NA
ACES scale ^{50,144}	2	482	0.06 (-0.40, 0.53)	85%	NA
BPRS scale ^{43,44,50,52,99,144}	6	1519	-0.14 (-0.61, 0.34)	0%	NA
HAM-A scale ⁹⁶	1	256	0.60 (-0.87, 2.07)	NE	NA

Note: bolded results are statistically significant; * = binary outcome; ABS = Agitated Behavior Scale; ACES = Agitation-Calmness Evaluation Scale; BPRS = Brief Psychiatric Rating Scale; CDS-S = Calgary Depression Scale for Schizophrenia; CGI-I = Clinical Global Impressions-Improvement; CGI-S = Clinical Global Impression-Severity; CI = confidence intervals; COWAT = Controlled Word Association Test; CRT = cognitive remediation treatment; CVLT = California Verbal Learning Test; DS-CPT = Degraded Stimuli-Continuous Performance Test; DSC = dynamic susceptibility contrast; GAF = Global Assessment of Functioning; GCI = General Cognitive Index; GPT = Gorham Proverbs Test; HAM-A = Hamilton Rating Scale for Anxiety; HAM-D = Hamilton Rating Scale for Depression; I² = I-squared; LNS = Letter-Number Sequencing; MADRS = Montgomery-Asberg Depression Rating Scale; MANSA = Manchester Short Assessment of Quality of Life; MMSE = Mini-Mental State Examination; NA = not applicable; NE = not estimable; NR = not reported; PANSS = Positive and Negative Syndrome Scale; PEC = Positive and Negative Syndrome Scale Excited Component; PPI = Prepulse inhibition; pts = patients; QLS = Quality of Life Scale; QoL = Quality of Life; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; SNST = Stroop Neuropsychological Screening Test; SRT = Story Recall Test; STM = Short term memory; UKU = Udvalg for Kliniske Undersøgelser; VCCQ = Voris Cocaine Craving Questionnaire; WAIS = Wechsler Adult Intelligence Scale; WCS = Work Readiness Cognitive Screen; WCST = Wisconsin Card Sort Test; YMRS = Young Mania Rating Scale

Table 18. Evidence summary table: haloperidol versus olanzapine (continued)

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
BPRS: anergia ⁸³	1	182	0.33 (-0.60, 1.26)	NE	NA
PANSS: negative factor ¹⁴²	1	76	-0.37 (-0.74, 0.00)	NE	NA
SANS: composite ⁴³	1	267	2.93 (-1.35, 7.21)	NE	NA
General symptoms					
Scales					
BPRS scale ¹³⁸	1	1996	0.89 (0.44, 1.34)	NE	olanzapine
PANSS scale ^{44,48,83,100,105,107,121,133,142}	9	1160	0.46 (-1.40, 2.31)	57%	NA
Subscales/ composite outcomes					
BPRS: Psychosis subscale ¹⁰¹	1	32	-1.10 (-2.59, 0.39)	NE	NA
BPRS: thought disorder subscale ⁸³	1	182	0.25 (-0.72, 1.22)	NE	NA
PANSS: Cognitive factor ¹⁴²	1	76	-0.26 (-0.57, 0.05)	NE	NA
PANSS: Depression/ anxiety factor ¹⁴²	1	76	-0.19 (-0.56, 0.18)	NE	NA
Subjective well-being: emotional regulation subscale ⁷²	1	24	1.70 (-1.07, 4.47)	NE	NA
Subjective well-being: mental functioning subscale ⁷²	1	24	0.80 (-2.92, 4.52)	NE	NA
Subjective well-being: physical functioning subscale ⁷²	1	24	1.80 (-0.62, 4.22)	NE	NA
Subjective well-being: self-control subscale ⁷²	1	24	3.20 (0.75, 5.65)	NE	olanzapine
Total score					
Scales					
BPRS scale ^{37,43-45,50,52,65,83,99,101,138,144,288}	13	4014	0.59 (-1.10, 2.28)	82%	NA
CGI-I scale ^{72,144}	2	281	0.11 (-0.30, 0.51)	36%	NA
CGI-S scale ^{43,44,49,52,65,86,106,138}	9	3564	NR	87%	NA
CGI-S scale ^{43,44,49,52,86,105,138,289} with outlier removed	8	3485	0.20 (0.08, 0.31)	24%	olanzapine
GAF scale ⁸⁶	1	208	-4.00 (-13.70, 5.70)	NE	NA
MADRS ^{72,96,105,106,138}	4	2539	2.25 (1.28, 3.21)	22%	olanzapine
PANSS scale ^{44,45,48,72,83,86,96,99,100,106,107,125,138,142}	14	4181	2.69 (0.77, 4.60)	32%	olanzapine
Subjective Well-Being under Neuroleptics Scale ⁷²	1	24	0.60 (-5.36, 6.56)	NE	NA
Functional outcomes					
Functional capacity					
Attention Span ¹²¹	1	44	-0.22 (-0.59, 0.15)	NE	NA
Block Design ¹⁰⁰	1	73	-0.61 (-1.15, -0.07)	NE	olanzapine
Brief test of attention (correct responses) ⁶⁵	1	111	-0.76 (-1.88, 0.36)	NE	NA
Continuous performance test (correct responses) ⁶⁵	1	111	-2.78 (-7.30, 1.74)	NE	NA
Cognitive composite score ⁶⁹	1	208	-0.10 (-0.28, 0.08)	NE	NA
COWAT: category/ semantic ¹⁰⁷	1	38	-5.13 (-10.26, 0.00)	NE	NA
COWAT: letter fluency ¹⁰⁷	1	38	-3.03 (-10.23, 4.17)	NE	NA

Table 18. Evidence summary table: haloperidol versus olanzapine (continued)

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
COWAT: Verbal Fluency ¹⁰⁷	1	44	-7.30 (-11.91, -2.69)	NE	olanzapine
COWAT ¹³¹	1	60	7.20 (0.57, 13.83)	NE	haloperidol
CRT ⁴⁸	1	25	-50.00 (-163.48, 63.48)	NE	NA
CVLT ¹³¹	1	60	4.60 (-1.91, 11.11)	NE	NA
D2 Test of Attention ⁴⁸	1	25	-1.71 (-37.40, 33.98)	NE	NA
Declarative verbal learning and memory ¹⁴²	1	76	-0.34 (-0.74, 0.06)	NE	NA
Design List Learning ¹²¹	1	44	-4.68 (-9.30, -0.06)	NE	olanzapine
Digit Span ¹²¹	1	44	-0.70 (-2.80, 1.40)	NE	NA
Digit Span Backward ⁴⁸	1	25	0.82 (-0.82, 2.46)	NE	NA
Digit Span Distractibility Test ⁴⁸	1	25	7.99 (-13.85, 29.83)	NE	NA
Digit Symbol Subtest ¹²¹	1	44	-4.20 (-9.76, 1.36)	NE	NA
Discrimination of self-generated words ⁹⁵	1	11	0.07 (-0.53, 0.67)	NE	NA
Disorientation ¹⁰⁰	1	73	-0.41 (-0.87, 0.05)	NE	NA
Distractibility task: no. correct ¹⁰⁷	1	38	-2.33 (-7.59, 2.93)	NE	NA
DS-CPT ¹³¹	1	60	0.05 (-0.01, 0.11)	NE	NA
DSC ¹³¹	1	60	2.60 (-4.01, 9.21)	NE	NA
Executive function ¹⁰⁰	1	73	-0.03 (-0.29, 0.23)	NE	NA
Executive skills ¹²¹	1	44	-0.33 (-0.96, 0.30)	NE	NA
Fagerstrom Tolerance Questionnaire ⁹⁷	1	67	2.60 (1.52, 3.68)	NE	haloperidol
FAS verbal Fluency (# words in time limit) ⁶⁵	1	111	-5.86 (-9.81, -1.91)	NE	olanzapine
Finger Tapping ^{48,121}	2	69	-4.02 (-10.66, 2.62)	36%	NA
Finger tapping test (mean taps/10 sec) ⁶⁵	1	111	0.27 (-3.15, 3.69)	NE	NA
GCI ¹⁰⁰	1	73	-0.49 (-0.77, -0.21)	NE	olanzapine
GPT ¹³¹	1	60	-14.80(42.36,12.76)	NE	NA
Hooper Visual Organization Test ¹²¹	1	44	-0.85 (-1.84, 0.14)	NE	NA
Immediate recall ¹²¹	1	44	-0.63 (-1.03, -0.23)	NE	olanzapine
Iowa gambling task ⁶⁵	1	111	-16.02 (-31.31, -0.73)	NE	olanzapine
Level of Functioning Scale ⁵²	1	63	0.00 (-2.87, 2.87)	NE	NA
LNS ^{48,107,131}	3	123	0.53 (-2.04, 3.10)	65%	NA
Memory ¹²⁵	1	309	-0.19 (-0.39, 0.01)	NE	NA
MMSE ¹⁰⁰	1	73	-3.89 (-6.32, -1.46)	NE	olanzapine
Motor Battery ^{100,121,125,142}	1	502	-0.43 (-0.80, -0.06)	68%	olanzapine
Neurocognitive composite score ^{96,105,142}	3	595	-0.06 (-0.44, 0.32)	86%	NA
Neurocognitive testing: General executive and perceptual organization ¹⁴²	1	76	-0.45 (-0.76, -0.14)	NE	olanzapine
Nonverbal Fluency ¹²¹	1	44	-3.40 (-6.52, -0.28)	NE	olanzapine
Nonverbal Fluency and Construction ¹²¹	1	44	-0.66 (-1.36, 0.04)	NE	NA
Peabody Picture Vocabulary Test ¹²¹	1	44	-2.68 (-9.54, 4.18)	NE	NA
Pegboard ^{48,65,69,121}	4	388	3.14 (-2.03, 8.31)	76%	NA
Poor attention ¹⁰⁰	1	73	-0.59 (-1.05, -0.13)	NE	olanzapine

Table 18. Evidence summary table: haloperidol versus olanzapine (continued)

Outcome or Subgroup	Studies	Participants	Effect Estimate	I2	Favors
Processing speed and attention ¹⁴²	1	76	-0.49 (-0.87, -0.11)	NE	olanzapine
Rey auditory verbal learning (# words recalled) ⁶⁵	1	111	-3.09 (-7.35, 1.17)	NE	NA
Rey auditory verbal learning (# words recalled from list after delay) ⁶⁵	1	111	-1.40 (-2.69, -0.11)	NE	olanzapine
Rey Auditory Verbal Learning Test, sum of trials 1–5 ¹⁰⁷	1	38	-19.61 (-28.11, -11.11)	NE	olanzapine
Rey Auditory Verbal Learning Test, recognition form ^{69,107}	2	246	-0.21 (-0.35, -0.06)	0%	olanzapine
Rey complex figure test (long term recall) ⁶⁵	1	111	0.10 (-2.60, 2.80)	NE	NA
Rey–Taylor Complex Figure Copy ¹²¹	1	44	-1.92 (-5.53, 1.69)	NE	NA
Rey–Taylor Complex Figure Immediate Recall ¹²¹	1	44	-0.08 (-3.89, 3.73)	NE	NA
Similarities subtest ¹²¹	1	44	0.50 (-1.47, 2.47)	NE	NA
SRT ^{48,121}	2	69	-2.98 (-8.21, 2.24)	0%	NA
SNST ⁴⁸	1	25	0.22 (-4.48, 4.92)	NE	NA
Trail Making Test: A ^{69,100,107}	3	319	-0.38 (-1.17, 0.42)	76%	NA
Trail Making Test: B ^{65,69,107,121}	4	401	9.76 (-6.02, 25.54)	69%	NA
Neurocognitive Composite Score ¹⁰⁷	1	263	0.16 (0.04, 0.28)	NE	haloperidol
Verbal STM ⁴⁸	1	25	-4.22 (-11.62, 3.18)	NE	NA
Verbal Memory ¹⁰⁰	1	73	-0.82 (-1.26, -0.38)	NE	olanzapine
Verbal Fluency and Reasoning ¹²¹	1	44	-0.32 (-0.61, -0.03)	NE	olanzapine
Verbal List Learning ¹²¹	1	44	-8.52 (-14.18, -2.86)	NE	olanzapine
Visual Memory Span Backward ⁴⁸	1	25	0.11 (-1.64, 1.86)	NE	NA
Visual Memory Span Forward ⁴⁸	1	25	0.54 (-1.11, 2.19)	NE	NA
Visual Memory ¹⁰⁰	1	73	0.21 (-0.37, 0.79)	NE	NA
Visual Digit Coding Task ¹⁰⁷	1	38	-10.57 (-16.92, -4.22)	NE	olanzapine
Visual Reproduction ¹²¹	1	44	-0.90 (-2.78, 0.98)	NE	NA
Visual Span ¹²¹	1	44	-0.78 (-2.70, 1.14)	NE	NA
WAIS III backwards digits (total score) ⁶⁵	1	111	0.41 (-0.34, 1.16)	NE	NA
WAIS III digit symbol (total score) ^{65,69}	2	319	-0.29 (-0.83, 0.24)	28%	NA
WCST ¹³¹	1	60	0.80 (-0.15, 1.75)	NE	NA
WCST: perseverative errors ^{107,121}	2	82	0.05 (-0.06, 0.16)	0%	NA
WCST: total errors ¹³⁴	1	29	9.32 (2.63, 16.01)	NE	olanzapine
VCCQ: energy score ¹³³	1	31	11.50 (3.69, 19.31)	NE	olanzapine
VCCQ: intensity score ¹³³	1	31	-5.90 (-12.36, 0.56)	NE	NA
VCCQ: mood score ¹³³	1	31	8.20 (-1.79, 18.19)	NE	NA
VCCQ: sick ¹³³	1	31	11.20 (0.85, 21.55)	NE	olanzapine

Table 18. Evidence summary table: haloperidol versus olanzapine (continued)

Outcome or Subgroup	Studies	Participants	Effect Estimate	I2	Favors
Social relatedness/ functioning					
Facial Emotion Identification Test ¹³¹	1	60	-0.50 (-2.11, 1.11)	NE	NA
Half profile nonverbal sensitivity ¹³¹	1	60	1.80 (-2.67, 6.27)	NE	NA
Interpersonal Perception Task-15 ¹³¹	1	60	0.80 (-0.03, 1.63)	NE	NA
Subjective well-being, social functioning subscale ⁷²	1	24	-0.90 (-4.23, 2.43)	NE	NA
Voice Emotion Identification Test ¹³¹	1	60	0.20 (-1.76, 2.16)	NE	NA
Sexual function/ dysfunction					
Sexual dysfunction (UKU) ⁸⁶	1	208	0.80 (0.52, 1.24)*	NE	NA
Healthcare system utilization					
Rates of hospitalization/rehospitalization ⁸⁶	1	208	0.79 (0.42, 1.51)*	NE	NA
Mean hospital bed days ¹²⁴	1	309	-7.10 (-20.95, 6.75)	NE	NA
Other outcomes					
Response rates ^{43,65,83,86,96,99-101,105,107,128,138,144,288}	14	4099	0.86 (0.78, 0.96)*	55%	olanzapine
Remission rates ^{86,105}	2	471	0.60 (0.34, 1.06)*	77%	NA
Medication adherence ⁹⁶	1	256	1.00 (0.81, 1.22)*	NE	NA
Patient insight into illness ¹⁰⁵	1	263	-1.10 (-3.95, 1.75)	NE	NA
Encounters with the legal system					
Positive urine toxicology ¹³³	1	31	3.20 (0.76, 13.46)*	NE	NA
Health-related quality of life (QoL)					
MANSU ⁸⁶	1	208	0.00 (-1.38, 1.38)	NE	NA
QLS ^{43,52}	1	330	-2.62 (-6.39, 1.15)	0%	NA
Schizophrenia-specific QLS ⁹⁹	1	276	-3.62 (-8.94, 1.70)	NE	NA

Haloperidol versus Quetiapine

Thirty-six trials^{40,41,59,62,67,69,73,74,86,120,140} and one cohort study,¹⁰² involving 2,330 adults with schizophrenia, compared haloperidol with quetiapine. The results for key questions 1, 2, and 4 are presented in Table 19.

Key Question 1. Improving core illness symptoms.

Positive symptoms. Two trials^{40,73} (n=598) reported BPRS (positive) and found no significant difference between groups. Four trials^{59,73,120,187} (n=393) reported PANSS and found no significant difference between groups. One subscale (BPRS elated mood subscale) also showed no significant difference between groups.

Negative symptoms. Six trials examined negative symptoms using three different scales. No significant differences were found between groups in pooled estimates for the different scales.

One trial (n=288) examined the PANSS depressive subscale and found a significant difference favoring quetiapine.

General symptoms. Four trials examined general symptoms using two different scales. No significant differences were found between groups for either scale.

Total score. Ten studies examined total scores using five different scales. Four trials^{40,62,73,86} (n=1253) used the CGI-S scale and found a significant difference favoring haloperidol. No significant differences were found between groups for the other scales.

Key Question 2 and 4. Improvement in functional outcomes, decreasing health care system utilization, and other outcomes.

Functional outcomes. One trial⁸⁶ (n=207) reported sexual dysfunction and found no significant difference between groups.

A small number of studies examined a variety of functional tasks. One study showed a significant difference favoring haloperidol in terms of the complex figure recall test, whereas results favored quetiapine for four functional tasks (Story Recall Test, Trail-Making Test B, Wechsler Adult Intelligence Scale-III Digit Symbol tests).

Other outcomes. Six trials^{40,62,73,86,187,288} (n=1421) reported response rates and one trial⁸⁶ (n=207) reported remission rates. No significant differences were found between groups.

Key Question 5. Subgroups.

Sex. One trial⁴¹ examined 35 female patients undergoing treatment for their first psychotic episode and reported no significant difference on the BRPS (total) scale.

Table 19. Evidence summary table: haloperidol versus quetiapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Core symptoms					
Positive symptoms					
Scales					
BPRS scale ^{40,73}	2	598	0.17 (-0.46, 0.80)	59%	NA
PANSS scale ^{59,73,120,187}	4	393	0.68 (-0.14, 1.50)	0%	NA
Subscales/ composite outcomes					
BPRS: elevated mood subscale ⁷³	1	288	0.53 (-0.17, 1.23)	NE	NA
Negative symptoms					
Scales					
CDS-S ^{86,120}	2	232	0.03 (-0.52, 0.58)	NE	NA
PANSS scale ^{59,73,120,187}	4	393	1.36 (-0.41, 3.13)	76%	NA
SANS scale ⁴⁰	1	310	-0.94 (-2.04, 0.15)	NE	NA

Note: bolded results are statistically significant; * = binary outcome; BDI = Beck Depression Inventory; BPRS = Brief Psychiatric Rating Scale; CDS-S = Calgary Depression Scale for Schizophrenia; CGI = Clinical Global Impression; CI = confidence intervals; GAF = Global Assessment of Functioning; I² = I-squared; MANSA = Manchester Short Assessment of Quality of Life; NA = not applicable; NE = not estimable; PANSS = Positive and Negative Syndrome Scale; QoL = Quality of Life; SANS = Scale for the Assessment of Negative Symptoms; UKU = Udvalg for Kliniske Undersøgelser; WAIS = Wechsler Adult Intelligence Scale; WCST = Wisconsin Card Sort Test; WMS = Wechsler Memory Scale

Table 19. Evidence summary table: haloperidol versus quetiapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Subscales/ composite outcomes					
PANSS: depressive subscale ⁷³	1	288	1.06 (0.32, 1.80)	NE	quetiapine
General symptoms					
Scales					
BDI scale ¹²⁰	1	25	5.30 (-2.79, 13.39)	NE	NA
PANSS scale ^{59,73,120,187}	4	393	0.46 (-0.87, 1.78)	9%	NA
Total score					
Scales					
BPRS scale ^{40,41,73,288}	4	756	1.23 (-0.50, 2.96)	0%	NA
CGI-I scale ^{40,73,120}	3	623	0.02 (-0.24, 0.27)	0%	NA
CGI-S scale ^{40,62,73,86}	4	1253	-0.23 (-0.42, -0.04)	0%	haloperidol
GAF scale ⁸⁶	1	207	0.10 (-9.60, 9.80)	NE	NA
PANSS scale ^{37,59,62,73,86,120,187}	7	1083	0.84 (-0.97, 2.66)	13%	NA
Sexual function/ dysfunction					
Sexual dysfunction (UKU) ⁸⁶	1	207	1.01 (0.63, 1.62)	NE	NA
Functional capacity					
Cognition: attention Span ¹²⁰	1	25	-0.20 (-0.68, 0.28)	NE	NA
Cognition: executive skills/visuomotor tracking ¹²⁰	1	25	0.10 (-0.42, 0.62)	NE	NA
Cognition: general ¹²⁰	1	25	-0.10 (-0.49, 0.29)	NE	NA
Cognition: immediate recall ¹²⁰	1	25	-0.20 (-0.67, 0.27)	NE	NA
Cognition: motor speed/dexterity ¹²⁰	1	25	0.10 (-1.04, 1.24)	NE	NA
Cognition: verbal reasoning/fluency ¹²⁰	1	25	-0.20 (-0.58, 0.18)	NE	NA
Cognition: visuospatial fluency/construction ¹²⁰	1	25	-0.60 (-1.29, 0.09)	NE	NA
Cognitive: composite score ⁶⁹	1	207	-0.14 (-0.33, 0.05)	NE	NA
Cognitive: summary Score ¹⁴⁰	1	58	-0.11 (-0.61, 0.39)	NE	NA
Complex figure copy test ¹²⁰	1	25	-1.30 (-3.09, 0.49)	NE	NA
Complex figure recall test ¹²⁰	1	25	1.00 (0.10, 1.90)	NE	haloperidol
Design learning test ¹²⁰	1	25	-0.40 (-1.35, 0.55)	NE	NA
Finger tapping ¹²⁰	1	25	-0.40 (-1.56, 0.76)	NE	NA
Grooved pegboard ^{69,120}	2	232	-0.02 (-0.25, 0.21)	0%	NA
Hopkins verbal learning test ¹²⁰	1	58	-1.52 (-5.84, 2.80)	NE	NA
Nonverbal fluency ¹²⁰	1	25	-0.10 (-0.46, 0.26)	NE	NA
Paragraph recall ¹²⁰	1	58	-0.72 (-3.05, 1.60)	NE	NA
Rey's auditory verbal learning Test ⁶⁹	1	207	0.00 (-0.26, 0.26)	NE	NA
Story recall Test ¹²⁰	1	25	-1.00 (-1.91, -0.09)	NE	quetiapine
Stroop Color-Word ¹⁴⁰	1	58	-2.57 (-13.52, 8.37)	NE	NA
Symbol digit ¹⁴⁰	1	58	1.14 (-7.55, 9.83)	NE	NA
Trail-making test A ⁶⁹	1	207	-0.04 (-0.22, 0.14)	NE	NA
Trail-making test B ^{69,120}	2	232	-0.12 (-0.24, -0.01)	0%	quetiapine
Trails B-A ¹⁴⁰	1	32	-1.00(-41.43, 39.43)	NE	NA
Verbal fluency ^{120,140}	2	83	-0.42 (-1.02, 0.17)	0%	NA
Verbal learning test ¹²⁰	1	25	0.00 (-0.91, 0.91)	NE	NA

Table 19. Evidence summary table: haloperidol versus quetiapine (continued)

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
WAIS-III Digit Symbol ⁶⁹	1	207	-0.26 (-0.46, -0.06)	NE	quetiapine
WAIS-R Digit Symbol Test ¹²⁰	1	25	0.00 (-0.36, 0.36)	NE	NA
WAIS-R Similarities ¹²⁰	1	25	-0.30 (-0.77, 0.17)	NE	NA
WCST (perseverations) ¹²⁰	1	25	0.50 (-0.53, 1.53)	NE	NA
WMS Digit Span ¹²⁰	1	25	-0.10 (-0.53, 0.33)	NE	NA
WMS Visual Reproduction ¹²⁰	1	25	-0.10 (-1.44, 1.24)	NE	NA
WMS Visual Span ¹²⁰	1	25	-0.50 (-1.23, 0.23)	NE	NA
Healthcare system utilization					
Rates of hospitalization/rehospitalization ⁸⁶	1	207	1.01 (0.51, 2.01)*	NE	NA
Other outcomes					
Response rates ^{40,62,73,86,187,288}	6	1421	0.99 (0.76, 1.30)*	77%	NA
Remission rates ⁸⁶	1	207	0.72 (0.41, 1.25)*	NE	NA
Health-related quality of life (QoL)					
MANSAs ⁸⁶	1	207	0.00 (-1.38, 1.38)	NE	NA

Haloperidol versus Risperidone

Thirty-six trials^{39,46,47,53-56,58,65,66,71,75,76,80,85,94-97,103,108,110,111,114,115,117,121-123,127,129,131,132,136,139,142,143,145-148} and one cohort study,¹⁰² involving 14,078 adults with schizophrenia, compared haloperidol with risperidone. The results for key questions 1, 2, and 4 are presented in Table 20.

Key Question 1. Improving core illness symptoms.

Positive symptoms. Twenty-four trials reported on positive symptoms using five scales. There was no significant difference between the groups with the PANSS^{55,58,66,75,85,96,103,108,111,114,115,117,121,122,129,132,136,142,146,147} (n=4064), HAM-A⁹⁶ (n=255), SAPS,^{97,142} (n=193) and Startle Reactivity¹⁴⁵ (n=30) scales. The Prepulse Inhibition Scale (n=30) significantly favored risperidone.¹⁴⁵

Multiple subscales or composite outcomes were also not significantly different between groups with the following exceptions: the PANSS subscale (uncontrolled hostility or excitement) in one trial¹¹⁵ favored haloperidol; and four subscales of the Symptom Check List (SCL-90-R) (anxiety, phobic anxiety, anger or hostility, and obsessive or compulsive) in one trial¹¹⁰ favored risperidone.

Negative symptoms. Twenty-five trials reported on negative symptoms using five scales. There was no significant difference between the groups with the PANSS^{55,58,66,75,85,96,103,108,111,114,115,117,121,122,129,132,136,142,146,147} (n=4064), HAM-D^{65,85,115} (n=468), and CDS-S^{65,80,115} (n=483). Four trials^{47,65,97,115} reported a significant difference on the SANS scale (n=506) favoring risperidone.

Several subgroups or composite outcomes reported no significant differences between the groups except for one trial¹¹⁰ (n=63) reporting SCL-90-R (depression) and one trial⁸⁵ (n=62) reporting HAM-D (sleep disturbance), both favoring risperidone.

General symptoms. Fifteen trials^{55,58,75,103,114,115,117,121,129,132,136,142,146,147,147} (n=3032) reported PANSS (general psychopathology). Pooled results are not reported due to marked heterogeneity among the included trials ($I^2 = 96$ percent, 95% CI: 95 to 97). Removal of two outlying trials,^{132,136} both significantly in favor of haloperidol, from the analysis reduced the quantified heterogeneity to 27 percent, which was not explained by either intervention details (mode of administration or dosage) or patient population. Several subgroups or composite outcomes reported no significant differences between the groups, except for one trial⁵⁴ (n=62) significantly favored haloperidol for BPRS (Factor 1) and one trial¹¹⁰ significantly favoring risperidone for SCL-90-R (interpersonal sensitivity). The pooled estimate without the two outliers was not statistically significant.

Total score. Total scores were reported for 10 scales, including the PANSS (20 trials), BPRS (12 trials), CGI-S (7 trials), CGI-I (4 trials), YMRS (2 trials), Clinician-Administered Rating Scale for Mania scale (1 trial), MADRS (1 trial), Nurses' Observation Scale for Inpatient Evaluation scale (1 trial), Schedule for Affective Disorders and Schizophrenia (1 trial), and SCL-90-R (1 trial). All reported no significant difference between groups except for the SCL-90-R, favoring risperidone.

Key Question 2 and 4. Improvement in functional outcomes, decreasing health care system utilization, and other outcomes.

Functional outcomes. *Employment or personal earnings:* One trial¹³² (n=100) reported economic independence in patients; there was no significant difference between groups.

Encounters with legal system: One trial¹¹⁵ (n=289) reported attitudes regarding drugs; there was no significant difference between groups.

Functional capacity: A variety of functional tests were reported. Haloperidol was significantly favored for the Maze simple and complex task velocity in one trial.¹⁰³ Risperidone was significantly favored for the following outcomes: Controlled Word Association Test (one trial¹³¹), functional deterioration (one trial¹¹⁵), marked clinical deterioration (one trial¹¹⁵), Fagerstrom Tolerance Questionnaire (one trial⁹⁷), various neurocognitive tests, nonverbal fluency (one trial¹²¹), perception of emotion (one trial⁹⁴), processing speed (one trial¹²⁹), Rey Verbal Learning Test (one trial¹²⁹), verbal fluency and reasoning (one trial¹²¹), and verbal fluency (one trial¹²⁹). All other outcomes were not significant.

Social relatedness or functioning: A variety of social relatedness or functioning tests were reported. The half profile nonverbal sensitivity (one trial¹³¹) and the Social Adjustment Scale II-Intimate relationship (one trial¹¹¹) significantly favoring haloperidol. All other outcomes were not significant.

Health care system utilization. Three trials^{71,115,132} (n=422) reported rates of hospitalization or rehospitalization in 422 participants; there were no significant difference between groups.

Other outcomes. *Relapse, response, and remission rates:* Six trials^{66,71,110,115,129,132} (n=1405) reported relapse rates and risperidone was significantly favored. Sixteen trials^{47,53,55,58,75,85,96,111,114,117,129,132,142,143,147,288} (n=2936) reported response rates. Pooled results are not reported due to marked heterogeneity among the included trials ($I^2 = 89$ percent, 95% CI: 83 to 92), which was not explained by mode of administration, dosage, or patient population.

There were no outliers with two trials^{58,143} statistically favoring haloperidol, four trials^{114,117,132,288} statistically favoring risperidone. One trial⁵⁴ (n=62) reported remission rates; there were no significant difference between groups.

Medication adherence: Three trials^{66,96,146} (n=661) reported medication adherence; there was no significant difference between groups.

Health-related quality of life (QoL): Three trials^{110,111,115} reported health-related quality of life scales; there were no significant difference between groups.

Patient satisfaction: One trial¹⁴³ (n=67) reported on patient satisfaction; there was no significant difference between groups.

Key Question 5. Subgroups.

Race. Seven trials^{97,103,108,114,146-148} with 493 Asian patients reported no significant difference on PANSS (positive), SAPS, PANSS (negative), or SANS.

One trial⁶⁵ in 117 Caucasians reported no significant results for the YMRS, but a significant difference favoring risperidone on the SAPS (MD = 0.30, 95% CI: 0.12 to 0.48), CDS-S (MD = 0.80, 95% CI: 0.69 to 0.91), HAM-D (MD = 1.00, 95% CI: 0.75 to 1.25), SANS (MD = 0.60, 95% CI: 0.38 to 0.82), and the BPRS (total) (MD = 0.80, 95% CI: 0.29 to 1.31). On the other hand, it reported a significant difference in favor of haloperidol on the CGI-S scale (MD = -0.20, 95% CI: -0.24 to -0.16).

First episode. Six trials^{65,75,115,127,129,139} (n=1365) with patients undergoing treatment for their first psychotic episode found a significant difference on the SAPS and SANS scales favoring risperidone ([MD = 0.30, 95% CI: 0.12 to 0.48] and [MD = 0.60, 95% CI: 0.38 to 0.62], respectively). No significant differences were found for the PANSS (positive), CDS-S, HAM-D, PANSS (negative), PANSS (general psychopathology), BPRS (total), CGI-I, CGI-S, PANSS (total), and YMRS.

Treatment resistance. Three trials^{94,143,147} with treatment resistant patients reported no significant difference on PANSS (positive) or PANSS (negative).

Table 20. Evidence summary table: haloperidol versus risperidone

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Core symptoms					
Positive symptoms					
Scales					
HAM-A scale ⁹⁶	1	255	0.10 (-1.44, 1.64)	NE	NA
PANSS scale ^{55,58,66,75,85,96,103,108,111,114,115,117,121,122,129,132,136,142,146,147}	20	4064	0.51 (-0.15, 1.17)	50%	NA
PPI scale ¹⁴⁵	1	30	12.18 (6.35, 18.01)	NE	risperidone
SAPS scale ^{65,97}	2	193	-0.14 (-2.01, 1.73)	35%	NA
Startle Reactivity ¹¹⁰	1	30	-2.40 (-22.98, 18.18)	NE	NA
Subscales/ composite outcomes					
PANSS-derived BPRS: activity subscale ¹¹⁷	1	1362	0.30 (-0.11, 0.71)	NE	NA
BPRS: hostility/suspiciousness ¹¹¹	1	63	0.05 (-0.13, 0.23)	NE	NA
PANSS-derived BPRS: hostility subscale ¹¹⁷	1	1362	0.08 (-0.38, 0.54)	NE	NA
PANSS: hostility subscale ^{56,66,85}	3	505	0.48 (-0.09, 1.05)	0%	NA
PANSS: excitement factor ^{142,142}	1	78	-0.15 (-0.73, 0.43)	NE	NA
PANSS: positive factor ^{142,142}	1	78	0.03 (-0.38, 0.44)	NE	NA
PANSS: Uncontrolled hostility/excitement MADRS ¹¹⁵	1	289	-0.70 (-1.18, -0.22)	NE	haloperidol
SCL-90-R: anxiety ¹¹⁰	1	63	0.35 (0.13, 0.57)	NE	risperidone
SCL-90-R: phobic anxiety ¹¹⁰	1	63	0.33 (0.09, 0.57)	NE	risperidone
SCL-90-R: anger/ hostility subscale ¹¹⁰	1	63	0.22 (0.04, 0.40)	NE	risperidone
SCL-90-R: obsessive/ compulsive subscale ¹¹⁰	1	63	0.35 (0.13, 0.57)	NE	risperidone
SCL-90-R: paranoid ideation subscale ¹¹⁰	1	63	0.16 (-0.16, 0.48)	NE	NA
SCL-90-R: psychoticism subscale ¹¹⁰	1	63	0.17 (-0.09, 0.43)	NE	NA
Negative symptoms					
Scales					
CDS-S ^{65,80,115}	3	483	0.47 (-0.39, 1.32)	74%	NA
HAM-D scale ^{65,85,115}	3	468	0.00 (-1.73, 1.73)	73%	NA
PANSS scale ^{55,58,66,75,85,96,103,108,111,114,115,117,121,122,129,132,136,142,146,147}	20	4064	0.51 (-0.15, 1.17)	31%	NA
SANS (total) scale ^{47,65,97,115}	4	506	0.58 (0.37, 0.80)	0%	risperidone

Note: bold = statistically significant; * = binary outcome; BPRS = Brief Psychiatric Rating Scale; CARs-M = Clinician-Administered Rating Scale for Mania; CDS-S = Calgary Depression Scale for Schizophrenia; CGI-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression-Severity; CI = confidence intervals; CM = Complex Maze; COWAT = Controlled Word Association Test; CVLT = California Verbal Learning Test; DSC-CPT = Degraded Stimuli-Continuous Performance Test; GAF = Global Assessment of Functioning; GPT = Grooved Pegboard Test; HAM-A = Hamilton Rating Scale for Anxiety; HAM-D = Hamilton Rating Scale for Depression; I² = I-squared; LNS = Letter-Number Sequencing; LQLP = Lancashire Quality of Life Profile; MADRS = Montgomery-Asberg Depression Rating Scale; NA = not applicable; NE = not estimable; NOSIE = Nurses' Observation Scale for Inpatient Evaluation; NR = not reported; PANSS = Positive and Negative Syndrome Scale; PPI = Prepulse Inhibition; QLS = Quality of Life Scale; QoL = quality of life; RVLTL = Rey Verbal Learning Test; SADS-C = Schedule for Affective Disorders and Schizophrenia-Change; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; SCL = Symptom Check List; SM = simple maze; SOFAS = Social and Occupational Functioning Scale; SRM = Spatial Recognition Memory; SWM = Spatial Working Memory; WAIS-R = Wechsler Adult Intelligence Scale-Revised; WCST = Wisconsin Card Sort Test; WMS-RVR = Wechsler Memory Scale - Revised Visual Reproduction; YMRS = Young Mania Rating Scale

Table 20. Evidence summary table: haloperidol versus risperidone (continued)

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Subscales/ composite outcomes					
BPRS: emotional withdrawal subscale ¹¹¹	1	63	0.00 (-0.17, 0.17)	NE	NA
CDS-S: depression subscale ³⁹	1	20	2.30 (-0.42, 5.02)	NE	NA
HAM-D: core depression subscale ⁸⁵	1	62	1.70 (-1.13, 4.53)	NE	NA
HAM-D: Secondary symptoms ⁸⁵	1	62	1.00 (-0.62, 2.62)	NE	NA
HAM-D: Somatic symptoms ⁸⁵	1	62	0.70 (-0.44, 1.84)	NE	NA
HAM-D: Sleep disturbance ⁸⁵	1	62	1.80 (0.20, 3.40)	NE	risperidone
PANSS: negative factor ^{65,142}	1	78	-0.14 (-0.53, 0.25)	NE	NA
SCL-90 Depression ¹¹⁰	1	63	0.46 (0.22, 0.70)	NE	risperidone
PANSS-derived BPRS: anergia ¹¹⁷	1	1362	0.36 (-0.12, 0.84)	NE	NA
SANS: affective flattening subscale ¹¹⁰	1	63	-0.02 (-0.35, 0.31)	NE	NA
SANS: alogia subscale ¹¹⁰	1	63	-0.01 (-0.29, 0.27)	NE	NA
SANS: anhedonia subscale ¹¹⁰	1	63	0.11 (-0.24, 0.46)	NE	NA
SANS: avolition subscale ¹¹⁰	1	63	0.06 (-0.26, 0.38)	NE	NA
SANS: global subscale ¹¹⁰	1	63	0.04 (-0.21, 0.29)	NE	NA
General symptoms					
Scales					
PANSS (general psychopathology) scale ^{55,58,75,103,114,115,117,121,129,132,136,142,146,147,147}	15	3032	NR	96%	NE
PANSS (general psychopathology) after removal of outliers ^{132,136}	13	2896	0.21 (-1.00, 1.41)	27%	NA
Subscales/ composite outcomes					
BPRS: anxiety/ depression ^{111,114}	2	98	0.18 (-0.13, 0.49)	51%	NA
BPRS: Factor I ⁵⁴	1	62	-0.52 (-0.84, -0.20)	NE	haloperidol
BPRS: Factor II ⁵⁴	1	62	-0.17 (-0.46, 0.12)	NE	NA
BPRS: Factor III ⁵⁴	1	62	-0.11 (-0.51, 0.29)	NE	NA
BPRS: Factor IV ⁵⁴	1	62	-0.09 (-0.22, 0.04)	NE	NA
BPRS: Factor V ⁵⁴	1	62	-0.13 (-0.45, 0.19)	NE	NA
BPRS: thought disturbances ^{110,114}	2	98	-0.10 (-0.33, 0.12)	0%	NA
PANSS-5: factor solution ¹¹⁵	1	289	-1.40 (-2.93, 0.13)	NE	NA
PANSS: anxiety/ depression ^{66,85,115,142}	4	794	0.23 (-0.21, 0.67)	29%	NA
PANSS: cognitive ^{142,142}	1	78	-0.13 (-0.42, 0.16)	NE	NA
PANSS: disorganized thought ^{66,85,115}	3	716	-0.16 (-2.16, 1.84)	86%	NA
PANSS-derived BPRS: anxiety/ depression ¹¹⁷	1	912	0.33 (-0.17, 0.84)	NE	NA
PANSS-derived BPRS: thought disturbances ¹¹⁷	1	1362	-0.06 (-0.62, 0.50)	NE	NA
SANS: attention impairment score ¹¹⁵	1	289	-0.20 (-0.47, 0.07)	NE	NA
SCL-90-R: interpersonal sensitivity ¹¹⁰	1	63	0.33 (0.05, 0.61)	NE	risperidone
SCL-90-R: somatization ¹¹⁰	1	63	0.21 (-0.01, 0.43)	NE	NA

Table 20. Evidence summary table: haloperidol versus risperidone (continued)

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Total score					
Scales					
BPRS scale ^{47,54,55,65,75,80,110,111,114,117,143,288}	12	2551	0.45 (-0.18, 1.08)	41%	NA
CARS–M scale ⁸⁵	1	62	3.00 (-3.36, 9.36)	NE	NA
CGI–I scale ^{85,114,129,143}	4	719	-0.06 (-0.23, 0.12)	0%	NA
CGI–S scale ^{55,65,111,114,115,117,143}	7	1626	-0.06 (-0.21, 0.10)	39%	NA
MADRS scale ⁹⁶	1	255	0.50 (-1.58, 2.58)	NE	NA
NOSIE–30 scale ⁵⁸	1	42	-5.30(-21.61, 11.01)	NE	NA
PANSS scale ^{39,55,58,66,75,76,85,96,103,108,111,114,115,117,129,132,136,142,146,147}	20	4042	1.78 (-0.73, 4.28)	74%	
SADS–C scale ⁵⁸	1	42	-0.40 (-10.12, 9.32)	NE	NA
SCL–90–R scale ¹¹¹	1	63	0.31 (0.12, 0.50)	NE	risperidone
YMRS ^{65,115}	2	406	0.10 (-0.07, 0.26)	0%	NA
Subscales/composite outcomes					
CARS–M: Mania subscale ⁸⁵	1	62	4.00 (-1.66, 9.66)	NE	NA
Employment/personal earnings					
Economic independence ¹³²	1	100	0.94 (0.68, 1.29)*	NE	NA
Encounters with legal system					
Attitude regarding drugs ¹¹⁵	1	289	-0.80 (-2.12, 0.52)	NE	NA
Functional capacity					
Attention Span ¹²¹	1	44	0.08 (-0.24, 0.40)	NE	NA
Brief test of attention (correct responses) ⁶⁵	1	117	-0.51 (-1.54, 0.52)	NE	NA
Continuous performance test (correct responses) ⁶⁵	1	117	-2.45 (-6.83, 1.93)	NE	NA
COWA, Verbal Fluency ¹²¹	1	44	-3.45 (-7.44, 0.54)	NE	NA
COWAT ¹³¹	1	60	7.40 (0.15, 14.65)	NE	risperidone
CVLT ¹³¹	1	60	6.20 (-0.31, 12.71)	NE	NA
Design list learning ¹²¹	1	44	-3.78 (-9.34, 1.78)	NE	NA
Functional deterioration (Csernasky criterion) ¹¹⁵	1	289	0.87 (0.46, 1.64)	NE	risperidone
Marked clinical deterioration ¹¹⁵	1	289	0.84 (0.29, 2.44)	NE	risperidone
Digit span ¹²¹	1	44	0.20 (-1.42, 1.82)	NE	NA
Digit symbol subtest ¹²¹	1	44	0.20 (-4.34, 4.74)	NE	NA
Discrimination of self-generated words ⁹⁵	1	9	-0.01 (-0.12, 0.10)	NE	NA
DS CPT ¹³¹	1	60	-0.01 (-0.06, 0.04)	NE	NA
DSC ¹³¹	1	60	0.40 (-6.41, 7.21)	NE	NA
Executive Skills ¹²¹	1	44	0.11 (-0.51, 0.73)	NE	NA
Fagerstrom Tolerance Questionnaire ⁹⁷	1	76	1.90 (0.94, 2.86)	NE	risperidone
FAS verbal fluency (# words in time limit) ⁶⁵	1	117	-0.43 (-4.36, 3.50)	NE	NA
Finger tapping ^{65,121}	2	161	0.44 (-6.66, 7.54)	65%	NA
GAF ¹¹⁵	1	289	-2.20 (-5.64, 1.24)	NE	NA

Table 20. Evidence summary table: haloperidol versus risperidone (continued)

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
GPT ¹³¹	1	60	-1.40 (-25.41, 22.61)	NE	NA
Grooved pegboard ^{65,121}	2	161	-0.48 (-17.58, 16.61)	64%	NA
Hooper visual organization test ¹²¹	1	44	0.38 (-0.47, 1.23)	NE	NA
Immediate recall ¹²¹	1	44	-0.22 (-0.58, 0.14)	NE	NA
Iowa gambling ⁶⁵	1	117	-11.99 (-26.45, 2.47)	NE	NA
LNS ¹³¹	1	60	0.20 (-2.40, 2.80)	NE	NA
Maze tasks CM velocity ¹⁰³	1	20	-41.70 (-81.21, -2.19)	NE	haloperidol
Maze tasks SM velocity ¹⁰³	1	20	-48.00 (-94.88, -1.12)	NE	haloperidol
Mean activity count: morning ³⁹	1	20	-200.00 (-561.65, 161.65)	NE	NA
Mean activity count: afternoon ³⁹	1	20	-96.30 (-265.24, 72.64)	NE	NA
Mean activity count: early night ³⁹	1	20	244.45 (-49.52, 538.42)	NE	NA
Mean activity count: late night ³⁹	1	20	88.89 (-1.54, 179.32)	NE	NA
Motor Skills ¹²¹	1	44	-0.48 (-1.10, 0.14)	NE	NA
Neurocognitive: composite score ⁹⁶	1	255	-0.06 (-0.27, 0.15)	NE	NA
Neurocognitive: Global Score ^{65,142}	1	78	-0.46 (-0.73, -0.19)	NE	risperidone
Neurocognitive: Declarative verbal learning and memory ^{65,142}	1	78	-0.66 (-1.08, -0.24)	NE	risperidone
Neurocognitive: General executive and perceptual organization ^{65,142}	1	78	-0.44 (-0.77, -0.11)	NE	risperidone
Neurocognitive: simple motor functioning ^{65,142}	1	78	-0.24 (-0.72, 0.24)	NE	NA
Nonverbal fluency ¹²¹	1	44	-3.60 (-6.17, -1.03)	NE	risperidone
Nonverbal fluency and construction ¹²¹	1	44	0.24 (-0.24, 0.72)	NE	NA
Peabody picture vocabulary test ¹²¹	1	44	1.02 (-4.41, 6.45)	NE	NA
Perception of emotion ⁹⁴	1	18	-6.93 (-10.32, -3.54)	NE	risperidone
Neurocognitive: processing speed and attention ^{65,142}	1	78	-0.21 (-0.63, 0.21)	NE	NA
Processing speed: WAIS-R Digit Symbol age-corrected score ¹²⁹	1	555	-0.35 (-0.67, -0.03)	NE	risperidone
Rey's auditory verbal learning (# words recalled) ⁶⁵	1	117	-1.26 (-5.18, 2.66)	NE	NA
Rey's auditory verbal learning LTR (# words recalled from list after delay) ⁶⁵	1	117	-0.98 (-2.36, 0.40)	NE	NA
Rey's complex figure test (long term recall) ⁶⁵	1	117	-0.46 (-2.97, 2.05)	NE	NA
Rey-Taylor complex figure copy ¹²¹	1	44	2.31 (-0.36, 4.98)	NE	NA
Rey-Taylor complex figure immediate recall ¹²¹	1	44	-0.08 (-4.15, 3.99)	NE	NA
RVLT: trials 1-5 ¹²⁹	1	555	-1.47 (-3.08, 0.14)	NE	NA

Table 20. Evidence summary table: haloperidol versus risperidone (continued)

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
RVLT: long-delay free recall ¹²⁹	1	555	-0.63 (-1.12, -0.14)	NE	risperidone
RVLT: recognition discriminability ¹²⁹	1	555	-0.78 (-2.85, 1.29)	NE	NA
Similarities subtest ¹²¹	1	44	-0.65 (-2.11, 0.81)	NE	NA
Sleep time (hrs) ³⁹	1	20	-0.46 (-2.22, 1.30)	NE	NA
SRM 15s ¹⁴³	1	67	1.50 (-0.20, 3.20)	NE	NA
SRM 5s ¹⁴³	1	67	1.60 (-0.20, 3.40)	NE	NA
Story Recall Test ¹²¹	1	44	-2.45 (-7.44, 2.54)	NE	NA
SWM 15s ¹⁴³	1	67	-2.90 (-5.92, 0.12)	NE	NA
SWM 5s ¹⁴³	1	67	-1.50 (-4.69, 1.69)	NE	NA
Trail-making test B ^{65,121}	2	161	2.64 (-9.02, 14.30)	0%	NA
Verbal fluency and reasoning ¹²¹	1	44	-0.30 (-0.49, -0.11)	NE	risperidone
Verbal list learning ¹²¹	1	44	-2.27 (-7.50, 2.96)	NE	NA
Verbal fluency: category + letter ¹²⁹	1	555	-2.79 (-5.23, -0.35)	NE	risperidone
Visual reproduction ¹²¹	1	44	0.45 (-1.33, 2.23)	NE	NA
Visual span ¹²¹	1	44	0.47 (-1.31, 2.25)	NE	NA
Vigilance: Continuous Performance Test d' total ¹²¹	1	555	0.08 (-0.01, 0.17)	NE	NA
Waking bouts ³⁹	1	20	7.26 (-1.46, 15.98)	NE	NA
WAIS III backwards digits (total score) ⁶⁵	1	117	-0.07 (-0.84, 0.70)	NE	NA
WAIS III digit symbol (total score) ⁶⁵	1	117	-0.30 (-1.42, 0.82)	NE	NA
WCST Categories ^{103,129,131}	3	635	-0.21 (-0.84, 0.41)	37%	NA
WCST Nonperseverative errors ¹⁰³	1	20	19.10 (-10.11,48.31)	NE	NA
WCST Perseverative errors ^{103,121,129}	4	650	0.58 (-2.92, 4.08)	12%	NA
WCST Perseverative responses ¹⁰³	1	20	5.10 (-16.83, 27.03)	NE	NA
WMS-RVR: Delayed recall total ¹²⁹	1	555	-0.81 (-2.15, 0.53)	NE	NA
WMS-RVR: Immediate recall total score ¹²⁹	1	555	-0.05 (-1.07, 0.97)	NE	NA
Social relatedness/ functioning					
Facial Emotion Identification Test ¹³¹	1	60	-0.50 (-2.26, 1.26)	NE	NA
Half profile nonverbal sensitivity ¹³¹	1	60	5.20 (0.45, 9.95)	NE	haloperidol
Interpersonal Perception Task-15 ¹³¹	1	60	0.30 (-0.62, 1.22)	NE	NA
Social Adjustment Scale II-Instrumental role ¹¹⁰	1	63	-0.01 (-0.55, 0.53)	NE	NA
Social Adjustment Scale II-Intimate relationship ¹¹¹	1	63	0.47 (0.01, 0.93)	NE	haloperidol
Social Adjustment Scale II-Overall Social functioning ¹¹⁰	1	63	0.18 (-0.18, 0.54)	NE	NA
Social Adjustment Scale II-Sense of well being ¹¹⁰	1	63	0.12 (-0.20, 0.44)	NE	NA
Social Adjustment Scale II-Total social relatedness/ functioning ¹¹⁰	1	63	0.05 (-0.25, 0.35)	NE	NA
Social Adjustment Scale II-Social/ leisure ¹¹⁰	1	63	-0.06 (-0.42, 0.30)	NE	NA

Table 20. Evidence summary table: haloperidol versus risperidone (continued)

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Social relations ¹¹⁰	1	63	0.06 (-0.29, 0.41)	NE	NA
SOFAS ¹¹⁵	1	289	-1.80 (-5.14, 1.54)	NE	NA
Voice Emotion Identification Test ¹³¹	1	60	0.50 (-1.51, 2.51)	NE	NA
Healthcare system utilization					
Rates of hospitalization/rehospitalization ^{71,115,132}	3	422	1.94 (0.99, 3.79)*	24%	NA
Other outcomes					
Relapse rates ^{66,71,110,115,129,132}	6	1405	1.35 (1.17, 1.57)*	0%	risperidone
Response rates ^{47,53,55,58,65,75,85,96,111,114,117,129,132,143,147,288}	16	2936	NR	89%	NA
Remission rates ⁵⁴	1	62	1.00 (0.58, 1.73)*	NE	NA
Medication adherence ^{66,96,146}	3	661	0.99 (0.95, 1.02)*	0%	NA
Patient satisfaction ¹⁴³	1	67	0.67 (0.37, 1.20)*	NE	NA
Health-related quality of life (QoL)					
QLS: Total ¹¹¹	1	63	0.10 (-0.17, 0.37)	NE	NA
LQLP: total score ¹¹⁵	1	289	0.10 (-0.20, 0.40)	NE	NA
LQLP: general health ¹¹⁵	1	289	-0.10 (-0.43, 0.23)	NE	NA
QoL: common objects ¹¹⁰	1	63	0.04 (-0.25, 0.33)	NE	NA
QoL: Intrapsychic ¹¹⁰	1	63	0.09 (-0.14, 0.32)	NE	NA
QoL: role functioning ¹¹⁰	1	63	0.05 (-0.69, 0.79)	NE	NA
Subjective Well-being Under neuroleptic Scale ¹¹⁵	1	289	1.80 (-2.39, 5.99)	NE	NA

Haloperidol versus Ziprasidone

Nine trials^{51,63,67,69,78,81,86,113,119} including 2971 adults with schizophrenia, compared haloperidol versus ziprasidone. The results for key questions 1, 2, and 4 are presented in Table 21.

Key Question 1. Improving core illness symptoms.

Positive symptoms. One trial⁵¹ (n=567) reported the Covi Anxiety Scale and found no significant difference between groups.

Negative symptoms. Two trials^{81,119} (n=900) reported the PANSS scale and found no significant difference between groups. One trial⁸⁶ (n=185) reported the CDS-S scale and found no significant difference between groups.

Total score. Four trials^{51,78,81,288} (n=1078) reported the BPRS scale, four trials^{51,78,81,86} (n=1275) reported the CGI-S, three trials^{81,86,119} (n=1085) reported the GAF scale, one trial⁸¹ (n=301) reported the MADRS, and four trials^{63,81,86,119} (n=1105) reported the PANSS; no significant differences between groups were found for any of the scales.

Key Question 2 and 4. Improvement in functional outcomes, decreasing health care system utilization, and other outcomes.

Functional outcomes. One trial (n=185) reported functional capacity using the grooved pegboard test, and ziprasidone was significantly favored. No differences were observed for the other five functional capacity measures.

Health care system utilization. Two trials^{81,86} (n=486) reported rates of hospitalization or rehospitalization; there was no significant difference between groups.

Other outcomes. Response and remission rates: Six trials^{51,63,78,81,86,288} (n=1283) reported response rates; there was no significant difference between groups. Three trials^{81,86,119} (n=1085) reported remission rates; there was no significant difference between groups.

Health-related quality of life (QoL): One trial⁸⁶ (n=185) reported health-related quality of life scales using the Manchester Short Assessment of Quality of Life scale; there was no significant difference between groups.

Key Question 5. Subgroups.

Comorbidities. Two trials^{67,86} in patients with comorbid substance abuse reported no significant difference in the CDS-S, CGI-S, GAF, and PANSS (total).

Table 21. Evidence summary table: haloperidol versus ziprasidone

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Core symptoms					
Positive symptoms					
Scales					
Covi anxiety scale ⁵¹	1	567	0.63 (-1.23, 2.49)	NE	NA
Negative symptoms					
Scales					
PANSS scale ^{81,119}	2	900	0.56 (-0.30, 1.42)	0%	NA
CDS-S ⁸⁶	1	185	0.00 (-0.71, 0.71)	NE	NA
Total score					
Scales					
BPRS scale ^{51,78,81,288}	4	1078	0.24 (-0.57, 1.06)	0%	NA
CGI-S scale ^{51,78,81,86}	4	1143	-0.00 (-0.26, 0.26)	28%	NA
GAF scale ^{81,86,119}	3	1085	0.30 (-1.58, 2.19)	0%	NA
MADRS scale ⁸¹	1	301	0.10 (-1.85, 2.05)	NE	NA
PANSS scale ^{63,81,86,119}	4	1105	0.45 (-2.85, 3.75)	0%	NA
Sexual function/ dysfunction					
Sexual dysfunction (UKU) ⁸⁶	1	185	0.69 (0.45, 1.07)*	NE	NA

Note: bold = statistically significant; * = binary outcome; BPRS = Brief Psychiatric Rating Scale; CDS-S = Calgary Depression Scale for Schizophrenia; CGI-I = Clinical Global Impressions-Improvement; CGI-S = Clinical Global Impression-Severity; CI = confidence intervals; GAF = Global Assessment of Functioning; I² = I-squared; MADRS = Montgomery-Asberg Depression Rating Scale; MANSAs = Manchester Short Assessment of Quality of Life; NA = not applicable; NE = not estimable; PANSS = Positive and Negative Syndrome Scale; QoL = Quality of Life; RVLt = Rey's Auditory Verbal Learning Test; UKU = Udvalg for Kliniske Undersøgelser; WAIS = Wechsler Adult Intelligence Scale

Table 22. Evidence summary table: haloperidol versus ziprasidone (continued)

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Functional capacity					
Cognitive composite score ⁶⁹	1	185	-0.08 (-0.28, 0.12)	NE	NA
Grooved pegboard test ⁶⁹	1	185	0.30 (0.05, 0.55)*	NE	ziprasidone
RVLT ⁶⁹	1	185	-0.24 (-0.48, 0.00)	NE	NA
Trail-making test A ⁶⁹	1	185	-0.06 (-0.27, 0.15)	NE	NA
Trail-making test B ⁶⁹	1	185	-0.19 (-0.39, 0.01)	NE	NA
WAIS-III digit symbol test ⁶⁹	1	185	-0.19 (-0.41, 0.03)	NE	NA
Healthcare system utilization					
Rates of hospitalization/re-hospitalization ^{81,86}	2	486	2.62 (0.99, 6.97)*	0%	NA
Other outcomes					
Response rates ^{51,63,78,81,86,288}	6	1283	0.98 (0.74, 1.30)*	80%	NA
Remission rates ^{81,86,119}	3	1085	0.89 (0.71, 1.12)*	12%	NA
Health-related quality of life (QoL)					
MANSA scale ⁸⁶	1	185	-0.10 (-1.48, 1.28)	NE	NA

Perphenazine versus Olanzapine

One trial¹⁰⁴ in 597 patients with schizophrenia compared perphenazine with olanzapine. The results for key questions 1, 2, and 4 are presented in Table 22.

Key Question 1. Improving core illness symptoms.

The included trial¹⁰⁴ (n=597) reported on PANSS (positive), PANSS (negative), PANSS (general psychopathology), PANSS (total), and CGI-S scales. All the findings significantly favored olanzapine, except PANSS (total), which favored perphenazine, and PANSS (negative), which was not significantly different between groups.

Key Question 2 and 4. Improvement in functional outcomes, decreasing health care system utilization, and other outcomes.

Functional outcomes. One trial¹⁰⁴ (n=597) examined the number of patients with paid employment; there was no significant difference between groups.

Health care system utilization. One trial¹⁰⁴ (n=597) reported the rates of hospitalization or rehospitalization; there was no significant difference between groups.

Other outcomes. One trial¹⁰⁴ (n=597) reported the Quality of Life Scale (total score); there was no significant difference between groups.

Key Question 5. Subgroups.

Comorbidities. The only included trial¹⁰⁴ reported on a subgroup of patients with comorbid illicit substance use. There was a significant difference in favor of olanzapine on PANSS (positive) (MD = 1.91, 95% CI: 0.57 to 3.25), PANSS (negative) (MD = 1.67, 95% CI: 0.17 to 3.17), and CGI-S (MD = 0.43, 95% CI: 0.17 to 0.69). There was a significant difference in favor

of perphenazine for PANSS (total) (MD = -5.11, 95% CI: -9.31 to -0.91). No difference between groups was found for the PANSS (general psychopathology).

Table 22. Evidence summary table: perphenazine versus olanzapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Positive symptoms					
PANSS scale ¹⁰⁴	1	597	1.47 (0.55, 2.40)	NE	olanzapine
Negative symptoms					
PANSS scale ¹⁰⁴	1	597	0.43 (-0.55, 1.41)	NE	NS
General psychopathology					
PANSS Scale ¹⁰⁴	1	597	2.17 (0.66, 3.68)	NE	olanzapine
Total scores					
PANSS Scale ¹⁰⁴	1	597	-4.59 (-7.42, -1.77)	NE	perphenazine
CGI Scale ¹⁰⁴	1	597	0.25 (0.06, 0.43)	NE	olanzapine
Functional outcomes					
Employment/ personal earnings					
Paid employment in past month ¹⁰⁴	1	597	1.29 (0.70, 2.38)*	NE	NA
Healthcare system utilization					
Rates of hospitalization/ rehospitalization ¹⁰⁴	1	597	1.39 (0.92, 2.09)*	NE	NA
Other outcomes					
Health-related quality of life (QoL)					
QLS Total score ¹⁰⁴	1	597	0.00 (-0.16, 0.16)	NE	NA

Note: bold = statistically significant; * = binary outcome; CI = confidence intervals; I² = I-squared; NA = not applicable; NE = not estimable; QLS = Quality of Life Scale; QoL = Quality of Life

Perphenazine versus Quetiapine

One trial¹⁰⁴ in 598 patients with schizophrenia compared perphenazine with quetiapine. The results for key questions 1, 2, and 4 are presented in Table 24.

Key Question 1. Improving core illness symptoms.

One trial¹⁰⁴ (n=598) reported the PANSS (positive), PANSS (negative), PANSS (general psychopathology), PANSS (total), and CGI-S scales; there was no significant difference between groups.

Key Question 2 and 4. Improvement in functional outcomes, decreasing health care system utilization, and other outcomes.

Functional outcomes. One trial¹⁰⁴ (n=598) reported the incidence of paid employment in the past month; there was no significant difference between groups.

Health care system utilization. One trial¹⁰⁴ (n=598) reported on rates of hospitalization or rehospitalization; there was no significant difference between groups.

Other outcomes. One trial¹⁰⁴ (n=598) reported the Quality of Life Scale (total score); there was no significant difference between groups.

Key Question 5. Subgroups.

Comorbidities. The only included trial¹⁰⁴ reported on a subgroup of patients with comorbid illicit substance use. There was no significant difference between groups on PANSS (positive), PANSS (negative), PANSS (general psychopathology), PANSS (total), or CGI-S.

Table 23. Evidence summary table: perphenazine versus quetiapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Positive symptoms					
PANSS scale ¹⁰⁴	1	598	-0.93 (-1.92, 0.05)	NE	NA
Negative symptoms					
PANSS scale ¹⁰⁴	1	598	-0.70 (-1.65, 0.25)	NE	NA
General psychopathology					
PANSS Scale ¹⁰⁴	1	598	-0.54 (-2.09, 1.01)	NE	NA
Total scores					
PANSS Scale ¹⁰⁴	1	598	1.52 (-1.36, 4.41)	NE	NA
CGI Scale ¹⁰⁴	1	598	-0.17 (-0.35, 0.01)	NE	NA
Employment/ personal earnings					
Paid employment in past month ¹⁰⁴	1	598	1.75 (0.90, 3.43)*	NE	NA
Healthcare system utilization					
Rates of hospitalization/ rehospitalization ¹⁰⁴	1	598	0.78 (0.55, 1.11)*	NE	NA
Other outcomes					
Health-related quality of life (QoL)					
Quality of Life Scale Total score ¹⁰⁴	1	598	0.10 (-0.07, 0.27)	NE	NA

* = binary outcome; CI = confidence intervals; I² = I-squared; NA = not applicable; NE = not estimable; QLS = Quality of Life Scale; QoL = Quality of Life

Perphenazine versus Risperidone

One trial¹⁰⁴ in 602 patients compared perphenazine with risperidone. The results for key questions 1, 2, and 4 are presented in Table 25.

Key Question 1. Improving core illness symptoms.

One trial¹⁰⁴ (n=602) reported on PANSS (positive), PANSS (negative), PANSS (general psychopathology), PANSS (total), and CGI-S scales; there was no significant difference between groups.

Key Question 2 and 4. Improvement in functional outcomes, decreasing health care system utilization, and other outcomes.

Functional outcomes. One trial¹⁰⁴ (n=602) reported the incidence of paid employment in the past month; there was no significant difference between groups.

Health care system utilization. One trial¹⁰⁴ (n=602) reported on rates of hospitalization or rehospitalization; there was no significant difference between groups.

Other outcomes. One trial¹⁰⁴ (n=602) reported the Quality of Life Scale (total score); there was no significant difference between groups.

Key Question 5. Subgroups.

Comorbidities. The only included trial¹⁰⁴ reported on a subgroup of patients with comorbid illicit substance use. There was no significant difference between groups on PANSS (positive), PANSS (negative), PANSS (general psychopathology), PANSS (total), or CGI-S.

Table 24. Evidence summary table: perphenazine versus risperidone

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Positive symptoms					
PANSS scale ¹⁰⁴	1	602	-0.06 (-1.04, 0.93)	NE	NA
Negative symptoms					
PANSS scale ¹⁰⁴	1	602	-0.87 (-1.85, 0.11)	NE	NA
General psychopathology					
PANSS Scale ¹⁰⁴	1	602	0.24 (-1.38, 1.86)	NE	NA
Total scores					
PANSS Scale ¹⁰⁴	1	602	0.17 (-2.84, 3.19)	NE	NA
CGI Scale ¹⁰⁴	1	602	-0.06 (-0.24, 0.13)	NE	NA
Employment/ personal earnings					
Paid employment in past month ¹⁰⁴	1	602	1.38 (0.74, 2.57)*	NE	NA
Healthcare system utilization					
Rates of hospitalization/rehospitalization ¹⁰⁴	1	602	1.05 (0.72, 1.53)*	NE	NA
Other outcomes					
Health-related quality of life (QoL)					
Quality of Life Scale Total score ¹⁰⁴	1	602	-0.07 (-0.24, 0.10)	NE	NA

* = binary outcome; CI = confidence intervals; I² = I-squared; NA = not applicable; NE = not estimable; QLS = Quality of Life Scale; QoL = Quality of Life

Perphenazine versus Ziprasidone

One trial¹⁰⁴ in 446 patients with schizophrenia compared perphenazine with ziprasidone. The results for key questions 1, 2, and 4 are presented in Table 25.

Key Question 1. Improving core illness symptoms.

One trial¹⁰⁴ (n=446) reported on PANSS (positive), PANSS (negative), PANSS (total), and CGI-S; there were no significant differences between groups, except for PANSS (general psychopathology), which favored perphenazine.

Key Question 2 and 4. Improvement in functional outcomes, decreasing health care system utilization, and other outcomes.

Functional outcomes. One trial¹⁰⁴ (n=446) reported the incidence of paid employment in the past month; there was no significant difference between groups.

Health care system utilization. One trial¹⁰⁴ (n=446) reported on rates of hospitalization or rehospitalization; there was no significant difference between groups.

Other outcomes. One trial¹⁰⁴ (n=446) reported the Quality of Life Scale (total score); no significant difference between groups.

Key Question 5. Subgroups.

Comorbidities. The only included trial¹⁰⁴ reported on a subgroup of patients with comorbid illicit substance use. There was no significant difference between groups on PANSS (positive), PANSS (negative), PANSS (general psychopathology), PANSS (total), or CGI-S.

Table 25. Evidence summary table: perphenazine versus ziprasidone

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Positive symptoms					
PANSS scale ¹⁰⁴	1	446	-0.85 (-2.05, 0.35)	NE	NA
Negative symptoms					
PANSS scale ¹⁰⁴	1	446	-0.97 (-2.05, 0.10)	NE	NA
General psychopathology					
PANSS Scale ¹⁰⁴	1	446	-1.92 (-3.69, -0.15)	NE	perphenazine
Total scores					
PANSS Scale ¹⁰⁴	1	446	2.23 (-1.15, 5.61)	NE	NA
CGI Scale ¹⁰⁴	1	446	-0.12 (-0.34, 0.10)	NE	NA
Employment/ personal earnings					
Paid employment in past month ¹⁰⁴	1	446	1.22 (0.60, 2.51)*	NE	NA
Healthcare system utilization					
Rates of hospitalization/ rehospitalization ¹⁰⁴	1	446	0.88 (0.58, 1.34)*	NE	NA
Other outcomes					
Health-related quality of life (QoL)					
Quality of Life Scale Total score ¹⁰⁴	1	446	-0.07 (-0.27, 0.13)	NE	NA

Note: bold = statistically significant; * = point estimate reflex relative risk; CI = confidence intervals; I² = I-squared; KQ = key question; NA = not applicable; NE = not estimable; QLS = Quality of Life Scale; QoL = Quality of Life; RR = relative risk

Bipolar disorder

For bipolar disorder, we included 10 trials that enrolled a total of 2279 adult patients. The individual studies are described in Appendix H through J. The results from the studies and pooled analyses, where appropriate, are presented in Tables 26 to 29. The following sections provide an overview of results according to key question: 1) core illness symptoms; 2) functional outcomes and health care system utilization; 4) other outcomes; and 5) subgroup analyses. For key question 1, the outcomes are grouped as follows: positive symptoms, negative symptoms, general psychopathology, and total score. Additionally, overall scores for scales are presented prior to scores on subscales or composite scores. Key questions 2 and 4 were grouped and are reported together throughout the results section. Within all key questions, comparisons are presented in alphabetic order by drug name.

Haloperidol versus Olanzapine

Two trials^{116,137} (n=463) involving adults with bipolar disorder compared haloperidol with olanzapine. The results from the trials for key questions 1, 2, and 4 are presented in Table 27.

Key Question 1. Improving core illness symptoms.

Sleep: One trial¹¹⁶ (n=12) found no significant differences in number of awakenings, sleep efficiency, stage rapid eye movement, total rapid eye movement, or total sleep time.

Total score: Two trials^{117,137} (n=465) assessed total score using three different scales; no differences were found between groups.

Key Question 2 and 4. Improvement in functional outcomes, decreasing health care system utilization, and other outcomes.

Functional outcomes. One trial¹³⁷ (n=453) reported a significant difference on the number days worked for pay favoring olanzapine.

Other outcomes. One trial¹³⁷ (n=453) reported on relapse, response, and remission rates; no significant difference was found between groups for any of the outcomes. One trial¹³⁷ (n=453) assessed health-related quality of life using the Short Form (SF)-36. Results showed a significant difference on the mental summary score favoring haloperidol and a significant difference on the physical summary score favoring olanzapine.

Key Question 5. Subgroups.

Disorder subtype. One trial¹³⁷ in 453 patients with bipolar 1 disorder reported no significant difference on HAM-D or YMRS.

One trial¹¹⁶ in 12 patients with bipolar 2 disorder reported no significant difference on number of awakenings, sleep efficiency, rapid eye movement, rapid eye movement activity, total sleep time (minutes), the CGI-Bipolar (BP), or the YMRS.

Table 26. Evidence summary table: haloperidol versus olanzapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Core symptoms					
Sleep					
Scales					
Number of awakenings ¹¹⁶	1	12	11.40 (-10.44, 33.24)	NE	NA
Sleep efficiency (%) ¹¹⁶	1	12	-8.90 (-34.65, 16.85)	NE	NA
Stage REM (min) ¹¹⁶	1	12	-10.70 (-54.10, 32.70)	NE	NA
Total REM activity ¹¹⁶	1	12	-29.30 (-85.88, 27.28)	NE	NA
Total sleep time (min) ¹¹⁶	1	12	18.60 (-107.21, 144.41)	NE	NA
Total score					
Scales					
CGI-BP scale ¹¹⁶	1	12	-1.80 (-5.66, 2.06)	NE	NA
HAM-D scale ¹³⁷	1	453	0.90 (-0.64, 2.44)	NE	NA
YMRS scale ^{116,137}	2	465	-0.37 (-1.98, 1.24)	0%	NA
Functional outcomes					
Employment/ personal earnings					
Active workers: number working for pay ¹³⁷	1	453	0.50 (0.32, 0.79)*	NE	Olanzapine
SLICE/LIFE: household activities impairment score ¹³⁷	1	453	0.23 (-0.10, 0.56)	NE	NA
SLICE/LIFE: work activities impairment score ¹³⁷	1	453	0.00 (-0.33, 0.33)	NE	NA
Other outcomes					
Relapse rates ¹³⁷	1	453	0.80 (0.52, 1.24)*	NE	NA
Response rates ¹³⁷	1	453	0.98 (0.94, 1.02)*	NE	NA
Remission rates ¹³⁷	1	453	0.85 (0.70, 1.03)*	NE	NA
Health-related quality of life (QoL)					
SF-36 mental summary score ¹³⁷	1	453	17.30 (14.47, 20.13)	NE	Haloperidol
SF-36 physical summary score ¹³⁷	1	453	-3.74 (-5.46, -2.02)	NE	Olanzapine

Note: bolded results are statistically significant; * = binary outcome; CGI-BP = Clinical Global Impression-Bipolar; CI = confidence intervals; HAM-D = Hamilton Rating Scale for Depression; I² = I-squared; NA = not applicable; NE = not estimable; QoL = Quality of Life; REM = rapid eye movement; SF = Short Form; SLICE/LIFE = Streamlined Longitudinal Interview Clinical Evaluation from the Longitudinal Interval Follow-up Evaluation; YMRS = Young Mania Rating Scale

Haloperidol versus Quetiapine

One trial¹³ (n=463) of adults with bipolar disorder compared haloperidol with quetiapine. The results for key questions 1, 2, and 4 are presented in Table 28.

Key Question 1. Improving core illness symptoms.

The one relevant trial did not report core illness symptoms.

Key Question 2 and 4. Improvement in functional outcomes, decreasing health care system utilization, and other outcomes.

Other outcomes. The one trial showed no significant differences in response rates or remission rates.

Key Question 5. Subgroups.

No subgroups were examined in the one relevant trial.

Table 27. Evidence summary table: haloperidol versus quetiapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Other outcomes					
Response rates ¹¹²	1	201	1.03 (0.83, 1.28)*	NE	NA
Remission rates ¹¹²	1	201	1.14 (0.94, 1.40)*	NE	NA

* = binary outcome; CI = confidence intervals; I² = I-squared; NA = not applicable; NE = not estimable

Haloperidol versus Risperidone

Four trials^{126,130,135,133} involving 463 adults with bipolar disorder compared haloperidol with risperidone. The results from the trials for key questions 1, 2, and 4 are presented in Table 29.

Key Question 1. Improving core illness symptoms.

Total score. One trial¹³³ (n=30) reported BPRS (total) and found no differences between groups. Likewise, three trials^{126,130,135} (n=433) showed no differences based on the YMRS.

Key Question 2 and 4. Improvement in functional outcomes, decreasing health care system utilization, and other outcomes.

No additional outcomes were reported among the four relevant trials.

Key Question 5. Subgroups.

Disorder subtype. One trial¹³⁵ in 298 patients with bipolar 1 found no significant difference on the YMRS.

Table 28. Evidence summary table: haloperidol versus risperidone

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Core symptoms					
Total score					
Scales					
BPRS scale ¹³³	1	30	-1.60 (-7.11, 3.91)	NE	NA
YMRS scale ^{126,130,135}	3	433	1.08 (-0.95, 3.12)	0%	NA

BPRS = Brief Psychiatric Rating Scale; CI = confidence intervals; I² = I-squared; NA = not applicable; NE = not estimable; YMRS = Young Mania Rating Scale

Haloperidol versus Ziprasidone

Only one trial¹⁴¹ involving 350 adults with bipolar disorder compared haloperidol with ziprasidone. The results for key questions 1, 2, and 4 are presented in Table 29.

Key Question 1. Improving core illness symptoms.

Total score. The one trial¹⁴¹ (n=350) found a significant difference favoring haloperidol based on the YMRS.

Key Question 2 and 4. Improvement in functional outcomes, decreasing health care system utilization, and other outcomes.

Other outcomes. The one relevant trial found a significant difference in response rates favoring haloperidol but no difference in remission rates.

Key Question 5. Subgroups.

Disorder subtype. One trial¹⁴¹ in 350 patients with bipolar 1 compared the YMRS and reported a significant difference favoring haloperidol (MD = -5.52, 95% CI: -7.79 to -3.25).

Table 29. Evidence summary table: haloperidol versus ziprasidone

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Core symptoms					
Total score					
Scales					
YMRS scale ¹⁴¹	1	350	-5.52 (-7.79, -3.25)	NE	haloperidol
Other outcomes					
Response rates ¹⁴¹	1	350	1.09 (1.02, 1.16)*	NE	haloperidol
Remission rates ¹⁴¹	1	350	1.42 (1.00, 2.02)*	NE	NA

Note: bolded results are statistically significant; * = binary outcome; CI = confidence intervals; I² = I-squared; YMRS = Young Mania Rating Scale; NA = not applicable; NE = not estimable

Key Question 3. Adverse events.

This section reviews the evidence on the comparative harms of FGAs and SGAs. The results are organized in alphabetical order by drug comparison (Appendix M). Data are not presented separately for schizophrenia and related psychoses and bipolar disorder because adverse events associated with an antipsychotic are likely to be consistent regardless of the indication for which a drug is being taken. For each comparison, we report data on general and specific adverse events. We categorized the outcomes by systems. We extracted only binary data for adverse events (i.e., the number of patients who experienced a given event in each group), not continuous data (e.g., mean change in laboratory values).

A priori, we identified four adverse events (AEs) to be of most clinical importance: diabetes mellitus, tardive dyskinesia, metabolic syndrome, and mortality. Table 31 summarizes the results of studies that provided data for these AEs and the strength of evidence for each comparison. For the most part, the evidence was insufficient to allow conclusions, primarily as a result of only single studies providing data. For diabetes mellitus, two RCTs of haloperidol versus olanzapine provided moderate evidence of no difference between the groups. For metabolic syndrome, one trial provided data for haloperidol versus clozapine and showed significantly fewer cases for haloperidol. Two trials provided data for haloperidol versus olanzapine and no differences were found. For mortality, two RCTs comparing chlorpromazine with clozapine provided low evidence of no difference between the groups. The only other significant difference in any of these AEs showed a higher incidence of tardive dyskinesia for haloperidol compared with clozapine; however, the evidence for this finding was considered insufficient to draw firm conclusions.

Table 30. Summary of the strength of evidence for AEs

Comparison (number of studies)	Strength of evidence	Summary	Relative risk (95% CI)
Diabetes mellitus			
Haloperidol vs. olanzapine (1 cohort study)	Insufficient	No significant difference.	0.60 (0.45 to 0.79)
Haloperidol vs. olanzapine (1 RCT)	Insufficient	No significant difference.	0.85 (0.21 to 3.49)
Haloperidol vs. quetiapine (1 cohort)	Insufficient	No significant difference.	0.83 (0.51 to 1.36)
Haloperidol vs. risperidone (1 cohort study)	Insufficient	Significant difference with more events for risperidone.	0.61 (0.46, 0.81)
Perphenazine vs. olanzapine (1 RCT)	Insufficient	No significant difference.	0.81 (0.45 to 1.45)
Perphenazine vs. quetiapine (1 RCT)	Insufficient	No significant difference.	1.57 (0.79 to 3.12)
Perphenazine vs. risperidone (1 RCT)	Insufficient	No significant difference.	1.06 (0.57 to 1.96)
Perphenazine vs. ziprasidone (1 RCT)	Insufficient	No significant difference.	1.00 (0.49 to 2.05)
Tardive dyskinesia			
Chlorpromazine vs. clozapine (1 RCT)	Insufficient	No significant difference.	3.30 (0.14 to 76.46)
Chlorpromazine vs. ziprasidone (1 RCT)	Insufficient	No significant difference.	1.21 (0.61 to 2.44)
Haloperidol vs. clozapine (1 cohort study)	Insufficient	Significant difference with more events for haloperidol.	34.50 (2.07 to 573.55)
Haloperidol vs. olanzapine (1 RCT)	Insufficient	No significant difference.	11.75 (0.65 to 211.26)
Haloperidol vs. quetiapine (1 RCT)	Insufficient	Results not pooled due to zero events in both groups.	NE

Table 30. Summary of the strength of evidence for AEs (continued)

Comparison (number of studies)	Strength of evidence	Summary	Relative risk (95% CI)
Tardive dyskinesia (continued)			
Haloperidol vs. quetiapine (1 RCT)	Insufficient	Results not pooled due to zero events in both groups.	NE
Haloperidol vs. ziprasidone (1 RCT)	Insufficient	No significant difference.	4.84 (0.23 to 99.93)
Metabolic syndrome			
Haloperidol vs. clozapine (1 RCT)	Low	Significant difference with more events for clozapine.	0.27 (0.10 to 0.75)
Haloperidol vs. olanzapine (2 RCTs)	Low	No significant difference.	0.38 (0.06 to 2.51)
Perphenazine vs. olanzapine (1 RCT)	Insufficient	No significant difference.	0.88 (0.63 to 1.21)
Perphenazine vs. quetiapine (1 RCT)	Insufficient	No significant difference.	1.19 (0.84 to 1.70)
Perphenazine vs. risperidone (1 RCT)	Insufficient	No significant difference.	1.42 (0.98 to 2.06)
Perphenazine vs. ziprasidone (1 RCT)	Insufficient	No significant difference.	1.51 (0.96 to 2.39)
Mortality			
Chlorpromazine vs. clozapine (2 RCTs)	Low	No significant difference.	0.98 (0.10 to 9.19)
Chlorpromazine vs. ziprasidone (1 RCT)	Insufficient	Results not pooled due to zero events in both groups.	NE
Haloperidol vs. aripiprazole (1 RCT)	Insufficient	Results not pooled due to zero events in both groups.	NE

CI = confidence interval; RCT = randomized controlled trial; RR = relative risk; NE = not estimable

Chlorpromazine versus Clozapine (Table 31)

General Measures. Two trials^{106,153} reported on mortality and three trials^{82,106,287} reported withdrawals due to AEs; no differences were found.

Specific Measures. Behavior and psychosis. One trial¹⁵⁰ reported the incidence of patients with agitation, and another trial¹⁵¹ reported on increasing paranoia and excitement; no differences were found.

BMI and weight. One trial²⁸⁷ reported the incidence of weight changes (gain or loss); no difference between the groups was found. Another trial⁸² reported on weight gain >5 percent and weight loss and found no differences.

Cardiovascular. The incidence of patients with hypotension in four trials^{82,89,106,287} was more frequent with chlorpromazine. The incidence of patients with hypertension in one trial⁸⁹ was more frequent in patients receiving clozapine. The rest of the outcomes were not significantly different between groups, including abnormal electrocardiogram (ECG) (one trial), arrhythmia (one trial), cardiotoxic effects (one trial), orthostatic collapse (one trial), orthostatic hypotension (one trial), and tachycardia (two trials).

Cholinergic and anticholinergic. One trial²⁸⁷ reported a higher incidence of anticholinergic effects, and two trials^{82,89} reported a higher incidence of dry mouth in patients receiving chlorpromazine. Four trials^{89,151,155,287} reported a higher incidence of hypersalivation in patients

receiving clozapine. The other outcomes, ileus (one trial¹⁰⁶) and moderate-severe sialorrhea (one trial⁸²), were not significantly different between the groups.

CNS. Four trials^{287,82,150,89} reported the incidence of patients with CNS disturbances; no differences were found.

Dermatology. Four trials^{106,82,150,287} reported the incidence of patients with dermatologic reactions; no difference between the groups was found.

Endocrine (prolactin and thyroid). One trial²⁸⁷ reported that hyperprolactinemia occurred significantly more frequently in patients receiving chlorpromazine.

EPS. Two trials^{151,287} reported that dystonia occurred significantly more frequently in patients receiving clozapine. One trial²⁸⁷ reported that bradykinesia, dyskinesia, rigor, and tremor occurred significantly more frequently in patients receiving chlorpromazine.

Gastrointestinal. Two trials^{89,106} reported the incidence of constipation, and two trials^{82,89} reported the incidence of nausea or vomiting; no differences were found.

Hematology. Five trials^{89,106,82,89,151} reported the incidence of patients with hematologic disorders; no significant difference between the groups was found.

Metabolic. Two trials^{89,82} reported the incidence of patients with elevated hepatic enzymes, one trial²⁸⁷ reported the incidence of patients with dyslipidemia and glucose intolerance, and one trial⁸² reported the incidence of patients with jaundice; no differences were found.

Sleep. One trial¹⁵⁰ reported the incidence of patients with deep sleep, sleep disturbances, and tiredness or sleepiness; no significant differences between the groups were found.

Systemic AEs. Two trials^{106,151} reported the incidence of patients with hyperthermia, one trial⁸² reported the incidence of patients with falls (accident), and one trial⁸⁹ reported the incidence of patients with fever and headache. Fever occurred significantly more frequently in patients receiving clozapine. All other AEs did not differ across groups.

Table 31. Evidence summary table: chlorpromazine versus clozapine – specific AEs (KQ3)

Outcome	Studies	Participants	Relative Risk	I ²	Favors
Cardiovascular					
Hypertension ⁸⁹	1	268	0.41 (0.17, 0.98)	NE	Chlorpromazine
Hypotension ^{82,89,106,287}	4	692	3.36 (2.19, 5.15)	11%	Clozapine
Cholinergic/anticholinergic					
Anticholinergic effects ²⁸⁷	1	220	2.46 (1.32, 4.61)	NE	Clozapine
Dry mouth ^{82,89}	2	308	4.07 (1.96, 8.46)	0%	Clozapine
Hypersalivation ^{89,151,155,287}	4	528	0.25 (0.09, 0.72)	49%	Chlorpromazine
Endocrine (prolactin, thyroid)					
Hyperprolactinemia ²⁸⁷	1	220	9.86 (1.27, 76.49)	NE	Clozapine

Note: Bold = statistically significant; AE = adverse event; EPS = extra pyramidal symptoms/syndrom; I² = I-squared; KQ = key question; NE = not estimable

Table 31. Evidence summary table: chlorpromazine versus clozapine - specific AEs (KQ3) (continued)

Outcome	Studies	Participants	Relative Risk	I ²	Favors
EPS					
Bradykinesia ²⁸⁷	1	220	5.32 (3.19, 8.87)	NE	Clozapine
Dystonia ^{151,287}	2	235	0.09 (0.01, 0.80)	34%	Chlorpromazine
Dyskinesia ²⁸⁸	1	220	27.36 (1.64, 456.43)	NE	Clozapine
Rigor ²⁸⁷	1	220	42.68 (2.61, 698.16)	NE	Clozapine
Tremor ²⁸⁸	1	220	13.14 (3.18, 54.27)	NE	Clozapine
Systemic AE					
Fever ⁸⁹	1	268	0.33 (0.13, 0.82)	NE	Chlorpromazine

Chlorpromazine versus Olanzapine (Table 32)

General Measures. One trial⁶⁰ reported withdrawals due to AEs; no differences were found.

Specific Measures. Cardiovascular. One trial⁶⁰ reported the incidence of patients with orthostatic changes and tachycardia. Orthostatic changes were significantly more frequent with chlorpromazine.

Cholinergic and anticholinergic. One trial⁶⁰ reported the incidence of patients with dry mouth, which occurred significantly more frequently with chlorpromazine.

CNS. One trial⁶⁰ reported the incidence of patients with dizziness, drowsiness or lethargy, slurred speech, and unsteady gait. The only significant difference was for unsteady gait, which occurred significantly more frequently with chlorpromazine.

EPS. One trial⁶⁰ reported the incidence of patients with EPS; no significant difference between the groups was found.

Gastrointestinal. One trial⁶⁰ reported the incidence of patients with constipation, dyspepsia or heartburn, and nausea or vomiting. Constipation occurred significantly more frequently with chlorpromazine. All other AEs did not differ between the groups.

Genital, urinary, and breast. One trial⁶⁰ reported the incidence of patients with dysuria; no significant difference between the groups was found.

Ophthalmology. One trial⁶⁰ reported the incidence of patients with blurred vision; no significant difference between the groups was found.

Sleep. One trial⁶⁰ reported the incidence of patients with insomnia; no significant difference between the groups was found.

Systemic AEs. One trial⁶⁰ reported the incidence of patients with headache; no significant difference between the groups was found.

Table 32. Evidence summary table: chlorpromazine versus olanzapine – specific AEs (KQ3)

Outcome	Studies	Participants	Relative Risk	I ²	Favors
Cardiovascular					
Orthostatic changes ⁶⁰	1	84	7.50 (2.90, 19.42)	NE	Olanzapine
Cholinergic/anticholinergic					
Dry mouth ⁶⁰	1	84	1.94 (1.27, 2.97)	NE	Olanzapine
CNS					
Unsteady gait ⁶⁰	1	84	15.00 (2.07, 108.48)	NE	Olanzapine
GI					
Constipation ⁶⁰	1	84	2.60 (1.02, 6.65)	NE	Olanzapine

Note: Bold = statistically significant; CNS = Central Nervous System; GI = gastrointestinal; I² = I-squared; KQ = key question; NE = not estimable

Chlorpromazine versus Quetiapine (Table 33)

General Measures. One trial¹¹⁸ reported mortality and withdrawals due to AEs; no differences were found.

Specific Measures. Behavior and psychosis. One trial¹¹⁸ reported the incidence of patients with agitation, anxiety, and nervousness; no significant differences between the groups were found.

BMI and weight. One trial¹¹⁸ reported the incidence of patients with weight gain >7 percent; no significant difference between the groups was found.

Cardiovascular. One trial¹¹⁸ reported the incidence of patients with hypotension, postural hypotension, and tachycardia; no significant difference between the groups was found.

Cholinergic and anticholinergic. One trial¹¹⁸ reported the incidence of patients with dry mouth; no significant difference between the groups was found.

CNS. One trial¹¹⁸ reported the incidence of patients with dizziness; no significant difference between the groups was found.

EPS. One trial¹¹⁸ reported the incidence of patients with akathisia, hypertonia, and tremor; no significant difference between the groups was found.

Gastrointestinal. One trial¹¹⁸ reported the incidence of constipation; no significant difference between the groups was found.

Metabolic. One trial¹¹⁸ reported the incidence of patients with elevation of alanine aminotransferase (ALT); no significant difference between the groups was found.

Sleep. One trial¹¹⁸ reported the incidence of patients with insomnia and somnolence; no significant difference between the groups was found.

Systemic AEs. One trial¹¹⁸ reported the incidence of patients with headache; no significant difference between the groups was found.

Table 33. Evidence summary table: chlorpromazine versus quetiapine – specific AEs (KQ3)

Outcome	Studies	Participants	Relative Risk	I ²	Favors
Cardiovascular					
Postural hypotension ¹¹⁸	1	201	3.64 (1.40, 9.42)	NE	Quetiapine

Note: Bold = statistically significant; I² = I-squared; KQ = key question; NE = not estimable

Chlorpromazine versus Ziprasidone (Table 34)

General Measures. One trial⁹¹ reported on mortality and withdrawals due to AEs; no differences were found.

Specific Measures. BMI and weight. One trial⁹¹ reported the incidence of patients with weight gain or loss >7 percent; there was no significant difference between groups for weight gain, but significantly more patients experienced weight loss with ziprasidone.

Cardiovascular. One trial⁹¹ reported the incidence of patients with postural hypotension and QT interval >500 milliseconds; no significant difference between the groups was found.

CNS. One trial⁹¹ reported the incidence of dizziness; no significant difference between the groups was found.

Endocrine (prolactin and thyroid). One trial⁹¹ reported the incidence of patients with amenorrhea; no significant difference between the groups was found.

EPS. One trial⁹¹ reported the incidence of patients with akathisia, EPS, tardive dyskinesia, and tremor; no significant difference between the groups was found.

Gastrointestinal. One trial⁹¹ reported the incidence of vomiting; no significant difference between the groups was found.

Genital, urinary, and breast. One trial⁹¹ reported the incidence of male patients with sexual dysfunction; no significant difference between the groups was found.

Sleep. One trial⁹¹ reported the incidence of patients with somnolence; no significant difference between the groups was found.

Table 34. Evidence summary table: chlorpromazine versus ziprasidone – specific AEs (KQ3)

Outcome	Studies	Participants	Relative Risk	I ²	Favors
BMI/Weight					
Weight loss >7% ⁹¹	1	306	0.19 (0.06, 0.62)	NE	Chlorpromazine

Note: Bold = statistically significant; I² = I-squared; KQ = key question; NE = not estimable

Fluphenazine versus Olanzapine

General Measures. One trial⁸⁴ reported on incidence of patients with AEs and withdrawals due to AEs; no differences were found.

Specific Measures. Body mass index (BMI) and weight. One trial⁸⁴ reported the incidence of patients with weight gain; there was no significant difference between the groups.

Central nervous system (CNS). One trial⁸⁴ reported the incidence of patients with stupor; there was no significant difference between the groups.

Extrapyramidal symptoms (EPS). One trial⁸⁴ reported the incidence of patients with akathisia, dyskinesia, dyskinetic symptoms, hypertonia, parkinsonism, and tremor; there were no significant differences between the groups.

Sleep. One trial⁸⁴ reported the incidence of patients with insomnia; there was no significant difference between the groups.

Fluphenazine versus Quetiapine

General Measures. One trial⁶¹ reported on incidence of withdrawals due to AEs; no differences were found.

Specific Measures. Behavior and psychosis. One trial⁶¹ reported the incidence of patients with anxiety; no significant difference between the groups was found.

Cardiovascular. One trial⁶¹ reported the incidence of patients with abnormal electrocardiogram and orthostasis; there were no significant differences between the groups.

Cholinergic and anticholinergic. One trial⁶¹ reported the incidence of patients with dry mouth; there was no significant difference between the groups.

CNS. One trial⁶¹ reported the incidence of patients with dizziness and lethargy; there were no significant differences between the groups.

Endocrine (prolactin and thyroid). One trial⁶¹ reported the incidence of patients with abnormal thyroid stimulating hormone, amenorrhea, galactorrhea, and gynecomastia; there were no significant differences between the groups.

EPS. One trial⁶¹ reported the incidence of patients with tremor; no significant difference between the groups was found.

Gastrointestinal. One trial⁶¹ reported the incidence of patients with constipation, diarrhea, dyspepsia, increased appetite, and nausea; no significant difference between the groups was found.

Genital, urinary, and breast. One trial⁶¹ reported the incidence of patients with urinary frequency and hesitancy; no significant difference between the groups was found.

Ophthalmology. One trial⁶¹ reported the incidence of patients with blurred vision; no significant difference between the groups was found.

Sleep. One trial⁶¹ reported the incidence of patients with insomnia and somnolence; no significant difference between the groups was found.

Systemic AEs. One trial⁶¹ reported the incidence of patients with headache; no significant difference between the groups was found.

Fluphenazine versus Risperidone

General Measures. One trial⁶¹ reported on incidence of withdrawals due to AEs; no differences were found.

Specific Measures. Behavior and psychosis. One trial⁶¹ reported the incidence of patients with anxiety; no significant difference between the groups was found.

Cardiovascular. One trial⁶¹ reported the incidence of patients with abnormal electrocardiogram and orthostasis; no significant difference between the groups was found.

Cholinergic and anticholinergic. One trial⁶¹ reported the incidence of patients with dry mouth; no significant difference between the groups was found.

CNS. One trial⁶¹ reported the incidence of patients with dizziness and lethargy; no significant difference between the groups was found.

Endocrine (prolactin and thyroid). One trial⁶¹ reported the incidence of patients with abnormal thyroid stimulating hormone, amenorrhea, galactorrhea, and gynecomastia; no significant difference between the groups was found.

EPS. One trial⁶¹ reported the incidence of patients with tremor; no significant difference between the groups was found.

Gastrointestinal. One trial⁶¹ reported the incidence of patients with constipation, diarrhea, dyspepsia, increased appetite, and nausea; no significant difference between the groups was found.

Genital, urinary, and breast. One trial⁶¹ reported the incidence of patients with urinary frequency and hesitancy; no significant difference between the groups was found.

Ophthalmology. One trial⁶¹ reported the incidence of patients with blurred vision; no significant difference between the groups was found.

Sleep. One trial⁶¹ reported the incidence of patients with insomnia and somnolence; no significant difference between the groups was found.

Systemic AEs. One trial⁶¹ reported the incidence of patients with headache; no significant difference between the groups was found.

Haloperidol versus Aripiprazole (Table 35)

General Measures. One trial²⁸⁸ reported the incidence of patients with AEs, one trial³⁸ reported mortality, three trials^{38,70,87} reported serious AEs, and three trials^{38,70,87} reported withdrawals due to AEs; no differences were found.

Specific Measures. *Behavior and psychosis.* One trial³⁸ reported the incidence of patients with agitation, one trial⁸⁷ reported the incidence of patients with anxiety, and one trial²⁸⁸ reported the incidence of patients with psychological deterioration; no significant differences between groups were found.

BMI and weight. One trial⁸⁷ reported the incidence of weight gain; no significant difference between the groups were found.

Cardiovascular. One trial⁸⁷ reported the incidence of patients with increased QT interval and orthostatic hypotension; no significant difference between the groups was found.

CNS. Two trials^{38,87} reported that dizziness occurred significantly more frequently in patients receiving haloperidol.

Dermatology. One trial³⁸ reported the incidence of patients with injection site reaction; no significant difference between the groups was found.

EPS. Studies examined the incidence of akathisia (two trials^{70,87}), EPS (one trial³⁸), EPS-related AEs (two trials^{38,92}), hypertonia and tremor (one trial⁸⁷), and tremor of the extremities (one trial⁷⁰). EPS occurred significantly more frequently with patients receiving haloperidol.

Gastrointestinal. Two trials^{38,87} reported the incidence of patients with nausea, and one trial⁸⁷ reported the incidence of patients with abdominal pain and vomiting. Nausea occurred significantly more frequently in patients receiving haloperidol.

Ophthalmology. One trial⁸⁷ reported that blurred vision occurred significantly more frequently in patients receiving haloperidol.

Sleep. Three trials^{38,70,87} reported the incidence of patients with insomnia, and two trials^{38,87} reported the incidence of patients with somnolence; no significant differences between groups were found.

Systemic AEs. Two trials^{38,87} reported the incidence of patients with headache, and one trial⁸⁷ reported the incidence of patients with asthenia; no significant differences between the groups were found.

Table 35. Evidence summary table: haloperidol versus aripiprazole – specific AEs (KQ3)

Outcome	Studies	Participants	Relative Risk	I ²	Favors
CNS					
Dizziness ^{38,87}	2	668	0.48 (0.26, 0.89)	0%	Haloperidol
EPS					
EPS ³⁸	1	360	9.46 (1.22, 73.13)	NE	Aripiprazole
GI					
Nausea ^{38,87}	2	668	0.34 (0.16, 0.71)	0%	Haloperidol
Ophthalmology					
Blurred vision ⁸⁷	1	308	5.23 (1.42, 19.30)	NE	Aripiprazole

Note: Bold = statistically significant; CNS = central nervous system; EPS = extra pyramidal symptoms/syndrom; GI = gastrointestinal; I² = I-squared; KQ = key question; NE = not estimable

Haloperidol versus Asenapine (Table 36)

General Measures. One trial⁹² reported the incidence of patients with AEs, serious AEs, and withdrawals due to AEs; no differences were found.

Specific Measures. Behavior and psychosis. One trial⁹² reported the incidence of patients with agitation, anxiety, and worsening psychotic symptoms; no significant differences between the groups were found.

BMI and weight. One trial⁹² reported the incidence of patients with weight changes (loss or gain); no significant difference between the groups was found.

CNS. One trial⁹² reported the incidence of patients with oral hypoesthesia and sedation. Oral hypoesthesia occurred significantly more frequently in patients receiving asenapine.

Endocrine (prolactin and thyroid). One trial⁹² reported that prolactinemia occurred significantly more frequently with patients receiving haloperidol.

EPS. One trial⁹² reported the incidence of patients with dystonia and EPS, which both occurred significantly more frequently in patients receiving haloperidol. The other outcomes were not significantly different between groups.

Gastrointestinal. One trial⁹² reported the incidence of vomiting; no significant difference between the groups was found.

Metabolic. One trial⁹² reported the incidence of patients with fasting glucose >50 percent above the upper limit; no significant difference between the groups was found.

Sleep. One trial⁹² reported the incidence of patients with insomnia and somnolence. Somnolence occurred significantly more frequently with patients receiving asenapine.

Systemic AEs. One trial⁹² reported the incidence of headaches; no significant difference between the groups was found.

Table 36. Evidence summary table: haloperidol versus asenapine – specific AEs (KQ3)

Outcome	Studies	Participants	Relative Risk	I ²	Favors
CNS					
Oral hypoesthesia ⁹²	1	335	0.04 (0.00, 0.69)	NE	Haloperidol
Endocrine (prolactin, thyroid)					
Prolactinemia ⁹²	1	335	2.30 (1.02, 5.15)	NE	Asenapine
EPS					
Dystonia ⁹²	1	335	3.51 (1.33, 9.24)	NE	Asenapine
EPS ⁹²	1	335	2.07 (1.40, 3.07)	NE	Asenapine
Sleep					
Somnolence ⁹²	1	335	0.21 (0.05, 0.90)	NE	Haloperidol

Note: Bold = statistically significant; CNS = central nervous system; EPS = extra pyramidal symptoms; I² = I-squared; KQ = key question; NE = not estimable

Haloperidol versus Clozapine (Table 37)

General Measures. Six trials^{49,90,100,124,142,287} reported the incidence of withdrawals due to AEs; no differences were found.

Specific Measures. Behavior and psychosis. One trial¹⁴² reported the incidence of patients with clinical deterioration conducive to termination, and one trial¹⁵² reported the incidence of patients with irritability. Both outcomes occurred significantly more frequently with haloperidol. The other outcomes were not significantly different between groups.

BMI and weight. Three trials^{142,287,100} reported the incidence of patients with weight changes; no difference between the groups were found.

Cardiovascular. Four trials^{142,287,152,49} reported the incidence of patients with cardiovascular abnormalities; no difference between the groups were found.

Cholinergic and anticholinergic. One trial²⁸⁷ reported the incidence of patients with anticholinergic effects, two trials^{49,287} reported the incidence of patients with hypersalivation, and one trial¹⁵² reported the incidence of patients with sweating. All AEs occurred significantly more frequently with clozapine. Two trials^{49,152} reported the incidence of patients with dry mouth, which occurred significantly more frequently with haloperidol.

CNS. One trial⁴⁹ reported the incidence of patients with dizziness, which occurred significantly more frequently with clozapine. The other outcomes were not significantly different between groups.

Dermatology. Three trials^{49,287,152} reported the incidence of patients with dermatological abnormalities; no significant difference between the groups was found.

Endocrine (prolactin and thyroid). One trial²⁸⁷ reported that hyperprolactinemia occurred significantly more frequently with haloperidol. One trial¹⁵² reported the incidence of patients with abnormal menstruation; no significant difference between the groups were found.

EPS. One trial²⁸⁷ reported the incidence of patients with akathisia, dyskinesia, dystonia, rigor and, and tremor. Another trial¹⁵² reported the incidence of patients with hyperkinesias. One cohort study⁷⁷ reported the incidence of tardive dyskinesia. All outcomes occurred significantly more frequently with haloperidol. The other outcomes were not significantly different between groups.

Gastrointestinal. One trial⁴⁹ reported the incidence of patients with nausea, which occurred significantly more frequently with clozapine. The other outcomes were not significantly different between groups.

Hematology. Four trials^{124,142,287,49} reported the incidence of patients with hematologic disorders; no significant difference between the groups were found.

Metabolic. One trial¹⁰⁰ reported the incidence of patients with glucose levels >100 mg/dl and metabolic syndrome; both occurred significantly more frequently with clozapine. One trial²⁸⁷ reported the incidence of patients with dyslipidemia, which occurred significantly more frequently with haloperidol. The other outcomes were not significantly different between groups.

Ophthalmology. One trial¹⁵² reported the incidence of ophthalmic disturbances; no significant difference between groups.

Respiratory and airway. Two trials^{152,49} reported the incidence of patients with upper respiratory airway disturbances; no significant difference between the groups were found.

Sleep. One trial¹⁵² reported the incidence of patients with insomnia, which occurred significantly more frequently with haloperidol.

Systemic AEs. The incidence of the following AEs were reported: fever (two trials^{49,152}), headache and weakness (one trial¹⁵²), concurrent illnesses leading to termination (one trial¹⁴²), and malaise (one trial⁴⁹). No significant differences between the groups were found.

Table 37. Evidence summary table: haloperidol versus clozapine – specific AEs (KQ3)

Outcome	Studies	Participants	Relative Risk	I ²	Favors
Behavioral/psychosis					
Irritability ¹⁵²	1	88	3.21 (1.26, 8.15)	NE	Clozapine
Overt aggression ¹⁴³	1	77	1.66 (1.03, 2.66)	NE	Clozapine
Cholinergic/anticholinergic					
Anticholinergic effects ²⁸⁷	1	220	0.18 (0.04, 0.80)	NE	Haloperidol
Dry mouth ^{49,152}	2	163	2.81 (1.61, 4.92)	0%	Clozapine
Hypersalivation ^{49,287}	2	295	0.23 (0.12, 0.42)	0%	Haloperidol
Sweating ¹⁵²	1	88	0.13 (0.02, 0.96)	NE	Haloperidol
CNS					
Dizziness ⁴⁹	1	75	0.38 (0.18, 0.79)	NE	Haloperidol
Endocrine (prolactin, thyroid)					
Hyperprolactinemia ²⁸⁷	1	220	13.14(1.74, 99.35)	NE	Clozapine
EPS					
Akathisia ²⁸⁷	1	220	60.24 (8.49, 427.62)	NE	Clozapine
Dyskinesia ²⁸⁷	1	220	71.13(4.41, 1147.27)	NE	Clozapine
Dystonia ²⁸⁷	1	220	73.38(10.37, 519.26)	NE	Clozapine
Hyperkinesia ¹⁵²	1	88	2.01 (1.13, 3.56)	NE	Clozapine
Rigor ²⁸⁷	1	220	114.91(7.18,1838.32)	NE	Clozapine
Tardive dyskinesia ⁷⁷	1	333	34.50 (2.07, 573.55)	NE	Clozapine
Tremor ²⁸⁷	1	220	14.79 (3.60, 60.67)	NE	Clozapine
GI					
Nausea ⁴⁹	1	75	0.29 (0.11, 0.81)	NE	Haloperidol
Metabolic					
Glucose levels >100 mg/dl ¹⁰⁰	1	73	0.05 (0.00, 0.80)	NE	Haloperidol
Emergent metabolic syndrome ¹⁰⁰	1	73	0.27 (0.10, 0.75)	NE	Haloperidol
Sleep					
Insomnia ¹⁵²	1	88	3.44 (1.51, 7.84)	NE	Clozapine

Note: Bold = statistically significant; CNS = central nervous system; EPS = extra pyramidal symptoms/syndrom; GI = gastrointestinal; I² = I-squared; KQ = key question; mg/dl = milligrams per deciliter; NE = not estimable

Haloperidol versus Olanzapine (Table 38–39)

General Measures. Two trials^{124,288} reported the incidence of patients with AEs, 3 trials^{86,99,144} reported serious AEs, and 20 trials^{37,43,44,48,65,72,79,83,86,96,99,100,105,107,121,125,137,138,142,144} reported withdrawals due to AEs. Significantly more withdrawals due to AEs occurred with haloperidol. No other differences were found.

Specific Measures. Behavior and psychosis. Eleven trials^{43,65,79,83,96,103,107,138,142,144,288} reported the incidence of patients with behavioral disturbances or psychosis. One trial¹³⁸ reported a significantly higher incidence of patients with conversion symptoms receiving haloperidol. One trial¹⁴² reported a statistically higher incidence of patients with overt aggression. The other outcomes were not significantly different.

BMI and weight. Eight trials reported the incidence of patients with weight gain,^{43,83,99,125,137,138,142,214} seven trials reported the incidence of patients with weight gain >7%,^{65,86,100,105,127,138,139} and one trial⁸⁶ reported the incidence of overweight patients (BMI>25kg/m²); all were significantly higher for patients receiving quetiapine. The other outcomes were not significantly different between the groups.

Cardiovascular. One trial¹³⁸ reported that the incidence of palpitations were significantly higher in patients receiving haloperidol

CNS. One trial¹³⁸ reported the incidence of ataxia and drowsiness, and one trial⁸³ reported the incidence of patients with gait abnormal. Both outcomes occurred significantly more frequently with haloperidol. The other outcomes were not significantly different between groups.

Dermatology. One trial¹⁴⁴ reported the incidence of patients with maculopapular rash; no significant difference among the groups was found.

Endocrine (prolactin and thyroid). One trial¹⁰⁵ reported the incidence of patients with abnormal prolactin levels, two trials^{65,103} reported the incidence of patients with amenorrhea, and one trial¹³⁸ reported the incidence of patients with hot flashes. All outcomes occurred significantly more frequently with haloperidol. The other outcomes were not significantly different between groups.

EPS. The incidence of patients with EPS-related AEs, including acute dyskinesia (one trial¹³⁸), acute dystonia (one trial^{50,144}), akathisia (13 trials^{43,44,50,65,83,86,96,99,105,125,137,138,144}), any extrapyramidal event (one trial¹³⁸), bradykinesia (one trial⁸³), dyskinesia (three trials^{44,86,137}), dystonia (five trials^{43,44,86,99,137}), EPS (five trials^{44,99,101,144,103}), extrapyramidal syndrome (one trial¹³⁷), hypertonia (four trials^{43,44,137,138}), hypokinesia (three trials^{65,137,138}), hypotonia (one trial¹³⁸), parkinsonism (seven trials^{50,86,105,45,144,65,83}), and tremor (eight trials^{43,44,65,83,96,99,137,138}) were reported to be significantly higher in patients receiving haloperidol. The other outcomes were not significantly different between groups.

Gastrointestinal. One trial⁸³ reported the incidence of patients with anorexia, one trial¹³⁸ reported the incidence of increased or decreased appetite or excessive appetite, and two trials^{96,138} reported the incidence of vomiting. All outcomes occurred significantly more frequently with haloperidol. The other outcomes were not significantly different between groups.

Genital, urinary, and breast. One trial¹³⁸ reported that the incidence of patients with difficulty with micturition occurred significantly more often with patients receiving haloperidol. The other outcomes were not significantly different between groups.

Hematology. Three trials^{44,138,142} reported the incidence of patients with abnormal blood counts; no significant difference between the groups was found.

Metabolic. Two trials^{44,105} reported the incidence of patients with elevated liver transaminases, and one trial⁸⁶ reported the incidence of patients with hyperglycemia and hyperlipidemia. All outcomes occurred significantly more frequently with haloperidol. The other outcomes were not significantly different between groups. One large retrospective cohort¹⁰² reported a higher incidence of new-onset diabetes mellitus in patients receiving olanzapine.

Ophthalmology. One trial¹³⁸ reported the incidence of patients with blurred vision to be significantly higher in patients receiving haloperidol.

Respiratory and airway. Two trials^{43,96} reported on the incidence of patients with rhinitis; no significant difference between the groups were found.

Sleep. One trial¹³⁸ reported the incidence of patients having sleep disturbances (difficulty falling asleep, early awakening, increased dreams or nightmares, and interrupted sleep), and a second trial⁴⁴ reported the incidence of shortened sleep. These AEs occurred significantly more often

with patients receiving haloperidol. The other outcomes were not significantly different between groups.

Systemic AEs. Two trials^{43,65} reported the incidence of asthenia, and one trial¹³⁷ reported the incidence of fever and infection. These AEs occurred significantly more often with patients receiving quetiapine. One trial¹³⁸ reported the incidence of patients with chills; there was no significant difference between the groups. The other outcomes were not significantly different between the groups.

Table 38. Evidence summary table: haloperidol versus olanzapine – general measures of AEs (KQ3)

Outcome	Studies	Parti- cipants	Relative Risk	I ²	Favors
Withdrawals due to AE ^{37,43,44,48,65,72,79,83,86,96,99,100,105,107,121,125,137,138,142,144}	20	5324	1.87(1.54,2.26)	0%	Olanzapine

Note: Bold = statistically significant; AE = AEs; I² = I-squared; KQ = key question

Table 39. Evidence summary table: haloperidol versus olanzapine – specific AEs (KQ3)

Outcome	Studies	Participants	Relative Risk	I ²	Favors
Behavioral/psychosis					
Conversion symptoms ¹³⁸	1	1996	2.34 (1.12, 4.88)	NE	Olanzapine
Overt aggression ¹⁴²	1	76	1.73 (1.06, 2.82)	NE	Olanzapine
BMI/Weight					
Overweight (BMI>25kg/m ²) ⁸⁶	1	208	0.36 (0.22, 0.60)	NE	Haloperidol
Weight gain ^{43,83,99,125,137,138,142,214}	8	3815	0.46 (0.31, 0.69)	72%	Haloperidol
Weight gain >7% ^{65,86,100,103,105,127,138,139}	7	2574	0.42 (0.28, 0.64)	87%	Haloperidol
Cardiovascular					
Palpitations ¹³⁸	1	1996	1.48 (1.09, 2.02)	NE	Olanzapine
CNS					
Ataxia ¹³⁸	1	1996	1.84 (1.01, 3.35)	NE	Olanzapine
Drowsiness ¹³⁸	1	1996	1.19 (1.02, 1.38)	NE	Olanzapine
Gait abnormal ⁸³	1	182	8.36 (1.98, 35.32)	NE	Olanzapine
Cholinergic/anticholinergic					
Dry mouth ^{43,96,138}	3	2519	0.75 (0.61, 0.91)	0%	Haloperidol
Hypersalivation ^{44,65,83,137,138}	5	3171	3.64 (2.03, 6.55)	44%	Olanzapine
Increased perspiration ¹³⁸	1	1996	1.91 (1.44, 2.54)	NE	Olanzapine
Endocrine (prolactin, thyroid)					
Abnormal prolactin level ¹⁰⁵	1	263	1.36 (1.10, 1.68)	NE	Olanzapine
Hot flashes ¹³⁸	1	76	1.62 (1.06, 2.49)	NE	Olanzapine
EPS					
Acute dyskinesia ¹³⁸	1	1996	2.79 (1.85, 4.22)	NE	Olanzapine

Note: Bold = statistically significant; AE = adverse event; ALT = alanine transaminase; BMI = body mass index; CNS = central nervous system; EPS = extrapyramidal symptoms; GI = gastrointestinal; GU = genital/urinary; HDL = high density lipoprotein; I² = I-squared; KQ = key question; LDL = low density lipoprotein; Met S = metabolic syndrome; mg/dl = milligrams/deciliter; ms = milliseconds; NE = not estimable; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase

Table 39. Evidence summary table: haloperidol versus olanzapine – specific AEs (KQ3)

Outcome	Studies	Participants	Relative Risk	I ²	Favors
Acute dystonia ^{50,144}	2	482	21.07 (2.67, 166.25)	0%	Olanzapine
Akathisia ^{43,44,50,65,83,86,96,99,105,125,137,138,144}	13	4977	3.12 (2.39, 4.06)	47%	Olanzapine
Any extrapyramidal event ¹³⁸	1	1996	2.36 (2.05, 2.71)	NE	Olanzapine
Bradykinesia ⁸³	1	182	8.36 (1.98, 35.32)	NE	Olanzapine
Dyskinesia ^{44,86,137}	3	1092	8.57 (2.63, 27.87)	0%	Olanzapine
Dystonia ^{43,44,86,99,137}	5	1635	4.53 (2.20, 9.34)	7%	Olanzapine
EPS ^{44,99,101,144}	4	996	3.50 (2.18, 5.62)	0%	Olanzapine
Extrapyramidal syndrome ¹³⁷	1	453	11.11 (4.52, 27.30)	NE	Olanzapine
Hypertonia ^{43,44,137,138}	4	3147	2.54 (1.65, 3.91)	55%	Olanzapine
Hypokinesia ^{65,137,138}	3	2560	4.03 (1.55, 10.47)	37%	Olanzapine
Hypotonia ¹³⁸	1	1996	1.68 (1.03, 2.72)	NE	Olanzapine
Parkinsonism ^{50,86,105}	3	696	4.15 (1.52, 11.29)	73%	Olanzapine
Treatment-emergent Parkinsonism ^{45,144}	4	577	4.90 (2.74, 8.75)	0%	Olanzapine
Tremor ^{43,44,65,83,96,99,137,138}	8	3972	2.44 (1.63, 3.65)	63%	Olanzapine
GI					
Anorexia ⁸³	1	182	3.66 (1.25, 10.69)	NE	Olanzapine
Decreased appetite ¹³⁸	1	1996	1.56 (1.25, 1.96)	NE	Olanzapine
Excessive appetite ¹³⁸	1	1996	0.51 (0.41, 0.64)	NE	Haloperidol
Vomiting ^{96,138}	2	2252	1.78 (1.30, 2.43)	0%	Olanzapine
GU/breast					
Difficulty with micturition ¹³⁸	1	1996	16.8 (1.11, 2.54)	NE	Olanzapine
Metabolic					
Elevated ALT ^{44,290}	2	491	0.13 (0.02, 0.65)	0%	Haloperidol
High LDL ⁸⁶	1	208	0.47 (0.28, 0.79)	NE	Haloperidol
Hypercholesterolemia ⁸⁶	1	208	0.41 (0.24, 0.71)	NE	Haloperidol
Hyperglycemia ⁸⁶	1	208	0.32 (0.13, 0.77)	NE	Haloperidol
Hypertriglyceridemia ⁸⁶	1	208	0.51 (0.28, 0.94)	NE	Haloperidol
Low HDL ⁸⁶	1	208	0.38 (0.16, 0.94)	NE	Haloperidol
New onset Diabetes ¹⁰²	1	8989	0.60 (0.45, 0.79)	NE	Haloperidol
SGOT abnormality ≥ 1 ¹⁰⁵	1	263	0.41 (0.28, 0.58)	NE	Haloperidol
SGPT abnormality ≥ 1 ¹⁰⁵	1	263	0.45 (0.34, 0.61)	NE	Haloperidol
Treatment emergent Met S ¹²⁷	1	66	0.13 (0.02, 0.93)	NE	Haloperidol
Ophthalmology					
Blurred vision ¹³⁸	1	1996	1.40 (1.10, 1.78)	NE	Olanzapine
Sleep					
Difficulty falling asleep ¹³⁸	1	1996	1.24 (1.06, 1.45)	NE	Olanzapine
Early awakening ¹³⁸	1	1996	1.49 (1.24, 1.79)	NE	Olanzapine
Increased dreams/nightmares ¹³⁸	1	1996	1.31 (1.05, 1.63)	NE	Olanzapine
Interrupted sleep ¹³⁸	1	1996	1.58 (1.34, 1.85)	NE	Olanzapine
Shortened sleep ⁴⁴	1	1996	1.62 (1.35, 1.96)	NE	Olanzapine
Systemic AE					
Asthenia ^{43,65}	2	378	1.55 (1.06, 2.27)	0%	Olanzapine
Chills ¹³⁸	1	1996	1.74 (1.19, 2.52)	NE	Olanzapine
Fever ¹³⁷	1	453	0.05 (0.00, 0.86)	NE	Haloperidol
Infection ¹³⁷	1	453	0.27 (0.08, 0.93)	NE	Haloperidol
Heaviness in extremities ¹³⁹	1	1996	1.40 (1.11, 1.77)	NE	Olanzapine

Haloperidol versus Quetiapine (Table 40)

General Measures. Three trials^{62,73,288} reported the incidence of patients with AEs, one trial⁸⁶ on the serious AEs, and eight trials^{40,41,62,73,74,86,112,120} on withdrawals due to AEs; no differences were found.

Specific Measures. Behavior and psychosis. Six trials^{40,62,103,112,120,288} reported the incidence of patients with behavioral disturbances or psychosis; no significant difference between groups was found.

BMI and weight. Four trials^{40,86,103,120} reported the incidence of patients with weight gain and BMI>25kg/m²; no significant difference between the groups were observed.

Cardiovascular. Three trials^{40,62,112} reported the incidence of patients with postural hypotension, and three trials^{86,290,40} reported on QT interval prolongation; no significant difference between the groups were found.

Cholinergic and anticholinergic. Three trials^{62,112,120} reported that the incidence of patients with dry mouth was significantly higher in patients receiving quetiapine. Two trials^{62,120} reported no difference between groups regarding the incidence of hypersalivation.

CNS. Three trials^{40,62,120} reported the incidence of patients with AEs related to the CNS; no significant differences between the groups were found.

Dermatology. One trial¹²⁰ reported the incidence of patients with dry skin or rash; no significant differences between that groups were found.

Endocrine (prolactin and thyroid). Three trials^{62,73,86} reported that the incidence of patients with hyperprolactinemia was significantly higher with haloperidol. One trial⁶² reported that the incidence of patients with thyroid function test changes was significantly higher with quetiapine. There was no difference between the groups for other outcomes.

EPS. The incidence of akathisia (five trials^{40,62,73,86,112}), EPS (six trials^{40,73,74,103,62,112}), parkinsonism (two trials^{40,86}), and tremor (two trials^{62,112}) was significantly higher for patients receiving haloperidol. Two trials^{62,112} reported the incidence of patients with extrapyramidal syndrome was significantly higher for patients receiving quetiapine. The other outcomes were not significant between groups.

Gastrointestinal. Two trials^{40,62} reported that the incidence constipation was significantly higher in patients receiving quetiapine. One trial¹¹⁸ reported dyspepsia was not significantly different between the groups.

Genital, urinary, and breast. One trial¹⁰³ reported the incidence of patients with impotence, loss of libido, and sexual dysfunction; no significant difference between the groups were observed.

Hematology. One trial⁶² reported the incidence of patients with decreased white blood cell count, and one trial⁴⁰ reported on severe neutropenia and agranulocytosis; no significant difference between the groups were observed.

Metabolic. Three trials^{62,86,290} reported the incidence of patients with elevated liver transaminases and blood lipid levels; no significant differences between groups were found.

Multiple organ systems. One trial¹²⁰ reported the incidence of a two composite outcome measures consisting of patients with irritability, impotency, and elevated AST and ALT levels

(all occurring in the same patient) or nausea and vomiting, restlessness, appetite changes, EPS, akathisia (all occurring in the same patient); there were no significant differences between the groups.

Ophthalmology. One trial¹²⁰ reported the incidence of patients with blurred vision; no significant difference between the groups was found.

Sleep. Four trials^{40,62,112,120} reported the incidence of patients with insomnia or somnolence; there was no significant difference between the groups.

Systemic AEs. One trial⁶² reported the incidence of patients with asthenia, one trial¹²⁰ reported on cold flashes, one trial¹²⁰ reported on fatigue, and one trial^{40,62,112,120} reported on headache. No significant differences between the groups were found, except for significantly more frequent asthenia in patients receiving quetiapine.

Table 40. Evidence summary table: haloperidol versus quetiapine – specific AEs (KQ3)

Outcome	Studies	Participants	Relative Risk	I ²	Favors
Cardiovascular					
Postural hypotension ^{40,62,112}	3	959	0.49 (0.25, 0.94)	0%	Haloperidol
Cholinergic/anticholinergic					
Dry mouth ^{62,112,120}	3	674	0.32 (0.15, 0.65)	0%	Haloperidol
Endocrine (prolactin, thyroid)					
Hyperprolactinemia ^{62,73,86}	3	943	2.24 (1.04, 4.80)	89%	Quetiapine
Thyroid function test changes ⁶²	1	448	0.05 (0.00, 0.79)	NE	Haloperidol
EPS					
Akathisia ^{40,62,73,86,112}	5	1454	3.51 (1.84, 6.72)	68%	Quetiapine
EPS ^{40,73,74}	3	643	3.09 (1.60, 5.96)	72%	Quetiapine
EPS-related AE ¹¹²	1	201	4.68 (2.74, 7.97)	NE	Quetiapine
Extrapyramidal Syndrome ^{62,112}	2	649	0.32 (0.21, 0.49)	0%	Haloperidol
Parkinsonism ^{40,86}	2	517	4.04 (1.97, 8.26)	53%	Quetiapine
Tremor ^{62,112}	2	649	3.80 (2.12, 6.81)	0%	Quetiapine
GI					
Constipation ^{40,62}	2	758	0.45 (0.22, 0.93)	0%	Haloperidol
Sleep					
Somnolence ^{40,62,112,120}	4	984	0.57 (0.39, 0.84)	0%	Haloperidol
Systemic AE					
Asthenia ⁶²	1	448	0.29 (0.12, 0.71)	NE	Haloperidol

Note: Bold = statistically significant; AE = AEs; EPS = extrapyramidal symptoms; GI = gastrointestinal; I² = I-squared; KQ = key question; NE = not estimable

Haloperidol versus Risperidone (Table 41–42)

General Measures. One trial¹⁴⁸ reported the incidence of all AEs that spontaneously resolved by 24 hours; no differences were found. Eight trials^{66,75,80,114,126,133,148,288} reported the number of patients with AEs, and 22 trials^{53-55,58,65,66,75,76,80,85,96,115,117,126,129,135,142,143,146-148,291} reported withdrawals due to AEs; both significantly favored risperidone.

Specific Measures. Behavior and psychosis. Fourteen trials^{55,58,65,66,75,96,111,114,115,117,126,142,146,288} reported the incidence of patients with behavioral disturbances or psychosis; there was no significant difference between the groups.

BMI and weight. One trial⁹⁶ found significantly greater incidence of weight gain in patients receiving risperidone.

Cardiovascular. Three trials^{55,126,58} reported the incidence of patients with cardiovascular abnormalities; no significant difference between the groups was found.

Cholinergic and anticholinergic. Six trials^{54,58,65,80,96,146} reported the incidence of patients with AEs related to the cholinergic or anticholinergic properties; no significant difference between the groups was found.

CNS. Five trials^{58,96,111,126,148} reported the incidence of patients with AEs related to the CNS; no significant difference between the groups was found.

Endocrine (prolactin and thyroid). Six trials^{58,65,103,117,129,146} reported the incidence of patients with endocrine disturbances; there was no difference between the groups.

EPS. Akathisia (six trials^{54,65,96,136,143,146}), EPS (seven trials^{55,103,111,114,135,143,148}), and tremor (three trials^{80,96,126}) were significantly higher in patients receiving haloperidol; other outcomes were not significantly different between the groups.

Gastrointestinal. Nine trials^{47,55,58,80,96,111,117,126,146} reported the incidence of patients with gastrointestinal disturbances; there was no significant difference between the groups.

Genital, urinary, and breast. Decreased sexual desire (two trials^{117,146}), ejaculatory dysfunction (four trials^{58,65,117,146}), and erectile dysfunction (four trials^{58,65,117,143}) were not significantly different between the groups.

Hematology. One trial¹⁴² reported the incidence of patients with agranulocytosis; there was no significant difference between groups.

Metabolic. One trial²⁹⁰ reported the incidence of patients with elevated ALT and elevated AST; there was no significant difference between the groups.

Ophthalmology. Two trials^{54,58} reported the incidence of patients with blurred vision; there was no significant difference between the groups.

Respiratory and airway. One trial⁹⁶ reported the incidence of patients with rhinitis; there was no significant difference between the groups.

Sleep. Eight trials^{47,55,75,80,96,117,126,148} reported sleep-related outcomes; there was no difference between the groups.

Systemic AEs. The incidence of patients with asthenia (four trials^{54,58,65,117,146}), drug overdose (one trial¹¹⁵), headache (eight trials^{47,55,58,75,80,96,126,148}), infection (one trial⁴⁷), and pain (one trial⁹⁶) were not significantly different among the groups.

Table 41. Evidence summary table: haloperidol versus risperidone – general measures of AEs (KQ3)

Outcome	Studies	Participants	Relative Risk	I ²	Favors
Incidence of patients with AE ^{66,75,80,114,126,133,148,288}	8	1313	1.20 (1.01, 1.42)	84%	Risperidone
Withdrawals due to AE ^{53-55,58,65,66,75,76,80,85,96,115,117,126,129,135,142,143,146-148,291}	22	4380	1.27 (1.04, 1.55)	0%	Risperidone

Note: Bold = statistically significant; AE = AEs; I² = I-squared; KQ = key question

Table 42. Evidence summary table: haloperidol versus risperidone – specific AEs (KQ3)

Outcome	Studies	Participants	Relative Risk	I ²	Favors
BMI/Weight					
Weight gain ⁹⁶	1	255	0.19 (0.05, 0.81)	NE	Haloperidol
EPS					
Akathisia ^{54,65,96,136,143,146}	6	578	1.81 (1.32, 2.47)	0%	Risperidone
EPS ^{55,111,114,135,143,148}	6	604	1.86 (1.47, 2.37)	0%	Risperidone
Tremor ^{80,96,126}	3	437	2.27 (1.17, 4.41)	0%	Risperidone
Systemic AE					
Asthenia ^{65,65,146}	3	193	1.62 (1.05, 2.52)	0%	Risperidone

Note: Bold = statistically significant; AE = adverse event; BMI = body mass index; EPS = extrapyramidal symptoms; I² = I-squared; KQ = key question; NE = not estimable

Haloperidol versus Ziprasidone (Table 43 – 44)

General Measures. Seven trials^{51,63,78,81,141,288,292} reported on the number of patients with AEs and seven trials^{51,78,81,86,113,141} on withdrawals due to AEs; for both outcomes, ziprasidone had fewer events. Two trials^{113,141} reported on mortality and five trials^{51,81,86,141,292} on serious AEs; no differences were found.

Specific Measures. Behavior and psychosis. Five trials^{51,81,113,141,292} reported the incidence of patients with behavioral disturbances or psychosis; all the outcomes were not significantly different between groups.

BMI and weight. One trial⁸⁶ reported the incidence of patients with BMI > 25 kg/m² or weight gain > 7 percent; no difference between the groups was found. Another trial¹⁴¹ reported on weight change (gain or loss) and found no differences.

Cardiovascular. Six trials^{81,86,113,141,290,292} reported the incidence of patients with cardiovascular events with no significant difference between groups.

Cholinergic and anticholinergic. Two trials^{81,113} reported the incidence of patients with dry mouth and sweating with no significant difference between groups.

Central nervous system. One trial²⁹² reported the incidence of ataxia and seizures, and three trials^{81,113,141} reported on dizziness; there were no significant differences between groups.

Dermatology. One trial¹¹³ reported the incidence of injection-site pain with no significant difference between groups.

Endocrine (prolactin and thyroid). Two trials^{51,86} reported the incidence of patients with hyperprolactinemia; there was no significant difference between groups.

EPS. The incidence of patients with akathisia (seven trials^{51,81,86,113,119,141,292}), any movement disorder (one trial⁸¹), dystonia (four trials^{51,86,141,292}), EPS (six trials^{51,63,113,119,141,292}), hypertonia (four trials^{51,81,113,292}), hypokinesia (one trial¹⁴¹), muscular hypotonia (one trial¹⁴¹), and tremor (six trials^{51,81,113,119,141,292}) were significantly higher in patients receiving haloperidol. The other outcomes were not significantly different among the groups.

Gastrointestinal. The incidence of patients with nausea (two trials^{81,113}) was significantly higher with haloperidol. There was no difference in the incidence of dyspepsia (one trial¹⁴¹) and vomiting (two trials^{81,292}).

Hematology. One trial²⁹² reported no patients with hematologic toxicity.

Metabolic. Three trials^{86,290,292} reported the incidence of patients with metabolic disturbances; there was no difference between the groups.

Ophthalmology. One trial¹¹³ reported the incidence of abnormal vision; there was no difference between the groups.

Respiratory and airway. One trial reported the incidence of respiratory depression; there was no difference between the groups.

Sleep. Six trials^{51,81,113,119,141,292} reported the incidence of somnolence, and four trials^{51,81,113,119} reported on insomnia; there was no difference between the groups.

Systemic AEs. Two trials^{81,113} reported the incidence of asthenia, three^{81,113,141} trials reported on headaches, and one trial reported on malaise;¹¹³ there were no differences between the groups.

Table 43. Evidence summary table: haloperidol versus ziprasidone – general measures of AEs (KQ3)

Outcome	Studies	Participants	Relative Risk	I ²	Favors
Incidence of patients with AE ^{51,63,78,81,141,288,292}	7	1580	1.14 (1.05, 1.24)	26%	Ziprasidone
Withdrawals due to AE ^{51,78,81,86,113,141,292}	7	1683	1.7 (1.28, 2.26)	0%	Ziprasidone

Note: Bold = statistically significant; AE = AEs; I² = I-squared; KQ = key question

Table 44. Evidence summary table: haloperidol versus ziprasidone – specific AEs (KQ3)

Outcome	Studies	Participants	Relative Risk	I ²	Favors
Endocrine (prolactin, thyroid)					
High prolactin levels ⁵¹	1	567	2.65 (2.06, 3.42)	NE	Ziprasidone
EPS					
Treatment emergent akathisia ⁵¹	1	567	2.45 (1.75, 3.45)	NE	Ziprasidone
Any movement disorder ⁸¹	1	301	2.73 (1.77, 4.19)	NE	Ziprasidone
Dystonia ^{51,86,141,292}	4	1234	2.26 (1.51, 3.39)	0%	Ziprasidone
EPS ^{51,63,113,119,141}	5	1594	2.34 (1.56, 3.53)	63%	ziprasidone
Hypertonia ^{51,81,113,292}	4	1058	2.55 (1.63, 4.00)	0%	Ziprasidone
Hypokinesia ¹⁴¹	1	350	6.21 (1.41, 27.34)	NE	Ziprasidone
Muscular hypotonia ¹⁴¹	1	350	5.86 (1.75, 19.65)	NE	Ziprasidone
Tremor ^{51,81,113,119,141,292}	6	2007	2.61 (1.87, 3.66)	0%	Ziprasidone
GI					
Nausea ^{81,113}	2	359	0.43 (0.19, 0.95)	0%	Haloperidol

Note: Bold = statistically significant; EPS = extrapyramidal symptoms; GI = gastrointestinal; I² = I-squared; KQ = key question; NE = not estimable

Perphenazine versus Olanzapine

General Measures. One trial¹⁰⁴ reported the incidence of patients with AEs, serious AEs, and withdrawals due to AEs; no differences were found.

Specific Measures. Behavior and psychosis. One trial¹⁰⁴ reported the incidence of patients with suicidal ideation and suicide attempt; no differences were found.

BMI and weight. One trial¹⁰⁴ reported a higher incidence of weight gain >7 percent in patients receiving olanzapine.

Cardiovascular. One trial¹⁰⁴ reported the incidence of patients with new-onset hypertension, orthostatic faintness, and prolonged correct QT interval; there were no differences between the groups.

Cholinergic and anticholinergic. One trial¹⁰⁴ reported the incidence of patients with urinary hesitancy, dry mouth, and constipation; there were no differences between the groups.

Endocrine (prolactin and thyroid). One trial¹⁰⁴ reported the incidence of patients with gynecomastia or galactorrhea and menstrual irregularities; there were no differences between the groups.

EPS. One trial¹⁰⁴ reported the incidence of patients with acute dystonia, Abnormal Involuntary Movement Scale (AIMS) global severity score ≥ 2 , Barnes Akathisia Scale (BARS) global score ≥ 3 , and Simpson-Angus Scale (SAS) mean score ≥ 1 . The trial found a higher incidence of AIMS global severity score ≥ 2 in patients receiving perphenazine; no other differences were found.

Genital, urinary, and breast. One trial¹⁰⁴ reported the incidence of patients with decreased sex drive, arousal, or ability to reach orgasm, incontinence, and nocturia; there were no differences between the groups.

Metabolic. One trial¹⁰⁴ reported the incidence of patients with metabolic syndrome and new-onset diabetes mellitus; there were no differences between the groups.

Ophthalmology. One trial¹⁰⁴ reported the incidence of patients with new-onset cataracts; there was no difference between the groups.

Sleep. One trial¹⁰⁴ reported the incidence of patients with hypersomnia or sleepiness and insomnia. There was higher incidence of patients with insomnia receiving perphenazine.

Table 45. Evidence summary table: perphenazine versus olanzapine – specific AEs (KQ3)

Outcome	Studies	Participants	Relative Risk	I ²	Favors
BMI/Weight					
Weight gain >7% ¹⁰⁴	1	597	0.41 (0.28, 0.60)	NE	Perphenazine
EPS					
AIMS global severity score ≥ 2 ¹⁰⁴	1	597	1.65 (1.07, 2.54)	NE	Olanzapine
Sleep					
Insomnia ¹⁰⁴	1	597	1.54 (1.12, 2.13)	NE	Olanzapine

Note: Bold = statistically significant; BMI = body mass index; EPS = extrapyramidal symptoms; I² = I-squared; KQ = key question; NE = not estimable

Perphenazine versus Quetiapine

General Measures. One trial¹⁰⁴ reported the incidence of patients with AEs, serious AEs, and withdrawals due to AEs; no differences were found.

Specific Measures. Behavior and psychosis. One trial¹⁰⁴ reported the incidence of patients with suicidal ideation and suicide attempt; no differences were found.

BMI and weight. One trial¹⁰⁴ reported the incidence of weight gain >7 percent; no differences were found.

Cardiovascular. One trial¹⁰⁴ reported the incidence of patients with new-onset hypertension, orthostatic faintness, and prolonged corrected QT interval; no differences were found.

Cholinergic and anticholinergic. One trial¹⁰⁴ reported the incidence of patients with urinary hesitancy, dry mouth, and constipation; no differences were found.

Endocrine (prolactin and thyroid). One trial¹⁰⁴ reported the incidence of patients with gynecomastia or galactorrhea and menstrual irregularities; no differences were found.

EPS. One trial¹⁰⁴ reported the incidence of patients with acute dystonia, AIMS global severity score ≥ 2 , BARS global score ≥ 3 , and SAS mean score ≥ 1 . The incidence of AIMS global severity score ≥ 2 was higher in patients receiving perphenazine.

Genital, urinary, and breast. One trial¹⁰⁴ reported the incidence of patients with decreased sex drive, arousal, or ability to reach orgasm, incontinence, and nocturia; no differences were found.

Metabolic. One trial¹⁰⁴ reported the incidence of patients with metabolic syndrome and new-onset diabetes mellitus; no differences were found.

Ophthalmology. One trial¹⁰⁴ reported the incidence of patients with new-onset cataracts; no difference between the groups was found.

Sleep. One trial¹⁰⁴ reported the incidence of patients with hypersomnia or sleepiness and insomnia; no differences were found.

Table 46. Evidence summary table: perphenazine versus quetiapine – specific AEs (KQ3)

Outcome	Studies	Participants	Relative Risk	I ²	Favors
EPS					
AIMS global severity score ≥ 2 ¹⁰⁴	1	598	1.76 (1.13, 2.75)	NE	Quetiapine
Multitple organ systems					
Urinary hesitancy, dry mouth, constipation ¹⁰⁴	1	598	0.70 (0.53, 0.93)	NE	Perphenazine
Sleep					
Insomnia ¹⁰⁴	1	598	1.37 (1.01, 1.87)	NE	Quetiapine

Note: Bold = statistically significant; AIMS = Abnormal Involuntary Movement Scale; EPS = extrapyramidal symptoms; I² = I-squared; KQ = key question; NE = not estimable

Perphenazine versus Risperidone (Table 47)

General Measures. One trial¹⁰⁴ reported the incidence of patients with AEs, serious AEs, and withdrawals due to AEs; no differences were found.

Specific Measures. Behavior and psychosis. One trial¹⁰⁴ reported the incidence of patients with suicidal ideation and suicide attempt; no differences were found.

BMI and weight. One trial¹⁰⁴ reported the incidence weight gain >7 percent; there was no difference between the groups.

Cardiovascular. One trial¹⁰⁴ reported the incidence of patients with new-onset hypertension, orthostatic faintness, and prolonged correct QT interval; there were no differences between the groups.

Cholinergic and anticholinergic. One trial¹⁰⁴ reported the incidence of patients with urinary hesitancy, dry mouth, and constipation; no differences were found.

Endocrine (prolactin and thyroid). One trial¹⁰⁴ reported the incidence of patients with gynecomastia or galactorrhea and menstrual irregularities; no differences were found.

EPS. One trial¹⁰⁴ reported the incidence of patients with acute dystonia, AIMS global severity score ≥ 2 , BARS global score ≥ 3 , and SAS mean score ≥ 1 ; no differences were found.

Genital, urinary, and breast. One trial¹⁰⁴ reported the incidence of patients with decreased sex drive, arousal, or ability to reach orgasm, incontinence, and nocturia. There was a significantly higher incidence of incontinence and nocturia with patients receiving risperidone.

Metabolic. One trial¹⁰⁴ reported the incidence of patients with metabolic syndrome and new-onset diabetes mellitus; no differences were found.

Ophthalmology. One trial¹⁰⁴ reported the incidence of patients with new-onset cataracts; no differences were found.

Sleep. One trial¹⁰⁴ reported the incidence of patients with hypersomnia or sleepiness and insomnia; no differences were found.

Table 47. Evidence summary table: perphenazine versus risperidone – specific AEs (KQ3)

Outcome	Studies	Participants	Relative Risk	I ²	Favors
Genital, urinary, and breast					
Incontinence, nocturia ¹⁰⁴	1	602	0.31 (0.13, 0.75)	NE	perphenazine

Perphenazine versus Ziprasidone

General Measures. One trial¹⁰⁴ reported the incidence of patients with AEs, serious AEs, and withdrawals due to AEs; no differences were found.

Specific Measures. *Behavior and psychosis.* One trial¹⁰⁴ reported the incidence of patients with suicidal ideation and suicide attempt; no differences were found.

BMI and weight. One trial¹⁰⁴ reported the incidence weight gain >7 percent; no difference between the groups was found.

Cardiovascular. One trial¹⁰⁴ reported the incidence of patients with new-onset hypertension, orthostatic faintness, and prolonged correct QT interval; no differences were found.

Cholinergic and anticholinergic. One trial¹⁰⁴ reported the incidence of patients with urinary hesitancy, dry mouth, and constipation; no differences were found.

Endocrine (prolactin and thyroid). One trial¹⁰⁴ reported the incidence of patients with gynecomastia or galactorrhea and menstrual irregularities; no differences were found.

EPS. One trial¹⁰⁴ reported the incidence of patients with acute dystonia, AIMS global severity score ≥ 2 , BARS global score ≥ 3 , and SAS mean score ≥ 1 ; no differences were found.

Genital, urinary, and breast. One trial¹⁰⁴ reported the incidence of patients with decreased sex drive, arousal, or ability to reach orgasm, incontinence, and nocturia; no differences were found.

Metabolic. One trial¹⁰⁴ reported the incidence of patients with metabolic syndrome and new-onset diabetes mellitus; no differences were found.

Ophthalmology. One trial¹⁰⁴ reported the incidence of patients with new-onset cataracts; no difference between the groups was found.

Sleep. One trial¹⁰⁴ reported the incidence of patients with hypersomnia or sleepiness and insomnia; no differences were found.

Thioridazine versus Olanzapine

General Measures. None reported.

Specific Measures. *Cardiovascular.* One trial²⁹⁰ reported the incidence of patients with QT interval prolongation; no differences were found.

Metabolic. One trial²⁹⁰ reported the incidence of patients with elevated ALT and elevated aspartate aminotransferase (AST); no differences were found.

Thioridazine versus Risperidone

General Measures. None reported.

Specific Measures. *Cardiovascular.* One trial²⁹⁰ reported the incidence of patients with QT interval prolongation; no differences were found.

Metabolic. One trial²⁹⁰ reported the incidence of patients with elevated ALT and elevated AST; no differences were found.

Thioridazine versus Quetiapine

General Measures. None reported.

Specific Measures. *Cardiovascular.* One trial²⁹⁰ reported the incidence of patients with QT interval prolongation; no differences were found.

Metabolic. One trial²⁹⁰ reported the incidence of patients with elevated ALT and elevated AST; no differences were found.

Thioridazine versus Ziprasidone

General Measures. None reported.

Specific Measures. *Cardiovascular.* One trial²⁹⁰ reported the incidence of patients with QT interval prolongation; no differences were found.

Metabolic. One trial²⁹⁰ reported the incidence of patients with elevated ALT and elevated AST; no differences were found.

Summary and Discussion

This report provides a comprehensive synthesis of the evidence on the comparative effectiveness and safety of first- (FGAs) versus second-generation antipsychotics (SGAs) in adults with schizophrenia, schizophrenia-related psychoses, and bipolar disorder. The strength of evidence for core illness symptoms and key adverse events (AEs) is summarized by comparison in Tables 48–51.

We identified a large number of studies comparing individual FGAs with individual SGAs. For example, 111 studies provided data on 20 different comparisons for patients with schizophrenia or schizophrenia-related psychoses. Fewer studies provided evidence comparing antipsychotic drugs in patients with bipolar disorder (n=10). The most frequent comparisons involved haloperidol, with 42 studies comparing haloperidol with risperidone and 37 studies comparing haloperidol with olanzapine. Nevertheless, the number of studies available within each comparison and outcome was often limited. Although many studies reported data for core illness symptoms, a total of 95 scales and subscales or composite outcomes were used across studies. The heterogeneity in outcome assessment tools and the small number of studies within specific comparisons precluded drawing firm conclusions that may be directly relevant to front-line clinical decisions. Further, the primary outcomes may often have been selected based on expectations from the regulatory authorities and approval process. These outcomes may not always be the most relevant for clinical decision-making (e.g., patient employment, functioning). Outcomes potentially important to patients were rarely assessed in the studies, including health-related quality of life, social and occupational functioning, and legal interactions, thus limiting the potential applicability to real-life functions and naturalistic outcomes.

Data were provided primarily from randomized controlled trials (RCTs); however, in our quality assessment, most of the trials were found to have unclear risk of bias due to insufficient reporting of the methods used for sequence generation, concealment of allocation, and blinding.

Despite our efforts to identify long-term safety data from observational studies, only two retrospective cohort studies provided data for a minimum 2-year followup period. Short-term efficacy trials, which are accepted by the regulatory authorities, may not identify time-dependent AEs such as tardive dyskinesia for FGAs and diabetes mellitus and metabolic syndrome for SGAs. The optimal and minimal acceptable duration of followup in trials remains to be determined.

The majority of studies were industry funded (n = 86; 70%), which can increase the chance of pro-industry findings.²⁹³ Full disclosure of the nature and extent of industry involvement in the design, conduct, and analysis of such studies can help readers better evaluate the likelihood of industry bias in trial results. Of further note, funding for 19% of studies (n = 23) was not disclosed highlighting the need for transparency in reporting the nature and extent of financial support.

The evidence is summarized by key question in the sections that follow. Overall, there were few differences of clinical importance between the active drug comparisons. FGAs and SGAs were generally found to be comparable on symptom improvement. FGAs generally had poorer safety profiles.

Key Question 1: Core illness symptoms

The findings for core illness symptoms are presented for each condition in Table 48. Comparisons and outcomes for which there was insufficient evidence to draw a conclusion are not displayed in the tables. The evidence comparing individual FGAs and SGAs was insufficient to draw conclusions for the following comparisons: fluphenazine versus quetiapine, fluphenazine versus risperidone, haloperidol versus asenapine, and chlorpromazine versus olanzapine.

For schizophrenia or schizophrenia-related psychoses, seven studies provided data on core illness symptoms for chlorpromazine versus clozapine. No differences were found for positive symptoms. Moderate evidence showed benefits for clozapine for general symptoms. Moderate evidence also suggested benefits for clozapine in terms of total score; however, low evidence suggested benefits for chlorpromazine for total score.

One study provided data on core illness symptoms for fluphenazine versus olanzapine. The results showed significant differences in favor of olanzapine for positive symptoms, general symptoms, and total score. The strength of evidence was considered low for each outcome. No studies provided data for negative symptoms.

Five studies provided data on core illness symptoms for haloperidol versus aripiprazole. No differences were found for positive symptoms, negative symptoms, or total score. The strength of evidence was low for each outcome. No studies provided data for general symptoms.

Ten studies provided data on core illness symptoms for haloperidol versus clozapine. No significant differences were found for positive symptoms, negative symptoms, or general symptoms. The strength of evidence was low for these three outcomes. The findings were discordant for total score: low levels of evidence showed benefits for haloperidol in terms of the CGI-EI scale, whereas moderate levels of evidence favored clozapine in terms of the CGI-I and CGI-S scales.

Thirty-four studies provided data on core illness symptoms for haloperidol versus olanzapine. Results were discordant for positive symptoms: a significant difference favoring haloperidol was observed based on the Prepulse Inhibition test, whereas a significant benefit for olanzapine was found based on the Young Mania rating scale (YMRS). No differences were observed for the other five scales assessed. The strength of evidence was low for all outcomes. Olanzapine was favored for negative symptoms, general symptoms, and total score. The strength of evidence for these outcomes was low to moderate.

Ten studies provided data on core illness symptoms for haloperidol versus quetiapine. No significant differences were found for positive symptoms, negative symptoms, or general symptoms. A significant difference favoring haloperidol was found for total score. The strength of evidence for each of these outcomes was low.

Thirty-one studies provided data on core illness symptoms for haloperidol versus risperidone. The results showed significant benefits for risperidone in terms of positive symptoms and total score. The strength of evidence was low for positive symptoms, and low to moderate for total score depending on the scale used. There was no significant difference for negative symptoms and no studies provided data for general symptoms.

Seven studies provided data on core illness symptoms for haloperidol versus ziprasidone. There were no significant differences in terms of negative symptoms or total score. The strength of evidence was considered low. No studies provided data on positive symptoms or general symptoms.

One study provided data on core illness symptoms for perphenazine versus olanzapine. There were significant benefits for olanzapine in terms of positive symptoms and general symptoms. The results showed significant benefits for perphenazine for total score. The strength of evidence for each of these outcomes was low.

A total of 11 studies included patients with bipolar disorder. The most frequent comparison was haloperidol versus risperidone (four RCTs). No significant differences were found in total symptom score. Two studies compared haloperidol versus olanzapine and found no significant differences in total symptom score. One study compared haloperidol with ziprasidone and found a significant difference favoring haloperidol for total symptom score. The strength of evidence was considered low for all comparisons.

Table 48. Summary of the strength of evidence for core illness symptoms (KQ1)

Outcome	Comparison (number of studies)	Strength of evidence	Summary
Schizophrenia and schizophrenia-related psychoses			
Positive symptoms	Chlorpromazine vs. clozapine (2 RCTs)	Low	No significant difference.
	Fluphenazine vs. olanzapine (1 RCT)	Low	Significant difference favoring olanzapine for HAM–A and PANSS.
	Haloperidol vs. aripiprazole (3 RCTs)	Low	No significant difference.
	Haloperidol vs. clozapine (4 RCTs)	Low	No significant difference.
	Haloperidol vs. olanzapine (20 RCTs)	Low	Significant difference favoring haloperidol for PPI. Significant difference favoring olanzapine for YMRS. No differences in ACES, BPRS, PANSS, or SAPS.
	Haloperidol vs. quetiapine (5 RCTs)	Low	No significant difference.
	Haloperidol vs. risperidone (24 RCTs)	Low	Significant difference favoring risperidone for PPI. No difference for PANSS or SAPS.
	Perphenazine vs. olanzapine (1 RCT)	Low	Significant difference favoring olanzapine for PANSS.
	Negative symptoms	Haloperidol vs. aripiprazole (3 RCTs)	Low
Haloperidol vs. clozapine (5 RCTs)		Low	No significant difference.
Haloperidol vs. olanzapine (18 RCTs)		Low to moderate	Significant difference favoring olanzapine for BPRS, HAM–D, PANSS, and SANS (moderate). No difference for CDS–S (low).
Haloperidol vs. quetiapine (6 RCTs)		Low	No significant difference.
Haloperidol vs. risperidone (25 RCTs)		Low	No significant difference.
Haloperidol vs. ziprasidone (2 RCTs + 1 cohort)		Low	No significant difference.
General symptoms		Chlorpromazine vs. clozapine (2 RCTs)	Moderate
	Fluphenazine vs. olanzapine (1 RCT)	Low	Significant difference favoring olanzapine.
	Haloperidol vs. clozapine (3 RCTs)	Low	No significant difference.
	Haloperidol vs. olanzapine (11 RCTs)	Low	Significant difference favoring olanzapine for BPRS. No difference for PANSS.
	Haloperidol vs. quetiapine (4 RCTs)	Low	No significant difference.
	Perphenazine vs. olanzapine (1 RCT)	Low	Significant difference favoring olanzapine for PANSS.

Total score	Chlorpromazine vs. clozapine (6 RCTs)	Low to moderate	Significant difference favoring chlorpromazine based on CGI-EI scale (low). Significant difference favoring clozapine for CGI-S (moderate).
	Fluphenazine vs. olanzapine (1 RCT)	Low	Significant difference favoring olanzapine.
	Haloperidol vs. aripiprazole (4 RCTs)	Low	No significant difference.
	Haloperidol vs. clozapine (7 RCTs)	Low to moderate	Significant difference favoring haloperidol for CGI-EI (low). Significant differences favoring clozapine for CGI-I (moderate), and CGI-S (moderate). No differences for BPRS (low) and PANSS (low).
	Haloperidol vs. olanzapine (23 RCTs)	Low to moderate	Significant difference favoring olanzapine for MADRS (moderate) and PANSS (moderate). No difference for BPRS (low) or CGI-I (low).
	Haloperidol vs. quetiapine (10 RCTs)	Low	Significant difference favoring haloperidol for CGI-S. No differences for BPRS, CGI-I, or PANSS.
	Haloperidol vs. risperidone (23 RCTs)	Low to moderate	Significant difference favoring risperidone for SCL-90-R (low). No difference for BPRS (low), CGI-I (low), CGI-S (moderate), or YMRS (low).
	Haloperidol vs. ziprasidone (6 RCTs + 1 cohort)	Low	No significant difference.
	Perphenazine vs. olanzapine (1 RCT)	Low	Significant difference favoring perphenazine for PANSS.

Bipolar Disorder

Total score	Haloperidol vs. olanzapine (2 RCT)	Low	No significant difference.
	Haloperidol vs. risperidone (4 RCTs)	Low	No significant difference.
	Haloperidol vs. ziprasidone (1 RCT)	Low	Significant difference favoring haloperidol for YMRS.

ACES = Agitation-Calmness Evaluation Scale; BPRS = Brief Psychiatric Rating Scale; CDS-S = Calgary Depression Scale for Schizophrenia; CGI-EI = Clinical Global Impressions- Efficacy Index; CGI-I = Clinical Global Impressions-Improvement; CGI-S = Clinical Global Impression-Severity; HAM-A = Hamilton Rating Scale for Anxiety; HAM-D = Hamilton Rating Scale for Depression; MADRS = Montgomery-Asberg Depression Rating Scale; PANSS = Positive and Negative Syndrome Scale; PPI = Prepulse inhibition; pts = patients; RCT = randomized controlled trial; SAPS = Scale for the Assessment of Positive Symptoms; SCL = Symptom Check List; YMRS = Young Mania Rating Scale

Key Question 2: Functional outcomes and health care resource utilization

The findings for functional outcomes and health care system utilization are presented for each condition and comparison in Table 49. We did not assess the strength of evidence for outcomes in KQ2.

Results for functional outcomes were available from 13 head-to-head comparisons in studies of patients with schizophrenia or schizophrenia-related psychoses. No significant differences in functional outcomes were observed between groups for: fluphenazine versus olanzapine, quetiapine or risperidone; and perphenazine versus olanzapine, quetiapine, risperidone, and ziprasidone. However, in most cases evidence came from single studies.

Significant differences in functional outcomes were found in studies comparing haloperidol with SGAs (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone); however, the drug favored was not always consistent. Further, in several cases the proportion of

significant findings was small compared to the number of outcomes assessed. For example, 16 trials provided data on 79 different functional capacity measures for haloperidol versus olanzapine. In most cases, there were only single studies contributing to each measure. Overall, significant results were found for 24 of the measures; however, in some cases haloperidol was favored whereas in other cases olanzapine was favored. The variety of functional measures assessed across the studies precludes firm conclusions regarding the overall comparative effectiveness of individual drugs in terms of patient functioning.

Only one trial comparing haloperidol with olanzapine provided data on functional outcomes in patients with bipolar disorder. Significant differences were found favoring olanzapine in terms of the number of individuals actively working for pay. No differences were found for household or work activities impairment.

Table 49. Summary of evidence for functional outcomes, healthcare system utilization, and other outcomes (KQ2)

Outcome	Comparison (number of studies)	Summary
Schizophrenia and schizophrenia-related psychoses		
Functional outcomes	Fluphenazine vs. olanzapine (2 RCTs)	No significant difference in functional capacity.
	Fluphenazine vs. quetiapine (1 RCT)	No significant difference in sexual function/ dysfunction.
	Fluphenazine vs. risperidone (1 RCT)	No significant difference in sexual function/ dysfunction.
	Haloperidol vs. aripiprazole (1 RCT)	Significant difference favoring haloperidol for Fagerstrom Tolerance Questionnaire.
	Haloperidol vs. clozapine (4 RCTs)	Significant difference favoring clozapine for three functional capacity outcomes. No differences for remaining 27 functional capacity outcomes.
	Haloperidol vs. olanzapine (17 RCTs)	Significant difference favoring haloperidol for three functional capacity outcomes. Significant difference favoring olanzapine for 23 outcomes. No significant differences for remaining 53 reported functional capacity outcomes, social relatedness or functioning, sexual function or dysfunction, or encounters with the legal system.
	Haloperidol vs. quetiapine (3 RCTs)	Significant difference favoring haloperidol for one functional capacity outcome. Significant difference favoring quetiapine for three functional capacity measures. No significant differences for other 29 functional capacity outcomes or sexual function/ dysfunction.
	Haloperidol vs. risperidone (13 RCTs)	Significant difference favoring risperidone for 15 functional capacity measures and for one measure of social relatedness/ functioning. Significant difference favoring haloperidol for two functional capacity measures and one measure of social relatedness/ functioning. No significant differences for other 58 functional capacity outcomes, other 10 social relatedness/ functioning outcomes, economic independence, or attitude regarding drugs.
	Haloperidol vs. ziprasidone (1 RCTs)	Significant difference favoring ziprasidone for one functional capacity measure. No differences for five other functional capacity measures or sexual function/ dysfunction.

* For all comparisons reported, data were available on rates of hospitalization/rehospitalization; for haloperidol vs. olanzapine, data also available for mean hospital bed days. KQ = Key Question; RCT = Randomized Controlled Trial; WAIS = Weschler Adult Intelligence Scale

Table 49. Summary of evidence for functional outcomes, healthcare system utilization, and other outcomes (KQ2) (continued)

Outcome	Comparison (number of studies)	Summary
Schizophrenia and schizophrenia-related psychoses		
Functional outcomes (continued)	Perphenazine vs. olanzapine (1 RCT)	No significant difference in patients with paid employment.
	Perphenazine vs. quetiapine (1 RCT)	No significant difference in patients with paid employment.
	Perphenazine vs. risperidone (1 RCT)	No significant difference in patients with paid employment.
	Perphenazine vs. ziprasidone (1 RCT)	No significant difference in patients with paid employment.
Health care system use*	Chlorpromazine vs. clozapine (1 RCT)	No significant difference.
	Haloperidol vs. olanzapine (2 RCTs)	No significant difference.
	Haloperidol vs. quetiapine (1 RCT)	No significant difference.
	Haloperidol vs. risperidone (3 RCTs)	No significant difference.
	Haloperidol vs. ziprasidone (2 RCTs)	No significant difference.
	Perphenazine vs. olanzapine (1 RCT)	No significant difference.
	Perphenazine vs. quetiapine (1 RCT)	No significant difference.
	Perphenazine vs. risperidone (1 RCT)	No significant difference.
Perphenazine vs. ziprasidone (1 RCT)	No significant difference.	
Bipolar Disorder		
Functional outcomes	Haloperidol vs. olanzapine (1 RCT)	Significant difference favoring olanzapine for number of active workers (i.e., working for pay). No difference in household or work activities impairment.

Key Question 3: Medication-associated adverse events and safety

The findings for the adverse events that were deemed most clinically important are summarized in Table 50. The evidence comparing individual FGAs and SGAs was insufficient to draw conclusions for the following outcomes and comparisons: tardive dyskinesia (chlorpromazine versus clozapine, chlorpromazine versus ziprasidone, haloperidol versus clozapine, haloperidol versus quetiapine, haloperidol versus ziprasidone), mortality (chlorpromazine versus ziprasidone, haloperidol versus aripiprazole, haloperidol versus olanzapine), diabetes mellitus (haloperidol versus olanzapine, haloperidol versus quetiapine, haloperidol versus risperidone, perphenazine versus olanzapine, perphenazine versus quetiapine, perphenazine versus risperidone, perphenazine versus ziprasidone), and metabolic syndrome (perphenazine versus quetiapine, perphenazine versus risperidone, perphenazine versus ziprasidone).

Two trials provided data on mortality for chlorpromazine versus clozapine and no significant difference was found. For metabolic syndrome, one trial provided data for haloperidol versus clozapine and showed significantly fewer cases for haloperidol. The strength of evidence for these comparisons was low suggesting that further research may change the results and change our confidence in the results.

Data were also recorded for general measures of AEs, and specific AEs by physiological system (e.g., cardiovascular, endocrine); these outcomes were not assessed for strength of evidence. For general measures of AEs, significant differences were found in the incidence of patients with adverse events (AEs) and withdrawals due to AEs for several comparisons. Most

often the comparison included haloperidol, and the risk was consistently higher for the FGA. The most frequently reported AEs with significant differences were in the category of EPS and most often involved a comparison with haloperidol. In the vast majority of cases, the SGA had the preferred AE profile for EPS.

We were unable to examine persistence and reversibility of AEs due to the relatively short followup of the included studies: study followup periods averaged 8 weeks. It is unclear whether AE persistence and reversibility of several significant AEs could be reasonably examined during this time period (e.g., metabolic conditions, body mass index or weight, and cardiovascular).

Table 50. Summary of the strength of evidence for medication-associated adverse events and safety (KQ3)

Adverse event	Comparison (number of studies)	Strength of evidence	Summary
Schizophrenia and schizophrenia-related psychoses			
Mortality	Chlorpromazine vs. clozapine (2 RCTs)	Low	No significant difference.
Metabolic syndrome	Haloperidol vs. clozapine (1 RCTs)	Low	Significantly less frequent with haloperidol.
	Haloperidol vs. olanzapine (2 RCTs)	Low	No significant difference.

RCT = Randomized Controlled Trial

Key Question 4: Other outcomes

The findings for other outcomes are presented for each condition and comparison in Table 51. We did not assess the strength of evidence for outcomes in KQ4.

Results for other outcomes were available for 14 head-to-head comparisons in studies of patients with schizophrenia or schizophrenia-related psychoses. Few significant differences were found across the comparisons and outcomes examined. For all significant findings, the SGA was preferred. The most commonly reported other outcome was response rate. A significant difference in response rates based on three studies was found favoring clozapine versus chlorpromazine. Olanzapine was favored over haloperidol for response rates based on 15 studies. Significant differences were found favoring aripiprazole over haloperidol for caregiver satisfaction (n = 1 study) and patient satisfaction (n = 1 study). Risperidone was favored over haloperidol for relapse rates (n = 6 studies). Health-related quality of life was evaluated for the following comparisons and no significant differences were found: haloperidol versus olanzapine (4 RCTs), quetiapine (1 RCT), risperidone (3 RCTs) and ziprasidone (1 RCT); perphenazine versus olanzapine, quetiapine, risperidone and ziprasidone (1 RCT each).

Results for other outcomes were available for three head-to-head comparisons in studies of patients with bipolar disorder. Significant differences were found for health-related quality of life in one study comparing haloperidol versus olanzapine: haloperidol was favored for the mental summary score and olanzapine was favored for the physical summary score. One study showed a significant difference favoring haloperidol compared with ziprasidone for response rates.

Table 51. Summary of the evidence for other outcomes (KQ4)

Comparison (number of studies)	Summary
Schizophrenia and schizophrenia-related psychoses	
Chlorpromazine vs. clozapine (5 RCTs)	Significant difference in response rates favoring clozapine. No difference in remission rates.
Chlorpromazine vs. olanzapine (1 RCT)	No significant difference in response rates.
Chlorpromazine vs. quetiapine (1 RCT)	No significant difference in response rates.
Chlorpromazine vs. ziprasidone (1 RCT)	No significant difference in response rates.
Fluphenazine vs. olanzapine (1 RCT)	No significant difference in response rates.
Fluphenazine vs. quetiapine (1 RCT)	No significant difference in response rates.
Fluphenazine vs. risperidone (1 RCT)	No significant difference in response rates.
Haloperidol vs. aripiprazole (4 RCTs)	No significant difference in response rates or medication adherence. Significant difference favoring aripiprazole for caregiver satisfaction and patient satisfaction.
Haloperidol vs. asenapine (1 RCT)	No significant difference in response rates.
Haloperidol vs. clozapine (4 RCTs)	No significant differences in relapse rates, response rates, remission rates, or patient satisfaction.
Haloperidol vs. olanzapine (15 RCTs)	Significant difference favoring olanzapine for response rates. No significant difference for remission rates, medication adherence, patient insight into illness, or HRQoL.
Haloperidol vs. quetiapine (6 RCTs)	No significant difference in response rates, remission rates, or HRQoL.
Haloperidol vs. risperidone (22 RCTs)	Significant difference favoring risperidone for relapse rates. No significant difference for remission rates, medication adherence, patient satisfaction, or HRQoL.
Haloperidol vs. ziprasidone (7 RCTs)	No significant difference in response rates, remission rates, or HRQoL.
Perphenazine vs. olanzapine (1 RCT)	No significant difference in HRQoL.
Perphenazine vs. quetiapine (1 RCT)	No significant difference in HRQoL.
Perphenazine vs. risperidone (1 RCT)	No significant difference in HRQoL.
Perphenazine vs. ziprasidone (1 RCT)	No significant difference in HRQoL.
Bipolar Disorder	
Haloperidol vs. olanzapine (1 RCT)	No difference for relapse, response, or remission rates. Significant difference favoring haloperidol for HRQoL mental summary score. Significant difference favoring olanzapine for HRQoL physical summary score.
Haloperidol vs. quetiapine (1 RCT)	No significant difference in response or remission rates.
Haloperidol vs. ziprasidone (1 RCT)	Significant difference favoring haloperidol for response rates. No difference for remission rates.

KQ = Key Question; RCT = Randomized Controlled Trial; HRQoL = health-related quality of life

Key Question 5: Subgroups

A total of 38 studies compared outcomes for predefined subgroups. Among the studies of patients with schizophrenia and schizophrenia-related psychoses, data were most often available for race and treatment resistance. The race most often examined was Asian. No notable differences were observed for the subgroups compared to the overall findings.

The only subgroup available for analysis in studies of patients with bipolar disorder was disorder subtype, specifically bipolar 1 and bipolar 2. The results were consistent with the overall findings. A significant difference favoring haloperidol compared with ziprasidone in terms of core illness symptoms (YMRS and total score) was found for patients with bipolar 1 disorder.

Applicability

This report included studies that compared an individual FGA to an individual SGA. Placebo-controlled studies or studies comparing a FGA versus another FGA, or a SGA versus another SGA, were not included. Therefore, the evidence is focused on the comparative effectiveness of FGAs versus SGAs, but not on their effectiveness compared to placebo or other active agents. Overall, there were 20 head-to-head comparisons across the relevant studies; however, within most comparisons there were few studies.

The focus of FGA/SGA comparisons was on adults, aged 18 to 64 years, with schizophrenia or schizophrenia-related psychoses and bipolar disorder. The average age across studies ranged from 21 to 51 years (median = 38 years [interquartile range (IQR), 33 to 41]). Most studies were highly selective in patient enrolment and included patients who (1) met strict diagnostic criteria for case definition, (2) had few comorbidities, and (3) used few or no concomitant medications. Older adults, minorities, and the most seriously ill patients were also underrepresented. Such highly selective criteria may increase the likelihood of drug benefit and decrease the likelihood of AE occurrence. Almost half the studies involved hospitalized patients (inpatient treatment) (60 of 122 studies) or mixed inpatient and outpatient treatment populations (25 studies); relatively few studies examined only outpatient treatment populations (19 studies). As such we judge the results of this report to be applicable to patients in outpatient and inpatient treatment settings.

Another factor that restricts the applicability of results is the limited duration of followup. The lack of long-term (≥ 2 years) followup data precludes the ability to detect serious adverse effects that may develop over the course of several years. The average length of followup in the included studies was only 8 weeks. Further, a priori, we defined the following key adverse effects: diabetes mellitus, mortality, tardive dyskinesia, and major metabolic syndrome. In order to identify evidence for these important outcomes, we expanded our scope to search for and include cohort studies with a minimum of 2-year duration. Despite a comprehensive search, we only identified two cohort studies meeting our criteria. This is an important limitation that needs to be considered when interpreting the results and applying them in clinical practice.

Limitation of Existing Evidence

Inconsistency in treatment comparisons, outcomes, and outcome measurement across studies makes drawing firm clinical conclusions difficult. Few studies compared the same antipsychotic medications and dosage using similar measures; various scales and surrogate measures were used to assess efficacy for different outcomes and adverse events. Consensus is needed regarding outcomes and measures used to assess outcomes. Surrogate outcome measures may have been attractive alternatives in studies given their ability to save time (e.g., shorter followup durations) and ease to assess. However, they are associated with a main limitation when the medication indicates an AE in the surrogate, but may have no effect or have a harmful effect on the clinical outcome. This inconsistency can lead to recommendations of harmful medications or the exclusion of beneficial medications. Example surrogate outcome measures in this report include laboratory values to indicate treatment emergent metabolic syndrome, a clinical outcome.

Another important limitation in this body of evidence pertains to the instruments used to measure outcomes. Over 95 different scales and subscales or composite outcomes were used to assess efficacy outcomes across the studies. While some outcomes and scales were assessed

fairly consistently for core symptoms across conditions, such as the PANSS and BPRS for schizophrenia, measurement of core symptoms within global functioning scales was common and mixed using total scores, sub-scale scores, different criteria, and different measures. While the clinical global impressions reported across the studies make study outcomes relevant for clinicians, the heterogeneity in the different types of scales used to measure global improvements makes comparisons of patient improvement across studies and interventions challenging.

We also identified a vast array of different measures to assess functional capacity. For instance, 79 different measures were used among studies comparing haloperidol with olanzapine. For most measures, only single trials provided data. This is problematic in that when significant differences are found, we are not able to discern whether they are real differences or arise due to multiple statistical testing. Discussion and consensus are also needed on outcomes that can provide more information on patient functioning and well-being. This includes a systematic assessment of outcomes potentially important to patients such as health-related quality of life, social and occupational functioning, and legal interactions.

An important limitation to systematic reviews is the quality of the primary studies included in the review. We assessed risk of bias in RCTs using an empirically derived tool developed by The Cochrane Collaboration and assessed the methodological quality of cohort studies using the Newcastle-Ottawa Scale. The majority of studies providing data for this report were RCTs (n=120). Of these trials, none were identified as having a low risk of bias in their results. All of the trials had an unclear risk of bias (n=75; 65 percent) or high risk of bias (n=42; 35 percent). Only 14 RCTs (12 percent) were evaluated as having adequately generated the allocation sequence and 6 RCTs (5 percent) had an adequately concealed allocation processes. Measures employed by the study investigators to ensure that the allocation sequence was random and occurred without foreknowledge of treatment assignments was unclear in the majority of the trials. These features should be routinely employed in order to avoid selection bias.

Only 17 percent of RCTs (n=20) reported blinding study investigators and participants (26 percent had unclear reporting), which is another important limitation of this body of evidence as a lack of blinding can lead to exaggerated treatment effects. Blinding through use of matched placebo tablets that appear and taste similar to the study medication may reduce the risk that the knowledge of which intervention was received, rather than the active drug itself, affected outcomes. Studies should also consistently ensure and report that outcome assessors are blinded to treatment allocation. Incomplete outcome data was a limitation in almost half of the trials (unclear risk of bias, 26 percent; high risk of bias, 20 percent) due to loss to followup and inadequate handling of missing data in the reporting and analysis, which may have exaggerated reported treatment effects. The majority of trials were free of selective reporting (97 percent) and other sources of bias (e.g., significant baseline imbalances between study groups) (86 percent). Two cohort studies were included in this review given their focus on adverse events (new-onset diabetes mellitus and tardive dyskinesia, respectively). These studies were identified as being good quality cohorts, receiving a rating of 8 out of 9 points on the Newcastle-Ottawa Scale. However, these cohort studies are limited by their design; the lack of randomization for treatment allocation makes the results vulnerable to bias due to a lack of comparability between treatment groups.

This comparative effectiveness review has several limitations. Only English-language studies were eligible for inclusion in the review; therefore, it is possible that relevant studies published in other languages may have affected the review findings. The scope of this report was limited to the direct comparison of individual FGAs with individual SGAs. Therefore, we cannot make

conclusions on the comparison of antipsychotics within the same drug class or with placebo. In addition, evidence on the use of other drug classes (e.g., anticonvulsants) that are frequently used in the treatment of these patient populations is not considered in this report.

This report presents a synthesis of the available evidence on the effectiveness and safety of antipsychotics in the adult population. However, we do not make clinical recommendations on the use of these medications, as this is the purview of the user group. We trust that the evidence presented in this report will be helpful in the further development of clinical practice guidelines in this field.

Future Research

This review identified a growing body of literature examining the effectiveness of FGAs and SGAs for treating schizophrenia and related psychoses. However, for many of the individual comparisons there were few trials. There is a need for consensus on the most important FGA and SGA comparisons. For many of the comparisons, the FGA was haloperidol. As haloperidol is known to have a poor AE profile, using this as the standard comparison may exaggerate the apparent safety profile of the SGA being compared. Consensus is needed on which comparisons will be the most informative and provide the most valid and accurate information to inform clinical decisions.

More head-to-head trials are needed to compare the effectiveness of currently approved FGAs and SGAs for treating bipolar disorder. Given that antipsychotic medications are used to augment treatment with mood stabilizing medications to ensure effective treatment of core illness symptoms for various forms of the disorder (acute mania, bipolar depression) and maintenance treatment, further research is necessary to better understand the impact of treatment on patient safety and function.

More longitudinal research is also needed on the long-term comparative effectiveness of FGAs versus SGAs. Only two cohort studies were identified for this review that examined serious adverse events with long-term antipsychotic use; however, these studies only examined two serious events: new-onset diabetes mellitus and tardive dyskinesia. Studies examining the naturalistic and long-term efficacy and, particularly, the safety of antipsychotics over the course of several years and across a number of important adverse events are required.

Short- and long-term evaluations of the effectiveness of FGAs and SGAs with patient sub-populations including patients with medical and neurological comorbidities are needed. Further, there is a need for studies investigating how drug dose, age, and other factors such as comorbidities influence the occurrence of serious adverse events, which would help estimate possible risks in specific patient populations.

Future studies should examine functional naturalistic outcomes that are important to patients. These outcomes include health-related quality of life and other patient-reported outcomes, relationships, academic and occupational performance, and legal interactions.

Conclusions

This report provides a comprehensive synthesis of the evidence on the comparative effectiveness and safety of individual FDA-approved FGAs compared with individual FDA-approved SGAs. The focus of the report was adults aged 18 to 64 years with schizophrenia, schizophrenia-related psychoses, and bipolar disorder. The vast majority of relevant studies

involved patients with schizophrenia or schizophrenia-related psychoses. Studies most often involved haloperidol which was compared most frequently with risperidone (42 studies) and olanzapine (39 studies). Numerous studies provided data on core illness symptoms; however, many different scales were used to assess outcomes, which limited the quantitative pooling of data. Few notable differences of clinical importance were identified. In the majority of cases where significant differences were observed, the SGA showed greater improvement in core illness symptoms. Further, the strength of evidence was low for most comparisons suggesting that future research may change the results and change our confidence in the results.

Data on the relative effectiveness of individual FGAs and SGAs for functional outcomes, health care system utilization, and other outcomes were generally sparse. Numerous tasks and tests were used to assess functional capacity. In most cases only single studies contributed to each measure. The variety of functional measures assessed across studies precluded firm conclusions regarding the overall effectiveness of individual drugs in terms of patient functioning. Few studies reported on health care system utilization or patient-important outcomes. Where health-related quality of life was assessed, no differences were found.

The scope of this report included cohort studies with a minimum followup of two years in order to identify adverse effects of most clinical importance, including diabetes mellitus, mortality, tardive dyskinesia, and major metabolic syndrome. Only two studies with long-term followup were identified; hence, evidence on these important adverse effects is limited and urgently needed. A variety of adverse events associated with numerous physiological systems were reported. The adverse effects most often reported involved EPS, which occurred more frequently for FGAs, particularly haloperidol, than for SGAs.

The evidence for important subgroups was limited. The most frequently examined subgroups were race and treatment resistance. There were no notable differences in outcomes for these subgroups compared to the overall results.

Future research needs to incorporate design elements to minimize bias, in particular blinding of investigators, patients, and outcome assessors and adequate handling and reporting of missing data. Researchers need to ensure and report on appropriate methods for sequence generation and allocation concealment. Long-term longitudinal studies of at least 2-year duration are needed to detect important differences in the relative safety profile of individual FGAs and SGAs.

In summary, data on the comparative effectiveness of individual FGAs and SGAs precluded drawing firm conclusions for outcomes that are directly relevant to front-line clinical decisions. Overall, there were few statistically significant differences. Outcomes potentially important to patients were rarely assessed. Finally, data on long-term safety are lacking and urgently needed.

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