



Effective Health Care Program

Comparative Effectiveness Review
Number 63

First-Generation Versus Second-Generation Antipsychotics in Adults: Comparative Effectiveness



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First-Generation Versus Second-Generation Antipsychotics in Adults: Comparative Effectiveness

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Errata – On August 20, 2012, Appendix O was updated to clarify that the route of administration for INVEGA SUSTENNA is IM injection (dosage 39 mg - 234 mg) and the route of administration for RISPERIDOL CONSTA is IM injection (dosage 25 mg).

This report is based on research conducted by the University of Alberta Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2007-10021). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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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

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 are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email 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 Beth Collins Sharp at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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First-Generation Versus Second-Generation Antipsychotics in Adults: Comparative Effectiveness

Structured Abstract

Objectives. To compare individual first-generation antipsychotics (FGAs) with individual second-generation antipsychotics (SGAs) in adults (18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, with a focus on core illness symptoms, functional outcomes, health care system utilization, and adverse events.

Data Sources. We conducted comprehensive searches in 10 electronic databases up to July 2011. We hand-searched conference proceedings, clinical trials registers, and reference lists of relevant studies. We contacted content experts 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. We included 113 studies of schizophrenia (22 comparisons) and 11 studies of bipolar disorder (6 comparisons), and 1 study included both. Trials ($n = 123$) had an unclear (63 percent) or high (37 percent) risk of bias. Cohort studies ($n = 2$) had good methodological quality.

Core illness symptoms (global ratings and total scores). For schizophrenia, clozapine was more efficacious than chlorpromazine based on the one reported scale. Results for haloperidol versus olanzapine were discordant, with olanzapine favored for one scale but no differences based on two other scales. Haloperidol was favored over quetiapine based on one of four scales reported. No differences were found for haloperidol versus aripiprazole, clozapine, risperidone, and ziprasidone.

For bipolar disorder, haloperidol was favored over ziprasidone on the one scale reported. No differences were observed for haloperidol versus aripiprazole, olanzapine, or risperidone.

Functional outcomes and health care system utilization. Evidence came primarily from single studies and showed no differences between groups.

Adverse events. No differences were found in mortality for chlorpromazine versus clozapine and haloperidol versus aripiprazole, or in metabolic syndrome for haloperidol versus olanzapine. The most frequently reported adverse events with significant differences were extrapyramidal symptoms; in most cases, the SGA had fewer extrapyramidal symptoms than haloperidol.

Other outcomes. For schizophrenia, few differences were found across comparisons and outcomes. No differences were observed in health-related quality of life. For bipolar disorder, there were few comparisons or differences.

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

Conclusion. Few differences of clinical importance for outcomes of effectiveness were found. Patient-important outcomes were rarely assessed. Data were sparse for the four key adverse events 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. To date, FGAs have been classified according to their chemical structure, which includes serotonin-dopamine antagonists and multiacting receptor-targeted antipsychotics, whereas SGAs have been categorized according to their pharmacological properties as dopamine partial agonists. There is ongoing research testing the proposed mechanisms of action within each class with respect to the neurobiology of different psychiatric disorders.^{1,2}

According to findings from the 2004–05 Medical Expenditure Panel Survey, an estimated 2 million adult patients in the United States were prescribed an antipsychotic medication, three-quarters of whom were taking an SGA.³ In 2003, an estimated \$2.82 billion were spent in the country on these medications, with SGAs accounting for 93 percent of this expenditure.³ Today, 20 FGAs and SGAs are commercially available in the United States and approved by the Food and Drug Administration (FDA).

Individuals taking antipsychotics may stop taking their medication for a number of reasons, including adverse events (AEs) and a lack of improvement in their symptoms.⁴ As a result, ongoing evaluations of drug efficacy and models of patient decisionmaking 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. In contrast to previous reviews, this CER focuses on comparisons of individual medications rather than drug classes. This topic is important and timely, given the ongoing debate about the comparative benefits and harms of FGAs and SGAs.⁵ Moreover, the focus of this report complements other recent reviews investigating different SGAs,⁶ the off-label use of antipsychotics,⁷ and FGAs versus SGAs in the pediatric population.⁸ The focus of this report is adults age 18 to 64 years with schizophrenia, schizophrenia-related psychoses, and bipolar disorder. This age group is the normal demographic in which these illnesses have been shown to be prevalent. The illnesses are discussed in more detail in the sections that follow.

Key Questions

The following Key Questions (KQs) were investigated in the report:

1. For adults (age 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what are 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, general psychopathology (i.e., preoccupation, lack of insight, and motor retardation), and global ratings and total scores.
 - b. Core illness symptoms for bipolar disorder: mood, motor activity or energy, sleep, speech, behavior, and mood stability.

2. For adults (age 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 includes: time to hospitalization or rehospitalization because of mental illness and all other causes, rates of hospitalization or rehospitalization, 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 (age 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, do FGAs and SGAs differ in medication-associated AEs and safety? AEs included:
 - a. Overall AEs.
 - b. Specific AEs:
 - 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*: extrapyramidal symptoms (EPS), weight changes, agitation, constipation, sedation, elevated cholesterol, AEs related to prolactin elevations, galactorrhea or bloody galactorrhea, 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 AEs.
 - d. Persistence and reversibility of AEs.
4. For adults (age 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: endpoints 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 (age 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what are the comparative effectiveness and risks of FGAs versus SGAs in subgroups defined by the following variables?
 - a. Disorder subtypes.
 - b. Sex.
 - c. Age group (18–35 years, 36–54 years, and 55–64 years).
 - d. Race.
 - e. Comorbidities.
 - f. Drug dosage.
 - g. Followup period.
 - h. Treatment of a first episode versus treatment in the context of previous episodes (previous exposure to antipsychotics).
 - i. Treatment resistance.

Methods

In general, we followed methodologically rigorous methods for systematic reviews as described in recent standards documents.^{7,8} Detailed information on the reports prepared by Evidence-based Practice Centers can be found on the Agency for Healthcare Research and Quality Web site at www.effectivehealthcare.ahrq.gov/.

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 2011. For the questions on AEs, we also searched the 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 (2008–10), the International College of Neuropsychopharmacology (2008–10), and the International Society for Bipolar Disorders (2008–10). 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 for study design, population, interventions, and comparators. 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 2 years or greater; included adults age 18 to 64 years with schizophrenia or related psychoses or bipolar disorder; and compared a commercially available FDA-approved FGA with 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 and consensus or third-party adjudication. We assessed RCTs and nRCTs using the Cochrane Collaboration's Risk of Bias tool.⁵ We assessed cohort studies using the Newcastle-Ottawa Scale.⁷ A priori, the research team developed decision rules regarding application of the tools.

Two reviewers independently evaluated the overall strength of evidence (SoE) using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach used by Evidence-based Practice Centers 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 psychopathology, and global ratings and total scores. We provided a grade for each different scale that was used. We graded the following AEs, which were deemed to be most clinically important a priori: diabetes mellitus, mortality, tardive dyskinesia, and major metabolic syndrome. These outcomes were identified a priori as being the most clinically important for decisionmaking.

Data Extraction

Two reviewers independently extracted data using standardized data extraction forms and resolved discrepancies through discussion and consensus or by third-party adjudication. We extracted information on study characteristics, population, interventions and dosing regimens, outcomes assessed, results, and funding source. When studies incorporated multiple relevant treatment arms or multiple followup periods, we extracted data from all groups for the longest followup data. 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 KQs 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 comparison of FGA versus SGA. 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 the applicability of the results. These included patient characteristics (e.g., age, diagnostic criteria, severity of illness, comorbidities, concomitant medications, inpatient or outpatient status) and study characteristics (e.g., length of followup).

Results

Description of Included Studies

The searches identified 9,411 unique study reports. A total of 125 primary publications and 146 companion publications were included. The studies included 121 RCTs, 2 nRCTs, and 2 retrospective cohort studies. The studies were published between 1974 and 2010. The majority of studies were multicenter ($n = 70$, 56 percent) and involved inpatients ($n = 62$, 50 percent), and they were conducted more often in North America than elsewhere ($n = 57$, 46 percent). The number of participants in the studies ranged from 10 to 95,632 (median = 86 [interquartile range (IQR), 36 to 300]). The average age of study participants ranged from 21 to 50 years (median = 37 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 ($n = 88$) had some form of support from the pharmaceutical industry.

Overall, 113 studies examined schizophrenia or schizophrenia-related psychoses, 11 studies examined bipolar disorder, and 1 study included both. A total of 22 and 6 drug comparisons were made for schizophrenia and bipolar disorder, respectively (Table A).

Table A. Comparisons examined in the included studies

Schizophrenia or Schizophrenia-Related Psychoses		Bipolar Disorder	
<i>Comparison</i>	<i>n</i>	<i>Comparison</i>	<i>n</i>
Chlorpromazine vs. clozapine	12	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	5
Fluphenazine vs. quetiapine	1	Haloperidol vs. ziprasidone	1
Fluphenazine vs. risperidone	1		
Haloperidol vs. aripiprazole	8		
Haloperidol vs. asenapine	1		
Haloperidol vs. clozapine	11 ^a		
Haloperidol vs. olanzapine	35 ^a		
Haloperidol vs. quetiapine	11 ^a		
Haloperidol vs. risperidone	39 ^b		
Haloperidol vs. ziprasidone	9 ^c		
Perphenazine vs. aripiprazole	1		
Perphenazine vs. olanzapine	2		
Perphenazine vs. quetiapine	1		
Perphenazine vs. risperidone	2		
Perphenazine vs. ziprasidone	1		
Trifluoperazine vs. clozapine	1		
Thioridazine versus clozapine	1		
Thioridazine versus risperidone	1		

n = number of studies; nRCT = nonrandomized controlled trial

Note: $n = 125$.

^aIncludes 1 cohort study.

^bIncludes 1 cohort study and 1 nRCT.

^cIncludes 1 nRCT.

Methodological Quality of Included Studies

None of the 123 RCTs and nRCTs was rated as having a low risk of bias. The majority of the trials ($n = 78$, 63 percent) had an unclear risk of bias; the remaining trials ($n = 45$, 37 percent)

had a high risk of bias. In the majority of cases, trials were assessed as having 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 having 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 KQs they address. Within each KQ, we present results by condition and comparison. Tables with a summary of findings for efficacy and safety are presented below. It is important to note that lack of statistical significance does not equate to equivalence or noninferiority, nor does statistical significance equate to clinical significance.

KQ1: Core Illness Symptoms

The findings for core illness symptoms are presented for each condition in Table B. Comparisons and outcomes for which there was insufficient SoE to draw a conclusion (e.g., evidence from single trials) are not displayed in the tables. The SoE comparing individual FGAs and SGAs was insufficient to draw conclusions for the following comparisons: chlorpromazine versus olanzapine, quetiapine, and ziprasidone; fluphenazine versus olanzapine, quetiapine, and risperidone; haloperidol versus asenapine; perphenazine versus aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone; trifluoperazine versus clozapine.

For schizophrenia or related psychoses, seven studies provided data on core illness symptoms for chlorpromazine versus clozapine. No differences were found for positive or negative symptoms or general psychopathology. Clozapine showed benefits for total score (moderate SoE).

Eight studies provided data on core illness symptoms for haloperidol versus aripiprazole. No differences were found for positive symptoms or general psychopathology, global ratings, or total symptom score. The SoE was low for positive outcomes, global ratings, and total scores; the SoE was insufficient for general psychopathology. Aripiprazole showed benefits for negative symptoms (moderate SoE).

Eight studies provided data on core illness symptoms for haloperidol versus clozapine. No significant differences were found for positive symptoms, negative symptoms, or general psychopathology (low SoE). The findings were discordant for total symptom score: no difference was found based on the Brief Psychiatric Rating Scale (BPRS) and Positive and Negative Symptom Scale (PANSS) (low SoE); one study showed benefits for clozapine on the Clinical Global Impression–Improvement (CGI–I) and Clinical Global Impression–Severity (CGI–S) scales (insufficient SoE).

Twenty-seven studies provided data on core illness symptoms for haloperidol versus olanzapine. No differences were found for positive symptoms (low SoE). Olanzapine was favored for negative symptoms (moderate SoE). In terms of general psychopathology, a significant benefit for olanzapine was found based on the Hamilton Rating Scale for Depression (HAM–D), Montgomery–Asberg Depression Rating Scale (MADRS), and Young Mania Rating Scale (YMRS). No differences were observed for the other five scales of general symptoms assessed. The SoE varied across outcomes from insufficient to moderate. Olanzapine was favored for global ratings and total symptom scores based on the CGI–S and PANSS; however,

no differences were found for the other four scales assessed. The SoE for these outcomes also varied from insufficient to moderate.

Nine studies provided data on core illness symptoms for haloperidol versus quetiapine. No significant differences were found for positive or negative symptoms, or general psychopathology. A significant difference favoring haloperidol was found for one of the five global ratings (CGI-S) and total symptom scores assessed. The SoE across outcomes ranged from insufficient to moderate.

Thirty-one studies provided data on core illness symptoms for haloperidol versus risperidone. There were no differences for positive symptoms (low SoE). Risperidone was favored for negative symptoms based on the Scale for the Assessment of Negative Symptoms (SANS) (moderate SoE); in contrast, no difference for negative symptoms was found based on PANSS (low SoE). No differences were found for any of the six measures used to assess general psychopathology (low to insufficient SoE). Seven of the global ratings or total symptom scores showed no differences, whereas the Symptom Checklist (SCL-90-R) showed a benefit for risperidone (low to insufficient SoE).

Seven studies provided data on core illness symptoms for haloperidol versus ziprasidone. There were no significant differences in terms of negative symptoms, general psychopathology, global ratings, or total score (low to insufficient SoE). No studies provided data on positive symptoms.

A total of 12 studies included patients with bipolar disorder. The most frequent comparison was haloperidol versus risperidone (five RCTs). No significant differences were found for mood (mania), mood (depression), positive or negative symptoms, or global ratings and total scores (low to insufficient SoE). Two studies compared haloperidol versus olanzapine and found no significant differences in sleep, mood (mania), mood (depression), or global ratings and total scores (low or insufficient SoE). Two studies compared haloperidol with aripiprazole and found no differences in mood (mania), mood (depression), positive or negative symptoms, or global ratings and total scores (low or insufficient SoE). Single studies compared chlorpromazine versus clozapine and haloperidol versus quetiapine and ziprasidone (insufficient SoE).

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

Outcome	Comparison	SoE	Summary (Number of Studies)
<i>Schizophrenia and Schizophrenia-Related Psychoses</i>			
Positive symptoms	Haloperidol vs. aripiprazole	Low	No significant difference for PANSS (2 RCTs).
	Haloperidol vs. clozapine	Low	No significant difference for PANSS (2 RCTs).
	Haloperidol vs. olanzapine	Low	No difference for PANSS (14 RCTs) or SAPS (2 RCTs).
	Haloperidol vs. quetiapine	Low	No significant difference for PANSS (4 RCTs).
	Haloperidol vs. risperidone	Low	No difference for PANSS (20 RCTs) or SAPS (2 RCTs).

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

Outcome	Comparison	SoE	Summary (Number of Studies)
<i>Schizophrenia and Schizophrenia-Related Psychoses (continued)</i>			
Negative symptoms	Haloperidol vs. aripiprazole	Moderate	Significant difference favoring aripiprazole for PANSS (3 RCTs).
	Haloperidol vs. clozapine	Low	No significant difference for PANSS (2 RCTs) or SANS (2 RCTs).
	Haloperidol vs. olanzapine	Moderate	Significant difference favoring olanzapine for PANSS (14 RCTs) and SANS (5 RCTs).
	Haloperidol vs. quetiapine	Low	No significant difference for PANSS (4 RCTs).
	Haloperidol vs. risperidone	Low to moderate	Significant difference favoring risperidone for SANS (moderate SoE, 4 RCTs). No significant difference for PANSS (low SoE, 20 RCTs).
	Haloperidol vs. ziprasidone	Low	No significant difference for PANSS (2 RCTs).
General psychopathology	Haloperidol vs. clozapine	Low	No significant difference for PANSS (2 RCTs).
	Haloperidol vs. olanzapine	Low to moderate	Significant difference favoring olanzapine for HAM-D (moderate SoE, 3 RCTs) and MADRS (moderate SoE, 6 RCTs). No difference for ABS (low SoE, 2 RCTs), ACES (low SoE, 2 RCTs), CDS-S (low SoE, 3 RCTs), HAM-A (low SoE, 2 RCTs), or PANSS (low SoE, 10 RCTs).
	Haloperidol vs. quetiapine	Low	No significant difference for CDS-S (2 RCTs) or PANSS (4 RCTs).
Global ratings and total scores	Chlorpromazine vs. clozapine	Moderate	Significant difference favoring clozapine for BPRS (6 RCTs).
	Haloperidol vs. aripiprazole	Low	No significant difference for BPRS (3 RCTs) or CGI-S (5 RCTs).
	Haloperidol vs. clozapine	Low	No difference for BPRS (4 RCTs) or PANSS (3 RCTs).
	Haloperidol vs. olanzapine	Low to moderate	Significant difference favoring olanzapine for CGI-S (moderate SoE, 7 RCTs) and PANSS (moderate SoE, 14 RCTs). No difference for BPRS (low SoE, 13 RCTs) or CGI-I (low SoE, 2 RCTs).
	Haloperidol vs. quetiapine	Low to moderate	Significant difference favoring haloperidol for CGI-S (moderate SoE, 4 RCTs). No difference for BPRS (low SoE, 4 RCTs), CGI-I (low SoE, 3 RCTs), or PANSS (low SoE, 6 RCTs).
	Haloperidol vs. risperidone	Low	No difference for BPRS (13 RCTs), CGI-I (3 RCTs), CGI-S (8 RCTs), or PANSS (20 RCTs).
	Haloperidol vs. ziprasidone	Low	No significant difference for BPRS (4 RCTs), CGI-S (4 RCTs), GAF (3 RCTs), or PANSS (4 RCTs).

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

Outcome	Comparison	SoE	Summary (Number of Studies)
<i>Bipolar Disorder</i>			
Mood (mania)	Haloperidol vs. aripiprazole	Low	No significant difference in YMRS (2 RCTs).
	Haloperidol vs. olanzapine	Low	No significant difference in YMRS (2 RCTs).
	Haloperidol vs. risperidone	Low	No significant difference in YMRS (3 RCTs).
Mood (depression)	Haloperidol vs. aripiprazole	Low	No significant difference in MADRS (2 RCTs).
Global ratings and total scores	Haloperidol vs. aripiprazole	Low	No significant difference in CGI-BP (2 RCTs).

ABS = Agitated Behavior Scale; ACES = Agitation-Calmness Evaluation Scale; BPRS = Brief Psychiatric Rating Scale; CDS-S = Calgary Depression Scale for Schizophrenia; CGI-BP = Clinical Global Impression-Bipolar; CGI-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression-Severity; GAF = Global Assessment of Functioning; HAM-A = Hamilton Rating Scale for Anxiety; HAM-D = Hamilton Rating Scale for Depression; KQ = Key Question; MADRS = Montgomery-Asberg Depression Rating Scale; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; SoE = strength of evidence; YMRS = Young Mania Rating Scale

KQ2: 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 C. We did not assess the SoE for outcomes in KQ2.

Results for functional outcomes were available from nine 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 any of the comparisons. However, in most cases evidence came from single studies. Results for health care system utilization were available for 10 head-to-head comparisons, and no differences were found for any comparison.

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 impairment in household or work activities.

Table C. Summary of evidence for functional outcomes, health care system utilization, and other outcomes (KQ2)

Outcome	Comparison	Summary (Number of Studies)
<i>Schizophrenia and Schizophrenia-Related Psychoses</i>		
Functional outcomes	Fluphenazine vs. quetiapine	No significant difference for sexual dysfunction or improvement on treatment (1 RCT).
	Fluphenazine vs. risperidone	No significant difference for sexual dysfunction or improvement on treatment (1 RCT).
	Haloperidol vs. olanzapine	No significant difference for positive urine toxicology (1 RCT) or sexual dysfunction (1 RCT).
	Haloperidol vs. quetiapine	No significant difference for sexual dysfunction (1 RCT).
	Haloperidol vs. risperidone	No significant difference for economic independence (1 RCT) or attitude regarding drugs (1 RCT).
	Haloperidol vs. ziprasidone	No difference for sexual dysfunction (1 RCT).
	Perphenazine vs. quetiapine	No significant difference in patients with paid employment (1 RCT).
	Perphenazine vs. risperidone	No significant difference in patients with paid employment (1 RCT).

Table C. Summary of evidence for functional outcomes, health care system utilization, and other outcomes (KQ2) (continued)

Outcome	Comparison	Summary (Number of Studies)
Schizophrenia and Schizophrenia-Related Psychoses		
Functional outcomes (continued)	Perphenazine vs. ziprasidone	No significant difference in patients with paid employment (1 RCT).
Health care system use	Chlorpromazine vs. clozapine	No significant difference in rates of hospitalization or rehospitalization (1 RCT).
	Haloperidol vs. clozapine	No significant difference in mean hospital bed days (1 RCT).
	Haloperidol vs. olanzapine	No significant difference in mean hospital bed days or rates of hospitalization or rehospitalization (1 RCT).
	Haloperidol vs. quetiapine	No significant difference in rates of hospitalization or rehospitalization (1 RCT).
	Haloperidol vs. risperidone	No significant difference in rates of hospitalization or rehospitalization (3 RCTs).
	Haloperidol vs. ziprasidone	No significant difference in rates of hospitalization or rehospitalization (2 RCTs).
	Perphenazine vs. olanzapine	No significant difference in rates of hospitalization or rehospitalization (1 RCT).
	Perphenazine vs. quetiapine	No significant difference in rates of hospitalization or rehospitalization (1 RCT).
	Perphenazine vs. risperidone	No significant difference in rates of hospitalization or rehospitalization (1 RCT).
	Perphenazine vs. ziprasidone	No significant difference in rates of hospitalization or rehospitalization (1 RCT).
Bipolar Disorder		
Functional outcomes	Haloperidol vs. olanzapine	Significant difference favoring olanzapine for number of active workers (i.e., work for pay) (1 RCT). No difference in impairment in household or work activities (1 RCT).

KQ = Key Question; RCT = randomized controlled trial

KQ3: Medication-Associated AEs and Safety

The findings for the AEs that were deemed most clinically important are summarized in Table D. The SoE comparing individual FGAs and SGAs was insufficient to draw conclusions for the following outcomes and comparisons: tardive dyskinesia (chlorpromazine vs. clozapine and ziprasidone; haloperidol vs. clozapine, olanzapine, quetiapine, and ziprasidone); mortality (chlorpromazine vs. clozapine and ziprasidone; haloperidol vs. risperidone; thioridazine vs. clozapine and risperidone); diabetes mellitus (haloperidol vs. olanzapine; perphenazine vs. olanzapine, quetiapine, risperidone, and ziprasidone); and metabolic syndrome (haloperidol vs. clozapine; perphenazine vs. olanzapine, quetiapine, risperidone, and ziprasidone).

Two trials each provided data on mortality for chlorpromazine versus clozapine and haloperidol versus aripiprazole; no significant differences were found, although the length of followup of the trials for the latter comparison was only 24 hours. For metabolic syndrome, two trials provided data for haloperidol versus olanzapine and showed no significant difference in incidence of metabolic syndrome. The SoE 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 SoE. 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 they 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 adequately 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 measures).

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

Adverse Event	Comparison	SoE	Summary (Number of Studies)
Mortality	Chlorpromazine vs. clozapine	Low	No significant difference (2 RCTs, length of followup: 52 and 208 wks)
	Haloperidol vs. aripiprazole	Low	No significant difference (2 RCTs, length of followup: 24 hrs for both)
Metabolic syndrome	Haloperidol vs. olanzapine	Low	No significant difference (2 RCTs, length of followup: 6 and 12 wks)

KQ = Key Question; RCT = randomized controlled trial; SoE = strength of evidence

KQ4: Other Outcomes

The findings for other outcomes are presented for each condition and comparison in Table E. We did not assess the SoE for outcomes in KQ4.

Results for other outcomes were available for 19 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 compared with chlorpromazine. Olanzapine was favored over haloperidol for remission (3 trials) and response rates (14 trials). Significant differences were found favoring aripiprazole over haloperidol for caregiver satisfaction (one trial) and patient satisfaction (one trial). Risperidone was favored over haloperidol for relapse rates (six trials). Olanzapine was favored over perphenazine for time to all-cause medication discontinuation (one trial). Health-related quality of life was evaluated for the following comparisons, and no significant differences were found: haloperidol versus olanzapine, quetiapine, risperidone, and ziprasidone (one trial each); perphenazine versus aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone (one trial 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 trial 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 E. Summary of the evidence for other outcomes (KQ4)

Comparison	Summary ^a (Number of Studies)
Schizophrenia and Schizophrenia-Related Psychoses	
Chlorpromazine vs. clozapine	Significant difference favoring clozapine for response rates (3 RCTs). No difference in remission rates (2 RCTs).
Chlorpromazine vs. olanzapine	No significant difference in response rates (1 RCT).
Chlorpromazine vs. quetiapine	No significant difference in response rates (1 RCT).
Chlorpromazine vs. ziprasidone	No significant difference in response rates (1 RCT).

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

Comparison	Summary ^a (Number of Studies)
Schizophrenia and Schizophrenia-Related Psychoses	
Fluphenazine vs. olanzapine	No significant difference in response rates (1 RCT).
Fluphenazine vs. quetiapine	No significant difference in response rates (1 RCT).
Fluphenazine vs. risperidone	No significant difference in response rates (1 RCT).
Haloperidol vs. aripiprazole	No significant difference in response rates (5 RCTs) or medication adherence (1 RCT). Difference favoring aripiprazole for caregiver and patient satisfaction (1 RCT).
Haloperidol vs. asenapine	No significant difference in response rates (1 RCT).
Haloperidol vs. clozapine	No significant difference in relapse (1 RCT), response (2 RCTs) or remission (1 RCT) rates or patient satisfaction (1 RCT).
Haloperidol vs. olanzapine	Significant difference favoring olanzapine for response rates (14 RCTs) and remission rates (3 RCTs). No significant difference in medication adherence (1 RCT), patient insight into illness (1 RCT), or HRQoL (5 RCTs).
Haloperidol vs. quetiapine	No significant difference in response rates (6 RCTs), remission rates (1 RCT), or HRQoL (1 RCT).
Haloperidol vs. risperidone	Significant difference favoring risperidone for relapse rates (6 RCTs). No significant difference in remission rates (2 RCTs), response rates (16 RCTs), medication adherence (3 RCTs), patient satisfaction (1 RCT), or HRQoL (2 RCTs).
Haloperidol vs. ziprasidone	No significant difference in response rates (6 RCTs), remission rates (3 RCTs), or HRQoL (2 RCTs).
Perphenazine vs. aripiprazole	No significant difference in response rates (1 RCT) or HRQoL (1 RCT).
Perphenazine vs. olanzapine	No significant difference in HRQoL (1 RCT). Significant difference favoring olanzapine in time to all-cause medication discontinuation (1 RCT).
Perphenazine vs. quetiapine	No significant difference in HRQoL (1 RCT).
Perphenazine vs. risperidone	No significant difference in time to all-cause medication discontinuation (1 RCT) or HRQoL (1 RCT).
Perphenazine vs. ziprasidone	No significant difference in HRQoL (1 RCT).
Bipolar Disorder	
Haloperidol vs. aripiprazole	Significant difference in favor of haloperidol for relapse rates (1 RCT). No difference in remission (1 RCT) or response (2 RCTs) rates.
Haloperidol vs. olanzapine	No difference for relapse (1 RCT), response (1 RCT), or remission rates (1 RCT). Significant difference favoring haloperidol for HRQoL mental summary score (1 RCT). Significant difference favoring olanzapine for HRQoL physical summary score (1 RCT).
Haloperidol vs. quetiapine	No significant difference in response or remission rates (1 RCT).
Haloperidol vs. risperidone	No difference in response rates (1 RCT).
Haloperidol vs. ziprasidone	Significant difference favoring haloperidol for response rates (1 RCT). No difference for remission rates (1 RCT).

HRQoL = health-related quality of life; KQ = Key Question; RCT = randomized controlled trial

^aResponse rates were defined by authors of the primary studies and may have varied across trials.

KQ5: Subgroups

A total of 41 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 with the overall findings.

The only subgroup available for analysis in studies of patients with bipolar disorder was disorder subtype, specifically bipolar I and bipolar II. The results were consistent with the overall

findings. A significant difference favored haloperidol compared with ziprasidone for core illness symptoms (YMRS) in patients with bipolar I disorder.

Results in the Context of Other Research

The results of this review are similar in some respects to another recent systematic review of SGAs versus FGAs, although the present review is broader in scope in terms of medications included, patient populations, and outcomes.⁹ There were a number of methodological differences between the previous review and this one. The previous review included antipsychotics not approved by the FDA, restricted the analysis to only double-blinded trials, included only studies examining optimum SGA dosage and oral route of administration, and pooled data across efficacy outcome measures. The differences in the methodologies may have led to slightly different conclusions regarding individual SGAs.

The previous review compared nine SGAs (six of which are included in this report) with FGAs for overall efficacy (total symptom scores); positive, negative, and depressive symptoms; relapse; quality of life; EPS; weight gain; and sedation. The authors reported that the overall efficacy of the FDA-approved SGAs clozapine, olanzapine, and risperidone was better than that of FGAs. In terms of global ratings and total symptom scores, we found that clozapine was more efficacious than chlorpromazine but not haloperidol. We found that olanzapine performed better than haloperidol on one of the three total symptom scores assessed. We found no differences between haloperidol and risperidone for the five total symptom scores reported. The previous review found that SGAs were not superior to FGAs regarding the negative symptoms. We found no difference in negative symptoms for haloperidol versus clozapine; however, we found evidence that olanzapine was more efficacious than haloperidol for negative symptoms, whereas the evidence for risperidone compared with haloperidol was mixed. In general, the findings for AEs were consistent between reviews, showing poorer safety profiles with respect to EPS for FGAs (specifically haloperidol) and more weight gain among the SGAs (in particular, olanzapine and risperidone).

One of the unique features of our review was the SoE assessments, which provide information on how confident we can be in the results of existing studies and how likely it is that the estimates of treatment effects will change with future research. In most cases, the SoE was insufficient or low, highlighting the likelihood that future research will change the estimates of effect and the need for a stronger evidence base to inform clinical practice.

Applicability

This report included studies that compared an individual FGA with an individual SGA. Placebo-controlled studies or studies comparing an FGA versus another FGA or an 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 and safety compared with 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 our review was adults age 18 to 64 years with schizophrenia, schizophrenia-related psychoses, or bipolar disorder. The average age across studies ranged from 21 to 50 years (median = 37 years [IQR, 33 to 41]). Most studies were highly selective in patient enrollment 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 and the most seriously ill patients were 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) (62 of 125 studies) or mixed inpatient and outpatient populations (26 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 the minimum 2-year followup period.

Limitations of Existing Evidence

Inconsistency in treatment comparisons, outcomes, outcome measurement, and patient populations across studies makes it difficult to draw firm clinical conclusions. 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 AEs. Consensus is needed regarding outcomes and measures used to assess outcomes. Additionally, functional outcomes and symptomatic outcomes (e.g., sedation, restlessness) were rarely and unequally reported throughout the trial reports, even though these outcomes are often vital to patient compliance.

A key limitation and challenge in synthesizing and interpreting this body of evidence is the issue of heterogeneous patient populations across and within studies, which is in part driven by the complex nature of these disorders and their course over time. The studies we included had very mixed populations with respect to disorder subtypes, comorbid drug or alcohol use, treatment resistance, and number of previous episodes. These variables may create differential response to treatment, and this has been the basis for recommendations around personalized medicine in this area.⁸ We conducted extensive subgroup and sensitivity analyses to explore these varying features. The results of subgroup analyses should be interpreted as hypothesis generating rather than hypothesis confirming. Our findings may provide some information to make treatment decisions for individual patients but need to be confirmed in future research.

An additional limitation and challenge of synthesis in this area is that characteristics of the research may have changed over time, including drug doses (e.g., lower doses of FGAs in more recent studies) and patient populations (e.g., fewer patients already exposed to FGAs or proven treatment resistant to FGAs in recent studies).

An important limitation of this review and other systematic reviews is the design and quality of the primary included studies. The majority of studies providing data for this report were RCTs (n = 123); however, most were designed as superiority trials, often with an a priori hypothesis that the SGA would be more efficacious.¹⁰ The individual studies and, in many cases, the pooled results may not have sufficient power to detect equivalence or noninferiority between drugs. Further, all of the included trials had an unclear risk of bias (n = 78, 63 percent) or high risk of bias (n = 45, 37 percent). Of note, few trials (n = 20) reported blinding study investigators and participants (26 percent had unclear reporting), which is important in interpreting the results because lack of blinding has been shown to produce exaggerated treatment effects.⁹

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; these studies examined only two serious events: tardive

dyskinesia and mortality rates. The SoE for these AEs was insufficient to draw conclusions. 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 required. Further, consensus is needed on the most important comparisons of FGAs versus SGAs 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

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 report provides extensive details in terms of study characteristics and methodological features, which may help inform individual treatment decisions.

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 SoE was low or insufficient for most comparisons, suggesting that future research is likely to 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 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.

We included cohort studies with a minimum followup of 2 years in order to identify the 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 with 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. Finally, data on long-term safety are lacking and urgently needed.

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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}

According to findings from the 2004–2005 U.S. Medical Expenditure Panel Survey, an estimated 2 million adult patients in the United States were prescribed an antipsychotic medication; of which three-quarters of patients were taking a SGA.³ In 2003, an estimated \$2.82 billion was spent in the United States on these medications, with SGAs accounting for 93 percent of this expenditure.³

FGAs were first developed 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 Food and Drug Administration (FDA)-approved and commercially available FGAs in the U.S., with chlorpromazine, perphenazine, and haloperidol being the most frequently 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. SGAs have been proven effective for treating a variety of psychiatric conditions by blocking the cerebral dopamine pathways. Currently, nine SGAs are FDA-approved and commercially available in the U.S., with quetiapine, risperidone, aripiprazole, and olanzapine being the most frequently prescribed (Table 1).⁴

Individuals taking an antipsychotic may stop taking their medication for a number of reasons, including side effects and lack of improvement in their symptoms.⁵ As a result, ongoing evaluations of drug efficacy and models of patient decision-making are essential.

The disconnect between the research findings of well-known studies CUtLASS 1, CATIE, recent meta-analyses (showing few significant differences 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.

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. In contrast to previous reviews this CER focuses on comparisons of individual medications rather than drug classes. This topic is important and timely given the ongoing debate about the comparative benefits and harms of FGAs and SGAs.⁶ Moreover, the focus of this report complements other recent reviews investigating different SGAs,⁷ the off-label use of antipsychotics,⁸ and FGAs versus SGAs in the pediatric population.⁹ The focus of this report is adults age 18 to 64 years with schizophrenia, schizophrenia-related psychoses, and bipolar

disorder. This age group is the normal demographic in which these illnesses have been shown to be prevalent; 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 Droperidol Fluphenazine Haloperidol Loxapine Perphenazine Pimozide Prochlorperazine Thioridazine Thiothixene Trifluoperazine	<u>Monotherapy</u> Aripiprazole Asenapine Clozapine Iloperidone Lurasidone Olanzapine Paliperidone Quetiapine Risperidone Ziprasidone <u>Combination therapy</u> Olanzapine plus fluoxetine

* Multiple formulations (e.g., extended-release) are available for some antipsychotics. All drugs are FDA-approved and currently available at the time of this report.

Schizophrenia and Related Psychoses

Schizophrenia is a heterogeneous syndrome that includes disturbances in language, perception, cognition, social relatedness, and volition.¹⁰ Symptoms include positive (i.e., delusions and hallucinations), negative (i.e., passive or apathetic social withdrawal and blunted affect) symptoms and general psychopathology (i.e., preoccupation, lack of insight, and motor retardation) symptoms. Onset of symptoms typically occurs in late adolescence or early adulthood, with approximately 0.4 to 0.6 percent of the population affected worldwide.¹¹ 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.¹²

In the treatment of schizophrenia, FGAs act on the dopaminergic system by blocking the dopamine type 2 (D2) receptors.¹³ This mechanism, however, may lead to a variety of extrapyramidal symptoms (EPS) (e.g., tremor, slurred speech, akathisia, and dystonia), some of which appear after long-term exposure (e.g., tardive dyskinesia).^{14,15} Although these antipsychotics are effective against the positive symptoms of schizophrenia, they have been considered to be ineffective in treating negative symptoms.¹⁶ Such symptoms particularly play a critical role in producing the severe social and vocational disabilities experienced by many patients with schizophrenia.¹⁷

The search for antipsychotic medications that manage both the positive and negative symptoms of schizophrenia led to the emergence of second-generation antipsychotic drugs. SGAs 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, including sedation, hypotension, weight gain, and sexual dysfunction.¹⁸ SGAs have also been associated with metabolic side effects (e.g., elevated lipids and development of type II diabetes mellitus),¹⁸ 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.¹⁹

There is debate surrounding the efficacy of SGAs on negative symptoms, with several published reports indicating no clear advantage over FGAs.^{17,20} 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 symptoms²⁰ 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).¹⁷ Recent findings from the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1)^{21,22} and the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study^{23,24} found few differences in the effectiveness of SGAs and FGAs in patients with nonrefractory schizophrenia. Subsequent meta-analyses have generally confirmed these results²⁵ and have helped to provide a clearer picture of the comparative effectiveness of the two classes of antipsychotic medications.

Scales for Assessing the Core Symptoms of Schizophrenia

The most frequently used scales for measuring core illness symptoms in patients with schizophrenia are the Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression (CGI) scale, and Positive and Negative Symptom Scale (PANSS). Additionally, the Scale for the Assessment of Positive Symptoms (SAPS) and Scale for the Assessment of Negative Symptoms (SANS) 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–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 the 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).

Bipolar Disorder

Bipolar disorder is characterized by severe fluctuations in mood, activity, thought, and behavior.¹⁰ Bipolar I 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 II disorder is characterized by at least one hypomanic episode and at least one major depressive episode. The prevalence of bipolar disorder is 0.4 to 1.6 percent in community samples and has an average age of onset of 20 years.¹⁰ The APA (2002)²⁶ 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 recommendations state that SGAs are preferred over FGAs because of their side-effect profile.²⁶

Commonly used scales for measuring core illness 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.

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 Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program Web site. The Technical Expert Panel, Evidence-based Practice Center (EPC), 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. The focus of KQ1 was on the core symptoms and KQ2 was 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 (SAEs); see point 8 below), and systematic reviews that may answer the KQs.
8. To capture data on long-term SAEs, the inclusion criteria were modified to include cohort studies that compared FGAs with SGAs, had a followup period of at least 2 years, and

presented data on at least one SAE as determined by the Technical Expert Panel (i.e., type II diabetes mellitus, mortality, tardive dyskinesia, and major metabolic syndromes).

9. We added the following outcomes of interest:

Key symptoms:

- Core symptoms, including maintenance of mood stability (particularly for bipolar disorder).
- Measures for bipolar disorder symptoms: YMRS, MADRS, and CGI-BP.

Adverse events (AEs):

- Weight gain, hypotension, and metabolic changes (including changes in glucose levels, triglycerides, and lipids and the risk of developing diabetes).

Other outcomes:

- Comorbidity: endpoints 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 EPS.
- 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 KQs are as follows:

KQ 1: For adults (age 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 (age 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 (age 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 KQ1 above.

Interventions: See KQ1 above.

Comparators: See KQ1 above.

Outcomes:

1. 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.
2. Health care system utilization include: time to hospitalization or rehospitalization because of mental illness and all other causes, rates of hospitalization or rehospitalization, 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 KQ1 above.

Settings: See KQ1 above.

KQ 3: For adults (age 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 KQ1 above.

Interventions: See KQ1 above.

Comparators: See KQ1 above.

Outcomes: Disorder-specific and -nonspecific AEs:

1. Overall AEs.
2. Specific AEs:
 - 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:* EPS, weight gain, agitation, constipation, sedation, elevated cholesterol, AEs 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 AEs.
4. Persistence and reversibility of AEs.

Timing: See KQ1 above.

Settings: See KQ1 above.

KQ 4: For adults (age 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 KQ1 above.

Interventions: See KQ1 above.

Comparators: See KQ1 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: endpoints 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 EPS.
10. Patient preferences.

Timing: See KQ1 above.

Settings: See KQ1 above.

KQ 5: For adults (age 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. Sex.
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 KQ1 above.

Interventions: See KQ1 above.

Comparators: See KQ1 above.

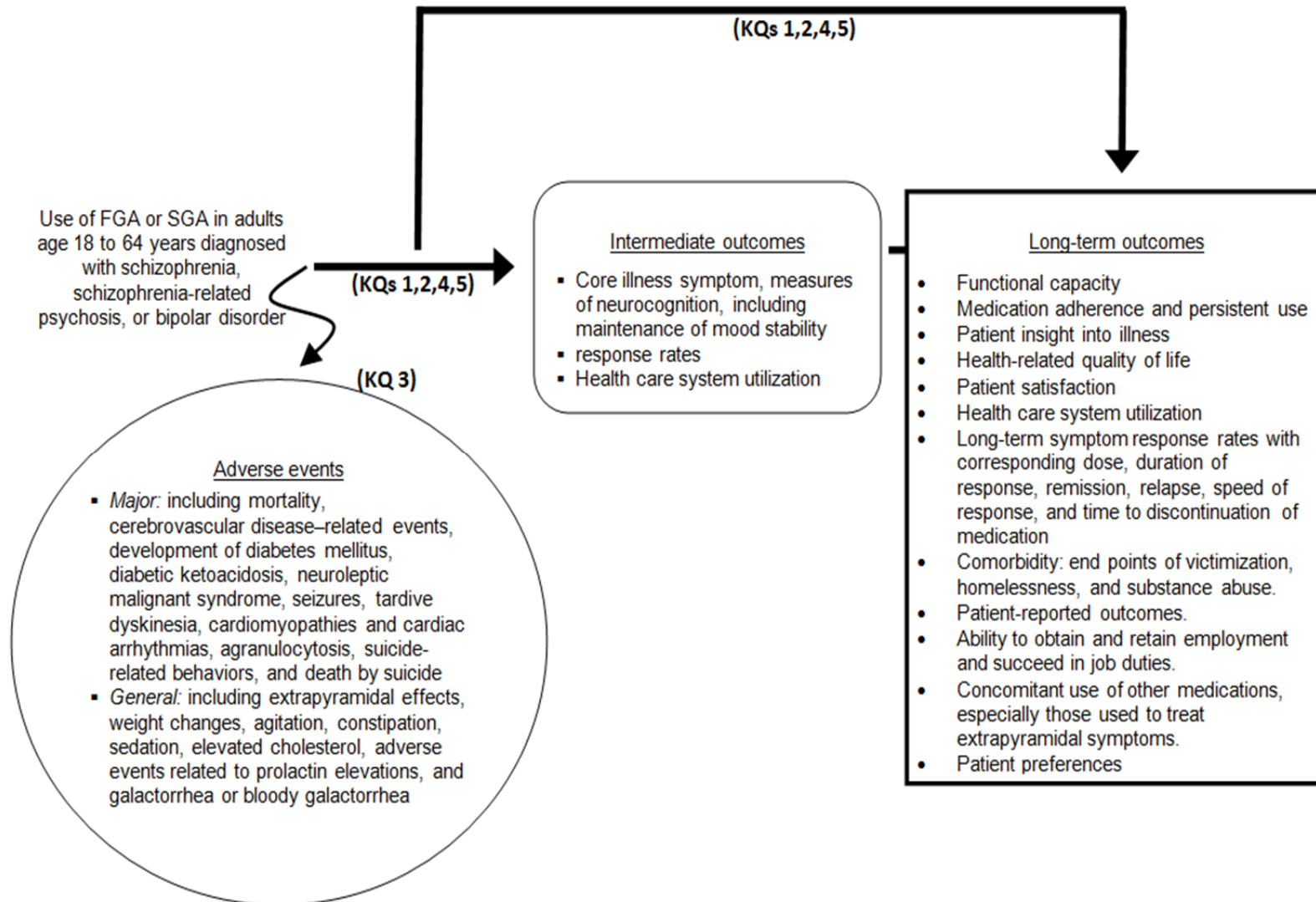
Outcomes: Core illness symptoms (see KQ1), functional capacity and decreasing health care-system utilization (see KQ2), AEs (see KQ3), or other outcomes (KQ4).

Timing: See KQ1 above.

Settings: See KQ1 above.

Figure 1 depicts the KQs within the context of an analytic framework.

Figure 1. Analytic framework for the comparative effectiveness of FGAs and SGAs



FGA = first-generation antipsychotic; KQ = Key Question; 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 (KQs). 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 strength of evidence of the overall body of evidence, and our approach to data analysis and synthesis. In general, we followed methodologically rigorous methods for systematic reviews as described in recent standards documents.^{27,28} and the EPC Methods Guide (www.effectivehealthcare.ahrq.gov/methodsguide.cfm/).

Topic Refinement and Technical Expert Panel

Our 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 KQs in consultation with AHRQ, the Scientific Resource Center, and a Technical Expert Panel. AHRQ posted the initial questions on their Web site for public comment for a period of 1 month. After reviewing the public comments, we revised the KQs, and AHRQ approved the final questions.

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

Literature Search Strategy

Our research librarian conducted comprehensive searches in the following electronic databases from 1950 to July 2011: Ovid's MEDLINE[®], Embase, PsycINFO, International Pharmaceutical Abstracts, Ebscohost CINAHL, ProQuest[®] Dissertations and Theses–Full Text, Cochrane Central Register of Controlled Trials (CENTRAL), and Scopus[™] (Appendix A–1 to A–5). We also searched the U.S. National Library of Medicine's TOXLINE[®] database and the MedEffect[™] Canada Adverse Drug Reaction Database from 1950 to July 2010 in order to identify additional data on adverse events (AEs). We restricted the searches to English-language randomized controlled trials (RCTs), nonrandomized controlled trials (nRCTs), cohort studies, and review articles examining 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, with periodic updates of the searches up to July 2011.

We hand searched conference proceedings of the American Psychiatric Association (APA) (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 by searching the U.S. Food and Drug Administration (FDA) Web site for relevant documents, and

soliciting “Scientific Information Packets” from manufacturers of the FGAs and SGAs through the Scientific Resource Center. We collected these materials asking the manufacturers for any material (published or unpublished) related to the KQs of the review. We made manufacturers aware that any materials submitted may become public through the Freedom of Information Act. The materials received from several manufacturers was reviewed for potential inclusion.

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 outcomes (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, interventions, and comparators. We rated each citation as: “include,” “exclude,” or “unclear.” Records rated as “include” or “unclear” were advanced to level 2 screening. For full-text screening (level 2 screening), two reviewers independently reviewed each retrieved 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.²⁹

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, we did not exclude studies examining patients taking other medications from 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 AEs section (KQ3). To be included, cohort studies were required to have a followup period of at least 2 years and present data on at least one serious adverse event (SAE), as determined by the Technical Expert Panel (i.e., type II diabetes mellitus, mortality, tardive dyskinesia, and major metabolic syndromes).

Table 2. Inclusion and exclusion criteria

	Inclusion Criteria	Exclusion Criteria
Publication type	English language, full-text publications from 1950 to present	Non-English language publications Conference abstracts
Study design	RCTs, nRCTs, and prospective and retrospective cohort studies	Observational study designs with no comparison group (e.g., case reports, case series, and cross-sectional studies) or case-control studies
Participants	Adults (age 18 to 64 years) with schizophrenia or related psychoses or bipolar disorder	Pediatric population (aged <18 years) Geriatric population (aged >64 years)
Interventions	Any currently available FDA-approved FGA (Table 1)	Currently unavailable or non-FDA-approved FGA or other interventions
Comparators	Any currently available FDA-approved SGA (Table 1)	Currently unavailable or non-FDA-approved SGA, placebo, or other interventions

Table 2. Inclusion and exclusion criteria (continued)

	Inclusion Criteria	Exclusion Criteria
Outcomes	Outcomes listed in the KQ; cohort studies must report on ≥ 1 SAE	None of the a priori identified outcomes were available from the trial report or communication with the study's corresponding author
Timing	All followup periods for trials; cohort studies ≥ 2 years followup	Cohorts with < 2 years followup
Setting	All settings	NA

FDA = Food and Drug Administration; FGA = first-generation antipsychotic; KQ = Key Question; NA = not applicable; nRCT = nonrandomized controlled trial; RCT = randomized controlled trial; SAE = serious adverse event; SGA = second-generation antipsychotic

Assessment of Methodological Quality

We assessed the risk of bias of RCTs and nRCTs using the Cochrane Collaboration's Risk of Bias tool.²⁷ We assessed the methodological quality of cohort studies using the Newcastle-Ottawa Scale.³⁰ 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 Risk of Bias 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.²⁷ In accordance with the guidance from the Cochrane Handbook for Systematic Reviewers, if one or more of the individual domains had a high risk of bias, we rated the overall risk of bias as high. 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 situations.

The Newcastle-Ottawa Scale, 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 and consensus 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 studies³¹⁻³³ and resolved any identified issues.

We extracted data on the following: general study characteristics (e.g., study design, inclusion and exclusion criteria, length of followup); population characteristics (e.g., age and sex); interventions and dosing regimens; numbers of patients allocated to 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 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.

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. We analyzed continuous data as post-treatment score or absolute difference (or change score) from baseline.³⁴ Since final scores and change scores can be mixed in a meta-analysis, change scores were not calculated, but extracted, when presented by the authors. Since many studies used multiple scales and scoring systems 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. For response rates, when multiple definitions were provided by authors, we chose the lower percentage reduction levels in order to standardize data extraction across all studies.

For AEs, we extracted the number of participants experiencing events and the total number of participants. We did not extract continuous measures (e.g. severity of AEs or plasma levels) because the primary concern was to define the comparative differences in AE incidence rather than severity. We counted each event as if it corresponded to a unique individual. Because an individual patient may have experienced more than one event during the course of the study, this assumption may have overestimated the number of patients that experienced an AE. We did not extract count data. All adverse events reported in the primary publication and companion papers were extracted to allow for comparative effectiveness of the adverse events profiles of FGAs and SGAs.

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.

Data Analysis

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

We pooled binary data using the Mantel-Haenszel method and a random-effects model (DerSimonian and Laird).³⁵ For continuous outcomes, we used the inverse variance method and a random-effects model (DerSimonian and Laird).³⁵ We used Chi-square to test for significant heterogeneity reduction in partitioned subgroups; $p < 0.1$ was considered to be significant. We generated forest plots for KQ1 when at least two trials provided evidence. 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.³⁶ For continuous summary estimates where the same measure of analysis was used, we calculated the MD with 95% confidence intervals (CI). We reported dichotomous summary estimates as relative risk with accompanying 95% CI.

For KQ3, data are not presented separately for schizophrenia and related psychoses and bipolar disorder because AEs associated with an antipsychotic are likely to be consistent regardless of the indication for which a drug is being administered.

We tested for heterogeneity using an I-squared (I^2) statistic and accompanying 95% uncertainty intervals.³⁷ 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. The I^2 statistic was interpreted based on the guidance in the Cochrane Handbook for Systematic Reviews of Interventions.²⁷

Variables that we considered important to explain heterogeneity included specific intervention details (e.g., type and quantity), study design, funding source, 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 (i.e., the measure used to estimate the differences in effect of an intervention against a comparator) or heterogeneity. A priori subgroup analyses included disorder subtypes, sex, 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 with at least 10 studies. Additionally, we quantitatively assessed publication bias using the Begg adjusted rank correlation test and Egger regression asymmetry test.³⁸

When pooled estimates were available, we considered clinical significance to be at least a 20 percent improvement between interventions on an individual scale.

Grading the Strength of a Body of Evidence

We evaluated the overall strength of evidence (SoE) for key outcomes identified a priori by the clinical experts (i.e., core illness symptoms in the categories of positive symptoms, negative symptoms, general psychopathology, global ratings and total scores, and clinically important serious AEs: diabetes mellitus, mortality, tardive dyskinesia, and major metabolic syndrome). We used the EPC GRADE³⁹ approach, which is based on the standard GRADE approach developed by the Grading of Recommendation Assessment, Development and Evaluation (GRADE) Working Group.⁴⁰ We assessed the SoE for the key core symptom scales and AEs (Table 3) by examining 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).

For each key outcome for each comparison of interest, we assigned an overall evidence grade based on the ratings for the individual domains. We graded the overall SoE 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, we graded the evidence as insufficient. 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.

Table 3. Outcomes assessed by GRADE*

Key Question	Outcome Category	Outcomes and/or Outcome Measures
KQ1 (Bipolar disorder)	Mood (anxiety)	Covi Anxiety Scale
	Mood (mania)	CARS–M, MRS, YMRS
	Mood (depression)	CDS–S, HAM–D, MADRS
	Sleep	Number of awakenings, sleep efficiency (%), stage REM (min), total REM activity, total sleep time (min)
	Global ratings and total scores	BRPS, CGI–BP, CGI–I, CGI–S, GAF, PANSS, PANSS-derived BPRS
KQ1 (Schizophrenia)	Positive symptoms	PANSS, SAPS
	Negative symptoms	PANSS, SANS
	General psychopathology	ABS, ACES, BDI, CABS, CDS–S, HAM–A, HAM–D, MADRS, MOAS, PANSS, PAS, YMRS
	Global ratings and total scores	BPRS, CGI–I, CGI–S, GAF, NOSIE–30, PANSS, PANSS-derived BPRS, SADS–C, SCL–90–R, SWBUN
KQ3 (conditions combined)	SAEs	Diabetes mellitus, major metabolic syndrome, mortality, tardive dyskinesia

* Based on outcomes available in the included studies; ABS = Agitated Behavior Scale; ACES = Agitation-Calmness Evaluation Scale; BDI = Beck Depression Inventory; BPRS = Brief Psychiatric Rating Scale; CABS = Corrigan Agitated Behavior Scale; CARS–M = Clinician-Administered Rating Scale for Mania; CDS–S = Calgary Depression Scale for Schizophrenia; CGI–BP = Clinical Global Impression–Bipolar; CGI–I = Clinical Global Impression–Improvement; CGI–S = Clinical Global Impression–Severity; GAF = Global Assessment of Functioning; GRADE = Grading of Recommendations Assessment, Development and Evaluation; HAM–D = Hamilton Rating Scale for Depression; KQ = Key Question; MADRS = Montgomery-Asberg Depression Rating Scale; min = minute; MOAS = Modified Overt Aggression Scale; MRS = Mania Rating Scale; NOSIE = Nurses’ Observation Scale for Inpatient Evaluation; PANSS = Positive and Negative Symptom Scale; PAS = Psychotic Anxiety Scale; REM = rapid eye movement; SADS = Schedule for Affective Disorders and Schizophrenia; SAE = serious adverse event; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; SCL = Symptom Check List; SWBUN = Subjective Well-Being Under Neuroleptics scale; YMRS = Young Mania Rating Scale

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, and efficacy studies.⁴¹ 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. We assessed the applicability of the body of evidence following the PICOTS (population, intervention, comparator, outcomes, timing of outcome measurement, and setting) format used to assess study characteristics. Specific characteristics we examined included those related to patients (e.g., age, diagnostic criteria, severity of illness, comorbidities, concomitant medications, inpatient or outpatient status) and those related to study design (e.g., length of followup). We reported clinically important outcomes and participant characteristics in the results.

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 (KQs) 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 KQ3 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% confidence intervals (CI), and I-squared (I^2) statistics, are available in evidence tables for each comparison.

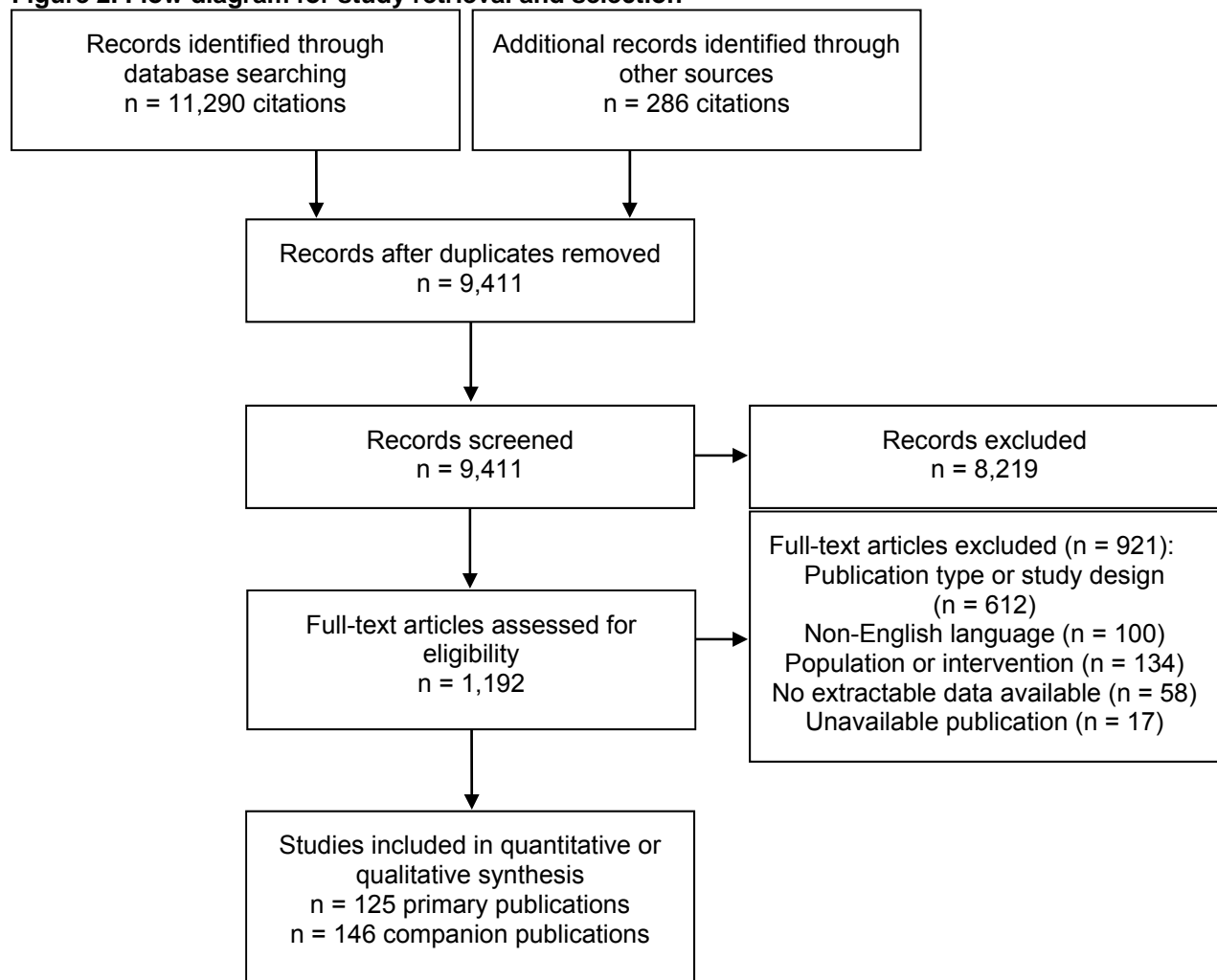
Several appendixes provide supporting information to the findings presented in this section. A list of citations for the excluded and unobtained studies and for companion studies are provided in Appendix C and D, respectively. Risk of bias assessments for trials are available in Appendix E and F, and quality assessments for cohort studies are available in Appendix G. A description of the general characteristics of the included studies and patient flow through the studies are provided in Appendix H and I, respectively. Forest plots for adverse events (AEs) (KQ3) and funnel plots for all comparisons and outcomes for which there were 10 or more studies are available in Appendix J and K, respectively. Appendix L contains evidence tables for core illness symptom subscales, composite outcomes, and measures of functional capacity (e.g., memory, recall, and motor skills). Appendix M contains evidence tables for subgroup and sensitivity analyses. Appendix N contains evidence tables for AEs.

Literature Search

All citations identified through electronic or hand searching and expert nomination were combined into a single database (Figure 2).⁴² Of the 11,576 citations identified, 2,165 were duplicates and 9,411 were unique study reports.

Following level 1 screening, 8,219 were excluded, and 1,192 were further evaluated for inclusion. Of these, 125 primary publications^{23,31-33,43-163} passed level 2 screening and were included in this comparative effectiveness review (CER). An additional 146 companion publications passed level 2 screening and are also included. The characteristics of the publications excluded at level 2 screening are presented in Figure 2 and Appendix C. The main reasons for exclusion 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 125 unique studies^{23,31-33,43-163} included in this review are described in detail in the evidence tables found in Appendixes H and I. An overview is provided in Table 4, Table 5, and Table 6. The 146 companion articles that met our inclusion criteria were used for data that were not provided in the primary report. The primary studies were published between 1974 and 2010 (median = 2002 [interquartile range (IQR), 1998 to 2006]). The majority of the studies were randomized controlled trials (RCTs) (97 percent) and were conducted in multicenter settings (56 percent). Studies were most frequently conducted in North America (46 percent). The number of enrolled participants ranged from 10 to 95,632 (median = 86 [IQR, 36 to 300]). The mean age of study participants ranged from 21 to 50 years (median = 37 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 = 88) had some form of support from the pharmaceutical industry.

A total of 113 studies examined adults with schizophrenia or related psychoses, 11 studies examined adults with bipolar disorder, and 1 study examined adults with either diagnosis. Overall, the studies examined 22 comparisons of individual first-generation antipsychotics (FGAs) and individual second-generation antipsychotics (SGAs) (Table 5 and Table 6).

Table 4. Characteristics of included studies

Category	Characteristic	Number of studies (%)
Study design	RCT	121 (96.8%)
	nRCT	2 (1.6%)
	Retrospective cohort study	2 (1.6%)
Number of centers	Multicenter	70 (56.0%)
	Single center	52 (41.6%)
	Two centers	3 (2.4%)
Setting	Inpatient	62 (49.6%)
	Outpatient	19 (15.2%)
	Mixed	26 (20.8%)
	Unclear or not reported	18 (14.4%)
Country	Africa	2 (1.6%)
	Asia	18 (14.4%)
	Australia	1 (0.8%)
	Europe	23 (18.4%)
	Middle East	1 (0.8%)
	North America	51 (40.8%)
	South America	5 (4.0%)
	International (including North America)	6 (4.8%)
	International (not including North America)	18 (14.4%)

nRCT = nonrandomized controlled trial; RCT = randomized controlled trial

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

	Aripiprazole	Asenapine	Clozapine	Olanzapine	Quetiapine	Risperidone	Ziprasidone
Chlorpromazine			13	1	1		1
Fluphenazine				2	1	1	
Haloperidol	10	1	11	37	12	43	10
Perphenazine	1			2	1	2	1
Trifluoperazine			1				
Thioridazine			1			1	

Table 6. Comparisons in the included studies by condition

Comparison	Schizophrenia (n)	Bipolar disorder (n)
Chlorpromazine vs. Clozapine	12	1
Chlorpromazine vs. Olanzapine	1	0
Chlorpromazine vs. Quetiapine	1	0
Chlorpromazine vs. Ziprasidone	1	0
Fluphenazine vs. Olanzapine	2	0
Fluphenazine vs. Quetiapine	1	0
Fluphenazine vs. Risperidone	1	0
Haloperidol vs. Aripiprazole	8	2
Haloperidol vs. Asenapine	1	0
Haloperidol vs. Clozapine	11	0
Haloperidol vs. Olanzapine	35	2
Haloperidol vs. Quetiapine	11	1
Haloperidol vs. Risperidone	39	5
Haloperidol vs. Ziprasidone	9	1
Perphenazine vs. Aripiprazole	1	0
Perphenazine vs. Olanzapine	2	0
Perphenazine vs. Quetiapine	1	0
Perphenazine vs. Risperidone	2	0
Perphenazine vs. Ziprasidone	1	0
Trifluoperazine vs. Clozapine	1	0
Thioridazine versus Clozapine	1	0
Thioridazine versus Risperidone	1	0

N = number; Vs. = versus

Methodological Quality of Included Studies

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

Randomized and Nonrandomized Controlled Trials

None of the 123 included trials^{23,31-33,43-161} were rated as having a low risk of bias. The majority of the trials (n = 78)^{23,31-33,43,44,46,47,49-56,59-61,64,66,67,70,72,74,78-81,84,85,87-89,93,94,96,97,99,101-110,112,113,115,117-127,131-134,138,143,145-147,150,153-155,158,160} were rated as having an unclear risk of bias due to under-reporting in the articles. The key potential biases in these studies were related to selection bias (i.e., random sequence generation and allocation concealment) and performance bias (i.e., proper blinding of participants and study personnel) (Appendix E and F). The remaining trials (n = 45)^{45,48,57,58,62,63,65,68,69,71,73,75-77,82,83,86,90-92,95,98,100,111,114,116,128-130,135-137,139-142,144,148,149,151,152,156,157,159,161} were considered to have a high risk of bias. The key potential biases in these studies were related to attrition bias (i.e., incomplete outcome data) and performance bias (i.e., proper blinding of participants and study personnel) (Appendix E and 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 (2.4%)	105 (85.4%)	15 (12.2%)
Allocation concealment	1 (0.8%)	116 (94.3%)	6 (4.9%)
Blinding	21 (17.1%)	83 (67.5%)	19 (15.4%)
Incomplete outcome data addressed	24 (19.5%)	32 (26.0%)	67 (54.5%)
Free of selective reporting	1 (0.8%)	3 (2.4%)	119 (96.7%)
Free of other bias	0 (0.0%)	20 (16.3%)	103 (83.7%)

Cohort Studies

Two cohort studies^{162,163} met the inclusion criteria. The methodological quality of the cohort studies was good (8 of a possible 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 (Key Questions 1, 2, 4, 5)

For schizophrenia, we included 113 studies that enrolled a total of 118,503 patients. The individual studies are described in Appendixes H and I. The results from the studies and pooled analyses are presented in Table 8 through Table 65. Within the forest plots, the studies are presented by year of publication. The following sections are organized by comparison and provide an overview of results according to the KQ: 1) core illness symptoms; 2) functional outcomes and health care system utilization; 4) other outcomes; and 5) subgroup analyses. For comparisons with more than one study, we highlight key points summarizing the overall findings prior to reporting detailed analyses.

For KQ1, the outcomes are grouped as follows: positive symptoms, negative symptoms, general psychopathology, global ratings, and total scores. Additionally, scores on subscales or composite scores, and functional capacity outcomes are presented in Appendix L. KQs 2 and 4

were grouped and are reported together throughout the results section. Within all KQs, comparisons are presented in alphabetic order by drug name.

Chlorpromazine Versus Clozapine

Key Points

- Nine RCTs comparing chlorpromazine with clozapine in patients with a range of illness severity were included; few studies examined the same outcomes.
- The most commonly reported outcome was total symptom score using the Brief Psychiatric Rating Scale (BPRS). Pooled results from six studies showed greater efficacy for clozapine, and the difference was considered clinically important (moderate strength of evidence (SoE)).
- Three trials assessed response rates and showed a significant difference favoring clozapine; two trials included treatment-resistant patients with followup between 6 and 12 weeks.
- Two trials assessed remission rates and found no significant difference; length of followup was 5 weeks (chronic schizophrenia) and 1 year (first-episode schizophrenia).
- The remaining outcomes were assessed in single trials; the majority showed no significant differences between antipsychotic effect.

Nine RCTs^{63,87,94,109,153,154,157,158,161} (n = 765) compared chlorpromazine versus clozapine. The doses varied across the studies ranging from 50 to 1800 mg/d for chlorpromazine and 25 to 900 mg/d for clozapine. Key characteristics of the included trials and summary of results are presented in Table 8 and Table 9. All the trials included patients with schizophrenia. One trial¹⁰⁹ also included patients with schizophreniform disorder. Another trial¹⁵³ only included males with paranoid/hallucinatory or catatonic type schizophrenia. Two trials^{87,94} were in patients considered to be treatment resistant; both studies assessed treatment resistance historically, whereas one of the studies⁹⁴ also confirmed treatment resistance with a run-in period. One study¹⁰⁹ focused on participants with first-episode schizophrenia. Three trials^{87,109,161} included only Asian participants. Two trials^{87,158} specifically excluded participants with drug or alcohol dependence.

The risk of bias was unclear for seven studies^{87,94,109,153,154,158,161} and high for two studies.^{63,157} Three studies had financial support from industry: in two studies^{94,154} the industry sponsors were producers of both drugs being compared, whereas the third study¹⁰⁹ was sponsored by a company that produces clozapine. Duration of followup was ≤ 6 weeks for five studies,^{94,153,154,157,158} between 6 weeks and 6 months for three studies,^{63,87,161} and >6 months for two studies.^{109,156}

Publication bias was not formally tested for any of the outcomes due the small number of included trials. The SoE for the majority of the evaluated outcomes was insufficient due to the small number of included trials (Table 10).

Table 8. Characteristics of RCTs comparing chlorpromazine versus clozapine in the treatment of schizophrenia and related psychoses

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout/ Run-in Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Claghorn et al. 1987 ⁶³ RCT (8 wks)	G1: CHL (50–1800mg/d); (76) G2: CLO (25–900mg/d); (75) Run-in phase: 2 wks	Sz w/ neurological reactions (either TD or EPS) induced by >2 prior AP	High, NR
Eklom et al. 1974 ¹⁵³ RCT (5 wks)	G1: CHL (65–700mg/d); (21) G2: CLO (65–600mg/d); (20) Washout period: 2 wks	Male w/ acute Sz; relapsed or exacerbated chronic Sz cases of the paranoid/ hallucinatory or catatonic type	Unclear, NR
Gelenberg et al. 1979 ¹⁵⁴ RCT (8 wks)	G1: CHL (50–1800mg/d); (8) G2: CLO (25–900mg/d); (7) Washout period: 48 hrs	Sz not further defined	Unclear, Industry
Hong et al. 1997 ⁸⁷ RCT (12 wks)	G1: CHL (50–1800mg/d); (19) G2: CLO (25–900mg/d); (21) Run-in phase: 6 wks	Tx refractory Sz; symptom hx ≥6 mo	Unclear, Academic
Kane et al. 1988 ⁹⁴ RCT (6 wks)	G1: CHL (1000–1800mg/d); (142) G2: CLO (500–900mg/d); (126) Run-in phase: 6 wks	Hx of tx resistance; ≥3 periods of tx in ≤5 yrs w/ AP from 2 different classes; 6 wks w/ doses equivalent to 1000mg/d CHL without relief; no period of functioning ≤5 yrs;	Unclear, Multiple sources including industry
Lieberman et al. 2003 ¹⁰⁹ RCT (52 wks)	G1: CHL (≤600mg/d); (83) G2: CLO (≤400mg/d); (81)	Sz or schizophreniform disorder; symptoms <60 mo; no prior AP tx	Unclear, Industry
Rinieris et al. 1980 ¹⁵⁷ RCT (6 wks)	G1: CHL (50–100mg/d); (16) G2: CLO (50–100mg/d); (5) Run-in phase: 1 wk	Sz not further defined	High, NR
Shopsin et al. 1979 ¹⁵⁸ RCT (5 wks)	G1: CHL (50–1600mg/d); (12) G2: CLO (25–900mg/d); (13) Washout period: ≥1 wks	Chronic Sz; recent acute exacerbation necessitating involuntary hospitalization; no spontaneous remission	Unclear, NR
Singer et al. 1974 ¹⁶¹ RCT (40 d)	G1: CHL (50–600mg/d); (20) G2: CLO (50–600mg/d); (20) Washout period: 2 wks	Acute Sz	Unclear, NR

AP(s) = antipsychotic(s); CHL = chlorpromazine; CLO = clozapine; D = days; EPS = extrapyramidal symptoms; G = group; Hr(s) = hour(s); Hx = history; Mg = milligrams; Mo = month; No. = number; NR = not reported; RCT = randomized controlled trial; Sz = schizophrenia; TD = tardive dyskinesia; Tx = treatment; W/ = with; Wk(s) = week(s); Yr(s) = year(s)

Key Question 1. Improving Core Illness Symptoms

Positive Symptoms

One trial⁸⁷ (n = 40) of patients with treatment-refractory schizophrenia and symptoms for greater than 6 months compared chlorpromazine (50–1800 mg/d) with clozapine (25–900 mg/d); there was no significant difference in positive symptoms based on the Positive and Negative Symptom Scale (PANSS) (Table 9). The SoE was graded insufficient (Table 10).

Negative Symptoms

One trial¹⁰⁹ (n = 164) of treatment-naïve patients with schizophrenia or schizophreniform disorder compared chlorpromazine (≤600 mg/d) with clozapine (≤400 mg/d) and reported no significant difference for negative symptoms using the Scale for the Assessment of Negative Symptoms (SANS) (Table 9). The SoE was graded as insufficient (Table 10).

General Psychopathology

One trial⁸⁷ (n = 40) of patients with treatment-refractory schizophrenia and symptoms for greater than 6 months compared chlorpromazine (50–1800 mg/d) with clozapine (25–900 mg/d) and found no significant difference for PANSS (general psychopathology) (Table 9). The SoE was graded as insufficient (Table 10).

Global Ratings and Total Scores

Seven trials^{63,87,94,109,154,157,161} (n = 699) reported total scores using five unique scales (Table 9). All seven trials reported total scores based on the BPRS. Two trials^{87,94} were in patients with treatment resistance. The dosages of chlorpromazine ranged from 50–1800 mg/d and clozapine from 25–900 mg/d.

Pooled results are not reported due to considerable heterogeneity among the included trials ($I^2 = 90$ percent) (Appendix M, Table 94). One trial¹⁰⁹ showed an effect in the opposite direction to the other studies: the point estimate favored chlorpromazine, although the difference between groups was not statistically significant. This trial was distinct from the other trials in that it specifically included patients with schizophreniform disorder and only those with a first episode, used relatively lower doses of both the FGA and SGA, and followed patients for 12 months. Removing this trial from the analysis reduced the heterogeneity to 20 percent.

Pooling of the remaining six trials showed a significant difference favoring clozapine (MD [mean difference] = 8.40; 95% CI, 5.92 to 10.88) (Table 9; Figure 3). This difference was considered to be clinically significant. The results of subgroup and sensitivity analyses showed some variation in the magnitude of effect based on population and study characteristics. A larger effect was observed for patients with treatment resistance and previous episodes, for trials with shorter followup periods, and for industry-funded trials. The effect in favor of clozapine was larger when higher doses of chlorpromazine were used (up to 1800 mg/d vs. 100 and 600 mg/day). Sensitivity analyses showed a larger effect when studies with imputed data were excluded, whereas no notable difference in effect was found based on risk of bias. Overall, the SoE for this outcome was graded as moderate (Table 10).

One trial,⁹⁴ (n = 268) in patients with a history of treatment resistance compared chlorpromazine (1000–1800 mg/d) with clozapine (500–900 mg/d) and reported Clinical Global Impression–Severity (CGI–S). The study found a significant difference favoring clozapine (Table 9). This difference was considered clinically significant; however, the SoE was graded as insufficient (Table 10).

One trial¹⁰⁹ (n = 164) in treatment-naïve patients comparing chlorpromazine (≤ 600 mg/d) with clozapine (≤ 400 mg) reported no significant difference based on the Clinical Global Impression–Improvement (CGI–I) and Global Assessment of Functioning (GAF) (Table 9). The SoE for these outcome measures was graded as insufficient (Table 10).

One trial⁸⁷ (n = 40) of patients with treatment-refractory schizophrenia and symptoms for greater than 6 months compared chlorpromazine (50–1800 mg/d) with clozapine (25–900 mg/d) and reported no significant difference in PANSS (total) (Table 9). The SoE was graded as insufficient (Table 10).

Key Questions 2 and 4. Improvement in Functional Outcomes, Decreasing Health Care System Utilization, and Other Outcomes

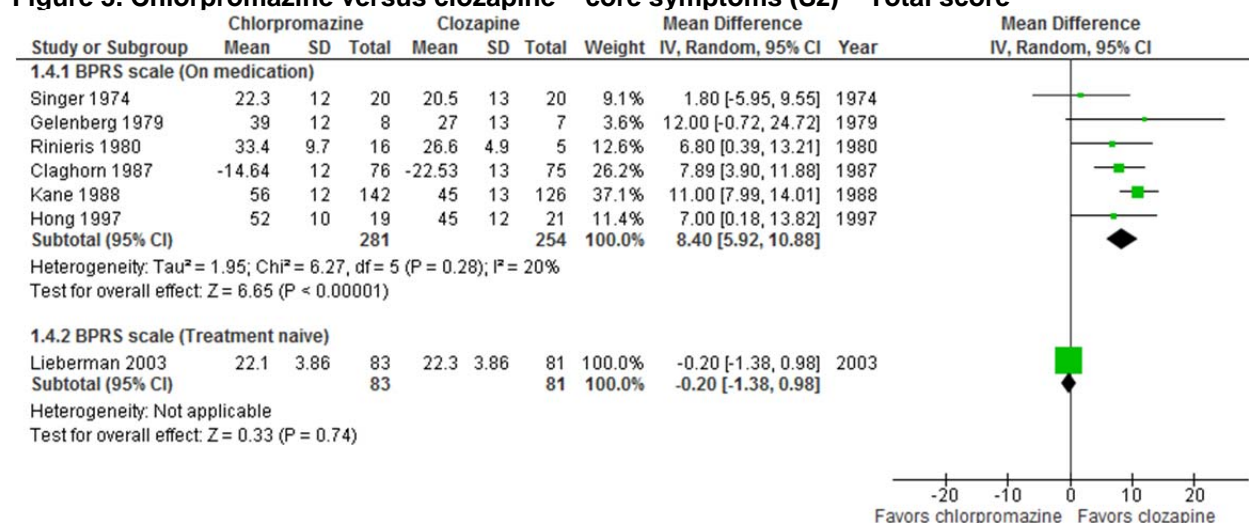
Health Care System Utilization

One trial¹⁰⁹ (n = 164) of treatment-naïve patients compared chlorpromazine (≤ 600 mg/d) with clozapine (≤ 400 mg) and found no significant differences in rates of hospitalization or rehospitalization (Table 9).

Other Outcomes. Three trials^{87,94,154} (n = 323) in patients with schizophrenia, including those with treatment resistance,^{87,94} compared chlorpromazine (50–1800 mg/d) with clozapine (25–900 mg/d) and reported a significant difference favoring clozapine for response rates (Table 9).

Two trials^{109,158} (n = 189) in treatment-naïve patients with schizophrenia or schizophreniform disorder¹⁰⁹ and chronic schizophrenics with an acute exacerbation necessitating involuntary hospitalization¹⁵⁸ compared chlorpromazine (50–1600 mg/d) with clozapine (25–900 mg/d). No significant differences were found in remission rates (Table 9).

Figure 3. Chlorpromazine versus clozapine – core symptoms (Sz) – Total score



BPRS = Brief Psychiatric Rating Scale; CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; SD = standard deviation; Sz = schizophrenia

Key Question 5. Subgroups

Race

Three trials^{87,109,161} (n = 244) were performed exclusively in Asian patients with schizophrenia and compared chlorpromazine (50–1800 mg/d) with clozapine (25–900 mg/d). There was no significant difference for the PANSS (positive),⁸⁷ SANS,¹⁰⁹ PANSS (general psychopathology),⁸⁷ or global ratings and global ratings and total scores (BPRS,^{87,109,161} CGI-I,¹⁰⁹ GAF,¹⁰⁹ and PANSS (total)).⁸⁷

Sex

One trial¹⁵³ (n = 41) examined males with acute schizophrenia or relapsed or exacerbated chronic schizophrenia of the paranoid/hallucinatory or catatonic types. The trial compared

chlorpromazine (65–700 mg/d) with clozapine (65–600 mg/d); however, there was no extractable data for KQs 1, 2, or 4.

Treatment Naïve and Treatment of First Episode

One trial¹⁰⁹ (n = 164) in treatment-naïve patients compared chlorpromazine (≤ 600 mg/d) with clozapine (≤ 400 mg). No significant differences were reported for negative symptoms using SANS and global rating scores based on BPRS and CGI-I.

Treatment Resistance. Two trials^{87,94} (n = 308) in patients with treatment resistance compared chlorpromazine (50–1800 mg/d) with clozapine (25–900 mg/d) and reported a significant difference favoring clozapine for BPRS (MD = 10.22; 95% CI, 7.12 to 13.33) and CGI-S (MD = 0.90; 95% CI, 0.67 to 1.13). The differences were considered to be clinically significant. The differences on the PANSS (positive), PANSS (general psychopathology), and PANSS (total) were not significantly different between groups.

Table 9. Evidence summary table: chlorpromazine versus clozapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Positive Symptoms					
PANSS ⁸⁷	1	40	2.00 (-0.79, 4.79)	NE	ND
Negative Symptoms					
SANS ¹⁰⁹	1	164	2.00 (-2.66, 6.66)	NE	ND
General Psychopathology					
PANSS ⁸⁷	1	40	5.00 (-3.68, 13.7)	NE	ND
Global Ratings and Total Scores					
BPRS (On treatment) ^{63,87,94,154,157,161}	6	535	8.40 (5.92, 10.90)	20%	clozapine
BPRS (Treatment naïve) ¹⁰⁹	1	164	-0.20 (-1.38, 0.98)	NE	ND
CGI-I ¹⁰⁹	1	164	-0.20 (-0.63, 0.23)	NE	ND
CGI-S ⁹⁴	1	268	0.90 (0.67, 1.13)	NE	clozapine
GAF ¹⁰⁹	1	164	-1.00 (-12.1, 10.1)	NE	ND
PANSS (total) ⁸⁷	1	40	12.00 (-4.48, 28.5)	NE	ND
Health Care System Utilization					
Rates of hospitalization/rehospitalization ¹⁰⁹	1	164	0.70 (0.23, 2.11)*	NE	ND
Other Outcomes					
Response rates ^{87,94,154}	3	323	0.13 (0.06, 0.28)*	0%	clozapine
Remission rates ^{109,158}	2	189	0.66 (0.25, 1.74)*	72%	ND

Note: bolded results are statistically significant; * = binary outcome; BPRS = Brief Psychiatric Rating Scale; CGI-I = Clinical Global Impression–Improvement; CGI-S = Clinical Global Impression–Severity; GAF = Global Assessment of Functioning; I² = I-squared; ND = no difference; NE = not estimable; PANSS = Positive and Negative Symptom Scale; SANS = Scale for the Assessment of Negative Symptoms

Table 10. Strength of evidence (GRADE): chlorpromazine versus clozapine

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Positive Symptoms						
PANSS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Negative Symptoms						
SANS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
General Psychopathology						
PANSS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
Global Ratings and Total Scores						
BPRS (on treatment)	6 RCT	Medium	Consistent	Direct	Precise	Moderate (favoring clozapine)
CGI-I	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
CGI-S	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
GAF	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
PANSS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
SANS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

BPRS = Brief Psychiatric Rating Scale; CGI-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression-Severity; GAF = Global Assessment of Functioning; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; RoB = risk of bias; SANS = Scale for the Assessment of Negative Symptoms; SoE = Strength of Evidence

Chlorpromazine Versus Olanzapine

One RCT⁶⁶ (n = 84) compared chlorpromazine (600–1200 mg/d) with olanzapine (12.5–25 mg/d) in patients with treatment-resistant schizophrenia (Table 11). There was no reported difference in core illness symptoms (negative symptoms, global ratings) and response rates between groups (Table 12). No other relevant outcomes were reported. The SoE for all reported outcomes was insufficient (Table 13).

Table 11. Characteristics of RCT comparing chlorpromazine versus olanzapine in the treatment of schizophrenia

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Run-in period	Main Inclusion Criteria	Risk of Bias, Financial Support
Conley et al. 1998 ⁶⁶ RCT (6 wks)	G1: CHL (600–1200mg/d); (42) G2: OLA (12.5–25mg/d); (42) Run-in phase: 6 wks	Tx resistant Sz; ≥2 periods of tx in ≤5 yrs with AP (≥2 classes, excluding HAL), at dosages ≥1000mg/d of CHL equivalents, for 6 wks	Unclear, Multiple sources

AP(s) = antipsychotic(s); CHL = chlorpromazine; D = days; G = group; HAL = haloperidol; Mg = milligrams; OLA = olanzapine; RCT = randomized controlled trial; Sz = schizophrenia; Tx = treatment; Wk(s) = week(s); Yr(s) = year(s)

Table 12. Evidence summary table: chlorpromazine versus olanzapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Negative Symptoms					
SANS ⁶⁶	1	84	0.90 (-2.90, 4.70)	NE	ND
Global Ratings					
BPRS ⁶⁶	1	84	2.80 (-2.74, 8.34)	NE	ND
CGI-S ⁶⁶	1	84	0.10 (-0.29, 0.49)	NE	ND
Other Outcomes					
Response rates ⁶⁶	1	84	0.14 (0.01, 2.68)*	NE	ND

* = binary outcome; BPRS = Brief Psychiatric Rating Scale; CGI-S = Clinical Global Impression-Severity; I² = I-squared; ND = no difference; NE = not estimable; SANS = Scale for the Assessment of Negative Symptoms

Table 13. Strength of evidence (GRADE): chlorpromazine versus olanzapine

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Negative Symptoms						
SANS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Global Ratings						
BPRS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
CGI-S	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

BPRS = Brief Psychiatric Rating Scale; CGI-S = Clinical Global Impression–Severity; RCT = randomized controlled trial; RoB = risk of bias; SoE = Strength of Evidence

Chlorpromazine Versus Quetiapine

One RCT¹²¹ (n = 201) compared chlorpromazine (75–750 mg/d) with quetiapine (75–750 mg/d) in patients with chronic or subchronic schizophrenia with an acute exacerbation or patients with schizophreniform disorder (Table 14). There was no reported difference in **response rates** between groups (Table 15). No other relevant outcomes were reported.

Table 14. Characteristics of RCT comparing chlorpromazine versus quetiapine in the treatment of schizophrenia and related psychoses

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Peuskens et al. 1997 ¹²¹ RCT (8 wks)	G1: CHL (75–750mg/d); (100) G2: QUE (75–750mg/d); (101) Washout period: 24 hrs	Acute exacerbation of chronic/ subchronic Sz, or schizophreniform disorder; not on depot AP	Unclear, Industry

AP(s) = antipsychotic(s); CHL = chlorpromazine; D = days; G = group; Hr(s) = hour(s); Mg = milligrams QUE = quetiapine; RCT = randomized controlled trial; Sz = schizophrenia; Wk(s) = week(s)

Table 15. Evidence summary table: chlorpromazine versus quetiapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Other Outcomes					
Response rates ¹²¹	1	201	0.81 (0.64, 1.02)*	NE	ND

* = binary outcome; I² = I-squared; ND = no difference; NE = not estimable

Chlorpromazine Versus Ziprasidone

One RCT⁹⁶ (n = 306) compared chlorpromazine (100–1200 mg/d) with ziprasidone (40–160 mg/d) in **Asian patients** with chronic or subchronic **treatment-resistant schizophrenia** (Table 16). There were no reported results for **core illness symptoms**. There was no difference in **response rates** between groups (Table 17). No other relevant outcomes were reported.

Table 16. Characteristics of RCT comparing chlorpromazine versus ziprasidone in the treatment of schizophrenia and related psychoses.

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Run-in Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Kane et al. 2006 ⁹⁶ RCT (12 wks)	G1: CHL (100–1200mg/d); (154) G2: ZIP (40–160mg/d); (152) Run-in phase: 6 wks	Chronic/ subchronic Sz; tx resistant; HAL nonresponders with no response to HAL during run-in phase	Unclear, Industry

AP(s) = antipsychotic(s); CHL = chlorpromazine; HAL = Haloperidol; G = group; Mg = milligrams; RCT = randomized controlled trial; Sz = schizophrenia; Tx = treatment; Wk(s) = week(s); ZIP = ziprasidone

Table 17. Evidence summary table: chlorpromazine versus ziprasidone

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Other Outcomes					
Response rates ⁹⁶	1	306	0.95 (0.78, 1.16)*	NE	ND

* = binary outcome; I² = I-squared; ND = no difference; NE = not estimable

Fluphenazine Versus Olanzapine

One RCT⁸⁹ (n = 60) compared fluphenazine (6–21 mg/d) with olanzapine (5–20 mg/d) in **Caucasian patients** with stable schizophrenia (Table 18). For **positive symptoms**, a significant difference favored olanzapine based on PANSS (positive) (Table 19). For **general psychopathology**, significant differences favoring olanzapine based on the Hamilton Rating Scale for Anxiety (HAM–A) and the PANSS (general psychopathology) were reported (Table 19). **Global Ratings** and **Total Scores** reported significant benefits favoring olanzapine for the BPRS, CGI–S, and PANSS (total) scales (Table 19). The results for the core illness symptoms were not considered to be clinically significant, and the SoE for all the evaluated outcomes was insufficient due to the inclusion of only a single trial (Table 20). No significant differences were found for **negative symptoms** based on PANSS (negative) and **response rates** (Table 19).

Table 18. Characteristics of RCT comparing fluphenazine versus olanzapine in the treatment of schizophrenia and related psychoses

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Jakovljevic et al. 1999 ⁸⁹ RCT (22 wks)	G1: FLU (6–21mg/d); (30) G2: OLA (5–20mg/d); (30) Washout period: 1–1.5 wks	SZ; no unstable illness hx or intolerance to OLA or FLU w/ depot AP; no previous trial with OLA	Unclear, Industry

AP(s) = antipsychotic(s); D = day; FLU = fluphenazine; G = group; Hx = history; Mg = milligrams; OLA = olanzapine; RCT = randomized controlled trial; Sz = schizophrenia; W/ = with; Wks = weeks

Table 19. Evidence summary table: fluphenazine versus olanzapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Positive Symptoms					
PANSS ⁸⁹	1	60	5.10 (0.57, 9.63)	NE	olanzapine
Negative Symptoms					
PANSS ⁸⁹	1	60	3.00 (-1.00, 7.00)	NE	ND
General Psychopathology					
HAM–A ⁸⁹	1	60	4.00 (0.28, 7.72)	NE	olanzapine
PANSS ⁸⁹	1	60	8.20 (0.83, 15.57)	NE	olanzapine
Global Ratings and Total Scores					
BPRS ⁸⁹	1	60	9.30 (0.57, 18.03)	NE	olanzapine
-CGI–S ⁸⁹	1	60	0.90 (0.17, 1.63)	NE	olanzapine
PANSS ⁸⁹	1	60	16.20 (1.22, 31.18)	NE	olanzapine
Other Outcomes					
Response rates ⁸⁹	1	60	0.74 (0.51, 1.07)*	NE	ND

Note: bolded outcomes are statistically significant; * = binary outcome; BPRS = Brief Psychiatric Rating Scale; CGI–S = Clinical Global Impression–Severity; HAM–A = Hamilton Rating Scale for Anxiety; I² = I-squared; ND = no difference; NE = not estimable; PANSS = Positive and Negative Symptom Scale

Table 20. Strength of evidence (GRADE): fluphenazine versus olanzapine

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Positive Symptoms						
PANSS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
Negative Symptoms						
PANSS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
General Psychopathology						
HAM-A	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
PANSS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
Global Ratings and Total Scores						
BPRS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
CGI-S	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
PANSS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient

BPRS = Brief Psychiatric Rating Scale; CGI-S = Clinical Global Impression–Severity; HAM-A = Hamilton Rating Scale for Anxiety; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; RoB = risk of bias; SoE = Strength of Evidence

Fluphenazine Versus Quetiapine

One RCT⁶⁷ (n = 25) compared fluphenazine (10–15 mg/d) versus quetiapine (300–500 mg/d) in patients with **treatment-resistant** schizophrenia (Table 21). No significant differences were reported between groups for **core illness symptoms** (global ratings), **sexual dysfunction**, and **response rates** (Table 22). The SoE for all the evaluated outcomes was insufficient due to the inclusion of only a single trial (Table 23).

Table 21. Characteristics of RCT comparing fluphenazine versus quetiapine in the treatment of schizophrenia and related psychoses

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Run-in Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Conley et al. 2005 ⁶⁷ RCT (12 wks)	G1: FLU (10–15mg/d); (13) G2: QUE (300–500mg/d); (12) Run-in phase: 4–6 wks	Tx resistant Sz; persistent positive psychotic symptoms; failed tx trials with 2 different APs	Unclear, Multiple sources

AP(s) = antipsychotic(s); D = day; FLU = fluphenazine; G = group; Mg = milligrams; QUE = quetiapine; RCT = randomized controlled trial; Sz = schizophrenia; Tx = Treatment; Wk(s) = week(s)

Table 22. Evidence summary table: fluphenazine versus quetiapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Global Ratings					
BPRS ⁶⁷	1	25	-1.98 (-12.96, 9.00)	NE	ND
CGI-S ⁶⁷	1	25	-0.03 (-0.92, 0.86)	NE	ND
Sexual Dysfunction					
Dysfunction ⁶⁷	1	25	2.15 (0.72, 6.48)*	NE	ND
Improvement on treatment ⁶⁷	1	25	0.46 (0.05, 4.46)*	NE	ND
Other Outcomes					
Response rates ⁶⁷	1	25	0.62 (0.12, 3.07)*	NE	ND

* = binary outcome; BPRS = Brief Psychiatric Rating Scale; CGI-S = Clinical Global Impression–Severity; I² = I-squared; ND = no difference; NE = not estimable

Table 23. Strength of evidence (GRADE): fluphenazine versus quetiapine

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Global Ratings						
BPRS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
CGI-S	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

BPRS = Brief Psychiatric Rating Scale; CGI-S = Clinical Global Impression–Severity; RCT = randomized controlled trial; RoB = risk of bias; SoE = Strength of Evidence

Fluphenazine Versus Risperidone

One RCT⁶⁷ (n = 26) compared fluphenazine (10–15 mg/d) with risperidone (3–5 mg/d) in patients with **treatment-resistant** schizophrenia (Table 24). No differences were found between groups for any of the **core illness symptom** assessments (global ratings), **sexual dysfunction**, and **response rates** (Table 25). The SoE for all the evaluated outcomes was insufficient due to the inclusion of only a single trial (Table 26).

Table 24. Characteristics of RCT comparing fluphenazine versus risperidone in the treatment of schizophrenia and related psychoses

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Run-in Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Conley et al. 2005 ⁶⁷ RCT (12 wks)	G1: FLU (10–15mg/d); (13) G2: RIS (3–5mg/d); (13) Run-in phase: 4–6 wks	Tx resistant Sz; persistent positive psychotic symptoms; failed tx trials with 2 different APs	Unclear, Multiple sources

AP(s) = antipsychotic(s); D = day; FLU = fluphenazine; G = group; Mg = milligrams; RCT = randomized controlled trial; RIS = risperidone; Sz = schizophrenia; Tx = treatment; Wk(s) = week(s)

Table 25. Evidence summary table: fluphenazine versus risperidone

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Global Ratings					
BPRS ⁶⁷	1	26	-0.30 (-10.80, 10.20)	NE	ND
CGI-S ⁶⁷	1	26	0.07 (-0.77, 0.91)	NE	ND
Sexual dysfunction					
Sexual dysfunction ⁶⁷	1	26	1.40 (0.60, 3.28)*	NE	ND
Improvement on treatment ⁶⁷	1	26	0.17 (0.02, 1.20)*	NE	ND
Other outcomes					
Response rates ⁶⁷	1	26	0.67 (0.13, 3.35)*	NE	ND

* = binary outcome; BPRS = Brief Psychiatric Rating Scale; CGI-S = Clinical Global Impression–Severity; I² = I-squared; ND = no difference; NE = not estimable

Table 26. Strength of evidence (GRADE): fluphenazine versus risperidone

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Global Ratings						
BPRS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
CGI-S	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

BPRS = Brief Psychiatric Rating Scale; CGI-S = Clinical Global Impression–Severity; RCT = randomized controlled trial; RoB = risk of bias; SoE = Strength of Evidence

Haloperidol Versus Aripiprazole

Key Points

- Eight RCTs compared haloperidol with aripiprazole among patients with varying disease severity.
- Six studies assessing global ratings using three different tools (BPRS, CGI-I, and CGI-S) found no differences between study groups. The SoE was graded as low or insufficient depending on the scale used.
- A significant difference in favor of aripiprazole was found for negative symptoms based on three studies that used the PANSS (negative) scale (moderate SoE). This finding was not considered to be clinically significant.
- No difference was found for positive symptoms based on two studies that used the PANSS (positive) scale (low SoE).
- Five studies assessed response rates and showed no differences between groups.

- The remaining outcomes were assessed in single trials, and the majority showed no significant differences.

Eight RCTs^{31,44,73,74,76,92,98,102} (n = 2,850) compared haloperidol with aripiprazole. Key characteristics of the included trials and summary of findings are presented in Table 27 and Table 28, respectively. Five trials^{31,73,74,76,92} specifically included patients with schizoaffective disorder, whereas one trial⁴⁴ specifically excluded patients with schizoaffective disorder. Five studies^{31,44,74,76,92} specifically excluded patients with drug and/or alcohol dependence. Two studies^{98,102} included only patients with multiple episodes, whereas the remaining studies included patients with both first and multiple episodes. Five studies^{31,44,73,74,98} included only patients with no treatment resistance; the remaining three studies included mixed populations with both treatment resistance and no treatment resistance. One trial¹⁰² included only Asian patients. In the majority of studies, the maximum dose of haloperidol was 10 mg/d; in two studies the maximum dose was 15 mg/d⁷⁶ and 30 mg/d.⁷³ The dosage for aripiprazole varied across studies ranging from 1 mg/d³¹ to 45 mg/d.⁷³

Risk of bias was unclear for five studies^{31,44,74,98,102} and high for three studies.^{73,76,92} The duration of followup was <6 weeks in five studies,^{31,44,73,74,92} between 6 weeks and 6 months in two studies,^{76,102} and >6 months in one study.⁹⁸ Six studies^{31,44,74,76,92,98} were funded by industry; in all cases the industry manufactured aripiprazole.

Publication bias was not formally tested for any of the outcomes due the small number of included trials. The SoE for the majority of the evaluated outcomes was insufficient due to the small number of trials (Table 29).

Table 27. Characteristics of RCTs comparing haloperidol versus aripiprazole in the treatment of schizophrenia and other related psychoses

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Andrezina et al. 2006 ⁴⁴ RCT (24 hrs)	G1: HAL (6.5mg/ 2 hrs; max 3/d); (185) G2: ARI (9.75mg/ 2 hrs; max 3/d); (175)	Sz or schizoaffective with agitation and no use of benzodiazepines or anticholinergics ≤4 hr; lack of response to previous AP	Unclear, Industry
Daniel et al. 2007 ⁷⁴ RCT (5 d)	G1: HAL (6.5mg/d); (151) G2: ARI (9.75mg/d); (153)	Acutely agitated Sz or schizoaffective disorder	Unclear, Industry
de Oliveira et al. 2009 ⁷⁶ RCT (8 wks)	G1: HAL (10–15mg/d); (33) G2: ARI (15–30mg/d); (66)	Sz/ schizoaffective disorder	High, Industry
Kane et al. 2002 ⁹² RCT (4 wks)	G1: HAL (10mg/d); (104) G2: ARI (15mg/d); (102) G3: ARI (30mg/d); (102) Washout period: <1 wks	Sz/ schizoaffective disorder not refractory to antipsychotics; improvement with AP besides CLO; OP >1 3–month period <1 yr	High, Industry
Kasper et al. 2003 ⁹⁸ RCT (52 wks)	G1: HAL (5–10mg/d); (433) G2: ARI (20–30mg/d); (861) Washout period: ≥5 d	Acute relapse of Sz; response to AP (except CLO); no hx tx resistance; ≥3 mo OP AP use in last yr; PANSS total ≥60	Unclear, Industry
Kim et al. 2010 ¹⁰² RCT (8 wks)	G1: HAL (15.9±7.1mg/d); (35) G2: ARI (21.7±5.5 mg/d); (31) Washout period: >4wks	Sz not further defined	Unclear, Foundation

Table 27. Characteristics of RCTs comparing haloperidol versus aripiprazole in the treatment of schizophrenia and other related psychoses (continued)

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout Period	Main Inclusion Criteria	Risk of Bias, Financial Support
McCue et al. 2006 ⁷³ RCT (3 wks)	G1: HAL (4–30mg); (61) G2: ARI (10–45mg); (63)	Sz, schizoaffective disorder or schizophreniform disorder; no hx of response or lack of response to AP, BP, major depression, or substance-induced psychotic disorder	High, No external funding
Tran-Johnson et al. 2007 ³¹ RCT (24 hrs)	G1: HAL (7.5mg/d); (60) G2: ARI (1mg/d); (57) G3: ARI (5.25mg/d); (63) G4: ARI (9.75mg/d); (57) G5: ARI (15mg/d); (58)	Sz, schizoaffective, or schizophreniform disorder; acute agitation	Unclear, Industry

AP(s) = antipsychotic(s); ARI = aripiprazole; BP = bipolar disorder; CLO = clozapine; D = day; G = group; HAL = haloperidol; Hr(s) = hour(s); Hx = history; Max = maximum; Mg = milligram; OP = outpatient; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; Sz = schizophrenia; Tx = treatment; Wk(s) = week(s); Yr(s) = year(s)

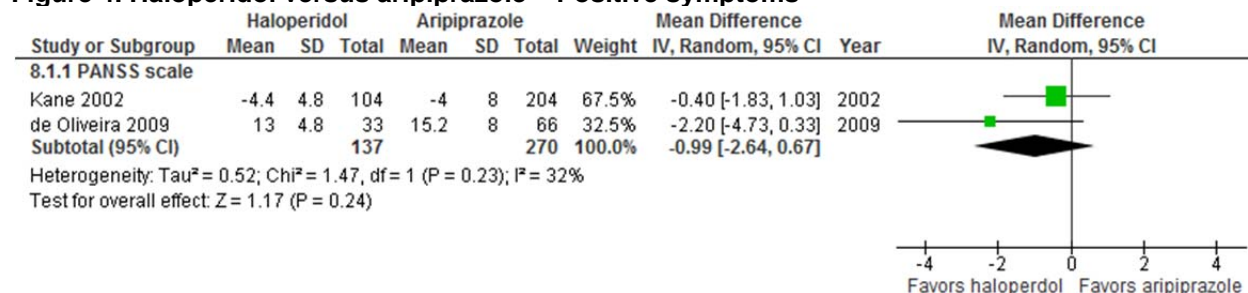
Key Question 1. Improving Core Illness Symptoms

Positive Symptoms

Three trials^{76,92,102} (n = 473) assessed positive symptoms using two different scales. Two of the studies^{76,92} included only patients with schizoaffective disorders and no alcohol and/or drug use; the third study¹⁰² only included Asians and a mixed population in terms of disorder subtypes and comorbid drug or alcohol use. Studies were consistent in the dosages of study drugs. Duration of followup was <6 weeks for one study⁹² and 8 weeks for two studies.^{76,102} Risk of bias was high for two studies^{76,92} and unclear for one study.¹⁰² Two of the studies were industry-funded.^{76,102}

No significant differences were found based on the PANSS (positive; two studies)^{76,92} and Scale for the Assessment of Positive Symptoms (SAPS; 1 study)¹⁰² (Table 28; Figure 4). There was moderate statistical heterogeneity between the two studies that reported PANSS scores; the only notable differences between these studies were duration of followup of 4 weeks⁹² versus 8 weeks⁷⁶ and risk of bias (high⁹² vs. unclear⁷⁶). The SoE was graded as low for PANSS (positive) and insufficient for SAPS (Table 29).

Figure 4. Haloperidol versus aripiprazole – Positive symptoms



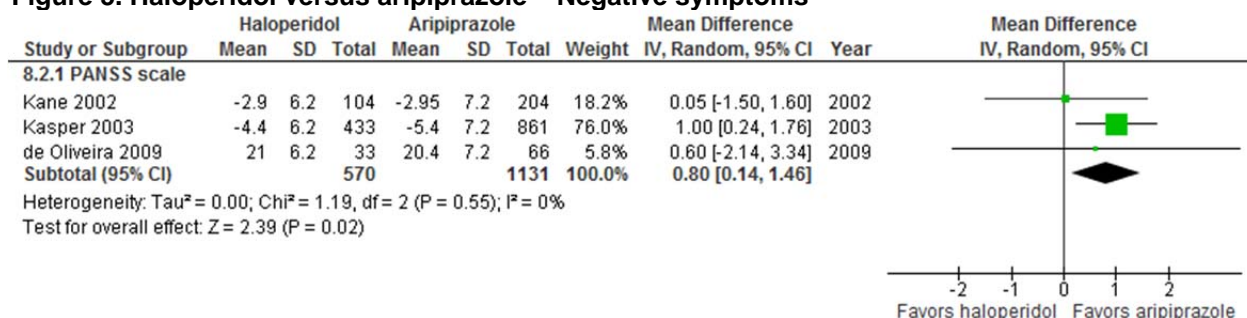
CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale; SD = standard deviation

Negative Symptoms. Four trials^{76,92,98,102} (n = 1767) reported on negative symptoms. Two trials^{76,92} specifically included patients with schizoaffective disorders and no comorbid drug or

alcohol use; two trials^{98,102} included mixed populations in terms of disorder subtype and comorbid drug or alcohol use. Two trials^{98,102} included only patients with multiple episodes, whereas two trials^{76,92} included mixed first and multiple episodes. One trial⁹⁸ specifically excluded treatment-resistant patients, and one study¹⁰² included only Asians. One trial¹⁰² included a higher range of haloperidol dose; the doses of aripiprazole were consistent across studies. Risk of bias was high for two studies^{76,92} and unclear for two studies.^{98,102} All studies were industry-funded except one.¹⁰²

There was a significant difference favoring aripiprazole based on PANSS (negative), with no evidence of statistical heterogeneity (Table 28; Figure 5).^{76,92,98} This difference was not considered to be clinically significant. There was no difference in the SANS¹⁰² based on one small study (Table 28). The SoE was graded as moderate for PANSS (negative) and insufficient for SANS (Table 29).

Figure 5. Haloperidol versus aripiprazole – Negative symptoms



CI = confidence intervals; df = degrees of freedom; I² = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale; SD = standard deviation

General Psychopathology

One trial comparing 7.5 mg/d haloperidol with 1 mg/d aripiprazole reported results for the Agitation-Calmness Evaluation Scale (ACES) and Corrigan Agitated Behavior Scale (CABS),³¹ and showed no differences between study groups. The study specifically included patients with schizoaffective disorders and no comorbid alcohol or drug use. The study excluded patients with treatment resistance and included both first and multiple episodes. Length of followup was only 24 hours. Risk of bias was unclear, and the study was industry-funded.

One trial⁷⁶ (n = 99) reported PANSS (general psychopathology) and found no differences between groups over the 8-week study period (Table 28). The trial included only patients with schizoaffective disorders and no comorbid alcohol or drug use; the trial included a mix of first and multiple episodes, as well as treatment-resistant and nonresistant patients. Risk of bias was high, and the trial was industry-funded.

The SoE for PANSS (negative), ACES, and CABS was graded as insufficient (Table 29).

Global Ratings and Total Scores

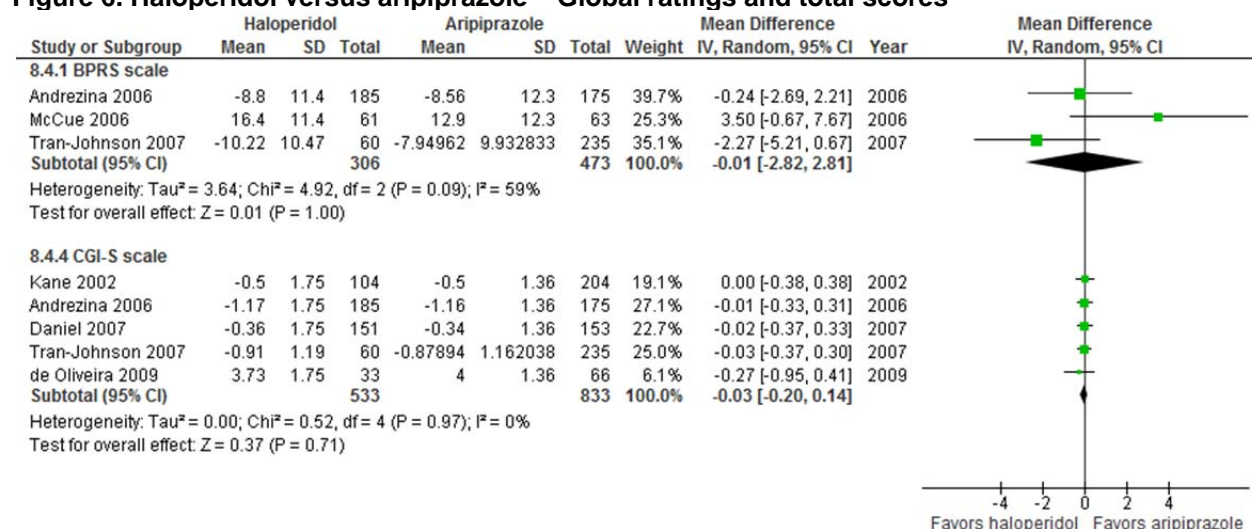
Six trials^{31,44,73,74,76,92} (n = 1,490) presented global rating scores. No differences were found for BPRS (3 studies),^{31,44,73} CGI-I (1 study),³¹ or CGI-S (5 studies)^{31,44,74,76,92} (Table 28; Figure 6). The SoE was graded as low for BPRS and CGI-S and insufficient for CGI-I (Table 29).

The three trials^{31,44,73} that reported BPRS were statistically heterogeneous: one trial had an effect estimate favoring aripiprazole, and the other two favored haloperidol (although 95% CIs in all cases included the null). All three trials specifically included patients with schizoaffective

disorders and no treatment resistance, and included mixed first and multiple episodes. The one trial differed in that it did not specifically exclude patients with comorbid drug or alcohol use, and it used relatively higher doses of both haloperidol (4-30 mg/d vs. 6.5 and 7.5 mg/d) and aripiprazole (10-45 mg/d vs. 1 and 9.75 mg/d). Further, the duration of followup was longer for the one trial (3 weeks vs. 24 hours). The trial⁷³ that differed had high risk of bias and was not industry-funded, while the other two trials had an unclear risk of bias and were industry-funded.

The five trials^{31,44,74,76,92} that reported CGI-S showed no evidence of statistical heterogeneity, but varied on several clinical and study characteristics. All studies specifically included patients with schizoaffective disorders except one⁴⁴ in which patients with schizoaffective disorders were excluded. Three studies^{31,44,74} specifically excluded treatment-resistant patients, whereas two studies^{76,92} had both treatment-resistant and nonresistant patients. All studies specifically excluded patients with comorbid drug or alcohol use. The range of dose for haloperidol was relatively consistent across studies; however, the dose for aripiprazole ranged from 1 mg/d³¹ to 15-30 mg/d.^{76,92} The duration of followup ranged from 24 hours^{31,44} to 8 weeks.⁷⁶ Risk of bias was unclear for all but one trial, which was high;⁹² all trials were industry-funded.

Figure 6. Haloperidol versus aripiprazole – Global ratings and total scores



BPRS = Brief Psychiatric Rating Scale; CGI-S = Clinical Global Impression–Severity; CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; SD = standard deviation

Key Questions 2 and 4. Improvement in Functional Outcomes, Decreasing Health Care System Utilization, and Other Outcomes

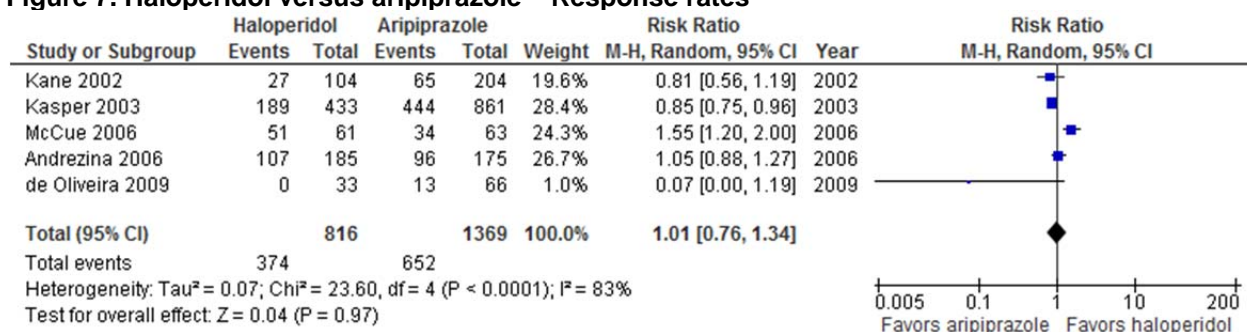
Other Outcomes

Five trials^{44,73,76,92,98} ($n = 2,185$) assessed treatment response rates and found no significant difference between groups (Table 28; Figure 7); however, there was considerable statistical heterogeneity (Appendix M, Table 95). The trials varied on characteristics of the patient populations: schizoaffective disorder included,^{73,76,92} schizoaffective disorder excluded,⁴⁴ mixed,⁹⁸ treatment-resistant patients excluded.^{44,73,98} All but one trial⁹⁸ excluded patients with comorbid drug or alcohol use and included mixed first and multiple episodes. Doses ranged across studies from 6.5 to 4-30 mg/d for haloperidol and from 1 mg to 10-45 mg/d for aripiprazole. Duration of followup also varied across studies from 24 hours⁴⁴ to 52 weeks.⁹⁸ All

but one study⁷³ were assessed as unclear risk of bias and were industry-funded. None of these variables explained the statistical heterogeneity in the pooled estimate of effect.

One trial⁷⁶ (n = 99) comparing 10–15 mg/d haloperidol with 15–30 mg/d aripiprazole examined medication adherence, caregiver satisfaction, and patient satisfaction. The study reported a significant difference for caregiver and patient satisfaction favoring aripiprazole. There was no significant difference between groups for compliance rates (Table 28). This study specifically included patients with schizoaffective disorder, no comorbid drug or alcohol use, and mixed first and multiple episodes. Length of followup was 8 weeks. Risk of bias was unclear, and the study was industry-funded.

Figure 7. Haloperidol versus aripiprazole – Response rates



CI = confidence intervals; df = degrees of freedom; I² = I-squared; IV = inverse variance; M-H = Mantel-Haenszel

Key Question 5. Subgroups

Race

One trial¹⁰² (n = 66) involving Korean patients with schizophrenia compared haloperidol (15.9±7.1 mg/d) with aripiprazole (21.7±5.5 mg/d) and reported no significant difference for positive (SAPS) or negative (SANS) core illness symptoms.

Table 28. Evidence summary table: haloperidol versus aripiprazole

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Positive Symptoms					
PANSS ^{76,92}	2	407	-0.99 (-2.64, 0.67)	32%	ND
SAPS ¹⁰²	1	66	-3.10 (-11.08, 4.88)	NE	ND
Negative Symptoms					
PANSS ^{76,92,98}	3	1701	0.80 (0.14, 1.46)	0%	aripiprazole
SANS ¹⁰²	1	66	-1.10 (-5.24, 3.04)	NE	ND
General Psychopathology					
ACES ³¹	1	295	0.46 (-0.03, 0.95)	NE	ND
CABS ³¹	1	295	-1.82 (-3.83, 0.18)	NE	ND
PANSS ⁷⁶	1	99	-1.60 (-5.28, 2.08)	NE	ND
Global Ratings					
BPRS ^{31,44,73}	3	779	-0.01 (-2.82, 2.81)	59%	ND
CGI-I ³¹	1	295	-0.08 (-0.40, 0.25)	NE	ND
CGI-S ^{31,44,74,76,92}	5	1366	-0.03 (-0.20, 0.14)	0%	ND

Table 28. Evidence summary table: haloperidol versus aripiprazole (continued)

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Other Outcomes					
Response rates ^{44,73,76,92,98}	5	2185	1.01 (0.76, 1.34)*	83%	ND
Low medication adherence ⁷⁶	1	99	0.66 (0.03, 15.70)*	NE	ND
Caregiver satisfaction ⁷⁶	1	99	0.32 (0.15, 0.67)*	NE	aripiprazole
Patient satisfaction ⁷⁶	1	99	0.33 (0.17, 0.66)*	NE	aripiprazole

Note: bolded results are statistically significant; * = binary outcome; ACES = Agitation-Calmness Evaluation Scale; BPRS = Brief Psychiatric Rating Scale; CABS = Corrigan Agitated Behavior Scale; CGI-I = Clinical Global Impression–Intensity; CGI-S = Clinical Global Impression–Severity; I² = I-squared; ND = no difference; NE = not estimable; PANSS = Positive and Negative Symptom Scale; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms

Table 29. Strength of evidence (GRADE): haloperidol versus aripiprazole

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Positive Symptoms						
PANSS	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
SAPS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Negative Symptoms						
PANSS	3 RCT	Medium	Consistent	Direct	Imprecise	Moderate (favoring aripiprazole)
SANS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
General Psychopathology						
ACES	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
CABS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
PANSS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Global Ratings and Total Scores						
BPRS	3 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
CGI-I	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
CGI-S	5 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)

ACES = Agitation-Calmness Evaluation Scale; BPRS = Brief Psychiatric Rating Scale; CABS = Corrigan Agitated Behavior Scale; CGI-S = Clinical Global Impression–Severity; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; RoB = risk of bias; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; SoE = Strength of Evidence; ND = no difference

Haloperidol Versus Asenapine

One RCT⁹⁷ (n = 335) compared haloperidol (4 mg/d) with asenapine (5–10 mg/d) in patients with schizophrenia with acute exacerbation of psychotic symptoms (Table 30). This study did not find any significant differences between groups for **core illness symptoms** (positive, negative, or general psychopathology symptoms and global ratings and total scores) or for **response rates** (Table 31). The SoE for all the evaluated outcomes was insufficient due to the inclusion of only a single trial (Table 32).

Table 30. Characteristics of RCTs comparing haloperidol versus asenapine in the treatment of schizophrenia

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Kane et al. 2010 ⁹⁷ RCT (6 wks)	G1: HAL (4mg/d); (115) G2: ASE (5mg/d); (114) G3: ASE (10mg/d); (106) Washout period: 1–3 d	Sz with acute exacerbation of psychotic symptoms	Unclear, Industry

ASE = Asenapine; D = day; G = group; HAL = haloperidol; Mg = milligrams; RCT = randomized controlled trial; Sz = schizophrenia; Wk = week

Table 31. Evidence summary table: haloperidol versus asenapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Positive Symptoms					
PANSS ⁹⁷	1	335	0.16 (-1.22, 1.54)	NE	ND
Negative Symptoms					
PANSS ⁹⁷	1	335	0.39 (-0.72, 1.51)	NE	ND
General Psychopathology					
CDS-S ⁹⁷	1	335	0.56 (-0.20, 1.32)	NE	ND
PANSS ⁹⁷	1	335	0.26 (-1.59, 2.10)	NE	ND
Global Ratings and Total Scores					
CGI-S ⁹⁷	1	335	0.01 (-0.24, 0.25)	NE	ND
PANSS ⁹⁷	1	335	0.23 (-2.50, 2.95)	NE	ND
Other Outcomes					
Response rates ⁹⁷	1	335	0.82 (0.64, 1.04)*	NE	ND

* = binary outcome; CDS-S = Calgary Depression Scale for Schizophrenia; CGI-S = Clinical Global Impression-Severity; I² = I-squared; ND = no difference; NE = not estimable; PANSS = Positive and Negative Symptom Scale

Table 32. Strength of evidence (GRADE): haloperidol versus asenapine

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Positive Symptoms						
PANSS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Negative Symptoms						
PANSS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
General Psychopathology						
CDS-S	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
PANSS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Global Ratings and Total Scores						
CGI-S	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
PANSS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

CDS-S = Calgary Depression Scale for Schizophrenia; CGI-S = Clinical Global Impression-Severity; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; RoB = risk of bias; SoE = Strength of Evidence

Haloperidol Versus Clozapine

Key Points

- Nine studies compared haloperidol with clozapine and involved patients with varying disease severity.
- Four studies assessed total scores using BPRS and three studies using PANSS. No differences were found between groups for either scale. Results were statistically heterogeneous for the PANSS total score, with one trial showing a significant difference favoring clozapine. This trial included patients with treatment-refractory schizophrenia and a history of high use of inpatient services; further, the study had a longer duration of followup (12 months vs. 12–14 weeks). The SoE was low for both BPRS and PANSS.
- The remaining outcomes were assessed in only one to two trials each; all showed no significant differences between study groups, except for CGI-I and CGI-S in a single study.

Nine RCTs^{55,62,70,95,103,105,126,145,155} (n = 1,000) compared haloperidol with clozapine. Key characteristics of the included trials and summary of findings are presented in Table 33 and Table 34, respectively. All trials included various disorder subtypes, except for one study¹⁰³ that included only patients with paranoid schizophrenia; four studies^{70,95,105,145} specifically included patients with schizoaffective disorders. Five trials^{55,62,95,126,145} included patients with treatment-resistant schizophrenia, and one study¹⁰⁵ specifically excluded treatment-resistant patients. Five

trials^{55,62,95,126,145} included only patients with multiple episodes. Two trials^{55,95} specifically excluded patients with comorbid drug or alcohol use. The dosages varied across studies, ranging from 2.25 to 30 mg/d for haloperidol and 12.5 to 900 mg/d for clozapine.

Risk of bias was unclear for all but two studies,^{62,95} which were high. Five studies were funded; by producers of clozapine,^{62,95} both haloperidol and clozapine,^{126,145} or makers of other antipsychotics.¹⁰⁵ Duration of followup varied: <6 weeks for one study;¹⁰³ between 6 weeks and 6 months for five studies;^{55,62,105,145,155} and >6 months for three studies.^{70,95,126}

Publication bias was not formally tested for any of the outcomes due to the small number of included trials. The SoE for the majority of the evaluated outcomes was insufficient to low due to the small number of trials in individual outcomes assessments (Table 35).

Table 33. Characteristics of RCTs comparing haloperidol versus clozapine in the treatment of schizophrenia and related psychoses

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Run-in Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Breier et al. 1994 ⁵⁵ RCT (10 wks)	G1: HAL (10–30mg/d); (37) G2: CLO (200–600mg/d); (38) Run-in phase: 6 wks	Chronic Sz not responding to 6 wks of FLU	Unclear, Government
Citrome et al. 2001 ⁶² RCT (14 wks)	G1: HAL (10–30mg/d); (37) G2: CLO (200–800mg/d); (40) Run-in phase: 1 wk	Sz w/ suboptimal tx response; no depot AP <1 mo	High, Industry
Covington et al. 2000 ⁷⁰ RCT (24 mo)	G1: HAL (NR); (42) G2: CLO (NR); (40)	Sz or schizoaffective disorder	Unclear, Government
Itoh et al. 1977 ¹⁵⁵ RCT (12 wks) Kane et al. 2001 ⁹⁵ RCT (29 wks)	G1: HAL (5–16mg/d); (34) G2: CLO (12.5–800mg/d); (37)	Sz/ schizoaffective disorder, poor response (tx failure in >2 trials of conventional AP)	High, Industry
Klieser et al. 1994 ¹⁰³ RCT (4 wks)	G1: HAL (16mg/d); (17) G2: CLO (350mg/d); (17)	Acute paranoid Sz; no previous AP tx	Unclear, NR
Krakowski et al. 2006 ¹⁰⁵ RCT (12 wks)	G1: HAL (10–30mg/d); (36) G2: CLO (200–800mg/d); (37) Run-in phase: 1–2 wks	Schizophrenia or schizoaffective disorder; not hospitalized >1 yr or hx of nonresponse to CLO, OLA, or HAL	Unclear, Multiple sources including industry
Rosenheck et al. 1997 ¹²⁶ RCT (12 mo)	G1: HAL (5–30mg/d); (218) G2: CLO (10–900mg/d); (205)	Tx refractory Sz; hx of high level of use of inpatient services	Unclear, Multiple sources including industry
Volavka et al. 2002 ¹⁴⁵ RCT (14 wks)	G1: HAL (10–30mg/d); (37) G2: CLO (200–800mg/d); (40)	Chronic Sz or schizoaffective disorder and suboptimal response to previous tx	Unclear, Multiple sources

AP(s) = antipsychotic(s); CLO = clozapine; D = days; FLU = fluphenazine; G = group; HAL = haloperidol; Hr(s) = hour(s); Hx = history; Mg = milligrams; Mo = month; NR = not reported; OLA = olanzapine; RCT = randomized controlled trial; Sz = schizophrenia; Tx = treatment; W/ = with; Wk(s) = week(s); Yr(s) = year(s)

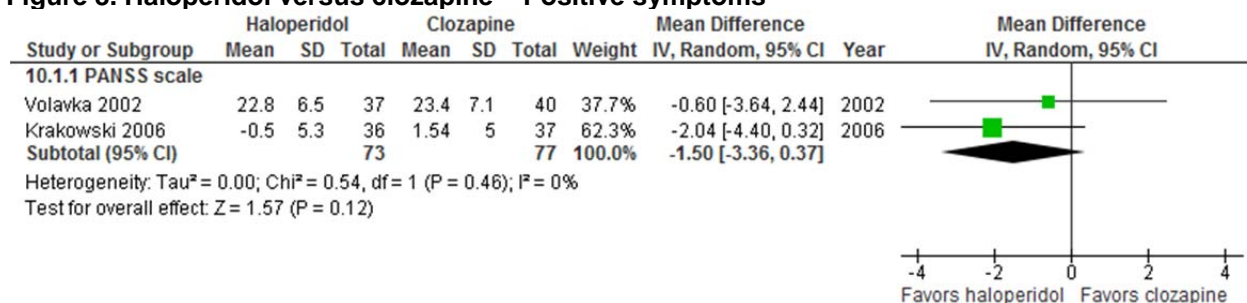
Key Question 1. Improving Core Illness Symptoms

Positive Symptoms

Two trials^{105,145} (n = 150) assessed positive symptoms using PANSS (positive) and found no significant differences between groups (Table 34; Figure 8). The studies specifically included schizoaffective patients. One study¹⁴⁵ specifically included patients with multiple episodes with treatment resistance whereas the other study¹⁰⁵ excluded patients with treatment resistance. The doses of haloperidol (10–30 mg/d) and clozapine (200–800 mg/d) were consistent across studies.

Duration of followup was relatively consistent, ranging from 12 to 14 weeks. Risk of bias was unclear for both studies, and both were industry-funded. The SoE was low for PANSS (positive) (Table 35).

Figure 8. Haloperidol versus clozapine – Positive symptoms



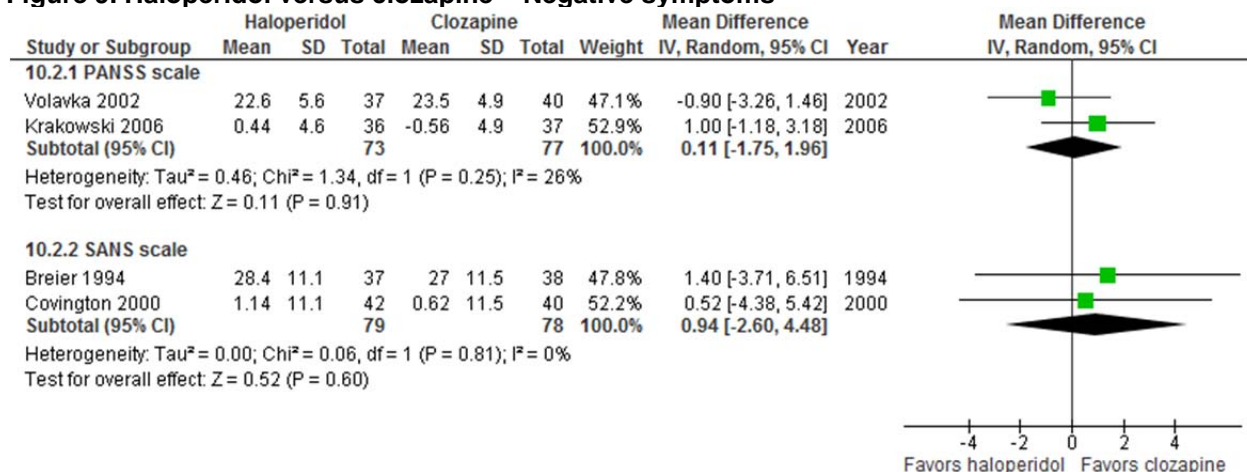
CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale; SD = standard deviation

Negative Symptoms

Four trials^{55,70,105,145} (n = 307) compared haloperidol (10–30 mg/d) with clozapine (200–800 mg/d). Three^{70,105,145} of the four trials specifically included patients with schizoaffective disorders. Two studies included only patients with multiple episodes,^{55,145} whereas the other two trials included mixed first and multiple episodes. Two studies included only treatment-resistant patients assessed by history¹⁴⁵ and run-in,⁵⁵ one study¹⁰⁵ specifically excluded treatment-resistant patients. One trial⁵⁵ specifically excluded patients with comorbid drug or alcohol use. The drug doses were consistent in three studies, but not reported in one.⁷⁰ Duration of followup was 10 to 14 weeks for three studies and 24 months for the fourth.⁷⁰ Risk of bias was unclear for all studies; two studies were industry-funded^{105,145} and two^{55,70} were government-funded.

No significant differences between groups were found based on PANSS (negative)^{55,70} and SANS^{55,70} (Table 34; Figure 9). The SoE for both scales was graded as low (Table 35).

Figure 9. Haloperidol versus clozapine – Negative symptoms



CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale; SANS = Scale for the Assessment of Negative Symptoms; SD = standard deviation

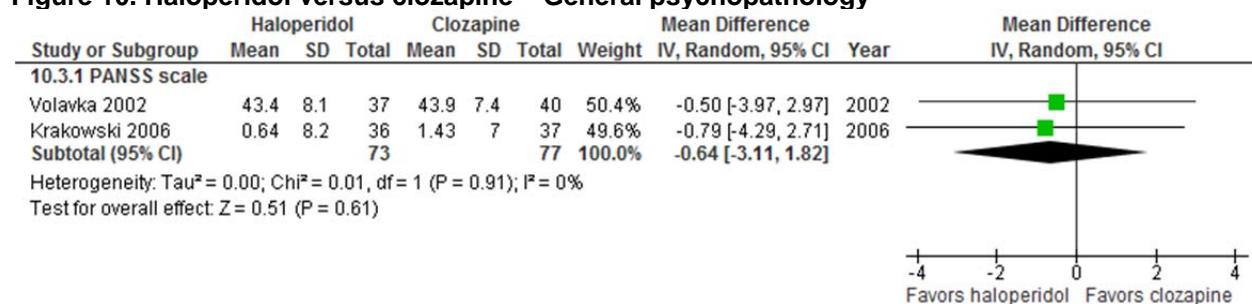
General Psychopathology

Two trials^{105,145} (n = 150) used the PANSS (general psychopathology). Both trials specifically included patients with schizoaffective disorders. One trial¹⁴⁵ included only patients with multiple episodes, whereas the other study included patients with both first and multiple episodes. Treatment-resistant patients were included in one study¹⁴⁵ and excluded in the other. Both trials used the same doses of study drugs. Duration of followup was also consistent (12 and 14 weeks, respectively). Both studies had unclear risk of bias and were industry-funded.

The studies were consistent in their treatment estimates, and pooled results showed no significant difference between groups for general psychopathology (Table 34; Figure 10). The SoE was graded as low (Table 35).

One¹⁰⁵ of the above studies also reported results of the Modified Overt Aggression Scale (MOAS) and found no difference between groups (insufficient SoE).

Figure 10. Haloperidol versus clozapine – General psychopathology



CI = confidence intervals; df = degrees of freedom; I² = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale; SD = standard deviation

Global Ratings and Total Score

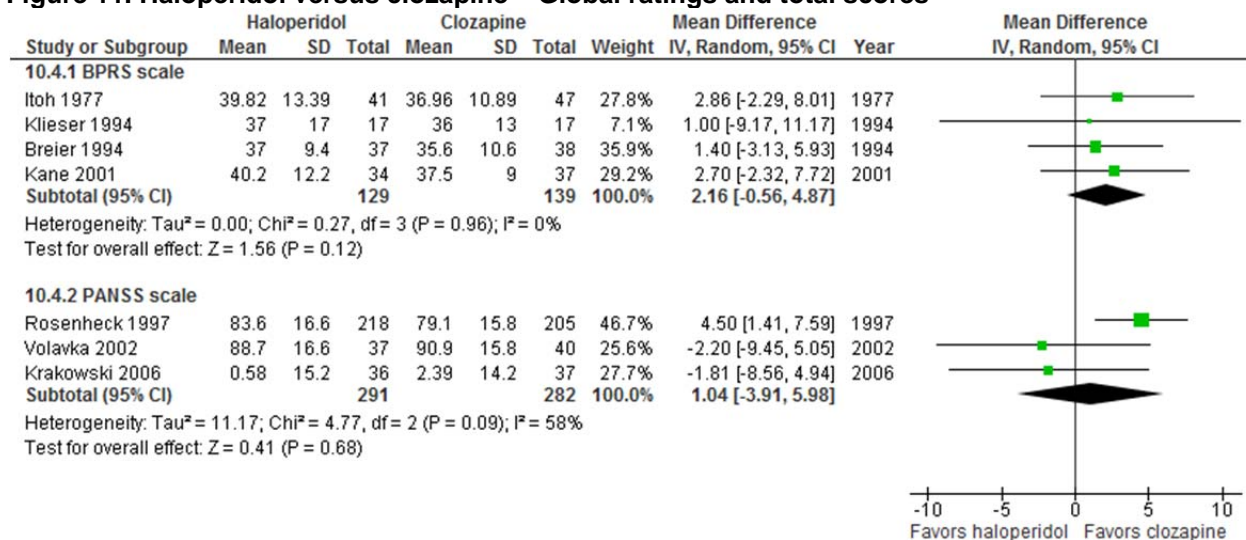
Seven trials^{55,95,103,105,126,145,155} (n = 841) reported global ratings and total scores using four different scales. Four studies^{55,95,103,155} used BPRS and reported consistent findings, with a pooled estimate showing no significant difference between groups (Table 34; Figure 11). These studies included varied disorder subtypes: paranoid schizophrenia,¹⁰³ schizoaffective disorders,⁹⁵ and mixed.^{55,155} Two studies^{55,95} included only patients with multiple episodes and treatment resistance and specifically excluded patients with comorbid alcohol or drug use. Duration of followup ranged from 4 weeks¹⁰³ to 29 weeks.⁹⁵ Risk of bias was unclear in all but one study,⁹⁵ which was high. Source of funding was not reported in two studies;^{103,155} one study⁹⁵ was industry-funded and one was government-funded.⁵⁵

Three studies used PANSS (total score).^{105,126,145} The pooled estimate showed no significant difference between groups (Table 34; Figure 11); however, the statistical heterogeneity was substantial. Moreover, one of the studies¹²⁶ showed a significant difference in favor of clozapine, whereas the other two studies showed no significant difference. Removing this one study from the analysis reduced the heterogeneity to 0 percent, and the result remained nonstatistically significant. The trial differed from the other two with respect to several clinical and study characteristics. The two studies with similar estimates specifically included patients with schizoaffective disorders. The study that differed had a greater range of dosing: 5–30 mg/d versus 10–30 mg/d for haloperidol and 100–900 mg/d versus 200–800 mg/d for clozapine. Duration of followup differed substantially: 12 to 14 weeks for the two similar studies^{105,145} versus 12 months.¹²⁶ All studies had unclear risk of bias and were funded by industry.

One study⁹⁵ assessed global rating scores using CGI-I and CGI-S (Table 34). The study included patients with schizoaffective disorder, multiple episodes, and treatment resistance. Patients with comorbid drug or alcohol use were specifically excluded. The doses were 5–16 mg/d for haloperidol and 12.5–800 mg/d for clozapine. Duration of followup was 29 weeks. The risk of bias was high, and the study was industry-funded. The results for both scales were statistically significant in favor of clozapine.

The SoE for BPRS and PANSS was graded as low; CGI-I and CGI-S were graded as insufficient (Table 35).

Figure 11. Haloperidol versus clozapine – Global ratings and total scores



BPRS = Brief Psychiatric Rating Scale; CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale; SD = standard deviation

Key Questions 2 and 4. Improvement in Functional Outcomes, Decreasing Health Care System Utilization, and Other Outcomes

Health Care System Utilization

One trial¹²⁶ ($n = 423$) in patients with treatment-refractory schizophrenia compared haloperidol (5–30 mg/d) with clozapine (10–900 mg/d) and reported no significant differences in duration of hospital stay between groups (Table 34).

Other Outcomes

One trial examining treatment-resistant patients with mixed disorder subtypes, multiple episodes, and no comorbid alcohol or drug use reported no significant difference in relapse rates (Table 34).⁵⁵ The study compared 5–16 mg/d haloperidol with 12.5–800 mg/d clozapine and followed patients for 29 weeks. Risk of bias was unclear, and the trial was government-funded.

Two studies assessed treatment response^{95,105} and found no significant difference overall; however, there was substantial statistical heterogeneity. One study⁹⁵ showing a positive effect in favor of clozapine included patients with schizoaffective disorders, multiple episodes, treatment resistance, and no comorbid drug or alcohol use. The study compared 5–16 mg/d haloperidol with 12.5–800 mg/d clozapine. Duration of followup was 29 weeks. The study had high risk of bias and was industry-funded. This study also examined remission rates and found no significant

difference between groups. The second study¹⁰⁵ showed no significant difference between groups. It also included patients with schizoaffective disorders and multiple episodes; however, it included patients with both first and multiple episodes and excluded treatment-resistant patients. The risk of bias was unclear, and the trial was industry-funded.

Finally, one study¹⁰³ assessed patient satisfaction and found no significant difference between groups. The study included mixed disorder subtypes and patients with multiple episodes, treatment resistance, and no comorbid alcohol or drug use. The study compared 10–30 mg/d haloperidol with 200–600 mg/d clozapine and followed patients for 10 weeks. The risk of bias was unclear, and the study was government-funded.¹⁰³

Key Question 5. Subgroups

Disorder Subtypes and Treatment Naïve

One trial¹⁰³ (n = 34) in treatment-naïve patients with paranoid schizophrenia compared 16 mg/d haloperidol with 12.5–800 mg/d clozapine and found no significant difference on BPRS.

Treatment Resistance

Five trials^{55,62,95,126,145} (n = 88) in patients with treatment-refractory schizophrenia compared 5–30 mg/d haloperidol with 12.5–900 mg/d clozapine and found no significant differences for positive symptoms (PANSS (positive)¹⁴⁵), negative symptoms (PANSS (negative),¹⁴⁵ SANS⁵⁵), general psychopathology (PANSS (general psychopathology)¹⁴⁵), or general ratings and total scores (BPRS,^{55,95} PANSS (total)^{126,145}). There were significant differences in favor of clozapine in one trial⁹⁵ for the general rating scale CGI-I (MD = 0.80; 95% CI, 0.26 to 1.34) and CGI-S (MD = 0.60; 95% CI, 0.13 to 1.07). This was not clinically significant.

Table 34. Evidence summary table: haloperidol versus clozapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Positive Symptoms					
PANSS ^{105,145}	2	147	-1.51 (-3.39, 0.37)	0%	ND
Negative Symptoms					
PANSS ^{105,145}	2	150	0.11 (-1.75, 1.96)	26%	ND
SANS ^{55,70}	2	157	0.94 (-2.60, 4.48)	0%	ND
General Psychopathology					
MOAS ¹⁰⁵	1	73	17.60 (-2.25, 37.45)	NE	ND
PANSS ^{105,145}	2	150	-0.64 (-3.11, 1.82)	0%	ND
Global Ratings and Total Scores					
BPRS ^{55,95,103,155}	4	268	2.16 (-0.56, 4.87)	0%	ND
CGI-I ⁹⁵	1	71	0.80 (0.26, 1.34)	NE	clozapine
CGI-S ⁹⁵	1	71	0.60 (0.13, 1.07)	NE	clozapine
PANSS ^{105,126,145}	3	573	1.04 (-3.91, 5.98)	58%	ND
Health Care System Utilization					
Mean hospital bed days ¹²⁶	1	423	-7.10 (-19.02, 4.82)	NE	ND
Other Outcomes					
Relapse rates ⁵⁵	1	75	0.68 (0.12, 3.87)*	NE	ND
Response rates ^{95,105}	2	144	0.64 (0.28, 1.47)*	72%	ND
Remission rates ⁹⁵	1	71	0.16 (0.02, 1.20)*	NE	ND
Patient satisfaction ¹⁰³	1	34	0.82 (0.46, 1.45)*	NE	ND

Note: bolded results are statistically significant; * = binary outcome; BPRS = Brief Psychiatric Rating Scale; CGI-I = Clinical Global Impression–Improvement; CGI-S = Clinical Global Impression–Severity; I² = I-squared; MOAS = Modified Overt Aggression Scale; ND = no difference; NE = not estimable; PANSS = Positive and Negative Symptom Scale; SANS = Scale for the Assessment of Negative Symptoms

Table 35. Strength of evidence (GRADE): haloperidol versus clozapine

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Positive Symptoms						
PANSS	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
Negative Symptoms						
PANSS	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
SANS	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
General Psychopathology						
MOAS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
PANSS	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
Global Ratings and Total Scores						
BPRS	4 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
CGI-I	1 RCT	Medium	Consistent	Direct	Precise	Insufficient
CGI-S	1 RCT	Medium	Consistent	Direct	Precise	Insufficient
PANSS	3 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)

BPRS = Brief Psychiatric Rating Scale; CGI-I = Clinical Global Impression–Improvement; CGI-S = Clinical Global Impression–Severity; MOAS = Modified Overt Aggression Scale; PANSS = Positive and Negative Symptom Scale; ND = No difference; RCT = randomized controlled trial; RoB = risk of bias; SANS = Scale for the Assessment of Negative Symptoms; SoE = Strength of Evidence

Haloperidol Versus Olanzapine

Key Points

- Twenty-nine studies compared haloperidol with olanzapine in patients with a range of illness severity.
- Sixteen studies reported positive symptoms using two different scales: PANSS (14 studies) and SAPS (2 studies). For both scales, the pooled results showed no differences between groups, and the SoE was low.
- Eighteen studies assessed negative symptoms using two scales: PANSS (14 studies) and SANS (5 studies). For both scales, results significantly favored olanzapine and in both cases the differences between groups were considered to be clinically important. The SoE was moderate for both scales.
- Eighteen studies reported general psychopathology using eight scales. Ten studies used the PANSS and found no differences between groups. Six studies used the Montgomery-Asberg Depression Rating Scale (MADRS) and found results significantly favored olanzapine, which was considered to be clinically relevant. Three studies used the Hamilton Rating Scale for Depression (HAM-D) and Calgary Depression Scale for Schizophrenia (CDS-S); only the HAM-D was found to significantly favor olanzapine. This difference was considered to be clinically significant. Two studies used the Agitated Behavior Scale (ABS), ACES, and HAM-A and found no differences. A single study used the Young Mania Rating Scale (YMRS) and showed no difference between groups. The SoE ranged from low to moderate.
- Twenty-two studies assessed global ratings and total scores using six scales: PANSS (15 studies), BPRS (13 studies), CGI-S (8 studies), CGI-I (2 studies), GAF (1 study), and Subjective Well-Being Under Neuroleptics scale (1 study). In all cases no significant differences were found except for the PANSS (total score), which showed a significant difference favoring olanzapine. This was considered to be clinically significant. Results for BPRS and CGI-S showed substantial statistical heterogeneity which may be partially explained by treatment resistance: when studies that included only patients with treatment resistance were removed from the analysis for BPRS, the results were homogeneous and

avored olanzapine. Removing one trial with first episode patients (not treatment resistant) from the analysis for CGI-S reduced the heterogeneity and results favored olanzapine. The SoE was moderate for PANSS and CGI-S, low for BPRS and CGI-I, and insufficient for the remaining scales.

- Response rates were assessed in 14 studies and showed a significant benefit for olanzapine. The statistical heterogeneity was substantial. As above, when studies that included only patients with treatment resistance were removed from the analysis, the results were homogeneous and favored olanzapine.
- Remission rates were assessed in three studies and showed a significant benefit for olanzapine.
- Five studies assessed health-related quality of life and showed no significant differences between groups.
- Other outcomes were assessed in single trials and showed no differences between groups.

Twenty-nine RCTs^{43,49-51,54,56,58,71,73,75,78,88,91,101,102,104-106,108,110,124,127,129,130,136,141,145,147,159} (n = 5,750) compared haloperidol with olanzapine. Key characteristics of the included trials and summary of findings are presented in Table 36 and Table 37, respectively. One trial⁴³ included patients with paranoid schizophrenia, five studies^{58,73,91,127,145} specifically included patients with schizoaffective disorder, and the remaining studies included mixed disorder subtypes. All studies included patients with both first and multiple episodes. Nine studies^{51,58,73,78,105,110,130,141,145} included only patients with treatment resistance, which was ascertained from history in all cases. Three studies^{91,124,129} specifically excluded patients with treatment resistance. Two studies^{130,136} specifically included patients with comorbid alcohol or drug use, whereas nine studies^{49-51,54,56,58,71,124,129} excluded patients with drug or alcohol use. Drug doses varied substantially across studies: from 1–4 mg/d⁷⁵ to 10–30 mg/d^{58,105} for haloperidol and from 1–17.5mg/d⁴⁹ to 5–40 mg/d⁷³ for olanzapine. All studies included adults ranging in age from 18 to 64, except one study⁷⁸ that included only patients 17 to 28 years of age. Two studies^{102,104} only included Asian patients.

Risk of bias was unclear for 19 studies^{43,49-51,54,56,78,88,101,102,104-106,108,110,124,127,145,147} and high for 10 studies.^{58,71,73,75,91,129,130,136,141,159} Duration of followup varied across studies: ≤6 weeks for 9 studies,^{51,56,71,73,78,106,129,136,147} between 6 weeks and 6 months for 11 studies;^{43,54,58,88,102,104,105,110,130,145,159} and ≥6 months for 9 studies.^{49,50,75,91,101,108,124,127,141} Source of funding included: government (3 studies);^{78,106,130} company that produces olanzapine (18 studies);^{43,49-51,54,56,58,101,104,105,108,110,124,127,136,141,147,159} multiple companies, including producer of haloperidol (2 studies);^{75,91} and multiple companies including producers of both drugs (1 studies).¹⁴⁵

Publication bias was assessed for outcomes with at least 10 studies, and results are reported in the sections that follow. The SoE for the evaluated outcomes varied from insufficient to moderate mainly depending on the number of included trials and heterogeneity among the included trials (Table 38).

For each outcome, we examined whether differences existed for the various clinical characteristics (disorder subtypes, inclusion or exclusion of patients with schizoaffective disorder, sex, age group, race, comorbidities, previous exposure to antipsychotics, and treatment resistance), study characteristics (drug dose, followup period, and study sponsorship), and analytic methods (risk of bias and imputed data). When pooled estimates showed evidence of statistical heterogeneity, we report on any subgroups that had an effect on heterogeneity. All

other subgroups showed no effect. Appendix M (Tables 96–102) provides detailed tables on all subgroup analyses.

Table 36. Characteristics of RCTs comparing haloperidol versus olanzapine in the treatment of schizophrenia and related psychoses

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout/ Run-in Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Altamura et al. 2002 ⁴³ RCT (14 wks)	G1: HAL (10–20mg/d); (15) G2: OLA (10–20mg/d); (13) Washout period: 1 wk	Paranoid Sz with partial response to AP after ≥ 6 wks of different classes	Unclear, Industry
Avasthi et al. 2001 ¹⁵⁹ RCT (12 wks)	G1: HAL (5–20mg/d); (10) G2: OLA (5–20mg/d); (17)	Sz; CGI–S score >3	Unclear, Industry
Beasley et al. 1996 ⁴⁹ RCT (1 yr)	G1: HAL (10–20mg/d); (69) G2: OLA (2.5–7.5mg/d); (65) G3: OLA (7.5–12.5mg/d); (64) G4: OLA (12.5–17.5mg/d); (69) Washout period: variable depending on medication Run-in phase: <1 wk	Sz with acute exacerbation	Unclear, Industry
Beasley et al. 1997 ⁵⁰ RCT (1 yr)	G1: HAL (15 \pm 5mg/d); (81) G2: OLA (1.0mg/d); (88) G3: OLA (5 \pm 2.5mg/d); (87) G4: OLA (10 \pm 2.5mg/d); (86) G5: OLA (15 \pm 2.5mg/d); (89) Washout period: oral: >2 d; depot: >2 wks Run-in phase: 4–7 d	Sz with acute exacerbation	Unclear, Industry
Bernardo et al. 2001 ⁵¹ RCT (4 wks)	G1: HAL (10mg/d); (13) G2: OLA (10mg/d); (14) Washout period: 1 wk	Sz/ schizophreniform disorder; no depot AP <6 mo	Unclear, Industry
Boulay et al. 2007 ⁵⁴ RCT (56 d)	G1: HAL (2.5–20mg/d); (11) G2: OLA (2.5–20mg/d); (14) Washout period: 3 d	Sz not further identified; no depot AP <6 mo	Unclear, Industry
Breier et al. 2002 ⁵⁶ RCT (24 hrs)	G1: HAL (7.5mg); (40) G2: OLA (2.5mg); (48) G3: OLA (5.0mg); (45) G4: OLA (7.5mg); (46) G5: OLA (10mg); (46) Washout period: 2–24 hrs	Hospitalized; Sz, schizophreniform disorder, schizoaffective disorder	Unclear, Industry
Buchanan et al. 2005 ⁵⁸ RCT (16 wks)	G1: HAL (10–30mg/d); (34) G2: OLA (10–30mg/d); (29) Run-in phase: 4 wks	Sz/ schizoaffective disorder with partial response to conventional APs, demonstrated $>30\%$ improvement on FLU, relapsed, or were intolerant of FLU during run-in phase	High, Multiple sources including industry
Crespo-Facorro et al. 2006 ⁷¹ RCT (6 wks)	G1: HAL (3–9mg/d); (56) G2: OLA (5–20mg/d); (55) Washout period: 3–5 d	Sz with no AP <6 wks	High, Multiple sources
Davidson et al. 2009 ⁷⁵ RCT (6 mo)	G1: HAL (1–4mg/d); (103) G2: OLA (5–20mg/d); (105)	<2 yrs since onset of positive symptoms; <2 wks exposure to AP <1 yr; <6 wks lifetime exposure to AP	High, Industry
de Haan et al. 2003 ⁷⁸ RCT (6 wks)	G1: HAL (2.5mg/d); (12) G2: OLA (7.5mg/d); (12)	Sz; hx of unresponsiveness to HAL or OLA; no IM AP <1 yr	Unclear, Government
Ishigooka et al. 2001 ⁸⁸ RCT (8 wks)	G1: HAL (4–12mg/d); (89) G2: OLA (5–15mg/d); (93) Washout period: 2–4 wks	Sz; no tx with HAL, OLA or other investigational AP <3 mo; study AP contraindications	Unclear, NR

Table 36. Characteristics of RCTs comparing haloperidol versus olanzapine in the treatment of schizophrenia and related psychoses (continued)

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout/ Run-in Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Keefe et al. 2006 ¹⁰¹ RCT (52 wks)	G1: HAL (2–19mg/d); (97) G2: OLA (5–20mg/d); (159)	Sz/ schizoaffective disorder; no previous AP \leq 1 mo	Unclear, Industry
Kim et al. 2010 ¹⁰² RCT (8 wks)	G1: HAL (15.9 \pm 7.1mg/d); (35) G2: OLA (15.9 \pm 4.3mg/d); (32) Washout period: >4wks	Sz not further defined	Unclear, Foundation
Kongsakon et al. 2006 ¹⁰⁴ RCT (24 wks)	G1: HAL (5–20 mg); (132) G2: OLA (5–20 mg); (144) Washout period: 2–9 d	Sz not further defined	Unclear, Industry
Krakowski et al. 2006 ¹⁰⁵ RCT (12 wks)	G1: HAL (10–30mg/d); (36) G2: OLA (10–35mg/d); (37) Run-in phase: 1–2 wks	Sz or schizoaffective disorder; not hospitalized >1 yr or hx of nonresponse to CLO, OLA, or HAL	Unclear, Multiple sources including industry
Lahti et al. 2009 ¹⁰⁶ RCT (6 wks)	G1: HAL (10–20mg/d); (14) G2: OLA (12.5–25mg/d); (18) Washout period: 2 wks	Sz defined by DSM–III–R	Unclear, Government
Lieberman et al. 2003 ¹⁰⁸ RCT (104 wks)	G1: HAL (2–20mg/d); (132) G2: OLA (5–20mg/d); (131) Washout period: <2 wks	Sz, schizophreniform, or schizoaffective disorder; onset <35 yrs; no AP drug tx >16 wks, previous CLO tx, or depot AP <3 dosing intervals	Unclear, Industry
Lindenmayer et al. 2007 ¹¹⁰ RCT (12 wks)	G1: HAL (5–20mg/d); (19) G2: OLA (5–20mg/d); (16) Washout period: 1 wk cross-titration from previous AP	Sz defined by DSM–IV–TR	Unclear, Industry
McCue et al. 2006 ⁷³ RCT (3 wks)	G1: HAL (4–30mg); (61) G2: OLA (5–40 mg); (58)	Sz, schizoaffective disorder, or schizophreniform disorder; no hx of response or lack of response to AP, BP, major depression, or substance-induced psychotic disorder	High, No external funding
Purdon et al. 2000 ¹²⁴ RCT (54 wks)	G1: HAL (5–20mg/d); (23) G2: OLA (5–20mg/d); (21) Washout period: 2–9 d Run-in phase: 1 mo	Sz <5 yrs of 1st exposure to AP; mild symptom severity	Unclear, Industry
Rosenheck et al. 2003 ¹²⁷ RCT (12 mo)	G1: HAL (5–20mg/d); (150) G2: OLA (5–20mg/d); (159)	Sz/ schizoaffective disorder; OP w/ hx of psychiatric hospitalization <2 yrs	Unclear, Industry
Saddichha et al. 2008 ¹²⁹ NRCT (6 wks)	G1: HAL (13.4 \pm 3.6mg/d); (31) G2: OLA (16.5 \pm 4.6mg/d); (35)	1st episode Sz; AP drug-naïve	High, NR
Sayers et al. 2005 ¹³⁰ RCT (26 wks)	G1: HAL (10–20mg/d); (12) G2: OLA (10–20mg/d); (12)	Sz and current cocaine abuse <6 mo; no depot AP <6 mo	High, Government
Smelson et al. 2006 ¹³⁶ RCT (6 wks)	G1: HAL (5–20mg/d); (15) G2: OLA (5–20mg/d); (16)	Sz; cocaine dependent; no DSM–IV criteria for other Axis I disorder	High, Industry
Tollefson et al. 1997 ¹⁴¹ RCT (14 mo)	G1: HAL (5–20mg/d); (660) G2: OLA (5–20mg/d); (1336)	Sz; intolerant of current AP therapy (excluding HAL)	High, Industry

Table 36. Characteristics of RCTs comparing haloperidol versus olanzapine in the treatment of schizophrenia and related psychoses (continued)

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout/ Run-in Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Volavka et al. 2002 ¹⁴⁵ RCT (14 wks)	G1: HAL (10–30mg/d); (37) G2: OLA (10–40mg/d); (39)	Chronic Sz or schizoaffective disorder and suboptimal response to previous tx	Unclear, Multiple sources
Wright et al. 2001 ¹⁴⁷ RCT (24 hrs)	G1: HAL (7.5 mg); (126) G2: OLA (10 mg); (131)	Sz, schizophreniform disorder, or schizoaffective disorder	Unclear, Industry

AP(s) = antipsychotic(s); BP = bipolar; CGI-S = Clinical Global Impression Severity Scale; CLO = clozapine; D = day; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders – IV; FLU = fluphenazine; G = group; HAL = haloperidol; Hr(s) = hour(s); Hx = history; IM = intramuscular; Mg = milligrams; Mo = month; NR = not reported; OLA = olanzapine; OP = outpatient; RCT = randomized controlled trial; Sz = schizophrenia; Tx = treatment; Wk(s) = week(s); Yr(s) = year(s)

Key Question 1. Improving Core Illness Symptoms

Positive Symptoms

Sixteen trials^{50,51,54,71,88,101,102,104,105,108,110,124,136,141,145,159} (n = 3,920) reported no difference in positive symptoms using two scales (Table 37; Figure 12). The SoE for both scales was graded as low (Table 38).

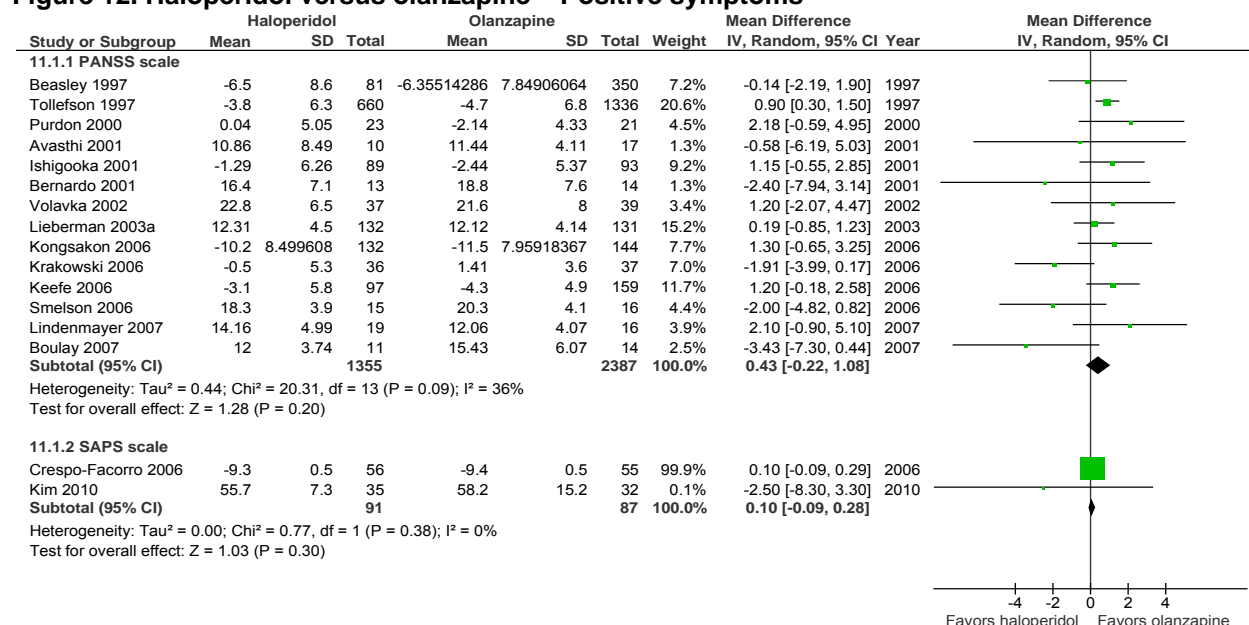
Fourteen trials^{50,51,54,88,101,104,105,108,110,124,136,141,145,159} (n = 3,742) used PANSS (positive). Pooled results showed no significant difference between groups; however, there was moderate statistical heterogeneity ($I^2 = 36$ percent). Restricting the analyses to the following subgroups reduced the heterogeneity:

- Mixed populations regarding comorbid drug or alcohol use: significantly favored olanzapine ($I^2 = 17$ percent);
- Olanzapine doses of ≤ 20 mg and haloperidol doses of ≤ 20 mg: significantly favored olanzapine ($I^2 = 23$ percent);
- Duration of followup > 6 months: significantly favored olanzapine ($I^2 = 0$ percent);
- No imputed data: significantly favored olanzapine ($I^2 = 17$ percent).

The tests for publication bias were not significant, although the funnel plot appeared slightly asymmetrical, with studies showing larger effects for haloperidol (Appendix K, Funnel plot 1).

Two trials^{71,102} (n = 178) showed no significant difference between groups based on SAPS. There was no evidence of statistical heterogeneity between the studies ($I^2 = 0$ percent).

Figure 12. Haloperidol versus olanzapine – Positive symptoms



CI = confidence intervals; df = degrees of freedom; I² = I-squared; IV = inverse variance; SD = standard deviation

Negative Symptoms

Eighteen trials,^{49-51,54,58,71,88,101,102,104,105,108,110,124,136,141,145,159} (n = 4,250) reported significant differences in favor of olanzapine on negative symptoms using two scales (Table 37; Figure 13). The SoE for these scales was graded as moderate (Table 38).

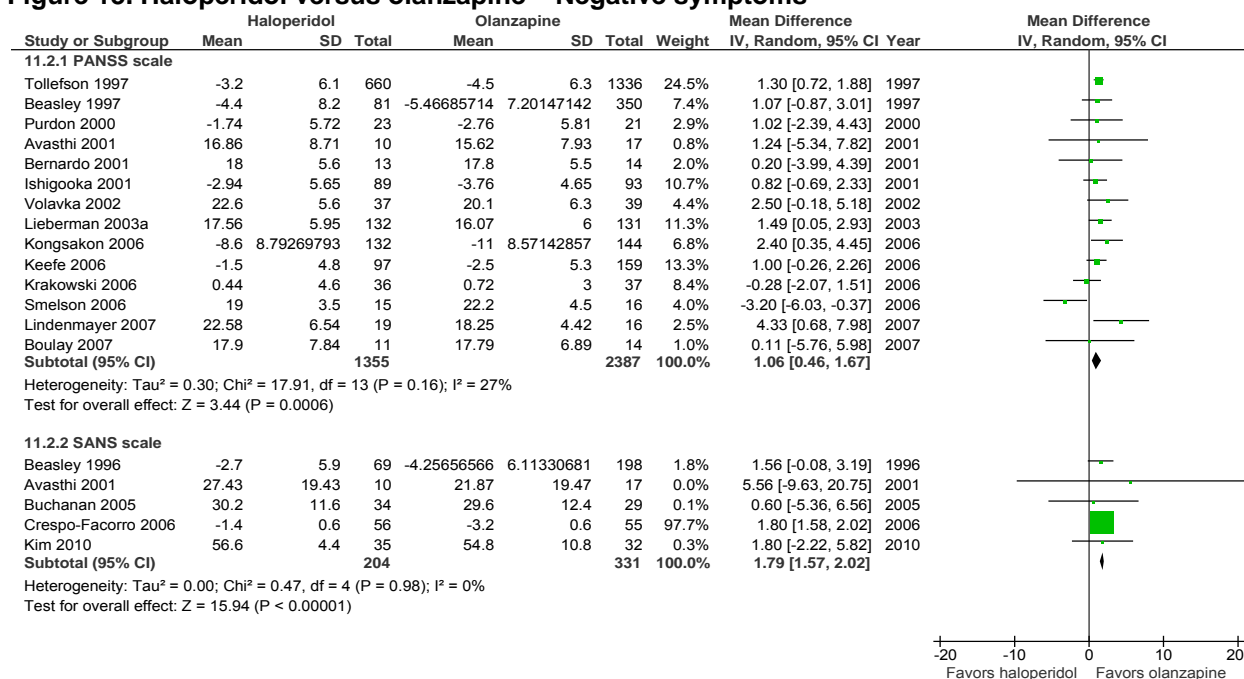
Fourteen studies (n = 3,742) used PANSS (negative).^{50,51,54,88,101,104,105,108,110,124,136,141,145,159} Pooled estimates were significantly different between groups in favor of olanzapine, which was considered to be clinically significant. The results showed moderate statistical heterogeneity (I² = 27 percent). Restricting the analyses to the following subgroups reduced the heterogeneity:

- Mixed populations regarding comorbid drug or alcohol use: significantly favored olanzapine (I² = 2 percent);
- Followup greater than 6 months (5 studies): significantly favored olanzapine (I² = 0 percent);
- Unclear risk of bias (11 studies): significantly favored olanzapine (I² = 0 percent).

There was no indication of publication bias based on statistical tests or visual examination of the funnel plot (Appendix K, Funnel plot 2).

Five trials^{49,58,71,102,159} (n = 535) used SANS and reported significant results favoring olanzapine, which was considered to be clinically significant. There was no evidence of statistical heterogeneity across trials (I² = 0 percent).

Figure 13. Haloperidol versus olanzapine – Negative symptoms



CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale; SANS = Scale for the Assessment of Negative Symptoms; SD = standard deviation

General Psychopathology

Eighteen studies^{50,54,56,58,71,78,88,91,101,105,108,110,124,136,141,145,147,159} ($n = 4,327$) assessed a range of other symptoms using eight scales (Table 37; Figure 14).

Ten trials^{50,54,88,105,108,110,124,136,145,159} ($n = 1,187$) showed no difference based on PANSS (general psychopathology); however, the statistical heterogeneity was substantial ($I^2 = 52$ percent). Restricting the analyses to the following subgroups reduced the heterogeneity:

- Mixed populations regarding comorbid drug or alcohol use: no difference between groups ($I^2 = 25$ percent);
- Studies that excluded comorbid drug or alcohol use: no difference between groups ($I^2 = 25$ percent);
- Followup >6 months (4 studies): significantly favored olanzapine ($I^2 = 0$ percent);
- Unclear risk of bias (8 studies): no difference between groups ($I^2 = 33$).

There was no suggestion of publication bias based on statistical tests or visual inspection of the funnel plot (Appendix K, Funnel plot 3).

Three trials^{58,71,110} ($n = 209$) used the HAM-D; the pooled results were significant in favor of olanzapine and showed no statistical heterogeneity ($I^2 = 0$ percent). This was considered to be clinically significant.

Six trials^{78,101,105,108,141,159} ($n = 2,639$) used the MADRS. The pooled estimate showed significant results favoring olanzapine; there was no statistical heterogeneity across the studies ($I^2 = 0$ percent). This was considered to be clinically significant.

Three trials^{54,71,91} ($n = 344$) reported CDS-S; the pooled result was not statistically significant, however the statistical heterogeneity was substantial ($I^2 = 73$ percent). One study⁷¹ showed a significant benefit of olanzapine, whereas the other studies^{54,91} showed no significant difference between groups. One study⁹¹ specifically included schizoaffective disorder. Two

studies^{54,71} excluded patients with comorbid drug or alcohol use. All studies included both treatment resistant and nonresistant patients. The dose of haloperidol varied across studies: 2.5–20 mg/d,⁵⁴ 3–9 mg/d,⁷¹ and 1–4 mg/d.⁹¹ The dose of olanzapine was more consistent with upper limits of 20 mg/d for all studies. Duration of followup varied from 6 weeks⁷¹ to 1 year.⁹¹ Risk of bias was high for two studies^{71,91} and unclear for one.⁵⁴ Two trials^{54,91} were industry-funded; the other⁷¹ did not report a funding source.

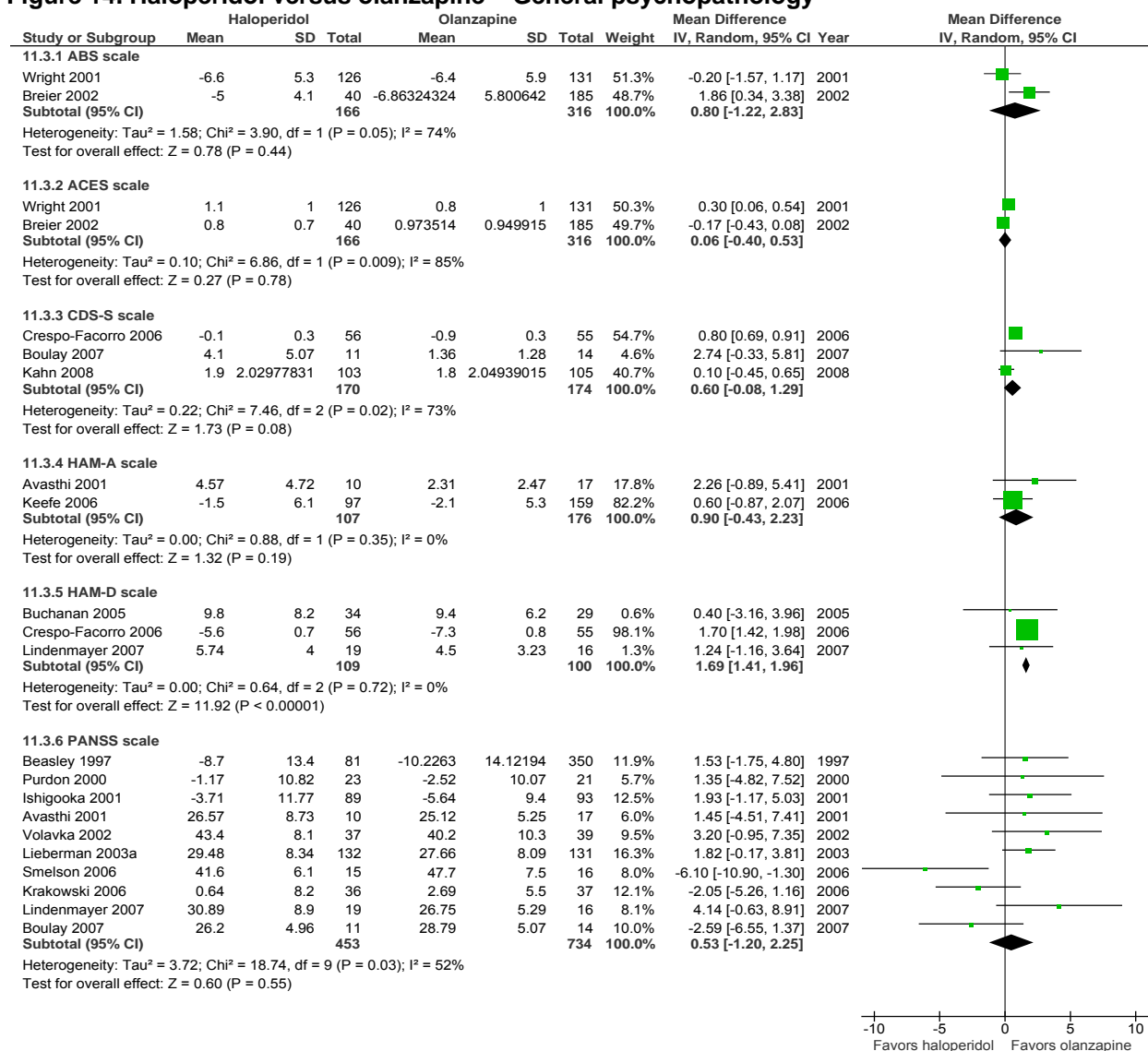
Two trials^{101,159} (n = 283) showed no significant difference between groups based on the HAM-A (Table 37; Figure 14). There was no statistical heterogeneity across the studies ($I^2 = 0$ percent).

Two trials^{56,147} (n = 482) found no significant difference based on the ABS and ACES. Statistical heterogeneity across studies was substantial ($I^2 = 74$ percent and 85 percent, respectively). Both studies included mixed populations in terms of disorder subtypes and treatment resistance. One study⁵⁶ specifically excluded patients with comorbid drug or alcohol use. Both studies used 7.5 mg/d of haloperidol and maximum 10 mg/d of olanzapine. Duration of followup was 24 hours for both studies. Both trials had unclear risk of bias and were funded by industry.

One study reported significant results favoring olanzapine based on the YMRS⁷¹ (n = 111); these results were considered not to be clinically important.

The SoE was graded as moderate for the HAM-D and MADRS, whereas the HAM-A, PANSS (general psychopathology), ABS, ACES, and CDS-S were graded as low SoE. The SoE for YMRS was graded as insufficient (Table 38).

Figure 14. Haloperidol versus olanzapine – General psychopathology



ABS = Agitated Behavior Scale; ACES = Agitation-Calmness Evaluation Scale; CDS-S = Calgary Depression Scale for Schizophrenia; CI = confidence intervals; df = degrees of freedom; HAM-A = Hamilton Rating Scale for Anxiety; HAM-D = Hamilton Rating Scale for Depression; I^2 = I-squared; IV = inverse variance; MADRS = Montgomery-Asberg Depression Rating Scale; PANSS = Positive and Negative Symptom Scale; SD = standard deviation

Global Ratings and Total Scores

Twenty-two trials,^{43,49-51,54,56,58,71,73,78,88,91,101,104-106,108,110,127,141,145,147} ($n = 5,283$) reported global ratings and total scores using six different scales (Table 37; Figure 15).

Fifteen trials^{43,50,51,54,78,88,91,101,104,105,108,110,127,141,145} ($n = 4,209$) reported a statistically significant difference in favor of olanzapine based on PANSS (total). The difference was considered to be clinically important; however, there was moderate statistical heterogeneity ($I^2 = 37$ percent). Restricting the analyses to the following subgroups reduced the heterogeneity:

- Specifically included schizoaffective disorder (3 studies): no difference between groups ($I^2 = 0$ percent);

- Specifically excluded patients with comorbid drug or alcohol use (3 studies): no difference between groups ($I^2 = 0$ percent);
- Included both treatment resistant and nonresistant patients (8 studies): no difference between groups ($I^2 = 23$ percent);
- Followed patients for less than 6 weeks (2 studies): no difference between groups ($I^2 = 0$ percent);
- Followed patients for longer than 6 months (6 studies): significantly favored olanzapine ($I^2 = 0$ percent);
- Maximum doses of haloperidol and olanzapine of 20 mg/d (13 studies): significantly favored olanzapine ($I^2 = 23$ percent);
- No industry funding (2 studies): no difference between groups ($I^2 = 0$ percent);
- Imputed data for the meta-analysis (3 studies): no difference between groups ($I^2 = 0$ percent); no imputed data (12 studies): significantly favored olanzapine ($I^2 = 5$ percent).

There was no suggestion of publication bias based on statistical tests and visual inspection of the funnel plot (Appendix K, Funnel plot 4).

Thirteen trials^{43,49-51,56,58,71,73,88,104,106,141,147} ($n = 4,014$) reported no significant difference between groups based on BPRS; however, the statistical heterogeneity was substantial ($I^2 = 82$ percent). Restricting the analyses to the following subgroups reduced the heterogeneity:

- Included patients with and without comorbid alcohol or drug use (7 studies): significantly favored olanzapine ($I^2 = 36$ percent);
- Included treatment resistant and non-treatment-resistant patients (9 studies) (i.e., removed studies with only treatment resistant patients): significantly favored olanzapine ($I^2 = 0$ percent);
- Followed patients for >6 weeks and up to 6 months (4 studies): significantly favored olanzapine ($I^2 = 0$ percent);
- Did not report funding or had funding from sources other than industry (4 studies): significantly favored olanzapine ($I^2 = 0$ percent).

There was no suggestion of publication bias based on statistical tests (Appendix K, Funnel plot 5).

Eight trials^{49,50,56,58,71,91,108,141} ($n = 3,564$) used the CGI-S, but pooled results are not presented due to substantial heterogeneity ($I^2 = 82$ percent) among the included trials. Restricting the analyses to the following subgroups reduced the heterogeneity:

- Patients with schizoaffective disorder (2 studies): no difference between groups ($I^2 = 34$ percent);
- Patients with and without comorbid drug or alcohol use (3 studies): significantly favored olanzapine ($I^2 = 0$ percent);
- Treatment-resistant patients (2 studies): significantly favored olanzapine ($I^2 = 32$ percent);
- Followed patients for >6 months (5 studies): significantly favored olanzapine ($I^2 = 7$ percent);
- Industry funding (7 studies): significantly favored olanzapine ($I^2 = 33$ percent);
- Unclear risk of bias (4 studies): no difference between groups ($I^2 = 11$ percent).

Further, one study appeared to be an outlier as it was the only study that significantly favored haloperidol. Removing this study reduced the heterogeneity to 33 percent and results

significantly favored olanzapine. This study included only patients with first episode and no treatment resistance.

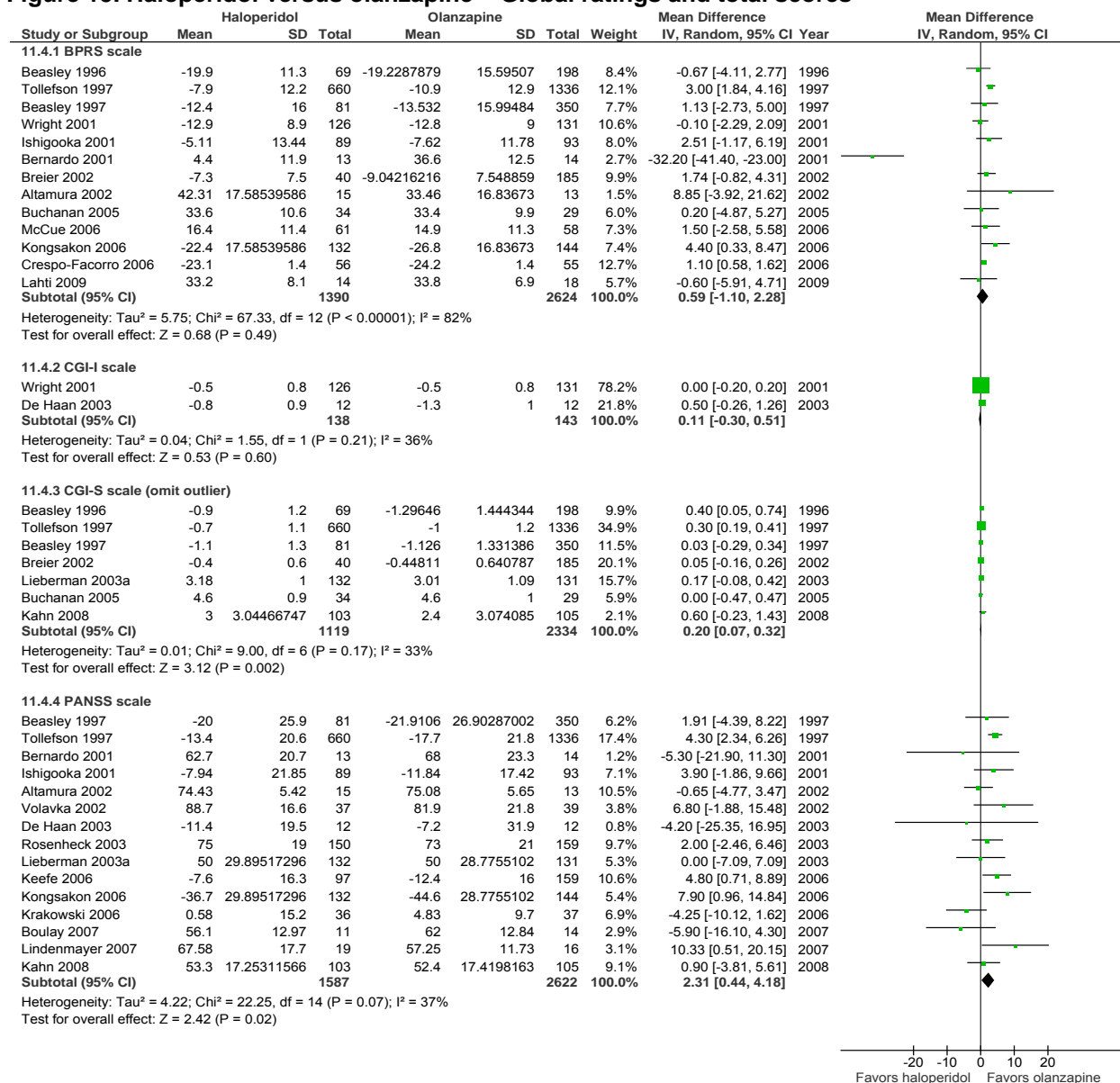
Two studies^{78,147} used the CGI-I and pooled results showed no difference between groups. Statistical heterogeneity was moderate ($I^2 = 36$ percent). One study⁷⁸ specifically included patients with schizoaffective disorder, treatment resistant by history, and young adults (17–28 years). Both studies included patients with and without comorbid drug or alcohol use. One study⁷⁸ compared 2.5 mg/d haloperidol with 7.5 mg/d olanzapine, whereas the other study¹⁴⁷ examined doses of 7.5 mg/d and 10 mg/d, respectively. Duration of followup was 6 weeks⁷⁸ and 8 weeks.¹⁴⁷ Risk of bias was unclear for both studies; one was funded by government⁷⁸ and the other by industry.¹⁴⁷

One study comparing 1–4 mg/d haloperidol with 5–20 mg/d olanzapine used the GAF and found no difference between groups.⁹¹

The Subjective Well-Being under Neuroleptics Scale was used in one study,⁷⁸ and no differences were found between groups.

The SoE for PANSS and CGI-S was graded as moderate; BPRS and CGI-I were graded as low; GAF and the Subjective Well-Being under Neuroleptics Scale were graded as insufficient (Table 38).

Figure 15. Haloperidol versus olanzapine – Global ratings and total scores



BPRS = Brief Psychiatric Rating Scale; CGI-I = Clinical Global Impression–Improvement; CGI-S = Clinical Global Impression–Severity; CI = confidence intervals; df = degrees of freedom; GAF = Global Assessment of Functioning; I^2 = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale; SD = standard deviation

Key Questions 2 and 4. Improvement in Functional Outcomes, Decreasing Health Care System Utilization, and Other Outcomes

Functional Outcomes

Encounters With Legal System

One trial¹³⁶ ($n = 31$) that enrolled cocaine dependent patients compared 5–20 mg/d haloperidol with 5–20 mg/d olanzapine and found no difference between the groups for positive

urine cocaine toxicology (Table 37). Duration of followup was 6 weeks. Risk of bias was high and the trial was industry-funded.

Sexual Dysfunction

One trial⁹¹ (n = 208) in patients with schizoaffective or schizophreniform disorder without treatment resistance compared 1–4 mg/d haloperidol with 5–20 mg/d olanzapine. The trial followed patients for one year and found no significant difference between groups regarding the incidence of sexual dysfunction (Table 37). The trial was considered high risk of bias and was industry-funded.

Health Care System Utilization

The same trial described above⁹¹ found no significant difference between groups in terms of rates of hospitalization or rehospitalization (Table 37). One trial¹²⁷ found no difference in mean hospital bed days (Table 37).

Other Outcomes

Pooled results from 14 trials^{49,71,73,88,91,101,104-106,108,110,130,141,147} (n = 4,099) showed a significant difference favoring olanzapine on response rates; however, statistical heterogeneity was substantial ($I^2 = 55$ percent) (Table 37; Figure 16). Restricting the analyses to the following subgroups reduced the heterogeneity:

- Mix of disorder subtypes (12 studies): significantly favored olanzapine ($I^2 = 26$ percent);
- Specifically excluded patients with comorbid drug or alcohol use (2 studies): no difference between groups ($I^2 = 29$ percent);
- Included treatment-resistant and nonresistant patients (8 studies): significantly favored olanzapine ($I^2 = 0$ percent);
- Followed patients for <6 weeks (4 studies): no difference between groups ($I^2 = 0$ percent);
- Followed patients for >6 weeks but <6 months (5 studies): no difference between groups ($I^2 = 22$ percent);
- No industry funding reported (5 studies): no difference between groups ($I^2 = 0$ percent);
- Unclear risk of bias (9 studies): significantly favored olanzapine ($I^2 = 7$ percent);
- Imputed data (3 studies): no difference between groups ($I^2 = 0$ percent).

There was no indication of publication bias based on statistical tests and visual inspection of the funnel plot (Appendix K, Funnel plot 6).

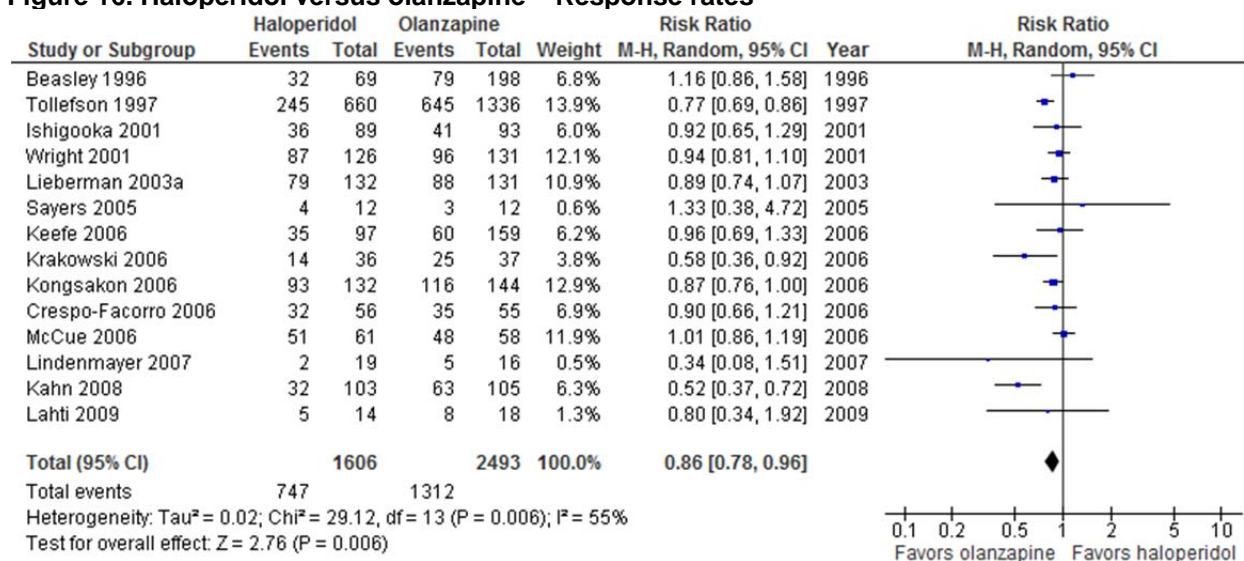
Three trials^{71,91,108} (n = 582) assessed remission rates (Table 37). The pooled result was significant favoring olanzapine; however, there was substantial statistical heterogeneity. Removing one trial⁹¹ from the analysis reduced the heterogeneity to 0 percent, and the result remained statistically significant. The trial differed from the other two in that it specifically included patients with schizoaffective disorder.

Single trials examined medication adherence¹⁰¹ (n = 256) and patient insight into illness¹⁰⁸ (n = 263) and reported no differences between groups (Table 37). Characteristics of these studies are described in Table 36.

Five trials^{49,58,91,104,159} examined health-related quality of life (HRQoL) using different scales; no differences were found between groups, and there was minimal statistical heterogeneity across the trials (Table 37). Two of the trials^{58,91} specifically included patients with schizoaffective disorders. Two trials^{49,58} specifically excluded patients with comorbid drug or alcohol use. One trial¹⁰⁴ included only patients of Asian descent. One study⁵⁸ used up to 30 mg/d

of both haloperidol and olanzapine and included only patients with treatment resistance. All studies followed patients for longer than 6 months. Risk of bias was unclear for two studies^{49,104} and high for three;^{58,91,159} all trials were industry-funded.

Figure 16. Haloperidol versus olanzapine – Response rates



CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; M-H = Mantel-Haenszel

Key Question 5. Subgroups

Age

One trial⁷⁸ ($n = 24$) in patients with schizophrenia aged 17–28 years found no differences between groups for general psychopathology (MADRS) or global ratings and total scores (CGI-I, PANSS (total), Subjective Well-Being under Neuroleptics Scale).

Comorbidities

Two trials^{130,136} ($n = 55$) in patients with comorbid cocaine use reported no significant difference on the PANSS (positive), but a significant difference in favor of haloperidol on the PANSS (negative) (MD = -3.20; 95% CI, -6.03 to -0.37) and the PANSS (general psychopathology) (MD = -6.10; 95% CI, -10.90 to -1.30). The results for PANSS negative and general psychopathology were considered to be clinically significant.

Disease Subgroup

One trial⁴³ ($n = 28$) in patients with paranoid schizophrenia reported no significant difference on global ratings using the BPRS scale.

Race

Three trials,^{88,102,104} ($n = 525$) in Asian patients reported no significant difference on PANSS (positive), SAPS, PANSS (negative), SANS, or PANSS (general psychopathology), but a significant difference in favor of olanzapine on BPRS (MD = 3.36; 95% CI, 0.63 to 6.09) and PANSS (total) (MD = 5.53; 95% CI, 1.10 to 9.96). The difference on BPRS and PANSS (total) were considered to be clinically significant.

Treatment of a First Episode

Four trials^{71,75,108,129} (n = 928) included patients undergoing treatment for their first schizophrenic episode. There was no significant difference on PANSS (positive), SAPS, PANSS (general psychopathology), and 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), HAM-D (MD = 1.70; 95% CI, 1.42 to 1.98), and BPRS (MD = 1.10; 95% CI, 0.58 to 1.62). There was a significant difference favoring haloperidol on the CGI-S scale (MD = 0.80; 95% CI, 0.69 to 0.91).

Treatment Resistance

Nine trials^{51,58,73,78,105,110,130,141,145} (n = 2,804) in treatment-resistant patients reported no difference in positive symptoms (PANSS [positive]),^{51,105,110,141,145} negative symptoms (SANS),⁵⁸ general psychopathology (HAM-D),⁵⁸ PANSS (general psychopathology),^{105,110,145} or global ratings and total scores (BPRS,^{51,58,73,141} CGI-I,⁷⁸ PANSS,^{51,78,105,110,141,145} and Subjective Well-Being under Neuroleptics Scale).⁷⁸ There was a significant difference favoring olanzapine for two scales: one measure general psychopathology (MADRS)^{78,105,141} and the other a global rating scale (CGI-S).^{58,141}

Table 37. Evidence summary table: haloperidol versus olanzapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Positive Symptoms					
PANSS ^{50,51,54,88,101,104,105,108,110,124,136,141,145,159}	14	3742	0.43 (-0.22, 1.08)	36%	ND
SAPS ^{71,102}	2	178	0.10 (-0.09, 0.28)	0%	ND
Negative Symptoms					
PANSS ^{50,51,54,88,101,104,105,108,110,124,136,141,145,159}	14	3742	1.06 (0.46, 1.67)	27%	olanzapine
SANS ^{49,58,71,102,159}	5	535	1.79 (1.57, 2.02)	0%	olanzapine
General Psychopathology					
ABS ^{56,147}	2	482	0.80 (-1.22, 2.83)	74%	ND
ACES ^{56,147}	2	482	0.06 (-0.40, 0.53)	85%	ND
CDS-S ^{54,71,91}	3	344	0.60 (-0.08, 1.29)	73%	ND
HAM-A ^{101,159}	2	283	0.90 (-0.43, 2.23)	0%	ND
HAM-D ^{58,71,110}	3	209	1.69 (1.41, 1.96)	0%	olanzapine
MADRS ^{78,101,105,108,141,159}	6	2639	2.46 (1.78, 3.14)	0%	olanzapine
PANSS ^{50,54,88,105,108,110,124,136,145,159}	10	1187	0.53 (-1.20, 2.25)	52%	ND
YMRS ⁷¹	1	111	0.40 (0.21, 0.59)	NE	olanzapine
Global Ratings and Total Scores					
BPRS ^{43,49-51,56,58,71,73,88,104,106,141,147}	13	4014	0.59 (-1.10, 2.28)	82%	ND
CGI-I ^{78,147}	2	281	0.11 (-0.30, 0.51)	36%	ND
CGI-S, ^{49,50,56,58,91,108,141} omit outlier	7	3453	0.20 (0.07, 0.32)	33%	olanzapine
GAF ⁹¹	1	208	-4.00 (-13.70, 5.70)	NE	ND
PANSS ^{43,50,51,54,78,88,91,101,104,105,108,110,127,141,145}	15	4209	2.31 (0.44, 4.18)	37%	olanzapine
Subjective Well-Being under Neuroleptics Scale ⁷⁸	1	24	7.00 (-3.55, 17.55)	NE	ND
Encounters With the Legal System					
Positive urine toxicology ¹³⁶	1	31	3.20 (0.76, 13.46)*	NE	ND
Sexual dysfunction					
Sexual dysfunction (UKU) ⁹¹	1	208	0.80 (0.52, 1.24)	NE	ND

Table 37. Evidence summary table: haloperidol versus olanzapine (continued)

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Health Care System Utilization					
Rates of hospitalization/rehospitalization ⁹¹	1	208	0.79 (0.42, 1.51)*	NE	ND
Mean hospital bed days ¹²⁷	1	309	-7.10 (-20.95, 6.75)	NE	ND
Other Outcomes					
Response rates ^{49,71,73,88,91,101,104-106,108,110,130,141,147}	14	4099	0.86 (0.78, 0.96)*	55%	olanzapine
Remission rates ^{71,91,108}	3	582	0.65 (0.45, 0.94)*	54%	olanzapine
Medication adherence ¹⁰¹	1	256	1.00 (0.81, 1.22)*	NE	ND
Patient insight into illness ¹⁰⁸	1	263	-1.10 (-3.95, 1.75)	NE	ND
Health-Related Quality of Life					
Health-related quality of life ¹⁵⁹	1	27	-2.05 (-25.81, 21.71)	NE	ND
MANSA ⁹¹	1	208	0.00 (-1.38, 1.38)	NE	ND
QLS ^{49,58}	2	330	-2.62 (-6.39, 1.15)	0%	ND
Schizophrenia-specific QLS ¹⁰⁴	1	276	-3.62 (-8.94, 1.70)	NE	ND

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 Impression-Improvement; CGI-S = Clinical Global Impression-Severity; GAF = Global Assessment of Functioning; HAM-A = Hamilton Rating Scale for Anxiety; HAM-D = Hamilton Rating Scale for Depression; I² = I-squared; MADRS = Montgomery-Asberg Depression Rating Scale; MANSA = Manchester Short Assessment of Quality of Life; ND = no difference; NE = not estimable; NR = not reported; PANSS = Positive and Negative Symptom Scale; QLS = Quality of Life Scale; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; YMRS = Young Mania Rating Scale

Table 38. Strength of evidence (GRADE): haloperidol versus olanzapine

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Positive Symptoms						
PANSS	14 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
SAPS	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
Negative Symptoms						
PANSS	14 RCT	Medium	Consistent	Direct	Precise	Moderate (favors OLA)
SANS	5 RCT	Medium	Consistent	Direct	Precise	Moderate (favors OLA)
General Psychopathology						
ABS	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
ACES	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
CDS-S	3 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
HAM-A	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
HAM-D	3 RCT	Medium	Consistent	Direct	Precise	Moderate (favors OLA)
MADRS	6 RCT	Medium	Consistent	Direct	Precise	Moderate (favors OLA)
PANSS	10 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
YMRS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient

Table 38. Strength of evidence (GRADE): haloperidol versus olanzapine (continued)

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
<i>Outcome</i>						
BPRS	13 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
CGI-I	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
CGI-S, omit outliers	7 RCT	Medium	Consistent	Direct	Precise	Moderate (favors OLA)
GAF	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
PANSS	15 RCT	Medium	Consistent	Direct	Precise	Moderate (favors OLA)
SWBUN	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

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 Impression-Improvement; CGI-S = Clinical Global Impression-Severity; GAF = Global Assessment of Functioning; HAM-A = Hamilton Rating Scale for Anxiety; HAM-D = Hamilton Rating Scale for Depression; MADRS = Montgomery-Asberg Depression Rating Scale; ND = no difference; OLA = olanzapine; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; RoB = risk of bias; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; SoE = Strength of Evidence; SWBUNS = Subjective Well-being Under Neuroleptics Scale; YMRS = Young Mania Rating Scale

Haloperidol Versus Quetiapine

Key Points:

- Nine studies compared haloperidol versus quetiapine in patients with a range of disease severity.
- Positive symptoms assessed using PANSS (4 trials) was not significantly different between groups (low SoE).
- Negative symptoms assessed using PANSS (4 trials) and SANS (1 trial) were not significantly different between groups. The results for PANSS were statistically heterogeneous with one of the trials (which was high risk of bias vs. unclear for the other three) showing a significant difference in favor of quetiapine. The SoE was low for PANSS and insufficient for SANS.
- General psychopathology was assessed using PANSS (general psychopathology) (4 trials), CDS-S (2 trials), and Beck Depression Inventory (BDI) (1 trial), and was not significantly different between groups. The SoE was low for PANSS and CDS-S and insufficient for BDI.
- Global ratings and total scores were assessed using PANSS (total) (6 trials), CGI-S (4 trials), BPRS (4 trials), CGI-I (3 trials), and GAF (1 trial). No differences were found for any scales except for CGI-S, which showed a significant benefit for haloperidol, which was not considered to be clinically significant. The SoE was low or insufficient for all scales except for CGI-S, which was moderate.
- Response rates were assessed in six studies and showed no difference between groups overall. One study was an outlier and showed a significant difference favoring haloperidol. This study of treatment-resistant patients used relatively higher doses of haloperidol (4–30 mg/d) and quetiapine (50–1200 mg/d) and followed patients for only 3 weeks.
- Other outcomes were assessed in a single trial and showed no differences between groups.

Nine RCTs,^{46,47,65,68,73,79,80,91,123} (n = 1,516) compared haloperidol (1–200 mg/d) with quetiapine (50–1200 mg/d). Key characteristics of the included trials and summary of findings are presented in Table 39 and Table 40. All studies included mixed populations in terms of first versus repeat episodes. One study⁸⁰ specifically included patients with schizoaffective disorder, whereas the others included mixed populations in terms of disorder subtypes. Three studies^{47,73,123} specifically excluded patients with comorbid drug or alcohol use; the others included patients with and without comorbid drug or alcohol use. Two studies^{73,79} included only treatment-resistant patients based on history; the other studies included mixed populations with respect to treatment resistance. One study⁴⁷ included only female patients, whereas the others included mixed male and female populations. The doses for haloperidol ranged from 1–4 mg/d⁹¹ to 4–30 mg/d.⁷³ Likewise the doses for quetiapine varied with maximum doses ranging from 500 mg/d⁶⁵ to 1200 mg/d.⁷³

Duration of followup was ≤6 weeks for four studies,^{46,47,68,73} between four weeks and 6 months for two studies,^{65,79} and ≥6 months for three studies.^{80,91,123} Risk of bias was unclear in five studies^{46,47,79,80,123} and high in four.^{65,68,73,91} All studies reported having industry support except for two^{47,73} that did not report their source of funding.

Publication bias was not formally tested for any of the outcomes due to the small number of included trials. The SoE for the majority of the evaluated outcomes was insufficient or low, largely due to the small number of trials (Table 41).

Table 39. Characteristics of RCTs comparing haloperidol versus quetiapine in the treatment of schizophrenia and related psychoses

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout/ Run-in Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Arvanitis et al. 1997 ⁴⁶ RCT (6 wks)	G1: HAL (12mg/d); (52) G2: QUE (75mg/d); (53) G3: QUE (150mg/d); (48) G4: QUE (300mg/d); (52) G5: QUE (600mg/d); (51) G6: QUE (750mg/d); (54) Washout period: 1 wk	Sz (chronic or subchronic) with no use of depot AP within one dosing interval	Unclear, Industry
Atmaca et al. 2002 ⁴⁷ RCT (6 wks)	G1: HAL (10mg/d); (17) G2: QUE (600mg/d); (18) Washout period: 2 wks	Sz defined by DSM–IV	Unclear, NR
Copolov et al. 2000 ⁶⁸ RCT (6 wks)	G1: HAL (1–16mg/d); (227) G2: QUE (50–800mg/d); (221) Washout period: 48 hrs	Acute exacerbation of chronic or subchronic Sz; no tx with a depot AP <1 dosing period	High, Industry
Emsley et al. 2000 ⁷⁹ RCT (12 wks)	G1: HAL (5–20mg/d); (145) G2: QUE (600mg/d); (143) Run-in phase: 4 wks	Sz; hx of partial response to conventional APs; persistent positive symptoms while previously taking AP; partial or no response to 1 mo FLU tx	Unclear, Industry
Emsley et al. 2005 ⁸⁰ RCT (2 yrs)	G1: HAL (5–20mg); (23) G2: QUE (100–800mg); (22)	Clinically stable Sz or schizoaffective disorder (DSM–IV); on stable dose of AP; had TD	Unclear, Multiple sources including industry
Glick et al. 2005 ⁶⁵ RCT (48 wks)	G1: HAL (200mg/wk); (14) G2: QUE (500mg/d); (21)	Sz requiring long-term therapy	High, Multiple sources including industry

Table 39. Characteristics of RCTs comparing haloperidol versus quetiapine in the treatment of schizophrenia and related psychoses (continued)

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout/ Run-in Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Kahn et al. 2008 ⁹¹ RCT (12 mo)	G1: HAL (1–4mg/d); (103) G2: QUE (200–750mg/d); (104)	Sz/ schizophreniform or schizoaffective disorder; <2 yrs since onset of positive symptoms; no AP > 2 wks in last 1 yr, or >6 wks at any time	High, Industry
McCue et al. 2006 ⁷³ RCT (3 wks)	G1: HAL (4–30mg); (61) G2: QUE (50–1200 mg); (62)	Sz, schizoaffective disorder, or schizophreniform disorder; no hx of response or lack of response to AP, BP, major depression, or substance-induced psychotic disorder	High, No external funding
Purdon et al. 2001 ¹²³ RCT (6 mo)	G1: HAL (10–20mg/d); (12) G2: QUE (300–600mg/d); (13) Washout period: 48 hrs	Sz defined by DSM–IV	Unclear, Industry

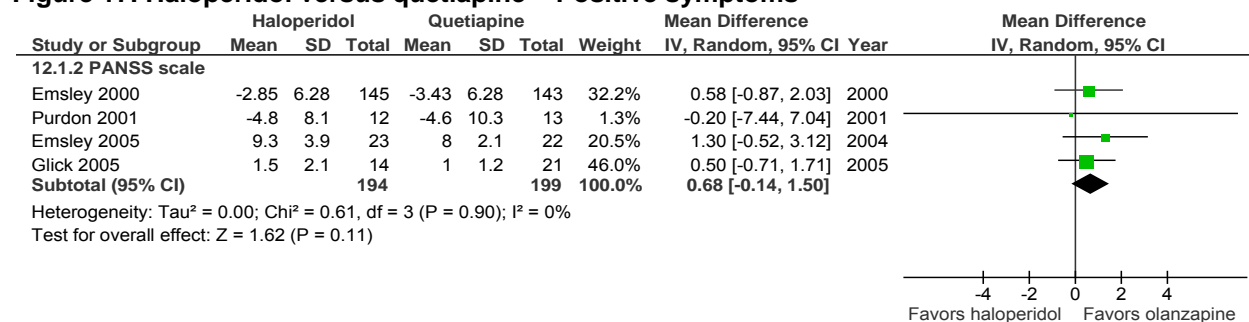
AP(s) = antipsychotic(s); BP = bipolar disorder; D = day; DSM–IV = Diagnostic and Statistical Manual of Mental Disorders – IV; FLU = fluphenazine; G = group; HAL = haloperidol; Hr(s) = hour(s); Hx = history; Mg = milligrams; Mo = month; NR = not reported; QUE = quetiapine; RCT = randomized controlled trial; Sz = schizophrenia; TD = tardive dyskinesia; Tx = treatment; Wk(s) = week(s); Yr(s) = year(s)

Key Question 1. Improving Core Illness Symptoms

Positive Symptoms

Four trials^{65,79,80,123} (n = 393) reported on positive symptoms using the PANSS (positive), and pooled results showed no significant difference between groups (Table 40; Figure 17); the trials were statistically homogenous. One of the studies⁸⁰ specifically included patients with schizoaffective disorder and treatment resistance based on history, whereas the others included mixed populations in terms of disorder subtypes and treatment resistance. One study¹²³ specifically excluded patients with comorbid drug or alcohol use. The dose of haloperidol was relatively consistent across studies except one⁶⁵ that gave 200 mg/wk. The dose of quetiapine ranged from 100–800 mg/d. Duration of followup was <6 months for two studies^{65,79} and ≥6 months for two studies.^{80,123} Risk of bias was high for one study⁶⁵ and unclear for the other three; all studies were industry-funded. The SoE for PANSS (positive) was graded as low (Table 41).

Figure 17. Haloperidol versus quetiapine – Positive symptoms



CI = confidence intervals; df = degrees of freedom; I² = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale; SD = standard deviation

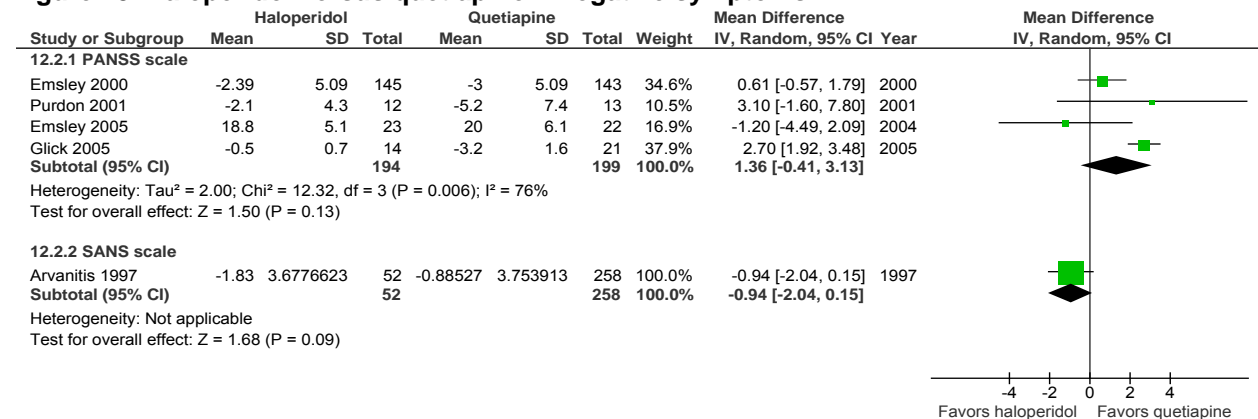
Negative Symptoms

Five trials,^{46,65,79,80,123} (n = 703) reported negative symptoms using two scales (Table 40; Figure 18). Four trials,^{65,79,80,123} (n = 393) reported no significant difference between groups using PANSS (negative); however, there was substantial statistical heterogeneity. We examined predefined subgroup and sensitivity analyses to explain the heterogeneity (Appendix M, Table 103). There was no change in heterogeneity based on disorder subtype, comorbid drug or alcohol use, treatment resistance, or duration of followup. Three studies had unclear risk of bias and had minimal statistical heterogeneity ($I^2 = 10$ percent); the pooled estimate showed no difference between groups. One study⁶⁵ with high risk of bias showed an important significant difference favoring quetiapine.

One trial⁴⁶ (n = 310) compared 12 mg/d haloperidol with 75–750 mg/d quetiapine and found no significant difference between groups using SANS (Table 40; Figure 18). This trial included mixed populations in terms of disorder subtypes, comorbid drug or alcohol use, and treatment resistance. Duration of followup was 6 weeks. Risk of bias was unclear, and the trial was industry-funded.

The SoE was low for PANSS (negative) and insufficient for SANS (Table 41).

Figure 18. Haloperidol versus quetiapine – Negative symptoms



CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale; SD = standard deviation

General Psychopathology

Four trials^{65,79,80,123} (n = 393) reported no significant difference between groups using PANSS (general psychopathology) (Table 40; Figure 19); there was minimal statistical heterogeneity across the studies. One of the studies⁸⁰ specifically included patients with schizoaffective disorder and treatment resistance based on history, whereas the others included mixed populations in terms of disorder subtypes and treatment resistance. One study¹²³ specifically excluded patients with comorbid drug or alcohol use. The dose of haloperidol was relatively consistent across studies except one⁶⁵ that gave 200 mg/d. The dose of quetiapine ranged from 100–800 mg/d. Duration of followup was <6 months for two studies^{65,79} and ≥6 months for two studies.^{80,123} Risk of bias was high for one study⁶⁵ and unclear for the other three; all studies were industry-funded.

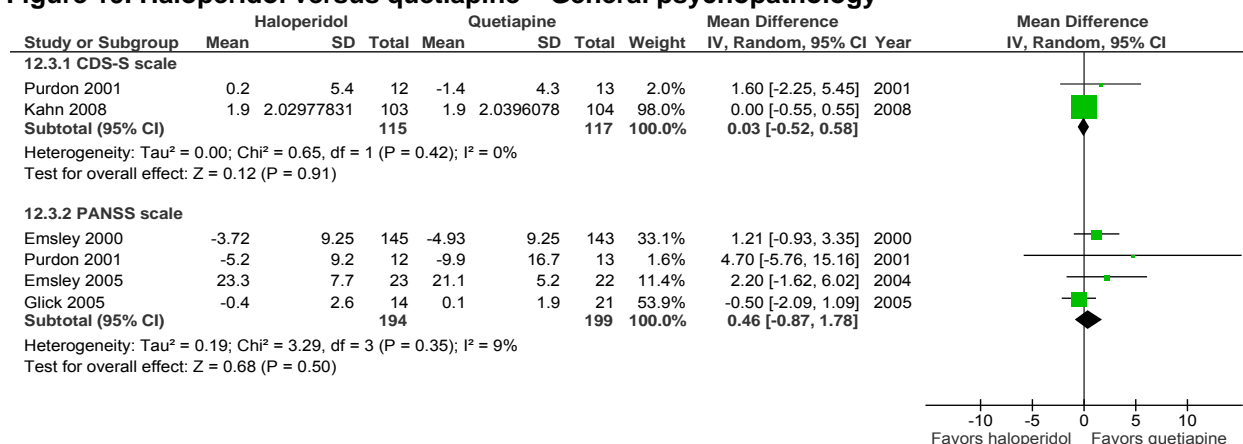
Two trials^{91,123} (n = 232) reported no significant difference between groups using CDS–S (Table 40; Figure 19). There was no statistical heterogeneity across these two studies. Both studies included mixed populations with respect to disorder subtype and treatment resistance.

One trial¹²³ specifically excluded patients with comorbid drug or alcohol use. Doses of haloperidol varied from 1–4 mg/d⁹¹ to 10–20 mg/d;¹²³ doses of quetiapine ranged from 200–750 mg/d⁹¹ and 300–600 mg/d.¹²³ Duration of followup was ≥ 6 months in both studies. Risk of bias was high⁹¹ and unclear;¹²³ both studies were industry-funded.

One of the trials described immediately above¹²³ (n = 25) reported results for the Beck Depression Inventory and found no significant difference between groups (Table 40).

The SoE for PANSS (general psychopathology) and CDS–S was graded as low, while the SoE for BDI was insufficient (Table 41).

Figure 19. Haloperidol versus quetiapine – General psychopathology



CDS–S = Calgary Depression Scale for Schizophrenia; CI = confidence intervals; df = degrees of freedom; I² = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale; SD = standard deviation

Global Ratings and Total Scores

Nine studies^{46,47,65,68,73,79,80,91,123} (n = 1,516) examined total scores using five scales (Table 40; Figure 20). Six trials^{65,68,79,80,91,123} (n = 1,048) reported no significant difference using PANSS (total) (Table 40; Figure 20); there was minimal statistical heterogeneity. One study⁸⁰ specifically included patients with schizoaffective disorders. One study⁷⁹ included only patients with treatment resistance based on history. One study¹²³ specifically excluded patients with comorbid drug or alcohol use. Doses of haloperidol ranged from 1–4 mg/d⁹¹ to 10–20 mg/d;¹²³ doses of quetiapine ranged from 50–800 mg/d across studies. Duration of followup was 6 weeks,⁶⁸ between 6 weeks and 6 months,^{65,79} and >6 months.^{80,91,123} Risk of bias was unclear for three studies^{79,80,123} and high for three;^{65,68,91} all were industry-funded.

Four trials^{46,68,79,91} reported a significant difference favoring haloperidol using CGI–S; the results were statistically homogeneous. All studies included mixed populations in terms of disorder subtype and comorbid drug or alcohol use. One study⁷⁹ only included treatment-resistant patients. Dose of haloperidol ranged from 1–20 mg/d with varying ranges across studies. Likewise, quetiapine ranged from 75–800 mg/d. Duration of followup was 6 weeks,^{46,68} 12 weeks,⁷⁹ and 1 year.⁹¹ Risk of bias was unclear for two trials^{46,79} and high for two trials;^{68,91} all trials were industry-funded.

Four trials^{46,47,73,79} reported no difference using BPRS (Table 40; Figure 20); the results were statistically homogeneous. All studies included mixed populations in terms of disorder subtypes. Two studies^{47,73} excluded patients with comorbid drug or alcohol use. Two studies^{73,79} included only patients with treatment resistance. One study⁴⁷ included only women. Doses of haloperidol and quetiapine were relatively consistent, although ranged from 4–30 mg/d and 50–1200 mg/d,

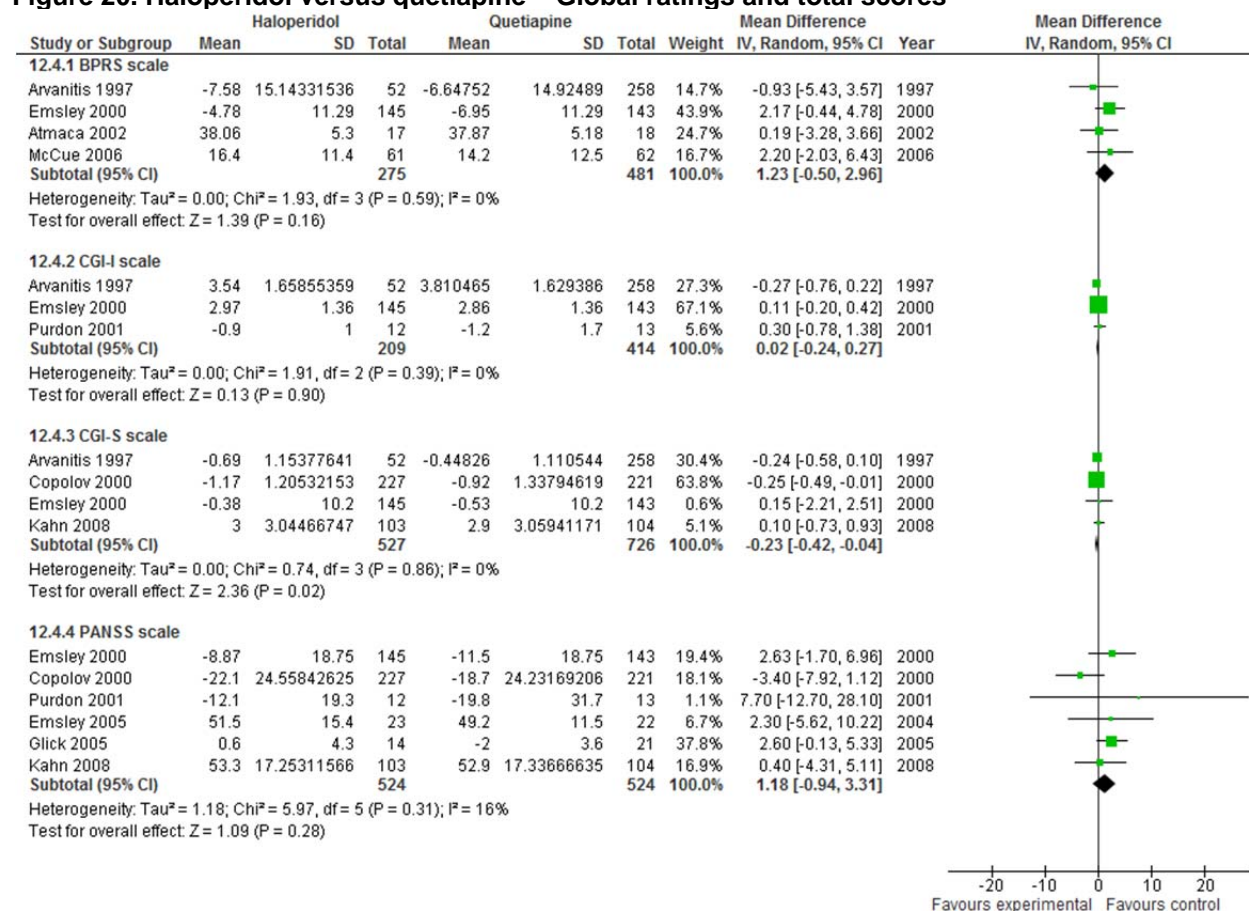
respectively, in one study.⁷³ Duration of followup was ≤ 6 weeks in three studies^{46,47,73} and 12 weeks in one study.⁷⁹ Risk of bias was unclear for three trials and high for one.⁷³ Two trials^{46,79} were industry-funded; two^{47,73} did not report source of funding.

Three trials^{46,79,123} (n = 623) showed no significant difference using CGI-I (Table 40; Figure 20); results were homogeneous across trials. All trials included mixed populations in terms of disorder subtypes. One study¹²³ excluded patients with comorbid drug or alcohol use. One study⁷⁹ included only patients with treatment resistance by history. Doses of haloperidol ranged from 5–20 mg/d; doses of quetiapine ranged from 75–750 mg/d. Risk of bias was unclear in all studies; all were industry-funded.

A single trial⁹¹ (n = 207) compared 1–4 mg/d haloperidol with 200–750 mg/d quetiapine and found no significant difference between groups using GAF (Table 40; Figure 20). The trial included mixed populations in terms of disorder subtypes, treatment resistance, and comorbid drug or alcohol use. Duration of followup was 1 year. Risk of bias was high, and the trial was industry-funded.

The SoE for CGI-S was graded as moderate (favoring haloperidol), for BPRS, CGI-I, and PANSS was graded as low (no difference), and for GAF was graded as insufficient (Table 41).

Figure 20. Haloperidol versus quetiapine – Global ratings and total scores



BPRS = Brief Psychiatric Rating Scale; CGI-I = Clinical Global Impression–Improvement; CGI-S = Clinical Global Impression–Severity; CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale; SD = standard deviation

Key Questions 2 and 4. Improvement in Functional Outcomes, Decreasing Health Care System Utilization, and Other Outcomes

Functional Outcomes

Sexual Dysfunction

One trial⁹¹ (n = 207) comparing 1–4 mg/d haloperidol with 200–750 mg/d quetiapine found no significant difference between groups with respect to sexual dysfunction (Table 40). The trial included mixed populations in terms of disorder subtypes, treatment resistance, and comorbid drug or alcohol use. Duration of followup was 1 year. Risk of bias was high, and the trial was industry-funded.

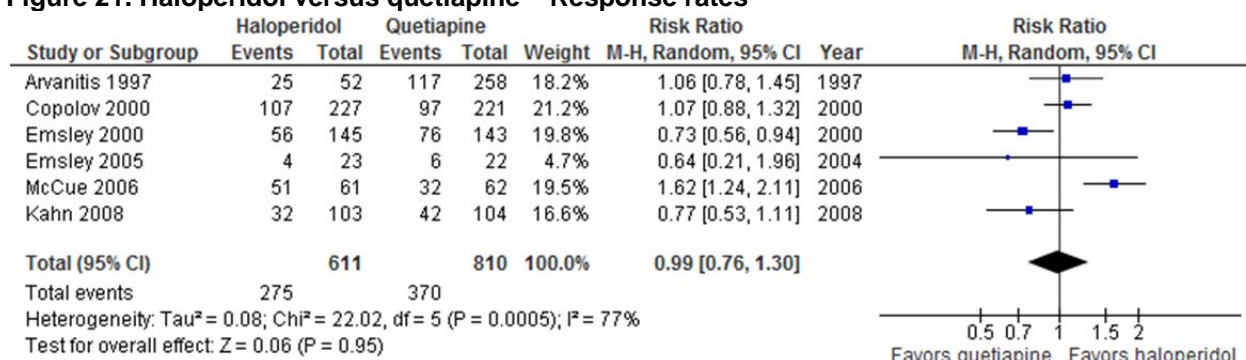
Health Care System Utilization

The same trial⁹¹ described immediately above found no significant difference between groups for rates of hospitalization or rehospitalization (Table 40).

Other Outcomes

Pooled results for six trials^{46,68,73,79,80,91} (n = 1,421) showed no significant difference in response rates (Table 40; Figure 21); however, the statistical heterogeneity was substantial ($I^2 = 77$ percent). We conducted predefined subgroup and sensitivity analyses to identify reasons for heterogeneous results across studies (Appendix M, Table 104). Heterogeneity was not explained by disorder subtypes or risk of bias. Three studies that followed patients for ≥ 6 months were homogeneous ($I^2 = 0$ percent), and pooled results favored quetiapine. Four studies that included both treatment-resistant and nonresistant patients showed reduced heterogeneity ($I^2 = 6$ percent), but no difference between groups. We examined one study⁷³ that was an outlier in that it showed a statistically significant benefit favoring haloperidol. This study was distinct from the others as it included doses of haloperidol ranging to 30 mg/d and it specifically excluded patients with comorbid drug or alcohol use. Further, the study did not report its source of funding, whereas the others declared industry support.

Figure 21. Haloperidol versus quetiapine – Response rates



CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; M-H = Mantel-Haenszel

One trial⁹¹ (n = 207) comparing 1–4 mg/d haloperidol with 200–750 mg/d quetiapine found no significant difference in remission rates (Table 40) or health-related quality of life. The trial included mixed populations in terms of disorder subtypes, treatment resistance, and comorbid

drug or alcohol use. Duration of followup was 1 year. Risk of bias was high, and the trial was industry-funded.

Key Question 5. Subgroups

Sex

One trial⁴⁷ (n = 35) in female schizophrenic patients showed no significant difference for the global rating scale BPRS.

Treatment Resistance

One trial⁷⁹ (n = 288) in patients with treatment-resistant schizophrenia showed no significant difference on PANSS (positive), PANSS (negative), PANSS (general psychopathology), and general ratings and total scores (BPRS,⁷⁹ CGI-I,⁷⁹ CGI-S,⁷⁹ PANSS (total)).

Table 40. Evidence summary table: haloperidol versus quetiapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Positive Symptoms					
PANSS ^{65,79,80,123}	4	393	0.68 (-0.14, 1.50)	0%	ND
Negative Symptoms					
PANSS ^{65,79,80,123}	4	393	1.36 (-0.41, 3.13)	76%	ND
SANS ⁴⁶	1	310	-0.94 (-2.04, 0.15)	NE	ND
General Psychopathology					
BDI ¹²³	1	25	5.30 (-2.79, 13.39)	NE	ND
CDS-S ^{91,123}	2	232	0.03 (-0.52, 0.58)	0%	ND
PANSS ^{65,79,80,123}	4	393	0.46 (-0.87, 1.78)	9%	ND
Global Ratings and Total Scores					
BPRS ^{46,47,73,79}	4	756	1.23 (-0.50, 2.96)	0%	ND
CGI-I ^{46,79,123}	3	623	0.02 (-0.24, 0.27)	0%	ND
CGI-S ^{46,68,79,91}	4	1253	-0.23 (-0.42, -0.04)	0%	haloperidol
GAF ⁹¹	1	207	0.10 (-9.60, 9.80)	NE	ND
PANSS ^{65,68,79,80,91,123}	6	1048	1.18 (-0.94, 3.31)	16%	ND
Sexual Dysfunction					
Sexual dysfunction (UKU) ⁹¹	1	207	1.01 (0.63, 1.62)	NE	ND
Health Care System Utilization					
Rates of hospitalization/rehospitalization ⁹¹	1	207	1.01 (0.51, 2.01)*	NE	ND
Health-Related Quality of Life					
MANSA ⁹¹	1	207	0.00 (-1.38, 1.38)	NE	ND
Other Outcomes					
Response rates ^{46,68,73,79,80,91}	6	1421	0.99 (0.76, 1.30)*	77%	ND
Remission rates ⁹¹	1	207	0.72 (0.41, 1.25)*	NE	ND

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-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression-Severity; GAF = Global Assessment of Functioning; I² = I-squared; MANSA = Manchester Short Assessment of Quality of Life; ND = no difference; NE = not estimable; PANSS = Positive and Negative Symptom Scale; SANS = Scale for the Assessment of Negative Symptoms

Table 41. Strength of evidence (GRADE): haloperidol versus quetiapine

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Positive Symptoms						
PANSS	4 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
Negative Symptoms						
PANSS	4 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
SANS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
General Psychopathology						
BDI	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
CDS-S	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
PANSS	4 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
Global Ratings and Total Scores						
BPRS	4 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
CGI-I	3 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
CGI-S	4 RCT	Medium	Consistent	Direct	Precise	Moderate (favoring haloperidol)
GAF	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
PANSS	6 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)

BDI = Beck Depression Inventory; BPRS = Brief Psychiatric Rating Scale; CDS-S = Calgary Depression Scale for Schizophrenia; CGI-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression-Severity; GAF = Global Assessment of Functioning; ND = no difference; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; RoB = risk of bias; SANS = Scale for the Assessment of Negative Symptoms; SoE = Strength of Evidence.

Haloperidol Versus Risperidone

Key Points:

- Thirty-three studies compared haloperidol with risperidone in patients with a range of illness severity.
- Twenty-two studies reported positive symptoms using two different scales: PANSS (20 studies) and SANS (2 studies). Pooled results showed no differences between groups, and the SoE was considered low.
- Twenty-three studies assessed negative symptoms using two different scales: PANSS (20 studies) and SANS (4 studies). Pooled results of findings from each scale showed significant benefits for risperidone. The SoE was moderate for both scales.
- Sixteen studies reported general psychopathology using PANSS (general psychopathology; 16 studies), CDS-S (3 studies), HAM-D (2 studies), YMRS (2 studies), HAM-A (1 study), and MADRS (1 study). For PANSS, pooled results for all 16 studies are not presented due to substantial heterogeneity. Three studies were outliers in that they favored haloperidol; pooling the remaining 13 trials showed no difference between groups. Results for HAM-D and CDS-S showed no significant differences; however, heterogeneity was substantial. No differences were found for YMRS, MADRS, and HAM-A. The SoE was low for PANSS, CDS-S, HAM-D, and YMRS; insufficient for MADRS and HAM-A.
- Twenty-seven studies assessed global ratings and total scores using eight scales: PANSS (total; 20 studies), BPRS (13 studies), CGI-S (8 studies), CGI-I (3 studies), Nurses Observation Scale for Inpatient Evaluation (NOISIE) (1 study), Schedule for Affective Disorders and Schizophrenia-Change (SADS-C) (1 study), SCL-90-R (1 study), and Subjective Well-being Under Neuroleptic Scale (1 study). In all cases where there were multiple studies, pooled results showed no significant differences between groups. The

SoE was low for all scales except those with only one trial, which were considered insufficient.

- Response rates were assessed in 16 studies and showed no difference between groups.
- Relapse rates were assessed in six studies and showed a significant benefit for risperidone.
- Remission rates were assessed in two studies and showed no difference between groups.
- Two studies assessed health-related quality of life (HRQoL) and showed no significant differences between groups.
- Other outcomes were assessed in few trials and showed no differences between groups.

Thirty-three RCTs,^{45,52,53,59-61,64,71-73,77,81,82,85,99,101,102,107,111,113,114,117,118,120,124,125,132,135,139,145,146,149,150} (n = 4,789) compared haloperidol with risperidone. Key characteristics of the included trials and summary findings are presented in Table 42 and Table 43. All studies included populations with mixed disorder subtypes. Five studies^{72,73,81,132,145} specifically included patients with schizoaffective disorder, whereas two studies^{52,114} excluded patients with schizoaffective disorder. One study⁸¹ included only patients with first episodes, 13 studies^{59,64,85,99,102,113,117,118,120,135,145,146,150} included only patients with multiple episodes, and the remaining studies included all patients. Five studies^{73,99,145,146,150} included only patients with treatment resistance, which was ascertained by history in all but one study,¹⁴⁶ which conducted a run-in period to the trial. Four studies^{72,81,118,124} included only patients with no treatment resistance. The remaining studies included all patients regardless of treatment resistance. Twenty studies^{45,52,53,59,61,71,72,77,81,82,107,111,117,118,120,124,125,132,149,150} specifically excluded patients with comorbid drug or alcohol use; the remaining studies included patients both with and without comorbid drug or alcohol use. Six studies^{102,107,111,117,149,150} included only patients of Asian descent. Doses of haloperidol ranged from 1 to 40 mg/d; doses ranged greater than 20 mg/d in two studies.^{73,145} Doses of risperidone ranged from 1 to 16 mg/d.

Duration of followup was ≤ 6 weeks in 8 studies,^{45,52,53,59,71,73,81,139} between 6 weeks and 6 months in 13 studies,^{60,61,64,102,107,111,114,117,120,145,146,149,150} and >6 months in 10 studies;^{72,77,82,101,113,118,124,125,132,135} 2 studies^{85,99} did not report length of followup. Risk of bias was high in 10 studies^{45,71,73,77,82,111,114,135,139,149} and unclear in the others. Eighteen studies^{53,59,61,64,77,82,85,99,101,113,114,118,124,125,132,145,146} were industry-funded, two^{107,149} were funded by government, one¹⁰² received institutional funding, and the others did not report funding source.

Publication bias was assessed for outcomes with at least 10 studies, and results are reported in the sections that follow. The SoE for the evaluated outcomes varied from insufficient to moderate mainly depending on the number of included trials (Table 44).

For each outcome, we examined whether differences existed for clinical characteristics (disorder subtypes, inclusion or exclusion of patients with schizoaffective disorder, sex, age group, race, comorbidities, previous exposure to antipsychotics, and treatment resistance), study characteristics (drug dose, followup period, and study sponsorship), and analytic methods (risk of bias and imputed data). When pooled estimates showed evidence of statistical heterogeneity, we report on any subgroups that had an effect on heterogeneity. All other subgroups showed no effect. Appendix M Tables 105 to 111 provides detailed tables on all subgroup analyses.

Table 42. Characteristics of RCTs comparing haloperidol versus risperidone in the treatment of schizophrenia

Study, Design (Followup)	Interventions, Dosages; No. randomized, Washout/ Run-in Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Apiquian et al. 2008 ⁴⁵ RCT (4 wks)	G1: HAL (2mg/d); (10) G2: RIS (1mg/d); (10)	Sz with psychosis	High, NR
Blin et al. 1996 ⁵² RCT (4 wks)	G1: HAL (4–12mg/d); (20) G2: RIS (4–12mg/d); (21)	Sz with acute exacerbation and anxiety symptoms; no depot AP <1 mo or short-acting AP <2 d	Unclear, NR
Borison et al. 1992 ⁵³ RCT (6 wks)	G1: HAL (4–20mg/d); (12) G2: RIS (2–10mg/d); (12) Run-in phase: 1 wk	Sz with acute exacerbation defined by DSM–III–R	Unclear, Industry
Cavallaro et al. 2001 ⁵⁹ RCT (6 wks)	G1: HAL (2.5–10mg/d); (16) G2: RIS (2.5–10mg/d); (17) Run-in phase: <=1 wk	Subchronic Sz; no AP <1 wk or depot APs in <1 mo	Unclear, Industry
Ceskova et al. 1993 ⁶⁰ RCT (8 wks)	G1: HAL (2–20mg/d); (31) G2: RIS (2–20mg/d); (31)	Acute Sz pts defined by ICD–9	Unclear, NR
Chouinard et al. 1993 ⁶¹ RCT (8 wks)	G1: HAL (20mg/d); (21) G2: RIS (2mg/d); (24) G3: RIS (6mg/d); (22) G4: RIS (10mg/d); (22) G5: RIS (16mg/d); (24) Washout period: 2 d – 2 wks	Sz; no depot AP for one tx cycle	Unclear, Industry
Claus et al. 1992 ⁶⁴ RCT (12 wks)	G1: HAL (1–10mg/d); (21) G2: RIS (1–10mg/d); (21) Washout period: 1 wk Run-in phase: 2 wks	Chronic Sz	Unclear, Industry
Crespo-Facorro et al. 2006 ⁷¹ RCT (6 wks)	G1: HAL (3–9mg/d); (56) G3: RIS (3–6mg/d); (61) Washout period: 3–5 d	Sz with no AP <6 wks	High, Multiple sources
Csernansky et al. 2002 ⁷² RCT (12 mo)	G1: HAL (5–20mg/d); (188) G2: RIS (2–8mg/d); (177) Washout period: <1 wks	Sz or schizoaffective disorder; no hx of AP refractoriness or depot AP for one tx cycle; clinically stable >30 d	Unclear, Industry
de Sena et al. 2003 ⁷⁷ RCT (12 mo)	G1: HAL (5–17mg/d); (13) G2: RIS (1–6mg/d); (20) Washout period: 3–7d	Sz pts defined by DSM–III–R	High, Industry
Emsley et al. 1999 ⁸¹ RCT (6 wks)	G1: HAL (2–10mg/d); (84) G2: RIS (2–10mg/d); (99)	Sz/ schizophreniform disorder without prior tx; psychotic symptoms requiring tx	Unclear, NR
Fakra et al. 2008 ⁸² RCT (50 wks)	G1: HAL (NR); (15) G2: RIS (NR); (15) Washout period: 1 wk	Sz defined by DSM–IV	High, Multiple sources including industry
Heck et al. 2000 ⁸⁵ RCT (NR)	G1: HAL (3–24mg/d); (37) G2: RIS (2–16mg/d); (40)	Clinically stable Sz on AP; >5 on ESRS or antiparkinson drug use	Unclear, Industry
Kee et al. 1998 ⁹⁹ RCT (NR)	G1: HAL (15mg/d); (9) G2: RIS (6mg/d); (9) Washout period: <1 wks Run-in phase: 3 wks	Sz; tx resistant defined by DSM–III–R	Unclear, Multiple sources
Keefe et al. 2006 ¹⁰¹ RCT (52 wks)	G1: HAL (2–19mg/d); (97) G2: RIS (2–10mg/d); (158)	Sz/ schizoaffective disorder; no previous AP <1 mo	Unclear, Industry
Kim et al. 2010 ¹⁰² RCT (8 wks)	G1: HAL (15.9±7.1mg/d); (35) G2: RIS (4.8±2.9mg/d); (41) Washout period: >4wks	Sz not further defined	Unclear, Foundation
Lee et al. 2007 ¹⁰⁷ RCT (8 wks)	G1: HAL (7.6±2.6mg/d); (10) G2: RIS (4.1±0.8mg/d); (10)	Sz defined by DSM–IV	High, Government

Table 42. Characteristics of RCTs comparing haloperidol versus risperidone in the treatment of schizophrenia (continued)

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout/ Run-in Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Liu 2000 ¹¹¹	G1: HAL (7.6±2.6mg/d); (28) G2: RIS (4.1±0.8mg/d); (28)	PANSS (total) >65; no pts with hx of physical illness or substance abuse	High, NR
Marder et al. 1994 ¹¹⁴ RCT (8 wks)	G1: HAL (20mg/d); (66) G2: RIS (2mg/d); (63) G3: RIS (6mg/d); (64) G4: RIS (10mg/d); (65) G5: RIS (16mg/d); (64) Washout period: 1 wk	Sz; no schizoaffective disorder	High, Industry
Marder et al. 2003 ¹¹³ RCT (2 yrs)	G1: HAL (2 mg t.i.d. for 1 wk then 6 mg h.s.); (30) G2: RIS (2 mg t.i.d. for 1 wk then 6 mg h.s.); (33) Run-in phase: 2 wk	>2 Sz episodes <2 yrs w/ continuing psychotic symptoms; OP >1 mo	Unclear, Multiple sources
McCue et al. 2006 ⁷³ RCT (3 wks)	G1: HAL (4–30mg); (61) G2: RIS (2–9 mg); (65)	Sz, schizoaffective disorder, or schizophreniform disorder; no hx of response or lack of response to AP, BP, major depression, or substance-induced psychotic disorder	High, No external funding
Min et al. 1993 ¹¹⁷ RCT (8 wks)	G1: HAL (2.5–5mg/d); (19) G2: RIS (2.5–5mg); (16) Washout period: 1 wk	Chronic Sz defined by DSM–III–R	Unclear, NR
Moller et al. 2008 ¹¹⁸ RCT (2 yrs)	G1: HAL (2–8mg/d); (146) G2: RIS (2–8mg/d); (143) Washout period: 1 wk	Sz recovered from a 1st episode (1st inpatient tx of psychotic symptoms)	Unclear, Multiple sources
Peuskens et al. 1995 ¹²⁰ RCT (8 wks)	G1: HAL (10mg/d); (226) G2: RIS (1mg/d); (229) G3: RIS (4mg/d); (227) G4: RIS (8mg/d); (230) G5: RIS (12mg/d); (226) G6: RIS (16mg/d); (224) Washout period: 3–7 d	Chronic Sz defined by DSM–III–R	Unclear, NR
Purdon et al. 2000 ¹²⁴ RCT (54 wks)	G1: HAL (5–20mg/d); (23) G2: RIS (2–6mg/d); (21) Washout period: 2–9 d Run-in phase: 1 mo	Sz <5 yrs of 1st exposure to AP; mild symptom severity	Unclear, Industry
Remillard et al. 2008 ¹²⁵ RCT (12 mo)	G1: HAL (2–40mg/d); (14) G2: RIS (2–6mg/d); (14)	Sz defined DSM–III–R	Unclear, Industry
Schooler et al. 2005 ¹³² RCT (2 yrs)	G1: HAL (1–8mg/d); (277) G2: RIS (1–8mg/d); (278) Washout period: 3–7 d	Sz, schizophreniform, or schizoaffective disorder <1 yr; <2 hospitalizations for psychosis; <12 wks of cumulative exposure to AP; required AP tx upon enrollment	Unclear, Industry
Shrivastava et al. 2000 ¹³⁵ RCT (12 mo)	G1: HAL (5–15mg/d); (50) G2: RIS (2mg/d); (50) Run-in phase: 2–4 wks	Hospitalized; acute Sz exacerbation	High, NR
Tamrakar et al. 2006 ¹³⁹ RCT (6 wks)	G1: HAL (10–20mg/d); (18) G2: RIS (4–6mg/d); (18) Washout period: 1 wk for oral; 4 wks for depot	Sz not further defined	High, NR
Volavka et al. 2002 ¹⁴⁵ RCT (14 wks)	G1: HAL (10–30mg/d); (37) G2: RIS (4–16mg/d); (41)	Chronic Sz or schizoaffective disorder and suboptimal response to previous tx	Unclear, Multiple sources

Table 42. Characteristics of RCTs comparing haloperidol versus risperidone in the treatment of schizophrenia (continued)

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout/ Run-in Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Wirshing et al. 1999 ¹⁴⁶ RCT (8 wks)	G1: HAL (15mg/d); (33) G2: RIS (6mg/d); (34) Washout period: 3–7 d Run-in phase: 3 wks	Tx resistant Sz; no functioning within last 5 yrs	Unclear, Multiple sources
Yen et al. 2004 ¹⁴⁹ RCT (12 wks)	G1: HAL (4–20mg/d); (20) G2: RIS (2–12mg/d); (21) Washout period: 7 d for oral AP; 4 wks for depot AP	Sz defined by DSM–III–R	High, Government
Zhang et al. 2001 ¹⁵⁰ RCT (12 wks)	G1: HAL (6mg/d); (37) G2: RIS (20mg/d); (41) Run-in phase: 2 wks	Sz; full dose conventional AP >3 mo; duration of illness >5 yrs	Unclear, NR

AP(s) = antipsychotic(s); BP = bipolar; D = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; ESRS = Extrapyramidal Syndrome Rating Scale; G = group; HAL = haloperidol; Hx = history; ICD–9 = International Classification of Diseases, 9th edition; Mg = milligrams; Mo = month; NR = not reported; OP = outpatient; Pts = patients; RCT = randomized controlled trial; RIS = risperidone; Sz = schizophrenia; T.i.d. = twice daily; Tx = treatment; W/ = with; Wk(s) = week(s); Yr(s) = years(s)

Key Question 1. Improving Core Illness Symptoms

Positive Symptoms

Twenty-two trials^{52,61,64,71,72,81,101,102,107,111,114,117,118,120,124,125,132,135,139,145,149,150} (n = 4,266) reported on positive symptoms using two scales (Table 43). Across 20 trials,^{52,61,64,72,81,101,107,111,114,117,118,120,124,125,132,135,139,145,149,150} (n = 4,043) there was no significant difference between groups on the PANSS (positive) (Table 43; Figure 22); however, there was substantial statistical heterogeneity among the studies ($I^2 = 53$ percent). Restricting the analyses to the following subgroups reduced the heterogeneity:

- Mixed populations with respect to comorbid drug use (6 studies): significantly favored risperidone ($I^2 = 0$ percent);
- Mixed populations with respect to first versus multiple episodes (11 studies): significantly favored risperidone ($I^2 = 34$ percent);
- Followed patients for >6 weeks and <6 months (10 studies); no difference between groups ($I^2 = 0$ percent);
- Asian patients only (5 studies): no difference between groups ($I^2 = 0$ percent);
- No industry funding or no funding source reported (12 studies): significantly favored risperidone ($I^2 = 28$ percent);
- High risk of bias (5 studies): significantly favored risperidone ($I^2 = 0$ percent).

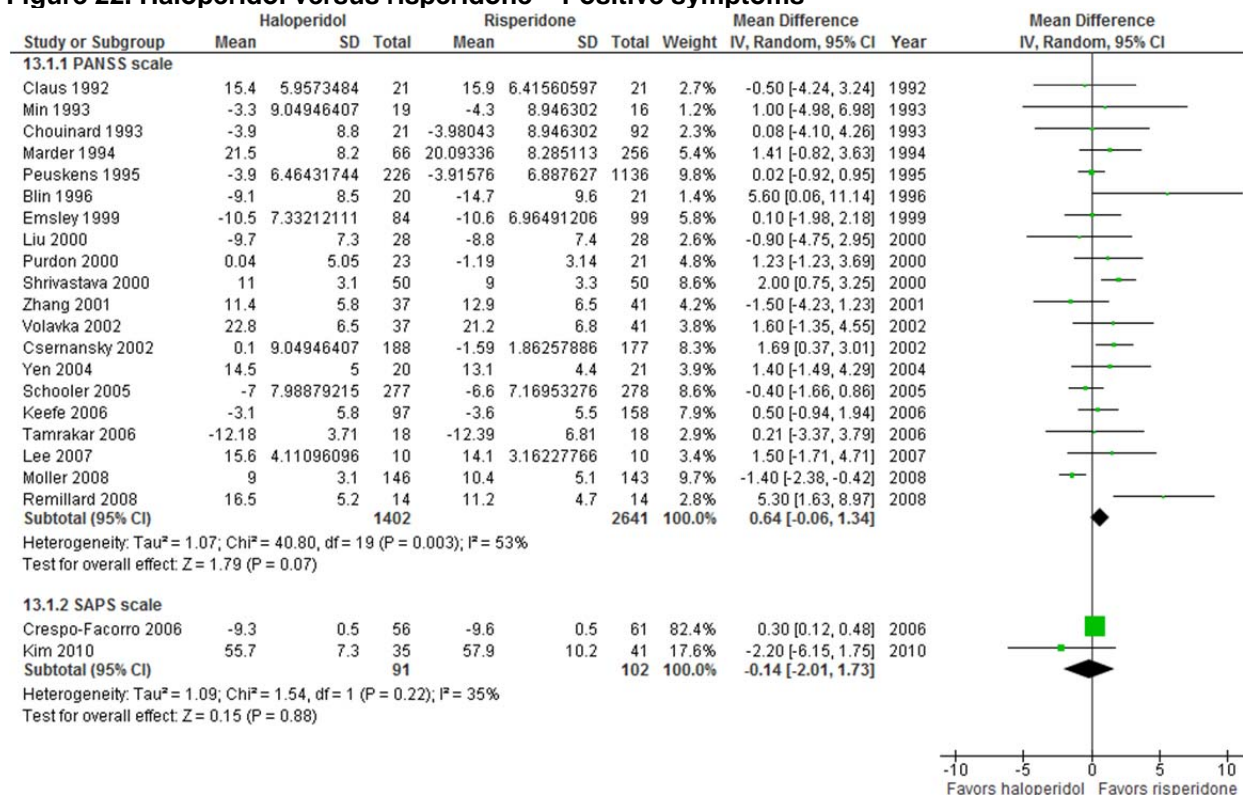
Tests for publication bias were not significant, although the funnel plot showed some asymmetry due to the two small studies that showed large effects for risperidone (Appendix K, Funnel plot 7).

Two trials^{71,102} (n = 193) reported on the SAPS, (Table 43; Figure 22) and pooled results showed no significant difference between groups. Statistical heterogeneity was moderate ($I^2 = 35$ percent). Crespo-Facorro et al.⁷¹ compared 3–9 mg/d haloperidol with 3–6 mg/d risperidone and showed a significant difference favoring risperidone. This study included mixed populations in terms of disorder subtypes, first and multiple episodes, and treatment resistance. The study excluded patients with comorbid drug or alcohol use. Duration of followup was 6 weeks; the study had high risk of bias and did not report on funding source. Kim et al.¹⁰² compared 15.9±7.1

mg/d haloperidol with 4.8 ± 2.9 mg/d risperidone and found no significant difference between groups. This study included mixed populations in terms of disorder subtypes, comorbid drug or alcohol use, and treatment resistance. The study included only patients of Asian descent with multiple episodes. Duration of followup was 8 weeks; risk of bias was unclear, and the study received institutional support.

The SoE for PANSS (positive) and SAPS was graded as low (Table 44).

Figure 22. Haloperidol versus risperidone – Positive symptoms



CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale; SAPS = Scale for the Assessment of Positive Symptoms; SD = standard deviation

Negative Symptoms

Twenty-three trials^{52,53,61,64,71,72,81,101,102,107,111,114,117,118,120,124,125,132,135,139,145,149,150} ($n = 4,260$) reported on negative symptoms using two scales (Table 43; Figure 23).

Twenty trials^{52,61,64,72,81,101,107,111,114,117,118,120,124,125,132,135,139,145,149,150} ($n = 4,043$) reported PANSS (negative). Pooled results showed a significant difference favoring risperidone; statistical heterogeneity was moderate ($I^2 = 30$ percent). This was considered not to be clinically significant. Restricting the analyses to the following subgroups reduced the heterogeneity:

- Specifically included patients with schizoaffective disorder (4 studies): significantly favored risperidone ($I^2 = 0$ percent);
- Specifically excluded patients with schizoaffective disorder (2 studies): significantly favored risperidone ($I^2 = 0$ percent);
- Included patients with both first and multiple episodes (13 studies): significantly favored risperidone ($I^2 = 0$ percent);

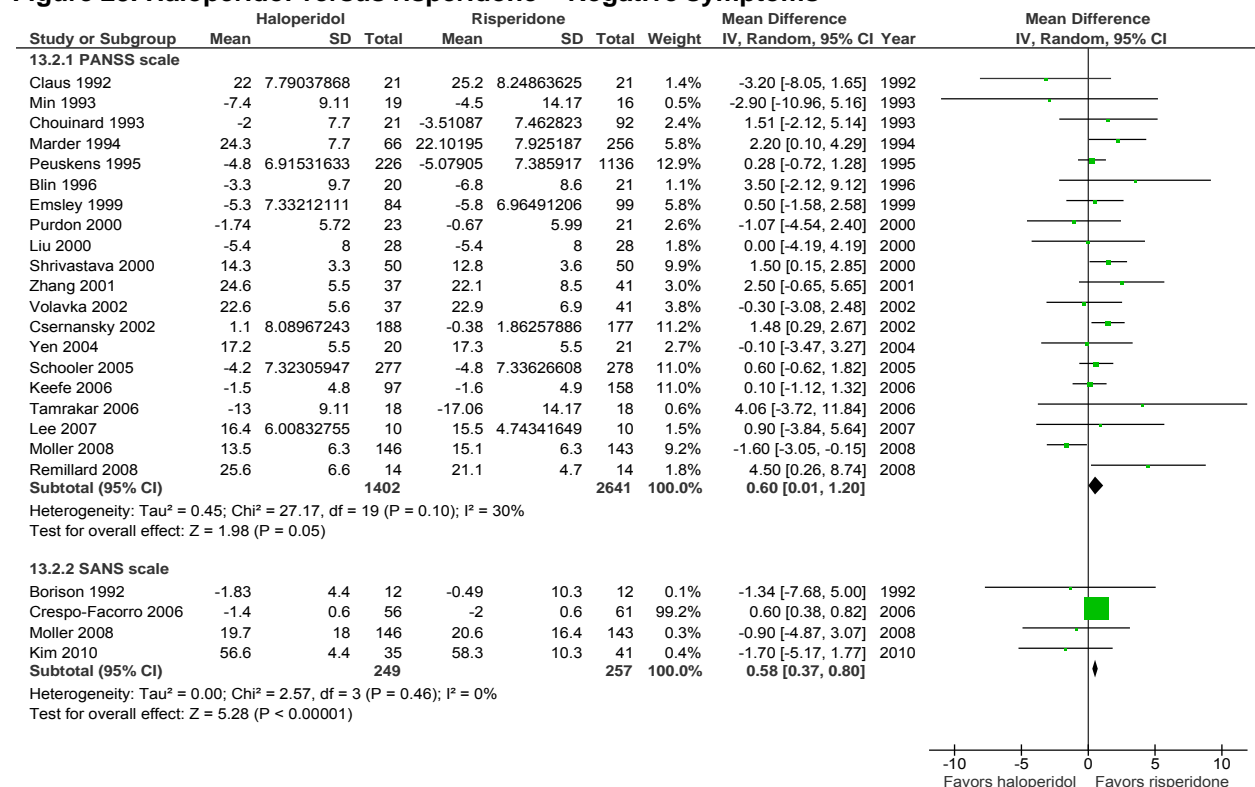
- Mixed populations with respect to treatment resistance (14 studies): significantly favored risperidone ($I^2 = 3$ percent);
- Followed patients for <6 weeks (3 studies): no difference between groups ($I^2 = 0$ percent);
- Followed patients for >6 weeks and <6 months (10 studies); no difference between groups ($I^2 = 0$ percent);
- Received funding from sources other than industry or did not report source of funding (10 studies): significantly favored risperidone ($I^2 = 0$ percent).
- High risk of bias (5 studies): significantly favored risperidone ($I^2 = 0$ percent);
- Patient populations of Asian descent (5 studies): significantly favored risperidone ($I^2 = 0$ percent);

There was no indication of publication bias based on statistical tests and visual inspection of the funnel plot (Appendix K, Funnel plot 8).

Pooled results from four trials^{53,71,102,118} (n = 506) showed a significant difference on the SANS scale favoring risperidone. This was considered to be clinically significant. There was no evidence of heterogeneity ($I^2 = 0$ percent).

The SoE for PANSS (negative) and SANS was graded as moderate (Table 44).

Figure 23. Haloperidol versus risperidone – Negative symptoms



CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale; SANS = Scale for the Assessment of Negative Symptoms; SD = standard deviation

General Psychopathology

Sixteen trials^{52,61,64,81,107,111,117,118,120,124,132,135,139,145,149,150} (n = 3,073) reported PANSS (general psychopathology) (Table 43; Figure 24). Pooled results are not reported due to marked heterogeneity among the included trials ($I^2 = 96$ percent; 95% CI, 94 to 97). Thirteen of the trials

(n = 2,648) showed no difference between groups; pooled results also showed no difference and had no statistical heterogeneity (MD = 0.90; 95% CI, -0.10 to 1.90; $I^2 = 0$ percent). The three trials that were removed from the analysis all favored haloperidol. There was substantial statistical heterogeneity among these three trials. All three studies included mixed disorder subtypes. Two studies^{118,135} only included patients with multiple episodes. One study¹¹⁸ excluded patients with comorbid drug or alcohol use and treatment resistance; this study showed the most conservative estimate of the three favoring haloperidol. Doses of haloperidol were 2–8 mg/d,¹¹⁸ 5–15 mg/d,¹³⁵ and 10–20¹³⁹ mg/d; doses of risperidone were 2–8 mg/d,¹¹⁸ 2 mg/d,¹³⁵ and 4–6 mg/d.¹³⁹ Duration of followup was 6 weeks,¹³⁹ 1 year,¹³⁵ and 2 years.¹¹⁸ Risk of bias was unclear for one study,¹¹⁸ which was industry-funded; the other two studies had high risk of bias and did not report source of funding. There was no indication of publication bias based on statistical tests (Appendix K, Funnel plot 9). The SoE was graded as low (Table 44).

Three studies used CDS–S^{71,85,118} (n = 483); pooled results showed no difference; however, there was substantial statistical heterogeneity. Crespo-Facorro⁷¹ described immediately above showed a significant effect favoring risperidone. The other two studies showed no difference and were statistically homogeneous. Both studies included mixed disorder subtypes and only patients with multiple episodes. One study¹¹⁸ excluded patients with treatment resistance, whereas the other included both treatment-resistant and nonresistant patients. One¹¹⁸ excluded patients with comorbid drug or alcohol use, the other included a mixed population.⁸⁵ One study¹¹⁸ used 2–8 mg/d of both drugs; the other compared 3–24 mg/d haloperidol with 2–16 mg/d risperidone. Duration of followup was 8 weeks in one study¹¹⁸ and not reported in the other.⁸⁵ Both studies had unclear risk of bias and industry funding.

Two studies used HAM–D^{71,118} (n = 468); pooled results showed no difference, although heterogeneity was substantial ($I^2 = 71$ percent). Crespo-Facorro et al.⁷¹ compared 3–9 mg/d haloperidol with 3–6 mg/d risperidone and showed a significant difference favoring risperidone. This study included mixed populations in terms of disorder subtypes, first and multiple episodes, and treatment resistance. The study excluded patients with comorbid drug or alcohol use. Duration of followup was 6 weeks; the study had high risk of bias and did not report funding source. Moller et al.¹¹⁸ compared 2–8 mg/d of both haloperidol and risperidone and found no difference between groups. The study included mixed populations in terms of disorder subtype. The study excluded patients with comorbid drug or alcohol use and treatment resistance; only patients with multiple episodes were included. Duration of followup was 2 years. Risk of bias was unclear, and the study was industry-funded.

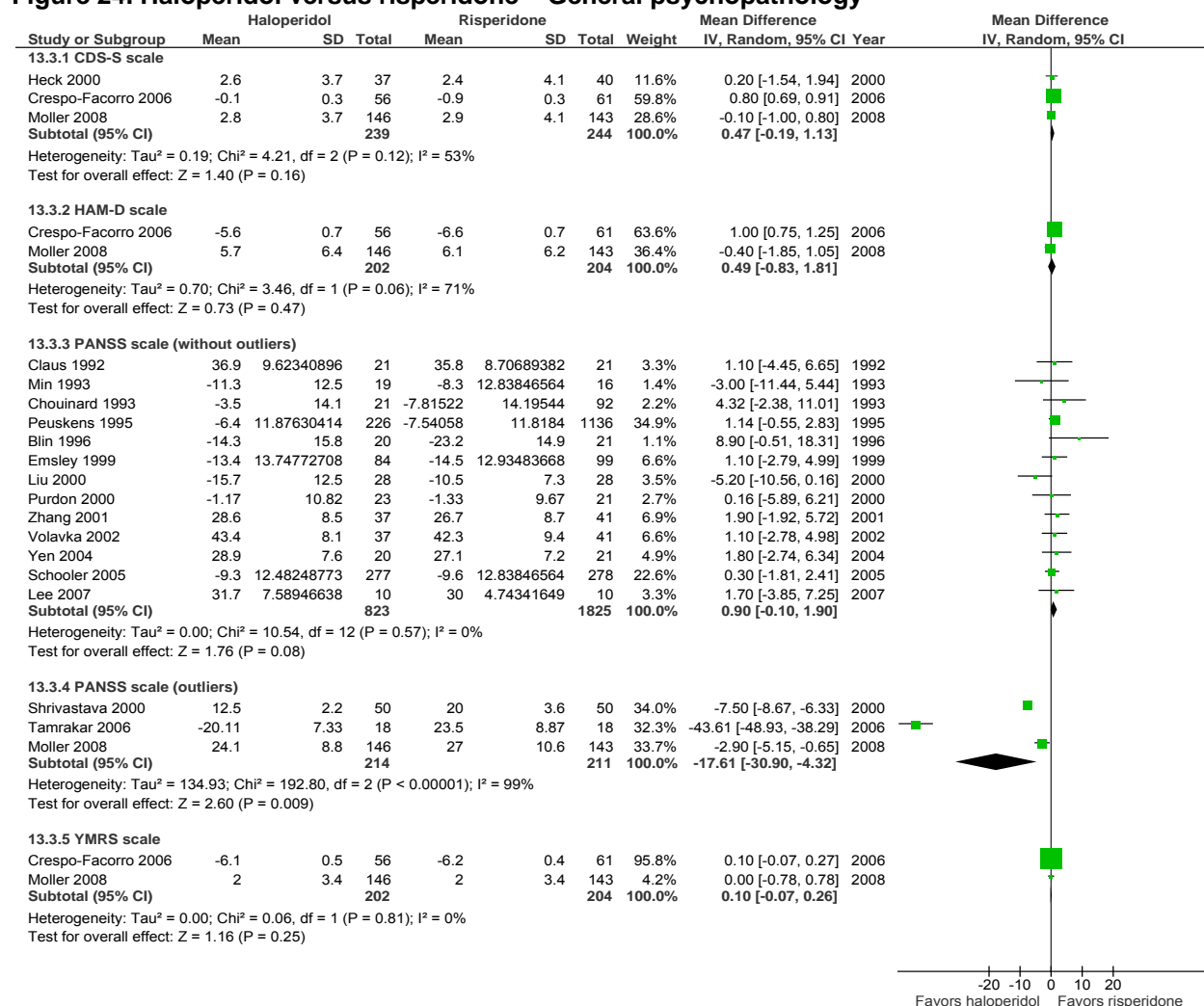
Two studies used the YMRS; results were consistent across studies and showed no difference between groups.^{71,118} There was no evidence of heterogeneity between the studies ($I^2 = 0$ percent).

One trial used HAM–A¹⁰¹ (n = 255) and found no difference between groups.

One study¹⁰¹ (n = 256) compared 2–19 mg/d haloperidol with 2–10 mg/d risperidone and reported no difference between groups based on the MADRS.

The SoE for the CDS–S, HAM–D, PANSS, and YMRS were graded as low and for the HAM–A and MADRS were graded as insufficient (Table 44).

Figure 24. Haloperidol versus risperidone – General psychopathology



CDS-S = Calgary Depression Scale for Schizophrenia; CI = confidence intervals; df = degrees of freedom; HAM-D = Hamilton Rating Scale for Depression; I^2 = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale; SD = standard deviation; YMRS = Young Mania Rating Scale

Global Ratings and Total Scores

Global ratings and total scores were reported in 27 trials^{45,52,53,60,61,64,71-73,81,82,85,101,107,111,113,114,117,118,120,132,135,139,145,146,149,150} ($n = 4,557$) using 8 different scales (Table 43; Figure 25).

Twenty studies ($n = 4,021$) used the PANSS (total).^{45,52,61,64,72,81,82,101,107,111,114,117,118,120,132,135,139,145,149,150} There was no significant difference between groups; however, heterogeneity was substantial ($I^2 = 75$ percent). All studies individually showed no difference or favored risperidone except for one study¹³⁵ favoring haloperidol. When this study, was removed from the analysis, the heterogeneity was minimal ($I^2 = 12$ percent). This study compared 5–15 mg/d haloperidol with 2 mg/d risperidone and included mixed populations with respect to disorder subtype, treatment resistance, and comorbid drug or alcohol use. The study only included patients with multiple episodes. Duration of followup was 1 year. Risk of bias was high, and source of funding was not reported. There was some suggestion of publication bias based on Egger's test ($p = 0.01$) and visual inspection of the funnel plot, with one small study showing a large effect for risperidone (Appendix K, Funnel plot 10).

Thirteen studies (n = 2592) used the BPRS.^{52,53,60,61,71,73,81,85,113,114,117,120,146} There was no significant difference between groups; statistical heterogeneity was moderate ($I^2 = 44$ percent). Restricting the analyses to the following subgroups reduced the heterogeneity:

- Excluded patients with comorbid drug or alcohol use (7 studies): significantly favored risperidone ($I^2 = 0$ percent);
- Included patients with multiple episodes only (5 studies): no difference between groups ($I^2 = 0$ percent);
- Duration of followup was ≤ 6 weeks (5 studies): significantly favored risperidone ($I^2 = 0$ percent);
- Industry funding (6 studies): no difference between groups ($I^2 = 0$ percent); Other sources of funding or source of funding not reported (7 studies): no difference between groups ($I^2 = 18$ percent);
- Unclear risk of bias (10 studies): no difference between groups ($I^2 = 0$ percent); High risk of bias (3 studies): significantly favored risperidone ($I^2 = 7\%$ percent);
- Some subgroups showed negligible heterogeneity, but the subgroups included very few studies (e.g., schizoaffective disorder, treatment resistance, and haloperidol >20 mg/d).

There was no indication of publication bias based on statistical tests and visual inspection of the funnel plot (Appendix K, Funnel plot 11).

Eight studies reported scores based on CGI-S;^{52,61,71,114,117,118,120,146} there were no differences between groups, but the results were statistically heterogeneous ($I^2 = 63$ percent). Most studies showed no difference between groups except for Crespo-Facorro et al.,⁷¹ which favored haloperidol and Blin et al.,⁵² which favored risperidone. Removing these two trials reduced the heterogeneity to 0 percent. Crespo-Facorro et al.⁷¹ compared 3–9 mg/d haloperidol with 3–6 mg/d risperidone and included mixed populations in terms of disorder subtypes, first and multiple episodes, and treatment resistance. The study excluded patients with comorbid drug or alcohol use. Duration of followup was 6 weeks; the study had high risk of bias and did not report funding source. Blin et al.⁵² compared similar doses of haloperidol and risperidone (4–12 mg/d). The study excluded patients with schizoaffective disorder and comorbid drug or alcohol use, and included mixed populations with respect to treatment resistance and first or multiple episodes. Duration of followup was 4 weeks. Risk of bias was unclear; funding source was not reported.

Three studies used the CGI-I;^{117,132,146} no difference between groups was found, but the studies were statistically heterogeneous ($I^2 = 48$ percent). One study¹³² specifically included patients with schizoaffective disorder. Two studies^{117,146} only included patients with multiple episodes. One study¹⁴⁶ only included patients with treatment resistance, ascertained by history and run-in to the trial. One study involved only Asian patients¹¹⁷ and excluded patients with comorbid drug or alcohol use. Doses of haloperidol were 2.5–5 mg/d,¹¹⁷ 1–8 mg/d¹³² and 15 mg/d;¹⁴⁶ doses of risperidone were 2.5–5 mg/d,¹¹⁷ 1–8 mg/d,¹³² and 6 mg/d.¹⁴⁶ Duration of followup was 8 weeks^{117,146} and 2 years.¹³² All studies had unclear risk of bias, and two declared industry funding.^{132,146}

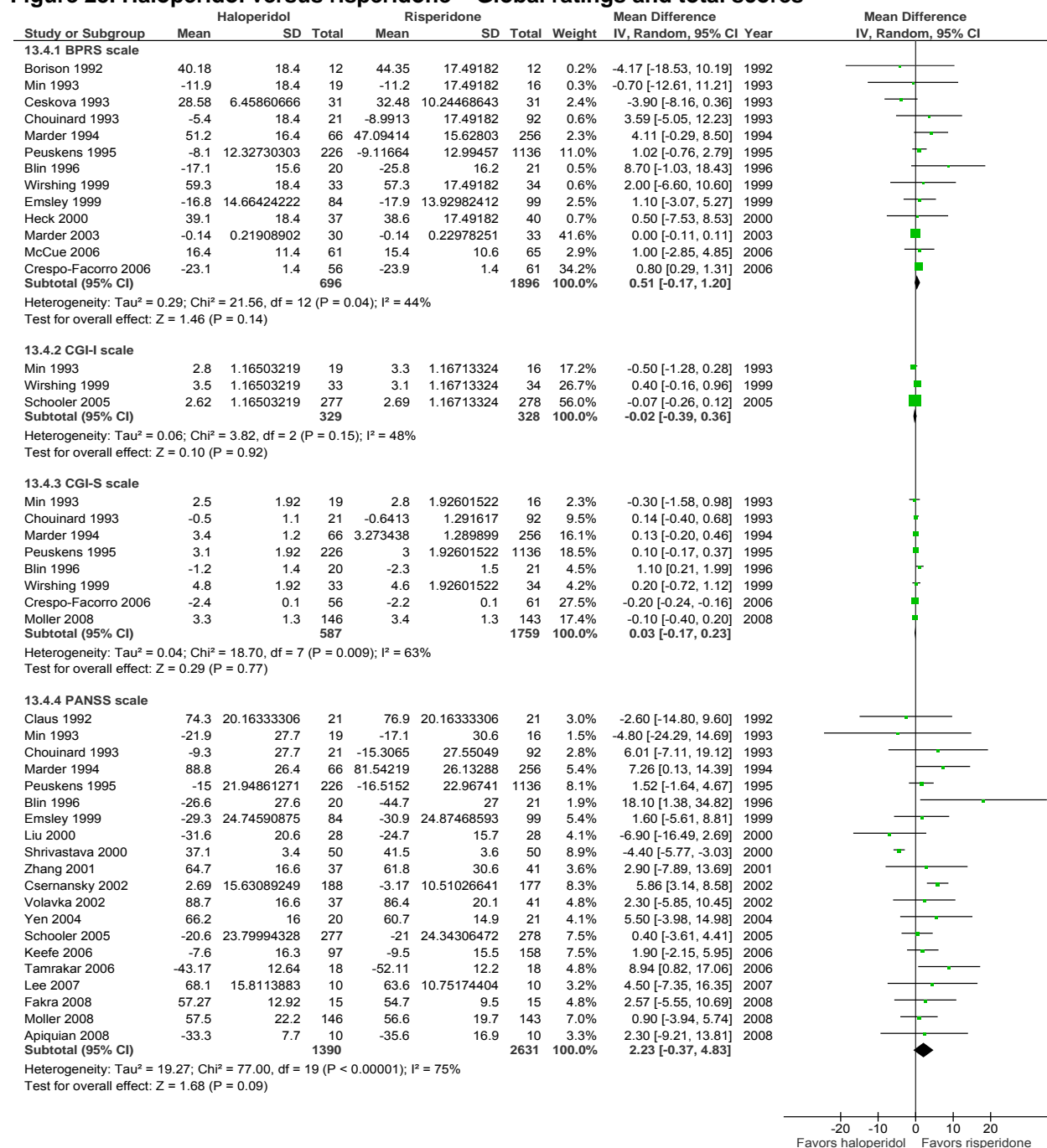
Single studies⁶⁴ (n = 42) compared 1–10 mg/d of haloperidol with 1–10 mg/d of risperidone and found no differences between groups on the NOISIE or SADS-C.

One study¹¹⁴ (n = 322) compared 20 mg/d haloperidol with 2–16 mg/d risperidone and found a significant difference in favor of risperidone for the Symptom Checklist (SCL-90-R). The difference was considered not to be clinically important.

One study¹¹⁸ (n = 289) compared 2–8 mg/d of haloperidol with 2–8 mg/d of risperidone and found no differences between groups on the Subjective Well-being Under Neuroleptic Scale.

The SoE was graded low for BPRS, CGI-I, CGI-S, and PANSS (total) and insufficient for NOISIE, SADS-C, SCL-90-R, and Subjective Well-being Under Neuroleptics Scale (Table 44).

Figure 25. Haloperidol versus risperidone – Global ratings and total scores



BPRS = Brief Psychiatric Rating Scale; CGI-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression-Severity; CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale

Key Questions 2 and 4. Improvement in Functional Outcomes, Decreasing Health Care System Utilization, and Other Outcomes

Functional Outcomes

Employment or Personal Earnings

One trial¹³⁵ (n = 100) comparing 5–15 mg/d haloperidol with 2 mg/d risperidone reported economic independence in patients and found no significant difference between groups (Table 43).

Encounters with Legal System

One trial¹¹⁸ (n = 289) comparing 2–8 mg/d haloperidol with 2–8 mg/d risperidone reported attitudes regarding drugs and found no significant difference between groups (Table 43).

Health Care System Utilization

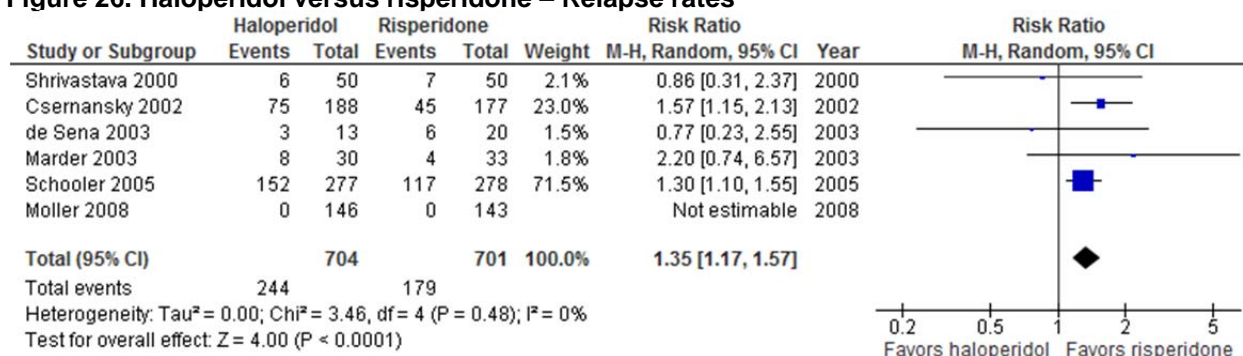
Pooled data from three trials^{77,118,135} (n = 422) showed no significant differences between groups for rates of hospitalization or rehospitalization ($I^2 = 24$ percent) (Table 43). Two studies^{77,118} excluded patients with comorbid drug or alcohol use. Two studies^{118,135} only included patients with multiple episodes. One¹¹⁸ study excluded patients with treatment resistance. Doses of haloperidol varied: 5–17 mg/d,⁷⁷ 2–8 mg/d,¹¹⁸ and 5–15 mg/d;¹³⁵ doses of risperidone were 1–6 mg/d,⁷⁷ 2–8 mg/d,¹¹⁸ and 2 mg/d.¹³⁵ Duration of followup was 1 year^{77,135} and 2 years.¹¹⁸ Risk of bias was high for two trials^{77,135} and unclear for one.¹¹⁸ Two studies were industry-funded,^{77,118} and one did not report funding source.

Other Outcomes

Relapse, Response, and Remission Rates

Pooled results from six trials^{72,77,113,118,132,135} (n = 1,405) showed a significantly lower relapse rate favoring risperidone (Table 43; Figure 26); the studies were statistically homogeneous ($I^2 = 0$ percent).

Figure 26. Haloperidol versus risperidone – Relapse rates

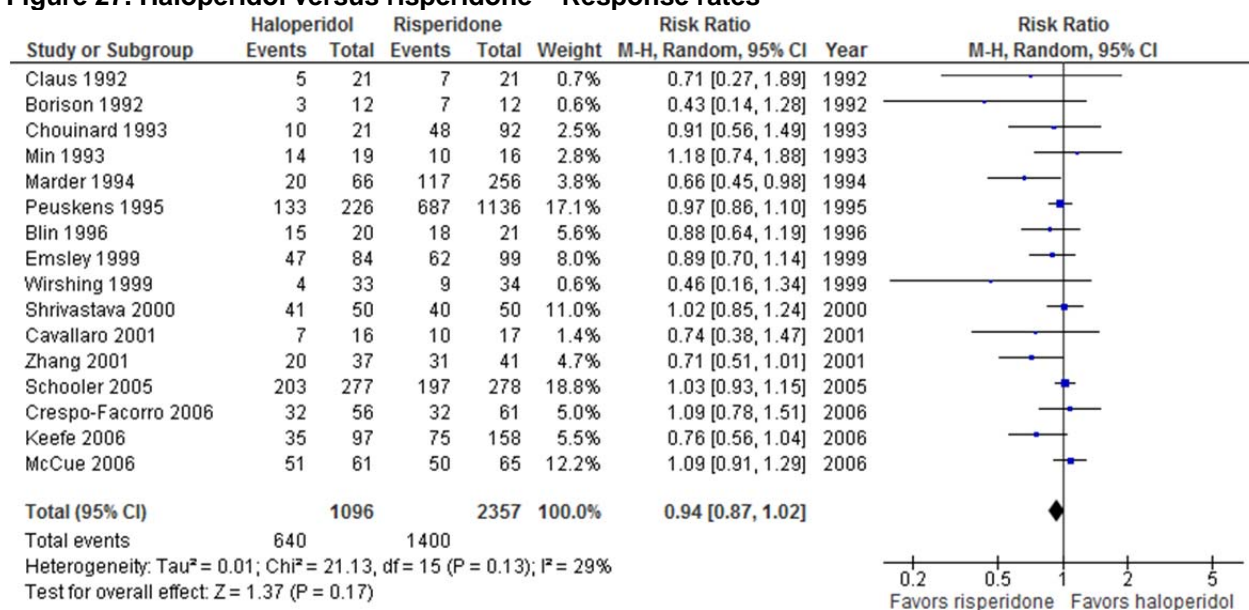


CI = confidence intervals; df = degrees of freedom; I² = I-squared; IV = inverse variance; M-H = Mantel-Haenszel

Two trials^{60,71} (n = 179) showed no significant difference between groups on treatment remission rates (Table 43); results were statistically homogeneous ($I^2 = 0$ percent)

Pooled results from 16 trials^{52,53,59,61,64,73,81,101,114,117,120,132,135,145,146,150} (n = 3,453) showed no significant difference between groups for treatment response rates (Table 43; Figure 27) there was no important statistical heterogeneity ($I^2 = 29$ percent). No important patterns were observed in the subgroup and sensitivity analyses; moreover, all subgroups showed no difference between groups (Appendix M, Table 111). All of the individual trials showed no differences except one study,¹¹⁴ which showed a significant benefit favoring risperidone. This trial compared 20 mg/d haloperidol with 2–16 mg/d risperidone, excluded patients with schizoaffective disorder, and included mixed populations with respect to comorbid drug or alcohol use, first or multiple episodes, and treatment resistance. Length of followup was 8 weeks. Risk of bias was high, and the study was industry-funded. There was suggestion of publication bias with more small trials favoring risperidone, based on Begg's rank correlation ($p = 0.03$) and Egger's ($p = 0.006$) tests, as well as visual inspection of the funnel plot (Appendix K, Funnel plot 12).

Figure 27. Haloperidol versus risperidone – Response rates



CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; M-H = Mantel-Haenszel

Medication Adherence

Three trials^{72,101,149} (n = 661) assessed medication adherence (Table 43); pooled results were homogeneous ($I^2 = 0$ percent) and showed no difference between groups.

Health-related Quality of Life

Two trials^{113,118} (n = 674) assessed health-related quality of life using a variety of measures and found no differences (Table 43).

Patient Satisfaction

One trial¹⁴⁶ (n = 67) comparing 15 mg/d haloperidol with 6 mg/d risperidone found no significant differences between groups for patient satisfaction (Table 43).

Key Question 5. Subgroups

Race

Six trials^{102,107,111,117,149,150} (n = 369) in Asian patients showed no significant difference on PANSS (positive), SAPS, PANSS (negative), or SANS.

First Episode

Pooled results from four trials^{71,81,118,132} (n = 1,365) in patients undergoing treatment for their first psychotic episode showed 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, CGI-I, CGI-S, PANSS (total), and YMRS.

Table 43. Evidence summary table: haloperidol versus risperidone

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Positive Symptoms					
PANSS ^{52,61,64,72,81,101,107,111,114,117,118,120,124,125,132,135,139,145,149,150}	20	4043	0.64 (-0.06, 1.34)	53%	ND
SAPS ^{71,102}	2	193	-0.14 (-2.01, 1.73)	35%	ND
Negative Symptoms					
PANSS ^{52,61,64,72,81,101,107,111,114,117,118,120,124,125,132,135,139,145,149,150}	20	4043	0.60 (0.01, 1.20)	30%	risperidone
SANS ^{53,71,102,118}	4	506	0.58 (0.37, 0.80)	0%	risperidone
General Psychopathology					
CDS-S ^{71,85,118}	3	483	0.47 (-0.19, 1.13)	53%	ND
HAM-A ¹⁰¹	1	255	0.10 (-1.44, 1.64)	NE	ND
HAM-D ^{71,118}	2	406	0.49 (-0.83, 1.81)	71%	ND
MADRS ¹⁰¹	1	255	0.50 (-1.58, 2.58)	NE	ND
PANSS (general psychopathology), ^{52,61,64,81,107,111,118,120,124,132,145,149,150} omit outliers	13	2648	0.90 (-0.10, 1.90)	0%	ND
YMRS ^{71,118}	2	406	0.10 (-0.07, 0.26)	0%	ND
Global Ratings and Total Scores					
BPRS ^{52,53,60,61,71,73,81,85,113,114,117,120,146}	13	2592	0.51 (-0.17, 1.20)	44%	ND
CGI-I ^{117,132,146}	3	657	-0.02 (-0.39, 0.36)	48%	ND
CGI-S ^{61,71,114,117,118,120,146}	8	1667	0.03 (-0.18, 0.23)	61%	ND
NOSIE-30 ⁶⁴	1	42	-5.30 (-21.61, 11.01)	NE	ND
PANSS ^{45,52,61,64,72,81,82,101,107,111,114,117,118,120,132,135,139,145,149,150}	20	4021	2.23 (-0.37, 4.83)	75%	ND
SADS-C ⁶⁴	1	42	-0.40 (-10.12, 9.32)	NE	ND
SCL-90-R ¹¹⁴	1	63	0.31 (0.12, 0.50)	NE	risperidone
Subjective Well-being Under Neuroleptic Scale ¹¹⁸	1	289	1.80 (-2.39, 5.99)	NE	ND
Employment or Personal Earnings					
Economic independence ¹³⁵	1	100	0.94 (0.68, 1.29)*	NE	ND
Encounters with legal system					
Attitude regarding drugs ¹¹⁸	1	289	-0.80 (-2.12, 0.52)	NE	ND
Health care system utilization					

Table 43. Evidence summary table: haloperidol versus risperidone (continued)

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Other Outcomes					
Relapse rates ^{72,77,113,118,132,135}	6	1405	1.35 (1.17, 1.57)*	0%	risperidone
Remission rates ^{60,71}	2	179	0.84 (0.56, 1.24)	0%	ND
Response rates ^{52,53,59,61,64,73,81,101,114,117,120,132,135,145,146,150}	16	3453	0.94 (0.87, 1.02)	29%	ND
Medication adherence ^{72,101,149}	3	661	0.99 (0.95, 1.02)*	0%	ND
Patient satisfaction ¹⁴⁶	1	67	0.67 (0.37, 1.20)*	NE	ND
Health-Related Quality of Life					
QLS: Total ¹¹³	1	63	0.10 (-0.17, 0.37)	NE	ND
LQLP: total score ¹¹⁸	1	289	0.10 (-0.20, 0.40)	NE	ND
LQLP: general health ¹¹⁸	1	289	-0.10 (-0.43, 0.23)	NE	ND
QoL: common objects ¹¹³	1	63	0.04 (-0.25, 0.33)	NE	ND
QoL: Intrapsychic ¹¹³	1	63	0.09 (-0.14, 0.32)	NE	ND
QoL: role functioning ¹¹³	1	63	0.05 (-0.69, 0.79)	NE	ND

Note: bold = statistically significant; * = binary outcome; BPRS = Brief Psychiatric Rating Scale; CDS-S = Calgary Depression Scale for Schizophrenia; CGI-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression-Severity; HAM-A = Hamilton Rating Scale for Anxiety; HAM-D = Hamilton Rating Scale for Depression; I² = I-squared; LQLP = Lancashire Quality of Life Profile; MADRS = Montgomery-Asberg Depression Rating Scale; ND = no difference; NE = not estimable; NOSIE = Nurses' Observation Scale for Inpatient Evaluation; PANSS = Positive and Negative Symptom Scale; QLS = Quality of Life Scale; QoL = quality of life; 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-90-R = Symptom Checklist-90-R; SWBUN = Subjective Well-Being Under Neuroleptics Scale; YMRS = Young Mania Rating Scale

Table 44. Strength of evidence (GRADE): haloperidol versus risperidone

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Positive Symptoms						
PANSS	20 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
SAPS	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
Negative Symptoms						
PANSS	20 RCT	Medium	Consistent	Direct	Precise	Moderate (favoring risperidone)
SANS	4 RCT	Medium	Consistent	Direct	Precise	Moderate (favoring risperidone)
General Psychopathology						
CDS-S	3 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
HAM-A	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
HAM-D	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
MADRS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
PANSS	13 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
YMRS	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
Global Ratings and Total Scores						
BPRS	13 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
CGI-I	3 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
CGI-S	8 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
NOSIE-30	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

Table 44. Strength of evidence (GRADE): haloperidol versus risperidone (continued)

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
<i>Global Ratings and Total Scores (continued)</i>						
PANSS	20 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
SADS-C	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
SCL-90-R	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
SWBUN	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

BPRS = Brief Psychiatric Rating Scale; CDS-S = Calgary Depression Scale for Schizophrenia; CGI-I = Clinical Global Impression-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; ND = no difference; NOSIE = Nurses' Observation Scale for Inpatient Evaluation; RoB = risk of bias; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; 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-90-R = Symptom Checklist-90-R; SoE = strength of evidence; YMRS = Young Mania Rating Scale

Haloperidol Versus Ziprasidone

Key Points:

- Eight RCTs compared haloperidol versus ziprasidone in patients with a range of disease severity.
- The most commonly reported outcome was global rating or total symptom scores using four different scales: BPRS (4 trials), CGI-S (4 trials), PANSS (4 trials), and GAF (3 trials). No differences were found between groups for any of the scales. The SoE was low for all scales.
- Six studies reported response rates and overall showed no difference; however, results showed substantial statistical heterogeneity, which was not fully explained through the predefined subgroup and sensitivity analyses. Moreover, some subgroups showed no differences (3 studies excluding patients with comorbid drug or alcohol use), one favored haloperidol (2 studies with duration of followup >6 months), and others favored ziprasidone (3 studies of patients with treatment resistance or mixed populations; 2 studies in which funding source was not reported).
- Three studies assessed remission rates and found no differences between groups.
- Other outcomes were assessed in only one to two studies, and in all but one case showed no differences between groups.

Eight RCTs^{57,69,73,75,83,86,91,122} (n = 2,067) compared haloperidol with ziprasidone. Key characteristics of the included trials and summary findings are presented in Table 45 and Table 46. All trials included mixed populations in terms of disorder subtypes. Three studies^{57,69,83} excluded patients with comorbid drug or alcohol use. One study included only patients with treatment resistance ascertained by history.⁷³ Three studies specifically excluded patients with treatment resistance.^{57,86,91} Doses of haloperidol ranged across studies and varied from 1–4 mg/d^{75,91} to 4–30 mg/day.⁷³ Doses of ziprasidone also varied across studies, ranging from 4–160 mg/d⁸³ to 40–240 mg/d.⁷³

Duration of followup was ≤6 weeks in four studies^{57,69,73,83} and ≥6 months in four studies;^{75,86,91,122} one study¹²² followed patients for 3.75 years. Risk of bias was unclear for two studies^{73,122} and high for the others. Seven studies were industry-funded, whereas two studies^{73,83} did not report their source of funding.

Publication bias was not formally tested for any of the outcomes due the small number of included trials. The SoE for the majority of the evaluated outcomes was insufficient due to the small number of trials (Table 47).

Table 45. Characteristics of RCTs comparing haloperidol versus ziprasidone in the treatment of schizophrenia and related psychoses

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout/ Run-in Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Brook et al. 2005 ⁵⁷ RCT (6 wks)	G1: HAL IM (2.5–10mg/d; Oral: 5–20mg/d); (138) G2: ZIP IM (10–40mg/d; Oral: 40–80mg/d); (429)	Acute exacerbation of Sz or schizoaffective disorder	High, Industry
Corripio et al. 2005 ⁵⁹ RCT (2 wks)	G1: HAL (5–20mg/d); (10) G2: ZIP (10–40mg/d); (10) Washout period: 2 wks	Sz manifesting acute psychotic exacerbation	High, Multiple sources
Davidson et al. 2009 ⁷⁵ RCT (6 mo)	G1: HAL (1–4mg/d); (103) G2: ZIP (40–160mg/d); (82)	<2 yrs since onset of positive symptoms; <2 wks exposure to AP <1 yr; <6 wks lifetime exposure to AP	High, Industry
Goff et al. 1998 ⁸³ RCT (4 wks)	G1: HAL (15mg/d); (17) G2: ZIP (4mg/d); (19) G3: ZIP (10mg/d); (17) G4: ZIP (40mg/d); (17) G5: ZIP (160mg/d); (20) Washout period: ≥1 wks	Hospitalized ≤2 wks for acute exacerbation; hospitalized or resided in an intermediate tx center ≥3 mo; partially responded to AP tx; no depot AP ≤2 mo or recent illicit drug	High, NR
Hirsch et al. 2002 ⁸⁶ NRCT (28 wks)	G1: HAL (5–15mg/d); (153) G2: ZIP (80–160mg/d); (148) Washout period: 2 wks Run-in phase: ≤2 wks	Chronic/ subchronic Sz; required AP maintenance tx; ≤2 AP tx failures ≤2 yrs; received investigational AP ≤4 wks or FLU ≤5 wks	High, Industry
Kahn et al. 2008 ⁹¹ RCT (12 mo)	G1: HAL (1–4mg/d); (103) G2: ZIP (40–160mg/d); (82)	Sz/ schizophreniform or schizoaffective disorder; ≤2 yrs since onset of positive symptoms; no AP ≥2 wks in last 1 yr, or ≥6 wks at any time	High, Industry
McCue et al. 2006 ⁷³ RCT (3 wks)	G1: HAL (4–30mg); (61) G2: ZIP (40–240 mg); (59)	Sz, schizoaffective disorder, or schizophreniform disorder; no hx of response or lack of response to AP, BP, major depression, or substance-induced psychotic disorder	High, No external funding
Potkin et al. 2009 ¹²² RCT (3.75 yrs)	G1: HAL (5–20mg/d); (151) G2: ZIP (80–120mg/d); (448) G3: ZIP (80–160mg/d) Washout period: 4 wks	Chronic/ subchronic Sz or schizoaffective disorder	Unclear, Industry

AP(s) = antipsychotic(s); BP = bipolar disorder; D = day; FLU = fluphenazine; G = group; HAL = haloperidol; Hx = history; IM = intramuscular; Mg = milligrams; Mo = month; NR = not reported; RCT = randomized controlled trial; Sz = schizophrenia; Tx = treatment; Wks = weeks; Yr(s) = year(s); ZIP = ziprasidone

Key Question 1. Improving Core Illness Symptoms

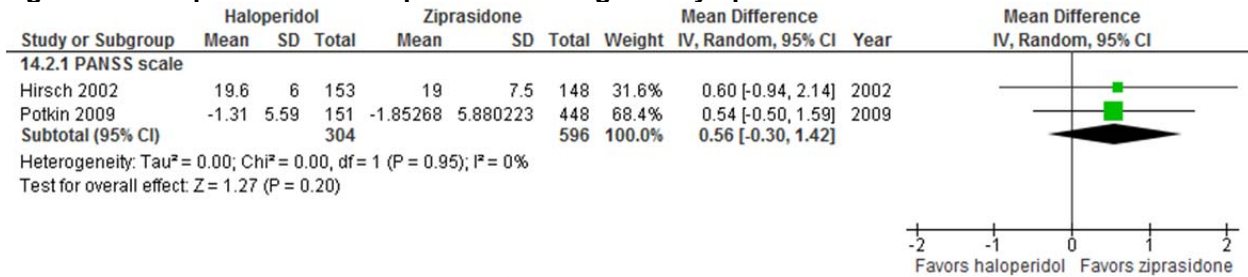
Positive Symptoms

None of the included trials reported positive symptoms.

Negative Symptoms

Two trials^{86,122} (n = 900) assessed negative symptoms using the PANSS (negative) and reported no significant difference between groups (Table 46; Figure 28); results showed no evidence of heterogeneity ($I^2 = 0$ percent). Both studies included mixed populations with respect to disorder subtypes and comorbid drug or alcohol use. Both studies used consistent doses of haloperidol (5–15 mg/d and 5–20 mg/d) and ziprasidone (80–160 mg/d). One study⁸⁶ excluded patients with treatment resistance. Duration of followup was 28 weeks⁸⁶ and 3.75 years.¹²² Risk of bias was high⁸⁶ and unclear;¹²² both were funded by industry. The SoE was low (Table 47).

Figure 28. Haloperidol versus ziprasidone – Negative symptoms



CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale; SD = standard deviation

General Psychopathology

One trial⁵⁷ (n = 567) compared 5–20 mg/d haloperidol with 10–40 mg/d ziprasidone and found no significant difference between groups using the Covi Anxiety Scale (Table 46). This trial included patients with mixed disorder subtypes. Patients with comorbid drug or alcohol use and those with treatment resistance were excluded. Duration of followup was 6 weeks. Risk of bias was high, and the trial was industry-funded.

One trial⁹¹ (n = 185) compared haloperidol (1–4 mg/d) with ziprasidone (40–60 mg/d) and found no significant difference between groups using the CDS–S (Table 46). The study included participants with mixed disorder subtypes and comorbid drug or alcohol use. Patients with treatment resistance were excluded. Duration of followup was 1 year. Risk of bias was high, and the study was industry-funded.

One trial⁸⁶ (n = 301) compared haloperidol (5–15 mg/d) with ziprasidone (80–160 mg/d) and found no significant difference between groups on MADRS (Table 46). The trial included a mix of disorder subtypes and comorbid drug or alcohol use. Patients with treatment resistance were excluded. Duration of followup was 28 weeks. Risk of bias was high, and the trial was industry-funded.

The SoE was insufficient for three scales used to assess general psychopathology (Table 47).

Global Ratings and Total Scores

Seven trials assessed total scores using four different tools. Four trials^{57,73,83,86} (n = 1,078) found no significant difference between groups on BPRS (Table 46; Figure 29); there was no statistical heterogeneity. All studies included a mix of disorder subtypes. Two studies^{57,83} excluded patients with comorbid drug or alcohol use. One study⁷³ included only patients with treatment resistance; two studies^{57,86} excluded patients with treatment resistance. Doses of haloperidol were relatively consistent, except for one study where the upper limit was 30 mg/d.⁷³ Upper limits for ziprasidone varied: 40 mg/d,⁵⁷ 160 mg/d,^{83,86} and 240 mg/d.⁷³ Duration of

followup was ≤ 6 weeks in three studies and 28 weeks in the other.⁸⁶ Risk of bias was high in three studies and unclear in one.⁷³ Two studies^{57,86} reported industry funding; two studies^{73,83} did not report funding source.

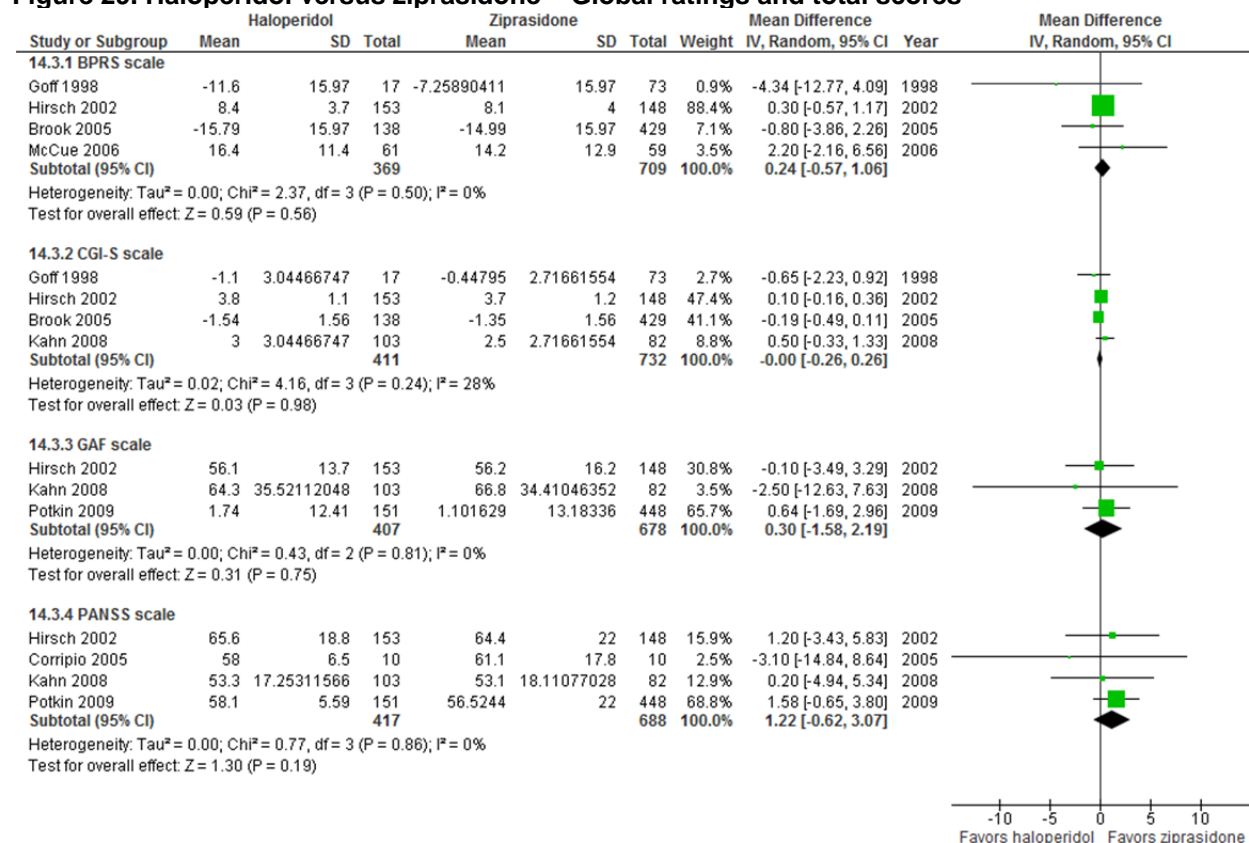
Four trials^{57,83,86,91} (n = 1,275) showed no significant difference between groups on CGI-S (Table 46; Figure 29); there was some statistical heterogeneity between studies. All studies included a mix of disorder subtypes. Two studies^{57,83} excluded patients with comorbid drug or alcohol use. Three studies^{57,86,91} excluded patients with treatment resistance. One study⁹¹ used a relatively lower dose of haloperidol (1–4 mg/d). Ziprasidone doses were relatively consistent; however, one study⁵⁷ had a lower maximum dose (40 vs. 160 mg/d). Duration of followup was ≤ 6 weeks in two studies,^{57,83} 28 weeks in one study,⁸⁶ and 1 year in one study.⁹¹ All studies were high risk of bias; three reported industry funding, and one did not report funding source.⁸³

Four trials^{69,86,91,122} (n = 1,105) showed no significant difference between groups on PANSS (total) (Table 46; Figure 29); there was no statistical heterogeneity among studies. All studies included a mix of disorder subtypes. One study⁶⁹ excluded patients with drug or alcohol use. Two studies^{86,91} excluded patients with treatment resistance. One study⁹¹ used a relatively lower dose of haloperidol (1–4 mg/d). Ziprasidone doses were relatively consistent; however, one study⁶⁹ had a lower maximum dose (40 vs. 160 mg/d). Duration of followup ranged from 2 weeks⁶⁹ to 3.75 years.¹²² Risk of bias was high for three studies and unclear for one;¹²² all studies were industry-funded.

Three trials^{86,91,122} (n = 1,085) showed no significant difference between groups on the GAF scale (Table 46; Figure 29); there was no statistical heterogeneity. All studies included patients with a mix of disorder subtypes and comorbid drug or alcohol use. Two studies^{86,91} excluded patients with treatment resistance. One study⁹¹ used a relatively lower dose of haloperidol (1–4 mg/d). Ziprasidone doses were consistent across studies. Followup ranged from 28 weeks⁸⁶ to 3.75 years.¹²² Risk of bias was high for two studies^{86,91} and unclear for one;¹²² all were industry-funded.

The SoE was graded as low for BPRS, CGI-S, PANSS (total), and GAF (Table 47).

Figure 29. Haloperidol versus ziprasidone – Global ratings and total scores



BPRS = Brief Psychiatric Rating Scale; CGI-S = Clinical Global Impression–Severity; CI = confidence intervals; df = degrees of freedom; GAF = Global Assessment of Functioning; I^2 = I-squared; IV = inverse variance; PANSS = Positive and Negative Symptom Scale; SD = standard deviation

Key Questions 2 and 4. Improvement in Functional Outcomes, Decreasing Health Care System Utilization, and Other Outcomes

Functional Outcomes

Sexual Dysfunction

One trial⁹¹ ($n = 185$) compared haloperidol (1–4 mg/d) and ziprasidone (40–160 mg/d) and found no differences between groups for incidence of sexual dysfunction (Table 46). The study included participants with mixed disorder subtypes and comorbid drug or alcohol use. Patients with treatment resistance were excluded. Duration of followup was 1 year. Risk of bias was high, and the study was industry-funded.

Health Care System Utilization

Pooled results for two trials^{86,91} ($n = 486$) showed no significant difference between groups for rates of hospitalization or rehospitalization (Table 46). Both trials included patients with a mix of disorder subtypes and comorbid drug or alcohol use. Both excluded patients with treatment resistance. One trial⁹¹ used a relatively lower dose of haloperidol (1–4 mg/d); ziprasidone doses were consistent. Duration of followup was 28 weeks⁸⁶ and 1 year.⁹¹ Risk of bias was high in both trials, and both were industry-funded.

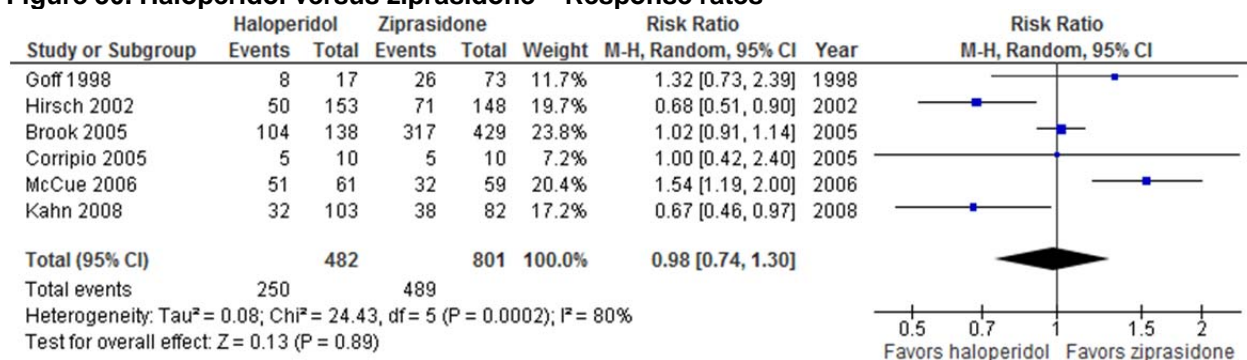
Other Outcomes

Response and Remission Rates

Six trials^{57,69,73,83,86,91} (n = 1,283) showed no significant difference between groups for treatment response rates (Table 46; Figure 30). However, statistical heterogeneity was substantial; therefore, the overall estimate may not be meaningful. We conducted predefined subgroup and sensitivity analyses to explain heterogeneity (Appendix M, Table 112). Three studies that excluded patients with comorbid drug or alcohol use had no heterogeneity ($I^2 = 0$ percent) and showed no difference. Two studies that followed patients for ≥ 6 months had no heterogeneity ($I^2 = 0$ percent) and showed significant results favoring haloperidol. Three studies had mixed treatment-resistant and nonresistant patients (2 studies) or included only treatment-resistant patients (1 study); when combined, these studies had no heterogeneity ($I^2 = 0$ percent) and showed significant results favoring ziprasidone. Two studies did not report their source of funding; these studies had no heterogeneity, and their pooled results favored ziprasidone. One study⁷³ appeared as an outlier, as it showed a statistically significant benefit for ziprasidone. This study included relatively larger doses of haloperidol (up to 30 mg/d) and included only treatment-resistant patients; the study had unclear risk of bias.

Three trials^{86,91,122} (n = 1,085) found no significant difference between groups for remission rates (Table 46); the statistical heterogeneity was minimal. These studies included a mix of populations with respect to disorder subtypes and comorbid drug or alcohol use. Two studies^{86,91} excluded patients with treatment resistance. One study⁹¹ used a relatively lower dose of haloperidol (1–4 mg/d); doses of ziprasidone were consistent across studies. All studies followed patients for >6 months, and one study¹²² followed patients for 3.75 years. Risk of bias was high for two studies and unclear for one;¹²² all studies declared industry support.

Figure 30. Haloperidol versus ziprasidone – Response rates



CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; M-H = Mantel-Haenszel

Health-related Quality of Life

A single trial⁹¹ (n = 185) comparing 1–4 mg/d haloperidol with 40–160 mg/d ziprasidone reported no significant difference between groups for health-related quality of life based on the Manchester Short Assessment of Quality of Life Scale. The study included participants with mixed disorder subtypes and comorbid drug or alcohol use. Patients with treatment resistance were excluded. Duration of followup was 1 year. Risk of bias was high, and the study was industry-funded. Another trial¹²² (n = 599) compared 5–20 mg/d haloperidol with 80–160 mg/d ziprasidone and found a significant difference favoring ziprasidone on the Quality of Life Scale (Table 46). This trial included a mix of patients with respect to disorder subtype, comorbid drug

or alcohol use, and treatment resistance. Duration of followup was 3.75 years. The trial had unclear risk of bias and was industry-funded.

Key Question 5. Subgroups

None of the included studies addressed the prespecified subgroups for the key core illness symptoms.

Table 46. Evidence summary table: haloperidol versus ziprasidone

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Negative Symptoms					
PANSS ^{86,122}	2	900	0.56 (-0.30, 1.42)	0%	ND
General Psychopathology					
CDS-S ⁹¹	1	185	0.00 (-0.71, 0.71)	NE	ND
Covi anxiety ⁵⁷	1	567	0.63 (-1.23, 2.49)	NE	ND
MADRS ⁸⁶	1	301	0.10 (-1.85, 2.05)	NE	ND
Global Ratings and Total Scores					
BPRS ^{57,73,83,86}	4	1078	0.24 (-0.57, 1.06)	0%	ND
CGI-S ^{57,83,86,91}	4	1143	-0.00 (-0.26, 0.26)	28%	ND
GAF ^{86,91,122}	3	1085	0.30 (-1.58, 2.19)	0%	ND
PANSS ^{69,86,91,122}	4	1105	1.22 (-0.62, 3.07)	0%	ND
Sexual Dysfunction					
Sexual dysfunction (UKU) ⁹¹	1	185	0.69 (0.45, 1.07)*	NE	ND
Health Care System Utilization					
Rates of hospitalization/re-hospitalization ^{86,91}	2	486	2.62 (0.99, 6.97)*	0%	ND
Other Outcomes					
Response rates ^{57,69,73,83,86,91}	6	1283	0.98 (0.74, 1.30)*	80%	ND
Remission rates ^{86,91,122}	3	1085	0.89 (0.71, 1.12)*	12%	ND
Health-Related Quality of Life					
MANSA scale ⁹¹	1	185	-0.10 (-1.48, 1.28)	NE	ND
QLS ¹²²	1	599	-12.12 (-22.06, -2.17)	NE	ziprasidone

BPRS = Brief Psychiatric Rating Scale; CDS-S = Calgary Depression Scale for Schizophrenia; CGI-S = Clinical Global Impression-Severity; GAF = Global Assessment of Functioning; I² = I-squared; MADRS = Montgomery-Asberg Depression Scale; MANSA = Manchester Short Assessment of Quality of Life; ND = no difference; NE = not estimable; PANSS = Positive and Negative Symptom Scale; QLS = Quality of Life scale; UKU = Udvalg for Kliniske Undersogelser

Note: bold = statistically significant.

*Binary outcome.

Table 47. Strength of evidence (GRADE): haloperidol versus ziprasidone

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Negative Symptoms						
PANSS	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
General Psychopathology						
CDS-S	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Covi nxiety	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
MADRS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Global Ratings and Total Scores						
BPRS	4 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
CGI-S	4 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
GAF	3 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
PANSS	4 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)

BPRS = Brief Psychiatric Rating Scale; CDS-S = Calgary Depression Scale for Schizophrenia; CGI-S = Clinical Global Impression-Severity; GAF = Global Assessment of Functioning; I² = I-squared; MADRS = Montgomery-Asberg Depression Scale; ND = no difference; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; RoB = risk of bias; SoE = strength of evidence

Perphenazine Versus Aripiprazole

One RCT⁹³ (n = 300) compared perphenazine (8–64 mg/d) with aripiprazole (15–30 mg/d) in patients with **treatment-resistant schizophrenia** (Table 48). There were no significant differences in **core illness symptoms** (global ratings/total scores) or **response rates** (Table 49). The SoE for all the evaluated outcomes was insufficient due to the inclusion of only a single trial (Table 50). A significant difference favoring perphenazine was reported showing a 20 percent improvement for **health-related quality of life**.

Table 48. Characteristics of RCT comparing perphenazine versus aripiprazole in the treatment of schizophrenia and related psychoses

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout/ Run-in Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Kane et al. 2007 ⁹³ RCT (6 wks)	G1: PER (8–64mg/d); (146) G2: ARI (15–30mg/d); (154) Washout period: 2–14 d Run-in phase: 4–6 wks	Tx resistant Sz with OLA or RIS; no schizoaffective disorder, residual schizophrenia, BP, refractory response to prior CLO or PER	Unclear, Industry

AP(s) = antipsychotic(s); ARI = aripiprazole; BP = bipolar disorder; CLO = clozapine; D = day; G = group; Mg = milligrams; No. = number; OLA = olanzapine; PER = perphenazine; RCT = randomized controlled trial; RIS = risperidone; Sz = schizophrenia; Tx = treatment; Wk(s) = week(s)

Table 49. Evidence summary table: perphenazine versus aripiprazole

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Global Ratings and Total Scores					
CGI-I ⁹³	1	300	-0.20 (-0.52, 0.12)	NE	ND
CGI-S ⁹³	1	300	0.00 (-0.25, 0.25)	NE	ND
PANSS scale ⁹³	1	300	-0.70 (-5.61, 4.21)	NE	ND
PANSS-derived BPRS ⁹³	1	300	0.00 (-0.99, 0.99)	NE	ND
Other Outcomes					
Response rates ⁹³	1	300	0.95 (0.64, 1.40)*	NE	ND
Health-Related Quality of Life					
Health-related quality of life (20% improvement) ⁹³	1	300	4.74 (2.58, 8.69)	NE	perphenazine

Note: bold = statistically significant; * = binary outcome; BPRS = Brief Psychiatric Rating Scale; CGI-I = Clinical Global Impression–Improvement; CGI-S = Clinical Global Impression–Severity; I² = I-squared; ND = no difference; NE = not estimable; PANSS = Positive and Negative Symptom Scale

Table 50. Strength of evidence (GRADE): perphenazine versus aripiprazole

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Global Ratings and Total Scores						
CGI-I	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
CGI-S	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
PANSS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
PANSS-derived BPRS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

BPRS = Brief Psychiatric Rating Scale; CGI-I = Clinical Global Impression–Improvement; CGI-S = Clinical Global Impression–Severity; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; RoB = risk of bias; SoE = Strength of Evidence

Perphenazine Versus Olanzapine

Two RCTs^{23,131} (n = 874) compared perphenazine with olanzapine. Key characteristics of the included trials and summary findings are presented in Table 51 and Table 52. Publication bias

was not formally tested due to the inclusion of a small number of trials. The SoE for all evaluated outcomes was insufficient due to the inclusion of only two trials (Table 53).

Table 51. Characteristics of RCTs comparing perphenazine versus olanzapine in the treatment of schizophrenia

Study, Design (Followup)	Interventions, Dosages; No. Randomized	Main Inclusion Criteria	Risk of Bias, Financial Support
Ascher-Svanum et al. 2008 ¹³¹ RCT (1 yr)	G1: PER (NR); (48) G2: OLA (NR); (229)	Sz, schizoaffective or schizophreniform disorders; BPRS >18	Unclear, Industry
Lieberman et al. 2005 ²³ RCT (18 mo)	G1: PER (8–32mg/d); (261) G2: OLA (7.5–30mg/d); (336)	Sz defined by DSM–IV	Unclear, Multiple sources including industry

BPRS = Brief Psychiatric Rating Scale; D = day; DSM–IV = Diagnostic and Statistical Manual, 4th edition; G = group; Mg = milligrams; Mo = month(s); No. = number; NR = not reported; OLA = olanzapine; PER = perphenazine; RCT = randomized controlled trial; Sz = schizophrenia; Yr(s) = year(s)

Key Question 1. Improving Core Illness Symptoms

One trial²³ (n = 597) including patients with schizophrenia compared perphenazine (8–32 mg/d) and olanzapine (7.5–30 mg/d) and 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 (Table 52). The differences were not considered to be clinically relevant, and the SoE for all outcomes was graded as insufficient (Table 53).

Key Questions 2 and 4. Improvement in Functional Outcomes, Decreasing Health Care System Utilization, and Other Outcomes

Employment or Personal Earnings

One trial²³ (n = 597) of patients with schizophrenia compared perphenazine (8–32 mg/d) with olanzapine (7.5–30 mg/d) and reported no significant difference between groups for the employment or personal earnings (Table 52).

Health Care System Utilization

One trial²³ (n = 597) of patients with schizophrenia compared perphenazine (8–32 mg/d) with olanzapine (7.5–30 mg/d) and reported no significant difference between groups for the rates of hospitalization or rehospitalization (Table 52).

Other Outcomes

One trial²³ (n = 597) of patients with schizophrenia compared perphenazine (8–32 mg/d) with olanzapine (7.5–30 mg/d) and reported no significant difference between groups for the Quality of Life Scale (total score) (Table 52). One trial¹³¹ of patients with schizophrenia, schizoaffective disorder, or schizophreniform disorder reported a significantly longer time to all-cause medication discontinuation (days) favoring olanzapine (Table 52).

Key Question 5. Subgroups

Comorbidities

One trial²³ (n = 597) of patients with schizophrenia compared perphenazine (8–32 mg/d) with olanzapine (7.5–30 mg/d) and 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). The differences were not considered to be clinically relevant.

Table 52. Evidence summary table: perphenazine versus olanzapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Positive Symptoms					
PANSS ²³	1	597	1.47 (0.55, 2.40)	NE	olanzapine
Negative Symptoms					
PANSS ²³	1	597	0.43 (-0.55, 1.41)	NE	ND
General Psychopathology					
PANSS ²³	1	597	2.17 (0.66, 3.68)	NE	olanzapine
Global Ratings and Total Scores					
CGI-S ²³	1	597	0.25 (0.06, 0.43)	NE	olanzapine
PANSS ²³	1	597	-4.59 (-7.42, -1.77)	NE	perphenazine
Employment/ Personal Earnings					
Paid employment in past month ²³	1	597	1.29 (0.70, 2.38)*	NE	ND
Health Care System Utilization					
Rates of hospitalization/rehospitalization ²³	1	597	1.39 (0.92, 2.09)*	NE	ND
Health-Related Quality of Life					
QLS Total score ²³	1	597	0.00 (-0.16, 0.16)	NE	ND
Medication Adherence					
Time to all-cause medication discontinuation (days) ¹³¹	1	277	-78.70 (-119.34, -38.06)	NE	olanzapine

Note: bold = statistically significant; * = binary outcome; CGI-S = Clinical Global Impression–Severity; I² = I-squared; ND = no difference; NE = not estimable; PANSS = Positive and Negative Symptom Scale; QLS = Quality of Life Scale

Table 53. Strength of evidence (GRADE): perphenazine versus olanzapine

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Positive Symptoms						
PANSS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
Negative Symptoms						
PANSS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
General Psychopathology						
PANSS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
Global Ratings and Total Scores						
PANSS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
CGI-S	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

CGI-S = Clinical Global Impression–Severity; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; RoB = risk of bias; SoE = Strength of Evidence

Perphenazine Versus Quetiapine

One RCT²³ (n = 598) compared perphenazine (8–32 mg/d) with quetiapine (200–800 mg/d) in patients with schizophrenia (Table 54). No significant differences between groups were found for **core illness symptoms** (positive or negative symptoms, general psychopathology, or total scores), **functional outcomes** (paid employment in past month), **health care system utilization**, or **quality of life scores** (Table 55). The SoE for all the evaluated outcomes was insufficient due to the inclusion of only a single trial (Table 56). For **subgroup** analysis investigating comorbidities, no significant differences were found between groups on PANSS (positive, negative, general psychopathology, or total score) or CGI–S.

Table 54. Characteristics of RCT comparing perphenazine versus quetiapine in the treatment of schizophrenia

Study, Design (Followup)	Interventions, Dosages; No. Randomized	Main Inclusion Criteria	Risk of Bias, Financial Support
Lieberman et al. 2005 ²³ RCT (18 mo)	G1: PER (8–32mg/d); (261) G2: QUE (200–800mg/d); (337)	Sz defined by DSM–IV	Unclear, Multiple sources including industry

D = day; DSM–IV = Diagnostic and Statistical Manual, 4th edition; G = group; Mg = milligrams; Mo = month(s); PER = perphenazine; QUE = quetiapine; RCT = randomized controlled trial; Sz = schizophrenia

Table 55. Evidence summary table: perphenazine versus quetiapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Positive Symptoms					
PANSS ²³	1	586	-0.93 (-1.93, 0.06)	NE	ND
Negative Symptoms					
PANSS ²³	1	586	-0.70 (-1.66, 0.26)	NE	ND
General Psychopathology					
PANSS ²³	1	586	-0.54 (-2.10, 1.02)	NE	ND
Global ratings and Total Scores					
CGI ²³	1	586	-0.17(-0.36, 0.01)	NE	ND
PANSS ²³	1	586	1.52 (-1.39, 4.43)	NE	ND
Employment/ Personal Earnings					
Paid employment in past month ²³	1	598	1.75 (0.90, 3.43)*	NE	ND
Health Care System Utilization					
Rates of hospitalization/ rehospitalization ²³	1	598	0.78 (0.55, 1.11)*	NE	ND
Health-related Quality of Life					
Quality of Life Scale Total score ²³	1	598	0.10 (-0.07, 0.27)	NE	ND

* = binary outcome; CGI = Clinical Global Impression; I² = I-squared; ND = no difference; NE = not estimable; PANSS = Positive and Negative Symptom Scale

Table 56. Strength of evidence (GRADE): perphenazine versus quetiapine

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Positive Symptoms						
PANSS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
Negative Symptoms						
PANSS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
General Psychopathology						
PANSS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
General Psychopathology						
PANSS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
CGI	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

CGI = Clinical Global Impression; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; RoB = risk of bias; SoE = Strength of Evidence

Perphenazine Versus Risperidone

Two RCTs^{23,131} (n = 871) in patients with schizophrenia compared perphenazine (8–32 mg/d) with risperidone (1.5–6.0 mg/d). Key characteristics of the included trials and summary findings are presented in Table 57 and Table 58. Publication bias was not formally tested due to the inclusion of a small number of trials. The SoE for all evaluated outcomes was insufficient due to the inclusion of only a small number of trials (Table 59).

Table 57. Characteristics of RCTs comparing perphenazine versus risperidone in the treatment of schizophrenia

Study, Design (Followup)	Interventions, Dosages; No. Randomized	Main Inclusion Criteria	Risk of Bias, Financial Support
Ascher-Svanum et al. 2008 ¹³¹ RCT (1 yr)	G1: PER (NR); (48) G2: RIS (NR); (221)	Sz, schizoaffective or schizophreniform disorders; BPRS >18	Unclear, Industry
Lieberman et al. 2005 ²³ RCT (18 mo)	G1: PER (8–32mg/d); (261) G2: RIS (1.5–6.0mg/d); (341)	Sz defined by DSM-IV	Unclear, Multiple sources including industry

BPRS = Brief Psychiatric Rating Scale; D = day; DSM-IV = Diagnostic and Statistical Manual, 4th edition; G = group; Mg = milligrams; Mo = month(s); NR = not reported; PER = perphenazine; RCT = randomized controlled trial; RIS = risperidone; Sz = schizophrenia; Yr(s) = year(s)

Key Question 1. Improving Core Illness Symptoms

One trial²³ (n = 602) including patients with schizophrenia and comparing perphenazine (8–32 mg/d) with risperidone (1.5–6.0 mg/d) reported no significant difference between groups on PANSS (positive), PANSS (negative), PANSS (general psychopathology), PANSS (total), and CGI-S (Table 58). The SoE for the outcomes was graded as insufficient (Table 59).

Key Questions 2 and 4. Improvement in Functional Outcomes, Decreasing Health Care System Utilization, and Other Outcomes

Employment or Personal Earnings

One trial²³ (n = 602) in patients with schizophrenia that compared perphenazine (8–32 mg/d) with risperidone (1.5–6.0 mg/d) reported no significant difference between groups for the employment or personal earnings (Table 58).

Health Care System Utilization

One trial²³ (n = 602) in patients with schizophrenia that compared perphenazine (8–32 mg/d) with risperidone (1.5–6.0 mg/d) reported no significant difference between groups on rates of hospitalization or rehospitalization (Table 58).

Other Outcomes

One trial²³ (n = 602) in patients with schizophrenia that compared perphenazine (8–32 mg/d) with risperidone (1.5–6.0 mg/d) reported no significant difference between groups on the Quality of Life Scale (total score) (Table 58). Another trial¹³¹ in patients with schizophrenia, schizoaffective disorder, or schizophreniform disorder reported no significant difference between groups for all-cause medication discontinuation (days) (Table 58).

Key Question 5. Subgroups

Comorbidities

One trial,²³ including patients with schizophrenia and comparing perphenazine (8–32 mg/d) with risperidone (1.5–6.0 mg/d), 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 58. Evidence summary table: perphenazine versus risperidone

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Positive Symptoms					
PANSS ²³	1	590	-0.06 (-1.04, 0.94)	NE	ND
Negative Symptoms					
PANSS ²³	1	590	-0.87 (-1.86, 0.12)	NE	ND
General Psychopathology					
PANSS ²³	1	590	0.24 (-1.39, 1.87)	NE	ND
Global Ratings and Total Scores					
CGI ²³	1	590	-0.06 (-0.25, 0.13)	NE	ND
PANSS ²³	1	590	0.17 (-2.84, 3.22)	NE	ND
Employment/ Personal Earnings					
Paid employment in past month ²³	1	602	1.38 (0.74, 2.57)*	NE	ND
Health Care System Utilization					
Rates of hospitalization/ rehospitalization ²³	1	602	1.05 (0.72, 1.53)*	NE	ND
Health-Related Quality of Life					
Quality of Life Scale Total score ²³	1	602	-0.07 (-0.24, 0.10)	NE	ND
Medication Adherence					
Time to all-cause medication discontinuation (days) ¹³¹	1	269	-33.40 (-75.18, 8.38)	NE	ND

CGI = Clinical Global Impression; I² = I-squared; ND = no difference; NE = not estimable; PANSS = Positive and Negative Symptom Scale; QLS = Quality of Life Scale

*Binary outcome.

Table 59. Strength of evidence (GRADE): perphenazine versus risperidone

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Positive Symptoms						
PANSS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
Negative Symptoms						
PANSS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
General Psychopathology						
PANSS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
Global Ratings and Total Scores						
PANSS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
CGI	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

CGI = Clinical Global Impression; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; RoB = risk of bias; SoE = Strength of Evidence

Perphenazine Versus Ziprasidone

One RCT²³ (n = 446) compared perphenazine (8–32 mg/d) with ziprasidone (40–160 mg/d) in patients with schizophrenia (Table 60). No significant differences were found between groups for **core illness symptoms** (positive, negative, and total scores); however, a significant difference favoring perphenazine for **core illness symptoms** (general psychopathology) was found, but was considered not clinically significant (Table 61). The SoE for all the evaluated outcomes was insufficient due to the inclusion of only a single trial (Table 62). No significant differences were found between groups for **functional outcomes** (paid employment in past month), **health care system utilization** (rates of hospitalization or rehospitalisation), **quality of life scores**, or for subgroup analysis investigating **comorbid** illicit substance use.

Table 60. Characteristics of RCT comparing perphenazine versus ziprasidone in the treatment of schizophrenia

Study, Design (Followup)	Interventions, Dosages; No. Randomized	Main Inclusion Criteria	Risk of Bias, Financial Support
Lieberman et al. 2005 ²³ RCT (18 mo)	G1: PER (8–32mg/d); (261) G2: ZIP (40–160mg/d); (185)	Sz defined by DSM–IV	Unclear, Multiple sources including industry

d = Day; DSM–IV = Diagnostic and Statistical Manual, 4th edition; G = group; Mg = milligrams; Mo = month(s); PER = perphenazine; RCT = randomized controlled trial; Sz = schizophrenia; ZIP = ziprasidone

Table 61. Evidence summary table: perphenazine versus ziprasidone

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Positive Symptoms					
PANSS ²³	1	440	-0.85 (-2.06, 0.35)	NE	ND
Negative Symptoms					
PANSS ²³	1	440	-0.97 (-2.05, 0.11)	NE	ND
General Psychopathology					
PANSS ²³	1	440	-1.92 (-3.71, -0.14)	NE	perphenazine
Global Ratings and Total Scores					
CGI ²³	1	440	-0.12 (-0.34, 0.10)	NE	ND
PANSS ²³	1	440	2.23 (-1.18, 5.63)	NE	ND
Employment or Personal Earnings					
Paid employment in past month ²³	1	446	1.22 (0.60, 2.51)*	NE	ND

Table 61. Evidence summary table: perphenazine versus ziprasidone (continued)

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Health Care System Utilization					
Rates of hospitalization or rehospitalization ²³	1	446	0.88 (0.58, 1.34)*	NE	ND
Health-Related Quality of Life					
Quality of Life Scale Total score ²³	1	446	-0.07 (-0.27, 0.13)	NE	ND

Note: bold = statistically significant; * = point estimate reflex relative risk; CGI = Clinical Global Impression; I² = I-squared; ND = no difference; NE = not estimable; PANSS = Positive and Negative Symptom Scale; QLS = Quality of Life Scale

Table 62. Strength of evidence (GRADE): perphenazine versus ziprasidone

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Positive Symptoms						
PANSS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
Negative Symptoms						
PANSS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
General Psychopathology						
PANSS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
Global Ratings and Total Scores						
PANSS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient
CGI	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

CGI = Clinical Global Impression; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; RoB = risk of bias; SoE = Strength of Evidence

Trifluoperazine Versus Clozapine

One RCT¹⁵⁷ (n = 25) compared trifluoperazine (7.5–15 mg/d) with clozapine (50–100 mg/d) in patients schizophrenia (Table 63). There was no reported difference in core illness symptoms (BPRS) (Table 64). No other relevant outcomes were reported. The SoE for BPRS was insufficient (Table 65).

Table 63. Characteristics of RCTs comparing trifluoperazine versus clozapine in the treatment of schizophrenia and related psychoses

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Run-in Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Rinieris et al. 1980 ¹⁵⁷ RCT (6 wks)	G1: TRI (7.5–15mg/d); (20) G2: CLO (50–100mg/d); (5) Run-in phase: 1 wk	Sz not further defined	High, NR

CLO = clozapine; D = days; G = group; Mg = milligrams; No. = number; NR = not reported; RCT = randomized controlled trial; Sz = schizophrenia; TRI = Trifluoperazine; Wk(s) = week(s)

Table 64. Evidence summary table: trifluoperazine versus clozapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Global Ratings					
BPRS ¹⁵⁷	1	25	2.50 (-4.19, 9.19)	NE	ND

BPRS = Brief Psychiatric Rating Scale; I² = I-squared; ND = no difference; NE = not estimable

Table 65. Strength of evidence (GRADE): trifluoperazine versus clozapine

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Global Ratings and Total Scores						
BPRS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

BPRS = Brief Psychiatric Rating Scale; RCT = randomized controlled trial; RoB = risk of bias; SoE = Strength of Evidence

Bipolar Disorder (Key Questions 1, 2, 4, 5)

For bipolar disorder, we included 11 trials that enrolled a total of 2,217 adult patients. The individual studies are described in Appendix H and I. The results from the studies and pooled analyses are presented in Table 66 to Table 82. Within the forest plots, the studies are presented by year of publication. The following sections provide an overview of results according to KQ: 1) core illness symptoms; 2) functional outcomes and health care system utilization; 4) other outcomes; and 5) subgroup analyses. For KQ1, the outcomes are grouped as follows: mood (mania), mood (depression), positive and negative symptoms, general psychopathology, and global ratings and total scores. KQs 2 and 4 were grouped and are reported together throughout the results section. Comparisons are presented in alphabetic order by drug name.

Chlorpromazine Versus Clozapine

One RCT⁴⁸ (n = 27) compared chlorpromazine (2–5 mg/d) with clozapine (25–175 mg/d) in patients with bipolar disorder and manic episodes (Table 66). No significant differences were found between groups for **mood (mania)** (YMRS scale) (Table 67). The SoE was insufficient due to the inclusion of only a single trial (Table 68). Other reported AEs were not different between groups (Appendix N, Tables 113 and 114).

Table 66. Characteristics of RCT comparing chlorpromazine versus clozapine in the treatment of bipolar disorder with manic episodes

Study, Design (Followup)	Interventions, Dosages; No. Randomized	Main Inclusion Criteria	Risk of Bias, Financial Support
Barbini et al. 1997 ⁴⁸ RCT (3 wks)	G1: CHL (2–5mg/kg/d); (12) G2: CLO (25–175mg/d); (15)	BP with manic episode; no depot AP <6 mo	High, NR

AP(s) = antipsychotic(s); BP = bipolar disorder; CHL = chlorpromazine; CLO = clozapine; D = days; G = group; Kg = kilograms; Mg = milligrams; Mo = month; NR = not reported; RCT = randomized controlled trial; Wk(s) = week(s);

Table 67. Evidence summary table: chlorpromazine versus clozapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Mood (Mania)					
YMRS scale ⁴⁸	1	27	3.94 (-0.11, 7.99)	NE	ND

I² = I-squared; ND = no difference; NE = not estimable; YMRS = Young Mania Rating Scale

Table 68. Strength of evidence (GRADE): chlorpromazine versus clozapine

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Mood (Mania)						
YMRS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

RCT = randomized controlled trial; RoB = risk of bias; SoE = Strength of Evidence; YMRS = Young Mania Rating Scale

Haloperidol Versus Aripiprazole

Two RCTs^{32,33} (n = 679) compared haloperidol with aripiprazole. Key characteristics of the included trials and findings are summarized in Table 69 and Table 70. Both studies included only patients with bipolar I disorder and no comorbid drug or alcohol use. Young et al.³³ only included patients with multiple episodes and no treatment resistance, whereas Vieta et al.³² had no restrictions regarding first versus multiple episodes or treatment resistance. Doses were the same for both studies: 10–15 mg/d haloperidol and 15–30 mg/d aripiprazole. Duration of followup was 12 weeks in both studies. Both trials had unclear risk of bias and were industry-funded.

Publication bias was not formally tested for any of the outcomes due the small number of included trials. The SoE for the evaluated outcomes was low or insufficient due to the small number of included trials (Table 71).

Table 69. Characteristics of RCTs comparing haloperidol versus aripiprazole in the treatment of bipolar disorder

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Vieta et al. 2005 ³² RCT (12 wks)	G1: HAL (10–15mg/d); (172) G2: ARI (15–30mg/d); (175) Washout period: 1–3 d	BP; no rapid-cycling BP I, current manic episode >4 wks, substance abuse, or unresponsive to previous AP	Unclear, Industry
Young et al. 2009 ³³ RCT (12 wks)	G1: HAL (5–15mg/d); (165) G2: ARI (15–30mg/d); (167) Washout period: 2–14 d	BP I manic or mixed type (with or without psychotic features)	Unclear, Industry

AP(s) = antipsychotic(s); ARI = aripiprazole; BP I = bipolar disorder type I; D = days; G = group; HAL = haloperidol; Hr(s) = hour(s); Mg = milligrams; Mo = month; RCT = randomized controlled trial; Wk(s) = week(s)

Key Question 1. Improving Core Illness Symptoms

Mood: Mania

Two trials^{32,33} (n = 679) assessed global ratings and total scores based on the YMRS; however, there was moderate heterogeneity for the YMRS. The study characteristics are described above which may explain some of the heterogeneity observed in effect estimates. Nevertheless, none of the studies individually showed significant effects. The SoE was graded as low for YMRS (Table 71).

Mood: Depression

Pooled results from the two included trials^{32,33} (n = 679) showed no significant difference in total scores based on the MADRS (Table 70); however, statistical heterogeneity was substantial across studies. The SoE was graded as low (Table 71).

Positive and Negative Symptoms

Young et al.³³ (n = 332) found no significant difference in positive symptoms based on the PANSS (positive) or negative symptoms on the PANSS (negative) (Table 70). The SoE was graded as insufficient for both scales (Table 71).

Global Ratings and Total Scores

Two trials^{32,33} (n = 679) assessed global ratings on the Clinical Global Impression–Bipolar (CGI–BP) version, with one study³³ also assessing PANSS (total) (Table 70). No significant differences were found on either scale; however there was substantial heterogeneity for the CGI–BP. The study characteristics are described above which may explain some of the heterogeneity observed in effect estimates. Nevertheless, none of the studies individually showed significant effects. The SoE was graded as low for CGI–BP and insufficient for PANSS (total) (Table 71).

Key Questions 2 and 4. Improvement in Functional Outcomes, Decreasing Health Care System Utilization, and Other Outcomes

Other Outcomes. The two relevant trials^{32,33} reported no significant difference in response rates overall; however, statistical heterogeneity was substantial (Table 70). Vieta et al.³² had no

restrictions regarding first versus multiple episodes or treatment resistance and showed a significant difference favoring haloperidol. In contrast, Young et al.³³ only included patients with multiple episodes and no treatment resistance and showed no difference between groups.

Vieta et al.³² (n = 347) found a significant difference in relapse rates favoring haloperidol (Table 70). Young et al.³³ (n = 332) found no significant difference in remission rates (Table 70).

Key Question 5. Subgroups

Neither study addressed the prespecified subgroups.

Table 70. Evidence summary table: haloperidol versus aripiprazole

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Mood (Mania)					
YMRS ^{32,33}	2	679	0.90 (-0.77, 2.58)	22%	ND
Mood (Depression)					
MADRS ^{32,33}	2	679	0.22 (-1.73, 2.18)	0%	ND
Positive/Negative Symptoms					
PANSS (positive) ³³	1	332	-0.50 (-1.61, 0.61)	NE	ND
PANSS (negative) ³³	1	332	-0.10 (-0.65, 0.45)	NE	ND
Global Ratings and Total Scores					
CGI-BP ^{32,33}	2	679	0.15 (-0.35, 0.65)	81%	ND
PANSS ³³	1	332	-1.90 (-4.95, 1.15)	NE	ND
Other Outcomes					
Relapse rates ³²	1	347	0.53 (0.40, 0.71)*	NE	haloperidol
Remission rates ³³	1	332	1.02 (0.89, 1.17)*	NE	ND
Response rates ^{32,33}	2	679	0.77 (0.42, 1.42)*	94%	ND

Note: bolded results are statistically significant; * = binary outcome; CGI-BP = Clinical Global Impression-Bipolar; I² = I-squared; MADRS = Montgomery-Asberg Depression Rating; ND = no difference; NE = not estimable; PANSS = Positive and Negative Symptom Scale; YMRS = Young Mania Rating Scale

Table 71. Strength of evidence (GRADE): haloperidol versus aripiprazole

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Mood (Mania)						
YMRS	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
Mood (Depression)						
MADRS	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
Positive/Negative Symptoms						
PANSS (positive)	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
PANSS (negative)	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Global Ratings and Total Scores						
CGI-BP	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
PANSS (total)	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

CGI-BP = Clinical Global Impression-Bipolar; MADRS = Montgomery-Asberg Depression Rating; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; RoB = risk of bias; SoE = Strength of Evidence; Total = total scores; YMRS = Young Mania Rating Scale; ND = no difference

Haloperidol Versus Olanzapine

Two trials^{119,140} (n = 463) compared haloperidol with olanzapine. Key trial characteristics and findings are summarized in Table 72 and Table 73. Moreno et al.¹¹⁹ included only patients with bipolar II disorder, whereas Tohen et al.¹⁴⁰ included only patients with bipolar I disorder. Both studies included only patients with no comorbid drug or alcohol use and included mixed

populations with respect to first versus multiple episodes and treatment resistance. Drug doses were consistent across studies: 3–15 mg/d haloperidol versus 5–20 mg/d olanzapine.

Moreno et al.¹¹⁹ and Tohen et al.¹⁴⁰ followed patients for 6 and 12 weeks, respectively. Moreno et al.¹¹⁹ had unclear risk of bias and was supported through foundation funding; Tohen et al.¹⁴⁰ had high risk of bias and was industry-funded.

Publication bias was not formally tested for any of the outcomes due the small number of included trials. The SoE for all the evaluated outcomes was insufficient due to the small number of included trials (Table 74).

Table 72. Characteristics of RCTs comparing haloperidol versus olanzapine in the treatment of bipolar disorder

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout Period	Main Inclusion criteria	Risk of Bias, Financial Support
Moreno et al. 2007 ¹¹⁹ RCT (6 wks)	G1: HAL (3–15mg/d); (5) G2: OLA (5–20mg/d); (7) Washout period: 4 d	BP; switched between depression and mania phase ≤ 1 mo before or after PSG procedure	Unclear, Foundation
Tohen et al. 2003 ¹⁴⁰ RCT (12 wks)	G1: HAL (3–15mg/d); (219) G2: OLA (5–20mg/d); (234)	BP defined by DSM–IV	High, Industry

AP(s) = antipsychotic(s); BP = bipolar disorder; D = days; DSM-IV = diagnostic and statistical manual of mental disorders; G = group; HAL = haloperidol; Hr(s) = hour(s); Mg = milligrams; Mo = month; OLA = olanzapine; PSG = polysomnographic studies; RCT = randomized controlled trial; Wk(s) = week(s);

Key Question 1. Improving Core Illness Symptoms

Mood: Mania

Both trials^{119,140} (n = 465) assessed total score using YMRS and found no differences between groups; results were statistically homogeneous across studies (Table 73). The SoE for YMRS was graded as low.

Mood: Depression

Tohen et al.¹⁴⁰ (n = 453) found no significant differences based on HAM–D (Table 73). The SoE was graded as insufficient (Table 74).

Sleep

Moreno et al.¹¹⁹ (n = 12) found no significant differences in number of awakenings, sleep efficiency, stage rapid eye movement, total rapid eye movement, or total sleep time (Table 73). The SoE was graded as insufficient (Table 74).

Global Ratings and Total Scores

Moreno et al.¹¹⁹ (n = 12) assessed total score with CGI–BP and showed no difference between groups. The SoE for CGI–BP was graded as insufficient (Table 74).

Key Questions 2 and 4. Improvement in Functional Outcomes, Decreasing Health Care System Utilization, and Other Outcomes

Functional Outcomes

Tohen et al.¹⁴⁰ (n = 453) examined patients with bipolar I and found a significant difference on the number of days worked for pay favoring olanzapine, but not for the Streamlined Longitudinal Interview Clinical Evaluation from the Longitudinal Interval Followup Evaluation household or work activities impairment scores (Table 73).

Other Outcomes

Tohen et al.¹⁴⁰ (n = 453) reported on relapse, response, and remission rates; no significant difference was found between groups for any of the outcomes (Table 73). The same trial¹⁴⁰ assessed health-related quality of life using the Short Form-36 (Table 73). Results showed a significant difference on the mental summary score favoring haloperidol and a significant difference on the physical summary score favoring olanzapine (Table 73).

Key Question 5. Subgroups

Disorder Subtype

Tohen et al.¹⁴⁰ included only patients with bipolar I disorder and found no significant difference on HAM-D or YMRS.

Moreno et al.¹¹⁹ included only patients with bipolar II disorder and found no significant difference on number of awakenings, sleep efficiency, rapid eye movement, rapid eye movement activity, total sleep time (minutes), the CGI-BP, or the YMRS.

Table 73. Evidence summary table: haloperidol versus olanzapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Mood (Mania)					
YMRS ^{119,140}	2	465	-0.37 (-1.98, 1.24)	0%	ND
Mood (Depression)					
HAM-D ¹⁴⁰	1	453	0.90 (-0.64, 2.44)	NE	ND
Sleep					
Number of awakenings ¹¹⁹	1	12	11.40 (-10.44, 33.24)	NE	ND
Sleep efficiency (%) ¹¹⁹	1	12	-8.90 (-34.65, 16.85)	NE	ND
Stage REM (min) ¹¹⁹	1	12	-10.70 (-54.10, 32.70)	NE	ND
Total REM activity ¹¹⁹	1	12	-29.30 (-85.88, 27.28)	NE	ND
Total sleep time (min) ¹¹⁹	1	12	18.60 (-107.21, 144.41)	NE	ND
Global Ratings and Total Scores					
CGI-BP ¹¹⁹	1	12	-1.80 (-5.66, 2.06)	NE	ND
Employment/ Personal Earnings					
Active workers: number working for pay ¹⁴⁰	1	453	0.50 (0.32, 0.79)*	NE	olanzapine
SLICE/LIFE: household activities impairment score ¹⁴⁰	1	453	0.23 (-0.10, 0.56)	NE	ND
SLICE/LIFE: work activities impairment score ¹⁴⁰	1	453	0.00 (-0.33, 0.33)	NE	ND

Table 73. Evidence summary table: haloperidol versus olanzapine (continued)

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Other Outcomes					
Relapse rates ¹⁴⁰	1	453	0.80 (0.52, 1.24)*	NE	ND
Remission rates ¹⁴⁰	1	453	0.85 (0.70, 1.03)*	NE	ND
Response rates ¹⁴⁰	1	453	0.98 (0.94, 1.02)*	NE	ND
Health-Related Quality of Life					
SF-36 mental summary score ¹⁴⁰	1	453	17.30 (14.47, 20.13)	NE	haloperidol
SF-36 physical summary score ¹⁴⁰	1	453	-3.74 (-5.46, -2.02)	NE	olanzapine

Note: bolded results are statistically significant; * = binary outcome; CGI-BP = Clinical Global Impression-Bipolar; HAM-D = Hamilton Rating Scale for Depression; I² = I-squared; ND = no difference; NE = not estimable; REM = rapid eye movement; SF = Short Form; SLICE/LIFE = Streamlined Longitudinal Interview Clinical Evaluation from the Longitudinal Interval Followup Evaluation; YMRS = Young Mania Rating Scale

Table 74. Strength of evidence (GRADE): haloperidol versus olanzapine

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Mood (Mania)						
YMRS	2 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
Mood (Depression)						
HAM-D	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Sleep						
Number of awakenings	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Sleep efficiency (%)	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Stage REM (min)	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Total REM activity	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Total sleep time (min)	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Global Ratings and Total Scores						
CGI-BP	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

CGI-BP = Clinical Global Impression-Bipolar; HAM-D = Hamilton Rating Scale for Depression; Min = minute; ND = no difference; RCT = randomized controlled trial; REM = rapid eye movement; RoB = risk of bias; SoE = Strength of Evidence; YMRS = Young Mania Rating Scale

Haloperidol Versus Quetiapine

One trial¹¹⁵ (n = 201) compared haloperidol (2–8 mg/d) with quetiapine (100–800 mg/d) in patients with bipolar disorder in a current manic episode with or without psychotic features (Table 75). This trial did not report **core illness symptoms**, or investigate **subgroups** (Table 76). No significant differences between groups were found for response rates or remission rates.

Table 75. Characteristics of RCT comparing haloperidol versus quetiapine in the treatment of bipolar disorder

Study, Design (Followup)	Interventions, Dosages; No. Randomized	Main Inclusion Criteria	Risk of Bias, Financial Support
McIntyre et al. 2005 ¹¹⁵ RCT (12 wks)	G1: HAL (2–8mg/d); (99) G2: QUE (100–800mg/d); (102)	BP I, current episode manic, with or without psychotic features; ≥1 manic or mixed episode; no tx with CLO ≤1 mo	Unclear, Industry

BP I = bipolar disorder type I; CLO = clozapine; D = days; DSM-IV = diagnostic and statistical manual of mental disorders; G = group; HAL = haloperidol; Hr(s) = hour(s); Mg = milligrams; Mo = month; QUE = quetiapine; RCT = randomized controlled trial; Wk(s) = week(s);

Table 76. Evidence summary table: haloperidol versus quetiapine

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
<i>Other Outcomes</i>					
Remission rates ¹¹⁵	1	201	1.14 (0.94, 1.40)*	NE	ND
Response rates ¹¹⁵	1	201	1.03 (0.83, 1.28)*	NE	ND

I² = I-squared; ND = no difference; NE = not estimable

*Binary outcome.

Haloperidol Versus Risperidone

Key Points:

- Four RCTs compared haloperidol with risperidone; three of the studies included both bipolar I and bipolar II patients, whereas one trial included only bipolar I disorder.
- The most commonly reported outcome was mood (mania) using the YMRS. Pooled results from three studies showed no differences between groups. The SoE was low.
- Other outcomes were assessed in single studies and no significant differences were reported.

Four trials^{90,128,133,138} involving 463 adults with bipolar disorder compared haloperidol with risperidone. Key characteristics of the included trials and summary findings are presented in Table 77 and Table 78. Three studies included mixed bipolar I and bipolar II disorder, whereas one study¹³⁸ included only patients with bipolar I disorder. All studies restricted inclusion to patients with no comorbid drug or alcohol use. Two studies^{128,138} only included patients with multiple episodes; two studies^{90,133} included both patients with first and multiple episodes. One study¹³⁸ specifically excluded patients with treatment resistance. Dosages for haloperidol ranged from 4–20 mg/d and for risperidone ranged from 2–10 mg/d.

Duration of followup was ≤6 weeks in three studies^{90,128,133} and 12 weeks in the fourth.¹³⁸ Risk of bias was high for two studies^{90,128} and unclear for two studies.^{133,138} All studies were funded by industry.

Publication bias was not formally tested for any of the outcomes due the small number of included trials. The SoE for all the evaluated outcomes was insufficient or low due to the small number of included trials (Table 79).

Table 77. Characteristics of RCTs comparing haloperidol versus risperidone in the treatment of bipolar disorder

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Janicak et al. 2001 ⁹⁰ RCT (6 wks)	G1: HAL (4–20mg); (32) G2: RIS (2–10mg); (30) Washout period: ~5 d	BP subtype, manic phase; no hypersensitivity hx to HAL or RIS	High, Industry
Sachs et al. 2002 ¹²⁸ RCT (3 wks)	G1: HAL (4–12mg/d); (53) G2: RIS (2–6mg/d); (52) Washout period: ≤3 d	BP and ≥1 prior manic episode; no CLO ≤1 month or depot AP within one cycle	High, Industry
Segal et al. 1998 ¹³³ RCT (28 d)	G1: HAL (10mg/d); (15) G2: RIS (6mg/d); (15)	BP with acute manic episode defined by DSM-IV	Unclear, Industry
Smulevich et al. 2005 ¹³⁸ RCT (12 wks)	G1: HAL (4–12mg/d); (144) G2: RIS (2–6mg/d); (154) Washout period: ≥3 d	BP I with ≥1 manic or mixed episode; no schizoaffective disorder, rapid-cycling BP, borderline or antisocial personality disorders	Unclear, Industry

AP(s) = antipsychotic(s); BP = bipolar disorder; CLO = clozapine; D = days; DSM-IV = diagnostic and statistical manual of mental disorders; G = group; HAL = haloperidol; Hr(s) = hour(s); Hx = history; Mg = milligrams; Mo = month; No = number; NR = not reported; RIS = risperidone; RCT = randomized controlled trial; Wk(s) = week(s)

Key Question 1. Improving Core Illness Symptoms

Mood: Mania

All four trials^{90,128,133,138} presented results for mood (mania) using two scales. One trial⁹⁰ (n = 62) assessed mania symptoms using the Clinician-Administered Rating Scale for Mania; no differences between groups were found. The study compared 4–20 mg/d haloperidol with 2–10 mg/d risperidone. The trial included mixed populations with respect to type of bipolar disorder (I and II), first and previous episodes, and treatment resistance. Patients with comorbid drug or alcohol use were excluded. Duration of followup was 6 weeks. Risk of bias was high, and the trial was industry-funded.

Three trials^{128,133,138} (n = 433) showed no differences based on the YMRS; the pooled results showed no statistical heterogeneity. Two of the studies included patients with both bipolar I and II disorders, whereas the third study¹³⁸ included only bipolar I disorder. Two studies^{128,138} included only patients with multiple episodes. One study¹³⁸ included patients with no treatment resistance. None of the studies included patients with comorbid drug or alcohol use. Dose ranged from 4–20mg/d for haloperidol and 2–6mg/d for risperidone. Duration of followup ranged from 3 weeks¹²⁸ to 12 weeks.¹³⁸ Risk of bias was high in one study¹²⁸ and unclear in two studies,^{133,138} all studies were industry-funded.

Mood: Depression

One trial⁹⁰ as above assessed depressive symptoms using the HAM-D; no differences between groups were found.

Positive and Negative Symptoms

One trial⁹⁰ described above assessed positive and negative symptoms. No significant difference was found using the PANSS.

Global Ratings and Total Scores

Two trials^{90,133} presented results for global ratings and total symptom scores using two scales. One trial¹³³ (n = 30) comparing 10 mg/d haloperidol with 6 mg/d risperidone reported BPRS and found no difference between groups. The study included patients with both bipolar I and II disorders and excluded patients with comorbid alcohol or drug use. The study population was mixed with respect to first and previous episodes as well as treatment resistance. Duration of followup was 12 weeks. Risk of bias was unclear, and the trial was industry-funded.

One trial⁹⁰ comparing 4–20 mg/d haloperidol with 2–10 mg/d risperidone found no differences on the CGI-I or PANSS (total) scale. This trial included mixed populations with respect to type of bipolar disorder (I and II), first and previous episodes, and treatment resistance. The trial excluded patients with comorbid drug or alcohol use. Duration of followup was 6 weeks. Risk of bias was high, and the trial was industry-funded.

Key Questions 2 and 4. Improvement in Functional Outcomes, Decreasing Health Care System Utilization, and Other Outcomes

Other Outcomes

One trial⁹⁰ comparing 4–20 mg/d haloperidol with 2–10 mg/d risperidone assessed response rates and found no difference between groups. This trial included mixed populations with respect to type of disorder (bipolar I and II), first and previous episodes, and treatment resistance. Patients with comorbid drug or alcohol use were excluded. Duration of followup was 6 weeks. Risk of bias was high, and the trial was industry-funded.

Key Question 5. Subgroups

Disorder Subtype. One trial¹³⁸ in 298 patients with bipolar disorder with acute mania compared haloperidol (4–12 mg/d) with risperidone (2–6 mg/d) and found no significant difference on the YMRS.

Table 78. Evidence summary table: haloperidol versus risperidone

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Mood (Mania)					
CARS-M ⁹⁰	1	62	3.00 (-3.36, 9.36)	NE	ND
YMRS ^{128,133,138}	3	433	1.08 (-0.95, 3.12)	0%	ND
Mood (Depression)					
HAM-D ⁹⁰	1	62	-5.00 (-10.86, 0.86)	NE	ND
Positive Symptoms					
PANSS ⁹⁰	1	62	-80 (-3.90, 2.30)	NE	ND
Negative Symptoms					
PANSS ⁹⁰	1	62	-1.30 (-4.33, 1.73)	NE	ND
Global Ratings and Total Scores					
BPRS ¹³³	1	30	-1.60 (-7.11, 3.91)	NE	ND
CGI-I ⁹⁰	1	62	0.00 (-0.42, 0.42)	NE	ND
PANSS ⁹⁰	1	62	-2.00 (-13.10, 9.10)	NE	ND
Other Outcomes					
Response rates ⁹⁰	1	62	1.07 (0.44, 2.59)	NE	ND

BPRS = Brief Psychiatric Rating Scale; CARS-M = Clinician-Administered Rating Scale for Mania; CGI-I = Clinical Global Impression-Improvement; HAM-D = Hamilton Rating Scale for Depression; I² = I-squared; ND = no difference; NE = not estimable; PANSS = Positive and Negative Symptom Scale; YMRS = Young Mania Rating Scale

Table 79. Strength of evidence (GRADE): haloperidol versus risperidone

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Mood (Mania)						
CARS-M	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
YMRS	3 RCT	Medium	Consistent	Direct	Imprecise	Low (ND)
Mood (Depression)						
HAM-D	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Positive Symptoms						
PANSS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Negative Symptoms						
PANSS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
Global Ratings and Total Scores						
BPRS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
CGI-I	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient
PANSS	1 RCT	Medium	Unknown	Direct	Imprecise	Insufficient

BPRS = Brief Psychiatric Rating Scale; CARS-M = Clinician-Administered Rating Scale for Mania; CGI-I = Clinical Global Impression-Improvement; HAM-D = Hamilton Rating Scale for Depression; ND = no difference; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; RoB = risk of bias; SoE = strength of evidence; YMRS = Young Mania Rating Scale

Haloperidol Versus Ziprasidone

One trial¹⁴⁴ (n = 350) compared haloperidol (8–30 mg/d) with ziprasidone (80–160 mg/d) in patients with bipolar I disorder and mixed or manic subtypes (Table 80). A significant difference favoring haloperidol was found for the improvement of **core illness symptoms**, **response rates**, and for **subgroup analysis** of disorder subtype (Table 81). The SoE for all the evaluated outcomes was insufficient due to the inclusion of only a single trial (Table 82). No difference between groups was found for **remission rates**.

Table 80. Characteristics of RCT comparing haloperidol versus ziprasidone in the treatment of bipolar disorder

Study, Design (Followup)	Interventions, Dosages; No. Randomized, Washout Period	Main Inclusion Criteria	Risk of Bias, Financial Support
Vieta et al. 2010 ¹⁴⁴ RCT (12 wks)	G1: HAL (8–30mg/d); (78) G2: ZIP (80–160mg/d); (73) Washout period: 2–10 d	BP I disorder, most recent episode manic or mixed	High, Industry

BP = bipolar; D = days; G = group; HAL = haloperidol; Hr(s) = hour(s); Mg = milligrams; RCT = randomized controlled trial; Wk(s) = week(s); ZIP = ziprasidone

Table 81. Evidence summary table: haloperidol versus ziprasidone

Outcome or Subgroup	Studies	Participants	Effect Estimate	I ²	Favors
Mood (Mania)					
YMRS ¹⁴⁴	1	350	-5.52 (-7.79, -3.25)	NE	haloperidol
Other Outcomes					
Remission rates ¹⁴⁴	1	350	1.42 (1.00, 2.02)*	NE	ND
Response rates ¹⁴⁴	1	350	1.09 (1.02, 1.16)*	NE	haloperidol

Note: bolded results are statistically significant; * = binary outcome; I² = I-squared; ND = no difference; NE = not estimable; YMRS = Young Mania Rating Scale

Table 82. Strength of evidence (GRADE): haloperidol versus ziprasidone

Outcome	Source	RoB	Consistency	Directness	Precision	SoE
Mood (Mania)						
YMRS	1 RCT	Medium	Unknown	Direct	Precise	Insufficient

RCT = randomized controlled trial; RoB = risk of bias; SoE = strength of evidence; YMRS = Young Mania Rating Scale

Adverse Events (Key Question 3)

This section reviews the evidence on the comparative harms of individual FGAs and SGAs. The results are organized in alphabetical order by drug comparison (Appendix N). For each comparison, we report data on general and specific AEs. We categorized the outcomes by systems. As detailed in the methods section, we extracted only binary data for AEs (i.e., the number of patients who experienced a given event in each group), not continuous data (e.g., mean change in laboratory values). In addition, we counted each event as if it corresponded to a unique individual. Because an individual patient may have experienced more than one event during the course of the study, this assumption may have overestimated the number of patients that experienced an AE.

A priori, we identified four AEs to be the most clinically important: diabetes mellitus, tardive dyskinesia, metabolic syndrome, and mortality. Table 83 summarizes the results of studies that provided data for these AEs and the SoE for each comparison. For metabolic syndrome, two RCTs comparing haloperidol with olanzapine found no difference in incidence of metabolic syndrome (low SoE). For mortality, two RCTs comparing chlorpromazine with clozapine and two RCTs comparing haloperidol with aripiprazole showed no difference between the groups (low SoE), although the length of followup of the trials for the latter comparison was only 24 hours. The evidence was insufficient to allow conclusions for the remaining comparisons, primarily because only single studies provided data. The only significant differences in the remaining comparisons showed less incidence with the SGAs with the exception of a higher incidence of patients developing metabolic syndrome with clozapine compared with haloperidol.

Table 83. Summary of the strength of evidence for AEs

Comparison (Number of Studies)	RR (95% CI)	Summary	SoE
<i>Diabetes Mellitus</i>			
Haloperidol vs. olanzapine (1 RCT)	0.85 (0.21 to 3.49)	No significant difference.	Insufficient
Perphenazine vs. olanzapine (1 RCT)	0.81 (0.45 to 1.45)	No significant difference.	Insufficient
Perphenazine vs. quetiapine (1 RCT)	1.57 (0.79 to 3.12)	No significant difference.	Insufficient
Perphenazine vs. risperidone (1 RCT)	1.06 (0.57 to 1.96)	No significant difference.	Insufficient
Perphenazine vs. ziprasidone (1 RCT)	1.00 (0.49 to 2.05)	No significant difference.	Insufficient
<i>Tardive Dyskinesia</i>			
Chlorpromazine vs. clozapine (1 RCT)	3.30 (0.14 to 76.46)	No significant difference.	Insufficient
Chlorpromazine vs. ziprasidone (1 RCT)	1.21 (0.61 to 2.44)	No significant difference.	Insufficient
Haloperidol vs. clozapine (1 cohort)	34.50 (2.07 to 573.55)	Significant difference, with more events for haloperidol.	Insufficient
Haloperidol vs. olanzapine (1 RCT)	11.75 (0.65 to 211.26)	No significant difference.	Insufficient
Haloperidol vs. quetiapine (1 RCT)	NE	Zero events in both groups.	Insufficient
Haloperidol vs. ziprasidone (1 RCT)	4.84 (0.23 to 99.93)	No significant difference.	Insufficient
<i>Metabolic Syndrome</i>			
Haloperidol vs. clozapine (1 RCT)	0.27 (0.10 to 0.75)	Significant difference, with more events for clozapine.	Insufficient
Haloperidol vs. olanzapine (2 RCTs)	0.38 (0.06 to 2.51)	No significant difference.	Low
Perphenazine vs. olanzapine (1 RCT)	0.88 (0.63 to 1.21)	No significant difference.	Insufficient
Perphenazine vs. quetiapine (1 RCT)	1.19 (0.84 to 1.70)	No significant difference.	Insufficient
Perphenazine vs. risperidone (1 RCT)	1.42 (0.98 to 2.06)	No significant difference.	Insufficient
Perphenazine vs. ziprasidone (1 RCT)	1.51 (0.96 to 2.39)	No significant difference.	Insufficient

Table 83. Summary of the strength of evidence for AEs (continued)

Comparison (Number of Studies)	RR (95% CI)	Summary	SoE
Mortality			
Chlorpromazine vs. clozapine (2 RCTs)	0.98 (0.10 to 9.19)	No significant difference.	Low
Chlorpromazine vs. clozapine (1 Cohort)	1.98 (1.30 to 3.00)	Significant difference, with more events for chlorpromazine.	Insufficient
Chlorpromazine vs. ziprasidone (1 RCT)	NE	Zero events in both groups.	Insufficient
Haloperidol vs. aripiprazole (2 RCT)	0.77 (0.04 to 15.91)	No significant difference.	Low
Haloperidol vs. risperidone (1 Cohort)	1.70 (1.31 to 2.20)	Significant difference, with more events for haloperidol.	Insufficient
Thioridazine vs. clozapine (1 Cohort)	2.12 (1.38 to 3.26)	Significant difference, with more events for thioridazine.	Insufficient
Thioridazine vs. risperidone (1 Cohort)	1.82 (1.37 to 2.40)	Significant difference, with more events for thioridazine.	Insufficient

CI = confidence interval; NE = not estimable; RCT = randomized controlled trial; RR = relative risk; SoE = strength of evidence

Chlorpromazine Versus Clozapine

Twelve trials^{48,63,87,94,109,152-154,156,158,160,161} reported on the incidence of AEs in patients receiving chlorpromazine compared with patients receiving clozapine (Table 84).

General Measures

The rates of mortality (2 trials)^{109,156} and withdrawals due to AEs (5 trials)^{63,87,109,152,160} were not different between groups.

Specific Measures

Behavior and Psychosis

No differences were found in single trials reporting the incidence of agitation,¹⁵³ depression,¹⁵² and increasing paranoia and excitement.¹⁵⁴

Body Mass Index (BMI) and Weight

A single trial⁸⁷ reported no differences in incidence of weight gain (>5 percent) and weight loss.

Cardiovascular

Hypertension occurred less frequently with chlorpromazine (2 trials).^{94,160} No difference between groups was found for abnormal electrocardiogram (ECG) (2 trials),^{154,160} cardiotoxic effects (1 trial),¹⁵³ hypotension (5 trials),^{48,87,94,109,160} orthostatic hypotension (3 trials),^{153,158,160} and tachycardia (2 trials).^{87,94}

Cholinergic and Anticholinergic

Dry mouth was reported less frequently with clozapine (5 trials),^{63,87,94,152,161} whereas hypersalivation was reported less frequently with chlorpromazine (9 trials).^{48,63,87,94,152,154,158,160,161} There was no difference in the incidence of ileus in one trial.¹⁰⁹

Central Nervous System (CNS)

Drowsiness was less frequent with chlorpromazine (5 trials).^{94,152,153,160,161} Dizziness (3 trials),^{94,160,161} sedation (3 trials),^{48,63,87} seizure (3 trials),^{63,87,153} and slurred speech (1 trial)¹⁶⁰ did not differ between groups.

Dermatology

There was no difference between groups in the incidence of dermatologic reactions (3 trials).^{87,109,153}

Endocrine (Prolactin and Thyroid)

One trial reported no difference in the incidence hyperprolactinemia.⁶³

Extrapyramidal Symptoms or Syndrome (EPS)

EPS were less frequent with clozapine (6 trials).^{48,63,87,109,158,160} There was no difference in the incidence of the following AEs: akathisia (3 trials),^{63,87,154} dystonia (2 trials),^{63,154} oculogyric crisis (1 trial),¹⁵⁴ parkinsonism (2 trials),^{153,154} rigidity (3 trials),^{63,152,160} staggering (1 trial),¹⁶⁰ deterioration of tardive dyskinesia (1 trial),⁸⁷ and tremor (3 trials).^{152,160,161}

Genitourinary

In a single trial⁶³ there was no difference in the incidence of impotence.

Gastrointestinal

No differences were found in the incidence of abdominal cramps (1 trial),¹⁶⁰ constipation (4 trials),^{63,94,109,152} diarrhea (1 trial),¹⁶⁰ heartburn (1 trial),¹⁶⁰ and nausea or vomiting (3 trials).^{87,94,160}

Hematology

No differences were found in the incidence of agranulocytosis (2 trials),^{63,94} abnormal blood cell count (1 trial),¹⁵⁴ neutropenia (1 trial),¹⁰⁹ elevated platelet count (1 trial),¹⁵⁴ and leukocytopenia (4 trials).^{48,63,87,94}

Hepatobiliary

No differences in the incidence of elevated hepatic enzymes (2 trials)^{87,94} or jaundice (1 trial)⁸⁷ were reported.

Sleep

No differences in the incidence of deep sleep or sleep disturbances were reported in a single trial.¹⁵³

Respiratory and Airway

No difference in the incidence of coughing was reported in one trial.¹⁶⁰

Systemic AEs

Fever or chills were reported less frequently with chlorpromazine (2 trials).^{94,160} There were no differences between groups in the incidence of accidental falls (1 trial),⁸⁷ headaches (2 trials),^{94,160} hyperthermia (3 trials),^{109,154,160} and tension (1 trial).¹⁶⁰

Table 84. Evidence summary table: chlorpromazine versus clozapine – specific AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I ²	Less With
Cardiovascular					
Hypertension ^{94,160}	2	312	0.39 (0.17, 0.90)	0%	chlorpromazine
Cholinergic and Anticholinergic					
Dry mouth ^{63,87,94,152,161}	5	563	3.00 (1.67, 5.40)	11%	clozapine
Hypersalivation ^{48,63,87,94,152,154,158,160,161}	9	674	0.25 (0.14, 0.45)	13%	chlorpromazine
CNS					
Drowsiness ^{94,152,153,160,161}	5	457	0.75 (0.58, 0.97)	0%	chlorpromazine
EPS					
EPS ^{48,63,87,109,158,160}	6	451	2.75 (1.48, 5.12)	0%	clozapine
Systemic AE					
Fever or chills ^{94,160}	2	312	0.35 (0.15, 0.83)	0%	chlorpromazine

AE = adverse event; CNS = central nervous system; EPS = extrapyramidal symptoms or syndrome; I² = I-squared; KQ = Key Question

Chlorpromazine Versus Olanzapine

A single trial⁶⁶ reported on the incidence of AEs in patients receiving chlorpromazine compared with patients receiving olanzapine (Table 85). The incidence of orthostatic hypotension, dry mouth, unsteady gait, and constipation was less frequent with olanzapine. Other reported AEs were not different between groups (Appendix N, Tables 115 and 116).

Table 85. Evidence summary table: chlorpromazine versus olanzapine – specific AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I ²	Less With
Cardiovascular					
Orthostatic hypotension ⁶⁶	1	84	7.50 (2.90, 19.42)	NE	olanzapine
Cholinergic and Anticholinergic					
Dry mouth ⁶⁶	1	84	1.94 (1.27, 2.97)	NE	olanzapine
CNS					
Unsteady gait ⁶⁶	1	84	15.00 (2.07, 108.48)	NE	olanzapine
GI					
Constipation ⁶⁶	1	84	2.60 (1.02, 6.65)	NE	olanzapine

AE = adverse event; CNS = Central Nervous System; GI = gastrointestinal; I² = I-squared; KQ = Key Question; NE = not estimable

Chlorpromazine Versus Quetiapine

A single trial¹²¹ reported on the incidence of AEs in patients receiving chlorpromazine compared with patients receiving quetiapine (Table 86). The incidence of orthostatic hypotension was less frequent with quetiapine. Other reported AEs did not differ between groups (Appendix N, Tables 117 and 118).

Table 86. Evidence summary table: chlorpromazine versus quetiapine – specific AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I ²	Less With
Cardiovascular					
Orthostatic hypotension ¹²¹	1	201	3.64 (1.40, 9.42)	NE	quetiapine

AE = adverse event; I² = I-squared; KQ = Key Question; NE = not estimable

Chlorpromazine Versus Ziprasidone

A single trial⁹⁶ reported on the incidence of AEs in patients receiving chlorpromazine compared with patients receiving ziprasidone (Table 87). The incidence of orthostatic hypotension was less frequent with chlorpromazine. Other reported AEs did not differ between groups (Appendix N, Tables 119 and 120).

Table 87. Evidence summary table: chlorpromazine versus ziprasidone – specific AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I ²	Less With
<i>BMI and Weight</i>					
Weight loss ⁹⁶	1	306	0.19 (0.06, 0.62)	NE	chlorpromazine

AE = adverse event; I² = I-squared; KQ = Key Question; NE = not estimable

Fluphenazine Versus Olanzapine

A single trial⁸⁹ comparing the incidence of AEs in patients receiving fluphenazine compared with patients receiving olanzapine showed no difference between groups (Appendix N, Tables 121 and 122).

Fluphenazine Versus Quetiapine

A single trial⁶⁷ reported on the incidence of AEs in patients receiving fluphenazine compared with patients receiving quetiapine; no difference in reported AEs or persistence and reversibility of AEs were found (Appendix N, Tables 123, 124, and 125).

Fluphenazine Versus Risperidone

A single trial⁶⁷ reported on the incidence of AEs in patients receiving fluphenazine compared with patients receiving quetiapine; no difference in reported AEs or persistence and reversibility of AEs were found (Appendix N, Tables 126, 127, and 128).

Haloperidol Versus Aripiprazole

Nine trials^{31-33,44,73,74,76,92,98} reported on the incidence of AEs in patients receiving haloperidol compared with patients receiving aripiprazole (Table 88). The statistically significant findings are presented in Table 89. Other reported AEs did not differ between groups (Appendix N, Tables 129 and 130).

General Measures

The incidence of patients with AEs (3 trials)^{31,73,98} and withdrawals due to AEs (7 trials)^{31-33,44,76,92,98} were less frequent with aripiprazole. Rates of mortality (2 trials)^{31,44} and serious adverse events (SAEs) (6 trials)^{31-33,44,76,92} were not different between groups.

Specific Measures

Behavior and Psychosis

The incidence of mania in a single trial³³ was less frequent with haloperidol. No differences between groups were found for agitation (4 trials),^{31,44,74,98} anxiety (4 trials),^{33,74,92,98} depression (2 trials),^{32,33} clinical deterioration (1 trial),⁷³ and psychosis (1 trial).⁹⁸

BMI and Weight

No difference between groups was found for weight gain (3 trials).^{33,92,98}

Cardiovascular

The incidence of ECG abnormalities (3 trials),^{31,32,92} orthostatic hypotension (1 trial),⁹² and tachycardia (1 trial)³¹ were not different between groups.

CNS

Dizziness (3 trials)^{31,44,92} was less frequent with haloperidol, and somnolence (6 trials)^{31,33,44,74,92,98} was less frequent with aripiprazole. No difference was reported for the incidence of seizures in a single trial.³¹

Dermatology

Two trials found no difference between groups in injection site reactions.^{31,44}

Endocrine (Prolactin and Thyroid)

Hyperprolactinemia (2 trials)^{32,33} was less frequent with aripiprazole.

EPS

Akathisia (7 trials),^{31-33,74,76,92,98} dystonia (1 trial),³¹ EPS (6 trials),^{32,33,44,74,92,98} rigidity (1 trial),³³ and tremor (5 trials)^{32,33,76,92,98} were less frequent with aripiprazole. No difference was found between groups for asthenia (1 trial)⁹² and hypertonia (1 trial).⁹²

Gastrointestinal

Dyspepsia (1 trial)⁷⁴ was less frequent with aripiprazole; nausea or vomiting (4 trials)^{31,44,74,92} was less frequent with haloperidol. There was no difference between groups in the incidence of abdominal pain (1 trial)⁹² and diarrhea (1 trial).⁷⁴

Hepatobiliary

A single trial found no difference in the incidence of liver damage.³²

Ophthalmology

A single trial found the incidence of blurred vision less frequent with aripiprazole.⁹²

Sleep

There was no difference between groups in the incidence of insomnia (7 trials).^{32,33,44,74,76,92,98}

Systemic AEs

There was no difference in the incidence of headache (7 trials).^{31-33,44,74,92,98}

Table 88. Evidence summary table: haloperidol versus aripiprazole – general adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less With
Incidence of patients with AEs ^{31,73,98}	3	1713	1.11 (1.06, 1.17)	0%	aripiprazole
Withdrawals due to AEs ^{31-33,44,76,92,98}	7	3035	1.25 (1.06, 1.47)	0%	aripiprazole

AE = adverse events; CI = confidence intervals; I² = I-squared

Table 89. Evidence summary table: haloperidol versus aripiprazole – specific AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I ²	Less With
Behavior and Psychosis					
Mania ³³	1	332	0.20 (0.05, 0.91)	NE	haloperidol
CNS					
Dizziness ^{31,44,92}	3	963	0.53 (0.31, 0.90)	0%	haloperidol
Somnolence ^{31,33,44,74,92,98}	6	2893	1.39 (1.03, 1.87)	0%	aripiprazole
Endocrine (Prolactin and Thyroid)					
Hyperprolactinemia ^{32,33}	2	679	3.67 (2.16, 6.24)	70%	aripiprazole
EPS					
Akathisia ^{31-33,74,76,92,98}	7	2979	2.04 (1.70, 2.44)	0%	aripiprazole
Dystonia ³¹	1	295	7.83 (1.47, 41.76)	NE	aripiprazole
EPS ^{32,33,44,74,92,98}	6	2945	2.22 (1.37, 3.59)	83%	aripiprazole
Rigidity ³³	1	332	8.10 (1.89, 34.66)	NE	aripiprazole
Tremor ^{32,33,76,92,98}	5	2380	1.99 (1.42, 2.78)	4%	aripiprazole
GI					
Dyspepsia ⁷⁴	1	304	9.12 (1.17, 71.10)	NE	aripiprazole
Nausea or vomiting ^{31,44,74,92}	4	1267	0.49 (0.28, 0.85)	0%	haloperidol
Ophthalmology					
Blurred vision ⁹²	1	308	5.23 (1.42, 19.30)	NE	aripiprazole

AE = adverse events; CNS = central nervous system; EPS = extrapyramidal symptoms or syndrome; GI = gastrointestinal; I² = I-squared; KQ = Key Question; NE = not estimable

Haloperidol Versus Asenapine

A single trial⁶⁷ reported on the incidence of AEs in patients receiving haloperidol compared with patients receiving asenapine. Oral hypoesthesia and somnolence were less frequent with haloperidol. Hyperprolactinemia, dystonia, and EPS were less frequent with asenapine (Table 90). There were no differences in the other reported AEs (Appendix N, Tables 131 and 132).

Table 90. Evidence summary table: haloperidol versus asenapine – specific AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I ²	Less With
CNS					
Oral hypoesthesia ⁹⁷	1	335	0.04 (0.00, 0.69)	NE	haloperidol
Somnolence ⁹⁷	1	335	0.21 (0.05, 0.90)	NE	haloperidol
Endocrine (Prolactin and Thyroid)					
Hyperprolactinemia ⁹⁷	1	335	2.30 (1.02, 5.15)	NE	asenapine
EPS					
Dystonia ⁹⁷	1	335	3.51 (1.33, 9.24)	NE	asenapine
EPS ⁹⁷	1	335	2.07 (1.40, 3.07)	NE	asenapine

AE = adverse event; CNS = central nervous system; EPS = extrapyramidal symptoms or syndrome; I² = I-squared; KQ = Key Question; NE = not estimable

Haloperidol Versus Clozapine

Six trials^{55,95,105,126,145,155} and two cohort studies^{162,163} reported on the incidence of AEs in patients receiving haloperidol compared with patients receiving clozapine (Table 91). The statistically significant findings are presented in Table 92. Other reported AEs did not differ between groups (Appendix N, Tables 133 and 134).

General Measures

A single cohort study found less incidence of mortality with clozapine.¹⁶³ The incidence of patients with AEs (1 trial)¹²⁶ and withdrawals due to AEs (5 trials),^{55,95,105,126,145} was not different between groups.

Specific Measures

Behavior and Psychosis

Single trials reported less frequent incidence of irritability¹⁵⁵ and overt aggression¹⁴⁵ with clozapine. One trial found no difference between groups in clinical deterioration conducive to termination.¹⁴⁵

BMI and Weight

No difference between groups was reported for weight gain (2 trials).^{105,145}

Cardiovascular

Single trials found no differences in incidence of hypertension,⁵⁵ hypertensive episodes,¹⁴⁵ intrathoracic oppression,¹⁵⁵ orthostatic hypotension,¹⁵⁵ and palpitation.¹⁵⁵

Cholinergic and Anticholinergic

Dry mouth (2 trials)^{55,155} was less frequent with clozapine. Hypersalivation (1 trial)⁵⁵ was less frequent with haloperidol.

CNS

No differences between groups were found for the incidence of CNS abnormalities, including dizziness (2 trials),^{55,155} drowsiness (1 trial),¹⁵⁵ dysarthria (1 trial),¹⁵⁵ sedation (1 trial),⁵⁵ seizures (1 trial),¹⁴⁵ and seizures conducive to termination (1 trial).¹⁴⁵

Dermatology

Single trials reported no difference in the incidence of pruritus¹⁵⁵ and rash.¹⁵⁵

Endocrine (Prolactin and Thyroid)

A single trial¹⁵⁵ reported no difference in the incidence of abnormal menstruation.

EPS

A single trial¹⁵⁵ found less frequent incidence of hyperkinesia with clozapine and no difference between groups in the incidence of hypertonia. One cohort study¹⁶² reported less frequent incidence of tardive dyskinesia with clozapine.

Gastrointestinal

The incidence of nausea or vomiting (2 trials)^{55,155} was less frequent with haloperidol. There was no difference in the incidence of constipation (2 trials),^{55,155} diarrhea (2 trials),^{55,155} loss of appetite (1 trial),¹⁵⁵ and other gastrointestinal abnormalities (1 trial).¹⁵⁵

Genital, Urinary, and Breast

A single trial⁵⁵ reported no difference in the incidence of enuresis.

Hematology

There were no differences between groups in the incidence of agranulocytosis (2 trials),^{126,145} bruising (1 trial),⁵⁵ hematological problems conducive to termination (1 trial),¹⁴⁵ leukopenia (1 trial),¹²⁶ and neutropenia (2 trials).^{126,145}

Metabolic

A single trial¹⁰⁵ reported less frequent incidence of abnormal glucose levels and emergent metabolic syndrome with haloperidol. The trial found no difference in hypercholesterolemia and hypertriglyceridemia.

Ophthalmology

A single trial¹⁵⁵ reported no difference in ophthalmic disturbances.

Respiratory and Airway

Two trials^{55,155} reported no difference in upper respiratory disturbances.

Sleep

A single trial¹⁵⁵ reported less frequent incidence of insomnia with clozapine.

Systemic AEs

The incidence of the following AEs was not different between groups: headache (1 trial),¹⁵⁵ fever (2 trials),^{55,155} intercurrent illnesses conducive to termination (1 trial),¹⁴⁵ malaise (1 trial),⁵⁵ sweating (1 trial),¹⁵⁵ and weakness (1 trial).¹⁵⁵

Table 91. Evidence summary table: haloperidol versus clozapine – general AEs (KQ3)

Outcome	Studies	Participants	Effect Estimate	I ²	Less With
Mortality (Cohort) ¹⁶³	1	49625	1.98 (1.30, 3.00)	NE	clozapine

AE = adverse events; I² = I-squared; KQ = Key Question; NE = not estimable

Table 92. Evidence summary table: haloperidol versus clozapine – specific AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I ²	Less With
Behavior and Psychosis					
Irritability ¹⁵⁵	1	88	3.21 (1.26, 8.15)	NE	clozapine
Overt aggression ¹⁴⁵	1	77	1.66 (1.03, 2.66)	NE	clozapine
Cholinergic and Anticholinergic					
Dry mouth ^{55,155}	2	163	2.81 (1.61, 4.92)	0%	clozapine
Hypersalivation ⁵⁵	1	75	0.23 (0.12, 0.46)	NE	haloperidol
EPS					
Hyperkinesia ¹⁵⁵	1	88	2.01 (1.13, 3.56)	NE	clozapine
Tardive Dyskinesia (Cohort) ¹⁶²	1	333	34.50 (2.07, 573.55)	NE	clozapine
GI					
Nausea or vomiting ^{55,155}	2	163	0.44 (0.21, 0.93)	17%	haloperidol
Metabolic					
Abnormal Glucose levels ¹⁰⁵	1	73	0.05 (0.00, 0.80)	NE	haloperidol
Metabolic syndrome (emergent) ¹⁰⁵	1	73	0.27 (0.10, 0.75)	NE	haloperidol
Sleep					
Insomnia ¹⁵⁵	1	88	3.44 (1.51, 7.84)	NE	clozapine

AE = adverse event; EPS = extrapyramidal symptoms or syndrome; GI = gastrointestinal; I² = I-squared; KQ = Key Question; NE = not estimable

Haloperidol Versus Olanzapine

Twenty-seven trials^{43,49-51,54,56,71,73,78,84,88,91,101,104-106,108,110,124,127,129,140-142,145,147,159} and two cohort studies^{162,163} reported on the incidence of AEs in patients receiving haloperidol compared with patients receiving olanzapine (Table 93). The statistically significant findings are presented in Table 94. Other reported AEs did not differ between groups (Appendix N, Tables 135 and 136).

General Measures

The incidence of withdrawals due to AEs (21 trials)^{43,49,50,54,71,78,84,88,91,101,104,105,108,110,124,127,140,141,145,147,159} was reported less frequently with olanzapine. There was some suggestion of publication bias based on Egger's test ($p = 0.02$) and some funnel plot asymmetry (Appendix K, Funnel plot 13). No difference was found for patients with AEs (1 trial),⁷³ persistence and reversibility of AE (1 trial),⁸⁸ and SAEs (3 trials).^{91,104,147}

Specific Measures

Behavior and Psychosis

In single trials, the incidence of anorexia,⁸⁸ decreased appetite,¹⁴¹ and conversion symptoms¹⁴¹ were less frequent with olanzapine, whereas the incidence of excessive appetite (1 trial)¹⁴¹ was less frequent with haloperidol. Other behavioral and psychotic-related AEs were not different between groups: abnormal thinking (1 trial),¹⁰¹ accommodation disturbance (1 trial),¹⁵⁹ agitation (2 trials),^{49,101} anxiety (4 trials),^{49,88,101,147} behavioral deterioration (2 trials),^{73,84} depression (1 trial),¹⁰¹ excitement (1 trial),⁸⁸ hallucinations (2 trials),^{84,101} nervousness (2 trials),^{49,101} overt aggression or violent behavior (3 trials),^{49,110,145} paranoia (1 trial),¹⁰¹ personality disorder (1 trial),⁴⁹ suicidal ideation (1 trial),¹¹⁰ and suicide (1 trial),⁸⁸ suicide attempt (1 trial).⁸⁸

BMI and Weight

The incidence of patients categorized as overweight or obese (2 trials)^{91,129} and weight gain (15 trials)^{49,71,88,91,101,104,105,108,127,129,140-142,145,159} was less frequent with haloperidol. There was no difference between groups in patients with weight loss (2 trials).^{88,141}

Cardiovascular

A single trial found fewer palpitations with olanzapine.¹⁴¹ No difference between groups was found for ECG abnormalities (2 trials),^{56,91} hypertensive episodes (1 trial),¹⁴⁵ and hypotension (1 trial).⁵⁶

Cholinergic and Anticholinergic

AEs. The incidence of dry mouth (5 trials)^{49,71,101,141,159} was less frequent with haloperidol. The incidence of hypersalivation (6 trials)^{50,71,88,140,141,159} was less frequent with olanzapine.

CNS

The incidence of drowsiness (1 trial),¹⁴¹ gait abnormalities (1 trial),⁸⁸ heaviness in the extremities (1 trial),¹⁴¹ hypokinesia (4 trials),^{71,140,141,159} and hypotonia (1 trial)¹⁴¹ was less frequent with olanzapine. There were no differences between groups for asthenia (3 trials),^{49,71,159} concentration difficulty (1 trial),⁷¹ dizziness (3 trials),^{49,101,140} seizures (1 trial),¹⁴⁵ and somnolence (6 trials).^{49,71,88,101,140,159}

Dermatology

A single trial¹⁴⁷ reported no difference in the incidence of maculopapular rash.

Endocrine (Prolactin and Thyroid)

In a single trial,¹⁴¹ the incidence of hot flashes was less frequent with olanzapine. There was no difference in the incidence of amenorrhea (1 trial).⁷¹ The pooled results for hyperprolactinemia (3 trials)^{50,91,108} were not reported because there was marked heterogeneity between the trials ($I^2 = 97$ percent).

EPS

The incidence of the following EPS-related AEs were less frequent with olanzapine: akathisia (14 trials),^{49-51,56,71,88,91,101,104,108,127,140,141,159} ataxia (1 trial),¹⁴¹ bradykinesia (1 trial),⁸⁸ dyskinesia (4 trials),^{50,91,140,141} dystonia (8 trials),^{49,50,56,91,104,140,147,159} EPS (6 trials),^{50,104,106,140,141,147} hypertonia (4 trials),^{49,50,140,141} parkinsonism (8 trials),^{51,56,71,84,88,91,108,147} rigidity (2 trials),^{71,159} and tremor (9 trials).^{49,50,71,88,101,104,140,141,159} Single trials found no difference in the incidence of neuroleptic malignant syndrome¹⁴⁷ and tardive dyskinesia.¹⁴⁰

Gastrointestinal

The incidence of nausea or vomiting (5 trials)^{49,88,101,141,141} was less frequent with olanzapine. There was no difference in the incidence of constipation (3 trials),^{49,101,159} diarrhea (1 trial),¹⁰¹ and dyspepsia (1 trial).⁴⁹

Genital, Urinary, and Breast

In single trials, difficult micturition¹⁴¹ was less frequent with olanzapine. No differences were found between groups for ejaculatory dysfunction,⁷¹ erectile dysfunction,⁷¹ and micturition disturbances.¹⁵⁹

Hematology

The incidence of the following hematological disorders were not different between groups: agranulocytosis (2 trials),^{141,145} eosinophilia (1 trial),⁵⁰ hematological problems conducive to termination (1 trial),¹⁴⁵ and neutropenia (1 trial).¹⁴⁵

Hepatobiliary

The incidence of abnormalities of serum glutamic oxaloacetic transaminase (1 trial)¹⁰⁸ and serum glutamic pyruvic transaminase (2 trials)^{49,108} were less frequent with haloperidol. In single trials, there was no difference in the incidence of elevated alanine aminotransferase⁵⁰ or increased gamma-glutamyl transpeptidase.⁵⁰

Metabolic

The incidence of the following metabolic disorders was less frequent with haloperidol: hypercholesterolemia (2 trials),^{91,105} hyperglycemia (2 trials),^{91,105} hypertriglyceridemia (2 trials),^{91,105} and low levels of high-density lipoprotein (1 trial).⁹¹ There were no differences between groups in the incidence of diabetes (1 trial)¹²⁹ or metabolic syndrome (2 trials).^{105,129}

Ophthalmology

A single trial¹⁴¹ reported less blurred vision with olanzapine.

Respiratory and Airway

The incidence of rhinitis was not different between groups (2 trials).^{49,101}

Sleep

The incidence of sleep disturbances, including early awakening (1 trial),¹⁴¹ increased dreams or nightmares (1 trial),¹⁴¹ and insomnia (7 trials),^{49,50,88,101,104,127,141} were less frequent with olanzapine.

Systemic AEs

In single trials, chills¹⁴¹ and increased perspiration¹⁴¹ were less frequent with olanzapine. In contrast, fever¹⁴⁰ and infection¹⁴⁰ were less frequent with haloperidol. No differences were found between groups for the following other systemic AEs: headache (3 trials),^{49,50,101} injury (1 trial),⁴⁹ intercurrent illnesses conducive to termination (1 trial),¹⁴⁵ malaise (1 trial),⁸⁸ pain (2 trials),^{49,101} and tension (1 trial).¹⁵⁹

Table 93. Evidence summary table: haloperidol versus olanzapine – general measures with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I ²	Less With
Withdrawals due to adverse events ^{43,49,50,54,71,78,84,88,91,101,104,105,108,110,124,127,140,141,145,147,159}	21	5351	1.87 (1.55, 2.27)	0%	olanzapine

I² = I-squared; KQ = Key Question

Table 94. Evidence summary table: haloperidol versus olanzapine – specific AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I ²	Less With
Behavior and Psychosis					
Anorexia ⁸⁸	1	182	3.66 (1.25, 10.69)	NE	olanzapine
Appetite (decreased) ¹⁴¹	1	1996	1.56 (1.25, 1.96)	NE	olanzapine
Appetite (excessive) ¹⁴¹	1	1996	0.51 (0.41, 0.64)	NE	haloperidol
Conversion symptoms ¹⁴¹	1	1996	2.34 (1.12, 4.88)	NE	olanzapine
BMI and Weight					
Overweight or obese ^{91,129}	2	274	0.35 (0.21, 0.58)	0%	haloperidol
Weight gain ^{49,71,88,91,101,104,105,108,127,129,140-142,145,159}	15	4600	0.47 (0.37, 0.61)	75%	haloperidol
Cardiovascular					
Palpitations ¹⁴¹	1	1996	1.48 (1.09, 2.02)	NE	olanzapine
Cholinergic and Anticholinergic					
Dry mouth ^{49,71,101,141,159}	5	2657	0.75 (0.62, 0.91)	0%	haloperidol
Hypersalivation ^{50,71,88,140,141,159}	6	3200	3.38 (1.79, 6.38)	49%	olanzapine
CNS					
Drowsiness ¹⁴¹	1	1996	1.19 (1.02, 1.38)	NE	olanzapine
Gait abnormalities ⁸⁸	1	182	8.36 (1.98, 35.32)	NE	olanzapine
Heaviness in extremities ¹⁴¹	1	1996	1.40 (1.11, 1.77)	NE	olanzapine
Hypokinesia ^{71,140,141,159}	4	2587	3.01 (1.88, 4.82)	7%	olanzapine
Hypotonia ¹⁴¹	1	1996	1.68 (1.03, 2.72)	NE	olanzapine
Endocrine (Prolactin and Thyroid)					
Hot flashes ¹⁴¹	1	1996	1.62 (1.06, 2.49)	NE	olanzapine

Table 94. Evidence summary table: haloperidol versus olanzapine – specific AEs with significant differences (KQ3) (continued)

Outcome	Studies	Participants	Effect Estimate	I ²	Less With
EPS					
Akathisia ⁴⁹⁻ 51,56,71,88,91,101,104,108,127,140,141,159	14	5031	3.11 (2.43, 3.98)	38%	olanzapine
Ataxia ¹⁴¹	1	1996	1.84 (1.01, 3.35)	NE	olanzapine
Bradykinesia ⁸⁸	1	182	8.36 (1.98, 35.32)	NE	olanzapine
Dyskinesia ^{50,91,140,141}	4	3088	3.55 (2.01, 6.27)	10%	olanzapine
Dystonia ^{49,50,56,91,104,140,147,159}	8	2144	5.01 (2.70, 9.28)	0%	olanzapine
EPS ^{50,104,106,140,141,147}	6	3445	3.88 (2.19, 6.85)	69%	olanzapine
Hypertonia ^{49,50,140,141}	4	3147	2.54 (1.65, 3.91)	55%	olanzapine
Parkinsonism ^{51,56,71,84,88,91,108,147}	8	1283	4.28 (2.49, 7.35)	50%	olanzapine
Rigidity ^{71,159}	2	138	10.65 (2.08, 54.50)	0%	olanzapine
Tremor ^{49,50,71,88,101,104,140,141,159}	9	3999	2.30 (1.59, 3.34)	58%	olanzapine
Genital, Urinary, and Breast					
Difficult micturition ¹⁴¹	1	1996	1.68 (1.11, 2.54)	NE	olanzapine
GI					
Nausea or vomiting ^{49,88,101,141,141}	5	4697	1.43 (1.06, 1.92)	34%	olanzapine
Hepatobiliary					
SGOT abnormality ¹⁰⁸	1	263	0.41 (0.28, 0.58)	NE	haloperidol
SGPT abnormality ^{49,108}	2	530	0.46 (0.35, 0.62)	0%	haloperidol
Metabolic					
Hypercholesterolemia ^{91,105}	2	281	0.43 (0.26, 0.72)	0%	haloperidol
Hyperglycemia ^{91,105}	2	281	0.28 (0.12, 0.66)	0%	haloperidol
Hypertriglyceridemia ^{91,105}	2	281	0.53 (0.30, 0.92)	0%	haloperidol
HDL (low) ⁹¹	1	208	0.38 (0.16, 0.94)	NE	haloperidol
Ophthalmology					
Blurred vision ¹⁴¹	1	1996	1.40 (1.10, 1.78)	NE	olanzapine
Sleep					
Early awakening ¹⁴¹	1	1996	1.49 (1.24, 1.79)	NE	olanzapine
Increased dreams/nightmares ¹⁴¹	1	1996	1.31 (1.05, 1.63)	NE	olanzapine
Insomnia ^{49,50,88,101,104,127,141}	7	3717	1.36 (1.03, 1.80)	49%	olanzapine
Systemic AE					
Chills ¹⁴¹	1	1996	1.74 (1.19, 2.52)	NE	olanzapine
Fever ¹⁴⁰	1	453	0.05 (0.00, 0.86)	NE	haloperidol
Infection ¹⁴⁰	1	453	0.27 (0.08, 0.93)	NE	haloperidol
Increased perspiration ¹⁴¹	1	1996	1.91 (1.44, 2.54)	NE	olanzapine

AE = adverse event; BMI = body mass index; CNS = central nervous system; EPS = extrapyramidal symptoms or syndrome; GI = gastrointestinal; HDL = high-density lipoprotein; I² = I-squared; KQ = Key Question; NE = not estimable; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase

Haloperidol Versus Quetiapine

Ten trials^{46,47,65,68,73,79,80,91,115,123} reported on the incidence of AEs in patients receiving haloperidol compared with patients receiving quetiapine. The statistically significant findings are presented in Table 95. Other reported AEs did not differ between groups (Appendix N, Tables 137 and 138).

General Measures

The incidences of patients with AEs (3 trials),^{68,73,79} SAEs (1 trial),⁹¹ and withdrawals due to AEs (8 trials)^{46,47,68,79,80,91,115,123} were not different between groups.

Specific Measures

Behavior and Psychosis

A single trial⁶⁸ reported less frequent asthenia with haloperidol. The following other AEs related to behavior and psychosis were not different between groups: agitation (4 trials),^{46,68,115,123} anxiety (1 trial),⁶⁸ depression (1 trial),¹¹⁵ deterioration (1 trial),⁷³ fatigue (1 trial),¹²³ and irritability (1 trial).¹²³

BMI and Weight

Weight gain (3 trials)^{46,91,123} was less frequent with haloperidol. A single trial⁹¹ reported no difference between groups in the incidence of overweight patients.

Cardiovascular

Orthostatic hypotension (3 trials),^{46,68,115} was less frequent with haloperidol. The incidence of ECG abnormalities (2 trials)^{46,91} was not different between groups.

Cholinergic and Anticholinergic

Dry mouth (3 trials)^{68,115,123} was less frequent with haloperidol; hypersalivation (2 trials)^{68,123} did not differ between groups.

CNS

Somnolence (4 trials)^{46,68,115,123} was less frequent with haloperidol. The incidence of other CNS abnormalities, including dizziness (2 trials),^{46,68} drowsiness (1 trial),¹²³ sedation (1 trial)¹²³ did not differ between groups.

Dermatology

A single trial¹²³ reported no difference in the incidence of dry skin or rash.

Endocrine (Prolactin and Thyroid)

Hyperprolactinemia (3 trials)^{68,79,91} was less frequent with quetiapine. A single trial found less frequent thyroid function test abnormalities with haloperidol.⁶⁸ Single trials reported no difference for the following endocrine abnormalities: amenorrhea or menstrual cycle irregularities,¹²³ cold flashes,¹²³ and galactorrhea.⁴⁷

EPS

Akathisia (5 trials),^{46,68,79,91,115} parkinsonism (2 trials),^{46,91} and tremors (2 trials)^{68,115} were less frequent with quetiapine. The following EPS-related AEs showed no difference between groups: akinesia (1 trial),⁶⁸ cogwheel rigidity (1 trial),⁶⁸ dyskinesia (1 trial),⁹¹ dystonia (3 trials),^{46,68,91} fine tremors (1 trial),¹²³ hypertonia (2 trials),^{68,79} involuntary movement of the jaw (1 trial),¹²³ neck rigidity (1 trial),⁶⁸ oculogyric crisis (1 trial),⁶⁸ stiffness (1 trial),¹²³ tardive dyskinesia (1 trial),⁶⁵ and twitching of the extremities (1 trial).¹²³ Pooled results for EPS (5 trials)^{46,68,79,80,115} were not reported because of marked heterogeneity between the trials ($I^2 = 90$ percent).

Gastrointestinal

Constipation (2 trials)^{46,68} was less frequent with haloperidol. A single trial⁴⁶ reported no difference in the rate of dyspepsia.

Hematology

Single trials found no differences in the incidence of agranulocytosis⁴⁶ or leucopenia.⁶⁸

Hepatobiliary

A single trial⁶⁸ reported no difference between groups in elevated liver transaminases.

Metabolic

Single trials reported no differences between groups in the incidence of low levels of high-density lipoprotein,⁹¹ hypercholesterolemia,⁹¹ hyperglycemia,⁹¹ and hypertriglyceridemia.⁹¹

Ophthalmology

A single trial¹²³ reported no difference in the incidence of blurred vision.

Sleep

The incidence of insomnia (4 trials)^{46,68,115,123} did not differ between groups.

Systemic AEs

The incidence of headaches (4 trials)^{46,68,115,123} did not differ between groups.

Table 95. Evidence summary table: haloperidol versus quetiapine – specific AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I ²	Less With
<i>Behavior and Psychosis</i>					
Asthenia ⁶⁸	1	448	0.29 (0.12, 0.71)	NE	haloperidol
<i>BMI and Weight</i>					
Weight gain ^{46,91,123}	3	542	0.59 (0.39, 0.89)	0%	haloperidol
<i>Cardiovascular</i>					
Orthostatic hypotension ^{46,68,115}	3	959	0.49 (0.25, 0.94)	0%	haloperidol
<i>Cholinergic and Anticholinergic</i>					
Dry mouth ^{68,115,123}	3	674	0.32 (0.15, 0.65)	0%	haloperidol
<i>CNS</i>					
Somnolence ^{46,68,115,123}	4	984	0.57 (0.39, 0.84)	0%	haloperidol
<i>Endocrine (Prolactin and Thyroid)</i>					
Hyperprolactinemia ^{68,79,91}	3	943	2.24 (1.04, 4.80)	89%	quetiapine
Thyroid function test abnormalities ⁶⁸	1	448	0.05 (0.00, 0.79)	NE	haloperidol

Table 95. Evidence summary table: haloperidol versus quetiapine – specific AEs with significant differences (KQ3) (continued)

Outcome	Studies	Participants	Effect Estimate	I ²	Less With
EPS					
Akathisia ^{46,68,79,91,115}	5	1454	3.51 (1.84, 6.72)	68%	quetiapine
Parkinsonism ^{46,91}	2	517	4.04 (1.97, 8.26)	53%	quetiapine
Tremor ^{68,115}	2	649	3.80 (2.12, 6.81)	0%	quetiapine
GI					
Constipation ^{46,68}	2	758	0.45 (0.22, 0.93)	0%	haloperidol

AE = adverse events; CNS = central nervous system; EPS = extrapyramidal symptoms or syndrome; GI = gastrointestinal; I² = I-squared; KQ = Key Question; NE = not estimable

Haloperidol Versus Risperidone

Twenty-eight trials^{52,53,59-61,64,71-73,81,82,85,90,101,117,118,120,124,128,132,136,138,139,145,146,149-151} and one cohort study¹⁶³ reported on the incidence of AEs in patients receiving haloperidol compared with patients receiving risperidone (Table 96). The statistically significant findings are presented in Table 97. Other reported AEs did not differ between groups (Appendix N, Tables 139 and 140).

General Measures

The incidences of patients with AEs (8 trials),^{72,73,81,85,117,128,136,151} mortality (1 cohort study),¹⁶³ and withdrawals due to AEs (23 trials),^{52,59-61,64,71,72,81,82,85,90,101,118,120,124,128,132,138,145,146,149-151} were less frequent with risperidone. There was no indication of publication bias for withdrawals due to AEs based on statistical tests and visual inspection of the funnel plot (Appendix K, Funnel plot 14). Single trials showed no difference for the incidence of AEs resolved spontaneously by 24 hours¹⁵¹ and SAEs.⁵²

Specific Measures

Behavior and Psychosis

Asthenia (5 trials),^{52,71,117,120,149} was less frequent with risperidone. No differences between groups were found for the following AEs: abnormal thinking (1 trial),¹⁰¹ accommodation disturbances (2 trials),^{120,149} agitation (4 trials),^{61,72,81,101} anxiety (3 trials),^{61,81,101} concentration difficulty (4 trials),^{64,71,117,120} decreased appetite (1 trial),⁶⁴ depression (2 trials),^{101,118} deterioration (1 trial),⁷³ drug overdose (1 trial),¹¹⁸ decreased sexual desire (2 trials),^{120,149} fatigue (2 trials),^{60,64} hallucination (1 trial),¹⁰¹ increased appetite (1 trial),⁶⁴ manic reaction (1 trial),¹²⁸ nervousness (1 trial),¹⁰¹ paranoia (1 trial),¹⁰¹ and sexual disturbances (1 trial).⁵²

BMI and Weight

A single trial¹⁰¹ reported less incidence of weight gain with haloperidol.

Cardiovascular

The groups did not differ in the incidence of the following cardiovascular abnormalities: ECG abnormalities (1 trial),¹²⁸ hypotension (1 trial),⁶¹ orthostatic tachycardia (1 trial),⁶¹ orthostatic hypotension (3 trials),^{52,61,64} and palpitations (2 trials).^{52,64}

Cholinergic and Anticholinergic

The incidence of decreased salivation (1 trial),⁷¹ dry mouth (4 trials),^{52,60,64,101} and hypersalivation (1 trial)⁸⁵ did not differ between groups.

CNS

No differences were found between groups for dizziness (3 trials),^{101,128,151} sedation (1 trial),⁶⁴ somnolence (5 trials),^{52,53,101,128,151} and vertigo (2 trials).^{52,64}

Endocrine (Prolactin and Thyroid)

The incidence of amenorrhea (4 trials)^{64,71,120,149} and galactorrhea (1 trial)¹³² did not differ between groups.

EPS

Akathisia (7 trials),^{52,60,71,101,139,146,149} EPS (5 trials),^{61,117,128,138,151} and tremor (4 trials)^{52,85,101,128} were less frequent with risperidone. There was no difference between groups for dystonia (3 trials)^{60,139,149} or oculogyric crisis (1 trial).⁸⁵

Gastrointestinal

The incidence of constipation (7 trials),^{52,53,64,101,120,128,149} diarrhea (1 trial),¹⁰¹ dyspepsia (1 trial),¹²⁸ nausea or vomiting (5 trials)^{53,61,64,85,101} did not differ between groups.

Genital, Urinary, and Breast

The incidence of breast tension (1 trial),⁶⁴ dry vagina (1 trial),¹⁴⁹ ejaculatory dysfunction (4 trials),^{64,71,120,149} erectile dysfunction (3 trials),^{64,71,120} gynecomastia (1 trial),¹³² and micturition disturbances (1 trial)⁵² did not differ between groups.

Hematology

A single trial¹⁴⁵ reported no difference in the incidence of agranulocytosis.

Ophthalmology

Two trials^{60,64} reported no difference in the incidence of blurred vision.

Respiratory and Airway

A single trial¹⁰¹ reported no difference in the incidence of rhinitis.

Sleep

The incidence of insomnia (6 trials)^{52,61,81,101,120,151} and sleep disorders (2 trials)^{52,85} did not differ between groups.

Systemic AEs

No differences were found between groups in the incidence headaches (9 trials),^{52,53,61,64,81,85,101,128,151} increased sweating (2 trials),^{52,64} infection (1 trial),⁵³ and pain (1 trial).¹⁰¹

Table 96. Evidence summary table: haloperidol versus risperidone – general measures of AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I ²	Less With
Incidence of patients with adverse events ^{72,73,81,85,117,128,136,151}	8	1313	1.20 (1.01, 1.42)	84%	risperidone
Mortality (Cohort) ¹⁶³	1	63352	1.70 (1.31, 2.20)	NE	risperidone
Withdrawals due to adverse events ^{52,59-61,64,71,72,81,82,85,90,101,118,120,124,128,132,138,145,146,149-151}	23	4421	1.27 (1.04, 1.55)	0%	risperidone

AE = adverse events; I² = I-squared; KQ = Key Question; NE = not estimable

Table 97. Evidence summary table: haloperidol versus risperidone – specific AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I ²	Less With
Behavior and Psychosis					
Asthenia ^{52,71,117,120,149}	5	1596	1.20 (1.02, 1.41)	0%	risperidone
BMI and Weight					
Weight gain ¹⁰¹	1	255	0.19 (0.05, 0.81)	NE	haloperidol
EPS					
Akathisia ^{52,60,71,101,139,146,149}	7	619	1.79 (1.31, 2.44)	0%	risperidone
EPS ^{61,117,128,138,151}	5	675	1.86 (1.46, 2.36)	0%	risperidone
Tremor ^{52,85,101,128}	4	478	2.09 (1.23, 3.53)	0%	risperidone

AE = adverse event; BMI = body mass index; EPS = extrapyramidal symptoms or syndrome; I² = I-squared; KQ = Key Question; NE = not estimable

Haloperidol Versus Ziprasidone

Nine trials^{57,69,73,83,86,91,116,122,144} reported on the incidence of AEs in patients receiving haloperidol compared with patients receiving ziprasidone (Table 98). The statistically significant findings are presented in Table 99. Other reported AEs did not differ between groups (Appendix N, Tables 141, 142, and 143).

General Measures

The incidences of patients with AEs (6 trials)^{57,69,73,83,86,144} and withdrawals due to AEs (6 trials)^{57,83,86,91,116,144} were less frequent with ziprasidone. No difference between groups was found for mortality (2 trials)^{116,144} and SAEs (4 trials).^{57,86,91,144}

Specific Measures

Behavior and Psychosis

The incidence of agitation (2 trials),^{86,116} anxiety (3 trials),^{86,116,144} asthenia (2 trials),^{86,116} depression (2 trials),^{86,144} clinical deterioration (1 trial),⁷³ and hallucinations (1 trial)⁸⁶ did not differ between groups.

BMI and Weight

The incidence of overweight patients (1 trial)⁹¹ and patients with weight gain (2 trials)^{91,144} or weight loss (1 trial)¹⁴⁴ did not differ between groups.

Cardiovascular

The incidence of cardiovascular AEs (1 trial),¹¹⁶ ECG abnormalities (6 trials),^{57,86,91,116,122,144} hypertension (1 trial),¹¹⁶ hypotension (1 trial),¹¹⁶ and syncope (1 trial)¹¹⁶ did not differ between groups.

Cholinergic and Anticholinergic

Two studies found no difference in the incidence of dry mouth.^{86,116}

CNS

A single trial¹⁴⁴ found that hypokinesia and hypotonia were less frequent with ziprasidone. The incidence of dizziness (3 trials)^{86,116,144} and somnolence (5 trials),^{57,86,116,122,144} did not differ between groups.

Dermatology

A single trial¹¹⁶ reported no difference in the incidence of injection-site pain.

Endocrine (Prolactin and Thyroid)

Two trials^{57,91} reported no difference in the incidence of hyperprolactinemia.

EPS

Dystonia (3 trials),^{57,91,144} EPS (5 trials),^{57,69,116,122,144} hypertonia (3 trials),^{57,86,116} movement disorder (1 trial),⁸⁶ and tremor (5 trials)^{57,86,116,122,144} were less frequent with ziprasidone. No differences between groups were found in the incidence of akathisia (6 trials),^{57,86,91,116,122,144} dyskinesia (1 trial),⁹¹ parkinsonism (1 trial),⁹¹ psychosis (1 trial),⁸⁶ and tardive dyskinesia (1 trial).⁸⁶

Gastrointestinal

The incidence of dyspepsia (1 trial)¹⁴⁴ and nausea or vomiting (2 trials)^{86,116} did not differ between groups.

Metabolic

A single study found no difference between groups in the incidence of low levels of high-density lipoprotein, hypercholesterolemia, hyperglycemia, and hypertriglyceridemia.⁹¹

Ophthalmology

A single trial¹¹⁶ reported no difference in the incidence of abnormal vision.

Sleep

The incidence of insomnia (4 trials)^{57,86,116,122} did not differ between groups.

Systemic AEs

The incidence of headaches (3 trials),^{86,116,144} malaise (1 trial),¹¹⁶ and sweating (1 trial)¹¹⁶ did not differ between groups.

Table 98. Evidence summary table: haloperidol versus ziprasidone – general measures with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I ²	Less With
Incidence of patients with adverse events ^{57,69,73,83,86,144}	6	1448	1.13 (1.03, 1.23)	31%	ziprasidone
Withdrawals due to adverse events ^{57,83,86,91,116,144}	6	1551	1.73 (1.30, 2.32)	0%	ziprasidone

I² = I-squared; KQ = Key Question

Table 99. Evidence summary table: haloperidol versus ziprasidone – specific AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I ²	Less With
CNS					
Hypokinesia ¹⁴⁴	1	350	6.21 (1.41, 27.34)	NE	ziprasidone
Hypotonia ¹⁴⁴	1	350	5.86 (1.75, 19.65)	NE	ziprasidone
EPS					
Dystonia ^{57,91,144}	3	1102	2.19 (1.34, 3.60)	15%	ziprasidone
EPS ^{57,69,116,122,144}	5	1594	2.34 (1.56, 3.53)	63%	ziprasidone
Hypertonia ^{57,86,116}	3	926	2.45 (1.52, 3.94)	0%	ziprasidone
Movement disorder ⁸⁶	1	301	2.73 (1.77, 4.19)	NE	ziprasidone
Tremor ^{57,86,116,122,144}	5	1875	2.55 (1.79, 3.63)	4%	ziprasidone

AE = adverse events; CNS = central nervous system; EPS = extrapyramidal symptoms or syndrome; GI = gastrointestinal; I² = I-squared; KQ = Key Question; NE = not estimable

Perphenazine Versus Aripiprazole

A single trial⁹³ reported on the incidence of AEs in patients receiving perphenazine compared with patients receiving aripiprazole (Table 100). The incidence of dizziness, ECG abnormalities, hyperprolactinemia, and injury was less frequent with aripiprazole. Other reported AEs were not different between groups (Appendix N, Tables 144 and 145).

Table 100. Evidence summary table: perphenazine versus aripiprazole – specific AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I ²	Less With
Behavior and Psychosis					
Dizziness ⁹³	1	300	5.27 (1.18, 23.66)	NE	aripiprazole
Cardiovascular					
ECG abnormalities ⁹³	1	300	15.82 (2.12, 118.27)	NE	aripiprazole
Endocrine (Prolactin and Thyroid)					
Hyperprolactinemia ⁹³	1	300	13.89 (6.25, 30.86)	NE	aripiprazole
Systemic AE					
Injury ⁹³	1	300	4.75 (1.04, 21.60)	NE	aripiprazole

AE = adverse event; ECG = electrocardiogram; I² = I-squared; KQ = Key Question; NE = not estimable

Perphenazine Versus Olanzapine

A single trial²³ reported on the incidence of AEs in patients receiving perphenazine compared with patients receiving olanzapine (Table 101). Weight gain was less frequent with perphenazine. The incidence of patients with Abnormal Involuntary Movement Scale (AIMS) global severity score ≥ 2 and insomnia was less frequent with olanzapine. Other reported AEs were not different between groups (Appendix N, Tables 146 and 147).

Table 101. Evidence summary table: perphenazine versus olanzapine – specific AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I ²	Less With
BMI and Weight					
Weight gain ²³	1	597	0.41 (0.28, 0.60)	NE	perphenazine
EPS					
AIMS global severity score ≥ 2 ²³	1	597	1.65 (1.07, 2.54)	NE	olanzapine
Sleep					
Insomnia ²³	1	597	1.54 (1.12, 2.13)	NE	olanzapine

AE = adverse events; AIMS = Abnormal Involuntary Movement Scale; BMI = body mass index; EPS = extrapyramidal symptoms or syndrome; I² = I-squared; KQ = Key Question; NE = not estimable

Perphenazine Versus Quetiapine

A single trial²³ reported on the incidence of AEs in patients receiving perphenazine compared with patients receiving quetiapine (Table 102). Anticholinergic AEs was less frequent with perphenazine. The incidence of patients with AIMS global severity score ≥ 2 was less frequent with quetiapine. Other reported AEs were not different between groups (Appendix N, Tables 148 and 149).

Table 102. Evidence summary table: perphenazine versus quetiapine – specific AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I ²	Less With
Cholinergic and Anticholinergic					
Anticholinergic side effects ²³	1	598	0.70 (0.53, 0.93)	NE	perphenazine
EPS					
AIMS global severity score ≥ 2 ²³	1	598	1.76 (1.13, 2.75)	NE	quetiapine

AE = adverse events; AIMS = Abnormal Involuntary Movement Scale; EPS = extrapyramidal symptoms or syndrome; I² = I-squared; KQ = Key Question; NE = not estimable

Perphenazine Versus Risperidone

A single trial²³ reported on the incidence of AEs in patients receiving perphenazine compared with patients receiving risperidone (Table 103). Incontinence or nocturia was less frequent with perphenazine. Other reported AEs were not different between groups (Appendix N, Tables 150 and 151).

Table 103. Evidence summary table: perphenazine versus risperidone – specific AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I ²	Less With
Genital, Urinary, and Breast					
Incontinence or nocturia ²³	1	602	0.31 (0.13, 0.75)	NE	perphenazine

AE = adverse events; I² = I-squared; KQ = Key Question; NE = not estimable

Perphenazine Versus Ziprasidone

A single trial²³ found no differences between perphenazine and ziprasidone in the incidence of any AEs (Appendix N, Tables 152 and 153).

Thioridazine Versus Clozapine

A single cohort study¹⁶³ found lower incidence of mortality with clozapine compared with thioridazine (Table 104; Appendix N, Table 154).

Table 104. Evidence summary table: thioridazine versus clozapine – general AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I ²	Less With
Mortality (Cohort) ¹⁶³	1	32280	2.12 (1.38, 3.26)	NE	clozapine

AE = adverse events I² = I-squared; KQ = Key Question; NE = not estimable

Thioridazine Versus Risperidone

A single cohort study¹⁶³ found lower incidence of mortality with risperidone compared with thioridazine (Table 105; Appendix N, Table 155).

Table 105. Evidence summary table: thioridazine versus risperidone – general AEs with significant differences (KQ3)

Outcome	Studies	Participants	Effect Estimate	I ²	Less With
Mortality (Cohort) ¹⁶³	1	46007	1.82 (1.37, 2.40)	NE	risperidone

AE = adverse event; I² = I-squared; KQ = Key Question; NE = not estimable

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. We included studies that directly compared one FGA versus one SGA. We did not include: studies comparing various FGAs or those comparing various SGAs; trials with no active comparator (e.g., no treatment or placebo-controlled trials); or those trials comparing antipsychotics not approved by the U.S. Food and Drug Administration (FDA) or no longer available in the U.S. (Appendix O). The strength of evidence (SoE) for core illness symptoms and key adverse events (AEs) is summarized by comparison in the tables below.

We identified a large number of studies comparing individual FGAs with individual SGAs, with the majority of studies being efficacy trials.⁴¹ The decision to limit the scope of the review to only randomized controlled trials (RCTs) and non-RCTs with additional input from long-term cohort studies was based on a previous literature search and expert opinion. The technical expert panel felt that there were sufficient RCTs in this area to adequately address the questions. To supplement the RCTs (which are often short-term), it was decided that long-term cohort studies would also be included as these could provide data on long-term outcomes (e.g. mortality, tardive dyskinesia, diabetes mellitus and metabolic syndrome), that are not usually available in the more rigorously designed RCTs. Overall, 113 studies provided data on 22 different comparisons for patients with schizophrenia or schizophrenia-related psychoses. Fewer studies provided evidence comparing antipsychotic drugs in patients with bipolar disorder (n = 11). One trial included patients with schizophrenia or bipolar disorder. The most frequent comparisons involved haloperidol, with 43 studies comparing haloperidol with risperidone and 37 studies comparing haloperidol with olanzapine. Nevertheless, the number of studies available for each comparison and outcome was often limited. Although many studies reported data for core illness symptoms, a total of 111 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 were most often for core illness symptoms and did not cover the full spectrum of outcomes that clinicians and patients need information about for medication decisionmaking (e.g., patient employment and functioning). Outcomes potentially important to patients were rarely assessed in the studies, including health-related quality of life, social and occupational functioning, legal interactions, and certain symptoms, such as depression or anxiety. This limits the potential applicability to real-life functions and naturalistic outcomes. For future reviews, these important outcomes may be searched for in long-term observational studies, but it is unclear whether these types of outcomes are assessed in the research literature.

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 to prevent selection bias (i.e., random sequence generation and allocation concealment) and performance bias (i.e., proper blinding of participants and study personnel). Inadequate randomization and allocation concealment have been associated with exaggerated estimates of treatment effects for a number of medications in different fields of on average 12 and 18 percent, respectively.^{164,165} Within this clinical field, trials that are single-blind or open-label have been found to favor the SGAs over FGAs;⁶ hence, results need to be interpreted in light of these limitations of the primary studies.

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. In contrast, we included eight RCTs providing data over a followup period of 2 or more years. Short-term efficacy trials, which are accepted by the regulatory authorities, may not identify time-dependent AEs, such as tardive dyskinesia, diabetes mellitus, metabolic syndrome or mortality. The optimal and minimal acceptable duration of followup in trials remains to be determined, but may arbitrarily be set at 2 years duration in order to capture important clinical and patient-related outcomes (e.g., occupational functioning measures and long-term safety). Even with long-term trials, it is important that researchers document and report these outcomes as it is so far evidenced that there is a gap in the literature with regards these outcomes.

The majority of studies were industry-funded (n = 88; 70 percent), which can increase the chance of pro-industry findings.¹⁶⁶ 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 was not disclosed for 19 percent of studies (n = 24), highlighting the need for transparency in reporting the nature and extent of financial support. Industry bias in the studies included in this review may include the choice of medication comparisons, dosages and outcomes being driven by the funder's interests and priorities. For instance, the largest volume of research within the report compared haloperidol with olanzapine or risperidone, whereas many other drugs have not been extensively examined.

The evidence is summarized by key question (KQ) in the sections that follow. Overall, there were few differences of clinical importance between the active drug comparisons. In general, few differences between FGAs and SGAs on symptom improvement were identified; however, we cannot assume that the drugs are equivalent. Rather, the analyses were unable to detect differences often as a result of small numbers of trials for any given comparison and outcome. Moreover, most of the trials were designed as superiority trials testing the a priori hypothesis that SGAs are more efficacious than FGAs; hence, the individual trials, and some of the pooled analyses, may not have adequate power to confirm equivalence. FGAs generally had poorer safety profiles during the studies' followup period.

Key Question 1: Core Illness Symptoms

The findings for core illness symptoms are presented for each condition in Table 106. Comparisons and outcomes for which there was insufficient strength of evidence (e.g., evidence from single trials) 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: chlorpromazine versus olanzapine, quetiapine, and ziprasidone; fluphenazine versus olanzapine, quetiapine, and risperidone; haloperidol versus asenapine; perphenazine versus aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone; trifluoperazine versus clozapine.

For schizophrenia or schizophrenia-related psychoses, seven studies provided data on core illness symptoms for chlorpromazine versus clozapine. No differences were found for positive, negative, or general psychopathology. Clozapine showed benefits for total score (moderate SoE).

Eight studies provided data on core illness symptoms for haloperidol versus aripiprazole. No differences were found for positive or general psychopathology, global ratings, or total symptom score. The SoE was low for positive outcomes, global ratings and total scores; the SoE was insufficient for general psychopathology. Aripiprazole showed benefits for negative symptoms (moderate SoE).

Eight studies provided data on core illness symptoms for haloperidol versus clozapine. No significant differences were found for positive symptoms, negative symptoms, or general psychopathology (low SoE). The findings were discordant for total symptom score: no difference was found based on Brief Psychiatric Rating Scale (BPRS) and Positive and Negative Symptom Scale (PANSS) (low SoE), whereas one study showed benefits for clozapine on the Clinical Global Impression–Improvement (CGI–I) and Severity (CGI–S) scales (insufficient SoE).

Twenty-seven studies provided data on core illness symptoms for haloperidol versus olanzapine. No differences were found for positive symptoms (low SoE). Olanzapine was favored for negative symptoms (moderate SoE). In terms of general psychopathology, a significant benefit for olanzapine was found based on the Hamilton Rating Scale for Depression (HAM–D), Montgomery–Asberg Depression Rating Scale (MADRS), and Young Mania Rating Scale (YMRS). No differences were observed for the other five scales of general symptoms assessed. The SoE varied across outcomes from insufficient to moderate. Olanzapine was favored for global ratings and total symptom scores based on the CGI–S and PANSS; however no differences were found for the other four scales assessed. The SoE for these outcomes also varied from insufficient to moderate.

Nine studies provided data on core illness symptoms for haloperidol versus quetiapine. No significant differences were found for positive, negative, or general psychopathology. A significant difference favoring haloperidol was found for one (CGI–S) of the five global ratings and total symptom scores assessed. The SoE across outcomes ranged from insufficient to moderate.

Thirty-one studies provided data on core illness symptoms for haloperidol versus risperidone. There were no differences for positive symptoms (low SoE). Risperidone was favored for negative symptoms based on the Scale for the Assessment of Negative Symptoms (SANS) and PANSS (negative) (moderate SoE). No differences were found for any of the six measures used to assess general psychopathology (low or insufficient SoE). Seven of the global ratings or total symptom scores showed no differences, whereas the Symptom Checklist (SCL–90–R) showed a benefit for risperidone (low or insufficient SoE).

Seven studies provided data on core illness symptoms for haloperidol versus ziprasidone. There were no significant differences in terms of negative symptoms, general psychopathology, global ratings, or total score (low or insufficient SoE). No studies provided data on positive symptoms.

A total of 11 studies examined patients with bipolar disorder. The most frequent comparison was haloperidol versus risperidone (four RCTs). No significant differences were found for mood (mania), mood (depression), positive or negative symptoms, or global ratings and total scores (low or insufficient). Two studies compared haloperidol versus olanzapine and found no significant differences in sleep, mood (mania), mood (depression), global ratings, or total symptom scores (low or insufficient SoE). Two studies compared haloperidol with aripiprazole and found no differences in mood (mania), mood (depression), positive or negative symptoms, or global ratings and total symptom scores (low or insufficient SoE). Single studies compared chlorpromazine versus clozapine and haloperidol versus quetiapine and ziprasidone (insufficient SoE).

Table 106. Summary of the strength of evidence for core illness symptoms (KQ1)

Outcome	Comparison (Number of Studies)	SoE	Summary
<i>Schizophrenia and Schizophrenia-Related Psychoses</i>			
Positive Symptoms	Haloperidol vs. aripiprazole	Low	No significant difference for PANSS (2 RCTs).
	Haloperidol vs. clozapine	Low	No significant difference for PANSS (2 RCTs).
	Haloperidol vs. olanzapine	Low	No differences in PANSS (14 RCTs) or SAPS (2 RCTs).
	Haloperidol vs. quetiapine	Low	No significant difference for PANSS (4 RCTs).
	Haloperidol vs. risperidone	Low	No difference for PANSS (20 RCTs) or SAPS (2 RCTs).
Negative Symptoms	Haloperidol vs. aripiprazole	Moderate	Significant difference favoring aripiprazole for PANSS (3 RCTs).
	Haloperidol vs. clozapine	Low	No significant difference for PANSS (2 RCTs) and SANS (2 RCTs).
	Haloperidol vs. olanzapine	Moderate	Significant difference favoring olanzapine for PANSS (14 RCTs) and SANS (5 RCTs).
	Haloperidol vs. quetiapine	Low	No significant difference for PANSS (4 RCTs).
	Haloperidol vs. risperidone	Moderate	Significant difference favoring risperidone for PANSS (moderate SoE, 20 RCTs) and SANS (moderate SoE, 4 RCTs).
	Haloperidol vs. ziprasidone	Low	No significant difference for PANSS (2 RCTs).
General Psycho-pathology	Haloperidol vs. clozapine	Low	No significant difference for PANSS (2 RCTs).
	Haloperidol vs. olanzapine	Low to moderate	Significant difference favoring olanzapine for HAM-D (moderate SoE, 3 RCTs) and MADRS (moderate SoE, 6 RCTs). No difference for ABS (low SoE, 2 RCTs), ACES (low SoE, 2 RCTs), CDS-S (low SoE, 3 RCTs), HAM-A (low SoE, 2 RCTs), and PANSS (low SoE, 10 RCTs).
	Haloperidol vs. quetiapine	Low	No significant difference for CDS-S (2 RCTs) or PANSS (4 RCTs).
	Haloperidol vs. risperidone	Low	No significant differences for CDS-S (3 RCTs), HAM-D (2 RCTs), PANSS (13 RCTs), and YMRS (2 RCTs).
Global Ratings and Total Scores	Chlorpromazine vs. clozapine	Moderate	Significant difference favoring clozapine for BPRS (6 RCTs).
	Haloperidol vs. aripiprazole	Low	No significant difference for BPRS (3 RCTs) and CGI-S (5 RCTs).
	Haloperidol vs. clozapine	Low	No differences for BPRS (4 RCTs) and PANSS (3 RCTs).
	Haloperidol vs. olanzapine	Low to moderate	Significant difference favoring olanzapine for CGI-S (moderate SoE, 7 RCTs) and PANSS (moderate SoE, 14 RCTs). No difference for BPRS (low SoE, 13 RCTs) or CGI-I (low SoE, 2 RCTs).

Table 106. Summary of the strength of evidence for core illness symptoms (KQ1) (continued)

Outcome	Comparison (Number of Studies)	SoE	Summary
Schizophrenia and Schizophrenia-Related Psychoses (continued)			
Global Ratings and Total Scores (continued)	Haloperidol vs. quetiapine	Low to moderate	Significant difference favoring haloperidol for CGI-S (moderate SoE, 4 RCTs). No differences for BPRS (low SoE, 4 RCTs), CGI-I (low SoE, 3 RCTs), or PANSS (low SoE, 6 RCTs).
	Haloperidol vs. risperidone	Low	No difference for BPRS (13 RCTs), CGI-I (3 RCTs), CGI-S (8 RCTs), PANSS (20 RCTs).
	Haloperidol vs. ziprasidone	Low	No significant difference for BPRS (4 RCTs), CGI-S (4 RCTs), GAF (3 RCTs), and PANSS (4 RCTs).
Bipolar Disorder			
Mood (mania)	Haloperidol vs. aripiprazole	Low	No significant difference in YMRS (2 RCTs).
	Haloperidol vs. olanzapine	Low	No significant difference in YMRS (2 RCT).
	Haloperidol vs. risperidone	Low	No significant difference in YMRS (3 RCTs).
Mood (depression)	Haloperidol vs. aripiprazole	Low	No significant difference in MADRS (2 RCTs).
Global Ratings and Total Scores	Haloperidol vs. aripiprazole	Low	No significant difference in CGI-BP (2 RCTs).

ABS = Agitated Behavior Scale; ACES = Agitation-Calmness Evaluation Scale; BPRS = Brief Psychiatric Rating Scale; CDS-S = Calgary Depression Scale for Schizophrenia; CGI-BP = Clinical Global Impression-Bipolar; CGI-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression-Severity; GAF = Global Assessment of Functioning; HAM-A = Hamilton Rating Scale for Anxiety; HAM-D = Hamilton Rating Scale for Depression; KQ = Key Question; MADRS = Montgomery-Asberg Depression Rating Scale; PANSS = Positive and Negative Symptom Scale; RCT = randomized controlled trial; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; SoE = Strength of Evidence; 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 107. We did not assess the SoE for outcomes in KQ2.

Results for functional outcomes were available from 9 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 most of the comparisons. However, in most cases evidence came from single studies. Results for health care system utilization were available for 10 head-to-head comparisons, and no differences were found for any comparison.

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

Table 107. Summary of evidence for functional outcomes, health care system utilization, and other outcomes (KQ2)

Outcome	Comparison	Summary (number of studies)
Schizophrenia and Schizophrenia-Related Psychoses		
Functional Outcomes	Fluphenazine vs. quetiapine	No significant differences for sexual dysfunction or improvement on treatment (1 RCT).
	Fluphenazine vs. risperidone	No significant differences for sexual dysfunction or improvement on treatment (1 RCT).
	Haloperidol vs. olanzapine	No significant difference for positive urine toxicology (1 RCT) or sexual dysfunction (1 RCT).
	Haloperidol vs. quetiapine	No significant difference for sexual dysfunction (1 RCT).
	Haloperidol vs. risperidone	No significant differences for economic independence (1 RCT) or attitude regarding drugs (1 RCT).
	Haloperidol vs. ziprasidone	No differences for sexual dysfunction (1 RCT).
	Perphenazine vs. quetiapine	No significant difference in patients with paid employment (1 RCT).
	Perphenazine vs. risperidone	No significant difference in patients with paid employment (1 RCT).
	Perphenazine vs. ziprasidone	No significant difference in patients with paid employment (1 RCT).
Health Care System Use	Chlorpromazine vs. clozapine	No significant difference in rates of hospitalization or rehospitalization (1 RCT).
	Haloperidol vs. clozapine	No significant difference in mean hospital bed days (1 RCT).
	Haloperidol vs. olanzapine	No significant difference in mean hospital bed days or rates of hospitalization or rehospitalization (1 RCT).
	Haloperidol vs. quetiapine	No significant difference in rates of hospitalization or rehospitalization (1 RCT).
	Haloperidol vs. risperidone	No significant difference in rates of hospitalization or rehospitalization (3 RCTs).
	Haloperidol vs. ziprasidone	No significant difference in rates of hospitalization or rehospitalization (2 RCTs).
	Perphenazine vs. olanzapine	No significant difference in rates of hospitalization or rehospitalization (1 RCT).
	Perphenazine vs. quetiapine	No significant difference in rates of hospitalization or rehospitalization (1 RCT).
	Perphenazine vs. risperidone	No significant difference in rates of hospitalization or rehospitalization (1 RCT).
	Perphenazine vs. ziprasidone	No significant difference in rates of hospitalization or rehospitalization (1 RCT).
Bipolar Disorder		
Functional outcomes	Haloperidol vs. olanzapine	Significant difference favoring olanzapine for number of active workers (i.e., working for pay) (1 RCT). No difference in household or work activities impairment (1 RCT).

KQ = Key Question; RCT = randomized controlled trial

Key Question 3: Medication-Associated Adverse Events and Safety

The findings for the AEs that were deemed most clinically important are summarized in Table 108. The evidence comparing individual FGAs and SGAs was insufficient to draw conclusions for the following outcomes and comparisons: tardive dyskinesia (chlorpromazine vs. clozapine and ziprasidone; haloperidol vs. clozapine, olanzapine, quetiapine, and ziprasidone), mortality (chlorpromazine vs. clozapine and ziprasidone; haloperidol vs. risperidone; thioridazine vs. clozapine and risperidone), diabetes mellitus (haloperidol vs. olanzapine; perphenazine vs. olanzapine, quetiapine, risperidone, and ziprasidone), and metabolic syndrome

(haloperidol vs. clozapine; perphenazine vs. olanzapine, quetiapine, risperidone, and ziprasidone).

Two trials each provided data on mortality for chlorpromazine versus clozapine and haloperidol versus aripiprazole; no significant differences were found, although the length of followup of the trials for the latter comparison was only 24 hours. For metabolic syndrome, two trials provided data for haloperidol versus olanzapine and showed no significant difference in incidence of metabolic syndrome. The SoE 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); these outcomes were not assessed for SoE. 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 extrapyramidal symptoms (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 adequately 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 108. Summary of the strength of evidence for medication-associated adverse events and safety (KQ3)

Adverse Event	Comparison	SoE	Summary (Number of Studies)
Mortality	Chlorpromazine vs. clozapine	Low	No significant difference (2 RCTs) (length of followup: 52 and 208 wks)
	Haloperidol vs. aripiprazole	Low	No significant difference (2 RCTs) (length of followup: 24 hrs for both)
Metabolic Syndrome	Haloperidol vs. olanzapine	Low	No significant difference (2 RCTs) (length of followup: 6 and 12 wks)

Hrs = hours; KQ = Key Question; RCT = randomized controlled trial; SoE = strength of evidence; wks = weeks; vs. = versus

Key Question 4: Other Outcomes

The findings for other outcomes are presented for each condition and comparison in Table 109. We did not assess the SoE for outcomes in KQ4.

Results for other outcomes were available for 19 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 most 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 compared with chlorpromazine. Olanzapine was favored over haloperidol for remission (3 trials) and response rates (14 trials). Significant differences were found favoring aripiprazole over haloperidol for caregiver satisfaction (1 trial) and patient satisfaction (1 trial). Risperidone was favored over haloperidol for relapse rates (6 trials). Olanzapine was favored over perphenazine for time to all-cause medication discontinuation (1 trial). Health-related quality of life was evaluated for the following comparisons, and no significant differences were found: haloperidol versus olanzapine, quetiapine, risperidone, and ziprasidone (1 trial each); olanzapine, quetiapine,

risperidone, and ziprasidone (1 trial each). There was a significant difference in HRQoL for perphenazine over aripiprazole (1 trial).

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 trial 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 109. Summary of the evidence for other outcomes (KQ4)

Comparison (Number of Studies)	Summary
Schizophrenia and Schizophrenia-Related Psychoses	
Chlorpromazine vs. clozapine	Significant difference favoring clozapine for response rates (3 RCTs). No difference in remission rates (2 RCTs).
Chlorpromazine vs. olanzapine	No significant difference in response rates (1 RCT).
Chlorpromazine vs. quetiapine	No significant difference in response rates (1 RCT).
Chlorpromazine vs. ziprasidone	No significant difference in response rates (1 RCT).
Fluphenazine vs. olanzapine	No significant difference in response rates (1 RCT).
Fluphenazine vs. quetiapine	No significant difference in response rates (1 RCT).
Fluphenazine vs. risperidone	No significant difference in response rates (1 RCT).
Haloperidol vs. aripiprazole	No significant difference in response rates (5 RCTs) or medication adherence (1 RCT). Difference favoring aripiprazole for caregiver and patient satisfaction (1 RCT).
Haloperidol vs. asenapine	No significant difference in response rates (1 RCT).
Haloperidol vs. clozapine	No significant difference in relapse (1 RCT), response (2 RCTs) or remission (1 RCT) rates, or patient satisfaction (1 RCT).
Haloperidol vs. olanzapine	Significant difference favoring olanzapine for response rates (14 RCTs) and remission rates (3 RCTs). No significant difference in medication adherence (1 RCT), patient insight into illness (1 RCT), or HRQoL (5 RCTs).
Haloperidol vs. quetiapine	No significant difference in response rates (6 RCTs), remission rates (1 RCT), or HRQoL (1 RCT).
Haloperidol vs. risperidone	Significant difference favoring risperidone for relapse rates (6 RCTs). No significant differences in remission rates (2 RCTs), response rates (16 RCTs), medication adherence (3 RCTs), patient satisfaction (1 RCT), or HRQoL (2 RCTs).
Haloperidol vs. ziprasidone	No significant difference in response rates (6 RCTs), remission rates (3 RCTs), or HRQoL (2 RCT).
Perphenazine vs. aripiprazole	No significant difference in response rates (1 RCT). Significant difference in HRQoL favoring perphenazine (1 RCT).
Perphenazine vs. olanzapine	No significant difference in HRQoL (1 RCT). Significant difference favoring olanzapine for time to all-cause medication discontinuation (1 RCT).
Perphenazine vs. quetiapine	No significant difference in HRQoL (1 RCT).
Perphenazine vs. risperidone	No significant difference in time to all-cause medication discontinuation (1 RCTs) and HRQoL (1 RCT).
Perphenazine vs. ziprasidone	No significant difference in HRQoL (1 RCT).

Table 109. Summary of the evidence for other outcomes (KQ4) (continued)

Comparison (Number of Studies)	Summary
<i>Bipolar Disorder</i>	
Haloperidol vs. aripiprazole	Significant difference in favor of haloperidol for relapse rates (1 RCT). No difference in remission (1 RCT) or response (2 RCTs) rates.
Haloperidol vs. olanzapine	No difference for relapse (1 RCT), response (1 RCT), or remission rates (1 RCT). Significant difference favoring haloperidol for HRQoL mental summary score (1 RCT). Significant difference favoring olanzapine for HRQoL physical summary score (1 RCT).
Haloperidol vs. quetiapine	No significant difference in response or remission rates (1 RCT).
<i>Schizophrenia and Schizophrenia-Related Psychoses</i>	
Haloperidol vs. risperidone	No difference in response rates (1 RCT).
Haloperidol vs. ziprasidone	Significant difference favoring haloperidol for response rates (1 RCT). No difference for remission rates (1 RCT).

KQ = Key Question; HRQoL = health-related quality of life; RCT = randomized controlled trial

Key Question 5: Subgroups

A total of 41 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 I and bipolar II. The results were consistent with the overall findings. A significant difference favored haloperidol compared with ziprasidone for core illness symptoms (YMRS) in patients with bipolar I disorder.

Results in the Context of Previous Literature

The results of this review are similar in some respects to another recent systematic review of SGAs versus FGAs, although the present review is broader in scope in terms of medications included, patient populations, and outcomes.⁶ There were a number of methodological differences between the previous review and this one; the previous review included non-FDA-approved antipsychotics, restricted the analysis to only double-blinded trials, included only studies examining optimum SGA dosage and oral route of administration, and pooled data across efficacy outcome measures. The differences in the methodologies may have led to slightly different conclusions regarding individual SGAs.

The previous review compared nine SGAs (six of which were included in this report) with FGAs for overall efficacy (total symptom scores), positive, negative, and depressive symptoms, relapse, quality of life, EPS, weight gain, and sedation. They reported that the overall efficacy of the FDA-approved SGAs clozapine, olanzapine, and risperidone fared better than FGAs. In terms of global ratings and total symptom scores, we found that clozapine was more efficacious than chlorpromazine, but not compared with haloperidol. We found that olanzapine performed better than haloperidol on one of the three total symptom scores assessed. We found no differences between haloperidol and risperidone for the five total symptom scores reported. The previous review found that SGAs were not superior to FGAs regarding the negative symptoms. We found no difference in negative symptoms for haloperidol versus clozapine; however, we found evidence that olanzapine was more efficacious than haloperidol for negative symptoms, whereas the evidence for risperidone compared with haloperidol was mixed. In general, the

findings for AEs were consistent between reviews showing poorer safety profiles with respect to EPS for FGAs (specifically haloperidol) and more weight gain among the SGAs (in particular, olanzapine and risperidone).

The general results of our review for schizophrenia are consistent with the results of two widely cited trials in this clinical field: Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)²³ and Cost Utility of the Latest Antipsychotic drugs in Schizophrenia Study (CUtLASS).²¹ The CATIE trial was included in this review and was designed to evaluate whether FGAs were inferior to SGAs in efficacy and safety. Findings from the CATIE trial suggested that the FGA perphenazine and various SGAs (olanzapine, quetiapine, risperidone, and ziprasidone) differed more in their side-effect profiles than therapeutic effects. The study, like this review, also demonstrated that effectiveness across medications varied, and in some cases, this difference was clinically important. For example, in CATIE, clozapine was most effective for patients whose symptoms did not improve with first-line treatment, but it had a worse side-effect profile, and quetiapine (SGA) was more effective for patients who did not tolerate perphenazine (FGA). The CUtLASS trial was not included in our review as this trial compared FGAs and SGAs as classes rather than as individual medications. However, this study like CATIE and our review found that differences between 13 grouped FGAs and four grouped SGAs for effectiveness were not significantly different. This body of work suggests that there are no clear-cut advantages of either medication class, and that there is a range of medication choice (both FGA and SGA) for prescribing clinicians and their patients to consider during treatment initiation and maintenance. Establishing how to use existing medications safely and effectively to optimize patient outcomes, and determining the role and effect of long-term antipsychotic use (> 2 years) remains urgently needed both for treating schizophrenia and use of antipsychotics for bipolar disorder.

In general, there were some differences between this review and the above-cited studies with respect to methods and scope. Our review was very broad in scope, including all patient populations and all FDA-approved medications, regardless of dose or route of administration. We also included an exhaustive list of outcomes. The extent of outcomes we examined was substantial; however, many outcomes were reported too sparsely to provide strong evidence. Moreover, one of the contributions of this comprehensive synthesis is that it highlights this problem of variable outcome selection across trials while providing extensive details to consider when making treatment choices on an individual basis. One of the unique features of our review was the SoE assessments. Although previous trials and reviews have found some significant findings, our SoE assessments provide information on how confident we can be in those results and how likely the effects may change with future research. In most cases, the SoE was insufficient or low, highlighting the likelihood that future research may change the estimates of effect and the need for a stronger evidence base to inform clinical practice.

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 and safety compared to placebo or other active agents. Overall, there were 22 head-to-head comparisons across the relevant studies; however, within most comparisons there were few studies.

The focus of this review was adults, age 18 to 64 years, with schizophrenia or schizophrenia-related psychoses and bipolar disorder. The average age across studies ranged from 21 to 50 years (median = 37 years [interquartile range (IQR), 33 to 41]). Most studies were highly selective in patient enrollment 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 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) (62 of 125 studies) or mixed inpatient and outpatient populations (26 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 limited long-term (≥ 2 years) followup data precludes the ability to detect serious adverse events (SAEs) that may develop over the course of several years. The average length of followup in the included studies was only 8 weeks (IQR, 6 to 26 weeks). Further, *a priori*, we defined the following key AEs: 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 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, outcome measurement, and patient populations 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 AEs. 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, their main limitation may be the lack of correlation between the results from surrogate and clinically meaningful outcomes. This inconsistency can lead to recommendations of harmful medications or the exclusion of beneficial medications. Examples of surrogate outcome measures in this report include laboratory values to indicate treatment emergent metabolic syndrome, a clinical outcome. Additionally, functional outcomes and symptomatic outcomes (e.g., sedation, restlessness) were rarely and unequally reported throughout the trial reports, even though these outcomes are often vital to patient compliance.

A key limitation and challenge in synthesizing and interpreting this body of evidence is the heterogeneous patient populations across and within studies, which is in part driven by the complex nature of these disorders and their course over time. The studies we included had very mixed populations with respect to disorder subtypes, comorbid drug/ or alcohol use, treatment resistance, and number of previous episodes. These variables may create differential response to treatment, and this has been the basis for recommendations around personalized medicine in this area.¹⁶⁷ We conducted extensive subgroup and sensitivity analyses to explore these varying features. In many cases, the subgroup analyses were consistent with the overall estimates of effect. In cases where some differences were found, these were often based on small numbers of studies within the subgroups. In any case, the results of subgroup analyses should be interpreted

as hypothesis generating rather than hypothesis confirming. Our findings may provide some information to make treatment decisions for individual patients, but need to be confirmed in future research. Moreover, treatment decisions and future research should take into consideration individual characteristics that can influence response to treatment including needs, preferences, past treatment history and response to previous medications, and clinical factors such as family history of medical conditions (e.g., diabetes, hypertension). Patients should have access to a range of options that meet their differing needs and response patterns, as well as changes in these over time.

An additional limitation and challenge of synthesis in this area is that characteristics of the research may have changed over time, including drug doses and patient populations. For instance, relatively higher doses of haloperidol may have been used in earlier studies. Further, patients in more recent studies may not have been exposed to an FGA, whereas in earlier studies patients may have been exposed, and have become resistant, to an FGA. An additional problem is that patient response to treatment may vary depending on what medication they were taking prior to entering the study.²³ Information on baseline medication was not often provided in the individual studies; this information should be collected and reported in future studies for clinicians who are reviewing study findings and should be acknowledged when considering treatment options for individual patients.

Another important limitation in this body of evidence pertains to the instruments used to measure outcomes. Over 100 different scales and subscales or composite outcomes were used to assess efficacy outcomes across the studies. Although 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 using subscale scores, different criteria, and different measures were common. The CGI reported across the studies make study outcomes relevant for clinicians; however, 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, 80 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 of this review and other systematic reviews is the design and quality of the primary included studies. The majority of studies providing data for this report were RCTs (n = 123); however, most were designed as superiority trials, often with an a priori hypothesis that the SGA would be more efficacious.²⁵ The individual studies and, in many cases, the pooled results may not have had sufficient power to detect equivalence or noninferiority between drugs. These study designs are consistent with CATIE superiority trial design, but given the well-regarded results of CATIE and the findings from this review and others,⁶ future trials need sound rationale for designing superiority trials versus using equivalence or inferiority designs. On another note, 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. All of the trials had an unclear risk of bias (n = 78; 63 percent) or high

risk of bias (n = 45; 37 percent). Only 15 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 has been shown to produce exaggerated treatment effects.⁶ 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) (84 percent).

Two cohort studies were included in this review, due to their focus on AEs (tardive dyskinesia and mortality rates). 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.

With regards to bipolar disorder, none of the included studies was limited to individuals with bipolar depression and therefore no conclusions can be made about the comparative effectiveness of interventions for this condition.

This comparative effectiveness review (CER) 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 although. However, our findings are consistent with a similar review that included non-English studies.⁶ The scope of this report was limited to the direct comparison of individual FGAs with individual SGAs. Although this produces results that are internally valid, there is a risk that findings of no difference lead to false conclusions of equal efficacy by the reader. Future research incorporating indirect analyses through mixed treatment comparisons may add more strength to the evidence base. Further, we cannot make conclusions on the comparison of antipsychotics within the same drug class or with placebo. Therefore, without formal indirect quantitative or qualitative comparisons, no conclusions can be made as to the comparative efficacy of drugs in the same class. 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. Finally, specific patient populations (e.g., patients with prior antipsychotic resistance) were under-studied in long-term trials, precluding firm conclusions relating to comparative effectiveness, response and remission rates, and side-effects profiles. The inclusion criteria of many studies were highly selective, primarily examining inpatients with no serious mental illness and who were not alcohol or substance users. This may not be generally reflective of patients with schizophrenia, as there is a high prevalence of comorbid disorders and alcohol or illicit drug use in this patient population.

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.

For treating bipolar disorder, more head-to-head trials are needed to compare the effectiveness of currently approved FGAs and SGAs. 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 (e.g., 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 long-term AEs. Only two cohort studies were identified for this review that examined SAEs with long-term antipsychotic use; however, these studies only provided evidence for two SAEs: tardive dyskinesia and mortality rates. 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 required. Such studies could be modeled after longitudinal cohort studies in other fields, such as the Framingham study¹⁶⁸ that has been ongoing for decades to examine risk factors for cardiovascular disease.

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 SAEs, 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 report provides extensive details in terms of study characteristics and methodological features, which may help inform individual treatment decisions. The focus of the report was adults age 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 (43 studies) and olanzapine (37 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 SoE was low or insufficient 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 2 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.

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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Abbreviations

AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
APA	American Psychiatric Association
BMI	Body mass index
BPRS	Brief Psychiatric Rating Scale
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CDS-S	Calgary Depression Scale for Schizophrenia
CER	Comparative effectiveness review
CGI-BP	Clinical Global Impression-Bipolar
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
CI	Confidence interval
CNS	Central nervous system
CUtLASS	Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study
ECG	Electrocardiogram
EPC	Evidence-based Practice Center
EPS	Extrapyramidal symptom or syndrome
FDA	Food and Drug Administration
FGA	First-generation antipsychotic
GAF	Global Assessment of Functioning
GAS	Global Assessment Scale
HAM-A	Hamilton Rating Scale for Anxiety
HAM-D	Hamilton Rating Scale for Depression
I^2	I-squared
IQR	Interquartile range
KQ	Key question
MADRS	Montgomery-Asberg Depression Rating Scale
MD	Mean difference
nRCTs	Nonrandomized controlled trial
PANSS	Positive and Negative Symptom Scale
RCT	Randomized controlled trial
SAE	Serious adverse event
SANS	Scale for the Assessment of Negative Symptoms
SAPS	Scale for the Assessment of Positive Symptoms
SCL	Symptom Checklist
SoE	Strength of evidence
SGA	Second-generation antipsychotic
YMRS	Young Mania Rating Scale

Appendix A. Literature Search Strategies

- Table A-1. MEDLINE®–Ovid Version
 Table A-2. PsycINFO–Ovid Version
 Table A-3. Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects–Wiley Version, International Pharmaceutical Abstracts (IPAB)
 Table A-4. CINAHL® (Cumulative Index to Nursing & Allied Health Literature)–EBSCO Version
 Table A-5. Scopus®–Elsevier B.V.

Table A-1. MEDLINE®–Ovid Version

Date searched: 15Jul10 (reviews); 22Jul10 (RCTs); 9Aug10 (cohort studies); 13April11 (all study designs); 11Jul11(all study designs)

Notes: limit to: RCT/CCT, cohort studies, systematic reviews, English only, 1950–present, adult (19–64 years)

1. exp Schizophrenia/	Sonapax or Thioridazin or Thioridazine or Thioridazinum or Tioridatsiini or Tioridazin or Tioridazina or Tioridazinas).mp.
2. Schizophrenia, Catatonic/	63. methotrimeprazine/
3. Schizophrenia, Disorganized/	64. 60-99-1.rn.
4. Schizophrenia, Paranoid/	65. (Dedoran or Hirnamin or Hirnamine or Levomepromazine or Levomepromazin or Levomepromazina or Levopromazoni or Levomepromazinum or Levoprome or Levotomin or Mepromazine or Methotrimeprazine or Neurocil or Neozine or Nirvan or Nocinan or Momizan or Nozinane or Sinogan or Levoram or Nozinan or Sinogan or Tisercin or Veractil).mp.
5. Psychotic Disorders/	66. Phenothiazines/ad, to, tu, ct, po, ae [Administration & Dosage, Toxicity, Therapeutic Use, Contraindications, Poisoning, Adverse Effects]
6. Schizotypal Personality Disorder/	67. Butyrophenones/ad, to, tu, ct, po, ae
7. schizophreniform.tw.	68. Thioxanthenes/ad, to, tu, ct, po, ae
8. (schizoaffective or schizo-affective).tw.	69. Dibenzoxazepines/ad, to, tu, ct, po, ae
9. schizophren\$.mp.	70. Indoles/ad, to, tu, ct, po, ae
10. (dementia adj (praecox or precox)).tw.	71. or/29-70
11. (delusional adj2 disorder*).tw.	72. atypical antipsychotic\$.tw.
12. ((negative or positive) adj syndrome*).tw.	73. ((second or 2nd) adj generation adj antipsychotic*).tw.
13. hebephrenia.tw.	74. ((third or 3rd) adj generation adj antipsychotic*).tw.
14. exp Bipolar Disorder/	75. Asenapine/
15. (((bipolar or manic) adj2 (I or II or illness or disorder or psychos?s or depress\$)) or mania*).tw.	76. 65576-45-6.rn.
16. (BPD or hypoman\$ or manic-depressive).tw.	77. (Asenapine or EINECS 265-829-4).mp.
17. (BP 1 or BP 2 or BP I or BP II).tw.	78. clozapine/
18. (cyclothym\$ or euthymic).tw.	79. 5786-21-0.rn.
19. (acute adj2 mania).tw.	80. (Clozapin or Clozapina or Clozapine or Clozapinum or Clorazil or Clozaril or FazaClo or Leponex or LX 100-129 or Zaponex).mp.
20. (acute adj2 mixed adj episode*).tw.	81. risperidone/
21. (rapid-cycling adj5 bipolar).tw.	82. 106266-06-2.rn.
22. (rapid adj2 cycling adj5 bipolar).tw.	83. (Apexidone or Psychodal or Risperdal or Risperidona or Risperidone or Risperidonum or Risperin or Risperilept or Rispolin or Spiron).mp.
23. (mixed adj2 state* adj3 bipolar).tw.	84. olanzapine.mp.
24. or/1-23	85. 132539-06-1.rn.
25. exp Antipsychotic Agents/	86. (Zyprexa or Olantsapiini or Olanzapin or Olanzapina
26. exp Tranquilizing Agents/	
27. (neuroleptic adj2 (agent* or drug*)).tw.	
28. or/25-27	
29. ((first or 1st) adj generation adj antipsychotic*).tw.	
30. chlorpromazine/	
31. 50-53-3.rn.	
32. (Aminazin or Aminazine or Ampliactil or BC 135 or Chlorpromazine or Chlorpromazinum or Clorpromazina or Chlor-Promanyl or Chlorpromados or Chlorderazin or Chlorpromazin or Contomin or Elmarin or Esmind or Fenactil or Fenaktyl or HL 5746 or Largactil or Largactilothiazine or Megaphen or Largactyl or Klooripromatsiini or Klorpromazin or 6 Copin or Trinalalm Forte or Diminex Balsamico Juven Tos or Largatrex or Phenactyl or Proma or Promactil or	

Promazil or Prozil or Psychozine or Sanpron or Thorazine or Torazina or Wintermin).mp.	or Olanzapinum or Olansek or Zalasta or Zypadhera or Symbyax).mp.
33. Droperidol/	87. quetiapine.mp.
34. 548-73-2.rn.	88. (111974-69-7 or 111974-72-2).rn.
35. (Dehydrobenzoperidol or Dehydrobenzperidol or Deidrobenzperidolo or Dridol or Droleptan or Droperidol or Droperidoli or Droperidolis or Droperidolum or Disifelit or Halkan or Inapsin or Inapsine or Inopsin or Thalamonal or Nilperidol or Properidol or Sintodril or Vetkalm).mp.	89. (Co-Quetiapine or HSDB 7557 or Seroquel).mp.
36. fluphenazine/	90. ziprasidone.mp.
37. 69-23-8.rn.	91. 146939-27-7.rn.
38. (Dapotum or Elinol or Flufenazina or Fluofenazine or Fluphenazine or Fluorphenazine or Fluphenazinum or Ftorphenazine or Moditen or Pacinol or Sevinol or Siqualon or Triflumethazine or Valamina or Vespazine).mp.	92. (Zeldox or zeldrox or geodon).mp.
39. haloperidol/	93. aripiprazole.mp.
40. 52-86-8.rn.	94. 129722-12-9.rn.
41. (Aldo or Aloperidin or Aloperidol or Aloperidolo or Brotopon or Dozic or Einalon S or Eukystol or Fortunan or Galoperidol or Haldol or Halojust or Halopal or Haloperidol or Haloperidoli or Haloperidolis or Haloperidolu or Halopoidol or Serenace or Halopidol or Haloper or Halperon or Keselan or Lealgin or Linton or Mixidol or Peluces or Pernox or Serenace or Serenefl or Sernas or Sernel or Serenase or Ulcolind or Uliolind or Vesalium).mp.	95. (Abilitat or Abilify or Aripiprazole or Discmelt or OPC 31 or OPC 14597).mp.
42. loxapine/	96. paliperidone.mp.
43. 1977-10-2.rn.	97. 144598-75-4.rn.
44. (Cloxazepine or CL 62362 or Dibenazepin or Dibenzoazepine or Hydrofluoride 3170 or LW 3170 or Lossapina or Loksapiini or Loxapin or Loxapina or Loxapine or Loxapinum or Oxilapine or Loxapac or SUM 3170 or Loxitane or Desconex).mp.	98. (9-Hydroxyrisperidone or Invega or R 76477 or RO76477).mp.
45. perphenazine/	99. loperidone/
46. 58-39-9.rn.	100. 133454-47-4.rn.
47. (Chlorperphenazine or Chlorpiprazine or Decentan or Emesinal or Etaperazin or Etaperazine or Ethaperazine or Etrafon or F-mon or Fentazin or Mutabon or Perfenazin or Perfenazina or Perfenazinas or Perfenazine or Perphenazin or Perphenazine or Perfenazyna or Perphenazinum or Pertriptyl or Sch 3940 or Thilatazin or Tranquisan or Trifaron or Trilafon or Trilifan or Triptafen or Triphenot or Triavil).mp.	101. (Fanapt or loperidone or HP 873 or Zomaril).mp.
48. Pimozide/	102. Isoxazoles/ad, to, tu, ct, po, ae
49. 2062-78-4.rn.	103. Dibenazepines/ad, to, tu, ct, po, ae
50. (Antalon or Opiran or Orap or Pimotsidi or Pimozid or Pimozida or Pimozidas or Pimozide or Pimozidum or Pimozyd).mp.	104. Pyrimidinones/ad, to, tu, ct, po, ae
51. Prochlorperazine/	105. Piperidines/ad, to, tu, ct, po, ae
52. 58-38-8.rn.	106. Dibenzothiazepines/ct, ad, to, tu, ae, po
53. (Apo-Prochlorazine or Capazine or Chlormeprazine or Compazine or Compro or Dhaperazine or Emelent or Kronocin or Nipodal or Novamin or Nu-Prochlor or Meterazin or Meterazine or Mitil or Prochlorpemazine or Prochlorperazinum or Prochlorperazina or Proklooriperatsiini or Proklorperazin or Prorazin or Phenothiazine or Seratil or Stemetil or Tementil or Temetid).mp.	107. Piperazines/ad, tu, to, ct, po, ae
54. thiothixene/	108. Pirenzepine/tu, ad, to, ct, po, ae
55. 5591-45-7.rn.	109. Thiazoles/ad, th, ct, po, to, ae
	110. Quinolones/to, po, ct, ad, tu, ae
	111. or/72-110
	112. and/71,111
	113. and/28,71,111
	114. or/112-113
	115. randomized controlled trial.pt.
	116. controlled clinical trial.pt.
	117. randomi?ed.ab.
	118. placebo*.ab.
	119. drug therapy.fs.
	120. randomly.ab.
	121. trial.ab.
	122. groups.ab.
	123. or/115-122
	124. humans/ not (animals and humans).hw,sh.
	125. 123 and 124
	126. and/24,114,125
	127. limit 126 to yr="1987 - 2010"
	128. limit 127 to english language
	129. limit 126 to yr="1950 - 1986"
	130. limit 129 to english language
	131. cohort studies/
	132. followup studies/
	133. longitudinal studies/
	134. prospective studies/
	135. Retrospective Studies/
	136. (observation\$ or prospectiv\$ or retrospectiv\$ or cohort\$ or control\$ or volunteer\$ or evaluat\$ or compar\$ or longitudinal or long term or long-term or longterm or followup or followup or followup).mp. and (study or studies or trial\$).ti,ab,sh.
	137. or/131-136
	138. humans.hw,sh.
	139. and/137-138
	140. meta-analysis.mp.pt.

56. (Navane or Navaron or Orbinamon or Thiothixene or Tiotikseeni or Tiotixen or Tiotixeno or Tiotixenum or Thixit or Tiotixene).mp.	141. review.pt.
57. trifluoperazine/	142. search:.tw.
58. 117-89-5.rn.	143. or/140-142
59. (Cuait D or Cuait N or eskazine or flupazine or Jatrosom or Jalonac or Parstelin or Parmodalin or stelazine or Stelabid or Stelapar or Sycot or Terfluzine or Trifluoperazine or Trifluoperazini Hydrochloridum or triftazin or Trinicalm Forte or Trinicalm Plus).mp.	144. and/24,114,139
60. thioridazine/	145. and/24,114,143
61. 50-52-2.rn.	146. limit 145 to yr="1987 - 2010"
62. (Aldazine or Dazithin or Detril or Elperil or Mallorol or Malloryl or Melleril or Meleril or Mellaril or Mellerets or Mellerette or Melleretten or Melleril or	147. limit 146 to english language
	148. limit 145 to yr="1950 - 1986"
	149. limit 148 to english language
	150. limit 144 to yr="1987-2010"
	151. limit 150 to english language
	152. limit 144 to yr="1950-1986"
	153. limit 152 to english language

CCT = controlled clinical trial; RCT = randomized controlled trial

Table A–2. PsycINFO–Ovid Version**Date searched:** 16Jul10; 13April11; 11Jul11**Notes: limit to:** RCT/CCT, cohort studies, systematic reviews, English only, 1950—present

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- | | |
|--|---|
| <ol style="list-style-type: none">1. exp schizophrenia/2. exp "fragmentation (schizophrenia)"/3. exp "positive and negative symptoms"/4. exp schizoaffective disorder/5. exp schizoid personality disorder/6. exp schizotypal personality disorder/7. exp psychosis/8. or/1-79. schizophren*.mp.10. (schizoaffective or schizo-affective).tw.11. (dementia adj praecox).tw.12. (delusional adj2 disorder*).tw.13. ((negative or positive) adj syndrome*).tw.14. hebephrenia.tw.15. or/9-1416. or/8,1517. exp Bipolar Disorder/18. affective psychosis/19. mania/20. exp affective disorders/21. or/17-2022. (((bipolar or manic) adj2 (I or II or illness or disorder or psychos?s or depress\$)) or mania*).tw.23. (BPD or hypoman\$ or manic-depressive).tw.24. (BP 1 or BP 2 or BP I or BP II).tw.25. (cyclothym\$ or euthymic).tw.26. (acute adj2 mania).tw.27. (acute adj2 mixed adj episode*).tw.28. (rapid-cycling adj5 bipolar).tw.29. (rapid adj2 cycling adj5 bipolar).tw.30. (mixed adj2 state* adj3 bipolar).tw.31. or/22-3032. or/21,3133. or/16,3234. exp Neuroleptic Drugs/35. ((first or 1st) adj generation adj antipsychotic*).tw.36. exp Chlorpromazine/37. (Aminazin or Aminazine or Ampliactil or BC 135 or Chlorpromazine or Chlorpromazinum or Clorpromazina or Chlor-Promanyl or Chlorpromados or Chlorderazin or Chlorpromazin or Contomin or Elmarin or Esmind or Fenactil or Fenaktyl or HL 5746 or Largactil or Largactilothiazine or Megaphen or Largactyl or Klooripromatsiini or Klorpromazin or 6 Copin or Trinicalm Forte or Diminex Balsamico Juven Tos or Largatrex or Phenactyl or Proma or Promactil or Promazil or Prozil or Psychozine or Sanpron or Thorazine or Torazina or Wintermin).mp.38. Droperidol.mp.39. (Dehydrobenzoperidol or Dehydrobenzperidol or Deidrobenezperidolo or Dridol or Droleptan or Droperidol or Droperidoli or Droperidolis or Droperidolum or Disifelit or Halkan or Inapsin or Inapsine or Inopsin or Thalamonal or Nilperidol or Properidol or Sintodril or Vetkalm).mp.40. exp Fluphenazine/41. (Dapotum or Elinol or Flufenazina or Fluofenazine or Fluphenazine or Fluorphenazine or Fluphenazinum or Ftorphenazine or Moditen or Pacinol or Sevinol or | <ol style="list-style-type: none">Thioridazin or Thioridazine or Thioridazinum or Tioridatsiini or Tioridazin or Tioridazina or Tioridazinas).mp.54. exp Thiothixene/55. (Navane or Navaron or Orbinamon or Tiotixene or Tiotikseeni or Tiotixen or Tiotixeno or Tiotixenum or Thixit or Tiotixene or Thiothixene).mp.56. exp Trifluoperazine/57. (Cuait D or Cuait N or eskazine or flupazine or Jatrosom or Jalonac or Parstelin or Parmodalin or stelazine or Stelabid or Stelapar or Sycot or Terfluzine or Trifluoperazine or Trifluoperazini Hydrochloridum or triflazin or Trinicalm Forte or Trinicalm Plus or Trifluperazine).mp.58. or/35-5759. ((second or 2nd) adj generation adj antipsychotic*).tw.60. ((third or 3rd) adj generation adj antipsychotic*).tw.61. exp Aripiprazole/62. (Abilitat or Abilify or Aripiprazole or Discmelt or OPC 31 or OPC 14597).mp.63. Asenapine.mp.64. (Blonanserin or AD 5423).mp.65. lloperidone.mp.66. (Fanapt or HP 873 or Zomaril).mp.67. exp Olanzapine/68. (Zyprexa or Olantsapiini or Olanzapin or Olanzapina or Olanzapinum or Olansek or Olanzapine or Zalasta or Zypadhera or Symbyax).mp.69. paliperidone.tw.70. (9-Hydroxyrisperidone or Invega or R 76477 or RO76477).mp.71. exp Quetiapine/72. (Co-Quetiapine or HSDB 7557 or Quetiapine or Seroquel).mp.73. exp Risperidone/74. (Apexidone or Psychodal or Risperdal or Risperidona or Risperidone or Risperidonum or Risperin or Risperilept or Rispolin or Spiron).mp.75. ziprasidone.tw.76. (Zeldox or zeldrox or geodon).mp.77. or/59-7678. or/34,58,7779. or/58,7780. or/78-7981. randomi?ed controlled trial.tw,pt.82. exp Clinical Trials/83. controlled clinical trial.tw,pt.84. randomi?ed.ab.85. placebo*.ab.86. randomly.ab.87. trial.ab.88. groups.ab.89. or/81-8890. exp Animals/91. 89 not 9092. and/33,80,9193. limit 92 to english language94. limit 93 to (adulthood <18+ years> and "300 |
|--|---|
-

Siqualon or Triflumethazine or Valamina or Vespazine).mp.	adulthood ")
42. exp Haloperidol/	95. exp Clinical Trials/
43. (Aldo or Aloperidin or Aloperidol or Aloperidolo or Brotopon or Dozic or Einalon S or Eukystol or Fortunan or Galoperidol or Haldol or Halojust or Halopal or Haloperidol or Haloperidoli or Haloperidolis or Haloperidolu or Halopoidol or Serenace or Halopidol or Haloper or Halperon or Keselan or Lealgin or Linton or Mixidol or Peluces or Pernox or Serenace or Sereneftl or Sernas or Sernel or Serenase or Ulcolind or Uliolind or Vesalium).mp.	96. clinical trial:.mp.
44. exp Loxapine/	97. random:.tw.
45. (Cloxazepine or CL 62362 or Dibenzacepin or Dibenzoazepine or Hydrofluoride 3170 or LW 3170 or Lossapina or Loksapiini or Loxapin or Loxapina or Loxapine or Loxapinum or Oxilapine or Loxapac or SUM Sinophenin or Talofen or Talofen or Tomil or Verophen).mp.	98. placebo:.mp.
46. exp Perphenazine/	99. double-blind:.mp.
47. (Chlorperphenazine or Chlorpiprazine or Decentan or Emesinal or Etaperazin or Etaperazine or Ethaperazine or Etrafon or F-mon or Fentazin or Mutabon or Perfenazin or Perfenazina or Perfenazinas or Perfenazine or Perphenazin or Perphenazine or Perfenazyna or Perphenazinum or Pertriptyl or Sch 3940 or Thilatazin or Tranquisan or Trifarone or Trilafon or Trilifan or Triptafen or Triphenot or Triavil).mp.	100. or/95-99
48. Pimozide/	101. and/33,80,100
49. (Antalon or Opiran or Orap or Pimotsidi or Pimozid or Pimozida or Pimozidas or Pimozide or Pimozidum or Pimozyd).mp.	102. limit 101 to english language
50. Prochlorperazine/	103. limit 102 to yr="1950 - 1986"
51. (Apo-Prochlorazine or Capazine or Chlormeprazine or Compazine or Comprone or Dhaperazine or Emelent or Kronocin or Nipodal or Novamin or Nu-Prochlor or Meterazin or Meterazine or Mitil or Prochlorpemazine or Prochlorperazinum or Prochlorperazina or Prochlorperazine or Proklooriperatsiini or Prokloorperazin or Prorazin or Phenothiazine or Seratil or Stemetil or Tementil or Temetid).mp.	104. limit 102 to (adulthood <18+ years> and "300 adulthood ")
52. exp Thioridazine/	105. limit 104 to "0100 journal"
53. (Aldazine or Dazithin or Detril or Elperil or Mallorol or Malloryl or Melleril or Meleril or Mellaril or Mellerets or Mellerette or Melleretten or Melleril or Sonapax or	106. exp Followup Studies/
	107. exp longitudinal studies/
	108. exp prospective studies/
	109. exp retrospective studies/
	110. (observation\$ or prospectiv\$ or cohort\$ or longitudinal or long term or long-term or longterm or followup or followup or followup).mp. and (study or studies or trial\$).ti,ab,sh.
	111. or/106-110
	112. exp Animals/
	113. 111 not 112
	114. and/33,80,113
	115. limit 114 to english language
	116. limit 115 to yr="1950 - 1986"
	117. limit 115 to "0100 journal"
	118. meta-analys?s.mp.
	119. search:.tw.
	120. review:.mp.
	121. or/118-120
	122. and/33,80,121
	123. and/33,80
	124. limit 123 to "0830 systematic review"
	125. or/122,124
	126. limit 125 to english language
	127. limit 126 to (adulthood <18+ years> and "300 adulthood ")
	128. limit 127 to "0100 journal"
	129. adult*.mp.
	130. 125 and 129
	131. limit 130 to "0100 journal"
	132. 128 or 131
	133. limit 132 to yr="1950 - 1986"

CCT = controlled clinical trial; RCT = randomized controlled trial

Table A–3. Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects–Wiley Version, International Pharmaceutical Abstracts (IPAB)

Date searched: 19Jul10; 4Oct10; 13April11; 11Jul11

Notes: text word searching for CDSR, CENTRAL, IPA

1. schizophren\$.mp.
2. (schizoaffective or schizo-affective).tw.
3. (delusional adj2 disorder*).tw.
4. ((negative or positive) adj syndrome*).tw.
5. hebephrenia.tw.
6. Schizo\$.mp.
7. or/1-6
8. bipolar\$.mp.
9. (manic or mania).mp.
10. (acute adj2 mixed adj episode*).tw.
11. (BP 1 or BP 2 or BP I or BP II).tw.
12. (BPD or hypoman\$ or manic-depressive).tw.
13. or/8-12
14. 7 or 13
15. (antipsychotic adj2 (drug* or agent*)).mp.
16. (neuroleptic adj2 (drug* or agent*)).mp.
17. or/15-16
18. (Aminazin or Aminazine or Ampliactil or BC 135 or Chlorpromazine or Chlorpromazinum or Clorpromazina or Chlor-Promanyl or Chlorpromados or Chlordazolin or Chlorpromazin or Contomin or Elmarin or Esmind or Fenactil or Fenaktyl or HL 5746 or Largactil or Largactilothiazine or Megaphen or Largactyl or Klooripromatsiini or Klorpromazin or 6 Copin or Trinicalm Forte or Diminex Balsamico Juven Tos or Largatrex or Phenactyl or Proma or Promactil or Promazil or Prozil or Psychozine or Sanpron or Thorazine or Torazina or Wintermin).mp.
19. (Dehydrobenzoperidol or Dehydrobenzperidol or Deidrobenezperidolo or Dridol or Droleptan or Droperidol or Droperidoli or Droperidolis or Droperidolum or Disifelit or Halkan or Inapsin or Inapsine or Inopsin or Thalamonal or Nilperidol or Properidol or Sintodril or Vetkalm).mp.
20. (Dapotum or Elinol or Flufenazina or Fluofenazine or Fluphenazine or Fluphenazinum or Ftorphenazine or Moditen or Pacinol or Sevinol or Squalon or Triflumethazine or Valamina or Vespazine).mp.
21. (Aldo or Aloperidin or Aloperidol or Aloperidolo or Brotopon or Dozic or Einalon S or Eukystol or Fortunan or Galoperidol or Haldol or Halojust or Halopal or Haloperidol or Haloperidoli or Haloperidolis or Haloperidolu or Halopoidol or Serenace or Halopidol or Haloper or Halperon or Keselan or Lealgin or Linton or Mixidol or Peluces or Pernox or Serenace or Serenefl or Sernas or Sernel or Serenase or Ulcolind or Uliolind or Vesalium).mp.
22. (Clozapine or CL 62362 or Dibenzacepin or Dibenzazepine or Hydrofluoride 3170 or LW 3170 or Lossapina or Loksapiini or Loxapin or Loxapina or Loxapine or Loxapinum or Oxilapine or Loxapac or SUM Sinophenin or
26. (Aldazine or Dazithin or Detril or Elperil or Mallorol or Malloryl or Melleril or Meleril or Mellaril or Mellerets or Mellerette or Melleretten or Melleril or Sonapax or Thioridazin or Thioridazine or Thioridazinum or Tioridatsiini or Tioridazin or Tioridazina or Tioridazinas).mp.
27. (Navane or Navaron or Orbinamon or Tiotixene or Tiotikseeni or Tiotixen or Tiotixeno or Tiotixenum or Thixit or Tiotixene or Thiothixene).mp.
28. (Cuait D or Cuait N or eskazine or flupazine or Jatrosom or Jalonac or Parstelin or Parmodalin or stelazine or Stelabid or Stelapar or Sycot or Terfluzine or Trifluoperazine or Trifluoperazini Hydrochloridum or triftazin or Trinicalm Forte or Trinicalm Plus or Trifluperazine).mp.
29. ((first or 1st) adj2 generation adj2 antipsychotic*).tw.
30. or/18-29
31. ((second or 2nd) adj generation adj antipsychotic*).tw.
32. ((third or 3rd) adj generation adj antipsychotic*).tw.
33. (Abilitat or Abilify or Aripiprazole or Discmelt or OPC 31 or OPC 14597).mp.
34. (Asenapine or Blonanserin or AD 5423).mp.
35. (Fanapt or HP 873 or lloperidone or Zomaril).mp.
36. (Zyprexa or Olantsapiini or Olanzapin or Olanzapina or Olanzapinum or Olansek or Olanzapine or Zalasta or Zypadhera or Symbyax).mp.
37. (9-Hydroxyrisperidone or Invega or Paliperidone or R 76477 or RO76477).mp.
38. (Co-Quetiapine or HSDB 7557 or Quetiapine or Seroquel).mp.
39. (Apexidone or Psychodal or Risperdal or Risperidona or Risperidone or Risperidonum or Risperin or Risperilept or Rispolin or Spiron).mp.
40. (Zeldox or zeldox or Ziprasidone or geodon).mp.
41. or/31-40
42. and/14,30,41
43. and/14,17,30,41
44. or/42-43
45. adult*.mp.
46. 44 and 45
47. (pediatric or child* or youth or teen* or adolescen* or elderly or aged).mp.
48. 44 not 47
49. or/46,48
50. randomi?ed.mp.
51. trial*.tw.
52. random:.tw.
53. or/50-52
54. and/49,53

	Talofen or Talofen or Tomil or Verophen).mp.	55. and/44,53
23.	(Chlorperphenazine or Chlorpiprazine or Decentan or Emesinal or Etaperazin or Etaperazine or Ethaperazine or Etrafon or F-mon or Fentazin or Mutabon or Perfenazin or Perfenazina or Perfenazinas or Perfenazine or Perphenazin or Perphenazine or Perfenazyna or Perphenazinum or Pertriptyl or Sch 3940 or Thilatazin or Tranquisan or Trifaron or Trilafon or Trilifan or Triptafen or Triphenot or Triavil).mp.	56. (cohort\$ or longitudinal or retrospective or prospective or followup or case-control).mp.
		57. and/49,56
		58. limit 57 to yr="1987 -current"
		59. limit 57 to yr="1950 -1986"
		60. review:.mp.
		61. search:.tw.
		62. meta-analys?s:.mp.
		63. or/60-62
		64. and/49,63
		65. and/44,63
24.	(Antalon or Opiran or Orap or Pimotsidi or Pimozid or Pimozida or Pimozidas or Pimozide or Pimozidum or Pimozyd).mp.	66. limit 55 to (english language and yr="1987 - Current") [Limit not valid in CCTR,CDSR; records were retained]
25.	(Apo-Prochlorazine or Capazine or Chlormeprazine or Compazine or Compro or Dhaperazine or Emelent or Kronocin or Nipodal or Novamin or Nu-Prochlor or Meterazin or Meterazine or Mitil or Prochlorpemazine or Prochlorperazinum or Prochlorperazina or Prochlorperazine or Proklooriperatsiini or Prokloorperazin or Prorazin or Phenothiazine or Seratil or Stemetil or Tementil or Temetid).mp.	67. limit 55 to yr="1950 -1986"
		68. limit 44 to (english language and yr="1987 - current") [Limit not valid in CCTR,CDSR; records were retained]
		69. limit 44 to yr="1950 -1986"

CDSR = Cochrane Database of Systematic Reviews; IPA = International Pharmaceutical Abstracts

Table A-4. CINAHL® (Cumulative Index to Nursing & Allied Health Literature)–EBSCO Version**Date searched:** 21Jul10; 13April11; 11Jul11

S1 (MH "Schizophrenia+")	S19 Thiothixene
S2 (MH "Schizotypal Personality Disorder")	S20 trifluoperazine
S3 schizophren* or schizotypal or (schizoaffective or schizo-affective) or (dementia praecox OR dementia precox) or negative syndrome or positive syndrome or hebephrenia	S21 ("trifluoperazine") or (MH "Trifluoperazine Hydrochloride")
S4 (MH "Bipolar Disorder+")	S22 ("Thioridazine") or (MH "Thioridazine
S5 bipolar illness* or bipolar disorder* or bipolar psychos* or bipolar depress* or (BPD OR BP1 or BP2 or BP I or BP II)	S23 methotrimeprazine
S6 manic illness* or manic disorder* or manic psychos* or (manic depress* or manic-depress*) or hypoman*	S24 S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23
S7 cyclothym* or euthymic or rapid-cycling or mixed state	S25 second generation antipsychotic* or 2nd generation antipsychotic*
S8 S1 or S2 or S3 or S4 or S5 or S6 or	S26 asenapine
S9 (MH "Antipsychotic Agents+")	S27 ("clozapine") or (MH "Clozapine
S10 first generation antipsychotic* or 1st generation antipsychotic	S28 ("risperidone") or (MH "Risperidone")
S11 MH chlorpromazine or TX chlorpromazine	S29 ("olanzapine") or (MH "Olanzapine")
S12 ("droperidol") or (MH "Droperidol")	S30 ("quetiapine") or (MH "Quetiapine")
S13 ("fluphenazine") or (MH "Fluphenazine")	S31 ziprasidone
S14 ("haloperidol") or (MH "Haloperidol")	S32 ("Aripiprazole") or (MH "Aripiprazole")
S15 loxapine	S33 paliperidone
S16 perphenazine	S34 iloperidone
S17 pimozide	S35 S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34
S18 ("prochlorperazine") or (MH "Prochlorperazine")	S36 randomi\$ed or random* or TX trial*
	S37 (MH "Clinical Trials+")
	S38 S36 or S37
	S40 S8 and S24 and S35 and S38 Limiters - Human; Language: English; Age Groups: Adult: 19-44 years, Middle Aged: 45-64 years
	S39 S8 and S24 and S35 and S38

Table A–5. SCOPUS**Date searched:** 1987–Present (22Jul10); 1950–1986 (04Oct10); 13April11; 11Jul11**1987–Present**

(((((TITLE-ABS-KEY((schizophren* OR schizotypal OR schizoaffective OR schizo-affective OR hebephrenia) OR (dementia PRE/1 pr?ecox) OR (bipolar W/2 disorder*) OR (bipolar W/2 illness*) OR (bipolar W/2 psychos?s) OR (bipolar W/2 depress*) OR (bpd OR bp1 OR bp2 OR bp i OR bp ii) OR (hypoman* OR manic-depress OR cyclothym* OR euthymic OR rapid-cycling))) AND (KEY(antipsychotic* OR neuroleptic*)) AND ((TITLE-ABS-KEY((first PRE/1 generation PRE/1 antipsychotic*) OR (1st PRE/1 generation PRE/1 antipsychotic) OR (first PRE/1 generation PRE/1 neuroleptic*) OR (1st PRE/1 generation PRE/1 neuroleptic*) OR (typical PRE/1 antipsychotic*) OR (typical PRE/1 neuroleptic*))) OR (TITLE-ABS-KEY((chlorpromazine) OR (droperidol) OR (fluphenazine) OR (haloperidol) OR (loxapine) OR (perphenazine) OR (pimozide) OR (prochlorperazine) OR (thiothixene OR tiotixene) OR (trifluoperazine) OR (thioridazine) OR (methotrimeprazine)))) AND ((TITLE-ABS-KEY((second PRE/1 generation PRE/1 antipsychotic*) OR (2nd PRE/1 generation PRE/1 antipsychotic) OR (second PRE/1 generation PRE/1 neuroleptic*) OR (2nd PRE/1 generation PRE/1 neuroleptic*) OR (atypical PRE/1 antipsychotic*) OR (atypical PRE/1 neuroleptic*))) OR (TITLE-ABS-KEY((asenapine) OR (clozapine) OR (risperidone) OR (olanzapine OR symbyax) OR (quetiapine) OR (ziprasidone OR zeldox OR geodon) OR (aripiprazole) OR (paliperidone) OR (iloperidone)))))) AND (LANGUAGE(english)) AND (PUBYEAR AFT 1986)) AND (SRCTYPE(j)) AND (TITLE-ABS-KEY((rct OR random* OR trial*) OR (control* PRE/2 trial*) OR (clinical PRE/2 trial*)))) AND (DOCTYPE(ar)) AND (KEY(human))

1950–1986

(((((TITLE-ABS-KEY((schizophren* OR schizotypal OR schizoaffective OR schizo-affective OR hebephrenia) OR (dementia PRE/1 pr?ecox) OR (bipolar W/2 disorder*) OR (bipolar W/2 illness*) OR (bipolar W/2 psychos?s) OR (bipolar W/2 depress*) OR (bpd OR bp1 OR bp2 OR bp i OR bp ii) OR (hypoman* OR manic-depress OR cyclothym* OR euthymic OR rapid-cycling))) AND (KEY(antipsychotic* OR neuroleptic*)) AND ((TITLE-ABS-KEY((first PRE/1 generation PRE/1 antipsychotic*) OR (1st PRE/1 generation PRE/1 antipsychotic) OR (first PRE/1 generation PRE/1 neuroleptic*) OR (1st PRE/1 generation PRE/1 neuroleptic*) OR (typical PRE/1 antipsychotic*) OR (typical PRE/1 neuroleptic*))) OR (TITLE-ABS-KEY((chlorpromazine) OR (droperidol) OR (fluphenazine) OR (haloperidol) OR (loxapine) OR (perphenazine) OR (pimozide) OR (prochlorperazine) OR (thiothixene OR tiotixene) OR (trifluoperazine) OR (thioridazine) OR (methotrimeprazine)))) AND ((TITLE-ABS-KEY((second PRE/1 generation PRE/1 antipsychotic*) OR (2nd PRE/1 generation PRE/1 antipsychotic) OR (second PRE/1 generation PRE/1 neuroleptic*) OR (2nd PRE/1 generation PRE/1 neuroleptic*) OR (atypical PRE/1 antipsychotic*) OR (atypical PRE/1 neuroleptic*))) OR (TITLE-ABS-KEY((asenapine) OR (clozapine) OR (risperidone) OR (olanzapine OR symbyax) OR (quetiapine) OR (ziprasidone OR zeldox OR geodon) OR (aripiprazole) OR (paliperidone) OR (iloperidone)))))) AND (LANGUAGE(english)) AND (PUBYEAR BEF 1986)) AND (SRCTYPE(j)) AND (TITLE-ABS-KEY((rct OR random* OR trial*) OR (control* PRE/2 trial*) OR (clinical PRE/2 trial*)))) AND (DOCTYPE(ar)) AND (KEY(human))) AND NOT (KEY(animal*))

Appendix B. Sample Data Extraction and Quality Assessment Forms

Comparative Effectiveness of FGA and SGA

RefID:

Reviewer's name:

Inclusion/ Exclusion:

(1) Is this a full-text manuscript published in English (e.i. not a conference proceeding, letter to the editor nor a foreign language publication) ?

(2) Is the study population same as our inclusion criteria?

If no, then please state the reason for exclusion (e.g., age, schizophrenia, bipolar disorder):

(3) Is there an intervention/ comparator of interest to this review?

(4) What was the study design?

(5) What is the study population?

<input type="checkbox"/> Schizophrenia	<input type="checkbox"/> Bipolar disorder
--	---

(6) What was the intervention?

<input type="checkbox"/> Chlorpromazine	<input type="checkbox"/> Pimozide
<input type="checkbox"/> Droperidol	<input type="checkbox"/> Prochlorperazine
<input type="checkbox"/> Fluphenazine	<input type="checkbox"/> Thioridazine
<input type="checkbox"/> Haloperidol	<input type="checkbox"/> Thiothixene
<input type="checkbox"/> Loxapine	<input type="checkbox"/> Trifluoperazine
<input type="checkbox"/> Perphenazine	Other... please describe:

(7) What was the control?

<input type="checkbox"/> Aripiprazole	<input type="checkbox"/> Paliperidone
<input type="checkbox"/> Asenapine	<input type="checkbox"/> Quetiapine
<input type="checkbox"/> Clozapine	<input type="checkbox"/> Risperidone
<input type="checkbox"/> Iloperidone	<input type="checkbox"/> Ziprasidone
<input type="checkbox"/> Olanzapine ± Fluoxetine	Other... please describe:

Reviewer's Decision:

Reviewer's Comments:

First versus Second Generation Antipsychotics (Adults)

Refid: Study Name: Reviewer's name:

Study Demographics:

<i>Study design</i>		<i>Registration # (if available)</i>	
<i>Country</i>		<i>Number of centers (n)</i>	()
<i>Setting</i>		<i>Funding (If pharm., company name)</i>	()
<i>Diagnosis</i>		<i>DSM classification</i>	If other, please state:
<i>Race</i>		<i>Co-morbidities (e.g. DM)</i>	
<i>Disease history:</i>	Occurrence: Resistance:	<i>History of prior antipsychotic exposure</i>	Naivety: Drug:
<i>Main inclusion criteria</i>		<i>Main exclusion criteria</i>	
<i>Use of concurrent standard medical therapies (e.g. Insulin)</i>		<i>Study period (month and year)</i>	to
<i>Washout period</i>	Check if Washout period was used. <input type="checkbox"/> Duration:	<i>Run-in phase</i>	Check if Run-in phase was used. <input type="checkbox"/> Drug used: Duration:
<i>Follow-up period</i>			

Reviewer's Comments:

Medication characteristics:								
	Intervention 1	Intervention 2	Intervention 3	Intervention 4	Intervention 5	Intervention 6	Intervention 7	Intervention 8
<i>Classification</i>								
<i>Drug</i>								
<i>Route of administration</i>								
<i>Dosage</i>								
<i>Dosage Intervals</i>								
<i>Other medications</i>								
Reviewer's Comments:								

Patient flow through trial:								
	Intervention 1	Intervention 2	Intervention 3	Intervention 4	Intervention 5	Intervention 6	Intervention 7	Intervention 8
<i>Number screened</i>								
<i>Number randomized</i>								
<i>Number completed</i>								
<i>Number analyzed (efficacy)</i>								
<i>Number analyzed (safety)</i>								
Reviewer's Comments:								

Patient Baseline Demographics:								
	Intervention 1	Intervention 2	Intervention 3	Intervention 4	Intervention 5	Intervention 6	Intervention 7	Intervention 8
<i>Age (yr) (random.)</i>								
<i>Mean ± SD</i>	±	±	±	±	±	±	±	±
<i>Body weight (Kg)</i>								
<i>Mean ± SD</i>	±	±	±	±	±	±	±	±

	Intervention 1	Intervention 2	Intervention 3	Intervention 4	Intervention 5	Intervention 6	Intervention 7	Intervention 8
<i>Height (cm)</i> <i>Mean ± SD</i>	±	±	±	±	±	±	±	±
<i>BMI (Kg/ m²)</i> <i>Mean ± SD</i>	±	±	±	±	±	±	±	±
<i>Gender</i> <i>Males</i>	/	/	/	/	/	/	/	/
<i>Ethnicity</i> <i>Caucasians</i>	/	/	/	/	/	/	/	/
<i>Education (yrs)</i> <i>Mean ± SD</i>	±	±	±	±	±	±	±	±
Reviewer's Comments:								
Disease characteristics:								
	Intervention 1	Intervention 2	Intervention 3	Intervention 4	Intervention 5	Intervention 6	Intervention 7	Intervention 8
<i>Age (yr) (diagnosis)</i> <i>Mean ± SD</i>	±	±	±	±	±	±	±	±
<i>Treatment (yr)</i> <i>Mean ± SD</i>	±	±	±	±	±	±	±	±
<i>Previous hospital admissions</i> <i>Mean ± SD</i>	±	±	±	±	±	±	±	±
Reviewer's Comments:								

Baseline severity:								
	Intervention 1	Intervention 2	Intervention 3	Intervention 4	Intervention 5	Intervention 6	Intervention 7	Intervention 8
<i>PANSS</i>	±	±	±	±	±	±	±	±
<i>BPRS</i>	±	±	±	±	±	±	±	±
<i>CGI-BP</i>	±	±	±	±	±	±	±	±
<i>CGI-EI</i>	±	±	±	±	±	±	±	±
<i>CGI-I</i>	±	±	±	±	±	±	±	±
<i>CGI-S</i>	±	±	±	±	±	±	±	±
<i>YMRS</i>	±	±	±	±	±	±	±	±
<i>GAS</i>	±	±	±	±	±	±	±	±
<i>MADRS</i>	±	±	±	±	±	±	±	±
Reviewer's Comments:								
Reviewer's Overall Comments: Overall comments								

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	A	B	C
1	Reviewer's name:		
2			
3	Study name:		
4			
5	Refid:		
6			
7	Intervention 1:	Drug name:	
8		Dose:	
9		# Randomized:	
10			
11	Intervention 2:	Drug name:	
12		Dose:	
13		# Randomized:	
14			
15	Intervention 3:	Drug name:	
16		Dose:	
17		# Randomized:	
18			
19	Intervention 4:	Drug name:	
20		Dose:	
21		# Randomized:	
22			
23	Intervention 5:	Drug name:	
24		Dose:	
25		# Randomized:	
26			
27	Intervention 6:	Drug name:	
28		Dose:	
29		# Randomized:	
30			
31	Intervention 7:	Drug name:	

Study name KQ1 - Core Symptoms (Sz) KQ1 - Core Symptoms (BP) KQ2,4 - Func. - Healthcare (Sz) KQ2,4 - Func. - Healthcare (BP) KQ3 - Adverse Events KQ5 - Subgroups

Ready 100%



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	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	W	AD	AK	AR	AY	BF
1			Intervention 1										Intervention 2 3 4 5 6 7 8									
2																						
3																						
4		Positive symptoms																				
11		Negative symptoms																				
12																						
19		General symptoms																				
20																						
27		Total Score																				
28																						
35		Mood																				
36																						
37		Scale name	If other, scale name	Mean	SD	SE	LCB	UCB	N	Mean	SD	SE	LCB	UCB	N							
38																						
39		CGI-BS																				
40		CGI-EI																				
41		CGI-I																				
42		CGI-S																				
43		GAS																				
44		HAMD-21																				
45		Hostility																				
46		MADRS																				
47																						
48		Motor activity/ energy																				
51																						
52		Speech																				
59																						
60		Sleep																				
67																						
68		Behaviour																				
75																						
76		Total score																				
83																						
84		Reviewer's comments																				

Study name KQ1 - Core Symptoms (Sz) KQ1 - Core Symptoms (BP) KQ2,4 - Func. - Healthcare (Sz) KQ2,4 - Func. - Healthcare (BP) KQ3 - Adverse Events KQ5 - Subgroups

Ready 100%

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Clipboard Font Alignment Number Styles Cells Editing

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	A	B	C	D	E	F	G	H	I	J	K	L	V	AF	AP	AZ	BJ	BT	CD
1																			
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Intervention 1 2 3 4 5 6 7 8

Functional capacity Continuous Binary

Healthcare system utilization Continuous Binary

Other outcomes Continuous Binary

Outcome	Scale name, if applicable	Mean	SD	SE	LCB	UCB	N	n	N
Relapse rates									
Response rates									
Remission rates									
Medication adherence									
Persistence									
Patient insight into illness									
Health-related quality of life (QoL)									
Care-giver satisfaction									
Patient satisfaction									

Reviewer's comments

Study name KQ1 - Core Symptoms (Sz) KQ1 - Core Symptoms (BP) KQ2,4 - Func. - Healthcare (Sz) KQ2,4 - Func. - Healthcare (BP) KQ3 - Adverse Events KQ5 - Subgroups

Ready 100%

Outcomes Data Extraction Template (v1.6)1 - Microsoft Excel

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Clipboard Font Alignment Number Styles Cells Editing

B2

	A	B	C	D	E	F	G	H	I	J	K	L	M
1	Is the whole a subgroup?												
2	If yes, which subgroup does it belong to?												
3	Please provide additional details:	Disorder subtypes											
4		Gender											
5		Age group (18-35yrs; 36-54yrs; 55-64yrs)											
6	Is data provided on of the review's subgroups?	Race											
7	If yes, which subgroup does it belong to?	Co-morbidities											
8	Please provide additional details:	Drug dosage											
9		Follow-up period											
10	Reviewer's comments												
11													
12													
13													
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Study name KQ1 - Core Symptoms (Sz) KQ1 - Core Symptoms (BP) KQ2,4 - Func. - Healthcare (Sz) KQ2,4 - Func. - Healthcare (BP) KQ3 - Adverse Events KQ5 - Subgroups

Ready 100%

**RISK OF BIAS (ROB)
RANDOMIZED CONTROLLED TRIALS**

<i>Item</i>	<i>Judgment</i>	<i>Description</i>
<i>Adequate sequence generation?</i>		
<i>Allocation concealment?</i>		
<i>Blinding?</i>		
<i>Incomplete outcome data addressed?</i>		
<i>Free of selective reporting?</i>		
<i>Free of other bias?</i>		

Appendix C. List of Excluded Studies

A total of 921 studies were excluded from the review during phase 2 screening. Reasons for exclusion included: a) publication type or study design (n = 612), b) non-English language (n = 100), c) population or intervention not of interest (n = 134), d) no extractable data related to the outcome of interest (n = 58), and e) publication unavailable through library service (n = 17).

Publication Type and Study Design

1. Abdollahian EM. Comparing the effects of risperidone and haloperidol in chronic schizophrenic patients. *Proceedings of the Thematic Conference of the World Psychiatric Association on "Treatments in Psychiatry: An Update"; 2004.*
2. Addington J, Addington D. Neurocognitive functioning in schizophrenia: a trial of risperidone versus haloperidol. *Can J Psychiatry* 1997;42(9):983. PMID:9429073
3. Addington J. Cognitive functioning in schizophrenia: a trial of risperidone versus haloperidol. 27th Collegium Internationale Neuro-psychopharmacologicum 2006.
4. Adetunji B, Basil B, Mathews M, et al. Methodological issues in a study of long-term maintenance therapy with quetiapine versus haloperidol decanoate. *J Clin Psychiatry* 2006;67(3):497-8. PMID:16649843
5. Agelink MW, Malessa R, Kamcili E, et al. Cardiovascular autonomic reactivity in schizophrenics under neuroleptic treatment: a potential predictor of short-term outcome? *Neuropsychobiology* 1998;38(1):19-24. PMID:9701718
6. Agid O, Kapur S, Arenovich T, et al. Delayed-onset hypothesis of antipsychotic action: a hypothesis tested and rejected. *Archives of General Psychiatry* 2003;60(12):1228-35. PMID:14662555
7. Aleman A, Kahn RS. Effects of the atypical antipsychotic risperidone on hostility and aggression in schizophrenia: a meta-analysis of controlled trials. *Eur Neuropsychopharmacol* 2001;11(4):289-93. PMID:11532383
8. Allan ER, Sison CE, Alpert M, et al. The relationship between negative symptoms of schizophrenia and extrapyramidal side effects with haloperidol and olanzapine. *Psychopharmacol Bull* 1998;34(1):71-4. PMID:9564201
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12. Amann BL, Pogarell O, Mergl R, et al. EEG abnormalities associated with antipsychotics: a comparison of quetiapine, olanzapine, haloperidol and healthy subjects. *Hum Psychopharmacol* 2003;18(8):641-6. PMID:14696024
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14. Ames D. Risperidone vs. haloperidol: relative liabilities for ocd and depression. *Schizophrenia Research (VIIIth Biennial Winter Workshop on Schizophrenia)* 1996;18(2-3):129.
15. Ames D. Subjective response to risperidone and haloperidol: preliminary results conference proceeding. *Schizophrenia Research (VIIIth Biennial Winter Workshop on Schizophrenia)* 1996;18(2-3):129.
16. Ames D. Treatment resistant schizophrenia: evaluation of risperidone vs. haloperidol. *Biol Psychiatry* 1997;72S-3S.
17. Ames D. Treatment-resistant schizophrenia: efficacy of risperidone versus haloperidol. 150th Annual Meeting of the American Psychiatric Association 2000.
18. Amin M, Shukla VS. Olanzapine vs haloperidol for treatment of schizophrenia. *JAMA* 2004;291(9):1065-6. PMID:14996767
19. Andersen SW, Tollefson GD, Sanger TM. Depressive signs and symptoms in schizophrenia: a prospective blinded trial of olanzapine and haloperidol [conference abstract]. *Schizophr Res* 1999;269.
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22. Arbaizar B, Gomez-Acebo I, Llorca J. Quality of reporting controlled clinical trials on treatment of the acute mania phase of bipolar disorder with new antipsychotic drugs. *Pharmacopsychiatry* 2008;41(6):240-1. PMID:19067261

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24. Ascher-Svanum H, Nyhuis A, Tunis S, et al. Time to all cause discontinuation following randomization to open-label olanzapine, risperidone, or conventional antipsychotic treatment for schizophrenia. 158th Annual Meeting of the American Psychiatric Association 2005.
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26. AstraZeneca. A multicenter, double-blind, randomized, comparison of quetiapine (seroquelA) and chlorpromazine in the treatment of subjects with treatment-resistant schizophrenia. <http://www.clinicalstudyresults.org/>
27. AstraZeneca. A multicentre, double-blind, randomised trial to compare the effects of seroquel and chlorpromazine in patients with treatment resistant schizophrenia (5077IL/0054 TRESS). <http://www.clinicalstudyresults.org/2000>.
28. AstraZeneca. An International, Multicenter, Double-blind, Randomized, Placebo-controlled Study of the Safety and Efficacy of Seroquel (Quetiapine Fumarate) and Haloperidol as Monotherapy in the Treatment of Acute Mania [5077IL/0104]. <http://www.clinicalstudyresults.org/>
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30. Atmaca M. The comparison of quetiapine and haloperidol effects on serum prolactin in patients with schizophrenia. *Eur Neuropsychopharmacol* 2001;11(3):S240.
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No Extractable Data Related to Outcomes of Interest

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Appendix D. List of Companion Studies

A total of 146 articles were companions to the included studies.

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Appendix E. Risk of Bias Assessment for Randomized Controlled Trials and Nonrandomized Controlled Trials

Guidelines and Decision Rules for Risk of Bias Assessments

Sequence generation:

- If computer-generated, random number list, flipping coins, randomly picking envelopes, etc. is specified → YES
- If the description only includes “random,” “randomly generated,” “randomized,” etc, do not assume additional details → UNCLEAR
- If the description is quasi-randomized (e.g. alternate randomization, day of the year, day of the month, birth date, birth month, beginning letter of last name, availability of investigator or specialist, etc) → NO

Allocation concealment:

- If the assignment is conducted by central telephone, pharmacy, etc → YES
- If dark (or opaque), sealed, sequentially-numbered envelopes are used → YES
- If the envelopes are not stated to dark and sealed, or sequentially-numbered → UNCLEAR

Note: sequential numbering of the envelopes is only required for adequate allocation concealment if the method of randomization was anything other than randomly picking envelopes (i.e., the envelopes were only used for allocation concealment and not as part of the randomization process).

Blinding:

- Describe who is blinded: patient, clinician, outcomes assessor, etc.
- If the study was stated to be blinded (masked), and the blinding is considered to be possible and not likely to be broken → YES
- If the study is only stated to be blinded, double-blinded, double-dummy, etc. without any further details → UNCLEAR
- If the study states the use of a placebo (dummy), but with no further details → UNCLEAR
- If no mention of blinding → UNCLEAR

Incomplete outcome data (longest time point):

- Look for intention-to-treat (ITT) analysis (all randomized patients are analyzed) → YES
- If all participants were accounted for (i.e., no dropouts or censored analysis conducted) → YES
- If the numbers and reasons for withdrawal or dropouts were described and comparable across groups (and \leq approximately 10 percent) → YES
- If there is between 10–30 percent dropout and no ITT analysis → UNCLEAR
- If there is greater 30 percent dropout and no ITT analysis → NO

Selective outcome reporting:

- If the study protocol is available (referenced in the manuscript), compare the outcomes reported in the publication to those specified in the protocol. If they match → YES
- If the study protocol is available (referenced in the manuscript), compare the outcomes reported in the publication to those specified in the protocol. If they do not match, but there is reference to another publication with this information presented → YES
- If the study protocol is not available, compare the outcomes reported in the methods and results sections. If they match → YES
- If the study protocol is not available, compare the outcomes reported in the methods and results sections. If they do not match → NO
- If the study protocol is not available, compare the outcomes reported in the methods and results sections. If they match but not in an extractable format (e.g., stating that there was no difference between the groups regarding the outcome) → UNCLEAR

Other sources of bias:

- Assess for baseline imbalances that could have biased the results (or were not accounted for)
- Assess for appropriateness of crossover design (e.g., inadequate wash-out period).
- Note any “other” sources of bias

Risk of Bias Assessments

A) Schizophrenia and Related Psychoses

Table 1. Risk of bias—chlorpromazine versus clozapine

Study	Item	Judgment	Description
Chiu et al. 1976 ¹⁵²	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details on sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment.
	Blinding?	UNCLEAR	Reported as a DB trial using identical capsules.
	Incomplete outcome data addressed?	NO	ITT principle was not used in the analyses with 43.8% of participants being excluded from the analyses. Attrition rate was high with 43.8% of participants not completing the trial.
	Free of selective reporting?	YES	Protocol was not available, but outcomes reported in methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Claghorn et al. 1987 ⁶³	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	YES	Reported as a DB trial, with medications that were identical in appearance and packaged uniformly.
	Incomplete outcome data addressed?	NO	ITT principle not utilized for analyses, and 42% of participants did not complete the study.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Ekblom et al. 1974 ¹⁵³	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details on sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment.
	Blinding?	YES	Reported as a DB trial using identical capsules.
	Incomplete outcome data addressed?	YES	ITT principle was used and attrition rate was low (9.8%).
	Free of selective reporting?	YES	Protocol was not available, but outcomes reported in methods and results are similar.
	Free of other bias?	UNCLEAR	Baseline characteristics were reported not reported. Other sources of bias were not detected.

Table 1. Risk of bias—chlorpromazine versus clozapine (continued)

Study	Item	Judgment	Description
Gelenberg et al. 1979 ¹⁵⁴	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details on sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding participant or physician blinding.
	Incomplete outcome data addressed?	YES	ITT principle was used in analyses with no reports of patients lost for followup.
	Free of selective reporting?	YES	Protocol was not available, but outcomes reported in methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Guirguis et al. 1977 ¹⁶⁰	Adequate sequence generation?	UNCLEAR	Reported as randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment.
	Blinding?	UNCLEAR	No mention of who was blinded, but used identical capsules prepared in pharmacy.
	Incomplete outcome data addressed?	UNCLEAR	No ITT, 35/50 (70%) analyzed.
	Free of selective reporting?	YES	Protocol not available, but methods and results sections match.
	Free of other bias?	UNCLEAR	Baseline imbalances on age, NOSIE score, and onset of schizophrenia.
Hong et al. 1997 ⁸⁷	Adequate sequence generation?	YES	Randomization was done using a table of random numbers.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial. Medications were identical in appearance and package, which ensured DB. No clear statement regarding blinding of assessors.
	Incomplete outcome data addressed?	YES	No use of ITT. 40 patients randomized, 38 patients analyzed (95%).
	Free of selective reporting?	YES	Outcomes in the method section match to the results.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Kane et al. 1988 ⁹⁴	Adequate sequence generation?	UNCLEAR	Reported patients were randomly assigned, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	YES	All medications were coded and administered under DB conditions; in addition to coded active antipsychotic medication in blue capsules, patients received either white benztropine tablets or identical white placebo tablets.
	Incomplete outcome data addressed?	UNCLEAR	No ITT. 10–30% (14%) dropouts.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

Table 1. Risk of bias—chlorpromazine versus clozapine (continued)

Study	Item	Judgment	Description
Leon et al. 1979 ¹⁵⁶	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding the methods used for blinding.
	Incomplete outcome data addressed?	NO	No ITT reported; 50 randomized and 37 analyzed at 3 year followup.
	Free of selective reporting?	YES	Protocol was not available, but all main outcomes were reported.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Lieberman et al. 2003 ¹⁰⁹	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial but only specified patients were blinded.
	Incomplete outcome data addressed?	YES	Use of modified ITT. Only 4 patients not considered in the analysis (2.43%).
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Rinieris et al. 1980 ¹⁵⁷	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	No information reported regarding patient or physician blinding status provided in trial report.
	Incomplete outcome data addressed?	NO	ITT principle was not used in analyses, with only 59% of randomized participants included in analyses.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results were similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Shopsin et al. 1979 ¹⁵⁸	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Blinding?	YES	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Incomplete outcome data addressed?	YES	ITT principle used during analyses, and there was no reporting of patients dropping out of the trial.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results sections are similar.
	Free of other bias?	UNCLEAR	Baseline characteristics were reported not reported. Other sources of bias were not detected.

Table 1. Risk of bias—chlorpromazine versus clozapine (continued)

Study	Item	Judgment	Description
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Singer et al. 1974¹⁶¹	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a blinded trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	One dropout from each group.
	Free of selective reporting?	YES	No protocol available, but outcomes in methods and results match.
	Free of other bias?	NO	No mention of baseline comparisons.

DB = double-blind; ITT = intention-to-treat analysis; NOSIE = Nurses' Observation Scale for Inpatient Evaluation

Table 2. Risk of bias—chlorpromazine versus olanzapine

Study	Item	Judgment	Description
Conley et al. 1998⁶⁶	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	YES	Reported as a DB trial, using matching medication.
	Incomplete outcome data addressed?	UNCLEAR	ITT reported. 70% completion.
	Free of selective reporting?	YES	Outcomes in the method section match to the results.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

DB = double-blind; ITT = intention-to-treat analysis

Table 3. Risk of bias—chlorpromazine versus quetiapine

Study	Item	Judgment	Description
Peuskens et al. 1997¹²¹	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding the methods used for blinding.
	Incomplete outcome data addressed?	YES	ITT performed on 196/201 (98%) of randomized patients.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

DB = double-blind; ITT = intention-to-treat analysis

Table 4. Risk of bias—chlorpromazine versus ziprasidone

Study	Item	Judgment	Description
Kane et al. 2006 ⁹⁶	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	ITT analysis. Response rates and safety evaluations are reported for the ITT population.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

DB = double-blind; ITT = intention-to-treat analysis

Table 5. Risk of bias—fluphenazine versus olanzapine

Study	Item	Judgment	Description
Jakovljevic et al. 1999 ⁸⁹	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding the methods used for blinding.
	Incomplete outcome data addressed?	YES	Modified ITT using LOCF on those who received drug and had at least one followup observation. 55/60 (92%) analyzed for efficacy, 100% for safety.
	Free of selective reporting?	YES	Protocol was not available, but all main outcomes were reported.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Ljubin et al. 2000 ¹¹²	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Physicians were blind to patient status, but no report of patients knowledge of treatment received.
	Incomplete outcome data addressed?	UNCLEAR	Only analyzed completers. Due to a dropout of some patients, the final olanzapine group had 10 patients, and the fluphenazine group 8 patients.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

DB = double-blind; ITT = intention-to-treat analysis; LOCF = last observation carried forward

Table 6. Risk of bias–fluphenapine versus quetiapine

Study	Item	Judgment	Description
Conley et al. 2005⁶⁷	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	ITT principle not used, but 71% of participants included in the analyses.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

DB = double-blind; ITT = intention-to-treat analysis;

Table 7. Risk of bias–fluphenapine versus risperidone

Study	Item	Judgment	Description
Conley et al. 2005⁶⁷	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	ITT principle not used, but 71% of participants included in the analyses.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

DB = double-blind; ITT = intention-to-treat analysis

Table 8. Risk of bias–haloperidol versus aripiprazole

Study	Item	Judgment	Description
Andrezina et al. 2006⁴⁴	Adequate sequence generation?	YES	Reported as using permuted block randomization.
	Allocation concealment?	YES	Reported as using a centralized call-in system.
	Blinding?	UNCLEAR	Reported as a DB, placebo-controlled trial, with no further details regarding the methods used for blinding.
	Incomplete outcome data addressed?	YES	ITT analysis was not used, but 99% of randomized participants were included in the analyses.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Daniel et al. 2007⁷⁴	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.

Table 8. Risk of bias–haloperidol versus aripiprazole (continued)

Study	Item	Judgment	Description
de Oliveira et al. 2009 ⁷⁶	Incomplete outcome data addressed?	UNCLEAR	Of the 448 patients who received IM formulations, 380 (85%) were transitioned to oral formulations. However, they did not report in this study the results obtained from people switching from placebo to aripiprazole.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias.
	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	Trial reported that investigators were provided with sealed, numbered, and coded envelopes containing the description of the treatment to be administered to the subject by a person who had no contact with the patients. There is no mention if the envelopes were opaque/ dark or not.
	Blinding?	NO	Reported as an open-label trial.
	Incomplete outcome data addressed?	YES	ITT principle not used, but 98% of participants included in analyses.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
Kane et al. 2002 ⁹²	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias.
	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding except that rater was blinded to treatment group.
	Incomplete outcome data addressed?	NO	ITT; reported 248/414 completed.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	UNCLEAR	It is unclear if baseline characteristics were similar.
	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
Kasper et al. 2003 ⁹⁸	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as DB, with no further information.
	Incomplete outcome data addressed?	YES	1294 patients randomized, 1289 analyzed; LOCF reported.
	Free of selective reporting?	YES	Methods match results reported.
	Free of other bias?	NO	No significant differences between treatment groups. Study funded by Bristol Myers Squibb.
	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial with no further details regarding sequence generation.
Kim et al. 2010 ¹⁰²	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a double blind trial. No further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	No ITT. No data regarding the number of dropouts.
	Free of selective reporting?	YES	Outcomes in the method section match to the results.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

Table 8. Risk of bias–haloperidol versus aripiprazole (continued)

Study	Item	Judgment	Description
McCue et al. 2006 ⁷³	Adequate sequence generation?	YES	Reported that randomization was performed using a website-based randomization scheme (www.randomization.com).
	Allocation concealment?	YES	Reported that the hospital staff with no clinical responsibilities and no knowledge of the patients oversaw the assignment procedure and assigned medications in sequential order, strictly following the randomized list. Also reported that the treating psychiatrist did not have access to this list.
	Blinding?	NO	Reported as an open-label study, with both the patient and the treating psychiatrist being aware of the antipsychotic being prescribed.
	Incomplete outcome data addressed?	YES	ITT principle not used during the analysis, but 98% of randomized participants analyzed.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	UNCLEAR	Reported that there was a significant difference in the age of participants among the 6 treatment groups and a significantly different proportion of patients received additional medications. Other sources of bias were not detected.
Tran-Johnson et al. 2007 ³¹	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding patient or physician blinding.
	Incomplete outcome data addressed?	YES	ITT principle not used in analyses, but 95% of participants were included in the analyses.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

DB = double-blind; IM = intramuscular; ITT = intention-to-treat analysis

Table 9. Risk of bias–haloperidol versus asenapine

Study	Item	Judgment	Description
Kane et al. 2010 ⁹⁷	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details.
	Allocation concealment?	UNCLEAR	Allocation concealment was not reported.
	Blinding?	UNCLEAR	Reported as a DB, placebo-controlled trial, with no further details regarding the methods used for blinding.
	Incomplete outcome data addressed?	YES	ITT analysis was not used, but 98% of randomized participants were included in the analyses.
	Free of selective reporting?	UNCLEAR	InterSePT and RDQ are reported as trial outcomes, but no extractable data is reported (i.e., only reported that changes from baseline to endpoint were small).
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

DB = double-blind; ITT = intention-to-treat analysis; RDQ = Readiness to Discharge Questionnaire

Table 10. Risk of bias—haloperidol versus clozapine

Study	Item	Judgment	Description
Breier et al. 2002 ⁵⁶	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	YES	Reported as a DB trial, with investigators, raters, clinical staff, and patients blinded by using identical unmarked syringes administered by trained, unblinded, third-party personnel, who played no role in evaluating patients.
	Incomplete outcome data addressed?	YES	ITT principle used in analyses. Attrition rate was low (0.7%).
	Free of selective reporting?	YES	Protocol was not available, but outcomes in methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Citrome et al. 2001 ⁶²	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with blinded raters performed all the clinical assessments and dosage changes requested by blinded psychiatrists, but no description of how the patients were blinded.
	Incomplete outcome data addressed?	NO	ITT principle was used during analyses, but attrition rate was high with only 58% of participants completing the trial.
	Free of selective reporting?	NO	Two outcomes (ESRS and NOSIE) are listed in the method section, but no results are presented.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Covington et al. 2000 ⁷⁰	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	No reporting of trial blinding.
	Incomplete outcome data addressed?	YES	ITT principle used during analyses and no dropouts were reported.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Itoh et al. 1977 ¹⁵⁵	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	Reported that those physicians who had conducted the trial or those who were related to the pharmaceutical company were excluded from the controllers who coded the DB trial and supervised the entire experiment.
	Blinding?	UNCLEAR	Reported that the 'coders' were independent of physicians supervising the trial. So it seems that they were blinded, but no report of the subjects' status.
	Incomplete outcome data addressed?	YES	All patients were analyzed.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

Table 10. Risk of bias—haloperidol versus clozapine (continued)

Study	Item	Judgment	Description
Kane et al. 2001 ⁹⁵	Adequate sequence generation?	YES	Reported as a randomized trial. Computer-generated randomization schedules (blocked by site) were provided to each site.
	Allocation concealment?	UNCLEAR	Use of sealed envelopes with treatment assignment were available to clinical personnel if needed to break the blind. Unsure whether they used sequentially numbered or opaque envelopes.
	Blinding?	UNCLEAR	Reported as a DB trial: medication was administered under DB conditions. To maintain the blind, all subjects had a weekly blood draw. No further details regarding blinding.
	Incomplete outcome data addressed?	NO	More than 30% were dropped out of the study, and no ITT was conducted.
	Free of selective reporting?	YES	Outcomes in the method section match to the results.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Kleiser et al. 1994 ¹⁰³	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	51 patients were randomized, 51 analyzed. No report of ITT.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	UNCLEAR	No significant differences between treatment groups. No declaration of funding source.
Krakowski et al. 2006 ¹⁰⁵	Adequate sequence generation?	UNCLEAR	Reported as a block randomization with no further detail.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	ITT performed on all participants.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Rosenheck et al. 1997 ¹²⁶	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	YES	Reported as a DB trial, with matching benztropine placebo. To maintain blinding, haloperidol- treated patients also received benztropine mesylate (2–10 mg/d) for extrapyramidal syndrome; clozapine patients received a matching benztropine placebo. Haloperidol patients participated in weekly blood counts as required for clozapine treatment.
	Incomplete outcome data addressed?	UNCLEAR	ITT principle not used in analyses and attrition rate was moderate, with 346/423 participants not included in analyses.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

Table 10. Risk of bias—haloperidol versus clozapine (continued)

Study	Item	Judgment	Description
Volakva et al. 2002 ¹⁴⁵	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial; clinicians who adjusted the dosing and outcome assessors were blinded. Patients were blinded to BDZ, not to the antipsychotics.
	Incomplete outcome data addressed?	YES	101 patients randomized, and 101 patients analyzed. No clear description of how many randomized.
	Free of selective reporting?	UNCLEAR	NOSIE and ESRS are in method section. But, no numeric data is reported in results, just F-values, degrees of freedom, and p-values are reported.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

BDZ = benzodiazepine; DB = double-blind; ESRS =Extrapyramidal Syndrome Rating Scale; ITT = intention-to-treat analysis; NOSIE = Nurses' Observation Scale for Inpatient Evaluation

Table 11. Risk of bias—haloperidol versus olanzapine

Study	Item	Judgment	Description
Altamura et al. 2002 ⁴³	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding the methods used for blinding.
	Incomplete outcome data addressed?	UNCLEAR	ITT principle was not used. 24/28 participants were included in the analyses using LOCF. Attrition rate was moderate (25%).
	Free of selective reporting?	UNCLEAR	Protocol was not available, but one of the main outcomes (CGI-S) was only reported to be not significantly different between the groups, without any extractable data presented.
	Free of other bias?	UNCLEAR	Baseline characteristics for the 2 groups was shown in tabular form, but no mention of similarity was presented.
Alvarez-Jimenez et al. 2006 ¹⁴²	Adequate sequence generation?	YES	Reported as a randomized trial using computer-generated blocks of random numbers.
	Allocation concealment?	YES	Allocation concealment was done by a member of the team not involved with either the assessment or the treatments.
	Blinding?	NO	Reported as single-blind trial, with research assessors and patients intended to be blind to intervention. It was difficult to keep assessors blinded.
	Incomplete outcome data addressed?	YES	ITT performed on all randomized patients.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Avasthi et al. 2001 ¹⁵⁹	Adequate sequence generation?	YES	Reported as a randomized trial, with no further details regarding sequence generation.

Table 11. Risk of bias—haloperidol versus olanzapine (continued)

Study	Item	Judgment	Description
Beasley et al. 1996 ⁴⁹	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	NO	Described as an open-label study.
	Incomplete outcome data addressed?	UNCLEAR	No ITT; 23/30 (76.7%) analyzed.
	Free of selective reporting?	YES	Study protocol not available, but outcomes reported in the methods and results sections match.
	Free of other bias?	UNCLEAR	No baseline comparison data reported.
	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB placebo-controlled trial, with no further details regarding blinding, except that dose ranges could be modified in a blinded manner.
	Incomplete outcome data addressed?	YES	ITT principle not used in the analyses, but 415/431 participants were included using LOCF. Attrition rate was low (16%).
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.
Beasley et al. 1997 ⁵⁰	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding the methods used for blinding.
	Incomplete outcome data addressed?	YES	ITT analysis using LOCF on 415/431 (96%) of patients.
	Free of selective reporting?	YES	Protocol was not available, but all main outcomes were reported.
Bernardo et al. 2001 ⁵¹	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further information regarding blinding.
	Incomplete outcome data addressed?	YES	ITT not used for analyses, with 27/28 participants included. Attrition was not reported.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
Boulay et al. 2007 ⁵⁴	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	ITT principle was not used, with 95% of participants included in analyses. Attrition rate was moderate (12.5%).
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.

Table 11. Risk of bias—haloperidol versus olanzapine (continued)

Study	Item	Judgment	Description
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Breier et al. 2002 ⁵⁶	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	YES	Reported as a DB trial, with investigators, raters, clinical staff, and patients blinded by using identical unmarked syringes administered by trained unblinded third-party personnel who played no role in evaluating patients.
	Incomplete outcome data addressed?	YES	ITT principle used in analyses. Attrition rate was low (0.7%).
	Free of selective reporting?	YES	Protocol was not available, but outcomes in methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Buchanan et al. 2005 ⁵⁸	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	NO	Reported as a DB trial, but adverse events were rated by a nonblinded pharmacist.
	Incomplete outcome data addressed?	YES	ITT principle is not used in analyses. Attrition rate was low 9.5%.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Citrome et al. 2001 ⁶²	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with blinded raters performed all the clinical assessments and dosage changes requested by blinded psychiatrists, but no description of how the patients were blinded.
	Incomplete outcome data addressed?	NO	ITT principle was used during analyses, but attrition rate was high, with only 58% of participants completing the trial.
	Free of selective reporting?	NO	Two outcomes (ESRS and NOSIE) are listed in the method section, but no results are presented.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Crespo-Faccoro et al. 2006 ⁷¹	Adequate sequence generation?	YES	Reported as a randomized trial using a computer-generated randomization list.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	NO	Reported as an open-label trial.
	Incomplete outcome data addressed?	YES	ITT principle not used, but attrition rate was low, and 172/182 were included in the analyses.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.

Table 11. Risk of bias—haloperidol versus olanzapine (continued)

Study	Item	Judgment	Description
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Davidson et al. 2009 ⁷⁵	Adequate sequence generation?	YES	Reported the use of a centralized computerized online randomization system.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	NO	Reported as an open-label trial.
	Incomplete outcome data addressed?	NO	ITT principle was not used, and attrition was high with 43% of participants not completing the trial.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
de Haan et al. 2003 ⁷⁸	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial using a randomized block design. No more details regarding sequence generation
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial. All analyses were performed blind to the clinical data.
	Incomplete outcome data addressed?	UNCLEAR	No ITT, 20% withdrawal.
	Free of selective reporting?	YES	Outcomes in the method section match to the results.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Goldman et al. 2004 ⁸⁴	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial; no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	No ITT, 7/10 completed.
	Free of selective reporting?	YES	Outcomes in the method section match to the results.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Ishigooka et al. 2001 ⁸⁸	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	No ITT. 127/174 completed the trial.
	Free of selective reporting?	YES	Outcomes in the method section match to the results.
	Free of other bias?	UNCLEAR	Significant difference in BPRS scores at baseline. Other sources of bias were not detected.
Kahn et al. 2008 ⁹¹	Adequate sequence generation?	YES	Trial reported patients were randomly assigned by a dedicated web-based online system developed inhouse by the Data Management Department of the Julius Center for Health Sciences and Primary Care.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	NO	Reported as an open-label trial. Patients and their treating psychiatrists were unmasked for the assigned treatment.
	Incomplete outcome data addressed?	YES	498 randomized. 498 analyzed. ITT reported. 342 completed followup.

Table 11. Risk of bias—haloperidol versus olanzapine (continued)

Study	Item	Judgment	Description
Keefe et al. 2006 ¹⁰¹	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	414 patients randomized. ITT reported. 414 analyzed.
Kim et al. 2010 ¹⁰²	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial. No further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	No ITT. No data regarding the number of dropouts.
Kongsakon et al. 2006 ¹⁰⁴	Free of selective reporting?	YES	Outcomes in the method section match to the results.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	YES	Drug kits were assigned a number according to a randomization list produced onsite, then these numbered kits were consecutively allocated to patients in blocks of four stratified by country.
	Blinding?	YES	Reported as a DB trial. All study medication was identical in appearance.
	Incomplete outcome data addressed?	YES	>90% (93% for PANSS and 98% for BPRS) were analyzed.
Krakowski et al. 2006 ¹⁰⁵	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias.
	Adequate sequence generation?	UNCLEAR	Reported as a block randomization with no further detail.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	ITT performed on all participants.
Lahti et al. 2009 ¹⁰⁶	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
Lahti et al. 2009 ¹⁰⁶	Blinding?	YES	Reported as a DB trial. Medications were prepared in similar-looking capsules by the hospital pharmacist.

Table 11. Risk of bias—haloperidol versus olanzapine (continued)

Study	Item	Judgment	Description
Lieberman et al. 2003 ¹⁰⁸	Incomplete outcome data addressed?	YES	ITT principle not used, but 29/32 (91%) of participants included in the analyses.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias.
	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial; no further details regarding the methods used for blinding.
	Incomplete outcome data addressed?	YES	ITT reported; 263 randomized; 262 analyzed.
	Free of selective reporting?	YES	Protocol was not available but all main outcomes were reported.
Lindenmayer et al. 2007 ¹¹⁰	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding procedure.
	Incomplete outcome data addressed?	UNCLEAR	ITT principle not used, 31/35 (89%) of participants included in the analyses.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
McCue et al. 2006 ⁷³	Adequate sequence generation?	YES	Reported that randomization was performed using a website-based randomization scheme (www.randomization.com).
	Allocation concealment?	YES	Reported that the hospital staff with no clinical responsibilities and no knowledge of the patients oversaw the assignment procedure and assigned medications in sequential order, strictly following the randomized list. Also reported that the treating psychiatrist did not have access to this list.
	Blinding?	NO	Reported as an open-label study with both the patient and the treating psychiatrist being aware of the antipsychotic being prescribed.
	Incomplete outcome data addressed?	YES	ITT principle not used during the analysis, but 98% of randomized participants analyzed.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	UNCLEAR	Reported that there was a significant difference in the age of participants among the 6 treatment groups, and a significantly different proportion of patients received additional medications. Other sources of bias were not detected.
Purdon et al. 2000 ¹²⁴	Adequate sequence generation?	YES	Reported as a randomized trial using a computer-generated random number table.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	65 randomized, 55 analyzed with LOCF. ITT reported.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

Table 11. Risk of bias—haloperidol versus olanzapine (continued)

Study	Item	Judgment	Description
Rosenheck et al. 2003 ¹²⁷	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	YES	Assignments were made from a coordinating center via telephone.
	Blinding?	YES	Reported as a DB trial using kits labelled with a random number; one group received a matching placebo (i.e. both groups took 2 drugs).
	Incomplete outcome data addressed?	YES	ITT analysis on all randomized patients.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Saddichha et al. 2008 ¹²⁹	Adequate sequence generation?	NO	Reported as randomized, but treatment was assigned by order in which patient arrived.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial. Assessments conducted by a single-blind investigator. No description of drug appearance to preserve the blinding.
	Incomplete outcome data addressed?	YES	Analyzed 99/110 (90%) enrolled patients.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	UNCLEAR	Baseline comparability was unclear. Other sources of bias were not detected.
Sayers et al. 2005 ¹³⁰	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding patient or physician blinding.
	Incomplete outcome data addressed?	NO	ITT principle not used in analyses; attrition rate was high, with 14/ 24 of participants not completing the trial.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Sergi et al. 2007 ¹³⁴	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	ITT not reported. 73/100 (73%) included in analysis.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias.
Smelson et al. 2006 ¹³⁶	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial using identical appearing capsules. No mention of who else blinded.
	Incomplete outcome data addressed?	NO	ITT not reported. 18/31 (58%) included in analysis .
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.

Table 11. Risk of bias—haloperidol versus olanzapine (continued)

Study	Item	Judgment	Description
Smith et al. 2001 ¹³⁷	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias.
	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	NO	ITT not reported. 53% to 73% included in analysis.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
Tollefson et al. 1997 ¹⁴¹	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	NO	Reported as an open-label trial.
	Incomplete outcome data addressed?	YES	ITT analysis on all randomized patients.
	Free of selective reporting?	YES	Protocol was not available, but all main outcomes were reported.
Volakva et al. 2002 ¹⁴⁵	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial; clinicians who adjusted the dosing and outcome assessors were blinded. Patients were blinded to BDZ, not to the antipsychotics.
	Incomplete outcome data addressed?	YES	101 patients randomized, and 101 patients analyzed. No clear description of how many randomized.
	Free of selective reporting?	UNCLEAR	NOSIE and ESRS are in method section. But, no numeric data is reported in results, just F-value, degrees of freedom, and p-value are reported.
Wright et al. 2001 ¹⁴⁷	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	YES	Reported as a DB trial. Drugs and placebo administered in identical, color-blinded, translucent syringes; raters and study personnel blind to treatment assignment.
	Incomplete outcome data addressed?	YES	ITT not reported but 285/311 (92%) included in analysis.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
Wynn et al. 2007 ¹⁴⁸	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.

Table 11. Risk of bias–haloperidol versus olanzapine (continued)

Study	Item	Judgment	Description
	Incomplete outcome data addressed?	NO	ITT not reported. 51/100 (51%) included in analysis.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

BDZ = benzodiazepine; BPRS = Brief Psychiatric Rating Scale; DB = double-blind; CGI-S = Clinical Global Impressions–Severity; ESRS = Extrapyramidal Symptom Rating Scale; ITT = intention-to-treat analysis; LOCF = last observation carried forward; NOSIE = Nurses’ Observation Scale for Inpatient Evaluation; PANSS = Positive and Negative Symptom Scale

Table 12. Risk of bias–haloperidol versus quetiapine

Study	Item	Judgment	Description
Arvantis et al. 1997⁴⁶	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	ITT principle not used, but 99% of participants included in the analyses.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Atmaca et al. 2002⁴⁷	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	This study was not reported as blinded, and there was not reporting of any blinding.
	Incomplete outcome data addressed?	UNCLEAR	Reported that all participants completed the study.
	Free of selective reporting?	YES	Protocol not available, but outcomes in methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Copolov et al. 2000⁶⁸	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	NO	ITT principle not used and attrition rate was high with 33% of participants dropping out from the trial.
	Free of selective reporting?	YES	Outcomes in the method section match with the results.
	Free of other bias?	UNCLEAR	Baseline characteristics were similar, with the exception for differences in the subgroup diagnoses of schizophrenia and AIMS scores. Other sources of bias were not detected.
Davidson et al. 2009⁷⁵	Adequate sequence generation?	YES	Reported the use of a centralized computerized online randomization system.

Table 12. Risk of bias–haloperidol versus quetiapine (continued)

Study	Item	Judgment	Description
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.

Study	Item	Judgment	Description
	Blinding?	NO	Reported as an open-label trial.
	Incomplete outcome data addressed?	NO	ITT principle was not used, and attrition was high, with 43% of participants not completing the trial.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Emsley et al. 2000 ⁷⁹	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	Modified ITT using LOCF on those who received drug and had at least one followup observation. 98% analyzed.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Emsley et al. 2005 ⁸⁰	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as investigator-blinded trial. No other details about blinding.
	Incomplete outcome data addressed?	YES	47 randomized; 33 analyzed; ITT reported (70% completion).
	Free of selective reporting?	YES	Outcomes in method section are matched to the results.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Glick et al. 2005 ⁸⁵	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	NO	Reported as an open-label trial.
	Incomplete outcome data addressed?	NO	ITT principle was not used, and attrition rate was high, with 66% of participants not available at the end of the trial.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Kahn et al. 2008 ⁹¹	Adequate sequence generation?	YES	Trial reported patients were randomly assigned by a dedicated web-based online system developed inhouse by the Data Management Department of the Julius Center for Health Sciences and Primary Care.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	NO	Reported as an open-label trial. Patients and their treating psychiatrists were unmasked for the assigned treatment.
	Incomplete outcome data addressed?	YES	498 randomized. 498 analyzed. ITT reported. 342 completed followup.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.

Table 12. Risk of bias—haloperidol versus quetiapine (continued)

Study	Item	Judgment	Description
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Study	Item	Judgment	Description
McCue et al. 2006 ⁷³	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
	Adequate sequence generation?	YES	Reported that randomization was performed using a website-based randomization scheme (www.randomization.com).
	Allocation concealment?	YES	Reported that the hospital staff with no clinical responsibilities and no knowledge of the patients oversaw the assignment procedure and assigned medications in sequential order, strictly following the randomized list. Also reported that the treating psychiatrist did not have access to this list.
	Blinding?	NO	Reported as an open-label study with both the patient and the treating psychiatrist being aware of the antipsychotic being prescribed.
	Incomplete outcome data addressed?	YES	ITT principle not used during the analysis, but 98% of randomized participants analyzed.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	UNCLEAR	Reported that there was a significant difference in the age of participants among the 6 treatment groups and a significantly different proportion of patients received additional medications. Other sources of bias were not detected.
Purdon et al. 2001 ¹²³	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	Unequal dropout between groups. Analyses included a range of 84% to 100% of patients.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Velligan et al. 2002 ¹⁴³	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	This is a substudy analysing 58/116 (50%) of eligible patients and excluded dropouts.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

AIMS = Abnormal Involuntary Movement Scale; DB = double-blind; ITT = intention-to-treat analysis; LOCF = last observation carried forward

Table 13. Risk of bias—haloperidol versus risperidone

Study	Item	Judgment	Description
Apiquain et al. 2008 ⁴⁵	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	NO	Reported as an open-label trial.
	Incomplete outcome data addressed?	NO	ITT principle not used during the analysis, and only data from 53% of participants were included in the analyses.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.
	Free of other bias?	UNCLEAR	Baseline characteristics were similar except for educational level, marital status, and occupational status. Other sources of bias were not detected.
Blin et al. 1996 ⁵²	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	ITT principle used during analysis, but attrition rate was moderate with 10/ 41 of participants not completing the trial.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Borison et al. 1992 ⁵³	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	ITT principle was used during analyses. Attrition was not reported to have occurred.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	UNCLEAR	Baseline characteristics are presented in tabular format but with no mention of similarity between the groups. Other sources of bias were not detected.
Cavallaro et al. 2001 ⁵⁹	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	YES	Reported as a DB trial using identical tablets.
	Incomplete outcome data addressed?	UNCLEAR	ITT principle not used in analyses with moderate attrition rate with 22% of participants not completing the trial.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

Table 13. Risk of bias—haloperidol versus risperidone (continued)

Study	Item	Judgment	Description
Cesková et al. 1993⁶⁰	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding patient or physician blinding status provided in trial report.
	Incomplete outcome data addressed?	YES	ITT principle not used during analyses, but attrition rate was low with 3/62 patients not completing the trial.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Chouinard et al. 1993⁶¹	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	YES	Reported as a DB trial using identical tablets.
	Incomplete outcome data addressed?	YES	ITT principle used during analyses and no reported dropouts.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Citrome et al. 2001⁶²	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with blinded raters performed all the clinical assessments and dosage changes requested by blinded psychiatrists, but no description of how the patients were blinded.
	Incomplete outcome data addressed?	NO	ITT principle was used during analyses, but attrition rate was high, with only 58% of participants completing the trial.
	Free of selective reporting?	NO	Two outcomes (ESRS and NOSIE) are listed in the method section, but no results are presented.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Claus et al. 1992⁶⁴	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	YES	Reported as a DB trial using matched oral solutions of each medication.
	Incomplete outcome data addressed?	YES	ITT principle not used, but 42 (95%) of participants included in the analyses.
	Free of selective reporting?	YES	Protocol was not available but all main outcomes were reported.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

Table 13. Risk of bias—haloperidol versus risperidone (continued)

Study	Item	Judgment	Description
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Study	Item	Judgment	Description
Crespo-Faccoro et al. 2006 ⁷¹	Adequate sequence generation?	YES	Reported as a randomized trial using a computer-generated randomization list.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	NO	Reported as an open-label trial.
	Incomplete outcome data addressed?	YES	ITT principle not used, but attrition rate was low, and 172/ 182 were included in the analyses.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Csernansky et al. 2002 ⁷²	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	YES	Reported as a DB trial using identical-appearing tablets.
	Incomplete outcome data addressed?	YES	ITT principle not used in analyses, but the attrition rate was low with 365/397 participants analyzed.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
de Sena et al. 2003 ⁷⁷	Adequate sequence generation?	NO	Reported that randomization was performed based on the time of inclusion assigning patients to groups to even and odd numbers (i.e., quasi-randomization).
	Allocation concealment?	NO	Allocation concealment was not possible because quasi-randomization was used.
	Blinding?	UNCLEAR	No details regarding patient or physician blinding was provided in the trial report.
	Incomplete outcome data addressed?	UNCLEAR	The number randomized was not provided, and there was no mention of dropouts.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Emsley et al. 1999 ⁸¹	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	ITT performed on all randomized patients.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Fakra et al. 2008 ⁸²	Adequate sequence generation?	UNCLEAR	Block randomization with no further details.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	NO	Reported as an open-label trial.
	Incomplete outcome data addressed?	UNCLEAR	12% dropout with no ITT.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

Table 13. Risk of bias—haloperidol versus risperidone (continued)

Study	Item	Judgment	Description
Heck et al. 2000 ⁸⁵	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	ITT analysis performed on all 77 (100%) patients.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Kee et al. 1998 ⁹⁹	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	20 randomized, 18 analyzed. No ITT reported.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Keefe et al. 2003 ¹⁰⁰	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	NO	ITT principle not used, 16/49 (33%) of participants included in the analyses, but number per treatment group were not reported.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Keefe et al. 2006 ¹⁰¹	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	414 patients randomized. ITT reported. 414 analyzed.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Kim et al. 2010 ¹⁰²	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial. No further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	No ITT. No data regarding the number of dropouts.
	Free of selective reporting?	YES	Outcomes in the method section match to the results.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

Table 13. Risk of bias—haloperidol versus risperidone (continued)

Study	Item	Judgment	Description
Lee et al. 2007 ¹⁰⁷	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	ITT analysis included all 20 patients.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Lim et al. 2010 ¹⁵¹	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial according to a predefined randomization code that was balanced to ensure even distribution of patients in each treatment group.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	NO	Reported as an open-label trial, but rater blinded.
	Incomplete outcome data addressed?	YES	ITT & LOCF reported. 124 randomized. 124 analyzed.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Liu et al. 2000 ¹¹¹	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial using block randomization in sizes of four with no further details.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	NO	ITT principle not used, 38/56 (68%) of participants included in the analyses.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Marder et al. 1994 ¹¹⁴	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding the methods used for blinding.
	Incomplete outcome data addressed?	NO	High attrition rates (53%) due to insufficient response, AEs, uncooperative etc.
	Free of selective reporting?	YES	Protocol was not available but all main outcomes were reported.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias.
Marder et al. 2003 ¹¹³	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	63 patients randomized, 29 completed the study, 63 patients analyzed. No ITT reported.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

Table 13. Risk of bias—haloperidol versus risperidone (continued)

Study	Item	Judgment	Description
McCue et al. 2006 ⁷³	Adequate sequence generation?	YES	Reported that randomization was performed using a website-based randomization scheme (www.randomization.com).
	Allocation concealment?	YES	Reported that the hospital staff with no clinical responsibilities and no knowledge of the patients oversaw the assignment procedure and assigned medications in sequential order, strictly following the randomized list. Also reported that the treating psychiatrist did not have access to this list.
	Blinding?	NO	Reported as an open-label study, with both the patient and the treating psychiatrist being aware of the antipsychotic being prescribed.
	Incomplete outcome data addressed?	YES	ITT principle not used during the analysis, but 98% of randomized participants analyzed.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	UNCLEAR	Reported that there was a significant difference in the age of participants among the 6 treatment groups and a significantly different proportion of patients received additional medications. Other sources of bias were not detected.
Min et al. 1993 ¹¹⁷	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	YES	All medication was identical and labeled with a protocol number.
	Incomplete outcome data addressed?	YES	ITT analysis performed on all 35 patients.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Moller et al. 2008 ¹¹⁸	Adequate sequence generation?	UNCLEAR	Block randomization with no further details.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	The ITT sample comprised all randomized patients except those whose initial diagnosis had been revised. 98% were analyzed.
	Free of selective reporting?	YES	Trial design described in a publication prior to results of trial. Methods match results reported.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias.
Peuskens et al. 1995 ¹²⁰	Adequate sequence generation?	YES	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	Randomized sequence transferred to sealed envelopes, but did not mention that envelopes were opaque.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding the methods used for blinding.
	Incomplete outcome data addressed?	UNCLEAR	No ITT reported. Analysis included 1019/1362 (75%) randomized patients.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

Table 13. Risk of bias—haloperidol versus risperidone (continued)

Study	Item	Judgment	Description
Purdon et al. 2000 ¹²⁴	Adequate sequence generation?	YES	Reported as a randomized trial using a computer-generated random number table.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	65 randomized, 55 analyzed with LOCF. ITT reported.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Remillard et al. 2008 ¹²⁵	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	The experimenter was blind to the participants' medication and psychopathological status; the clinician assessing psychopathology and EPS was blind to their cognitive performance and medication status.
	Incomplete outcome data addressed?	YES	All 28 were included in analyses.
	Free of selective reporting?	YES	Protocol was not available but all main outcomes were reported.
	Free of other bias?	UNCLEAR	Significant differences in baseline characteristics. Other sources of bias not found.
Schooler et al. 2005 ¹³²	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial using 1:1 randomization scheme balanced by site, with no further detail.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	State ITT principle used, but the denominator for primary outcome. They must have analyzed 521/559 (93%) of patients to obtain their result. Over the 2 yrs of trial, there was a 60.4% dropout rate.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias.
Sergi et al. 2007 ¹³⁴	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	ITT not reported. 73/100 (73%) included in analysis.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias.
Shrivastava et al. 2000 ¹³⁵	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	NO	Reported as an open-label study.
	Incomplete outcome data addressed?	UNCLEAR	ITT not reported. 100/125 (80%) included in analysis.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias.

Table 13. Risk of bias—haloperidol versus risperidone (continued)

Study	Item	Judgment	Description
Tamrakar et al. 2006 ¹³⁹	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	NO	Reported as a randomized open-label trial.
	Incomplete outcome data addressed?	UNCLEAR	ITT not reported. 36/45 (80%) included in analysis.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias.
Volakva et al. 2002 ¹⁴⁵	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial; clinicians who adjusted the dosing and outcome assessors were blinded. Patients were blinded to BDZ, not to the antipsychotics.
	Incomplete outcome data addressed?	YES	101 patients randomized, and 101 patients analyzed. No clear description of how many randomized.
	Free of selective reporting?	UNCLEAR	NOSIE and ESRS are in method section. But, no numeric data is reported in results, just F-value, degrees of freedom, and p-value are reported.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Wirshing et al. 1999 ¹⁴⁶	Adequate sequence generation?	YES	Reported as a randomized trial using a computerized random-number-generating program.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	10-30% dropout with no ITT.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias.
Wynn et al. 2007 ¹⁴⁸	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	NO	ITT not reported. 51/100 (51%) included in analysis.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias.
Yen et al. 2004 ¹⁴⁹	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	NO	Single-blind study (rater blinded).
	Incomplete outcome data addressed?	UNCLEAR	Used an endpoint LOCF, but it is not clear if used ITT (41 patients randomized, 14 dropped out) and included all patients.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias.

Table 13. Risk of bias—haloperidol versus risperidone (continued)

Study	Item	Judgment	Description
Zhang et al. 2001 ¹⁵⁰	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with blinded assessors. No detail about patient blinding.
	Incomplete outcome data addressed?	YES	ITT not reported but 75/80 (94%) included in analysis.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

AE = adverse events; BDZ = benzodiazepine; DB = double-blind; EPS = extrapyramidal symptoms; ESRS = Extrapyramidal Symptom Rating Scale; ITT = intention-to-treat analysis; LOCF = last observation carried forward; NOSIE = Nurses' Observation Scale for Inpatient Evaluation

Table 14. Risk of bias—haloperidol versus ziprasidone

Study	Item	Judgment	Description
Brook et al. 2005⁵⁷	Adequate sequence generation?	UNCLEAR	Reported as randomized trial using a 3:1 randomization ratio, with no further details in the trial report.
	Allocation concealment?	UNCLEAR	Reported as masked randomization schedule consisting of a list of numbers to which the study drugs had been randomly allocated, but there were no details on how the masking was performed.
	Blinding?	NO	Reported that this trial was an open-label, flexible-dose design trial, with all assessments conducted by evaluators blinded to drug allocation.
	Incomplete outcome data addressed?	NO	ITT principle was used with LOCF method used for missing data, but there was a high attrition rate with 33% of participants not completing the trial.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are consistent.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Corripio et al. 2005⁶⁹	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment.
	Blinding?	NO	Reported as a single-blinded trial, with physicians blinded to treatment status and patients not blinded.
	Incomplete outcome data addressed?	YES	ITT principle used with no reported dropouts.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Davidson et al. 2009⁷⁵	Adequate sequence generation?	YES	Reported the use of a centralized computerized online randomization system.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	NO	Reported as an open-label trial.
	Incomplete outcome data addressed?	NO	ITT principle was not used, and attrition was high with 43% of participants not completing the trial.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Goff et al. 1998⁸³	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	NO	ITT reported. Unknown number screened or randomized, 46/90 completed.
	Free of selective reporting?	YES	Outcomes in the method section match to the results.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

Table 14. Risk of bias—haloperidol versus ziprasidone (continued)

Study	Item	Judgment	Description
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Study	Item	Judgment	Description
Hirsch et al. 2002 ⁸⁶	Adequate sequence generation?	NO	Reported using a computer-generated pseudo-random code.
	Allocation concealment?	UNCLEAR	Reported use of 'envelope method,' but no further details provided.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	No ITT. 227/301 (75%) analyzed.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Kahn et al. 2008 ⁹¹	Adequate sequence generation?	YES	Trial reported patients were randomly assigned by a dedicated web-based online system developed inhouse by the Data Management Department of the Julius Center for Health Sciences and Primary Care.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	NO	Reported as an open-label trial. Patients and their treating psychiatrists were unmasked for the assigned treatment.
	Incomplete outcome data addressed?	YES	498 randomized. 498 analyzed. ITT reported. 342 completed followup.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
McCue et al. 2006 ⁷³	Adequate sequence generation?	YES	Reported that randomization was performed using a website-based randomization scheme (www.randomization.com).
	Allocation concealment?	YES	Reported that the hospital staff with no clinical responsibilities and no knowledge of the patients oversaw the assignment procedure and assigned medications in sequential order, strictly following the randomized list. Also reported that the treating psychiatrist did not have access to this list.
	Blinding?	NO	Reported as an open-label study with both the patient and the treating psychiatrist being aware of the antipsychotic being prescribed.
	Incomplete outcome data addressed?	YES	ITT principle not used during the analysis but 98% of randomized participants analyzed.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	UNCLEAR	Reported that there was a significant difference in the age of participants among the six treatment groups and a significantly different proportion of patients received additional medications. Other sources of bias were not detected.
Miceli et al. 2010 ¹¹⁶	Adequate sequence generation?	YES	Reported as a randomized trial: patients were randomly assigned, using a computer-generated protocol.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	NO	Reported as a single blind trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	59 patients randomized to treatment. 9 patients discontinued treatment (15.25%). Not reported use of ITT.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	UNCLEAR	Baseline comparability was unclear. Other sources of bias were not detected.

Table 14. Risk of bias—haloperidol versus ziprasidone (continued)

Study	Item	Judgment	Description
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Study	Item	Judgment	Description
Potkin et al. 2009 ¹²²	Adequate sequence generation?	YES	Randomization was by computer-generated schedule with a permuted block design.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	No ITT. The full analysis set included 536 subjects who had at least one post-baseline efficacy assessment. 536/599 (89%) analyzed at end of 40 week phase using LOCF, and 186/186 analyzed after 3 year extension using LOCF (Table 2.)
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

DB = double-blind; ITT = intention-to-treat; LOCF = last observation carried forward

Table 15. Risk of Bias – perphenazine versus aripiprazole

Study	Item	Judgment	Description
Kane et al. 2007 ⁹³	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	UNCLEAR	Modified ITT. Included only subjects who took 1 dose of medication (LOCF); 75% completed the 6 weeks treatment (25% dropouts).
	Free of selective reporting?	YES	Outcomes in the method section match to the results.
	Free of other bias?	UNCLEAR	It is unclear if baseline characteristics were similar.

DB = double-blind; ITT = intention-to-treat; LOCF = last observation carried forward

Table 16. Risk of bias—perphenazine versus olanzapine

Study	Item	Judgment	Description
Ascher-Svanum et al. 2008 ¹³¹	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	NO	Reported as an open-label treatment.
	Incomplete outcome data addressed?	YES	664 patients randomized. 648 analyzed. No ITT reported.
	Free of selective reporting?	YES	Methods match results reported.
Lieberman et al. 2005 ²³	Free of other bias?	YES	No significant differences between treatment groups.
	Adequate sequence generation?	UNCLEAR	Reported as a stratified randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment.
	Blinding?	YES	Reported as a DB: patients and assessors blinded.
	Incomplete outcome data addressed?	YES	ITT performed on 96% of patients.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	UNCLEAR	Baseline comparability was unclear. Other sources of bias were not detected.

DB = double-blind; ITT = intention-to-treat

Table 17. Risk of bias—perphenazine versus quetiapine

Study	Item	Judgment	Description
Lieberman et al. 2005 ²³	Adequate sequence generation?	UNCLEAR	Reported as a stratified randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment.
	Blinding?	YES	Reported as a DB: Patients and assessors blinded.
	Incomplete outcome data addressed?	YES	ITT performed on 96% of patients.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	UNCLEAR	Baseline comparability was unclear. Other sources of bias were not detected.

DB = double-blind; ITT = intention-to-treat

Table 18. Risk of bias—perphenazine versus risperidone

Study	Item	Judgment	Description
Ascher-Svanum et al. 2008 ¹³¹	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	NO	Reported as an open-label treatment.
	Incomplete outcome data addressed?	YES	664 patients randomized. 648 analyzed. No ITT reported.
	Free of selective reporting?	YES	Methods match results reported.
	Free of other bias?	YES	No significant differences between treatment groups.
Lieberman et al. 2005 ²³	Adequate sequence generation?	UNCLEAR	Reported as a stratified randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment.
	Blinding?	YES	Reported as a DB: patients and assessors blinded.
	Incomplete outcome data addressed?	YES	ITT performed on 96% of patients.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	UNCLEAR	Baseline comparability was unclear. Other sources of bias were not detected.

DB = double-blind; ITT = intention-to-treat

Table 19. Risk of bias—perphenazine versus ziprasidone

Study	Item	Judgment	Description
Lieberman et al. 2005 ²³	Adequate sequence generation?	UNCLEAR	Reported as a stratified randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment.
	Blinding?	YES	Reported as a DB: patients and assessors blinded.
	Incomplete outcome data addressed?	YES	ITT performed on 96% of patients.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	UNCLEAR	Baseline comparability was unclear. Other sources of bias were not detected.

DB = double-blind; ITT = intention-to-treat

Table 20. Risk of bias—trifluoperazine versus clozapine

Study	Item	Judgment	Description
Rinieris et al. 1980 ¹⁵⁷	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	No information reported regarding patient or physician blinding status.
	Incomplete outcome data addressed?	NO	ITT principle was not used in analyses with only 59% of randomized participants included in analyses.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results were similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias.

DB = double-blind; ITT = intention-to-treat

B) Bipolar Disorder

Table 21. Risk of bias—chlorpromazine versus clozapine

Study	Item	Judgment	Description
Barbini et al. 1997⁴⁸	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	NO	Reported as an open-label trial.
	Incomplete outcome data addressed?	YES	ITT principle not used, but 90% of randomized participants were included in the analyses.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	UNCLEAR	Treatment groups were similar except duration of last euthymic period, which was significantly longer in participants randomized to chlorpromazine. Other sources of bias were not detected.

ITT = intention-to-treat

Table 22. Risk of bias – haloperidol versus aripiprazole

Study	Item	Judgment	Description
Vieta et al. 2005³²	Adequate sequence generation?	UNCLEAR	Reported as using a fixed randomization schedule, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding patient or physician blinding.
	Incomplete outcome data addressed?	YES	ITT principle not used, but 338/ 347 participants were included in analyses.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Young et al. 2009³³	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	No information reported regarding patient or physician blinding status provided in trial report.
	Incomplete outcome data addressed?	YES	ITT principle not used and attrition rate was high with 43% of randomized participants not completing the trial.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

DB = double-blind; ITT = intention-to-treat

Table 23. Risk of bias—haloperidol versus olanzapine

Study	Item	Judgment	Description
Moreno et al. 2007 ¹¹⁹	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	YES	Reported as a DB trial. The two drugs to be compared had the same appearance and were packaged identically, and matched in order to satisfy the requirements of a DB study.
	Incomplete outcome data addressed?	YES	All 12 patients included in the analyses.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	UNCLEAR	Patients did have statistically significant differences between groups. Other sources of bias were not detected.
Tohen et al. 2003 ¹⁴⁰	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial. Not clear how the sequence was generated.
	Allocation concealment?	YES	Allocation concealment was done using a call-in interactive voice response system.
	Blinding?	UNCLEAR	Blinding was not reported.
	Incomplete outcome data addressed?	NO	ITT reported 256/453 completed.
	Free of selective reporting?	YES	All outcomes in methods are apparently reported in results.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

DB = double-blind; ITT = intention-to-treat

Table 24. Risk of bias—haloperidol versus quetiapine

Study	Item	Judgment	Description
McIntyre et al. 2005 ¹¹⁵	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial; medication was identical in number, form, and color but no mention of assessor blinding.
	Incomplete outcome data addressed?	YES	ITT performed on 299/302 randomized patients.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

DB = double-blind; ITT = intention-to-treat

Table 25. Risk of bias—haloperidol versus risperidone

Study	Item	Judgment	Description
Janicak et al. 2001 ⁹⁰	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	YES	Described as DB using identical-appearing preparations supplied by Janssen Pharmaceutical Products.
	Incomplete outcome data addressed?	NO	Results tables have no Ns reported, but Table 1 indicates that 25/62 (40%) finished the trial.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results match.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Sachs et al. 2002 ¹²⁸	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding patient or physician blinding.
	Incomplete outcome data addressed?	NO	ITT principle not used in analyses and attrition rate was high with 59/ 105 of participants not completing the trial.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Segal et al. 1998 ¹³³	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding patient or physician blinding.
	Incomplete outcome data addressed?	YES	ITT principle used in analyses.
	Free of selective reporting?	YES	Protocol is not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.
Smulevich et al. 2005 ¹³⁸	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB trial, with no further details regarding blinding.
	Incomplete outcome data addressed?	YES	ITT not reported but 297/297 (100%) included in analysis.
	Free of selective reporting?	YES	Protocol was not available, but outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

DB = double-blind; ITT = intention-to-treat

Table 26. Risk of bias—haloperidol versus ziprasidone

Study	Item	Judgment	Description
Vieta et al. 2010 ¹⁴⁴	Adequate sequence generation?	UNCLEAR	Reported as a randomized trial, with no further details regarding sequence generation in the trial report.
	Allocation concealment?	UNCLEAR	No information reported regarding allocation concealment in the trial report.
	Blinding?	UNCLEAR	Reported as a DB, double-dummy, with no further details regarding blinding.
	Incomplete outcome data addressed?	NO	ITT principle used in the analyses, but the attrition rate was high with 57% of participants did not complete the trial.
	Free of selective reporting?	YES	Protocol not available, but the outcomes in the methods and results are similar.
	Free of other bias?	YES	No significant differences in baseline characteristics or other sources of bias detected.

DB = double-blind; ITT = intention-to-treat

Appendix F. Summary Risk of Bias Assessments

Table 27. Study-level distribution

	Number of studies
Low risk of bias	0 (0%)
Unclear risk of bias	79 (64%)
High risk of bias	44 (36%)

Table 28. Domain-level distribution

Domain	High	Unclear	Low
Adequate sequence generation	3 (2.4%)	105 (85.4%)	15 (12.2%)
Allocation concealment	1 (0.8%)	116 (94.3%)	6 (4.9%)
Blinding	21 (17.1%)	83 (67.5%)	19 (15.4%)
Incomplete outcome data addressed	24 (19.5%)	32 (26.0%)	67 (54.5%)
Free of selective reporting	1 (0.8%)	3 (2.4%)	119 (96.7%)
Free of other bias	0 (0.0%)	20 (16.3%)	103 (83.7%)

Appendix G. Newcastle-Ottawa Scale Assessment of Cohort Studies

Table 29. Quality assessment of cohort studies

Author, year	Study design	Representative-ness of cohort	Selection of non-exposed cohort	Ascertainment of exposure	Selection		Comparability		Outcome	
					Outcome of interest	Comparability of cohorts	Assessment of outcome	Adequate duration of followup	Adequate follow-up of cohort	Total score
Gaszner 2004 ¹⁶²	Retrospective cohort study	A (1*)	A (1*)	A (1*)	A (1*)	A (1*)	B (1*)	A (1*)	A (1*)	8
Hennessy 2002 ¹⁶³	Retrospective cohort study	A (1*)	A (1*)	A (1*)	A (1*)	A (1*)	B (1*)	A (1*)	A (1*)	8

Appendix H. General Study Characteristics

A) Schizophrenia and Related Psychoses

Table 30. Patient characteristics—chlorpromazine versus clozapine

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Chiu et al. 1976 ¹⁵²	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: NR Study period: NR Number of centers: Single center Setting: Inpatient Country: Australia Financial support: Industry (Sandoz)</p> <p>Washout period performed: yes (5d) Run-in phase performed: no Followup period: 6 wks</p>	<p>Main inclusion criteria: Pts (<60 yrs) with acute episodes of Sz (moderate to severe symptomatology); not suffering from any major medical illnesses Main exclusion criteria: NR</p>	<p>G1: Age (mean±SD): 30.00±NR Males (n(%)): 4/14 (28.57%) Ethnicity: NR BL symptom scores: NR</p> <p>G2: Age (mean±SD): 32.60±NR Males (n(%)): 12/22 (54.55%) Ethnicity: NR BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Chlorpromazine Dosage: 50–300mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Clozapine Dosage: 50–300mg/d Intervals: NR</p>
Claghorn et al. 1987 ⁶³	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM II Study period: NR Number of centers: Multicenter (n = 6) Setting: Inpatient Country: USA Financial support: NR</p> <p>Washout period performed: NA Run-in phase performed: yes (2 wks) Followup period: 8 wks</p>	<p>Main inclusion criteria: Pts (18–65 yrs) with Sz (DSM–II); good physical health, exhibited neurological reactions (either tardive dyskinesia or extrapyramidal effects) induced by prior medication with at least two different AP; hospitalization under 6 months; BPRS score of at least 4 Main exclusion criteria: Pts with medical disorders that could alter the metabolism of the test agents; sensitivities to AP; organic mental disease, recent Hx of ECT; pregnancy</p>	<p>G1: Age (mean±SD): NR Males (n(%)): NR Ethnicity: NR BL symptom scores: BPRS (mean±SD): 54.94±14.24</p> <p>G2: Age (mean±SD): NR Males (n(%)): NR Ethnicity: NR BL symptom scores: BPRS (mean±SD): 58.05±14.64</p>	<p>G1: Classification: FGA Drug: Chlorpromazine Dosage: 50mg–1800mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Clozapine Dosage: 25mg–900mg/d Intervals: NR</p>

Table 30. Patient characteristics—chlorpromazine versus clozapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Eklblom et al. 1974 ¹⁵³	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: NR Study period: NR Number of centers: Single center Setting: Inpatient Country: Sweden Financial support: NR</p> <p>Washout period performed: yes (2 wks) Run-in phase performed: no Followup period: 5.71 wks</p>	<p>Main inclusion criteria: Male acute Sz, and relapsed or exacerbated chronic Sz cases of the paranoid/hallucinatory or catatonic type Main exclusion criteria: Pt age (over sixty or under fifteen); pts suffering from certain previously defined other illness, such as hypertonia, liver disease, etc</p>	<p>G1: Age (mean±SD): 28.00±NR Males (n(%)): 21/21 (100%) Ethnicity: NR BL symptom scores: NR</p> <p>G2: Age (mean±SD): 33.00±NR Males (n(%)): 20/20 (100%) Ethnicity: NR BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Chlorpromazine Dosage: 65–700mg/d</p> <p>G2: Classification: SGA Drug: Clozapine Dosage: 65–600mg/d</p>
Gelenberg et al. 1979 ¹⁵⁴	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM II Study period: NR Number of centers: Single center Setting: Inpatient Country: USA Financial support: Industry (Sandoz)</p> <p>Washout period performed: yes (48 h) Run-in phase performed: no Followup period: 4–8 wks</p>	<p>Main inclusion criteria: Pts (18–65 yrs) with Sz (DSM–II); BPRS rating of at least moderate on at least 3 of the items; Hx of neurologic reaction associated with previous antipsychotic drug use; suitability for treatment with oral medication; good physical health Main exclusion criteria: NR</p>	<p>G1: Age (mean±SD): 30.80±NR Males (n(%)): 4/8 (50%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 47±NR</p> <p>G2: Age (mean±SD): 28.30±NR Males (n(%)): 4/7 (57.14%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 45±NR</p>	<p>G1: Classification: FGA Drug: Chlorpromazine Dosage: 50–1800mg/d Intervals: TID</p> <p>G2: Classification: SGA Drug: Clozapine Dosage: 25–900mg/d Intervals: TID</p>
Guirguis et al. 1977 ¹⁶⁰	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: NR Study period: NR Number of centers: Single center Setting: Inpatient Country: Canada Financial support: NR</p> <p>Washout period performed: no Run-in phase performed: no Followup period: 7 wks</p>	<p>Main inclusion criteria: Dx with acute Sz; previously untreated acute Sz, acutely relapsed Sz and acute exacerbations in chronic Sz Main exclusion criteria: Severe somatic illnesses; drug allergies; pathological changes in blood picture; Hx of Parkinsonism, epilepsy or problems in micturition; disturbance in consciousness; glaucoma; pregnant</p>	<p>G1: Age (mean±SD): 34.7±2.0 Males (n(%)): 20/28 (71.4%) Ethnicity: NR BL symptom scores: NR</p> <p>G2: Age (mean±SD): 41.5±2.5 Males (n(%)): 15/22 (68.1%) Ethnicity: NR BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Chlorpromazine Dosage: 150–900mg/d Intervals: TID</p> <p>G2: Classification: SGA Drug: Clozapine Dosage: 75–450mg/d Intervals: TID</p>

Table 30. Patient characteristics—chlorpromazine versus clozapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Hong et al. 1997 ⁸⁷	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: 1995 to NA Number of centers: Single center Setting: Inpatient Country: China Financial support: Academic</p> <p>Washout period performed: NA Run-in phase performed: yes (6 wks) Followup period: 12 wks</p>	<p>Main inclusion criteria: Sz pt, treatment refractory, Hx of symptoms for 6 months, no less than 2 on BPRS Main exclusion criteria: Pt with: Hx drug abuse, alcoholism, organic brain disorder, mental retardation, or condition that contraindicates clozapine</p>	<p>G1: Age (mean±SD): 37.10±8.70 Males (n(%)): 7/19 (36.84%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 53.1±9.1 PANSS (mean±SD): 113±22</p> <p>G2: Age (mean±SD): 39.70±8.40 Males (n(%)): 7/21 (33.33%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 52.7±6.9 PANSS (mean±SD): 109±18</p>	<p>G1: Classification: FGA Drug: Chlorpromazine Dosage: 50–1800mg/d</p> <p>G2: Classification: SGA Drug: Clozapine Dosage: 25–900mg/d</p>
Kane et al. 1988 ⁹⁴	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM III Study period: NR Number of centers: Multicenter (n = 16) Setting: Inpatient Country: USA Financial support: Industry</p> <p>Washout period performed: NA Run-in phase performed: Drug: yes (6 wks) Followup period: 6 wks</p>	<p>Main inclusion criteria: total BPRS score at least 45 and a minimum CGI rating of 4; item scores of at least (moderate) were required on 2 of the items: conceptual disorganization, suspiciousness, hallucination behavior, and unusual thought content; Hx of Tx resistance; Tx refractory Sz Pts; 3 periods of Tx in the last 5 yrs w/neuroleptics from 2 different chemical classes; doses equivalent to 1000mg/d chlorpromazine for 6 wks without relief and no period of functioning within the preceding 5 yrs Main exclusion criteria: NR</p>	<p>G1: Age (mean±SD): 35.70±8.87 Males (n(%)): 114/142 (80.28%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 61±11</p> <p>G2: Age (mean±SD): 35.70±8.87 Males (n(%)): 101/126 (80.16%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 61±12</p>	<p>G1: Classification: FGA Drug: Chlorpromazine Dosage: 1000–1800mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Clozapine Dosage: 500–900mg/d Intervals: NR</p>

Table 30. Patient characteristics—chlorpromazine versus clozapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Leon et al. 1979 ¹⁵⁶	Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: WHO 1973 / APA Study period: NR Number of centers: Single center Setting: Outpatient Country: Columbia Financial support: Industry (Sandoz) Washout period performed: NA Run-in phase performed: no Followup period: 208 wks	Main inclusion criteria: Sz pts Main exclusion criteria: NR	G1: Age (mean±SD): 27.30±NR Males (n(%)): 15/25 (60%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 41.5±9.3 G2: Age (mean±SD): 30.00±NR Males (n(%)): 14/25 (56%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 40.5±10	G1: Classification: FGA Drug: Chlorpromazine Dosage: 100–1600mg/d Intervals: TID G2: Classification: SGA Drug: Clozapine Dosage: 100–1600mg/d Intervals: TID
Lieberman et al. 2003 ¹⁰⁹	Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: Oct 1995 to Dec 1998 Number of centers: Single center Setting: Inpatient Country: China Financial support: Industry (Novartis) Washout period performed: NA Run-in phase performed: no Followup period: 12 mo	Main inclusion criteria: Dx of Sz or schizophreniform disorder; duration of symptoms not longer than 60 mo; no prior Tx with antipsychotic medication or, if previously treated, a total lifetime usage of less than 14 d; between 16–40 yrs of age; current psychotic symptoms of moderate severity or greater measured by one of the five psychotic items in the (BPRS). Main exclusion criteria: NR	G1: Age (mean±SD): 28.70±6.90 Males (n(%)): 42/80 (52.5%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 44.4±NR G2: Age (mean±SD): 28.70±6.90 Males (n(%)): 42/80 (52.5%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 43.3±NR	G1: Classification: FGA Drug: Chlorpromazine Dosage: max of 600mg/d G2: Classification: SGA Drug: Clozapine Dosage: max of 400mg/d

Table 30. Patient characteristics—chlorpromazine versus clozapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Rinieris et al. 1980 ¹⁵⁷	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: NR Study period: NR Number of centers: Single center Setting: Inpatient Country: Greece Financial support: NR</p> <p>Washout period performed: NA Run-in phase performed: yes (1 wk) Followup period: 6 wks</p>	<p>Main inclusion criteria: Sz pts with absence of clinical symptoms; no Hx of thyroid or endocrinological disease; no use of psychotropic meds Main exclusion criteria: NR</p>	<p>G1: Age (mean±SD): 27.30±9.00 Males (n(%)): NR Ethnicity: NR BL symptom scores: BPRS (mean±SD): 41.5±9.3</p> <p>G2: Age (mean±SD): 27.30±9.00 Males (n(%)): NR Ethnicity: NR BL symptom scores: BPRS (mean±SD): 40.5±10</p> <p>G3: Age (mean±SD): 27.30±9.00 Males (n(%)): NR Ethnicity: NR BL symptom scores: BPRS (mean±SD): 36.4±11.4</p>	<p>G1: Classification: FGA Drug: Chlorpromazine Dosage: 50–100mg Intervals: TID</p> <p>G2: Classification: FGA Drug: Trifluoperazine Dosage: 2.5–5mg Intervals: TID</p> <p>G3: Classification: SGA Drug: Clozapine Dosage: 50–100mg Intervals: TID</p>
Shopsin et al. 1979 ¹⁵⁸	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: NR Study period: NR Number of centers: Single center Setting: Inpatient Country: USA Financial support: NR</p> <p>Washout period performed: yes (≥1 wks) Run-in phase performed: NR Followup period: 5 wks</p>	<p>Main inclusion criteria: Chronically ill Pts with Sz with a recent Hx of acute exacerbation necessitating involuntary hospitalization; those showing minimal criteria under disturbances of affect, thought, and behavior included Main exclusion criteria: Acute or chronic brain syndromes; alcohol/drug addiction; epilepsy; pregnancy; unwillingness to participate in the study; unmanageable ward behavior; refusal to take oral medications; medicolegal difficulties; spontaneous remission during the baseline placebo period</p>	<p>G1: Age (mean±SD): NR Males (n(%)): NR Ethnicity: NR BL symptom scores: NR</p> <p>G2: Age (mean±SD): NR Males (n(%)): NR Ethnicity: NR BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Chlorpromazine Dosage: 50–1600mg/d Intervals: TID</p> <p>G2: Classification: SGA Drug: Clozapine Dosage: 25–900mg/d Intervals: TID</p>

Table 30. Patient characteristics—chlorpromazine versus clozapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Singer et al. 1974 ¹⁶¹	Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: NR Study period: NR Number of centers: Single center Setting: Inpatient Country: Hong Kong Financial support: NR Washout period performed: Yes (2wks) Run-in phase performed: no Followup period: 40 days	Main inclusion criteria: Dx with acute Sz; Main exclusion criteria: Pts with severe somatic illnesses (hepatic, renal and cardiovascular disturbances including compensated and decompensated cardiac diseases, hypotension and, hypertension); drug allergies, histories of epileptic seizures and severe disturbances of consciousness, possibility of pregnancy or pregnant; closed angle glaucoma.	G1: Age (mean±SD): NR Males (n(%)): NR Ethnicity: NR BL symptom scores: NR G2: Age (mean±SD): NR Males (n(%)): NR Ethnicity: NR BL symptom scores: NR	G1: Classification: FGA Drug: Chlorpromazine Dosage: 50–600mg/d Intervals: QID G2: Classification: SGA Drug: Clozapine Dosage: 0–600mg/d Intervals: QID

AP = antipsychotic; APA = American Psychiatric Association; BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; ECT = electroconvulsive therapy; FGA = first-generation antipsychotic; Hx = history; mg = milligram; mo = month; n = number; NA = not applicable; NR = not reported; pts = patients; QID = Four times daily; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; TID = Three times daily; Tx = treatment; WHO = World Health Organization; wk = week; yr = year

Table 31. Patient characteristics—chlorpromazine versus olanzapine

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Conley et al. 1998 ⁶⁶	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM–III–R Study period: NR Number of centers: Multicenter (n = 3) Setting: Inpatient Country: USA Financial support: Multiple sources (Eli Lilly)</p> <p>Washout period performed: yes (NA) Run-in phase performed: yes (6 wks) Followup period: 12 wks</p>	<p>Main inclusion criteria: Pts with Sz (DSM–III–R) with Tx resistance; ≥ 2 periods of Tx in preceding 5 yrs with AP (from at ≥2 chemical classes, excluding haloperidol), at dosages ≥1000mg/d of chlorpromazine equivalents, for 6 wks without significant symptomatic relief; no period of good functioning within past 5 yrs; BPRS (total) score ≥45; CGI–S score ≥4 on at least two of the BPRS psychosis items</p> <p>Main exclusion criteria: resistance to clozapine</p>	<p>G1: Age (mean±SD): 42.63±10.89 Males (n(%)): 28/42 (66.7%) Ethnicity: Caucasian 29/42 (69.1%) BL symptom scores: BPRS (mean±SD): 55.1±8.3</p> <p>G2: Age (mean±SD): 42.91±8.57 Males (n(%)): 34/42 (81%) Ethnicity: Caucasian 28/42 (66.7%) BL symptom scores: BPRS (mean±SD): 55.5±7.8</p>	<p>G1: Classification: FGA Drug: Chlorpromazine Dosage: 600–1200mg/d Intervals: BID</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 12.5–25mg/d Intervals: BID</p>

AP = antipsychotic; BID = Twice daily; BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; FGA = first-generation antipsychotic; mg = milligram; n = number; NA = not applicable; NR = not reported; pts = patients; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; Tx = treatment; wk = week; yr = year

Table 32. Patient characteristics—chlorpromazine versus quetiapine

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Peuskens et al. 1997 ¹²¹	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM–III–R Study period: NR Number of centers: Multicenter (n = 28) Setting: Inpatient Country: Belgium, UK, Spain, France, South Africa Financial support: Industry (Zeneca)</p> <p>Washout period performed: yes (24 h) Run-in phase performed: no Followup period: 6 wks</p>	<p>Main inclusion criteria: Age 18–65; acute exacerbation of chronic or subchronic Sz, or schizophreniform disorder; BPRS score = 27; BPRS pos score = 3 on two or more of 'conceptual disorganization', 'suspiciousness', 'hallucinatory behavior' and 'unusual thought content'; a score of = 4 on CGI–S.</p> <p>Main exclusion criteria: Any medical condition or laboratory abnormality that might confound the trial results; had received long-acting depot medication; had participated in another investigational drug trial during the 4 wks prior to randomization; evidence of significant alcohol or other drug abuse within the previous 12 mo.</p>	<p>G1: Age (mean±SD): 34.00±11.00 Males (n(%)): 66/100 (66%) Ethnicity: Caucasian 80/100(80%) BL symptom scores: BPRS (mean±SD): 44±11 PANSS (mean±SD): 27.8±8</p> <p>G2: Age (mean±SD): 32.00±10.00 Males (n(%)): 63/101 (62.4%) Ethnicity: Caucasian 81/101 (80.2%) BL symptom scores: BPRS (mean±SD): 46±10 PANSS (mean±SD): 28±8</p>	<p>G1: Classification: FGA Drug: Chlorpromazine Dosage: 75–750mg/d Intervals: TID</p> <p>G2: Classification: SGA Drug: Quetiapine Dosage: 75–750mg/d Intervals: TID</p>

AP = antipsychotic; BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; FGA = first-generation antipsychotic; mg = milligram; mo = month; n = number; NA = not applicable; NR = not reported; PANSS = Positive and Negative Syndrome Scale; pts = patients; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; TID = Three times daily; Tx = treatment; wk = week; yr = year

Table 33. Patient characteristics—chlorpromazine versus ziprasidone

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Kane et al. 2006 ⁹⁶	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM–III–R Study period: NR Number of centers: Multicenter (n = 8) Setting: Outpatient Country: India Financial support: Industry (Pfizer)</p> <p>Washout period performed: NA Run-in phase performed: yes (6 wks) Followup period: 12 wks</p>	<p>Main inclusion criteria: Men and Women ≥18yrs with chronic or subchronic Sz; Tx resistant; Haloperidol nonresponders; total score ≥45 on the BPRS; a score ≥4 on at least two PANSS core psychosis items (conceptual disorganization, hallucinatory behavior, delusions and suspiciousness); and a score ≥4 on the CGI–S scale.</p> <p>Main exclusion criteria: Respond to haloperidol during run in phase</p>	<p>G1: Age (mean±SD): 34.40±8.20 Males (n(%)):122/154 (79.2%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 50.54±NR</p> <p>G2: Age (mean±SD): 35.60±9.50 Males (n(%)):103/152 (67.8%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 50.47±NR</p>	<p>G1: Classification: FGA Drug: Chlorpromazine Dosage: 100–1200mg/d Intervals: BID</p> <p>G2: Classification: SGA Drug: Ziprasidone Dosage: 40–160mg/d Intervals: BID</p>

AP = antipsychotic; BID = Twice daily; BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; FGA = first-generation antipsychotic; mg = milligram; NA = not applicable; n = number; NR = not reported; PANSS = Positive and Negative Syndrome Scale; pts = patients; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; Tx = treatment; wk = week; yr = year

Table 34. Patient Characteristics—fluphenazine versus olanzapine

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Jakovljevic et al. 1999 ⁸⁹	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Multicenter (n = 3) Setting: Inpatient Country: Croatia Financial support: Industry (Eli Lilly)</p> <p>Washout period performed: yes (1 to 1.5 wks) Run-in phase performed: no Followup period: 22 wks</p>	<p>Main inclusion criteria: Age 18–65 yrs; Dx with Sz; BPRS score≥42; CGI–S score≥4; PANSS≥42 Main exclusion criteria: Hx of unstable illness, intolerance to Olanzapine or Fluphenazine, substance dependence, abnormal liver function, hepatitis, jaundice. Tx with depot neuroleptics; suicidal ideation, pregnant or lactating, previous trial with olanzapine.</p>	<p>G1: Age (mean±SD): 36.00±9.80 Males (n(%)): 14/30 (46.7%) Ethnicity: Caucasian 30/30 (100%) BL symptom scores: BPRS (mean±SD): 42.7±10.3 PANSS (mean±SD): 106.9±18.5</p> <p>G2: Age (mean±SD): 34.80±11.10 Males (n(%)): 14/30 (46.7%) Ethnicity: Caucasian 81/101 (100%) BL symptom scores: BPRS (mean±SD): 43.7±8.7 PANSS (mean±SD): 110.5±16.4</p>	<p>G1: Classification: FGA Drug: Fluphenazine Dosage: 6–21mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 5–20mg/d Intervals: NR</p>

Table 34. Patient Characteristics–fluphenazine versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Ljubin et al. 2000 ¹¹²	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Single center Setting: Outpatient Country: Croatia Financial support: Industry (Eli Lilly)</p> <p>Washout period performed: NA Run-in phase performed: yes (2–9 d) Followup period: 22 wks</p>	<p>Main inclusion criteria: Outpatients Dx with Sz and CGI–S score = 4; females must be using a medically accepted means of contraception; must have a level of understanding to communicate intelligently with the investigators and nurses; must be reliable and understand the nature of the study</p> <p>Main exclusion criteria: Dx of DSM–IV organic mental disorder or substance use disorder within past 3 mo.; serious suicidal risk; pregnant or lactating; serious unstable co–morbidity condition; life expectancy = 3 yrs; exposure to olanzapine or fluoxetine = 4 wks, remoxipride = 6 mo; Tx with non–reversible monoamine oxidase inhibitor = 2 wks; lithium, anticonvulsants, benzodiazepines, antidepressants, psychostimulants, reversible monoamine oxidase inhibitor, reserpine, guanethidine, or guanadrel = 1 wk.</p>	<p>G1: Age (mean±SD): 37.00±NR Males (n(%)): NR Ethnicity: NR BL symptom scores: NR</p> <p>G2: Age (mean±SD): 37.00±NR Males (n(%)): NR Ethnicity: NR BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Fluphenazine Dosage: 6–21mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 5–20mg/d Intervals: NR</p>

AP = antipsychotic; BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; Dx = Diagnosis; FGA = first-generation antipsychotic; mg = milligram; mo = month; n = number; NA = not applicable; NR = not reported; PANSS = Positive and Negative Syndrome Scale; pts = patients; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; Tx = treatment; wk = week; yr = year

Table 35. Patient characteristics–fluphenazine versus quetiapine

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Conley et al. 2005 ⁶⁷	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Single center Setting: Inpatient Country: USA Financial support: Multiple sources (Janssen)</p> <p>Washout period performed: NA Run-in phase performed: yes (4–6 wks) Followup period: 12 wks</p>	<p>Main inclusion criteria: Age 18–65yrs; Dx with Sz; medically healthy, considered treatment resistant; persistent positive psychotic symptoms (≥ 4 points on 2 of 4 psychosis items on BPRS); BPRS ≥ 45 pts; CGI–S ≥ 4; 2 failed Tx trials with 2 different APs; no stable period of good social/occupational functioning within the previous 5 yrs; non response to run-in Tx.</p> <p>Main exclusion criteria: NR</p>	<p>G1: Age (mean\pmSD): 44.20\pm8.8 Males (n(%)): 11/13 (84.6%) Ethnicity: Caucasian 7/13 (53.9%) BL symptom scores: BPRS (mean\pmSD): 54.69\pm13.67</p> <p>G2: Age (mean\pmSD): 43.70\pm5.90 Males (n(%)): 10/12 (83.3%) Ethnicity: Caucasian 6/12 (50%) BL symptom scores: BPRS (mean\pmSD): 53.5\pm7.37</p> <p>G3: Age (mean\pmSD): 46.30\pm8.70 Males (n(%)): 9/13 (69.2%) Ethnicity: Caucasian 7/13 (53.9%) BL symptom scores: BPRS (mean\pmSD): 56\pm14.08</p>	<p>G1: Classification: FGA Drug: Fluphenazine Dosage: 10–15mg/d</p> <p>G2: Classification: SGA Drug: Quetiapine Dosage: 300–500mg/d</p> <p>G3: Classification: SGA Drug: Risperidone Dosage: 3–5mg/d</p>

AP = antipsychotic; BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; Dx = Diagnosis; FGA = first-generation antipsychotic; mg = milligram; n = number; NA = not applicable; NR = not reported; pts = patients; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; Tx = treatment; WHO = World Health Organization; wk = week; yr = year

Table 36. Patient characteristics–fluphenazine versus risperidone

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Conley et al. 2005 ⁶⁷	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Single center Setting: Inpatient Country: USA Financial support: Multiple sources (Janssen)</p> <p>Washout period performed: NA Run-in phase performed: yes (4–6 wks) Followup period: 12 wks</p>	<p>Main inclusion criteria: Age 18–65yrs; Dx with Sz; medically healthy, considered treatment resistant; persistent positive psychotic symptoms (≥ 4 points on 2 of 4 psychosis items on BPRS); BPRS ≥ 45 pts; CGI–S ≥ 4; 2 failed Tx trials with 2 different APs; no stable period of good social/occupational functioning within the previous 5 yrs; non response to run-in Tx.</p> <p>Main exclusion criteria: NR</p>	<p>G1: Age (mean\pmSD): 44.20\pm8.80 Males (n(%)): 11/13 (84.6%) Ethnicity: Caucasian 7/13 (53.9%) BL symptom scores: BPRS (mean\pmSD): 54.69\pm13.67</p> <p>G2: Age (mean\pmSD): 43.70\pm5.90 Males (n(%)): 10/12 (83.3%) Ethnicity: Caucasian 6/12 (50%) BL symptom scores: BPRS (mean\pmSD): 53.5\pm7.37</p> <p>G3: Age (mean\pmSD): 46.30\pm8.70 Males (n(%)): 9/13 (69.2%) Ethnicity: Caucasian 7/13 (53.9%) BL symptom scores: BPRS (mean\pmSD): 56\pm14.08</p>	<p>G1: Classification: FGA Drug: Fluphenazine Dosage: 10–15mg/d</p> <p>G2: Classification: SGA Drug: Quetiapine Dosage: 300–500mg/d</p> <p>G3: Classification: SGA Drug: Risperidone Dosage: 3–5mg/d</p>

AP = antipsychotic; BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; Dx = Diagnosis; FGA = first-generation antipsychotic; mg = milligram; n = number; NA = not applicable; NR = not reported; pts = patients; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; Tx = treatment; wk = week; yr = year

Table 37. Patient characteristics—haloperidol versus aripiprazole

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Andrezina et al. 2006 ⁴⁴	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: Dec 2003 to Jun 2004 Number of centers: Multicenter (n = 68) Setting: Inpatient Country: USA, Czech Republic, France, Estonia, Latvia, Poland, Croatia, Italy, Puerto Rico, South Africa, and Spain Financial support: Industry (Bristol–Myers Squibb, Otsuka)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 24h</p>	<p>Main inclusion criteria: Pts (18 yrs or older) experiencing acute agitation and Dx of Sz or schizoaffective disorder (DSM–IV); PEC scores >15 and <32; score of >4 on at least two of the five PEC items.</p> <p>Main exclusion criteria: Dx of schizophreniform disorder or other psychiatric Dx; Pts with significant risk of suicide; clinically significant neurologic diagnoses; Hx of seizures; Hx of abnormal EEG, severe head trauma, or stroke or evidence of other unstable medical conditions; substance or alcohol dependence within 2 months before the study; suspected substance–induced psychiatric disorder or behavioral disturbance; Hx of neuroleptic malignant syndrome from antipsychotic agents; use of benzodiazepines or anticholinergics within 4 h before the first injection of study medication; and lack of response to previous antipsychotic medication</p>	<p>G1: Age (mean±SD): 41.80±NR Males (n(%)): 59/185 (31.89%) Ethnicity: Caucasian 61/185 (33%) BL symptom scores: NR</p> <p>G2: Age (mean±SD): 41.90±NR Males (n(%)): 63/175 (36%) Ethnicity: Caucasian 70/175 (40%) BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 6.5mg Intervals: every 2 hrs (max 3/d)</p> <p>G2: Classification: SGA Drug: Aripiprazole Dosage: 9.75mg Intervals: every 2 hrs (max 3/d)</p>

Table 37. Patient characteristics—haloperidol versus aripiprazole (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Daniel et al. 2007 ⁷⁴	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Multicenter Setting: Inpatient Country: USA Financial support: Industry (Bristol–Myers Squibb)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 5 d</p>	<p>Main inclusion criteria: Acutely agitated Pts (18–69 yrs) with Sz or schizoaffective disorder (DSM–IV) and confirmed by the MINI; PEC = 15–32, greater than 4 on at least 2 PEC items Main exclusion criteria: Pts with Axis I (DSM–IV) Dx of schizophreniform disorder, Dx other than Sz or schizoaffective disorder requiring pharmacotherapy or suicidal; Hx of seizure or other neurologic disorders or abnormal EEG or other significant medical Hx; substance dependence/abuse; clinically significant lab value or baseline ECG findings; Hx of hypersensitivity to AP; need or potential need for St. John's Wort, carbamazepine, rifampicin, phenytoin, or ECT or use 2 wks prior to the trial; use of benzodiazepines within 4 hrs prior to the study; nonresponse to previous AP; need for restraints; pregnant/lactating women</p>	<p>G1: Age (mean±SD): 41.80±NR Males (n(%)): 110/185 (59.5%) Ethnicity: Caucasian 113/185 (61.1%) BL symptom scores: NR</p> <p>G2: Age (mean±SD): 41.90±NR Males (n(%)): 110/ 175 (62.9%) Ethnicity: Caucasian 122/175 (69.7%) BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 6.5mg/d Intervals: max 3 inj every 2 hrs</p> <p>G2: Classification: SGA Drug: Aripiprazole Dosage: 9.75mg/d Intervals: max 3 inj every 2 hrs</p>

Table 37. Patient characteristics—haloperidol versus aripiprazole (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
de Oliveira et al. 2009 ⁷⁶	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: Jul–03 to Mar–05 Number of centers: Multicenter (n = 10) Setting: Outpatient Country: Brazil Financial support: Industry (Bristol–Myers Squibb)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 8 wks</p>	<p>Main inclusion criteria: Pts (18–65 yrs) with Sz or schizoaffective disorder (DSM–IV–TR); PANSS (total) score >60 Main exclusion criteria: Clinically significant organic or neurologic disorders; epilepsy; psychiatric disorders other than Sz and schizoaffective disorder; Hx of alcohol/drug abuse in the previous 3 months; participated in trials using investigational drugs over the last 12 months; pregnant/nursing mothers and those of childbearing potential without adequate contraceptive methods</p>	<p>G1: Age (mean±SD): 34.20±9.70 Males (n(%)): 21/33 (63.6%) Ethnicity: Caucasian 15/33 (45.5%) BL symptom scores: CGI-BP (mean±SD): 4.7±0.75 PANSS (mean±SD): 85.1±14.9</p> <p>G2: Age (mean±SD): 34.50±13.20 Males (n(%)): 33/ 66 (50%) Ethnicity: Caucasian 37/66 (56.1%) BL symptom scores: CGI-BP (mean±SD): 4.85±0.92 PANSS (mean±SD): 87.7±15.3</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 10–15mg/d Intervals: Once daily</p> <p>G2: Classification: SGA Drug: Aripiprazole Dosage: 15–30mg/d Intervals: Once daily</p>

Table 37. Patient characteristics—haloperidol versus aripiprazole (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Kane et al. 2002 ⁹²	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: Jul–97 to Jun–98 Number of centers: Multicenter (n = 36) Setting: Inpatient Country: USA Financial support: Industry (Bristol–Myers Squibb and Otsuka)</p> <p>Washout period performed: yes (<1 wks) Run-in phase performed: no Followup period: 4 wks</p>	<p>Main inclusion criteria: Age (18–65) Dx Sz, or Sz–affective according to DSM–IV; not refractory to antipsychotics, had improvement with agents besides clozapine; outpatient for at least one 3–month period in last yr Main exclusion criteria: Psychotic disorder other than schizophrenia or schizoaffective disorder, Hx of violence, suicidal attempts, serious suicidal ideation, a clinically significant neurologic abnormality other than tardive dyskinesia or EPS, drug abuse or dependence. Tx with investigational drug in last month.</p>	<p>G1: Age (mean±SD): 38.90±9.18 Males (n(%)): 68/104 (65.4%) Ethnicity: NR BL symptom scores: PANSS (mean±SD): 99.3±17.34</p> <p>G2: Age (mean±SD): 37.80±10.10 Males (n(%)): 76/102 (74.5%) Ethnicity: NR BL symptom scores: PANSS (mean±SD): 98.5±17.17</p> <p>G3: Age (mean±SD): 39.30±10.10 Males (n(%)): 70/102 (68.6%) Ethnicity: NR BL symptom scores: PANSS (mean±SD): 99±19.19</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 10mg/d Intervals: once daily</p> <p>G2: Classification: SGA Drug: Aripiprazole Dosage: 15mg/d Intervals: once daily</p> <p>G3: Classification: SGA Drug: Aripiprazole Dosage: 30mg/d Intervals: once daily</p>

Table 37. Patient characteristics—haloperidol versus aripiprazole (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Kasper et al. 2003 ⁹⁸	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Multicenter (n = 133) Setting: NR Country: Austria Financial support: Bristol–Myers Squibb</p> <p>Washout period performed: yes (5 days) Run-in phase performed: no Followup period: 52 wks</p>	<p>Main inclusion criteria: Experiencing an acute relapse; Hx of previous response to antipsychotic medication (other than clozapine) and not considered refractory to typical antipsychotic medication Main exclusion criteria: initial episode of schizophrenia, currently or recently (<1 month)</p>	<p>G1: Age (mean±SD): 36.80±0.40 Males (n(%)): 247/433 (57.0%) Ethnicity: NR BL symptom scores: NR</p> <p>G2: Age (mean±SD): 36.80±0.50 Males (n(%)): 511/861 (59.3%) Ethnicity: NR BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 5–10mg Intervals: once daily</p> <p>G2: Classification: SGA Drug: Aripiprazole Dosage: 20–30mg Intervals: once daily</p>

Table 37. Patient characteristics—haloperidol versus aripiprazole (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Kim et al. 2010 ¹⁰²	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: NR Study period: NR Number of centers: Two—center Setting: Outpatient Country: South Korea Financial support: Other (Choi Shine Hae 2008–2009)</p> <p>Washout period performed: yes (>4wks) Run-in phase performed: no Followup period: 8 wks</p>	<p>Main inclusion criteria: Patients with schizophrenia, aged 20–64 yrs, attending outpatient departments at two sites in Korea; all participants were smokers; clinically stable, with no changes in their antipsychotic medication prescriptions Main exclusion criteria: NR</p>	<p>G1: Age (mean±SD): 42.50±8.70 Males (n(%)): 25/35 (71.4%) Ethnicity: NR BL symptom scores: NR</p> <p>G2: Age (mean±SD): 37.10±4.80 Males (n(%)): 23/31 (74.2%) Ethnicity: NR BL symptom scores: NR</p> <p>G3: Age (mean±SD): 41.80±11.40 Males (n(%)): 23/32 (71.9%) Ethnicity: NR BL symptom scores: NR</p> <p>G4: Age (mean±SD): 39.90±12.80 Males (n(%)): 28/41 (68.3%) Ethnicity: NR BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 15.9+/-7.1mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Aripiprazole Dosage: 21.7+/-5.5 mg/d Intervals: NR</p> <p>G3: Classification: SGA Drug: Olanzapine Dosage: 15.9+/-4.3mg/d Intervals: NR</p> <p>G4: Classification: SGA Drug: Risperidone Dosage: 4.8+/-2.9mg/d Intervals: NR</p>

Table 37. Patient characteristics—haloperidol versus aripiprazole (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
McCue et al. 2006 ⁷³	<p>Study design: Randomized controlled trial</p> <p>Registration #: NR</p> <p>Study population: Schizophrenia</p> <p>DSM Classification: DSM IV</p> <p>Study period: Jan 2004 to Feb 2005</p> <p>Number of centers: Single center</p> <p>Setting: Inpatient</p> <p>Country: USA</p> <p>Financial support: NR</p> <p>Trial characteristics:</p> <p>Washout period performed: NA</p> <p>Run-in phase performed: no</p> <p>Followup period: 3 wks</p>	<p>Main inclusion criteria: Pts (≥ 18 yrs) newly admitted for Sz, schizoaffective disorder or schizophreniform disorder</p> <p>Main exclusion criteria: Pregnant/lactating women; medical condition in which pharmacotherapy would prove a significant clinical risk; Hx of response or lack of response to AP; Dx of BP, major depressive disorder, substance-induced psychotic disorder</p>	<p>G1:</p> <p>Age (mean\pmSD): 37.50\pm10.80</p> <p>Males (n(%)): 42/57 (73.7%)</p> <p>Ethnicity: NR</p> <p>BL symptom scores: BPRS (mean\pmSD): 42\pm11.3</p> <p>G2:</p> <p>Age (mean\pmSD): 40.50\pm12.60</p> <p>Males (n(%)): 27/ 53 (51.0%)</p> <p>Ethnicity: NR</p> <p>BL symptom scores: BPRS (mean\pmSD): 41.3\pm10.2</p>	<p>G1:</p> <p>Classification: FGA</p> <p>Intervention: Haloperidol</p> <p>Dosage: 4-30mg</p> <p>Intervals: NR</p> <p>G2:</p> <p>Classification: SGA</p> <p>Intervention: Aripiprazole</p> <p>Dosage: 10-45mg</p> <p>Intervals: NR</p>

Table 37. Patient characteristics—haloperidol versus aripiprazole (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Tran-Johnson et al. 2007 ³¹	<p>Study design: RCT Registration #: NCT00036127 Study population: Schizophrenia DSM Classification: DSM IV Study period: Apr–02 to Jan–03 Number of centers: Multicenter (n = 50) Setting: NR Country: USA and 20 others Financial support: Industry (Bristol–Meyers Squibb Co., Otsuka Inc)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 24 h</p>	<p>Main inclusion criteria: Symptoms of acute agitation; Dx with Sz, schizoaffective disorder, or schizophreniform disorder; PANSS–PEC score 15 and 32; moderate score on 2/5 PEC items; 18 yrs; appropriate for IM Tx for acute agitation</p> <p>Main exclusion criteria: Pts who had psychoactive substance dependence within 2 months of study start; required involuntary restraint; were suicidal; had a neurologic or psychiatric condition other than Sz, schizoaffective disorder, or schizophreniform disorder; had a significant medical condition; were known nonresponders to antipsychotic medication</p>	<p>G1: Age (mean±SD): 40.85±10.16 Males (n(%)): 39/60 (65%) Ethnicity: Caucasian 43/60 (71.7%) BL symptom scores: BPRS (mean±SD): 58.93±NR</p> <p>G2: Age (mean±SD): 41.46±10.12 Males (n(%)): 37/57 (64.9%) Ethnicity: Caucasian 39/57 (68.4%) BL symptom scores: BPRS (mean±SD): 57.79±NR</p> <p>G3: Age (mean±SD): 39.46±10.19 Males (n(%)): 35/63 (55.6%) Ethnicity: Caucasian 47/63 (74.6%) BL symptom scores: BPRS (mean±SD): 57.03±NR</p> <p>G4: Age (mean±SD): 41.18±10.88 Males (n(%)): 36/57 (63.2%) Ethnicity: Caucasian 41/57 (71.9%) BL symptom scores: BPRS (mean±SD): 58.66±NR</p> <p>G5: Age (mean±SD):</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 7.5mg/d Intervals: 2–20 hrs</p> <p>G2: Classification: SGA Drug: Aripiprazole Dosage: 1mg/d Intervals: 2–20 hrs</p> <p>G3: Classification: SGA Drug: Aripiprazole Dosage: 5.25mg/d Intervals: 2–20 hrs</p> <p>G4: Classification: SGA Drug: Aripiprazole Dosage: 9.75mg/d Intervals: 2–20 hrs</p> <p>G5: Classification: SGA Drug: Aripiprazole Dosage: 15mg/d Intervals: 2–20 hrs</p>

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
			44.24±9.96 Males (n(%)): 35/ 58 (60.3%) Ethnicity: Caucasian 40/58 (69%) BL symptom scores: BPRS (mean±SD): 58.16±NR	

AP = antipsychotic; BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; Dx = Diagnosis; ECG = Electrocardiography; ECT = Electroconvulsive therapy; EEG = Electroencephalography; EPS = Extrapyrarnidal symptoms; FGA = first-generation antipsychotic; hr = hour; inj = injection; mg = milligram; n = number; NA = not applicable; NR = not reported; PANSS = Positive and Negative Syndrome Scale; PEC = Positive excitement component; pts = patients; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; Tx = treatment; wk = week; yr = year

Table 38. Patient characteristics—haloperidol versus asenapine

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Kane et al. 2010 ⁹⁷	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: Jun 2005 to Sep 2006 Number of centers: Multicenter (n = 43) Setting: Mixed Country: USA, Canada, Russia, India, Romania, Croatia Financial support: Industry (Schering-Plough)</p> <p>Washout period performed: yes (1–3d) Run-in phase performed: no Followup period: 6 wks</p>	<p>Main inclusion criteria: At least 18 Yrs; DSM–IV Sz with acute exacerbation of psychotic symptoms; PANSS score ≥ 60; scores ≥ 4 on 2 of 5 predefined PANSS pos subscale items (delusions, conceptual disorganization, hallucinatory behavior, grandiosity, and suspiciousness/persecution); CGI–S score ≥ 4.</p> <p>Main exclusion criteria: Clinically significant medical condition or abnormal laboratory or physical examination findings; Dx of residual–type Sz, schizoaffective disorder, or coexisting psychiatric disorder coded on Axis I; current or past substance abuse; 20% or higher decrease in PANSS total score from screening to baseline; known allergy or sensitivity to haloperidol; imminent risk of self–harm or harm to others; and previous participation in an asenapine trial.</p>	<p>G1: Age (mean\pmSD): NR Males (n(%)): NR Ethnicity: NR BL symptom scores: NR</p> <p>G2: Age (mean\pmSD): NR Males (n(%)): NR Ethnicity: NR BL symptom scores: NR</p> <p>G3: Age (mean\pmSD): NR Males (n(%)): NR Ethnicity: NR BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 4mg/d Intervals: BID</p> <p>G2: Classification: SGA Drug: Asenapine Dosage: 5mg/d Intervals: BID</p> <p>G3: Classification: SGA Drug: Asenapine Dosage: 10mg/d Intervals: BID</p>

AP = antipsychotic; BID = Twice daily; BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; FGA = first-generation antipsychotic; mg = milligram; n = number; NR = not reported; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; Tx = treatment; wk = week; yr = year

Table 39. Patient characteristics—haloperidol versus clozapine

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Breier et al. 1994 ⁵⁵	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM–III–R Study period: NR Number of centers: Single center Setting: Outpatient Country: USA Financial support: Government</p> <p>Washout period performed: NA Run-in phase performed: yes (6 wks) Followup period: 10 wks</p>	<p>Main inclusion criteria: Pts (18–55 yrs) chronic Sz (DSM–III–R) who had not responded to a 6–week trial of fluphenazine Main exclusion criteria: Concurrent drug/alcohol abuse, organic brain disorders, mental retardation, or a medical condition that contraindicates clozapine use</p>	<p>G1: Age (mean±SD): 35.00±8.00 Males (n(%)): 15/20 (75%) Ethnicity: Caucasian 14/20 (70%) BL symptom scores: BPRS (mean±SD): 38.1±8.2</p> <p>G2: Age (mean±SD): 34.00±6.00 Males (n(%)): 13/19 (68.4%) Ethnicity: Caucasian 15/19 (79%) BL symptom scores: BPRS (mean±SD): 36.7±10.6</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 10–30mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Clozapine Dosage: 200–600mg/d Intervals: NR</p>

Table 39. Patient characteristics—haloperidol versus clozapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Citrome et al. 2001 ⁶²	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: 1996 to 2000 Number of centers: Multicenter (n = 4) Setting: Inpatient Country: USA Financial support: Multiple sources (Janssen, Eli Lilly, Novartis, Merck)</p> <p>Washout period performed: NA Run-in phase performed: yes (1 wk) Followup period: 14 wks</p>	<p>Main inclusion criteria: Pts with Sz (18–60 yrs); Hx of suboptimal treatment response; PANSS minimum score of 60; persistent positive symptoms after six wks with one or more conventional antipsychotics (600 mg chlorpromazine equivalent or more); poor level of functioning over past two yrs Main exclusion criteria: Hx of not responding to clozapine, risperidone, or olanzapine; Hx of intolerance to any of the study drugs; receipt of depot AP during last 30 d</p>	<p>G1: Age (mean±SD): 40.80±9.20 Males (n(%)): 31/37 (83.8%) Ethnicity: Caucasian 11/37 (29.7%) BL symptom scores: NR</p> <p>G2: Age (mean±SD): 40.80±9.20 Males (n(%)): 34/40 (85%) Ethnicity: Caucasian 12/40 (30%) BL symptom scores: NR</p> <p>G3: Age (mean±SD): 40.80±9.20 Males (n(%)): 33/39 (84.6%) Ethnicity: Caucasian 12/39 (30.8%) BL symptom scores: NR</p> <p>G4: Age (mean±SD): 40.80±9.20 Males (n(%)): 35/41 (85.4%) Ethnicity: Caucasian 13/41 (31.7%) BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 10–30mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Clozapine Dosage: 200–800mg/d Intervals: NR</p> <p>G3: Classification: SGA Drug: Olanzapine Dosage: 10–40mg/d Intervals: NR</p> <p>G4: Classification: SGA Drug: Risperidone Dosage: 4–16mg/d Intervals: NR</p>

Table 39. Patient characteristics—haloperidol versus clozapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Covington et al. 2000 ⁷⁰	Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM–III–R Study period: NR Number of centers: Single center Setting: Unclear Country: USA Financial support: Government Washout period performed: yes (NA) Run-in phase performed: no Followup period: 24 mo	Main inclusion criteria: Pts with Sz or schizoaffective disorder (DSM–III–R) Main exclusion criteria: NR	G1: Age (mean±SD): 24.10±5.05 Males (n(%)): 34/42 (81%) Ethnicity: NR BL symptom scores: NR G2: Age (mean±SD): 25.30±5.65 Males (n(%)): 27/40 (67.5%) Ethnicity: NR BL symptom scores: NR	G1: Classification: FGA Drug: Haloperidol Dosage: NR Intervals: NR G2: Classification: SGA Drug: Clozapine Dosage: NR Intervals: NR
Gaszner et al. 2004 ¹⁶²	Study design: Retrospective cohort study Registration #: NR Study population: Schizophrenia DSM Classification: DSM–IV–TR Study period: 1980 to 2002 Number of centers: Single center Setting: NR Country: Hungary Financial support: NR Washout period performed: NA Run-in phase performed: no Followup period: 22 yrs	Main inclusion criteria: Pts with Sz (DSM–IV–TR); Clozapine Tx ≥1 yr Main exclusion criteria: NR	G1: Age (mean±SD): 43.10±4.00 Males (n(%)): 55/152(36.1%) Ethnicity: NR BL symptom scores: NR G2: Age (mean±SD): 42.40±7.44 Males (n(%)): 72/181 (39.8%) Ethnicity: NR BL symptom scores: NR	G1: Classification: FGA Drug: Haloperidol Dosage: 1.5–4.5mg/d Intervals: Once daily G2: Classification: SGA Drug: Clozapine Dosage: 50–200mg/d Intervals: Once daily

Table 39. Patient characteristics—haloperidol versus clozapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Hennessy et al. 2002 ¹⁶³	<p>Study design: Retrospective cohort study</p> <p>Registration #: NR</p> <p>Study population: Schizophrenia</p> <p>DSM Classification: NR</p> <p>Study period: 1993 to 1996</p> <p>Number of centers: Multicenter</p> <p>Setting: outpatient</p> <p>Country: USA</p> <p>Financial support: Industry (Pfizer)</p> <p>Washout period performed: NA</p> <p>Run-in phase performed: no</p> <p>Followup period: Until end of prescription duration</p>	<p>Main inclusion criteria: Individuals with more >1 prescription for oral thioridazine, haloperidol, risperidone, or clozapine plus at least 2 instances of a Sz Dx</p> <p>Main exclusion criteria: NR</p>	<p>G1: Age (mean±SD): NR Males (n(%)): NR Ethnicity: NR BL symptom scores: NR</p> <p>G2: Age (mean±SD): NR Males (n(%)): NR Ethnicity: NR BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: NR Intervals: NR</p> <p>G2: Classification: SGA Drug: Clozapine Dosage: NR Intervals: NR</p>
Itoh et al. 1977 ¹⁵⁵	<p>Study design: RCT</p> <p>Registration #: NR</p> <p>Study population: Schizophrenia</p> <p>DSM Classification: NR</p> <p>Study period: NR</p> <p>Number of centers: Multicenter (n = 7)</p> <p>Setting: Inpatient</p> <p>Country: Japan</p> <p>Financial support: Unclear (NR)</p> <p>Washout period performed: NA</p> <p>Run-in phase performed: no</p> <p>Followup period: 12 wks</p>	<p>Main inclusion criteria: Sz pts</p> <p>Main exclusion criteria: NR</p>	<p>G1: Age (mean±SD): NR Males (n(%)): NR Ethnicity: NR BL symptom scores: NR</p> <p>G2: Age (mean±SD): NR Males (n(%)): NR Ethnicity: NR BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 2.25–15mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Clozapine Dosage: 75–500mg/d Intervals: NR</p>

Table 39. Patient characteristics—haloperidol versus clozapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Kane et al. 2001 ⁹⁵	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM–III–R Study period: NR Number of centers: Multicenter (n = 3) Setting: Mixed Country: USA Financial support: Multiple sources (Novartis)</p> <p>Washout period performed: NA Run-in phase performed: yes Followup period: 29 wks</p>	<p>Main inclusion criteria: DSM–III–R Dx of Sz or schizoaffective disorder, 20–55 yrs of age, and living in the community or judged clinically treatable in the community; partial or poor response was defined by documented treatment failure in 2 trials of conventional antipsychotics at dosages equivalent to or greater than chlorpromazine hydrochloride, 600mg/d, for at least 6 wks (high-dose qualification) and 1 trial of a conventional agent at dosages equivalent to chlorpromazine hydrochloride, 250–500mg/d, for the same length of time (low-dose qualification).</p> <p>Main exclusion criteria: Use psychotropic medication therapy other than antipsychotics (eg, antidepressants or mood stabilizers) that could not be discontinued, documented Hx of intolerance to haloperidol at dosages of 4mg/d or more because of disabling extrapyramidal adverse effects, Dx of neuroleptic malignant syndrome with recurrence on rechallenge, evidence that refractoriness was related to medication noncompliance, organic brain disease (eg, epilepsy or brain tumor), mental retardation that precluded understanding study participation or assessment procedures, chronic medical illness that made study participation inappropriate, DSM–III–R diagnosis of substance abuse or dependence within 6 months, current treatment with medication(s) for other medical</p>	<p>G1: Age (mean±SD): 40.00±8.00 Males (n(%)): 24/34 (70.6%) Ethnicity: Caucasian 24/34 (70.6%) BL symptom scores: BPRS (mean±SD): 44.7±9.3</p> <p>G2: Age (mean±SD): 41.00±10.00 Males (n(%)): 26/37 (70.3%) Ethnicity: Caucasian 25/37 (67.6%) BL symptom scores: BPRS (mean±SD): 47.4±10.3</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 5–16mg/d Interval: NR</p> <p>G2: Classification: SGA Drug: Clozapine Dosage: 12.5–800mg/d Interval: NR</p>

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
		conditions that may have psychotropic effects or agranulocytosis risk or may interfere with drug absorption or metabolism, total white blood cell count below 3.5_103/ μ L (3500/mm ³), and pregnancy		
Kleiser et al. 1994 ¹⁰³	Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM III Study period: NR Number of centers: Single center Setting: Unclear Country: Germany Financial support: NR Washout period performed: NA Run-in phase performed: no Followup period: 4 wks	Main inclusion criteria: Pts who had not received any neuroleptic pretreatment suffering from an acute Sz paranoid type (ICD-9 295.3) Main exclusion criteria: NR	G1: Age (mean\pmSD): 33.70 \pm 9.70 Males (n(%)): 7/17 (41.2%) Ethnicity: NR BL symptom scores: BPRS (mean \pm SD): 55 \pm 12 G2: Age (mean\pmSD): 31.10 \pm 11.10 Males (n(%)): 6/17 (35.3%) Ethnicity: NR BL symptom scores: BPRS (mean \pm SD): 58 \pm 10	G1: Classification: FGA Drug: Haloperidol Dosage: 16mg/d Intervals: NR G2: Classification: SGA Drug: Clozapine Dosage: 350mg/d Intervals: NR Dosage: 10-35mg/d

Table 39. Patient characteristics—haloperidol versus clozapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Krakowski et al. 2006 ¹⁰⁵	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: Jun 1999 to Nov 2004 Number of centers: Multicenter (n = 2) Setting: Inpatient Country: USA Financial support: Multiple sources (Eli Lilly)</p> <p>Washout period performed: NA Run-in phase performed: yes (1–2 wks) Followup period: 12 wks</p>	<p>Main inclusion criteria: Aged 18–60 yrs and Dx with Sz or schizoaffective disorder using diagnostic criteria DSM–IV; patients were required to have a clearly confirmed episode of physical assault directed at another person during this hospitalization and some persistence of aggression, as evidenced by the presence of some other aggressive event, whether physical or verbal or against property.</p> <p>Main exclusion criteria: Hospitalized for more than a yr; if they had a Hx of nonresponse to clozapine, olanzapine, or haloperidol; if they had a history of clozapine, olanzapine, or haloperidol intolerance; or if they had medical conditions that would be adversely affected by any of these 3 medications; received a depot antipsychotic within 30 d before randomization</p>	<p>G1: Age (mean±SD): 32.70±10.60 Males (n(%)): 30/36 (83.3%) Ethnicity: Caucasian 7/36 (19.4%) BL symptom scores: PANSS (mean±SD): 85.5±13.2</p> <p>G2: Age (mean±SD): 35.10±12.30 Males (n(%)): 31/37 (83.8%) Ethnicity: Caucasian 7/37 (18.9%) BL symptom scores: PANSS (mean±SD): 86.4±14.4</p> <p>G3: Age (mean±SD): 35.60±9.40 Males (n(%)): 29/37 (78.4%) Ethnicity: Caucasian 5/37 (13.5%) BL symptom scores: PANSS (mean±SD): 83.7±14.1</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 10–30mg/d Interval: NR</p> <p>G2: Classification: SGA Drug: Clozapine Dosage: 200–800mg/d Interval: NR</p> <p>G3: Classification: SGA Drug: Olanzapine Dosage: 10–35mg/d Interval: NR</p>

Table 39. Patient characteristics—haloperidol versus clozapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Rosenheck et al. 1997 ¹²⁶	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM–III–R Study period: Mar 1993 to Apr 1995 Number of centers: Multicenter (n = 15) Setting: Inpatient Country: USA Financial support: Multiple sources (Sandoz)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 12 mo</p>	<p>Main inclusion criteria: The study targeted Pts with Sz refractory to Tx and a Hx of a high level of use of inpatient services, defined as 30 to 364 d of hospitalization for schizophrenia during the previous yr; clinical eligibility criteria consisted of a Dx of Sz, as defined in the (DSM–IIIR)</p> <p>Main exclusion criteria: Unable to give informed consent, had been treated previously with clozapine, had a current myeloproliferative disorder, pregnant</p>	<p>G1: Age (mean±SD): 43.90±8.30 Males (n(%)): 211/218 (96.8%) Ethnicity: Caucasian 145/218 (66.5%) BL symptom scores: PANSS (mean±SD): 92.2±14.5</p> <p>G2: Age (mean±SD): 43.20±7.70 Males (n(%)): 202/205 (98.5%) Ethnicity: Caucasian 135/205 (65.9) BL symptom scores: PANSS (mean±SD): 91±14.9</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 5 to 30mg/d Interval: NR</p> <p>G2: Classification: SGA Drug: Clozapine Dosage: 100 to 900mg/d Interval: NR</p>

Table 39. Patient characteristics—haloperidol versus clozapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Volakva et al. 2002 ¹⁴⁵	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: June 1996 to NR Number of centers: Multicenter (n = 4) Setting: Inpatient Country: USA Financial support: Multiple sources (Janssen, Eli Lilly, Novartis, Merck)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 14 wks</p>	<p>Main inclusion criteria: Dx of DSM–IV chronic Sz or schizoaffective disorder and suboptimal response to previous treatment, which was defined by two criteria that needed to be present (persistent positive symptoms after at least 6 contiguous wks of treatment, presently or documented in the past, with one or more typical antipsychotics at doses =600 mg/d in chlorpromazine equivalents, and poor level of functioning over the past 2 yrs, defined by the lack of competitive employment or enrollment in an academic or vocational program and not having age–expected interpersonal relations with someone outside the biological family of origin with whom ongoing regular contacts were maintained), a baseline total score =60 on the PANSS</p> <p>Main exclusion criteria: A Hx of nonresponse to clozapine, risperidone, or olanzapine, defined as an unambiguous lack of improvement despite a contiguous adequate trial of risperidone or olanzapine for at least 6 wks, or clozapine for at least 14 wks, a history of clozapine, olanzapine, risperidone, or haloperidol intolerance as well as those who received a depot antipsychotic within 30 d before randomization</p>	<p>G1: Age (mean±SD): 40.80±9.20 Males (n(%)): 133/167 (79.6%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 90.4±11.6</p> <p>G2: Age (mean±SD): 40.80±9.20 Males (n(%)): 133/167 (79.6%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 97.6±17.1</p> <p>G3: Age (mean±SD): 40.80±9.20 Males (n(%)): 133/167 (79.6%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 91±13.5</p> <p>G4: Age (mean±SD): 40.80±9.20 Males (n(%)): 133/167 (79.6%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 89.5±13.8</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 10–30mg/d Intervals: BID</p> <p>G2: Classification: SGA Drug: Clozapine Dosage: 200–800mg/d Intervals: BID</p> <p>G3: Classification: SGA Drug: Olanzapine Dosage: 10–40mg/d Intervals: BID</p> <p>G4: Classification: SGA Drug: Risperidone Dosage: 4–16mg/d Intervals: BID</p>

AP = antipsychotic; BID = Twice daily; BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; DX = diagnosis; FGA = first-generation antipsychotic; Hx = history; mg = milligram; n = number; NA = not applicable; NR = not reported; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; Tx = treatment; wk = week; yr = year

Table 40. Patient characteristics—haloperidol versus olanzapine

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Altamura et al. 2002 ⁴³	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Multicenter Setting: NR Country: Italy Financial support: Industry (Eli Lilly)</p> <p>Washout period performed: yes (1 wk) Run-in phase performed: no Followup period: 14 wks</p>	<p>Main inclusion criteria: Dx of paranoid Sz who showed partial response to neuroleptics after ≥6wks of doses of different classes. Main exclusion criteria: NR</p>	<p>G1: Age (mean±SD): 38.30±8.00 Males (n(%)): 7/11 (63.6%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 50.5±14.4</p> <p>G2: Age (mean±SD): 39.30±12.40 Males (n(%)): 6/13 (46.2%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 61.4±15</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 10–20mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 10–20mg/d Intervals: NR</p>
Alvarez–Jimenez et al. 2006 ¹⁴²	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Single center Setting: Mixed Country: Spain Financial support: Foundation</p> <p>Washout period performed: yes (3–5 d) Run-in phase performed: no Followup period: 3 mo</p>	<p>Main inclusion criteria: aged 15–60 yrs; DSM–IV criteria for Sz, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief reactive psychosis, or psychosis not otherwise specified; lived in the catchment area; and provided written informed consent; pts were experiencing their first episode of psychosis and had not received more than 6 wks of adequate neuroleptic Tx Main exclusion criteria: A Hx of neurologic disease, head injury, mental retardation (DSM–IV criteria), or drug dependence (DSM–IV criteria)</p>	<p>G1: Age (mean±SD): 26.80±7.70 Males (n(%)): 46/61 (75.4%) Ethnicity: NR BL symptom scores: NR</p> <p>G2: Age (mean±SD): 26.80±7.70 Males (n(%)): 46/61 (75.4%) Ethnicity: NR BL symptom scores: NR</p> <p>G3: Age (mean±SD): 26.80±7.70 Males (n(%)): 46/61 (75.4%) Ethnicity: NR BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 3 to 9mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 5–20mg/d Intervals: NR</p> <p>G3: Classification: SGA Drug: Risperidone Dosage: 3–6mg/d Intervals: NR</p>

Table 40. Patient characteristics—haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Avasthi et al. 2001 ¹⁵⁹	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Single center Setting: Mixed Country: India Financial support: Industry (Eli Lilly)</p> <p>Washout period performed: no Run-in phase performed: no Followup period: 3 mo</p>	<p>Main inclusion criteria: Male or female aged 18–65 yrs; Dx with Sz; CGI–S score ≥ 3 Main exclusion criteria: Positive for hepatitis surface antigen (HBs Ag), IgM fraction of the hepatitis core antibody (anti–HBcIgMD or had jaundice, current agranulocytosis (absolute neutrophil count < 500 mm³)</p>	<p>G1: Age (mean\pmSD): NR Males (n(%)): NR Ethnicity: NR BL symptom scores: BPRS (mean\pmSD): 25.00\pm4.56</p> <p>G2: Age (mean\pmSD): NR Males (n(%)): NR Ethnicity: NR BL symptom scores: BPRS (mean\pmSD): 23.31\pm9.94</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 5 to 20mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 5–20mg/d Intervals: NR</p>

Table 40. Patient characteristics—haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Beasley et al. 1996 ⁴⁹	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM–III–R Study period: 1991 to 1993 Number of centers: Multicenter (n = 22) Setting: Mixed Country: USA, Canada Financial support: Industry (Eli Lilly)</p> <p>Washout period performed: yes (variable depending on medication) Run-in phase performed: yes (≤1 wk) Followup period: 1 yr</p>	<p>Main inclusion criteria: Pts with Sz with acute exacerbation; BPRS score at least 24 Main exclusion criteria: Organic mental disorders; substance abuse; suicidal risk; unstable mental illnesses; Parkinson disease; myasthenia gravis; illness contraindicating use of anticholinergics; Hx of seizures, leukopenia or abnormal liver function; placebo responders</p>	<p>G1: Age (mean±SD): 36.00±9.00 Males (n(%)): 62/69 (89.9%) Ethnicity: Caucasian 40/69 (58%) BL symptom scores: BPRS (mean±SD): 41.8±11.4</p> <p>G2: Age (mean±SD): 36.00±9.00 Males (n(%)): 60/65 (92.3%) Ethnicity: Caucasian 42/65 (64.6%) BL symptom scores: BPRS (mean±SD): 41.2±11.7</p> <p>G3: Age (mean±SD): 36.00±9.00 Males (n(%)): 56/64 (87.5%) Ethnicity: Caucasian 46/64 (71.9%) BL symptom scores: BPRS (mean±SD): 42.8±10</p> <p>G4: Age (mean±SD): 36.00±9.00 Males (n(%)): 54/69 (78.3%) Ethnicity: Caucasian 54/69 (78.3%) BL symptom scores: BPRS (mean±SD): 42.6±10.9</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 10–20mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 2.5–7.5mg/d Intervals: NR</p> <p>G3: Classification: SGA Drug: Olanzapine Dosage: 7.5–12.5mg/d Intervals: NR</p> <p>G4: Classification: SGA Drug: Olanzapine Dosage: 12.5–17.5mg/d Intervals: NR</p>

Table 40. Patient characteristics—haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Beasley et al. 1997 ⁵⁰	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM–III–R Study period: Nov–91 to Nov–93 Number of centers: Multicenter (n = 50) Setting: Inpatient Country: Europe, South Africa, Israel, Australia Financial support: Industry (Eli Lilly)</p> <p>Washout period performed: yes (≥2d for oral and ≥2wks for depot APs) Run-in phase performed: yes (4–7d) Followup period: 1 yr</p>	<p>Main inclusion criteria: Age 18–65 yrs; Dx with Sz and an acute exacerbation; BPRS total score ≥ 24; CGI_S ≥4 (moderate) Main exclusion criteria: DSM–III–R organic mental disorder or substance use disorder in last 3 mo.; at risk of suicide; had Parkinson's disease, myasthenia gravis, or unstable medical illness that contraindicated the use of anticholinergics; Hx of seizures or leukopenia; elevated liver function tests, active hepatitis B, or jaundice; placebo responder during run-in phase</p>	<p>G1: Age (mean±SD): 36.00±10.00 Males (n(%)): 48/81 (59.3%) Ethnicity: Caucasian 66/81 (81.5%) BL symptom scores: BPRS (mean±SD): 41.2±10.7 PANSS (mean±SD): 105.3±18.5</p> <p>G2: Age (mean±SD): 34.00±10.00 Males (n(%)): 58/88 (65.9%) Ethnicity: Caucasian 77/88 (87.5%) BL symptom scores: BPRS (mean±SD): 39.5±10.3 PANSS (mean±SD): 100.9±17.9</p> <p>G3: Age (mean±SD): 34.00±12.00 Males (n(%)): 57/87 (65.5%) Ethnicity: Caucasian 75/87 (86.2%) BL symptom scores: BPRS (mean±SD): 40.1±11.2 PANSS (mean±SD): 102.7±19.4</p> <p>G4: Age (mean±SD): 36.00±11.00 Males (n(%)): 55/86 (64%) Ethnicity: Caucasian 74/86 (86.1%)</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 15±5mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 1.0mg/d Intervals: NR</p> <p>G3: Classification: SGA Drug: Olanzapine Dosage: 5±2.5mg/d Intervals: NR</p> <p>G4: Classification: SGA Drug: Olanzapine Dosage: 10±2.5mg/d Intervals: NR</p> <p>G5: Classification: SGA Drug: Olanzapine Dosage: 15±2.5mg/d Intervals: NR</p>

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
			BL symptom scores: BPRS (mean±SD): 40.4±9.5 PANSS (mean±SD): 102.2±16.9 G5: Age (mean±SD): 36.00±11.00 Males (n(%)): 57/89 (64%) Ethnicity: Caucasian 80/89 (90%) BL symptom scores: BPRS (mean±SD): 42.3±10.9 PANSS (mean±SD): 105.6±18.9	

Table 40. Patient characteristics—haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Bernardo et al. 2001 ⁵¹	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Single center Setting: Inpatient Country: Spain Financial support: Industry (Lilly SA)</p> <p>Washout period performed: yes (1 wk) Run-in phase performed: no Followup period: 4 wks</p>	<p>Main inclusion criteria: Pts with Sz/schizophreniform disorder (DSM–IV) with acute psychosis Main exclusion criteria: Significant organic disorders; substance abuse; resistance to antipsychotics; treatment with depot neuroleptics in last 6 mo</p>	<p>G1: Age (mean±SD): 29.90±9.80 Males (n(%)): 10/13 (76.9%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 52.7±13.3 PANSS (mean±SD): 96.1±25.5</p> <p>G2: Age (mean±SD): 26.90±5.40 Males (n(%)): 7/14 (50%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 55.5±11.5 PANSS (mean±SD): 101.3±21</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 10mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 10mg/d Intervals: NR</p>
Boulay et al. 2007 ⁵⁴	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Single center Setting: Mixed Country: Canada Financial support: Industry (Eli Lilly)</p> <p>Washout period performed: yes (0.43 wks) Run-in phase performed: no Followup period: 56 d</p>	<p>Main inclusion criteria: Pts within 5 yrs of Sz Dx (DSM–IV); were in a medication transition phase; PANSS (total) between 60–100 Main exclusion criteria: Hx of seizure disorder, traumatic brain injury resulting in loss of consciousness; current alcohol/drug abuse; received depot neuroleptic treatment within past 6 months; developmentally delayed</p>	<p>G1: Age (mean±SD): 34.73±10.62 Males (n(%)): 8/11 (72.7%) Ethnicity: NR BL symptom scores: PANSS (mean±SD): 72.38±13.76</p> <p>G2: Age (mean±SD): 32.86±12.08 Males (n(%)): 10/14 (71.4%) Ethnicity: NR BL symptom scores: PANSS (mean±SD): 76.14±10.07</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 2.5–20mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 2.5–20mg/d Intervals: NR</p>

Table 40. Patient characteristics—haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Breier et al. 2002 ⁵⁶	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Multicenter (n = 14) Setting: Inpatient Country: Croatia, Italy, Romania, South Africa Financial support: Industry (Eli Lilly)</p> <p>Washout period performed: yes (2–24 hrs) Run-in phase performed: no Followup period: 24 hrs</p>	<p>Main inclusion criteria: Recently hospitalized pts (18 yrs and older); Dx of Sz, schizophreniform disorder, schizoaffective disorder; PANSS–EC score at least 14 with at least 4 on at least 1 item; acutely agitated and required parenteral AP Tx</p> <p>Main exclusion criteria: Significant medical disorders, including alcohol/drug dependency, unable to give consent and cooperate</p>	<p>G1: Age (mean±SD): 37.40±10.60 Males (n(%)): 22/40 (55%) Ethnicity: Caucasian 25/40 (62.5%) BL symptom scores: PANSS (mean±SD): 19.3±3.1</p> <p>G2: Age (mean±SD): 36.20±10.50 Males (n(%)): 31/48 (64.6%) Ethnicity: Caucasian 29/48 (60.42%) BL symptom scores: PANSS (mean±SD): 18.3±2.4</p> <p>G3: Age (mean±SD): 35.10±10.10 Males (n(%)): 27/45 (60%) Ethnicity: Caucasian 31/45 (68.9%) BL symptom scores: PANSS (mean±SD): 19.7±3.4</p> <p>G4: Age (mean±SD): 35.90±11.30 Males (n(%)): 26/46 (56.5%) Ethnicity: Caucasian 29/46 (63%) BL symptom scores: PANSS (mean±SD): 18.9±2.6</p> <p>G5: Age (mean±SD):</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 7.5mg Intervals: max 3 doses/d (every 2–4 hrs)</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 2.5mg Intervals: max 3 doses/d (every 2–4 hrs)</p> <p>G3: Classification: SGA Drug: Olanzapine Dosage: 5.0mg Intervals: max 3 doses/d (every 2–4 hrs)</p> <p>G4: Classification: SGA Drug: Olanzapine Dosage: 7.5mg Intervals: max 3 doses/d (every 2–4 hrs)</p> <p>G5: Classification: SGA Drug: Olanzapine Dosage: 10mg Intervals: max 3 doses/d (every 2–4 hrs)</p>

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
			36.70±12.10 Males (n(%)): 26/46 (56.5%) Ethnicity: Caucasian 32/46 (69.6%) BL symptom scores: PANSS (mean±SD): 19.3±2.6	

Table 40. Patient characteristics—haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Buchanan et al. 2005 ⁵⁸	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Single center Setting: Outpatient Country: USA Financial support: Multiple sources (Eli Lilly)</p> <p>Washout period performed: NA Run-in phase performed: yes (4 wks) Followup period: 16 wks</p>	<p>Main inclusion criteria: Pts with Sz/schizoaffective disorder with partial response to conventional APs; BPRS (positive) score at least 8 or score of at least 4 on any single item Main exclusion criteria: Concurrent drug/alcohol abuse; organic brain disorders/mental retardation; demonstrated at least 30% improvement on fluphenazine, relapsed or were intolerant of fluphenazine during run-in</p>	<p>G1: Age (mean±SD): 46.40±9.00 Males (n(%)): 24/34 (70.6%) Ethnicity: Caucasian 16/34 (47.1%) BL symptom scores: BPRS (mean±SD): 34.7±8.8</p> <p>G2: Age (mean±SD): 41.90±7.00 Males (n(%)): 22/29 (75.9%) Ethnicity: Caucasian 18/29 (62.1%) BL symptom scores: BPRS (mean±SD): 35.5±9.1</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 10–30mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 10–30mg/d Intervals: NR</p>

Table 40. Patient characteristics—haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Citrome et al. 2001 ⁶²	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: 1996 to 2000 Number of centers: Multicenter (n = 4) Setting: Inpatient Country: USA Financial support: Multiple sources (Janssen, Eli Lilly, Novartis, Merck)</p> <p>Washout period performed: NA Run-in phase performed: yes (1 wk) Followup period: 14 wks</p>	<p>Main inclusion criteria: Pts with Sz (18–60 yrs); Hx of suboptimal treatment response; PANSS minimum score of 60; persistent positive symptoms after six wks with one or more conventional antipsychotics (600 mg chlorpromazine equivalent or more); poor level of functioning over past two yrs Main exclusion criteria: Hx of not responding to clozapine, risperidone, or olanzapine; Hx of intolerance to any of the study drugs; receipt of depot AP during last 30 d</p>	<p>G1: Age (mean±SD): 40.80±9.20 Males (n(%)): 31/37 (83.8%) Ethnicity: Caucasian 11/37 (29.7%) BL symptom scores: NR</p> <p>G2: Age (mean±SD): 40.80±9.20 Males (n(%)): 34/40 (85%) Ethnicity: Caucasian 12/40 (30%) BL symptom scores: NR</p> <p>G3: Age (mean±SD): 40.80±9.20 Males (n(%)): 33/39 (84.6%) Ethnicity: Caucasian 12/39 (30.8%) BL symptom scores: NR</p> <p>G4: Age (mean±SD): 40.80±9.20 Males (n(%)): 35/41 (85.4%) Ethnicity: Caucasian 13/41 (31.7%) BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 10–30mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Clozapine Dosage: 200–800mg/d Intervals: NR</p> <p>G3: Classification: SGA Drug: Olanzapine Dosage: 10–40mg/d Intervals: NR</p> <p>G4: Classification: SGA Drug: Risperidone Dosage: 4–16mg/d Intervals: NR</p>

Table 40. Patient characteristics—haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Crespo-Facorro et al. 2006 ⁷¹	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: Feb-01 to Feb-05 Number of centers: Single center Setting: Mixed Country: Spain Financial support: Multiple sources (NR)</p> <p>Washout period performed: yes (3–5d) Run-in phase performed: no Followup period: 6 wks</p>	<p>Main inclusion criteria: Pts (15–60 yrs) with Sz (DSM-IV); no AP within 6 wks; SAPS of moderate severity Main exclusion criteria: Mental retardation; drug dependence</p>	<p>G1: Age (mean±SD): 28.30±8.70 Males (n(%)): 36/56 (64.3%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 62.4±10.9 YMRS (mean±SD): 9.3±4.3</p> <p>G2: Age (mean±SD): 27.50±6.90 Males (n(%)): 33/55 (60%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 59.9±12.1 YMRS (mean±SD): 9.2±4.7</p> <p>G3: Age (mean±SD): 26.10±7.60 Males (n(%)): 38/61 (62.3%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 56.8±10.3 YMRS (mean±SD): 8.8±4.8</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 3–9mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 5–20mg/d Intervals: NR</p> <p>G3: Classification: SGA Drug: Risperidone Dosage: 3–6mg/d Intervals: NR</p>

Table 40. Patient characteristics—haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Davidson et al. 2009 ⁷⁵	<p>Study design: RCT Registration #: ISRCTN68736636 Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Multicenter (n = 50) Setting: NR Country: 13 European countries and Israel Financial support: Industry (AstraZeneca, Pfizer, U.S. Group, and Sanofi)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 6 mo</p>	<p>Main inclusion criteria: recent onset of psychosis with <2 yrs between the onset of positive symptoms and recruitment into the trial; <2 wks exposure to AP during the preceding yr; <6 wks lifetime exposure to AP Main exclusion criteria: NR</p>	<p>G1: Age (mean±SD): 26.03±5.80 Males (n(%)): 32/52 (61.5%) Ethnicity: Caucasian 48/52 (92.3%) BL symptom scores: PANSS (mean±SD): 91.35±19.4</p> <p>G2: Age (mean±SD): 26.18±5.20 Males (n(%)): 40/60 (66.7%) Ethnicity: Caucasian 59/60 (98.3%) BL symptom scores: PANSS (mean±SD): 90.08±21.7</p> <p>G3: Age (mean±SD): 26.07±5.60 Males (n(%)): 42/74 (56.8%) Ethnicity: Caucasian 70/74 (94.6%) BL symptom scores: PANSS (mean±SD): 86.8±21.4</p> <p>G4: Age (mean±SD): 25.56±5.90 Males (n(%)): 21/45 (46.7%) Ethnicity: Caucasian 43/45 (95.6%) BL symptom scores: PANSS (mean±SD): 86.76±19.5</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 1–4mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 5–20mg/d Intervals: NR</p> <p>G3: Classification: SGA Drug: Quetiapine Dosage: 200–750mg/d Intervals: NR</p> <p>G4: Classification: SGA Drug: Ziprasidone Dosage: 40–160mg/d Intervals: NR</p>

Table 40. Patient characteristics—haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
de Haan et al. 2003 ⁷⁸	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Single center Setting: Mixed Country: Netherlands Financial support: Government</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 6 wks</p>	<p>Main inclusion criteria: Pts (17–28 yrs) with Sz (DSM–IV) Main exclusion criteria: Neurological or endocrine disease, mental retardation, the use of adjunctive medications such as mood stabilizers or antidepressants; Hx of Tx with clozapine; Hx of unresponsiveness to haloperidol or olanzapine; IM AP within the last yr</p>	<p>G1: Age (mean±SD): 21.00±2.79 Males (n(%)): 12/12 (100%) Ethnicity: NR BL symptom scores: NR</p> <p>G2: Age (mean±SD): 21.00±2.33 Males (n(%)): 11/12 (91.7%) Ethnicity: NR BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 2.5mg/d Intervals: once daily</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 7.5mg/d Intervals: once daily</p>
Goldman et al. 2004 ⁸⁴	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Single center Setting: Inpatient Country: USA Financial support: Industry (Eli Lilly)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 8 wks</p>	<p>Main inclusion criteria: Pts with Sz or schizoaffective disorder (DSM–IV); polyuria in absence of recognized factors Main exclusion criteria: NR</p>	<p>G1: Age (mean±SD): 41.00±14.70 Males (n(%)): 4/5 (80%) Ethnicity: NR BL symptom scores: PANSS (mean±SD): 86.6±22</p> <p>G2: Age (mean±SD): 35.40±4.40 Males (n(%)): 5/5 (100%) Ethnicity: NR BL symptom scores: PANSS (mean±SD): 79±31.4</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 5–20mg/d Intervals: 5–mg increments</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 5–20mg/d Intervals: 5–mg increments</p>

Table 40. Patient characteristics—haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Ishigooka et al. 2001 ⁸⁸	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: ICD-10 DCR Study period: NR Number of centers: Multicenter (n = 67) Setting: Mixed Country: Japan Financial support: NR</p> <p>Washout period performed: yes (2–4 wks) Run-in phase performed: no Followup period: 8 wks</p>	<p>Main inclusion criteria: Men and women between the ages of 18–65 yrs; met the F.20 category in the ICD-10 DCR classification Main exclusion criteria: Tx with Haloperidol, Olanzapine or other investigational drug in last 3 months, contraindicated to study medications, Hx liver, kidney, heart disease; pregnant or nursing; neuroleptic malignant syndrome; leukopenia or granulocytopenia; Parkinson's; abnormal transaminase; jaundice</p>	<p>G1: Age (mean±SD): 42.90±NR Males (n(%)): 56/89 (62.9%) Ethnicity: Caucasian 0/89 (0%) BL symptom scores: BPRS (mean±SD): 45.5±11.7 PANSS (mean±SD): 83.5±21.2</p> <p>G2: Age (mean±SD): 42.90±NR Males (n(%)): 58/93 (62.4%) Ethnicity: Caucasian 0/93 (0%) BL symptom scores: BPRS (mean±SD): 47.9±12.2 PANSS (mean±SD): 88.3±21.3</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 4–12mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 5–15mg/d Intervals: NR</p>

Table 40. Patient characteristics—haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Kahn et al. 2008 ⁹¹	<p>Study design: RCT Registration #: ISRCTN68736636 Study population: Schizophrenia DSM Classification: DSM IV Study period: Dec 2002 to Jan 2006 Number of centers: Multicenter (n = 50) Setting: Mixed Country: European countries, Israel Financial support: Industry (AstraZeneca, Pfizer, Sanofi–Aventis)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 12 mo</p>	<p>Main inclusion criteria: Pts (18–40 yrs) with Sz, schizophreniform disorder, or schizoaffective disorder (DSM–IV) and confirmed by MINI Main exclusion criteria: More than 2 yrs had passed since the onset of positive symptoms; if any AP had been used for more than 2 wks in the previous yr, or for 6 wks at any time; if Pts had a known intolerance to one of the study drugs; or if Pts met any of the contraindications for any of the study drugs, as mentioned in the (local) package insert texts</p>	<p>G1: Age (mean±SD): 25.40±5.60 Males (n(%)): 64/103 (62.1%) Ethnicity: Caucasian 93/103 (90.3%) BL symptom scores: PANSS (mean±SD): 88.9±19.8</p> <p>G2: Age (mean±SD): 26.30±5.90 Males (n(%)): 67/105 (63.8%) Ethnicity: Caucasian 100/105(95.2%) BL symptom scores: PANSS (mean±SD): 87.5±21.1</p> <p>G3: Age (mean±SD): 26.40±5.70 Males (n(%)): 68/104 (65.4%) Ethnicity: Caucasian 97/104 (93.3%) BL symptom scores: PANSS (mean±SD): 91.5±22.6</p> <p>G4: Age (mean±SD): 26.70±5.70 Males (n(%)): 41/82 (50%) Ethnicity: Caucasian 77/82 (93.9%) BL symptom scores: PANSS (mean±SD): 88.3±20.1</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 1–4mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 5–20mg/d Intervals: NR</p> <p>G3: Classification: SGA Drug: Quetiapine Dosage: 200–750mg/d Intervals: NR</p> <p>G4: Classification: SGA Drug: Ziprasidone Dosage: 40–16mg/d Intervals: NR</p>

Table 40. Patient characteristics—haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Keefe et al. 2006 ¹⁰¹	<p>Study design: RCT Registration #: F1D–MC–HGGN Study population: Schizophrenia DSM Classification: DSM IV Study period: July 1999–Nov 2000 to July 1999–Nov 2001 Number of centers: Multicenter (n = 39) Setting: Mixed Country: USA, Canada Financial support: Industry (Eli Lilly)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 52 wks</p>	<p>Main inclusion criteria: 18–55yrs; Sz or schizoaffective disorder; PANSS score ≥ 4 on at least 2 positive items; BPRS score ≥ 18; English speaking; have a level of understanding sufficient to agree to all tests and examinations; had illness duration of at least 2 yrs from first hospitalization and/or diagnosis/treatment; female patients of childbearing potential must have been using a medically accepted means of contraception</p> <p>Main exclusion criteria: Previous participation in present study, participated in a clinical trial of another investigational drug within 1 mo.; participated in a study within the past 3 mo. that included the neurocognitive battery; significant neurological disorder, head injury with loss of consciousness; serious illness such that death was anticipated within 1 yr or intensive care hospitalization was anticipated within 6 mo, QTc interval greater than 450 ms, uncorrected hypo– or hyperthyroidism, current agranulocytosis, female patients who were either pregnant or nursing, allergic reaction to study medication, DSM–IV substance dependence) within past 2 mo, Tx with depot antipsychotics, reversible MAO inhibitor within 2 wks, or clozapine or ECT within 1 mo</p>	<p>G1: Age (mean\pmSD): 39.80\pm8.32 Males (n(%)): 69/97 (71.1%) Ethnicity: Caucasian 51/97 (52.6%) BL symptom scores: MADRS (mean\pmSD): 14.4\pm10.2 PANSS (mean\pmSD): 82.7\pm14.1</p> <p>G2: Age (mean\pmSD): 38.40\pm7.90 Males (n(%)): 115/159 (72.3%) Ethnicity: Caucasian 95/159 (59.8%) BL symptom scores: MADRS (mean\pmSD): 13.2\pm8.7 PANSS (mean\pmSD): 82.6\pm13.1</p> <p>G3: Age (mean\pmSD): 39.50\pm8.25 Males (n(%)): 111/158 (70.3%) Ethnicity: Caucasian 101/158 (63.9%) BL symptom scores: MADRS (mean\pmSD): 14.1\pm9.3 PANSS (mean\pmSD): 84.1\pm14.7</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 2–19mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 5–20mg/d Intervals: NR</p> <p>G3: Classification: SGA Drug: Risperidone Dosage: 2–10mg/d Intervals: NR</p>

Table 40. Patient characteristics—haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Kim et al. 2010 ¹⁰²	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: NR Study period: NR Number of centers: Two—center Setting: Outpatient Country: South Korea Financial support: Other (Choi Shine Hae 2008–2009)</p> <p>Washout period performed: yes (>4wks) Run-in phase performed: no Followup period: 8 wks</p>	<p>Main inclusion criteria: Pts with Sz, aged 20–64 yrs, attending outpatient departments at two sites in Korea; all pts were smokers; they were clinically stable, with no changes in their antipsychotic medication prescriptions. Main exclusion criteria: NR</p>	<p>G1: Age (mean±SD): 42.50±8.70 Males (n(%)): 25/35 (71.43%) Ethnicity: NR BL symptom scores: NR</p> <p>G2: Age (mean±SD): 37.10±4.80 Males (n(%)): 23/31 (74.2%) Ethnicity: NR BL symptom scores: NR</p> <p>G3: Age (mean±SD): 41.80±11.40 Males (n(%)): 23/32 (71.9%) Ethnicity: NR BL symptom scores: NR</p> <p>G4: Age (mean±SD): 39.90±12.80 Males (n(%)): 28/41 (68.3%) Ethnicity: NR BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 15.9+/-7.1mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Aripiprazole Dosage: 21.7+/-5.5 mg/d Intervals: NR</p> <p>G3: Classification: SGA Drug: Olanzapine Dosage: 15.9+/-4.3mg/d Intervals: NR</p> <p>G4: Classification: SGA Drug: Risperidone Dosage: 4.8+/-2.9mg/d Intervals: NR</p>

Table 40. Patient characteristics—haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Kongsakon et al. 2006 ¹⁰⁴	<p>Study design: RCT Registration #: F1D–SN–S010 Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Multicenter (n = 22) Setting: Outpatient Country: Philippines, Pakistan, Malaysia, Thailand, and Singapore Financial support: Industry (Eli Lilly)</p> <p>Washout period performed: yes (2–9d) Run-in phase performed: no Followup period: 24 wks</p>	<p>Main inclusion criteria: outpatients aged between 18–65 yrs, DSM–IV diagnostic criteria for Sz; a BPRS total score of > 18, patients and their caregivers to be reliable and in possession of a sufficient level of understanding to achieve compliance with the protocol; female patients on contraception.</p> <p>Main exclusion criteria: NR</p>	<p>G1: Age (mean±SD): 31.80±10.00 Males (n(%)): 83/132 (62.9%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 42.85±17.32 PANSS (mean±SD): 104.85±30.2</p> <p>G2: Age (mean±SD): 32.70±10.00 Males (n(%)): 73/144 (50.7%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 42.45±16.58 PANSS (mean±SD): 104.19±28.15</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 5–20 mg Intervals: 5 mg increments with 7 d between successive increases</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 5–20 mg Intervals: 5 mg increments with 7 d between successive increases</p>

Table 40. Patient characteristics—haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Krakowski et al. 2006 ¹⁰⁵	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: Jun 1999 to Nov 2004 Number of centers: Multicenter (n = 2) Setting: Inpatient Country: USA Financial support: Multiple sources (Eli Lilly)</p> <p>Washout period performed: NA Run-in phase performed: yes (1–2 wks) Followup period: 12 wks</p>	<p>Main inclusion criteria: Aged 18–60 yrs and Dx with Sz or schizoaffective disorder using diagnostic criteria DSM–IV; Pts were required to have a clearly confirmed episode of physical assault directed at another person during this hospitalization and some persistence of aggression, as evidenced by the presence of some other aggressive event, whether physical or verbal or against property</p> <p>Main exclusion criteria: Hospitalized for more than a yr; Hx of nonresponse to clozapine, olanzapine, or haloperidol; Hx of clozapine, olanzapine, or haloperidol intolerance; or if they had medical conditions that would be adversely affected by any of these 3 medications; received a depot antipsychotic within 30 d before randomization</p>	<p>G1: Age (mean±SD): 32.70±10.60 Males (n(%)): 30/36 (83.3%) Ethnicity: Caucasian 7/36 (19.4%) BL symptom scores: PANSS (mean±SD): 85.5±13.2</p> <p>G2: Age (mean±SD): 35.10±12.30 Males (n(%)): 31/37 (83.8%) Ethnicity: Caucasian 7/37 (18.9%) BL symptom scores: PANSS (mean±SD): 86.4±14.4</p> <p>G3: Age (mean±SD): 35.60±9.40 Males (n(%)): 29/37 (78.4%) Ethnicity: Caucasian 5/37 (13.5%) BL symptom scores: PANSS (mean±SD): 83.7±14.1</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 10–30mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Clozapine Dosage: 200–800mg/d Intervals: NR</p> <p>G3: Classification: SGA Drug: Olanzapine Dosage: 10–35mg/d Intervals: NR</p>

Table 40. Patient characteristics—haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Lahti et al. 2009 ¹⁰⁶	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Single center Setting: Inpatient Country: USA Financial support: Government</p> <p>Washout period performed: yes (2 wks) Run-in phase performed: no Followup period: 6 wks</p>	<p>Main inclusion criteria: Medically healthy individuals with Sz on the basis of the clinical interview and all other sources of data using DSM IV criteria Main exclusion criteria: NR</p>	<p>G1: Age (mean±SD): 38.30±12.20 Males (n(%)): 10/12 (83.3%) Ethnicity: Caucasian 5/12 (41.7%) BL symptom scores: BPRS (mean±SD): 34.4±7.6</p> <p>G2: Age (mean±SD): 36.10±10.50 Males (n(%)): 12/17 (70.6%) Ethnicity: Caucasian 3/17 (17.7%) BL symptom scores: BPRS (mean±SD): 37.3±8.9</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 10–20mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 12.5–25mg/d Intervals: NR</p>

Table 40. Patient characteristics—haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Lieberman et al. 2003 ¹⁰⁸	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Multicenter (n = 14) Setting: Mixed Country: north America, Western Europe Financial support: Industry (Eli Lilly)</p> <p>Washout period performed: yes (≤2wks) Run-in phase performed: no Followup period: 104 wks</p>	<p>Main inclusion criteria: ages 16–40 yrs; had onset of psychotic symptoms before age 35 yrs; DSM–IV diagnostic criteria for Sz, schizophreniform disorder, or schizoaffective disorder; research experienced psychotic symptoms (delusions, hallucinations, thought disorder, and grossly bizarre behavior) for at least 1 month but not more than 60 months, 5); scored =4 on at least two PANSS (24) psychosis items (P1, P2, P3, P5, or P6) or scored =5 on one psychosis item; 6) had a (CGI) severity score =4 (moderately ill); 7) required treatment with antipsychotic drugs on a clinical basis</p> <p>Main exclusion criteria: Previous AP drug Tx≥ 16 wks.; clozapine Tx at anytime; injectable depot neuroleptic within < three dosing intervals before study entry; pregnant or nursing; serious, unstable medical illnesses or findings that contraindicate AP drug Tx; Hx of allergic or severe adverse reactions to study medications; substance dependence <1 mo.; serious suicidal risk; required concurrent Tx with anticonvulsants, benzodiazepines (except for agitation/control of extrapyramidal signs), antidepressants, psychostimulants, AP drugs beyond those permitted; had contraindications for neuron imaging; had Hx of DSM–IV psychotic disorder with recovery; premorbid IQ of =70; ECT < 30 d</p>	<p>G1: Age (mean±SD): 24.00±4.90 Males (n(%)): 111/132 (84.1%) Ethnicity: Caucasian 72/132 (54.6%) BL symptom scores: PANSS (mean±SD): 73.57±17.5</p> <p>G2: Age (mean±SD): 23.50±4.60 Males (n(%)): 104/131 (79.4%) Ethnicity: Caucasian 67/131 (51.2%) BL symptom scores: PANSS (mean±SD): 75.9±18.07</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 2–20mg/d Intervals: once daily</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 5–20mg/d Intervals: once daily</p>

Table 40. Patient characteristics—haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Lindenmayer et al. 2007 ¹¹⁰	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM-IV-TR Study period: Sep 98 to May 2005 Number of centers: Single center Setting: Mixed Country: USA Financial support: Industry (Eli Lilly)</p> <p>Washout period performed: yes (Assignment after 1 wk of cross-titration from previous antipsychotic medication) Run-in phase performed: no Followup period: 12 wks</p>	<p>Main inclusion criteria: Male and female, 18–60 yrs inpatients and outpatients at a state psychiatric hospital in New York who met DSM-IV-TR criteria for schizophrenia; Ps were required to have a PANSS total score of greater than 50, with a PANSS negative subscale score of greater than 20; negative symptom score was required to contain at least 3 out of 7 negative item scores of greater than 3; all pts fulfilled the criteria for the SDS.</p> <p>Main exclusion criteria: PANSS positive subscale score of greater than 20; SAS akathisia—item score of greater than 2; Hx of Tx failure on antipsychotics (persistent positive symptoms after 8 wks of treatment with adequate dosages of 1 or more antipsychotics); significant medical disorder; positive substance—abuse Dx in the last 3 months; PANSS depression item score (exclusion level greater than 4) was used to exclude patients with significant levels of depression as a secondary negative symptom; pregnant or breast feeding women and women of childbearing age not using adequate contraception</p>	<p>G1: Age (mean±SD): 39.77±9.49 Males (n(%)): 19/19 (100%) Ethnicity: Caucasian 1/19 (5.3%) BL symptom scores: PANSS (mean±SD): 70.79±9.86</p> <p>G2: Age (mean±SD): 39.02±10.48 Males (n(%)): 1/16 (6.3%) Ethnicity: Caucasian 67/131 (51.2%) BL symptom scores: PANSS (mean±SD): 71.25±17.46</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 5–20mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 5–20mg/d Intervals: NR</p>

Table 40. Patient characteristics—haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
McCue et al. 2006 ⁷³	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: Jan 2004 to Feb 2005 Number of centers: Single center Setting: Inpatient Country: USA Financial support: NR</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 3 wks</p>	<p>Main inclusion criteria: Pts (≥ 18 yrs) newly admitted for Sz, schizoaffective disorder or schizophreniform disorder Main exclusion criteria: pregnant/lactating women; medical condition in which pharmacotherapy would prove a significant clinical risk; Hx of response or lack of response to AP; Dx of BP, major depressive disorder, substance-induced psychotic disorder</p>	<p>G1: Age (mean\pmSD): 35.70\pm10.80 Males (n(%)): 42/57 (73.7%) Ethnicity: NR BL symptom scores: BPRS (mean\pmSD): 42\pm11.3</p> <p>G2: Age (mean\pmSD): 40.50\pm12.60 Males (n(%)): 27/53 (51%) Ethnicity: NR BL symptom scores: BPRS (mean\pmSD): 41.3\pm10.2</p> <p>G3: Age (mean\pmSD): 39.00\pm11.00 Males (n(%)): 32/50 (64%) Ethnicity: NR BL symptom scores: BPRS (mean\pmSD): 43.6\pm10.4</p> <p>G4: Age (mean\pmSD): 33.80\pm10.10 Males (n(%)): 37/52 (71.2%) Ethnicity: NR BL symptom scores: BPRS (mean\pmSD): 41.1\pm11</p> <p>G5: Age (mean\pmSD): 38.60\pm12.90 Males (n(%)): 34/57 (59.7%) Ethnicity: NR BL symptom scores: BPRS (mean\pmSD): 42.3\pm9</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 4–30mg Intervals: NR</p> <p>G2: Classification: SGA Drug: Aripiprazole Dosage: 10–45mg Intervals: NR</p> <p>G3: Classification: SGA Drug: Olanzapine Dosage: 5–40 mg Intervals: NR</p> <p>G4: Classification: SGA Drug: Quetiapine Dosage: 50–1200 mg Intervals: NR</p> <p>G5: Classification: SGA Drug: Risperidone Dosage: 2–9 mg Intervals: NR</p> <p>G6: Classification: SGA Drug: Ziprasidone Dosage: 40–240 mg Intervals: NR</p>

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
			G6: Age (mean±SD): 38.30±11.90 Males (n(%)): 26/50 (52%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 43.4±11	

Table 40. Patient characteristics—haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Purdon et al. 2000 ¹²⁴	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Multicenter (n = 19) Setting: Outpatient Country: Canada Financial support: Industry (Eli Lilly)</p> <p>Washout period performed: yes (2–9d) Run-in phase performed: yes (1 month) Followup period: 54 wks</p>	<p>Main inclusion criteria: Men and women aged 18–65 yrs who were within 5 yrs of their first exposure to neuroleptic treatment and had symptom severity at least in the mild range Main exclusion criteria: Pregnant or lactating, had prior medical histories of central nervous system disease or severe head injury, or if they had active serious illness or substance abuse disorders in the previous 30 d</p>	<p>G1: Age (mean±SD): 28.83±6.52 Males (n(%)): 15/23 (65.2%) Ethnicity: NR BL symptom scores: PANSS (mean±SD): 33.17±7.88</p> <p>G2: Age (mean±SD): 26.01±5.76 Males (n(%)): 17/21 (81%) Ethnicity: NR BL symptom scores: PANSS (mean±SD): 32.9±7.88</p> <p>G3: Age (mean±SD): 31.77±11.24 Males (n(%)): 14/21 (66.7%) Ethnicity: NR BL symptom scores: PANSS (mean±SD): 30.29±6.73</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 5–20mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 5–20mg/d Intervals: NR</p> <p>G3: Classification: SGA Drug: Risperidone Dosage: 2–6mg/d Intervals: NR</p>

Table 40. Patient characteristics—haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Rosenheck et al. 2003 ¹²⁷	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: June 1998 to June 2000 Number of centers: Multicenter (n = 17) Setting: Mixed Country: USA Financial support: Industry (Eli Lilly, AstraZeneca)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 12 mo</p>	<p>Main inclusion criteria: Dx with SZ DSM–IV, schizoaffective disorder; outpatients with Hx of psychiatric hospitalization in previous 2 yrs; BPRS score \geq 36; serious symptoms and dysfunction for previous 2 yrs with inability to work or social constriction; Main exclusion criteria: Serious medical illness; unexplained seizures; severe medication allergies; had previously participated in olanzapine research.</p>	<p>G1: Age (mean\pmSD): 46.20\pm7.70 Males (n(%)): 144/150 (96%) Ethnicity: Caucasian 59/150 (39.3%) BL symptom scores: BPRS (mean\pmSD): 48.7\pm8.5 PANSS (mean\pmSD): 85.2\pm15.5</p> <p>G2: Age (mean\pmSD): 46.80\pm9.50 Males (n(%)): 154/159 (96.9%) Ethnicity: Caucasian 66/159 (41.5%) BL symptom scores: BPRS (mean\pmSD): 49.7\pm8.6 PANSS (mean\pmSD): 87.5\pm15.4</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 5–20mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 5–20mg/d Intervals: NR</p>

Table 40. Patient characteristics—haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Saddichha et al. 2008 ¹²⁹	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: Jun 2006 to Dec 2006 Number of centers: Single center Setting: Inpatient Country: India Financial support: Declared no funding</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 6 wks</p>	<p>Main inclusion criteria: Dx of Sz DSM–IV; first episode; were completely drug–naïve Main exclusion criteria: Other psychiatric comorbidity; Hx of severe physical illness; alcohol, and substance abuse or dependence; Hx of preexisting diabetes or hypertension or family Hx of hypertension or diabetes mellitus</p>	<p>G1: Age (mean±SD): 26.00±5.50 Males (n(%)): 16/31 (51.6%) Ethnicity: NR BL symptom scores: NR</p> <p>G2: Age (mean±SD): 26.00±5.50 Males (n(%)): 18/35 (51.4%) Ethnicity: NR BL symptom scores: NR</p> <p>G3: Age (mean±SD): 26.00±5.50 Males (n(%)): 18/33 (54.6%) Ethnicity: NR BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 13.4+/-3.6mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 16.5+/-4.6mg/d Intervals: NR</p> <p>G3: Classification: SGA Drug: Risperidone Dosage: 4.4+/-1.2mg/d Intervals: NR</p>
Sayers et al. 2005 ¹³⁰	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Single center Setting: Mixed Country: USA Financial support: Government</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 26 wks</p>	<p>Main inclusion criteria: DSM–IV diagnosis of schizophrenia and current cocaine abuse in the last 6 months; age 18–60; ability to provide informed consent Main exclusion criteria: use of depot medication within the past 6 months; Hx of sensitization to haloperidol or olanzapine or Hx of neuroleptic malignant syndrome; female pts who was pregnant, lactating, or not using contraceptives; unstable medical problems; homicidality or suicidality</p>	<p>G1: Age (mean±SD): 45.90±6.20 Males (n(%)): NR Ethnicity: NR BL symptom scores: NR</p> <p>G2: Age (mean±SD): 45.90±6.20 Males (n(%)): NR Ethnicity: NR BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 10 to 20mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 10 to 20mg/d Intervals: NR</p>

Table 40. Patient characteristics—haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Sergi et al. 2007 ¹³⁴	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Multicenter Setting: Outpatient Country: USA Financial support: Multiple sources (Janssen and Forest, and Eli Lilly)</p> <p>Washout period performed: no (No washout period was used) Run-in phase performed: no Followup period: 8 wks</p>	<p>Main inclusion criteria: Sz patients DSM–IV age between 18–60 yrs old, competence to provide informed consent, no identifiable neurological conditions or mental retardation, and no alcohol or substance dependence in the last 6 months Main exclusion criteria: NR</p>	<p>G1: Age (mean±SD): 50.00±5.80 Males (n(%)): 13/13 (100%) Ethnicity: Caucasian 4/13 (30.8%) BL symptom scores: NR</p> <p>G2: Age (mean±SD): 48.20±7.70 Males (n(%)): 24/28 (85.7%) Ethnicity: Caucasian 16/28 (57.1%) BL symptom scores: NR</p> <p>G3: Age (mean±SD): 49.20±6.70 Males (n(%)): 28/32 (87.5%) Ethnicity: Caucasian 9/32 (28.1%) BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 8mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 15mg/d Intervals: NR</p> <p>G3: Classification: SGA Drug: Risperidone Dosage: 4mg/d Intervals: NR</p>

Table 40. Patient characteristics—haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Smelson et al. 2006 ¹³⁶	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Single center Setting: NR Country: USA Financial support: Multiple sources (Eli Lilly)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 6 wks</p>	<p>Main inclusion criteria: Met DSM–IV diagnostic criteria for cocaine dependence and Sz (made independently by a psychiatrist and a psychologist); showed any positive change in baseline craving following the presentation of cocaine cues</p> <p>Main exclusion criteria: met DSM–IV criteria for an additional Axis I disorder other than schizophrenia and cocaine dependence (subjects who abused, but were not dependent, on other substances were allowed in the study due to the high rate of polysubstance use among this population.); were taking other prescribed medications that could affect the central nervous system; Hx of seizures; were pregnant females; evidenced chronic disease of the central nervous system other than Sz</p>	<p>G1: Age (mean±SD): 43.30±7.10 Males (n(%)): NR Ethnicity: NR BL symptom scores: NR</p> <p>G2: Age (mean±SD): 42.50±6.30 Males (n(%)): NR Ethnicity: NR BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 5–20mg/d Intervals: 5mg/d for the first 4 d, increased by 5mg/d every 4 d to a maximum dose of 20mg/d by d 12 and a target dose of 10mg/d.</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 5–20mg/d Intervals: 5mg/d for the first 4 d, increased by 5mg/d every 4 d to a maximum dose of 20mg/d by d 12 and a target dose of 10mg/d.</p>

Table 40. Patient characteristics—haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Smith et al. 2001 ¹³⁷	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: NR Study period: NR Number of centers: Single center Setting: Inpatient Country: USA Financial support: Multiple sources (Lilly)</p> <p>Washout period performed: yes (5–14d) Run-in phase performed: no Followup period: 8 wks</p>	<p>Main inclusion criteria: Medication refractory Pts with a Dx of Sz or schizoaffective psychosis, defined as a poor clinical response to at least two typical neuroleptics, with current active positive and/or severe negative symptoms which impacted on functioning and prevented discharge, patients had to be continuously hospitalized for at least 1 yr</p> <p>Main exclusion criteria: NR</p>	<p>G1: Age (mean±SD): 43.00±6.70 Males (n(%)): 31/34 (91.2%) Ethnicity: Caucasian 9/34 (26.5%) BL symptom scores: PANSS (mean±SD): 80.4±8.2</p> <p>G2: Age (mean±SD): 43.00±6.70 Males (n(%)): 31/34 (91.2%) Ethnicity: Caucasian 9/34 (26.5%) BL symptom scores: PANSS (mean±SD): 80.4±8.2</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 5–40mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 5–20mg/d Intervals: NR</p>

Table 40. Patient characteristics—haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Tollefson et al. 1997 ¹⁴¹	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM–III–R Study period: NR Number of centers: Multicenter (n = 174) Setting: Mixed Country: International (North America and Europe) Financial support: Industry (Eli Lilly)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 14 mo</p>	<p>Main inclusion criteria: Pts were required to have a minimum (BPRS) score of 18 (items extracted from the Positive and Negative Syndrome Scale and scored 0–6) and/or be intolerant of current antipsychotic therapy (excluding haloperidol) Main exclusion criteria: NR</p>	<p>G1: Age (mean±SD): 38.30±11.10 Males (n(%)): NR Ethnicity: NR BL symptom scores: BPRS (mean±SD): 34.1±11 MADRS (mean±SD): 16.7±8.7 PANSS (mean±SD): 92.1±20</p> <p>G2: Age (mean±SD): 38.70±11.60 Males (n(%)): NR Ethnicity: NR BL symptom scores: 33.1±10.6 MADRS (mean±SD): 16.6±8.9 PANSS (mean±SD): 90.1±19.2</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 5–20mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 5–20mg/d Intervals: NR</p>

Table 40. Patient characteristics—haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Volakva et al. 2002 ¹⁴⁵	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: June 1996 to NR Number of centers: Multicenter (n = 4) Setting: Inpatient Country: USA Financial support: Multiple sources (Janssen, Eli Lilly, Novartis, Merck)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 14 wks</p>	<p>Main inclusion criteria: Dx of DSM–IV chronic Sz or schizoaffective disorder and suboptimal response to previous treatment, which was defined by two criteria that needed to be present (persistent positive symptoms after at least 6 contiguous wks of treatment, presently or documented in the past, with one or more typical antipsychotics at doses =600 mg/d in chlorpromazine equivalents, and poor level of functioning over the past 2 yrs) defined by the lack of competitive employment or enrollment in an academic or vocational program and not having age–expected interpersonal relations with someone outside the biological family of origin with whom ongoing regular contacts were maintained), a baseline total score =60 on the PANSS</p> <p>Main exclusion criteria: Hx of nonresponse to clozapine, risperidone, or olanzapine, defined as an unambiguous lack of improvement despite a contiguous adequate trial of risperidone or olanzapine for at least 6 wks, or clozapine for at least 14 wks, a history of clozapine, olanzapine, risperidone, or haloperidol intolerance as well as those who received a depot antipsychotic within 30 d before randomization</p>	<p>G1: Age (mean±SD): 40.80±9.20 Males (n(%)): 133/167 (79.6%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 90.4±11.6</p> <p>G2: Age (mean±SD): 40.80±9.20 Males (n(%)): 133/167 (79.6%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 97.6±17.1</p> <p>G3: Age (mean±SD): 40.80±9.20 Males (n(%)): 133/167 (79.6%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 91±13.5</p> <p>G4: Age (mean±SD): 40.80±9.20 Males (n(%)): 133/167 (79.6%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 89.5±13.8</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 10–30mg/d Intervals: BID</p> <p>G2: Classification: SGA Drug: Clozapine Dosage: 200–800mg/d Intervals: BID</p> <p>G3: Classification: SGA Drug: Olanzapine Dosage: 10–40mg/d Intervals: BID</p> <p>G4: Classification: SGA Drug: Risperidone Dosage: 4–16mg/d Intervals: BID</p>

Table 40. Patient characteristics—haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Wright et al. 2001 ¹⁴⁷	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Multicenter Setting: Inpatient Country: International (Australia, Austria, Belgium, Canada, Czech Republic, France, Greece, Hungary, Israel, South Africa, Spain, the United Kingdom, and United States) Financial support: Industry (Eli Lilly)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 24 h</p>	<p>Main inclusion criteria: 18 yrs old or older, with a DSM–IV Dx of Sz, schizophreniform disorder, or schizoaffective disorder, an excited component score greater than or equal to 14 on the PANSS with a score of 4 or more on at least one item (1–7 point scale), clinically agitated and appropriate candidates for intramuscular treatment</p> <p>Main exclusion criteria: Pregnant or lactating women and patients with serious medical illnesses in which pharmacotherapy posed a substantial clinical risk or confounded Dx</p>	<p>G1: Age (mean±SD): 38.20±11.60 Males (n(%)): NR Ethnicity: NR BL symptom scores: BPRS (mean±SD): NR</p> <p>G2: Age (mean±SD): 38.20±11.60 Males (n(%)): NR Ethnicity: NR BL symptom scores: BPRS (mean±SD): NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 7.5 mg Intervals: 1–3 injections over a 24–hour period, optional second and third injections 2 or more and 4 or more hrs following the first injection</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 10 mg Intervals: 1–3 injections over a 24–hour period, optional second and third injections 2 or more and 4 or more hrs following the first injection</p>

Table 40. Patient characteristics—haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Wynn et al. 2007 ¹⁴⁸	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Multicenter (n = 3) Setting: Unclear Country: USA Financial support: Multiple sources (Eli Lilly, Janssen, F.P. Medications)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 8 wks</p>	<p>Main inclusion criteria: Age 18–60 yrs.; Dx with Sz, schizoaffective disorder (bipolar and depressive subtypes); competent to provide informed consent. Main exclusion criteria: Mental retardation, identifiable neurological conditions; alcohol and substance dependence in the last six months</p>	<p>G1: Age (mean±SD): 50.30±6.20 Males (n(%)): 11/11 (100%) Ethnicity: Caucasian 4/11 (36.4%) BL symptom scores: NR</p> <p>G2: Age (mean±SD): 49.80±7.20 Males (n(%)): 17/21 (81%) Ethnicity: Caucasian 14/21 (66.7%) BL symptom scores: NR</p> <p>G3: Age (mean±SD): 46.80±8.30 Males (n(%)): 15/19 (79%) Ethnicity: Caucasian 6/19 (31.6%) BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 8mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 15mg/d Intervals: NR</p> <p>G3: Classification: SGA Drug: Risperidone Dosage: 4mg/d Intervals: NR</p>

AP = antipsychotic; BID = Twice daily; BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; DX = diagnosis; ECT = Electroconvulsive therapy; FGA = first-generation antipsychotic; Hx = history; MADRS = Montgomery-Asberg Depression Rating Scale; MAO = Monoamine oxidase; mg = milligram; n = number; NA = not applicable; NR = not reported; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; SAPS = Scale for the Assessment of Positive Symptoms; SAS = Simpson-Angus Scale; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; Tx = treatment; wk = week; YMRS = Young Mania Rating Scale; yr = year

Table 41. Patient characteristics—haloperidol versus quetiapine

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Arvanitis et al. 1997 ⁴⁶	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM–III–R Study period: NR Number of centers: Multicenter (n = 26) Setting: Inpatient Country: USA, Canada, International Financial support: Industry (Zeneca)</p> <p>Washout period performed: yes (1 wk) Run-in phase performed: no Followup period: 6 wks</p>	<p>Main inclusion criteria: Pts with Sz (18–65 yrs old) with acute exacerbation of chronic or subchronic Sz (DSM–III–R); BPRS score >26 with score of 3 on at least two items from BPRS positive symptom cluster (conceptual disorganization, suspiciousness, hallucinatory behavior, unusual thought content), score of 4 on the CGI–S.</p> <p>Main exclusion criteria: Concurrent Axis I DSM–III–R diagnoses; Hx of seizure disorder; any clinically significant medical condition within 30 d; use of depot antipsychotics within one dosing interval; pregnancy</p>	<p>G1: Age (mean±SD): 37.00±10.00 Males (n(%)): 42/52 (80.8%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 44±9</p> <p>G2: Age (mean±SD): 37.00±10.00 Males (n(%)): 39/53 (73.6%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 45.7±10.9</p> <p>G3: Age (mean±SD): 38.00±9.00 Males (n(%)): 39/48 (81.3%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 47.2±10.1</p> <p>G4: Age (mean±SD): 38.00±9.00 Males (n(%)): 37/52 (71.2%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 45.3±10.9</p> <p>G5: Age (mean±SD): 39.00±8.00 Males (n(%)): 38/51 (74.5%) Ethnicity: NR BL symptom scores: BPRS (mean±SD):</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 12mg/d Intervals: three equally divided doses</p> <p>G2: Classification: SGA Drug: Quetiapine Dosage: 75mg/d Intervals: three equally divided doses</p> <p>G3: Classification: SGA Drug: Quetiapine Dosage: 150mg/d Intervals: three equally divided doses</p> <p>G4: Classification: SGA Drug: Quetiapine Dosage: 300mg/d Intervals: three equally divided doses</p> <p>G5: Classification: SGA Drug: Quetiapine Dosage: 600mg/d Intervals: three equally divided doses</p> <p>G6: Classification: SGA Drug: Quetiapine Dosage: 750mg/d Intervals: three equally divided doses</p>

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
			43.5±11.3 G6: Age (mean±SD): 35.00±10.00 Males (n(%)): 38/54 (70.4%) Ethnicity: Caucasian 54/69 (78.3%) BL symptom scores: BPRS (mean±SD): 45.7±11	
Atmaca et al. 2002 ⁴⁷	Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: Oct 2000 to Dec 2000 Number of centers: Single center Setting: Mixed Country: Turkey Financial support: NR Washout period performed: yes (2 wks) Run-in phase performed: no Followup period: 6 wks	Main inclusion criteria: Female Sz (DSM–IV) pts; 18–45 yrs old Main exclusion criteria: Severe physical illness; Hx of alcohol/substance abuse or dependence; presence of any endocrinological state, or taking oral contraceptives	G1: Age (mean±SD): 29.44±10.08 Males (n(%)): NR Ethnicity: NR BL symptom scores: BPRS (mean±SD): 49.67±4.23 PANSS (mean±SD): 90.54±7.34 G2: Age (mean±SD): 27.62±9.23 Males (n(%)): NR Ethnicity: NR BL symptom scores: BPRS (mean±SD): 48.35±3.68 PANSS (mean±SD): 92.42±7.12	G1: Classification: FGA Drug: Haloperidol Dosage: 10mg/d Intervals: NR G2: Classification: SGA Drug: Quetiapine Dosage: 600mg/d Intervals: NR

Table 41. Patient characteristics—haloperidol versus quetiapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Copolov et al. 2000 ⁶⁸	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM–III–R Study period: NR Number of centers: Multicenter (n = 55) Setting: Inpatient Country: 14 countries (Europe, Australia, South Africa) Financial support: Industry (AstraZeneca)</p> <p>Washout period performed: yes (48h) Run-in phase performed: no Followup period: 6 wks</p>	<p>Main inclusion criteria: Acute exacerbation of chronic or subchronic Sz; ≥18 yrs; CGI–S ≥ 4; PANSS ≥60; ≥4 on 2 or more PANSS items: delusions, conceptual disorganization, hallucinatory behavior, and suspiciousness/persecution.</p> <p>Main exclusion criteria: Significant co–morbidity, lab or ECG findings; epilepsy; WBC < the lower limit of the center's reference range; pregnant or lactating women, or not using adequate contraception; Tx with a long–acting depot medication < 1 dosing period prior to randomization; or participation in other investigational drug trial < 4 wks prior to randomization.</p>	<p>G1: Age (mean±SD): 37.00±12.00 Males (n(%)): 147/227 (64.8%) Ethnicity: NR BL symptom scores: NR</p> <p>G2: Age (mean±SD): 37.00±10.00 Males (n(%)): 158/221 (71.5%) Ethnicity: NR BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 1–16mg/d Intervals: BID</p> <p>G2: Classification: SGA Drug: Quetiapine Dosage: 50–800mg/d Intervals: BID</p>

Table 41. Patient characteristics—haloperidol versus quetiapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Davidson et al. 2009 ⁷⁵	<p>Study design: RCT Registration #: ISRCTN68736636 Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Multicenter (n = 50) Setting: NR Country: 13 European countries and Israel Financial support: Industry (AstraZeneca, Pfizer, U.S. Group, and Sanofi)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 6 mo</p>	<p>Main inclusion criteria: recent onset of psychosis with <2 yrs between the onset of positive symptoms and recruitment into the trial; <2 wks exposure to AP during the preceding yr; <6 wks lifetime exposure to AP Main exclusion criteria: NR</p>	<p>G1: Age (mean±SD): 26.03±5.80 Males (n(%)): 32/52 (61.5%) Ethnicity: Caucasian 48/52 (92.3%) BL symptom scores: PANSS (mean±SD): 91.35±19.4</p> <p>G2: Age (mean±SD): 26.18±5.20 Males (n(%)): 40/60 (66.7%) Ethnicity: Caucasian 59/60 (98.3%) BL symptom scores: PANSS (mean±SD): 90.08±21.7</p> <p>G3: Age (mean±SD): 26.07±5.60 Males (n(%)): 42/74 (56.8%) Ethnicity: Caucasian 70/74 (94.6%) BL symptom scores: PANSS (mean±SD): 86.8±21.4</p> <p>G4: Age (mean±SD): 25.56±5.90 Males (n(%)): 21/45 (46.7%) Ethnicity: Caucasian 43/45 (95.6%) BL symptom scores: PANSS (mean±SD): 86.76±19.5</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 1–4mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 5–20mg/d Intervals: NR</p> <p>G3: Classification: SGA Drug: Quetiapine Dosage: 200–750mg/d Intervals: NR</p> <p>G4: Classification: SGA Drug: Ziprasidone Dosage: 40–160mg/d Intervals: NR</p>

Table 41. Patient characteristics—haloperidol versus quetiapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Emsley et al. 2000 ⁷⁹	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Multicenter Setting: NR Country: South Africa, international Financial support: Industry (AstraZeneca)</p> <p>Washout period performed: NA Run-in phase performed: Drug: yes (4 wks) Followup period: 12 wks</p>	<p>Main inclusion criteria: Pts (≥ 18 yrs) with Sz; Hx of partial response to conventional APs; persistent positive symptoms while previously taking AP; PANSS score ≥ 15 with ≥ 4 on one or more on following items: delusions, conceptual disorganization, hallucinatory behavior and suspiciousness/persecution; CGI–S score ≥ 3; partial or no response to 1 mo Tx with fluphenazine</p> <p>Main exclusion criteria: Known to be resistant to standard AP medication or clozapine; had acute exacerbation within past 3 mos.; known sensitivity to study drugs; Hx of idiopathic/drug–induced agranulocytosis</p>	<p>G1: Age (mean\pmSD): 38.80\pm11.30 Males (n(%)): 101/145 (69.7%) Ethnicity: Caucasian 117/145 (80.7%) BL symptom scores: BPRS (mean\pmSD): 49.2\pmNR PANSS (mean\pmSD): 88.1\pmNR</p> <p>G2: Age (mean\pmSD): 37.70\pm10.80 Males (n(%)): 102/143 (71.3%) Ethnicity: Caucasian 113/143 (79%) BL symptom scores: BPRS (mean\pmSD): 49.4\pmNR PANSS (mean\pmSD): 88.2\pmNR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 5–20mg/d Intervals: BID</p> <p>G2: Classification: SGA Drug: Quetiapine Dosage: 600mg/d Intervals: BID</p>
Emsley et al. 2005 ⁸⁰	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: Apr 2000 to Mar 2002 Number of centers: Multicenter Setting: Mixed Country: South Africa Financial support: Multiple sources (AstraZeneca)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: Apr 2000 to Mar 2002</p>	<p>Main inclusion criteria: Pts (18–65 yrs) with clinically stable Sz or schizoaffective disorder (DSM–IV); on stable dose of AP; had TD</p> <p>Main exclusion criteria: another Axis I DSM–IV Dx; significant or unstable general medical condition; receiving clozapine</p>	<p>G1: Age (mean\pmSD): 50.10\pm8.60 Males (n(%)): 15/23 (65.2%) Ethnicity: NR BL symptom scores: PANSS (mean\pmSD): 57\pm14.1</p> <p>G2: Age (mean\pmSD): 49.20\pm14.50 Males (n(%)): 14/22 (63.6%) Ethnicity: NR BL symptom scores: PANSS (mean\pmSD): 55.5\pm12.9</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 5–20mg Intervals: 2.5 mg increments</p> <p>G2: Classification: SGA Drug: Quetiapine Dosage: 100–800mg Intervals: 100 mg increments</p>

Table 41. Patient characteristics—haloperidol versus quetiapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Glick et al. 2005 ⁶⁵	Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: 1998 to 2001 Number of centers: Multicenter (n = 3) Setting: NR Country: USA Financial support: Multiple sources (AstraZeneca) Washout period performed: NA Run-in phase performed: no Followup period: 48 wks	Main inclusion criteria: Pts requiring long-term therapy Main exclusion criteria: NR	G1: Age (mean±SD): 44.00±12.80 Males (n(%)): 7/9 (77.8%) Ethnicity: Caucasian 4/9 (44.4%) BL symptom scores: NR G2: Age (mean±SD): 41.30±13.00 Males (n(%)): 13/16 (81.3%) Ethnicity: Caucasian 5/16 (31.3%) BL symptom scores: NR	G1: Classification: FGA Drug: Haloperidol Dosage: 200mg/wk Intervals: NR G2: Classification: SGA Drug: Quetiapine Dosage: 500mg/d Intervals: NR

Table 41. Patient characteristics—haloperidol versus quetiapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Kahn et al. 2008 ⁹¹	<p>Study design: RCT Registration #: ISRCTN68736636 Study population: Schizophrenia DSM Classification: DSM IV Study period: Dec 2002 to Jan 2006 Number of centers: Multicenter (n = 50) Setting: Mixed Country: European countries, Israel Financial support: Industry (AstraZeneca, Pfizer, Sanofi–Aventis)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 12 mo</p>	<p>Main inclusion criteria: Pts (18–40 yrs) with Sz, schizophreniform disorder, or schizoaffective disorder (DSM–IV) and confirmed by MINI Main exclusion criteria: More than 2 yrs had passed since the onset of positive symptoms; if any AP had been used for more than 2 wks in the previous yr, or for 6 wks at any time; if Pts had a known intolerance to one of the study drugs; or if Pts met any of the contraindications for any of the study drugs, as mentioned in the (local) package insert texts</p>	<p>G1: Age (mean±SD): 25.40±5.60 Males (n(%)): 64/103 (90.3%) Ethnicity: Caucasian 93/103 (92.3%) BL symptom scores: PANSS (mean±SD): 88.9±19.8</p> <p>G2: Age (mean±SD): 26.30±5.90 Males (n(%)): 67/105 (65.4%) Ethnicity: Caucasian 100/105 (95.2%) BL symptom scores: PANSS (mean±SD): 87.5±21.1</p> <p>G3: Age (mean±SD): 26.40±5.70 Males (n(%)): 68/104 (50%) Ethnicity: Caucasian 97/104 (93.3%) BL symptom scores: PANSS (mean±SD): 91.5±22.6</p> <p>G4: Age (mean±SD): 26.70±5.70 Males (n(%)): 41/82 (46.7%) Ethnicity: Caucasian 77/82 (93.9%) BL symptom scores: PANSS (mean±SD): 88.3±20.1</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 1–4mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 5–20mg/d Intervals: NR</p> <p>G3: Classification: SGA Drug: Quetiapine Dosage: 200–750mg/d Intervals: NR</p> <p>G4: Classification: SGA Drug: Ziprasidone Dosage: 40–16mg/d Intervals: NR</p>

Table 41. Patient characteristics—haloperidol versus quetiapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
McCue et al. 2006 ⁷³	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: Jan 2004 to Feb 2005 Number of centers: Single center Setting: Inpatient Country: USA Financial support: NR</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 3 wks</p>	<p>Main inclusion criteria: Pts (≥ 18 yrs) newly admitted for Sz, schizoaffective disorder or schizophreniform disorder Main exclusion criteria: Pregnant/lactating women; medical condition in which pharmacotherapy would prove a significant clinical risk; Hx of response or lack of response to AP; Dx of BP, major depressive disorder, substance-induced psychotic disorder</p>	<p>G1: Age (mean\pmSD): 35.70\pm10.80 Males (n(%)): 42/57 (73.7%) Ethnicity: NR BL symptom scores: BPRS (mean\pmSD): 42\pm11.3</p> <p>G2: Age (mean\pmSD): 40.50\pm12.60 Males (n(%)): 27/53 (51%) Ethnicity: NR BL symptom scores: BPRS (mean\pmSD): 41.3\pm10.2</p> <p>G3: Age (mean\pmSD): 39.00\pm11.00 Males (n(%)): 32/50 (64%) Ethnicity: NR BL symptom scores: BPRS (mean\pmSD): 43.6\pm10.4</p> <p>G4: Age (mean\pmSD): 33.80\pm10.10 Males (n(%)): 37/52 (71.2%) Ethnicity: NR BL symptom scores: BPRS (mean\pmSD): 41.1\pm11</p> <p>G5: Age (mean\pmSD): 38.60\pm12.90 Males (n(%)): 34/57 (59.7%) Ethnicity: NR BL symptom scores: BPRS (mean\pmSD): 42.3\pm9</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 4–30mg Intervals: NR</p> <p>G2: Classification: SGA Drug: Aripiprazole Dosage: 10–45mg Intervals: NR</p> <p>G3: Classification: SGA Drug: Olanzapine Dosage: 5–40 mg Intervals: NR</p> <p>G4: Classification: SGA Drug: Quetiapine Dosage: 50–1200 mg Intervals: NR</p> <p>G5: Classification: SGA Drug: Risperidone Dosage: 2–9 mg Intervals: NR</p> <p>G6: Classification: SGA Drug: Ziprasidone Dosage: 40–240 mg Intervals: NR</p>

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
			G6: Age (mean±SD): 38.30±11.90 Males (n(%)): 26/50 (52%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 43.4±11	

Table 41. Patient characteristics—haloperidol versus quetiapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Purdon et al. 2001 ¹²³	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Multicenter (n = 3) Setting: NR Country: Canada Financial support: Industry (Astra–Zeneca)</p> <p>Washout period performed: yes (48 h) Run-in phase performed: no Followup period: 6 mo</p>	<p>Main inclusion criteria: Dx of Sz Main exclusion criteria: Hx of a serious medical disease or neurological disorder (including a history of serious head injury); active substance abuse in the 30–d period before enrollment.</p>	<p>G1: Age (mean±SD): 25.40±5.60 Males (n(%)): 64/103 (90.3%) Ethnicity: Caucasian 93/103 (92.3%) BL symptom scores: PANSS (mean±SD): 88.9±19.8</p> <p>G2: Age (mean±SD): 26.30±5.90 Males (n(%)): 67/105 (65.4%) Ethnicity: Caucasian 100/105 (95.2%) BL symptom scores: PANSS (mean±SD): 87.5±21.1</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 10–20mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Quetiapine Dosage: 300–600mg/d Intervals: NR</p>

Table 41. Patient characteristics—haloperidol versus quetiapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Velligan et al. 2002 ¹⁴³	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM–III–R Study period: NR Number of centers: Multicenter (n = 34) Setting: Outpatient Country: USA Financial support: Industry (AstraZeneca)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 24 wks</p>	<p>Main inclusion criteria: Conventional antipsychotic doses equivalent to 30mg/d or less of haloperidol; patients with full or partial remission; scores of 3 or less on BPRS; scores of moderately ill on the CGI–S Main exclusion criteria: Physical disorder or laboratory finding that made it inappropriate for them to receive study medication.</p>	<p>G1: Age (mean±SD): 36.00±9.70 Males (n(%)): 13/15 (86.7%) Ethnicity: Caucasian 10/15 (66.7%) BL symptom scores: NR</p> <p>G2: Age (mean±SD): 39.12±10.76 Males (n(%)): 12/17 (70.6%) Ethnicity: Caucasian 9/17 (52.9%) BL symptom scores: NR</p> <p>G3: Age (mean±SD): 41.77±11.49 Males (n(%)): 18/26 (69.2%) Ethnicity: Caucasian 20/26 (76.9%) BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 12mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Quetiapine Dosage: 300mg/d Intervals: NR</p> <p>G3: Classification: SGA Drug: Quetiapine Dosage: 600mg/d Intervals: NR</p>

AP = antipsychotic; BID = Twice daily; BL = baseline; BP = Bipolar Disorder; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; DX = diagnosis; ECG = Electrocardiography; FGA = first-generation antipsychotic; Hx = history; MADRS = Montgomery-Asberg Depression Rating Scale; MAO = Monoamine oxidase; mg = milligram; n = number; NA = not applicable; NR = not reported; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; TD = Tardive dyskinesia; Tx = treatment; WBC = White blood count; wk = week; yr = year

Table 42. Patient characteristics—haloperidol versus risperidone

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Apiquian et al. 2008 ⁴⁵	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Single center Setting: Outpatient Country: Mexico Financial support: NR</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 4 wks</p>	<p>Main inclusion criteria: Pts (17–50 yrs) Dx with Sz (DSM–IV), with acute psychosis; PANSS (positive) >16, score of at least 4 on at least two subscale items Main exclusion criteria: Other primary psychiatric or physical illnesses, current substance abuse or dependence, high risk for suicide or violence; or severe akathisia</p>	<p>G1: Age (mean±SD): 28.50±7.20 Males (n(%)): 13/15 (86.7%) Ethnicity: NR BL symptom scores: PANSS (mean±SD): 77.8±10.5</p> <p>G2: Age (mean±SD): 28.50±7.20 Males (n(%)): 12/17 (70.6%) Ethnicity: NR BL symptom scores: PANSS (mean±SD): 85.1±11.3</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 2mg/d Intervals: nightly dosing</p> <p>G2: Classification: SGA Drug: Risperidone Dosage: 1mg/d Intervals: nightly dosing</p>
Blin et al. 1996 ⁵²	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM–III–R Study period: NR Number of centers: Single center Setting: Inpatient Country: France Financial support: NR</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 4 wks</p>	<p>Main inclusion criteria: Pts (18–50 yrs) with Sz (DSM–III–R) with acute exacerbation and symptoms of anxiety (Psychotic Anxiety Scale score at least 34) Main exclusion criteria: Schizo–affective disorders; severe somatic disorders; abnormal lab results; Hx of drug/alcohol abuse; pregnant/lactating women; pts receiving long–acting antipsychotic agents during last 4 wks or short–acting antipsychotics during last 48 hrs or other treatments that might interfere with the trial medication or pt's emotional state</p>	<p>G1: Age (mean±SD): 33.90±NR Males (n(%)): 11/20 (86.7%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 66.3±15.8 CGI-BP (mean±SD): 4.5±0.8 PANSS (mean±SD): 119±21.8</p> <p>G2: Age (mean±SD): 34.80±NR Males (n(%)): 14/21 (66.7%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 70.1±12.2 CGI-BP (mean±SD): 4.6±0.8 PANSS (mean±SD): 124.4±19.7</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 4–12mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Risperidone Dosage: 4–12mg/d Intervals: NR</p>

Table 42. Patient characteristics—haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Borison et al. 1992 ⁵³	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM–III–R Study period: NR Number of centers: Multicenter Setting: NR Country: USA Financial support: Industry (Janssen)</p> <p>Washout period performed: NA Run-in phase performed: yes (1 wk) Followup period: 6 wks</p>	<p>Main inclusion criteria: Pts with Sz (DSM–III–R); BPRS score at least 30, with 2 or more positive symptom items (unusual thought content, hallucinations, conceptual disorganization, suspiciousness); Baseline CGI of moderate or greater Main exclusion criteria: Clinically significant medical/neurological problems or concomitant psychiatric diagnoses, substance abuse or dependence</p>	<p>G1: Age (mean±SD): 37.00±6.00 Males (n(%)): 12/12 (100%) Ethnicity: Caucasian 6/12 (50%) BL symptom scores: BPRS (mean±SD): 50±6</p> <p>G2: Age (mean±SD): 43.00±9.00 Males (n(%)): 12/12 (100%) Ethnicity: Caucasian 6/12 (50%) BL symptom scores: BPRS (mean±SD): 52±5</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 4–20mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Risperidone Dosage: 2–10mg/d Intervals: NR</p>
Cavallaro et al. 2001 ⁵⁹	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM–III–R Study period: NR Number of centers: Single center Setting: Inpatient Country: Italy Financial support: Industry (Janssen)</p> <p>Washout period performed: NA Run-in phase performed: yes (≤1 wk) Followup period: 6 wks</p>	<p>Main inclusion criteria: Pts with subchronic Sz (DSM–II–R); able to consent; not treated with neuroleptics in past wk. or depot APs in past mo. Main exclusion criteria: Other major morbidity; substance/alcohol abuse; known hypersensitivity to included Tx; IQ <80.</p>	<p>G1: Age (mean±SD): 23.20±2.30 Males (n(%)): 10/14 (71.4%) Ethnicity: NR BL symptom scores: NR</p> <p>G2: Age (mean±SD): 25.40±5.10 Males (n(%)): 12/15 (80%) Ethnicity: NR BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 2.5–10mg/d Intervals: BID</p> <p>G2: Classification: SGA Drug: Risperidone Dosage: 2.5–10mg/d Intervals: BID</p>

Table 42. Patient characteristics—haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Ceskova et al. 1993 ⁶⁰	Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: ICD-9 Study period: NR Number of centers: Single center Setting: Inpatient Country: Czech Republic Financial support: NR Washout period performed: NA Run-in phase performed: no Followup period: 8 wks	Main inclusion criteria: Pts with Sz (ICD-9) Main exclusion criteria: NR	G1: Age (mean±SD): 37.00±6.00 Males (n(%)): 12/12 (100%) Ethnicity: Caucasian 6/12 (50%) BL symptom scores: BPRS (mean±SD): 50±6 G2: Age (mean±SD): 43.00±9.00 Males (n(%)): 12/12 (100%) Ethnicity: Caucasian 6/12 (50%) BL symptom scores: BPRS (mean±SD): 52±5	G1: Classification: FGA Drug: Haloperidol Dosage: 2–20mg/d Intervals: NR G2: Classification: SGA Drug: Risperidone Dosage: 2–20mg/d Intervals: NR

Table 42. Patient characteristics—haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Chouinard et al. 1993 ⁶¹	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM–III–R Study period: NR Number of centers: Multicenter (n = 6) Setting: Inpatient Country: Canada Financial support: Industry (Janssen)</p> <p>Washout period performed: yes (2 d to 2 wks) Run-in phase performed: no Followup period: 8 wks</p>	<p>Main inclusion criteria: Pts (18–65 yrs) with Dx of Sz; PANSS score 60–120; hospitalized for first 3 wks of the study; no depot neuroleptics for one treatment cycle Main exclusion criteria: Women: pregnant/lactating/without adequate contraception; mental disorder other than Sz; epilepsy; Hx of psychoactive substance/alcohol abuse; significant abnormal lab or ECG results</p>	<p>G1: Age (mean±SD): 37.00±10.00 Males (n(%)): NR Ethnicity: NR BL symptom scores: BPRS (mean±SD): 55.7±14.5 PANSS (mean±SD): 95.4±23.5</p> <p>G2: Age (mean±SD): 37.00±10.00 Males (n(%)): NR Ethnicity: NR BL symptom scores: BPRS (mean±SD): 53.6±14.9 PANSS (mean±SD): 93.9±22.7</p> <p>G3: Age (mean±SD): 37.00±10.00 Males (n(%)): NR Ethnicity: NR BL symptom scores: BPRS (mean±SD): 57.5±13.1 PANSS (mean±SD): 98±22.6</p> <p>G4: Age (mean±SD): 37.00±10.00 Males (n(%)): NR Ethnicity: NR BL symptom scores: BPRS (mean±SD): 50.8±12.7 PANSS (mean±SD):</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 20mg/d Intervals: BID</p> <p>G2: Classification: SGA Drug: Risperidone Dosage: 2mg/d Intervals: BID</p> <p>G3: Classification: SGA Drug: Risperidone Dosage: 6mg/d Intervals: BID</p> <p>G4: Classification: SGA Drug: Risperidone Dosage: 10mg/d Intervals: BID</p> <p>G5: Classification: SGA Drug: Risperidone Dosage: 16mg/d Intervals: BID</p>

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
			89.9±19.2 G5: Age (mean±SD): 37.00±10.00 Males (n(%)): NR Ethnicity: NR BL symptom scores: BPRS (mean±SD): 54.5±12.6 PANSS (mean±SD): 94.3±21.3	

Table 42. Patient characteristics—haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Citrome et al. 2001 ⁶²	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: 1996 to 2000 Number of centers: Multicenter (n = 4) Setting: Inpatient Country: USA Financial support: Multiple sources (Janssen, Eli Lilly, Novartis, Merck)</p> <p>Washout period performed: NA Run-in phase performed: yes (1 wk) Followup period: 14 wks</p>	<p>Main inclusion criteria: Pts with Sz (18–60 yrs); Hx of suboptimal treatment response; PANSS minimum score of 60; persistent positive symptoms after six wks with one or more conventional antipsychotics (600 mg chlorpromazine equivalent or more); poor level of functioning over past two yrs Main exclusion criteria: Hx of not responding to clozapine, risperidone, or olanzapine; Hx of intolerance to any of the study drugs; receipt of depot AP during last 30 d</p>	<p>G1: Age (mean±SD): 40.80±9.20 Males (n(%)): 31/37 (83.8%) Ethnicity: Caucasian 11/37 (29.7%) BL symptom scores: NR</p> <p>G2: Age (mean±SD): 40.80±9.20 Males (n(%)): 34/40 (85%) Ethnicity: Caucasian 12/40 (30%) BL symptom scores: NR</p> <p>G3: Age (mean±SD): 40.80±9.20 Males (n(%)): 33/39 (84.6%) Ethnicity: Caucasian 12/39 (30.8%) BL symptom scores: NR</p> <p>G4: Age (mean±SD): 40.80±9.20 Males (n(%)): 35/41 (85.4%) Ethnicity: Caucasian 13/41 (31.7%) BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 10–30mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Clozapine Dosage: 200–800mg/d Intervals: NR</p> <p>G3: Classification: SGA Drug: Olanzapine Dosage: 10–40mg/d Intervals: NR</p> <p>G4: Classification: SGA Drug: Risperidone Dosage: 4–16mg/d Intervals: NR</p>

Table 42. Patient characteristics—haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Claus et al. 1992 ⁶⁴	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM–III–R Study period: NR Number of centers: Multicenter (n = 5) Setting: Inpatient Country: Belgium Financial support: Industry (Janssen)</p> <p>Washout period performed: yes (1 wk) Run-in phase performed: yes (2 wks) Followup period: 12 wks</p>	<p>Main inclusion criteria: Pts (18–67 yrs) with chronic Sz (DSM–III–R); hospitalized <10 yrs Main exclusion criteria: Pts with clinically relevant organic diseases; pregnant/lactating women or in their reproductive phase without adequate contraceptive measures</p>	<p>G1: Age (mean±SD): 39.00±NR Males (n(%)): 13/21 (61.9%) Ethnicity: NR BL symptom scores: PANSS (mean±SD): 79.8±21.12</p> <p>G2: Age (mean±SD): 37.40±NR Males (n(%)): 15/21 (71.4%) Ethnicity: NR BL symptom scores: PANSS (mean±SD): 91.1±18.79</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 1–10mg/d Intervals: BID</p> <p>G2: Classification: SGA Drug: Risperidone Dosage: 1–10mg/d Intervals: BID</p>

Table 42. Patient characteristics—haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Crespo-Facorro et al. 2006 ⁷¹	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: Feb–01 to Feb–05 Number of centers: Single center Setting: Mixed Country: Spain Financial support: Multiple sources (NR)</p> <p>Washout period performed: yes (3–5d) Run-in phase performed: no Followup period: 6 wks</p>	<p>Main inclusion criteria: Pts (15–60 yrs) with Sz (DSM–IV); no AP within 6 wks; SAPS of moderate severity Main exclusion criteria: Mental retardation; drug dependence</p>	<p>G1: Age (mean±SD): 28.30±8.70 Males (n(%)): 36/56 (64.3%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 62.4±10.9 YMRS (mean±SD): 9.3±4.3</p> <p>G2: Age (mean±SD): 27.50±6.90 Males (n(%)): 33/55 (60%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 59.9±12.1 YMRS (mean±SD): 9.2±4.7</p> <p>G3: Age (mean±SD): 26.10±7.60 Males (n(%)): 38/61 (62.3%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 56.8±10.3 YMRS (mean±SD): 8.8±4.8</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 3–9mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 5–20mg/d Intervals: NR</p> <p>G3: Classification: SGA Drug: Risperidone Dosage: 3–6mg/d Intervals: NR</p>

Table 42. Patient characteristics—haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Csernansky et al. 2002 ⁷²	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: May–96 to Sep–98 Number of centers: Multicenter (n = 40) Setting: Inpatient Country: USA Financial support: Industry (Janssen)</p> <p>Washout period performed: yes (≤ 1 wks) Run-in phase performed: no Followup period: 12 mo</p>	<p>Main inclusion criteria: Pts (18–65 yrs) with of Sz or schizoaffective disorder (DSM–IV) requiring hospitalization; clinically stable within last 30 d Main exclusion criteria: Another current DSM–IV Axis I Dx, an Axis II Dx of borderline personality disorder or antisocial personality disorder; substance dependence/abuse; clinically significant or unstable medical illness; current treatment with clozapine; Hx of refractoriness to AP; Tx with depot neuroleptic injections within one treatment cycle; allergic to either risperidone or haloperidol; pregnant/nursing women</p>	<p>G1: Age (mean\pmSD): 40.10\pm10.40 Males (n(%)): 128/188 (68.1%) Ethnicity: Caucasian 93/188 (49.5%) BL symptom scores: PANSS (mean\pmSD): 67.3\pm17.4</p> <p>G2: Age (mean\pmSD): 40.30\pm10.60 Males (n(%)): 127/77 (71.8%) Ethnicity: Caucasian 81/177 (45.8%) BL symptom scores: PANSS (mean\pmSD): 65\pm15.9</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 5–20mg/d Intervals: once/d</p> <p>G2: Classification: SGA Drug: Risperidone Dosage: 2–8mg/d Intervals: once/d</p>
de Sena et al. 2003 ⁷⁷	<p>Study design: NonRCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM–III–R Study period: Mar–95 to Nov–97 Number of centers: Single center Setting: Unclear Country: Brazil Financial support: Industry (Janssen–Cilag)</p> <p>Washout period performed: yes (3–7d) Run-in phase performed: no Followup period: 12 mo</p>	<p>Main inclusion criteria: Pts (15–40 yrs) with Sz (DSM–III–R) Main exclusion criteria: Long hospitalization (≥ 12 months); other Axis I disorders; drug dependence; significant neurological or organic disorders; Pts difficult to follow-up; participation in a trial during 4 wks prior to the study; use of depot neuroleptics with one treatment cycle before the start of the study</p>	<p>G1: Age (mean\pmSD): 27.40\pmNR Males (n(%)): 13/13 (100%) Ethnicity: Caucasian 2/13 (15.4%) BL symptom scores: NR</p> <p>G2: Age (mean\pmSD): 27.90\pmNR Males (n(%)): 20/20 (100%) Ethnicity: Caucasian 4/20 (20%) BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 5–17mg/d Intervals: BID</p> <p>G2: Classification: SGA Drug: Risperidone Dosage: 1–6mg/d Intervals: BID</p>

Table 42. Patient characteristics—haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Emsley et al. 1999 ⁸¹	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM–III–R Study period: NR Number of centers: Multicenter (n = 61) Setting: Inpatient Country: Australia, Belgium, Canada, France, Germany, Great Britain, Korea, The Netherlands, South Africa, Sweden Financial support: NR</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 6 wks</p>	<p>Main inclusion criteria: Pts (15–45 yrs) with Sz or schizophreniform disorder (DSM–III–R) without prior Tx; had psychotic symptoms requiring Tx; had received a maximum of 3 d of ED Tx for this disorder; had no clinically relevant neurological, ECG or lab test abnormalities; informed consent Main exclusion criteria: Pregnant/lactating women or of reproductive age not using adequate contraception; other mental illness; psychoactive substance abuse; previous depot antipsychotic Tx; clinically significant organic disease; participated in clinical trials of investigational drugs within 4 wks</p>	<p>G1: Age (mean±SD): 24.00±NR Males (n(%)): 54/84 (64.3%) Ethnicity: Caucasian 62/84 (73.8%) BL symptom scores: BPRS (mean±SD): 89.6±20.16 CGI-S (mean±SD): 51.5±8.62</p> <p>G2: Age (mean±SD): 26.00±NR Males (n(%)): 68/99 (68.7%) Ethnicity: Caucasian 62/99 (62.6%) BL symptom scores: BPRS (mean±SD): 89.1±18.81 CGI-S (mean±SD): 51.1±10.89</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 2–10mg/d Intervals: BID</p> <p>G2: Classification: SGA Drug: Risperidone Dosage: 2–10mg/d Intervals: BID</p>
Fakra et al. 2008 ⁸²	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM–IV–TR Study period: NR Number of centers: Single center Setting: Inpatient Country: France Financial support: Multiple sources (Janssen)</p> <p>Washout period performed: yes (1 wk) Run-in phase performed: no Followup period: 50 wks</p>	<p>Main inclusion criteria: Pts (18–55 yrs) with Sz (DSM–IV) Main exclusion criteria: Hx of alcohol/drug abuse; comorbidity with depressive or anxiety disorders; chronic medical illness other than Sz; facial TD; taking depot antipsychotics</p>	<p>G1: Age (mean±SD): 37.80±11.40 Males (n(%)): 12/14 (85.7%) Ethnicity: Caucasian 13/14 (92.9%) BL symptom scores: PANSS (mean±SD): 75.21±8.65</p> <p>G2: Age (mean±SD): 33.90±9.50 Males (n(%)): 7/11 (63.6%) Ethnicity: Caucasian 10/11 (90.9%) BL symptom scores: PANSS (mean±SD): 76.1±15.46</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: NR Intervals: NR</p> <p>G2: Classification: SGA Drug: Risperidone Dosage: NR Intervals: NR</p>

Table 42. Patient characteristics—haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Heck et al. 2000 ⁸⁵	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM–III–R Study period: 1993 to 1995 Number of centers: Multicenter (n = 12) Setting: Mixed Country: Netherlands Financial support: Industry (Janssen–Cilag)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: NR</p>	<p>Main inclusion criteria: Pts (18–70 yrs) with Sz (DSM–III–R); clinically stable on current meds; score of at least 5 on ESRS or use anti-Parkinson medication Main exclusion criteria: NR</p>	<p>G1: Age (mean±SD): 44.50±NR Males (n(%)): 12/22 (54.6%) Ethnicity: NR BL symptom scores: NR</p> <p>G2: Age (mean±SD): 40.00±NR Males (n(%)): 13/25 (52%) Ethnicity: NR BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 3–24mg/d Intervals: BID</p> <p>G2: Classification: SGA Drug: Risperidone Dosage: 2–16mg/d Intervals: BID</p>
Kee et al. 1998 ⁹⁹	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM–III–R Study period: NR Number of centers: Single center Setting: Inpatient Country: USA Financial support: Multiple sources (Janssen)</p> <p>Washout period performed: yes (<1 wks) Run-in phase performed: yes (3 wks) Followup period: NR</p>	<p>Main inclusion criteria: Sz disorder based on the Structured Clinical Interview for DSM–III–R, treatment-resistant Main exclusion criteria: NR</p>	<p>G1: Age (mean±SD): 37.67±8.37 Males (n(%)): 7/9 (77.8%) Ethnicity: Caucasian 5/9 (55.6%) BL symptom scores: NR</p> <p>G2: Age (mean±SD): 35.00±9.72 Males (n(%)): 5/9 (55.6%) Ethnicity: Caucasian 5/9 (55.6%) BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 15mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Risperidone Dosage: 6mg/d Intervals: NR</p>

Table 42. Patient characteristics—haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Keefe et al. 2003 ¹⁰⁰	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Single center Setting: NR Country: USA Financial support: Multiple sources (Janssen)</p> <p>Washout period performed: yes (<1 wks) Run-in phase performed: no Followup period: NR</p>	<p>Main inclusion criteria: Dx with Sz by DSM–IV criteria were assessed; Pts were included in the study only if their age ranged between 18–55 Main exclusion criteria: If English was not their first language, not having any of the target symptoms (autonoetic agnosia: thought insertion, voices arguing, voices commenting, made feelings, made acts, or made impulses)</p>	<p>G1: Age (mean±SD): 33.90±11.70 Males (n(%)): NR Ethnicity: NR BL symptom scores: BPRS (mean±SD): 36.6±6</p> <p>G2: Age (mean±SD): 33.90±11.70 Males (n(%)): NR Ethnicity: NR BL symptom scores: BPRS (mean±SD): 36.6±6</p> <p>G3: Age (mean±SD): NR Males (n(%)): NR Ethnicity: NR BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 2.5–10.0mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 2.5–10.0mg/d Intervals: NR</p> <p>G3: Classification: SGA Drug: Risperidone Dosage: 2.0–8.0mg/d Intervals: NR</p>

Table 42. Patient characteristics—haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Keefe et al. 2006 ¹⁰¹	<p>Study design: RCT Registration #: F1D–MC–HGGN Study population: Schizophrenia DSM Classification: DSM IV Study period: July 1999–Nov 2000 to July 1999–Nov 2001 Number of centers: Multicenter (n = 39) Setting: Mixed Country: USA, Canada Financial support: Industry (Eli Lilly)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 52 wks</p>	<p>Main inclusion criteria: 18–55yrs; schizophrenia or schizoaffective disorder; PANSS score ≥ 4 on at least 2 positive items; BPRS score ≥ 18; English speaking; have a level of understanding sufficient to agree to all tests and examinations; had illness duration of at least 2 yrs from first hospitalization and/or diagnosis/treatment; female pts of childbearing potential must have been using a medically accepted means of contraception.</p> <p>Main exclusion criteria: Previous participation in present study, participated in a clinical trial of another investigational drug within 1 mo.; participated in a study within the past 3 mo. that included the neurocognitive battery; significant neurological disorder, head injury with loss of consciousness; serious illness such that death was anticipated within 1 yr or intensive care hospitalization was anticipated within 6 mo, QTc interval greater than 450 ms, uncorrected hypo– or hyperthyroidism, current agranulocytosis, female patients who were either pregnant or nursing, allergic reaction to study medication, DSM–IV substance dependence) within past 2 mo, Tx with depot antipsychotics, reversible MAO inhibitor within 2 wks, or clozapine or ECT within 1 mo.</p>	<p>G1: Age (mean\pmSD): 39.80\pm8.32 Males (n(%)): 69/97 (71.1%) Ethnicity: Caucasian 51/97 (52.6%) BL symptom scores: MADRS (mean\pmSD): 14.4\pm10.2 PANSS (mean\pmSD): 82.7\pm14.1</p> <p>G2: Age (mean\pmSD): 38.40\pm7.90 Males (n(%)): 115/159 (72.3%) Ethnicity: Caucasian 95/159 (59.8%) BL symptom scores: MADRS (mean\pmSD): 13.2\pm8.7 PANSS (mean\pmSD): 82.6\pm13.1</p> <p>G3: Age (mean\pmSD): 39.50\pm8.25 Males (n(%)): 111/158 (70.3%) Ethnicity: Caucasian 101/158 (63.9%) BL symptom scores: MADRS (mean\pmSD): 14.1\pm9.3 PANSS (mean\pmSD): 84.1\pm14.7</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 2–19mg/d</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 5–20mg/d</p> <p>G3: Classification: SGA Drug: Risperidone Dosage: 2–10mg/d</p>

Table 42. Patient characteristics—haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Kim et al. 2010 ¹⁰²	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: NR Study period: NR Number of centers: Two—center Setting: Outpatient Country: South Korea Financial support: Other (Choi Shine Hae 2008–2009)</p> <p>Washout period performed: yes (>4wks) Run-in phase performed: no Followup period: 8 wks</p>	<p>Main inclusion criteria: Pts with Sz, aged 20–64 yrs, attending outpatient departments at two sites in Korea; all participants were smokers; they were clinically stable, with no changes in their antipsychotic medication prescriptions. Main exclusion criteria: NR</p>	<p>G1: Age (mean±SD): 42.50±8.70 Males (n(%)): 25/35 (71.4%) Ethnicity: NR BL symptom scores: NR</p> <p>G2: Age (mean±SD): 37.10±4.80 Males (n(%)): 23/31 (74.2%) Ethnicity: NR BL symptom scores: NR</p> <p>G3: Age (mean±SD): 41.80±11.40 Males (n(%)): 23/32 (71.9%) Ethnicity: NR BL symptom scores: NR</p> <p>G4: Age (mean±SD): 39.90±12.80 Males (n(%)): 28/41 (68.3%) Ethnicity: NR BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 15.9+/-7.1mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Aripiprazole Dosage: 21.7+/-5.5 mg/d Intervals: NR</p> <p>G3: Classification: SGA Drug: Olanzapine Dosage: 15.9+/-4.3mg/d Intervals: NR</p> <p>G4: Classification: SGA Drug: Risperidone Dosage: 4.8+/-2.9mg/d Intervals: NR</p>

Table 42. Patient characteristics—haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Lee et al. 2007 ¹⁰⁷	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Two-center Setting: Inpatient Country: Taiwan Financial support: Government</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 8 wks</p>	<p>Main inclusion criteria: Sz Pt identified on the basis of ICD-9 Main exclusion criteria: no previous Hx of other functional psychosis, neurological illnesses/insults, substance abuse within the past 2 yrs; Hx of substance dependence, electroconvulsive therapy within the past 6 months, or any other significant current medical conditions</p>	<p>G1: Age (mean±SD): 27.20±10.40 Males (n(%)): 10/10 (100%) Ethnicity: NR BL symptom scores: PANSS (mean±SD): 89.5±15.2</p> <p>G2: Age (mean±SD): 25.90±7.25 Males (n(%)): 10/10 (100%) Ethnicity: NR BL symptom scores: PANSS (mean±SD): 94.2±9.8</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 7.6+/-2.6mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Risperidone Dosage: 4.1+/-0.8mg/d Intervals: NR</p>

Table 42. Patient characteristics—haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Lim et al. 2010 ¹⁵¹	<p>Study design: RCT Registration #: NR Study population: Bipolar disorder and Schizophrenia DSM Classification: DSM IV Study period: Dec 2005 to Sept 2006 Number of centers: Single center Setting: Inpatient Country: South Korea Financial support: Industry (Janssen)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 24 h</p>	<p>Main inclusion criteria: Age 18–65 yrs; manifestation of acute psychotic agitation in the ED or inpatient ward; Sz or schizoaffective disorder, bipolar I disorder with or without psychotic features, delusional disorders, or psychotic disorder not otherwise specified; symptom score of ≥ 14 on the 5-item acute agitation cluster derived from the PANSS–EC; score of ≥ 3 on the CGI–S</p> <p>Main exclusion criteria: Neurological disorders or severe medical diseases; alcohol or other psychoactive substance abusers; treated with any antipsychotics or benzodiazepines within 6 h of enrollment; Hx of neuroleptic malignant syndrome or hypersensitivity to trial medications; treated with a depot antipsychotic within 1 Tx cycle of enrollment; eligible women were tested for pregnancy; pregnant and lactating women</p>	<p>G1: Age (mean\pmSD): 34.70\pm10.20 Males (n(%)): 32/62 (51.6%) Ethnicity: NR BL symptom scores: NR</p> <p>G2: Age (mean\pmSD): 32.30\pm9.80 Males (n(%)): 34/62 (54.8%) Ethnicity: NR BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 5–15mg Intervals: could repeat every 2 hr (max 15mg/24 hr)</p> <p>G2: Classification: SGA Drug: Risperidone Dosage: 2–6mg Intervals: could repeat every 2 hr (max 6mg/24 hr)</p>

Table 42. Patient characteristics—haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Liu et al. 2000 ¹¹¹	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM-III-R Study period: NR Number of centers: Single center Setting: Mixed Country: Taiwan Financial support: NR</p> <p>Washout period performed: yes (1 wk) Run-in phase performed: no Followup period: 12 wk</p>	<p>Main inclusion criteria: Prominent clinical symptoms as revealed by a total score of > 65 on the PANSS Main exclusion criteria: Patients with a previous history of physical illness or substance abuse that cast the Dx in doubt</p>	<p>G1: Age (mean±SD): 35.10±13.00 Males (n(%)): 6/19 (31.6%) Ethnicity: NR BL symptom scores: PANSS (mean±SD): 86.1±14.9</p> <p>G2: Age (mean±SD): 32.70±8.40 Males (n(%)): 9/19 (47.4%) Ethnicity: NR BL symptom scores: PANSS (mean±SD): 76±16.1</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: NR Intervals: NR</p> <p>G2: Classification: SGA Drug: Risperidone Dosage: NR Intervals: NR</p>

Table 42. Patient characteristics—haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Marder et al. 1994 ¹¹⁴	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM–III–R Study period: NR Number of centers: Multicenter (n = 20) Setting: Inpatient Country: USA Financial support: Industry (Janssen–Ortho)</p> <p>Washout period performed: yes (1 wk) Run-in phase performed: no Followup period: 8 wks</p>	<p>Main inclusion criteria: Dx of Sz otherwise physically healthy; PANSS total score ≥ 60, ≤ 120 Main exclusion criteria: Schizoaffective disorder; women with childbearing potential</p>	<p>G1: Age (mean\pmSD): 38.00\pm10.00 Males (n(%)): 60/66 (90.9%) Ethnicity: Caucasian 41/66 (62.1%) BL symptom scores: BPRS (mean\pmSD): 54.6\pm10.7 PANSS (mean\pmSD): 92.9\pm17.4</p> <p>G2: Age (mean\pmSD): 39.30\pm10.90 Males (n(%)): 54/63 (85.7%) Ethnicity: Caucasian 41/63 (65.1%) BL symptom scores: BPRS (mean\pmSD): 51.5\pm10.2 PANSS (mean\pmSD): 87.4\pm17.6</p> <p>G3: Age (mean\pmSD): 10.00\pm11.10 Males (n(%)): 55/64 (85.9%) Ethnicity: Caucasian 42/64 (65.6%) BL symptom scores: BPRS (mean\pmSD): 54.1\pm11.7 PANSS (mean\pmSD): 93.8\pm19.1</p> <p>G4: Age (mean\pmSD): 36.20\pm9.80 Males (n(%)): 61/65 (93.9%) Ethnicity: Caucasian 42/65 (64.6%)</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 20mg/d</p> <p>G2: Classification: SGA Drug: Risperidone Dosage: 2mg/d</p> <p>G3: Classification: SGA Drug: Risperidone Dosage: 6mg/d</p> <p>G4: Classification: SGA Drug: Risperidone Dosage: 10mg/d</p> <p>G5: Classification: SGA Drug: Risperidone Dosage: 16mg/d</p>

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
			BL symptom scores: BPRS (mean±SD): 54±11.8 PANSS (mean±SD): 92.5±19.4 G5: Age (mean±SD): 36.50±10.40 Males (n(%)): 53/64 (82.8%) Ethnicity: Caucasian 38/64 (59.4%) BL symptom scores: BPRS (mean±SD): 54.2±10.5 PANSS (mean±SD): 93.8±17.2	

Table 42. Patient characteristics—haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Marder et al. 2003 ¹¹³	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Multicenter (n = 3) Setting: Outpatient Country: USA Financial support: Multiple sources (Janssen Research Foundation) Washout period performed: NA Run-in phase performed: yes (2 wks) Followup period: 2 yrs</p>	<p>Main inclusion criteria: All subjects were 18–60 yrs of age; had at least two documented episodes of acute schizophrenic illness or at least 2 yrs of continuing psychotic symptoms; had been outpatients for at least 1 month; and were considered candidates for maintenance therapy with an antipsychotic Main exclusion criteria: NR</p>	<p>G1: Age (mean±SD): 43.30±8.40 Males (n(%)): 29/30 (96.7%) Ethnicity: Caucasian 14/30 (46.7%) BL symptom scores: NR G2: Age (mean±SD): 43.70±9.20 Males (n(%)): 29/33 (87.9%) Ethnicity: Caucasian 14/33 (42.4%) BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 2mg TID. for the first week and then 6mg h.s. G2: Classification: SGA Drug: Risperidone Dosage: 2mg TID. for the first week and then 6mg h.s.</p>

Table 42. Patient characteristics—haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
McCue et al. 2006 ⁷³	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: Jan 2004 to Feb 2005 Number of centers: Single center Setting: Inpatient Country: USA Financial support: NR</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 3 wks</p>	<p>Main inclusion criteria: Pts (≥ 18 yrs) newly admitted for Sz, schizoaffective disorder or schizophreniform disorder Main exclusion criteria: Pregnant/lactating women; medical condition in which pharmacotherapy would prove a significant clinical risk; Hx of response or lack of response to AP; Dx of BP, major depressive disorder, substance-induced psychotic disorder</p>	<p>G1: Age (mean\pmSD): 35.70\pm10.80 Males (n(%)): 42/57 (73.7%) Ethnicity: NR BL symptom scores: BPRS (mean\pmSD): 42\pm11.3</p> <p>G2: Age (mean\pmSD): 40.50\pm12.60 Males (n(%)): 27/53 (51%) Ethnicity: NR BL symptom scores: BPRS (mean\pmSD): 41.3\pm10.2</p> <p>G3: Age (mean\pmSD): 39.00\pm11.00 Males (n(%)): 32/50 (64%) Ethnicity: NR BL symptom scores: BPRS (mean\pmSD): 43.6\pm10.4</p> <p>G4: Age (mean\pmSD): 33.80\pm10.10 Males (n(%)): 37/52 (71.2%) Ethnicity: NR BL symptom scores: BPRS (mean\pmSD): 41.1\pm11</p> <p>G5: Age (mean\pmSD): 38.60\pm12.90 Males (n(%)): 34/57 (59.7%) Ethnicity: NR BL symptom scores: BPRS (mean\pmSD): 42.3\pm9</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 4–30mg</p> <p>G2: Classification: SGA Drug: Aripiprazole Dosage: 10–45mg</p> <p>G3: Classification: SGA Drug: Olanzapine Dosage: 5–40 mg</p> <p>G4: Classification: SGA Drug: Quetiapine Dosage: 50–1200 mg</p> <p>G5: Classification: SGA Drug: Risperidone Dosage: 2–9 mg</p> <p>G6: Classification: SGA Drug: Ziprasidone Dosage: 40–240 mg</p>

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
			G6: Age (mean±SD): 38.30±11.90 Males (n(%)): 26/50 (52%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 43.4±11	

Table 42. Patient characteristics—haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Min et al. 1993 ¹¹⁷	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM–III–R Study period: NR Number of centers: Single center Setting: Mixed Country: Korea Financial support: NR</p> <p>Washout period performed: yes (1 wk) Run-in phase performed: no Followup period: 8 wks</p>	<p>Main inclusion criteria: Chronic Sz; age 18–65 yrs.; PANSS score >60 and <120; normal laboratory and ECG tests; hospitalized d 6–14 if possible</p> <p>Main exclusion criteria: Other mental disorder; clinically significant co–morbidity; epilepsy; Hx of alcohol–or drug abuse within 12–month; included in other investigational drug trial within 4 wks; women not on adequate contraception, pregnant or lactating</p>	<p>G1: Age (mean±SD): 34.10±NR Males (n(%)): NR Ethnicity: NR BL symptom scores: BPRS (mean±SD): 48.8±14.8 PANSS (mean±SD): 88.2±28.2</p> <p>G2: Age (mean±SD): 34.10±NR Males (n(%)): NR Ethnicity: NR BL symptom scores: BPRS (mean±SD): 53.4±18.4 PANSS (mean±SD): 92±30</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 2.5–5mg/d Intervals: BID</p> <p>G2: Classification: SGA Drug: Risperidone Dosage: 2.5–5mg/d Intervals: BID</p>

Table 42. Patient characteristics—haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Moller et al. 2008 ¹¹⁸	<p>Study design: RCT Registration #: NCT00159081 Study population: Schizophrenia DSM Classification: ICD-10 F20 Study period: Nov 2000 to May 2004 Number of centers: Multicenter (n = 13) Setting: Inpatient Country: Germany Financial support: Multiple sources (Janssen—Cilag)</p> <p>Washout period performed: yes (1 wk) Run-in phase performed: no Followup period: 2 yrs</p>	<p>Main inclusion criteria: Having recovered from a first illness episode with a diagnosis according to ICD-10 F20, whereas first episode was pragmatically defined as the first inpatient treatment of psychotic symptoms; age between 18–55 yrs; having either participated in the acute Tx study or being suited for lateral entry; being sufficiently able in German language; having given consent after extensive information about the various phases and ramifications of the 2-yr study Main exclusion criteria: Pregnancy; insufficient response to pretreatment with risperidone or haloperidol; other contraindications for risperidone or haloperidol; mental retardation; organic brain disease; substance abuse; Hx of suicidal behavior; severe physical disease; participation in other trials</p>	<p>G1: Age (mean±SD): 30.70±10.00 Males (n(%)): 80/146 (54.8%) Ethnicity: NR BL symptom scores: PANSS (mean±SD): 80.8±24.8 YMRS (mean±SD): 5.5±5.5</p> <p>G2: Age (mean±SD): 29.50±9.50 Males (n(%)): 92/143 (64.3%) Ethnicity: NR BL symptom scores: PANSS (mean±SD): 77.3±23 YMRS (mean±SD): 5±5.2</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 2–8mg/d Intervals: Once daily</p> <p>G2: Classification: SGA Drug: Risperidone Dosage: 2–8mg/d Intervals: Once daily</p>

Table 42. Patient characteristics—haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Peuskens et al. 1995 ¹²⁰	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM–III–R Study period: NR Number of centers: Multicenter (n = 110) Setting: Inpatient Country: International (15 countries) Financial support: NR</p> <p>Washout period performed: yes (3–7d) Run-in phase performed: no Followup period: 8 wks</p>	<p>Main inclusion criteria: Dx of chronic Sz disorder according to DSM–III–R with a total score between 60–120 on the PANSS Main exclusion criteria: Clinically significant organic or neurological disorders, epilepsy, psychiatric disorders other than chronic schizophrenia, a history of alcohol or drug abuse in the previous 12 months, or had participated in trials of investigational drugs in the preceding 4 wks; pregnant or lactating women and those of reproductive age without adequate contraception</p>	<p>G1: Age (mean±SD): 38.10±NR Males (n(%)): 150/226 (66.4%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 48.1±10.22 PANSS (mean±SD): 90.1±17.86</p> <p>G2: Age (mean±SD): 38.40±NR Males (n(%)): 166/229 (72.5%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 48.9±10.59 PANSS (mean±SD): 32.9±7.88</p> <p>G3: Age (mean±SD): 38.10±NR Males (n(%)): 152/227 (67%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 48.6±10.09 PANSS (mean±SD): 89.6±17.48</p> <p>G4: Age (mean±SD): 37.60±NR Males (n(%)): 144/230 (62.6%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 48.1±10.92 PANSS (mean±SD):</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 10mg/d Intervals: 2 times per d distributed evenly</p> <p>G2: Classification: SGA Drug: Risperidone Dosage: 1mg/d Intervals: 2 times per d distributed evenly</p> <p>G3: Classification: SGA Drug: Risperidone Dosage: 4mg/d Intervals: 2 times per d distributed evenly</p> <p>G4: Classification: SGA Drug: Risperidone Dosage: 8mg/d Intervals: 2 times per d distributed evenly</p> <p>G5: Classification: SGA Drug: Risperidone Dosage: 12mg/d Intervals: 2 times per d distributed evenly</p> <p>G6: Classification: SGA Drug: Risperidone Dosage: 16mg/d Intervals: 2 times per d distributed evenly</p>

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
			<p>89.2±18.81</p> <p>G5: Age (mean±SD): 37.90±NR Males (n(%)): 142/226 (62.8%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 49.1±10.07 PANSS (mean±SD): 90.5±18.04</p> <p>G6: Age (mean±SD): 38.50± Males (n(%)): 140/224 (62.5%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 49.5±10.63 PANSS (mean±SD): 89.8±17.96</p>	

Table 42. Patient characteristics—haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Purdon et al. 2000 ¹²⁴	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Multicenter (n = 19) Setting: Outpatient Country: Canada Financial support: Industry (Eli Lilly)</p> <p>Washout period performed: yes (2–9d) Run-in phase performed: yes (1 month) Followup period: 54 wks</p>	<p>Main inclusion criteria: Men and women aged 18–65 yrs who were within 5 yrs of their first exposure to neuroleptic treatment and had symptom severity at least in the mild range Main exclusion criteria: Pregnant or lactating, had prior medical histories of central nervous system disease or severe head injury, or if they had active serious illness or substance abuse disorders in the previous 30 d</p>	<p>G1: Age (mean±SD): 28.83±6.52 Males (n(%)): 15/23 (65.2%) Ethnicity: NR BL symptom scores: PANSS (mean±SD): 33.17±7.88</p> <p>G2: Age (mean±SD): 26.01±5.76 Males (n(%)): 17/21 (81%) Ethnicity: NR BL symptom scores: PANSS (mean±SD): 32.9±7.88</p> <p>G3: Age (mean±SD): 31.77±11.24 Males (n(%)): 14/21 (66.7%) Ethnicity: NR BL symptom scores: PANSS (mean±SD): 30.29±6.73</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 5–20mg/d</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 5–20mg/d</p> <p>G3: Classification: SGA Drug: Risperidone Dosage: 2–6mg/d</p>
Remillard et al. 2008 ¹²⁵	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM–III–R Study period: NR Number of centers: Multicenter Setting: Outpatient Country: Canada, France Financial support: Industry (Janssen–Ortho)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 12 mo</p>	<p>Main inclusion criteria: Dx of Sz with DSM–III–R Main exclusion criteria: no Hx of drug or alcohol abuse or neurological disease</p>	<p>G1: Age (mean±SD): 44.10±9.40 Males (n(%)): 11/14 (78.6%) Ethnicity: NR BL symptom scores: NR</p> <p>G2: Age (mean±SD): 40.60±9.90 Males (n(%)): 11/14 (78.6%) Ethnicity: NR BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 2–40mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Risperidone Dosage: 2–6mg/d Intervals: BID</p>

Table 42. Patient characteristics—haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Schooler et al. 2005 ¹³²	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: Nov 1996 to Jan 2000 Number of centers: Multicenter (n = 12) Setting: Outpatient Country: Australia, Austria, Canada, Finland, France, Germany, Israel, Netherlands, New Zealand, South Africa, UK, USA Financial support: Industry (Johnson and Johnson) Washout period performed: yes (3–7d) Run-in phase performed: no Followup period: 2 yrs</p>	<p>Main inclusion criteria: Age 16–45yrs; Sz, schizophreniform disorder, or schizoaffective disorder ≤ 1 yr; no more than two psychiatric hospitalizations for psychosis; <12 wks of cumulative exposure to APs; required AP Tx upon enrollment Main exclusion criteria: Meeting DSM–IV criteria for another axis I diagnosis, including substance dependence or abuse; needing another nonantipsychotic psychotropic medication at enrollment; having a serious or unstable medical illness</p>	<p>G1: Age (mean±SD): 25.70±6.87 Males (n(%)): 200/277 (72.2%) Ethnicity: Caucasian 208/277 (75.1%) BL symptom scores: PANSS (mean±SD): 81.1±20.1 G2: Age (mean±SD): 25.20±6.84 Males (n(%)): 196/278 (70.5%) Ethnicity: Caucasian 205/277 (73.7%) BL symptom scores: PANSS (mean±SD): 83.7±20.22</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 1–8mg/d Intervals: NR G2: Classification: SGA Drug: Risperidone Dosage: 1–8mg/d Intervals: NR</p>

Table 42. Patient characteristics—haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Sergi et al. 2007 ¹³⁴	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Multicenter Setting: Outpatient Country: USA Financial support: Multiple sources (Janssen and Forest, and Eli Lilly)</p> <p>Washout period performed: no (No washout period was used) Run-in phase performed: no Followup period: 8 wks</p>	<p>Main inclusion criteria: Sz patients DSM–IV age between 18–60 yrs old, competence to provide informed consent, no identifiable neurological conditions or mental retardation, and no alcohol or substance dependence in the last 6 months Main exclusion criteria: NR</p>	<p>G1: Age (mean±SD): 50.00±5.80 Males (n(%)): 13/13 (100%) Ethnicity: Caucasian 4/13 (30.8%) BL symptom scores: NR</p> <p>G2: Age (mean±SD): 48.20±7.70 Males (n(%)): 24/28 (85.7%) Ethnicity: Caucasian 16/28 (57.1%) BL symptom scores: NR</p> <p>G3: Age (mean±SD): 49.20±6.70 Males (n(%)): 28/32 (87.5%) Ethnicity: Caucasian 9/32 (28.1%) BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 8mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 15mg/d Intervals: NR</p> <p>G3: Classification: SGA Drug: Risperidone Dosage: 4mg/d Intervals: NR</p>
Shrivastava et al. 2000 ¹³⁵	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Single center Setting: Inpatient Country: India Financial support: NR</p> <p>Washout period performed: NA Run-in phase performed: yes (2–4 wks) Followup period: 12 mo</p>	<p>Main inclusion criteria: Admitted for acute exacerbation of Sz Main exclusion criteria: NR</p>	<p>G1: Age (mean±SD): 31.80±4.80 Males (n(%)): 30/50 (60%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 89.1±4.8</p> <p>G2: Age (mean±SD): 36.20±3.50 Males (n(%)): 29/50 (58%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 91.9±5.9</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 5–15mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Risperidone Dosage: 2mg/d Intervals: NR</p>

Table 42. Patient characteristics—haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Tamrakar et al. 2006 ¹³⁹	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: ICD-10 Study period: Jan 2002 to Jun 2002 Number of centers: Single center Setting: NR Country: Nepal Financial support: NR</p> <p>Washout period performed: yes (1 wk for oral; 4 wks for depot) Run-in phase performed: no Followup period: 6 wks</p>	<p>Main inclusion criteria: Pts between 18–45 yrs of age Dx with Sz according to ICD-10 Main exclusion criteria: Pts with comorbid psychiatric and medical illnesses</p>	<p>G1: Age (mean±SD): 28.67±4.16 Males (n(%)): 10/18 (55.6%) Ethnicity: NR BL symptom scores: PANSS (mean±SD): 88.56±13.35</p> <p>G2: Age (mean±SD): 27.28±4.38 Males (n(%)): 12/18 (66.7%) Ethnicity: NR BL symptom scores: PANSS (mean±SD): 88.17±15.7</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 10–20mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Risperidone Dosage: 4–6mg/d Intervals: NR</p>

Table 42. Patient characteristics—haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Volakva et al. 2002 ¹⁴⁵	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: June 1996 to NR Number of centers: Multicenter (n = 4) Setting: Inpatient Country: USA Financial support: Multiple sources (Janssen, Eli Lilly, Novartis, Merck)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 14 wks</p>	<p>Main inclusion criteria: Dx of DSM–IV chronic Sz or schizoaffective disorder and suboptimal response to previous treatment, which was defined by two criteria that needed to be present (persistent positive symptoms after at least 6 contiguous wks of Tx presently or documented in the past, with one or more typical antipsychotics at doses =600 mg/d in chlorpromazine equivalents, and poor level of functioning over the past 2 yrs, defined by the lack of competitive employment or enrollment in an academic or vocational program and not having age–expected interpersonal relations with someone outside the biological family of origin with whom ongoing regular contacts were maintained), a baseline total score =60 on the PANSS</p> <p>Main exclusion criteria: Hx of nonresponse to clozapine, risperidone, or olanzapine, defined as an unambiguous lack of improvement despite a contiguous adequate trial of risperidone or olanzapine for at least 6 wks, or clozapine for at least 14 wks, a history of clozapine, olanzapine, risperidone, or haloperidol intolerance as well as those who received a depot antipsychotic within 30 d before randomization</p>	<p>G1: Age (mean±SD): 40.80±9.20 Males (n(%)): 133/167 (79.6%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 90.4±11.6</p> <p>G2: Age (mean±SD): 40.80±9.20 Males (n(%)): 133/167 (79.6%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 97.6±17.1</p> <p>G3: Age (mean±SD): 40.80±9.20 Males (n(%)): 133/167 (79.6%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 91±13.5</p> <p>G4: Age (mean±SD): 40.80±9.20 Males (n(%)): 133/167 (79.6%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 89.5±13.8</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 10–30mg/d Intervals: BID</p> <p>G2: Classification: SGA Drug: Clozapine Dosage: 200–800mg/d Intervals: BID</p> <p>G3: Classification: SGA Drug: Olanzapine Dosage: 10–40mg/d Intervals: BID</p> <p>G4: Classification: SGA Drug: Risperidone Dosage: 4–16mg/d Intervals: BID</p>

Table 42. Patient characteristics—haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Wirshing et al. 1999 ¹⁴⁶	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM–III–R Study period: NR Number of centers: Two–center Setting: Inpatient Country: USA Financial support: Multiple sources (Janssen)</p> <p>Washout period performed: yes (3–7d) Run-in phase performed: yes (3 wks) Followup period: 8 wks</p>	<p>Main inclusion criteria: Age 18–60 yrs; Dx of Sz; considered Tx resistant; able to take oral medication; BPRS \geq 45; minimum score of 4 on two BPRS items: conceptual disorganization, suspiciousness, hallucinations, or unusual thought content; CGI \geq 4. Meet treatment refractory requirement.</p> <p>Main exclusion criteria: Had experienced a period of good functioning within 5 yrs; clinically significant neurologic disease; seizure disorder; Hx of head injury; physical, cognitive, or language impairment that would affect ratings; substance abuse within 6 mo.; previous trial of risperidone sufficient to determine clinical response; Tx with investigational drugs or clozapine within 4 wks; depot neuroleptics within 8 wks; behavior that posed significant danger to self or others; significant clinical improvement between the initial screening and the start of the study.</p>	<p>G1: Age (mean\pmSD): 40.00\pm8.20 Males (n(%)): 29/33 (87.9%) Ethnicity: Caucasian 16/33 (48.5%) BL symptom scores: BPRS (mean\pmSD): 70.8\pm14.6</p> <p>G2: Age (mean\pmSD): 41.00\pm9.40 Males (n(%)): 26/34 (76.5%) Ethnicity: Caucasian 20/34 (58.8%) BL symptom scores: BPRS (mean\pmSD): 66.8\pm14.3</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 15mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Risperidone Dosage: 6mg/d Intervals: NR</p>

Table 42. Patient characteristics–haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Wynn et al. 2007 ¹⁴⁸	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Multicenter (n = 3) Setting: Unclear Country: USA Financial support: Multiple sources (Eli Lilly, Janssen, F.P. Medications)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 8 wks</p>	<p>Main inclusion criteria: Age 18–60 yrs.; Dx with Sz, schizoaffective disorder (bipolar and depressive subtypes); competent to provide informed consent. Main exclusion criteria: Mental retardation, identifiable neurological conditions; alcohol and substance dependence in the last six months</p>	<p>G1: Age (mean±SD): 50.30±6.20 Males (n(%)): 11/11 (100%) Ethnicity: Caucasian 4/11 (36.4%) BL symptom scores: NR</p> <p>G2: Age (mean±SD): 49.80±7.20 Males (n(%)): 17/21 (81%) Ethnicity: Caucasian 14/21 (66.7%) BL symptom scores: NR</p> <p>G3: Age (mean±SD): 46.80±8.30 Males (n(%)): 15/19 (79%) Ethnicity: Caucasian 6/19 (31.6%) BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 8mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 15mg/d Intervals: NR</p> <p>G3: Classification: SGA Drug: Risperidone Dosage: 4mg/d Intervals: NR</p>

Table 42. Patient characteristics—haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Yen et al. 2004 ¹⁴⁹	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM–III–R Study period: NR Number of centers: Single center Setting: NR Country: Taiwan Financial support: Government</p> <p>Washout period performed: yes (7 d from oral neuroleptics; 4 wks for depot preparations) Run-in phase performed: no Followup period: 12 wks</p>	<p>Main inclusion criteria: Age 18–65 yrs.; Dx with Sz; total PANSS score >60 Main exclusion criteria: Suffering from psychoses other than Sz, with early childhood brain damage, unable to comply with the medication, with a severe illness (including hematological, hepatic, or cardiovascular disease; pulmonary embolism; alcoholism or addiction), and pregnant or lactating women.</p>	<p>G1: Age (mean±SD): 34.00±6.61 Males (n(%)): 11/20 (55%) Ethnicity: NR BL symptom scores: PANSS (mean±SD): 90.2±16.4</p> <p>G2: Age (mean±SD): 32.90±10.30 Males (n(%)): 15/21 (71.4%) Ethnicity: NR BL symptom scores: PANSS (mean±SD): 90.5±16.5</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 4–20mg/d Intervals: Once daily</p> <p>G2: Classification: SGA Drug: Risperidone Dosage: 2–12mg/d Intervals: Once daily</p>
Zhang et al. 2001 ¹⁵⁰	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM–III–R Study period: NR Number of centers: Single center Setting: Inpatient Country: China Financial support: NR</p> <p>Washout period performed: NA Run-in phase performed: yes (2 wks) Followup period: 12 wks</p>	<p>Main inclusion criteria: Inpatients in Beijing Huilongguan Hospital; DSM–III–R criteria for schizophrenia; Pts Tx with three conventional neuroleptics for at least 3 months at full dose; duration of illness for at least 5 yrs; age between 25–60 yrs, with a CGI scale ratings of a score of 4 or higher Main exclusion criteria: Significant medical illness or were actively abusing alcohol or illegal drugs</p>	<p>G1: Age (mean±SD): 43.70±8.10 Males (n(%)): 30/37 (81.1%) Ethnicity: Caucasian 0/37 (0%) BL symptom scores: PANSS (mean±SD): 79.3±21.7</p> <p>G2: Age (mean±SD): 43.80±6.40 Males (n(%)): 30/41 (73.2%) Ethnicity: Caucasian 0/41 (0%) BL symptom scores: PANSS (mean±SD): 82.4±22.4</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 6mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Risperidone Dosage: 20mg/d Intervals: NR</p>

AP = antipsychotic; BID = Twice daily; BL = baseline; BP = Bipolar Disorder; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; DX = diagnosis; ECG = Electrocardiography; ; ED = Emergency Department; FGA = first-generation antipsychotic; Hx = history; MADRS = Montgomery-Asberg Depression Rating Scale; MAO = Monoamine oxidase; mg = milligram; n = number; NA = not applicable; NR = not reported; PANSS = Positive and Negative Syndrome Scale; QTc = Corrected QT interval; RCT = randomized controlled trial; SAPS = Scale for the Assessment of Positive Symptoms; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; TD = Tardive dyskinesia; Tx = treatment; wk = week; YMRS = Young Mania Rating Scale; yr = year

Table 43. Patient characteristics—haloperidol versus ziprasidone

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Brook et al. 2005 ⁵⁷	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: 1996 to NR Number of centers: Multicenter Setting: Inpatient Country: International Financial support: Industry (Pfizer)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 6 wks</p>	<p>Main inclusion criteria: Pts (18–70 yrs) with acute exacerbation of Sz or schizoaffective disorder (DSM–IV); BPRS score of 40 or more Main exclusion criteria: Previous Tx with other psychoactive drugs including antidepressants/mood stabilizers and/or significant past medical Hx; previous substance abuse or organic mental disease; Immediate risk of harm to oneself or others</p>	<p>G1: Age (mean±SD): 34.60±10.50 Males (n(%)): 91/138 (65.9%) Ethnicity: Caucasian 110/138 (79.7%) BL symptom scores: BPRS (mean±SD): 57±9.6</p> <p>G2: Age (mean±SD): 34.00±10.50 Males (n(%)): 286/429 (66.7%) Ethnicity: Caucasian 338/429 (78.8%) BL symptom scores: BPRS (mean±SD): 57±10.5</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: IM: 2.5–10mg/d; Oral: 5–20mg/d Intervals: IM: every 2 h (if needed); Oral: BID</p> <p>G2: Classification: SGA Drug: Ziprasidone Dosage: IM: 10–40mg/d; Oral: 40–80mg/d Intervals: IM: every 2 h (if needed); Oral: BID</p>
Corripio et al. 2005 ⁶⁹	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Single center Setting: Inpatient Country: Spain Financial support: Multiple sources (Pfizer)</p> <p>Washout period performed: yes (2 wks) Run-in phase performed: no Followup period: 2 wks</p>	<p>Main inclusion criteria: Pts with Sz (DSM–IV) manifesting acute psychotic exacerbation Main exclusion criteria: Hx of substance abuse; past or present neurological disease; other organic disturbance; pregnancy</p>	<p>G1: Age (mean±SD): 36.00±9.00 Males (n(%)): 4/10 (40%) Ethnicity: NR BL symptom scores: PANSS (mean±SD): 79.6±16.5</p> <p>G2: Age (mean±SD): 30.70±5.00 Males (n(%)): 6/10 (60%) Ethnicity: NR BL symptom scores: PANSS (mean±SD): 74.7±9.7</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 5–20mg/d Intervals: ≤4 inj (5mg) every 2hr for 2–3 d</p> <p>G2: Classification: SGA Drug: Ziprasidone Dosage: 10–40mg/d Intervals: ≤4 inj (5mg) every 2hr for 2–3 d</p>

Table 43. Patient characteristics—haloperidol versus ziprasidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Davidson et al. 2009 ⁷⁵	<p>Study design: RCT Registration #: ISRCTN68736636 Study population: Schizophrenia DSM Classification: DSM IV Study period: NR Number of centers: Multicenter (n = 50) Setting: NR Country: 13 European countries and Israel Financial support: Industry (AstraZeneca, Pfizer, U.S. Group, and Sanofi)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 6 mo</p>	<p>Main inclusion criteria: recent onset of psychosis with <2 yrs between the onset of positive symptoms and recruitment into the trial; <2 wks exposure to AP during the preceding yr; <6 wks lifetime exposure to AP Main exclusion criteria: NR</p>	<p>G1: Age (mean±SD): 26.03±5.80 Males (n(%)): 32/52 (61.5%) Ethnicity: Caucasian 48/52 (92.3%) BL symptom scores: PANSS (mean±SD): 91.35±19.4</p> <p>G2: Age (mean±SD): 26.18±5.20 Males (n(%)): 40/60 (66.7%) Ethnicity: Caucasian 59/60 (98.3%) BL symptom scores: PANSS (mean±SD): 90.08±21.7</p> <p>G3: Age (mean±SD): 26.07±5.60 Males (n(%)): 42/74 (56.8%) Ethnicity: Caucasian 70/74 (94.6%) BL symptom scores: PANSS (mean±SD): 86.8±21.4</p> <p>G4: Age (mean±SD): 25.56±5.90 Males (n(%)): 21/45 (46.7%) Ethnicity: Caucasian 43/45 (95.6%) BL symptom scores: PANSS (mean±SD): 86.76±19.5</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 1–4mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 5–20mg/d Intervals: NR</p> <p>G3: Classification: SGA Drug: Quetiapine Dosage: 200–750mg/d Intervals: NR</p> <p>G4: Classification: SGA Drug: Ziprasidone Dosage: 40–160mg/d Intervals: NR</p>

Table 43. Patient characteristics—haloperidol versus ziprasidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Goff et al. 1998 ⁸³	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM–III–R Study period: NR Number of centers: Multicenter (n = 6) Setting: Mixed Country: USA Financial support: NR</p> <p>Washout period performed: yes (≥1 wks) Run-in phase performed: no Followup period: 4 wks</p>	<p>Main inclusion criteria: Hospitalized ≤2 wks for acute exacerbation; hospitalized or resided in an intermediate treatment center ≥ 3 mo; had partially responded to neuroleptic Tx; BPRS total score ≥ 25; score ≥ 4 on one or more of the core items of the Psychosis subscale (suspiciousness, conceptual disorganization, hallucinatory behavior, unusual thought content);</p> <p>Main exclusion criteria: Women of child-bearing potential; comorbid Axis I psychiatric disorders; significant medical or neurologic disorders; had received a depot neuroleptic within 2 months or had recently used an illicit drug.</p>	<p>G1: Age (mean±SD): 35.50±7.50 Males (n(%)): 16/17 (94.1%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 35.4±NR</p> <p>G2: Age (mean±SD): 41.70±9.00 Males (n(%)): 17/19 (89.5%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 34.2±NR</p> <p>G3: Age (mean±SD): 39.20±10.00 Males (n(%)): 16/17 (94.1%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 33.4±NR</p> <p>G4: Age (mean±SD): 38.10±7.90 Males (n(%)): 16/17 (94.1%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 31.5±NR</p> <p>G5: Age (mean±SD): 41.70±9.00 Males (n(%)): 19/20 (95%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 36.3±NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 15mg/d Intervals: BID</p> <p>G2: Classification: SGA Drug: Ziprasidone Dosage: 4mg/d Intervals: BID</p> <p>G3: Classification: SGA Drug: Ziprasidone Dosage: 10mg/d Intervals: BID</p> <p>G4: Classification: SGA Drug: Ziprasidone Dosage: 40mg/d Intervals: BID</p> <p>G5: Classification: SGA Drug: Ziprasidone Dosage: 160mg/d Intervals: BID</p>

Table 43. Patient characteristics—haloperidol versus ziprasidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Hirsch et al. 2002 ⁸⁶	<p>Study design: NonRCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM–III–R Study period: NR Number of centers: Multicenter (n = 52) Setting: Outpatient Country: Europe Financial support: Industry (Pfizer)</p> <p>Washout period performed: yes (2 wks) Run-in phase performed: yes (≤2 wks) Followup period: 28 wks</p>	<p>Main inclusion criteria: Pts (18–64 yrs) with chronic/subchronic Sz; required AP maintenance Tx; PANSS–negative score = >10; GAF score >30; women unable to conceive or were reliably using contraception and were not pregnant or lactating Main exclusion criteria: Having an acute exacerbation; hospitalized for psychosis in previous 12 wks; score of ≥ 5 on PANSS item P7 or G8; deteriorated between baseline and screening (CGI–I score > 6); Hx of substance abuse or dependence in past 3 mo.; at significant risk of suicide or homicide; Hx of allergy to any neuroleptic; neuroleptic malignant syndrome; failure to experience therapeutic response to APs at least twice in the previous 2 yrs; had taken part in a ziprasidone trial or had received an investigational drug within 4 wks, fluoxetine within 5 wks, monoamine oxidase inhibitors within 2 wks, or antidepressants or lithium within 1 week; relevant medical illness, epilepsy, neurologic disorders, HIV seropositivity, serological evidence of hepatitis infection, or clinically significant ECG or lab abnormalities</p>	<p>G1: Age (mean±SD): 39.40±NR Males (n(%)): NR Ethnicity: Caucasian 93/103 (90.3%) BL symptom scores: BPRS (mean±SD): 9.7±3.6 MADRS (mean±SD): 14.1±7.9 PANSS (mean±SD): 74.4±16.1</p> <p>G2: Age (mean±SD): 39.20±NR Males (n(%)): NR Ethnicity: Caucasian 100/105(95.2%) BL symptom scores: BPRS (mean±SD): 9.6±3.7 MADRS (mean±SD): 15±8.3 PANSS (mean±SD): 72.9±17.1</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 5–15mg/d Intervals: BID</p> <p>G2: Classification: SGA Drug: Ziprasidone Dosage: 80–160mg/d Intervals: BID</p>

Table 43. Patient characteristics—haloperidol versus ziprasidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Kahn et al. 2008 ⁹¹	<p>Study design: RCT Registration #: ISRCTN68736636 Study population: Schizophrenia DSM Classification: DSM IV Study period: Dec 2002 to Jan 2006 Number of centers: Multicenter (n = 50) Setting: Mixed Country: European countries, Israel Financial support: Industry (AstraZeneca, Pfizer, Sanofi–Aventis)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 12 mo</p>	<p>Main inclusion criteria: Pts (18–40 yrs) with Sz, schizophreniform disorder, or schizoaffective disorder (DSM–IV) and confirmed by MINI Main exclusion criteria: More than 2 yrs had passed since the onset of positive symptoms; if any AP had been used for more than 2 wks in the previous yr, or for 6 wks at any time; if Pts had a known intolerance to one of the study drugs; or if Pts met any of the contraindications for any of the study drugs, as mentioned in the (local) package insert texts</p>	<p>G1: Age (mean±SD): 25.40±5.60 Males (n(%)): 64/103 (62.1%) Ethnicity: Caucasian 93/103 (90.3%) BL symptom scores: PANSS (mean±SD): 88.9±19.8</p> <p>G2: Age (mean±SD): 26.30±5.90 Males (n(%)): 67/105 (63.8%) Ethnicity: Caucasian 100/105(95.2%) BL symptom scores: PANSS (mean±SD): 87.5±21.1</p> <p>G3: Age (mean±SD): 26.40±5.70 Males (n(%)): 68/104 (65.4%) Ethnicity: Caucasian 97/104 (93.3%) BL symptom scores: PANSS (mean±SD): 91.5±22.6</p> <p>G4: Age (mean±SD): 26.70±5.70 Males (n(%)): 41/82 (50%) Ethnicity: Caucasian 77/82 (93.9%) BL symptom scores: PANSS (mean±SD): 88.3±20.1</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 1–4mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 5–20mg/d Intervals: NR</p> <p>G3: Classification: SGA Drug: Quetiapine Dosage: 200–750mg/d Intervals: NR</p> <p>G4: Classification: SGA Drug: Ziprasidone Dosage: 40–16mg/d Intervals: NR</p>

Table 43. Patient characteristics—haloperidol versus ziprasidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
McCue et al. 2006 ⁷³	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: Jan 2004 to Feb 2005 Number of centers: Single center Setting: Inpatient Country: USA Financial support: NR</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 3 wks</p>	<p>Main inclusion criteria: Pts (≥ 18 yrs) newly admitted for Sz, schizoaffective disorder or schizophreniform disorder Main exclusion criteria: Pregnant/lactating women; medical condition in which pharmacotherapy would prove a significant clinical risk; Hx of response or lack of response to AP; Dx of BP, major depressive disorder, substance-induced psychotic disorder</p>	<p>G1: Age (mean\pmSD): 35.70\pm10.80 Males (n(%)): 42/57 (73.7%) Ethnicity: NR BL symptom scores: BPRS (mean\pmSD): 42\pm11.3</p> <p>G2: Age (mean\pmSD): 40.50\pm12.60 Males (n(%)): 27/53 (51%) Ethnicity: NR BL symptom scores: BPRS (mean\pmSD): 41.3\pm10.2</p> <p>G3: Age (mean\pmSD): 39.00\pm11.00 Males (n(%)): 32/50 (64%) Ethnicity: NR BL symptom scores: BPRS (mean\pmSD): 43.6\pm10.4</p> <p>G4: Age (mean\pmSD): 33.80\pm10.10 Males (n(%)): 37/52 (71.2%) Ethnicity: NR BL symptom scores: BPRS (mean\pmSD): 41.1\pm11</p> <p>G5: Age (mean\pmSD): 38.60\pm12.90 Males (n(%)): 34/57 (59.7%) Ethnicity: NR BL symptom scores: BPRS (mean\pmSD): 42.3\pm9</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 4–30mg Intervals: NR</p> <p>G2: Classification: SGA Drug: Aripiprazole Dosage: 10–45mg Intervals: NR</p> <p>G3: Classification: SGA Drug: Olanzapine Dosage: 5–40 mg Intervals: NR</p> <p>G4: Classification: SGA Drug: Quetiapine Dosage: 50–1200 mg Intervals: NR</p> <p>G5: Classification: SGA Drug: Risperidone Dosage: 2–9 mg Intervals: NR</p> <p>G6: Classification: SGA Drug: Ziprasidone Dosage: 40–240 mg Intervals: NR</p>

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
			G6: Age (mean±SD): 38.30±11.90 Males (n(%)): 26/50 (52%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 43.4±11	

Table 43. Patient characteristics—haloperidol versus ziprasidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Miceli et al. 2010 ¹¹⁶	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: NR Study period: NR Number of centers: Single center Setting: Inpatient Country: USA Financial support: Industry (Pfizer)</p> <p>Washout period performed: yes (10 d) Run-in phase performed: no Followup period: 2–3 d</p>	<p>Main inclusion criteria: The study included adults (aged ≥18 yrs) with a Hx of Sz or schizoaffective disorder in whom long-term antipsychotic therapy was indicated; Pts were also required to have had normal findings on screening and baseline clinical laboratory testing</p> <p>Main exclusion criteria: Ps were excluded if they had a Hx of acute exacerbation of psychosis within 3 months before the study; had clinically significant abnormal findings on ECG or a condition with a potential to affect ECG findings; had received electroconvulsive therapy within 6 months before the study; had used fluphenazine decanoate or haloperidol decanoate within 4 months before the study; had used fluoxetine within 5 wks before the study; had used clozapine or investigational drugs within 4 wks before the study; or had used other anTIDepressants or lithium, mood stabilizers, or anticonvulsants within 2 wks before the study</p>	<p>G1: Age (mean±SD): 43.60±NR Males (n(%)): 21/27 (77.8%) Ethnicity: Caucasian 12/27 (44.4%) BL symptom scores: NR</p> <p>G2: Age (mean±SD): 43.70±NR Males (n(%)): 25/31 (80.7%) Ethnicity: Caucasian 13/31 (41.9%) BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 7.5–10 mg Intervals: every 4 hrs</p> <p>G2: Classification: SGA Drug: Ziprasidone Dosage: 20–30 mg Intervals: every 4 hrs</p>

Table 43. Patient characteristics—haloperidol versus ziprasidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Potkin et al. 2009 ¹²²	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM–III–R Study period: July 1994 to Sep 2000 Number of centers: Multicenter (n = 40) Setting: NR Country: USA, Canada Financial support: Industry (Pfizer)</p> <p>Washout period performed: yes (4 wk) Run-in phase performed: no Followup period: 3.75 yrs</p>	<p>Main inclusion criteria: A chronic or subchronic Sz or schizoaffective disorder (DSM–III–R) Dx, no hospitalization for psychosis for at least 12 wk prior to screening, PANSS negative score >10, PANSS hostility and uncooperativeness item scores <4 (moderate), CGI–I score <6 (much worse) at baseline (compared to screening), GAF Scale score >30 Main exclusion criteria: NR</p>	<p>G1: Age (mean±SD): 40.00±NR Males (n(%)): NR Ethnicity: Caucasian 110/151 (72.9%) BL symptom scores: PANSS (mean±SD): 72.6±18.1</p> <p>G2: Age (mean±SD): 39.30±NR Males (n(%)): NR Ethnicity: Caucasian 146/221 (66.1%) BL symptom scores: PANSS (mean±SD): 72.5±17.7</p> <p>G3: Age (mean±SD): 39.90±NR Males (n(%)): NR Ethnicity: Caucasian 165/227 (72.7%) BL symptom scores: PANSS (mean±SD): 73.7±18.3</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 5–20mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Ziprasidone Dosage: 80–120mg/d Intervals: NR</p> <p>G3: Classification: SGA Drug: Ziprasidone Dosage: 80–160mg/d Intervals: NR</p>

AP = antipsychotic; BID = Twice daily; BL = baseline; BP = Bipolar Disorder; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; DX = diagnosis; ECG = Electrocardiography; ; ED = Emergency Department; FGA = first-generation antipsychotic; GAF = Global Assessment of Functioning; Hx = history; MADRS = Montgomery-Asberg Depression Rating Scale; MAO = Monoamine oxidase; mg = milligram; n = number; NA = not applicable; NR = not reported; PANSS = Positive and Negative Syndrome Scale; QTc = Corrected QT interval; RCT = randomized controlled trial; SAPS = Scale for the Assessment of Positive Symptoms; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; TD = Tardive dyskinesia; Tx = treatment; WBC = White blood count; wk = week; YMRS = Young Mania Rating Scale; yr = year

Table 44. Patient characteristics—perphenazine versus aripiprazole

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Kane et al. 2007 ⁹³	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: Aug 2000 to Mar 2001 Number of centers: Multicenter (n = 59) Setting: Outpatient Country: USA, Canada Financial support: Industry (Bristol–Myers Squibb)</p> <p>Washout period performed: yes (2–14d) Run-in phase performed: yes (4–6 wks) Followup period: 6 wks</p>	<p>Main inclusion criteria: > 18 yrs. Sz; Tx resistant with Olanzapine, Risperidone; PANSS≥75. CGI–S≥4; At least 2 of: conceptual disorganization, suspiciousness, hallucinatory behavior, delusions. Tx as outpatient for one 3 month period in last 2 yrs. Main exclusion criteria: Dx of schizoaffective disorder; residual Sz; bipolar disorder; presentation or Hx consistent with delirium; dementia; amnesia or other cognitive disorders; refractory response to prior clozapine or perphenazine; likely to require prohibited concomitant therapy; current or recent psychoactive drug or alcohol abuse or dependence; Hx of suicidal attempts or thoughts; known allergy to study drugs; Tx with an investigational drug within 4 wk of washout phase; previous enrollment in an aripiprazole clinical study; had other acute or unstable medical condition; pregnant or lactating</p>	<p>G1: Age (mean±SD): 41.60±10.87 Males (n(%)): 94/146 (64.4%) Ethnicity: Caucasian 75/146 (51.4%) BL symptom scores: BPRS (mean±SD): 17.6±3.34 PANSS (mean±SD): 99.5±15.61</p> <p>G2: Age (mean±SD): 42.60±12.40 Males (n(%)): 114/154 (74%) Ethnicity: Caucasian 76/154 (49.4%) BL symptom scores: BPRS (mean±SD): 17.2±2.86 PANSS (mean±SD): 97.5±15.62</p>	<p>G1: Classification: FGA Drug: Perphenazine Dosage: 8–64mg/d Intervals: BID if > 8mg/d</p> <p>G2: Classification: SGA Drug: Aripiprazole Dosage: 15–30mg/d Intervals: NR</p>

AP = antipsychotic; BID = Twice daily; BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; DX = diagnosis; FGA = first-generation antipsychotic; Hx = history; mg = milligram; n = number; NA = not applicable; NR = not reported; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; Tx = treatment; wk = week; yr = year

Table 45. Patient characteristics—perphenazine versus olanzapine

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Ascher-Svanum et al. 2008 ¹³¹	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: May–98 to Sep–02 Number of centers: Multicenter (n = 21) Setting: Mixed Country: USA Financial support: Multiple sources (NR)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 12 mo</p>	<p>Main inclusion criteria: aged >18 years; DSM–IV criteria for Sz, schizoaffective or schizophreniform disorders based on the SCID; minimum score of 18 on BPRS Main exclusion criteria: serious or unstable physical illnesses; high risk of suicide; lactating or pregnant women and individuals with medical conditions contraindicating use of any study medication</p>	<p>G1: Age (mean±SD): 44.20±11.90 Males (n(%)): 28/48 (58.3%) Ethnicity: Caucasian 27/48(52.3%) BL symptom scores: BPRS (mean±SD): 28.9±31.90 PANSS (mean±SD): 81.0±18.9</p> <p>G2: Age (mean±SD): 42.70±12.20 Males (n(%)): 138/222 (62.1%) Ethnicity: Caucasian 124/222 (55.9%) BL symptom scores: BPRS (mean±SD): 31.9±11.30 PANSS (mean±SD): 87.10±19.60</p>	<p>G1: Classification: FGA Drug: Perphenazine Dosage: NR Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: NR Intervals: NR</p>

Table 45. Patient characteristics—perphenazine versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Lieberman et al. 2005 ²³	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: Jan–01 to Dec–04 Number of centers: Multicenter (n = 57) Setting: Outpatient Country: USA Financial support: Multiple sources (AstraZeneca, Bristol–Myers Squibb, Forest, Janssen, Eli Lilly, Otsuka, Pfizer, Zenith Goldline, Schering–Plough, and Novartis)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 18 mo</p>	<p>Main inclusion criteria: Age 18–65 yrs; Dx of Sz; able to take oral AP medication Main exclusion criteria: Schizoaffective disorder, mental retardation, other cognitive disorders; Hx of serious adverse reactions to study drugs; had only one Sz episode; Hx of Tx resistance; pregnant or breast feeding; other serious and unstable medical condition</p>	<p>G1: Age (mean±SD): 40.00±11.10 Males (n(%)): 199/261 (76.3%) Ethnicity: Caucasian 152/261 (58.2%) BL symptom scores: PANSS (mean±SD): 74.3±18.1</p> <p>G2: Age (mean±SD): 40.80±10.80 Males (n(%)): 244/336 (72.6%) Ethnicity: Caucasian 196/336 (58.3%) BL symptom scores: PANSS (mean±SD): 76.1±18.2</p> <p>G3: Age (mean±SD): 40.90±11.20 Males (n(%)): 255/337 (75.7%) Ethnicity: Caucasian 213/337 (63.2%) BL symptom scores: PANSS (mean±SD): 75.7±16.9</p> <p>G4: Age (mean±SD): 40.60±11.30 Males (n(%)): 253/341 (74.2%) Ethnicity: Caucasian 204/301 (59.8%) BL symptom scores: PANSS (mean±SD):</p>	<p>G1: Classification: FGA Drug: Perphenazine Dosage: 8–32mg/d Intervals: once daily</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 7.5–30mg/d Intervals: once daily</p> <p>G3: Classification: SGA Drug: Quetiapine Dosage: 200–800mg/d Intervals: BID</p> <p>G4: Classification: SGA Drug: Risperidone Dosage: 1.5–6.0mg/d Intervals: once daily</p> <p>G5: Classification: SGA Drug: Ziprasidone Dosage: 40–160mg/d Intervals: BID</p>

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
			76.4±16.6 G5: Age (mean±SD): 40.10±11.00 Males (n(%)): 129/185 (69.7%) Ethnicity: Caucasian 109/185 (58.9%) BL symptom scores: PANSS (mean±SD): 75.4±18.6	

AP = antipsychotic; BID = Twice daily; BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; DX = diagnosis; FGA = first-generation antipsychotic; Hx = history; mg = milligram; n = number; NA = not applicable; NR = not reported; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; wk = week; yr = year

Table 46. Patient characteristics—perphenazine versus quetiapine

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Lieberman et al. 2005 ²³	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: Jan–01 to Dec–04 Number of centers: Multicenter (n = 57) Setting: Outpatient Country: USA Financial support: Multiple sources (AstraZeneca, Bristol–Myers Squibb, Forest, Janssen, Eli Lilly, Otsuka, Pfizer, Zenith Goldline, Schering–Plough, and Novartis)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 18 mo</p>	<p>Main inclusion criteria: Age 18–65 yrs; Dx of Sz; able to take oral AP medication Main exclusion criteria: Schizoaffective disorder, mental retardation, other cognitive disorders; Hx of serious adverse reactions to study drugs; had only one schizophrenic episode; Hx of treatment resistance; pregnant or breast feeding; other serious and unstable medical condition</p>	<p>G1: Age (mean±SD): 40.00±11.10 Males (n(%)): 199/261 (76.3%) Ethnicity: Caucasian 152/261 (58.2%) BL symptom scores: PANSS (mean±SD): 74.3±18.1</p> <p>G2: Age (mean±SD): 40.80±10.80 Males (n(%)): 244/336 (72.6%) Ethnicity: Caucasian 196/336 (58.3%) BL symptom scores: PANSS (mean±SD): 76.1±18.2</p> <p>G3: Age (mean±SD): 40.90±11.20 Males (n(%)): 255/337 (75.7%) Ethnicity: Caucasian 213/337 (63.2%) BL symptom scores: PANSS (mean±SD): 75.7±16.9</p> <p>G4: Age (mean±SD): 40.60±11.30 Males (n(%)): 253/341 (74.2%) Ethnicity: Caucasian 204/301 (59.8%) BL symptom scores: PANSS (mean±SD):</p>	<p>G1: Classification: FGA Drug: Perphenazine Dosage: 8–32mg/d Intervals: once daily</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 7.5–30mg/d Intervals: once daily</p> <p>G3: Classification: SGA Drug: Quetiapine Dosage: 200–800mg/d Intervals: BID</p> <p>G4: Classification: SGA Drug: Risperidone Dosage: 1.5–6.0mg/d Intervals: once daily</p> <p>G5: Classification: SGA Drug: Ziprasidone Dosage: 40–160mg/d Intervals: BID</p>

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
			76.4±16.6 G5: Age (mean±SD): 40.10±11.00 Males (n(%)): 129/185 (69.7%) Ethnicity: Caucasian 109/185 (58.9%) BL symptom scores: PANSS (mean±SD): 75.4±18.6	

AP = antipsychotic; BID = Twice daily; BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; DX = diagnosis; FGA = first-generation antipsychotic; Hx = history; mg = milligram; n = number; NA = not applicable; NR = not reported; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; wk = week; yr = year

Table 47. Patient characteristics—perphenazine versus risperidone

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Ascher-Svanum et al. 2008 ¹³¹	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: May–98 to Sep–02 Number of centers: Multicenter (n = 21) Setting: Mixed Country: USA Financial support: Multiple sources (NR)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 12 mo</p>	<p>Main inclusion criteria: aged >18 years; DSM–IV criteria for Sz, schizoaffective or schizophreniform disorders based on the SCID; minimum score of 18 on BPRS Main exclusion criteria: serious or unstable physical illnesses; high risk of suicide; lactating or pregnant women and individuals with medical conditions contraindicating use of any study medication</p>	<p>G1: Age (mean±SD): 44.20±11.90 Males (n(%)): 28/48 (58.3%) Ethnicity: Caucasian 27/48(52.3%) BL symptom scores: BPRS (mean±SD): 28.9±31.90 PANSS (mean±SD): 81.0±18.9</p> <p>G2: Age (mean±SD): 42.00±11.80 Males (n(%)): 130/217 (60.0%) Ethnicity: Caucasian 118/217 (54.3%) BL symptom scores: BPRS (mean±SD): 32.4±12.20 PANSS (mean±SD): 87.40±20.70</p>	<p>G1: Classification: FGA Drug: Perphenazine Dosage: NR Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: NR Intervals: NR</p>

Table 47. Patient characteristics—perphenazine versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Lieberman et al. 2005 ²³	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: Jan–01 to Dec–04 Number of centers: Multicenter (n = 57) Setting: Outpatient Country: USA Financial support: Multiple sources (AstraZeneca, Bristol–Myers Squibb, Forest, Janssen, Eli Lilly, Otsuka, Pfizer, Zenith Goldline, Schering–Plough, and Novartis)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 18 mo</p>	<p>Main inclusion criteria: Age 18–65 yrs; Dx of Sz; able to take oral AP medication Main exclusion criteria: Schizoaffective disorder, mental retardation, other cognitive disorders; Hx of serious adverse reactions to study drugs; had only one schizophrenic episode; Hx of treatment resistance; pregnant or breast feeding; other serious and unstable medical condition.</p>	<p>G1: Age (mean±SD): 40.00±11.10 Males (n(%)): 199/261 (76.3%) Ethnicity: Caucasian 152/261 (58.2%) BL symptom scores: PANSS (mean±SD): 74.3±18.1</p> <p>G2: Age (mean±SD): 40.80±10.80 Males (n(%)): 244/336 (72.6%) Ethnicity: Caucasian 196/336 (58.3%) BL symptom scores: PANSS (mean±SD): 76.1±18.2</p> <p>G3: Age (mean±SD): 40.90±11.20 Males (n(%)): 255/337 (75.7%) Ethnicity: Caucasian 213/337 (63.2%) BL symptom scores: PANSS (mean±SD): 75.7±16.9</p> <p>G4: Age (mean±SD): 40.60±11.30 Males (n(%)): 253/341 (74.2%) Ethnicity: Caucasian 204/301 (59.8%) BL symptom scores: PANSS (mean±SD):</p>	<p>G1: Classification: FGA Drug: Perphenazine Dosage: 8–32mg/d Intervals: once daily</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 7.5–30mg/d Intervals: once daily</p> <p>G3: Classification: SGA Drug: Quetiapine Dosage: 200–800mg/d Intervals: BID</p> <p>G4: Classification: SGA Drug: Risperidone Dosage: 1.5–6.0mg/d Intervals: once daily</p> <p>G5: Classification: SGA Drug: Ziprasidone Dosage: 40–160mg/d Intervals: BID</p>

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
			76.4±16.6 G5: Age (mean±SD): 40.10±11.00 Males (n(%)): 129/185 (69.7%) Ethnicity: Caucasian 109/185 (58.9%) BL symptom scores: PANSS (mean±SD): 75.4±18.6	

AP = antipsychotic; BID = Twice daily; BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; DX = diagnosis; FGA = first-generation antipsychotic; Hx = history; mg = milligram; n = number; NA = not applicable; NR = not reported; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; wk = week; yr = year

Table 48. Patient characteristics—perphenazine versus ziprasidone

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Lieberman et al. 2005 ²³	<p>Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: DSM IV Study period: Jan–01 to Dec–04 Number of centers: Multicenter (n = 57) Setting: Outpatient Country: USA Financial support: Multiple sources (AstraZeneca, Bristol–Myers Squibb, Forest, Janssen, Eli Lilly, Otsuka, Pfizer, Zenith Goldline, Schering–Plough, and Novartis)</p> <p>Washout period performed: NA Run-in phase performed: no Followup period: 18 mo</p>	<p>Main inclusion criteria: Age 18–65 yrs; Dx of Sz; able to take oral AP medication Main exclusion criteria: Schizoaffective disorder, mental retardation, other cognitive disorders; Hx of serious adverse reactions to study drugs; had only one schizophrenic episode; Hx of treatment resistance; pregnant or breast feeding; other serious and unstable medical condition.</p>	<p>G1: Age (mean±SD): 40.00±11.10 Males (n(%)): 199/261 (76.3%) Ethnicity: Caucasian 152/261 (58.2%) BL symptom scores: PANSS (mean±SD): 74.3±18.1</p> <p>G2: Age (mean±SD): 40.80±10.80 Males (n(%)): 244/336 (72.6%) Ethnicity: Caucasian 196/336 (58.3%) BL symptom scores: PANSS (mean±SD): 76.1±18.2</p> <p>G3: Age (mean±SD): 40.90±11.20 Males (n(%)): 255/337 (75.7%) Ethnicity: Caucasian 213/337 (63.2%) BL symptom scores: PANSS (mean±SD): 75.7±16.9</p> <p>G4: Age (mean±SD): 40.60±11.30 Males (n(%)): 253/341 (74.2%) Ethnicity: Caucasian 204/301 (59.8%) BL symptom scores: PANSS (mean±SD):</p>	<p>G1: Classification: FGA Drug: Perphenazine Dosage: 8–32mg/d Intervals: once daily</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 7.5–30mg/d Intervals: once daily</p> <p>G3: Classification: SGA Drug: Quetiapine Dosage: 200–800mg/d Intervals: BID</p> <p>G4: Classification: SGA Drug: Risperidone Dosage: 1.5–6.0mg/d Intervals: once daily</p> <p>G5: Classification: SGA Drug: Ziprasidone Dosage: 40–160mg/d Intervals: BID</p>

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
			76.4±16.6 G5: Age (mean±SD): 40.10±11.00 Males (n(%)): 129/185 (69.7%) Ethnicity: Caucasian 109/185 (58.9%) BL symptom scores: PANSS (mean±SD): 75.4±18.6	

AP = antipsychotic; BID = Twice daily; BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; DX = diagnosis; FGA = first-generation antipsychotic; Hx = history; mg = milligram; n = number; NA = not applicable; NR = not reported; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; wk = week; yr = year

Table 49. Patient characteristics—trifluoperazine versus clozapine

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Rinieris et al. 1980 ¹⁵⁷	Study design: RCT Registration #: NR Study population: Schizophrenia DSM Classification: NR Study period: NR Number of centers: Single center Setting: Inpatient Country: Greece Financial support: NR Washout period performed: NA Run-in phase performed: yes (1 wk) Followup period: 6 wks	Main inclusion criteria: Sz pts with absence of clinical symptoms; no Hx of thyroid or endocrinological disease; no use of psychotropic meds Main exclusion criteria: NR	G1: Age (mean±SD): 27.30±9.00 Males (n(%)): NR Ethnicity: NR BL symptom scores: BPRS (mean±SD): 41.5±9.3 G2: Age (mean±SD): 27.30±9.00 Males (n(%)): NR Ethnicity: NR BL symptom scores: BPRS (mean±SD): 40.5±10 G3: Age (mean±SD): 27.30±9.00 Males (n(%)): NR Ethnicity: NR BL symptom scores: BPRS (mean±SD): 36.4±11.4	G1: Classification: FGA Drug: Chlorpromazine Dosage: 50–100mg Intervals: TID G2: Classification: FGA Drug: Trifluoperazine Dosage: 2.5–5mg Intervals: TID G3: Classification: SGA Drug: Clozapine Dosage: 50–100mg Intervals: TID

AP = antipsychotic; BL = baseline; BPRS = Brief Psychiatric Rating Scale; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; DX = diagnosis; FGA = first-generation antipsychotic; Hx = history; mg = milligram; n = number; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; TID = Three times daily; wk = week; yr = year

B) Bipolar Disorder

Table 50. Patient characteristics—chlorpromazine versus clozapine

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Barbini et al. 1997 ⁴⁸	Study design: RCT Registration #: NR Study population: Bipolar DSM Classification: DSM IV Study period: NR Number of centers: Single center Setting: Inpatient Country: Italy Financial support: NR Washout period performed: no Run-in phase performed: no Followup period: 3 wks	Main inclusion criteria: Bipolar inpatients with a manic episode, according to DSM IV criteria Main exclusion criteria: Other axis I diagnoses, history of alcohol or substance abuse, medication with long-acting neuroleptics during a period of 6 months before the study	G1: Age (mean±SD): 40.90±8.90 Males (n(%)): 2/12 (16.7%) Ethnicity: NR BL symptom scores: YMRS (mean±SD): 34.10±8.00 G2: Age (mean±SD): 33.20±10.90 Males (n(%)): 8/15 (53.3%) Ethnicity: NR BL symptom scores: YMRS (mean±SD): 38.30±4.20	G1: Classification: FGA Drug: Chlorpromazine Dosage: 2mg/kg/d Intervals: NR G2: Classification: SGA Drug: Clozapine Dosage: 25mg/d Intervals: NR

AP = antipsychotic; BL = baseline; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; DX = diagnosis; FGA = first-generation antipsychotic; Hx = history; mg = milligram; n = number; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; TID = Three times daily; wk = week; YMRS = Young Mania Rating Scale; yr = year

Table 51. Patient characteristics—haloperidol versus aripiprazole

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Vieta et al. 2005 ³²	<p>Study design: RCT Registration #: NR Study population: Bipolar DSM Classification: DSM IV Study period: Dec 2003 to Jun 2004 Number of centers: Multicenter (n = 76) Setting: Inpatient Country: Spain Financial support: Industry (Bristol–Myers Squibb, Otsuka)</p> <p>Washout period performed: yes (1–3 days) Run-in phase performed: no Followup period: 12 wks</p>	<p>Main inclusion criteria: DSM–IV Dx of bipolar I disorder. Main exclusion criteria: Presence of rapid–cycling bipolar I disorder; duration of the current manic episode of more than 4 weeks; proven substance misuse; Pts considered unresponsive to antipsychotics.</p>	<p>G1: Age (mean±SD): 41.00 ± 11.80 Males (n(%)): 57/172 (31.9%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 4.90 ± 1.31 YMRS (mean±SD): 31.50 ± 7.87</p> <p>G2: Age (mean±SD): 40.80±10.80 Males (n(%)): 244/336 (72.6%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 5.00 ± 1.32 YMRS (mean±SD): 31.10 ±6.61</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 10–15mg Intervals: NR</p> <p>G2: Classification: SGA Drug: Aripiprazole Dosage: 15–30mg Intervals: NR</p>

Table 51. Patient characteristics—haloperidol versus aripiprazole (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Young et al. 2009 ³³	<p>Study design: RCT Registration #: NR Study population: Bipolar DSM Classification: DSM IV Study period: NR Number of centers: Multicenter (n = 59) Setting: Inpatient Country: Bulgaria, Croatia, Mexico, Peru, Russia, South Africa, USA Financial support: Industry (Bristol–Myers Squibb, Otsuka)</p> <p>Washout period performed: yes (2–4 wks) Run-in phase performed: no Followup period: 12 wks</p>	<p>Main inclusion criteria: with bipolar I disorder manic or mixed type (with or without psychotic features), who were experiencing an acute relapse requiring hospitalization Main exclusion criteria: Sz or schizoaffective disorder, or if they were experiencing their first manic or mixed episode; previously unresponsive to Tx for manic symptoms</p>	<p>G1: Age (mean±SD): 41.60 ± NR Males (n(%)): 72/165 (43.6%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 454.10 ± 10.15 CGI (mean±SD): 4.40 ± 1.27 YMRS (mean±SD): 27.60 ± 5.67</p> <p>G2: Age (mean±SD): 40.50 ± NR Males (n(%)): 72/167 (43.1%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 554.80 ± 10.31 CGI (mean±SD): 4.50 ± 1.29 YMRS (mean±SD): 28.01 ± 5.77</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 5–10mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Aripiprazole Dosage: 15–30mg/d Intervals: NR</p>

AP = antipsychotic; BL = baseline; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; DX = diagnosis; FGA = first-generation antipsychotic; mg = milligram; n = number; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; wk = week; YMRS = Young Mania Rating Scale; yr = year

Table 52. Patient characteristics—haloperidol versus olanzapine

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Moreno et al. 2007 ¹¹⁹	<p>Study design: RCT Registration #: NR Study population: Bipolar DSM Classification: DSM–IV Study period: NR Number of centers: Single center Setting: outpatient Country: Brazil Financial support: Foundation (NR)</p> <p>Washout period performed: yes (4 days) Run-in phase performed: no Followup period: 6 wk</p>	<p>Main inclusion criteria: Bipolar pts had not switched from a depression phase to mania or from mania phase to depression, within 1 month Main exclusion criteria: A serious general medical condition or neurological disease, evidence of primary sleep disorder or a previous history of drug or alcohol abuse</p>	<p>G1: Age (mean±SD): 39.20 ± 11.20 Males (n(%)): 59/185 (31.9%) Ethnicity: Caucasian 61/185 (33%) BL symptom scores: CGI-BP (mean±SD): 13.00 ± 2.00 YMRS (mean±SD): 30.60 ± 8.60</p> <p>G2: Age (mean±SD): 38.60 ± 14.20 Males (n(%)): 63/175 (42.8%) Ethnicity: Caucasian 70/175 (40%) BL symptom scores: CGI-BP (mean±SD): 11.30 ± 1.80 YMRS (mean±SD): 30.60 ± 5.00</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 3–15mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Olanzapine Dosage: 5–20mg/d Intervals: NR</p>

Table 52. Patient characteristics—haloperidol versus olanzapine (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Tohen et al. 2003 ¹⁴⁰	Study design: RCT Registration #: NR Study population: Bipolar DSM Classification: DSM–IV Study period: NR Number of centers: Multicenter (n = 58) Setting: Mixed Country: International (North America and Europe) Financial support: Industry (Eli Lilly) Washout period performed: yes (7 days) Run-in phase performed: no Followup period: 12 wk	Main inclusion criteria: DSM–IV criteria for bipolar disorder manic or mixed type (with or without psychotic features) Main exclusion criteria: DSM–IV substance dependence	G1: Age (mean±SD): 40.00 ± 13.00 Males (n(%)): 94/219 (42.9%) Ethnicity: NR BL symptom scores: CGI-BP (mean±SD): 30.60 ± 7.68 G2: Age (mean±SD): 41.00 ± 13.00 Males (n(%)): 86/234 (36.8%) Ethnicity: NR BL symptom scores: CGI-BP (mean±SD): 31.10 ± 7.57	G1: Classification: FGA Drug: Haloperidol Dosage: 3–15mg/d Intervals: NR G2: Classification: SGA Drug: Olanzapine Dosage: 5–20mg/d Intervals: NR

AP = antipsychotic; BL = baseline; CGI = Clinical Global Impressions; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; FGA = first-generation antipsychotic; mg = milligram; n = number; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; wk = week; YMRS = Young Mania Rating Scale; yr = year

Table 53. Patient characteristics—haloperidol versus quetiapine

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
McIntyre et al. 2005 ¹¹⁵	<p>Study design: RCT Registration #: NR Study population: Bipolar DSM Classification: DSM-IV Study period: Jan-01 to Apr-02 Number of centers: Multicenter (n = 4) Setting: Inpatient Country: International Financial support: Industry (AstraZeneca)</p> <p>Washout period performed: no Run-in phase performed: no Followup period: 12 wks</p>	<p>Main inclusion criteria: DSM-IV diagnosis of bipolar I disorder, current episode manic, with or without psychotic features.</p> <p>Main exclusion criteria: Received treatment with clozapine within 28 days of the start of the trial, had an index manic episode judged to be the direct physiological consequence of a medical condition, treatment, or substance abuse</p>	<p>G1: Age (mean±SD): 45.10 ± NR Males (n(%)): 36/98 (36.7%) Ethnicity: NR BL symptom scores: YMRS (mean±SD): 32.30 ± NR</p> <p>G2: Age (mean±SD): 42.80 ± NR Males (n(%)): 37/101 (36.6%) Ethnicity: NR BL symptom scores: YMRS (mean±SD): 34.00 ± NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 2–8mg/d Intervals: BID</p> <p>G2: Classification: SGA Drug: Quetiapine Dosage: 100–800mg/d Intervals: BID</p>

AP = antipsychotic; BID = Twice daily; BL = baseline; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; FGA = first-generation antipsychotic; mg = milligram; n = number; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; wk = week; YMRS = Young Mania Rating Scale; yr = year

Table 54. Patient characteristics—haloperidol versus risperidone

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Janicak et al. 2001 ⁹⁰	<p>Study design: RCT Registration #: NR Study population: Bipolar DSM Classification: DSM–IV Study period: NR Number of centers: Multicenter (n=3) Setting: Inpatient Country: USA Financial support: Industry (Janssen)</p> <p>Washout period performed: yes (4–6d) Run-in phase performed: no Followup period: 6 wks</p>	<p>Main inclusion criteria: bipolar subtype/manic phase, had not received depot antipsychotics or fluoxetine in the 4 weeks before Main exclusion criteria: A Dx of alcohol or substance abuse within 6 months of admission, hypersensitivity to haloperidol or risperidone</p>	<p>G1: Age (mean±SD): 41.80 ± NR Males (n(%)): 59/185 (31.9%) Ethnicity: Caucasian 61/185 (33%) BL symptom scores: NR</p> <p>G2: Age (mean±SD): 41.90 ± NR Males (n(%)): 63/175 (36%) Ethnicity: Caucasian 70/175 (40%) BL symptom scores: NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 5–17mg/d Intervals: BID</p> <p>G2: Classification: SGA Drug: Risperidone Dosage: 1–6mg/d Intervals: BID</p>
Sachs et al. 2002 ¹²⁸	<p>Study design: RCT Registration #: NR Study population: Bipolar DSM Classification: DSM–IV Study period: NR Number of centers: Multicenter (NR) Setting: Inpatient Country: USA Financial support: Industry (Janssen)</p> <p>Washout period performed: no Run-in phase performed: no Followup period: 3 wks</p>	<p>Main inclusion criteria: bipolar disorder and at least 1 prior manic episode Main exclusion criteria: alcohol or substance abuse</p>	<p>G1: Age (mean±SD): 42.70 ± 12.38 Males (n(%)): 30/53 (56.6%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 41.20 ± 10.92 YMRS (mean±SD): 27.30 ± 5.82</p> <p>G2: Age (mean±SD): 41.40 ± 10.82 Males (n(%)): 26/52 (50.0%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 42.50 ± 10.82 YMRS (mean±SD): 28.00 ± 5.77</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 3–12mg/d Intervals: BID</p> <p>G2: Classification: SGA Drug: Risperidone Dosage: 2–6mg/d Intervals: BID</p>

Table 54. Patient characteristics—haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Segal et al. 1998 ¹³³	<p>Study design: RCT Registration #: NR Study population: Bipolar DSM Classification: DSM–IV Study period: NR Number of centers: Single center Setting: Inpatient Country: South Africa Financial support: Industry (Janssen)</p> <p>Washout period performed: no Run-in phase performed: no Followup period: 28 days</p>	<p>Main inclusion criteria: bipolar with acute manic episode</p> <p>Main exclusion criteria: NR</p>	<p>G1: Age (mean±SD): 29.50 ± NR Males (n(%)): 5/15 (33.3%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 15.20 ± NR CGI (mean±SD): 3.60 ± NR GAS (mean±SD): 40.20 ± NR</p> <p>G2: Age (mean±SD): 34.3 ± NR Males (n(%)): 2/15 (13.3%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 17.60 ± NR CGI (mean±SD): 4.000 ± NR GAS (mean±SD): 33.80 ± NR</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 10mg/d Intervals: BID</p> <p>G2: Classification: SGA Drug: Risperidone Dosage: 6mg/d Intervals: BID</p>

Table 54. Patient characteristics—haloperidol versus risperidone (continued)

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Smulevich et al. 2005 ¹³⁸	<p>Study design: RCT Registration #: NR Study population: Bipolar DSM Classification: DSM–IV Study period: NR Number of centers: Multicenter Setting: Mixed Country: International Financial support: Industry (Johnson & Johnson)</p> <p>Washout period performed: yes (3 days) Run-in phase performed: no Followup period: 12 wks</p>	<p>Main inclusion criteria: bipolar I disorder; Hx of at least one documented manic or mixed episode; met DSM–IV criteria for a current manic episode. Main exclusion criteria: Schizoaffective disorder; rapid cycling bipolar disorder; borderline or antisocial personality disorder; recent substance abuse or dependence; poor antimanic response to antipsychotic monotherapy</p>	<p>G1: Age (mean±SD): 38.50 ± 12.20 Males (n(%)): 83/154 (53.9%) Ethnicity: Caucasian 95/154 (65.9%) BL symptom scores: BPRS (mean±SD): 32.50 ± 7.30 CGI-S (mean±SD): 3.70 ± 0.80 YMRS (mean±SD): 31.30 ± 6.50</p> <p>G2: Age (mean±SD): 41.30 ± 13.10 Males (n(%)): 78/144 (54.2%) Ethnicity: Caucasian 102/154 (66.2%) BL symptom scores: BPRS (mean±SD): 32.30 ± 7.80 CGI-S (mean±SD): 3.80 ± 0.80 YMRS (mean±SD): 32.10 ± 6.90</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 2–12mg/d Intervals: NR</p> <p>G2: Classification: SGA Drug: Risperidone Dosage: 1–6mg/d Intervals: NR</p>

AP = antipsychotic; BID = Twice daily; BL = baseline; BPRS = Brief Psychiatric Rating Scale; ; CGI = Clinical Global Impression; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; FGA = first-generation antipsychotic; GAS = Global Assessment Scale; mg = milligram; n = number; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; wk = week; YMRS = Young Mania Rating Scale; yr = year

Table 55. Patient characteristics—haloperidol versus ziprasidone

Author, Year	Study Characteristics	Inclusion and Exclusion Criteria	Population	Interventions
Vieta et al. 2005 ³²	<p>Study design: RCT Registration #: NR Study population: Bipolar DSM Classification: DSM IV Study period: NR Number of centers: Multicenter (n = 76) Setting: Inpatient Country: Spain Financial support: Industry (Bristol–Myers Squibb, Otsuka)</p> <p>Washout period performed: yes (1–3 days) Run-in phase performed: no Followup period: 12 wks</p>	<p>Main inclusion criteria: DSM–IV Dx of bipolar I disorder Main exclusion criteria: Presence of rapid–cycling bipolar I disorder; duration of the current manic episode of more than 4 weeks; proven substance misuse; pts considered unresponsive to antipsychotics; recent Tx with a long–acting antipsychotic, lithium or divalproate</p>	<p>G1: Age (mean±SD): 41.00 ± 11.80 Males (n(%)): 57/172 (31.9%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 4.90 ± 1.31 YMRS (mean±SD): 31.50 ± 7.87</p> <p>G2: Age (mean±SD): 40.80±10.80 Males (n(%)): 244/336 (72.6%) Ethnicity: NR BL symptom scores: BPRS (mean±SD): 5.00 ± 1.32 YMRS (mean±SD): 31.10 ±6.61</p>	<p>G1: Classification: FGA Drug: Haloperidol Dosage: 10–15mg Intervals: NR</p> <p>G2: Classification: SGA Drug: Aripiprazole Dosage: 15–30mg Intervals: NR</p>

AP = antipsychotic; BID = Twice daily; BL = baseline; BPRS = Brief Psychiatric Rating Scale; d = day; DSM = Diagnostic and Statistical Manual of Mental Disorders; FGA = first-generation antipsychotic; mg = milligram; n = number; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; SGA = second-generation antipsychotic; Sz = schizophrenia; wk = week; YMRS = Young Mania Rating Scale; yr = year

Appendix I. Patient Flow Through Trials

A) Schizophrenia and Related Psychoses

Table 56. Patient flow through trials—chlorpromazine versus clozapine

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Chiu et al. 1976 ¹⁵²	Classification	FGA	SGA				
	Medication	Chlorpromazine	Clozapine				
	Dosage	50–300mg/d	50–300mg/d				
	No screened:	NR					
	No randomized:	33	31				
	No completed:	14	22				
	No analyzed (E):	NR	NR				
	No analyzed (S):	14	22				
Claghorn et al. 1987 ⁶³	Classification	FGA	SGA				
	Medication	Chlorpromazine	Clozapine				
	Dosage	50mg–1800mg/d	25mg–900mg/d				
	No screened:	NR					
	No randomized:	76	75				
	No completed:	40	48				
	No analyzed (E):	76	75				
	No analyzed (S):	76	75				
Ekblom et al. 1974 ¹⁵³	Classification	FGA	SGA				
	Medication	Chlorpromazine	Clozapine				
	Dosage	65–700mg/d	65–600mg/d				
	No screened:	NR					
	No randomized:	21	20				
	No completed:	19	17				
	No analyzed (E):	21	20				
	No analyzed (S):	21	20				

Table 56. Patient flow through trials—chlorpromazine versus clozapine (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Gelenberg et al. 1979 ¹⁵⁴	Classification	FGA	SGA				
	Medication	Chlorpromazine	Clozapine				
	Dosage	50–1800mg/d	25–900mg/d				
	No screened:	NR					
	No randomized:	8	7				
	No completed:	NR	NR				
	No analyzed (E):	8	7				
Guirguis et al. 1977 ¹⁶⁰	No analyzed (S):	NR	6				
	Classification	FGA	SGA				
	Medication	chlorpromazine	Clozapine				
	Dosage	150–900mg/d	75–450mg/d				
	No screened:	NR					
	No randomized:	28	22				
	No completed:	19	16				
Hong et al. 1997 ⁸⁷	No analyzed (E):	19	16				
	No analyzed (S):	19	16				
	Classification	FGA	SGA				
	Medication	Chlorpromazine	Clozapine				
	Dosage	50–1800mg/d	25–900mg/d				
	No screened:	NR					
	No randomized:	19	21				
Kane et al. 1988 ⁹⁴	No completed:	17	19				
	No analyzed (E):	19	21				
	No analyzed (S):	19	21				
	Classification	FGA	SGA				
	Medication	Chlorpromazine	Clozapine				
	Dosage	1000–1800mg/d	500–900mg/d				
	No screened:	NR					
	No randomized:	142	126				
	No completed:	124	111				
	No analyzed (E):	139	126				
	No analyzed (S):	142	126				

Table 56. Patient flow through trials—chlorpromazine versus clozapine (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Leon et al. 1979 ¹⁵⁶	Classification	FGA	SGA				
	Medication	Chlorpromazine	Clozapine				
	Dosage	100–1600mg/d	100–1600mg/d				
	No screened:	NR					
	No randomized:	25	25				
	No completed:	17	14				
	No analyzed (E):	25	25				
	No analyzed (S):	25	25				
Lieberman et al. 2003 ¹⁰⁹	Classification	FGA	SGA				
	Medication	Chlorpromazine	Clozapine				
	Dosage	max of 600 mg/d	max of 400 mg/d				
	No screened:	2708					
	No randomized:	83	81				
	No completed:	62	68				
	No analyzed (E):	80	80				
	No analyzed (S):	80	80				
Rinieris et al. 1980 ¹⁵⁷	Classification	FGA	FGA	SGA			
	Medication	Chlorpromazine	Trifluoperazine	Clozapine			
	Dosage	50–100mg	2.5–5mg	50–100mg			
	No screened:	NR					
	No randomized:	16	20	5			
	No completed:	10	9	5			
	No analyzed (E):	10	9	5			
	No analyzed (S):	10	9	5			
Shopsin et al. 1979 ¹⁵⁸	Classification	FGA	SGA				
	Medication	Chlorpromazine	Clozapine				
	Dosage	50–1600mg/d	25–900mg/d				
	No screened:	50					
	No randomized:	12	13				
	No completed:	12	13				
	No analyzed (E):	12	13				
	No analyzed (S):	12	13				

Table 56. Patient flow through trials—chlorpromazine versus clozapine (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Singer et al. 1974¹⁶¹	Classification	FGA	SGA				
	Medication	chlorpromazine	Clozapine				
	Dosage	50–600mg/d	50–600mg/d				
	No screened:	NR					
	No randomized:	20	20				
	No completed:	19	19				
	No analyzed (E):	19	19				
	No analyzed (S):	19	19				

d = day; E = efficacy; FGA = first-generation antipsychotic; max = maximum; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 57. Patient flow through trials—chlorpromazine versus olanzapine

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Conley et al. 1998⁶⁶	Classification	FGA	SGA				
	Medication	Chlorpromazine	Olanzapine				
	Dosage	600–1200mg/d	12.5–25mg/d				
	No screened:	103					
	No randomized:	42	42				
	No completed:	29	30				
	No analyzed (E):	42	42				
	No analyzed (S):	42	42				

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 58. Patient flow through trials—chlorpromazine versus quetiapine

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Peuskens et al. 1997¹²¹	Classification	FGA	SGA				
	Medication	Chlorpromazine	Quetiapine				
	Dosage	75–750mg/d	75–750mg/d				
	No screened:	NR					
	No randomized:	100	101				
	No completed:	64	70				
	No analyzed (E):	100	101				
	No analyzed (S):	100	101				

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 59. Patient flow through trials—chlorpromazine versus ziprasidone

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Kane et al. 2006 ⁹⁶	Classification	FGA	SGA				
	Medication	Chlorpromazine	Ziprasidone				
	Dosage	100–1200mg/d	40–160mg/d				
	No screened:	NR					
	No randomized:	489	154	152			
	No completed:	135	136				
	No analyzed (E):	154	152				
	No analyzed (S):	154	152				

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 60. Patient flow through trials—fluphenazine versus olanzapine

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Jakovljevic et al. 1999 ⁸⁹	Classification	FGA	SGA				
	Medication	Fluphenazine	Olanzapine				
	Dosage	6–21mg/d	5–20mg/d				
	No screened:	64					
	No randomized:	30	30				
	No completed:	22	29				
	No analyzed (E):	28	27				
	No analyzed (S):	30	30				
Ljubin et al. 2000 ¹¹²	Classification	FGA	SGA				
	Medication	Fluphenazine	Olanzapine				
	Dosage	6–21mg/d	5–20mg/d				
	No screened:	NR					
	No randomized:	30	30				
	No completed:	8	10				
	No analyzed (E):	8	10				
	No analyzed (S):	NR	NR				

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 61. Patient flow through trials – fluphenazine versus quetiapine

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Conley et al. 2005 ⁶⁷	Classification	FGA	SGA	SGA			
	Medication	Fluphenazine	Quetiapine	Risperidone			
	Dosage	10–15mg/d	300–500mg/d	3–5mg/d			
	No screened:	52					
	No randomized:	13	12	13			
	No completed:	4	8	8			
	No analyzed (E):	13	12	13			
	No analyzed (S):	12	12	13			

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 62. Patient flow through trials – fluphenazine versus risperidone

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Conley et al. 2005 ⁶⁷	Classification	FGA	SGA	SGA			
	Medication	Fluphenazine	Quetiapine	Risperidone			
	Dosage	10–15mg/d	300–500mg/d	3–5mg/d			
	No screened:	52					
	No randomized:	13	12	13			
	No completed:	4	8	8			
	No analyzed (E):	13	12	13			
	No analyzed (S):	12	12	13			

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 63. Patient flow through trials–haloperidol versus aripiprazole

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Andrezina et al. 2006⁴⁴	Classification	FGA	SGA				
	Medication	Haloperidol	Aripiprazole				
	Dosage	6.5mg	9.75mg				
	No screened:	448					
	No randomized:	185	175				
	No completed:	185	175				
	No analyzed (E):	185	175				
	No analyzed (S):	183	175				
Daniel et al. 2007⁷⁴	Classification	FGA	SGA				
	Medication	Haloperidol	Aripiprazole				
	Dosage	6.5mg/d	9.75mg/d				
	No screened:	NR					
	No randomized:	185	175				
	No completed:	136	140				
	No analyzed (E):	151	153				
	No analyzed (S):	150	155				
de Oliveira et al. 2009⁷⁶	Classification	FGA	SGA				
	Medication	Haloperidol	Aripiprazole				
	Dosage	10–15mg/d	15–30mg/d				
	No screened:	NR					
	No randomized:	33	66				
	No completed:	21	53				
	No analyzed (E):	31	66				
	No analyzed (S):	31	66				
Kane et al. 2002⁹²	Classification	FGA	SGA	SGA			
	Medication	Haloperidol	Aripiprazole	Aripiprazole			
	Dosage	10mg/d	15mg/d	30mg/d			
	No screened:	502					
	No randomized:	104	102	102			
	No completed:	62	68	60			
	No analyzed (E):	104	102	102			
	No analyzed (S):	103	102	101			

Table 63. Patient flow through trials—haloperidol versus aripiprazole (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Kasper et al. 2003⁹⁸	Classification	FGA	SGA				
	Medication	Haloperidol	Aripiprazole				
	Dosage	5–10mg/d	20–30mg/d				
	No screened:	1294					
	No randomized:	433	861				
	No completed:	128	367				
	No analyzed (E):	428	851				
	No analyzed (S):	428	851				
Kim et al. 2010¹⁰²	Classification	FGA	SGA	SGA	SGA		
	Medication	Haloperidol	Aripiprazole	Olanzapine	Risperidone		
	Dosage	15.9+/-7.1mg/d	21.7+/-5.5mg/d	15.9+/-4.3mg/d	4.8+/-2.9mg/d		
	No screened:	NR					
	No randomized:	35	31	32	41		
	No completed:	NR	NR	NR	NR		
	No analyzed (E):	NR	NR	NR	NR		
	No analyzed (S):	NR	NR	NR	NR		
McCue et al. 2006⁷³	Classification	FGA	SGA	SGA	SGA	SGA	SGA
	Medication	Haloperidol	Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone
	Dosage	4–30mg	10–45mg	5–40mg	50–1200mg	2–9mg	40–240mg
	No screened:	584					
	No randomized:	61	63	62	58	65	59
	No completed:	53	49	50	50	55	45
	No analyzed (E):	57	53	50	52	57	50
	No analyzed (S):	57	53	50	52	57	50
Tran–Johnson et al. 2007³¹	Classification	FGA	SGA	SGA	SGA	SGA	
	Medication	Haloperidol	Aripiprazole	Aripiprazole	Aripiprazole	Aripiprazole	
	Dosage	7.5mg/d	1mg/d	5.25mg/d	9.75mg/d	15mg/d	
	No screened:	NR					
	No randomized:	60	57	63	57	58	
	No completed:	NR	NR	NR	NR	NR	
	No analyzed (E):	57	56	62	56	58	
	No analyzed (S):	57	56	62	56	58	

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 64. Patient flow through trials—haloperidol versus asenapine

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Kane et al. 2010 ⁹⁷	Classification	FGA	SGA	SGA			
	Medication	Haloperidol	Asenapine	Asenapine			
	Dosage	4mg/d	5mg/d	10mg/d			
	No screened:	513					
	No randomized:	115	114	106			
	No completed:	65	68	70			
	No analyzed (E):	112	109	105			
	No analyzed (S):	115	111	106			

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 65. Patient flow through trials—haloperidol versus clozapine

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Breier et al. 1994 ⁵⁵	Classification	FGA	SGA				
	Medication	Haloperidol	Clozapine				
	Dosage	10–30mg/d	200–600mg/d				
	No screened:	NR					
	No randomized:	NR	NR				
	No completed:	20	19				
	No analyzed (E):	20	19				
	No analyzed (S):	20	19				
Citrome et al. 2001 ⁶²	Classification	FGA	SGA	SGA	SGA		
	Medication	Haloperidol	Clozapine	Olanzapine	Risperidone		
	Dosage	10–30mg/d	200–800mg/d	10–40mg/d	4–16mg/d		
	No screened:	NR					
	No randomized:	37	40	39	41		
	No completed:	27	32	30	28		
	No analyzed (E):	37	40	39	41		
	No analyzed (S):	37	40	39	41		
Covington et al. 2000 ⁷⁰	Classification	FGA	SGA				
	Medication	Haloperidol	Clozapine				
	Dosage	NR	NR				
	Patient flow through trial						
	No screened:	NR					
	No randomized:	42	40				
	No completed:	NR	NR				
	No analyzed (E):	42	40				
	No analyzed (S):	42	40				
Itoh et al. 1977 ¹⁵⁵	Classification	FGA	SGA				
	Medication	Haloperidol	Clozapine				
	Dosage	2.25–15mg/d	75–500mg/d				
	No screened:	NR					
	No randomized:	41	47				
	No completed:	NR	NR				
	No analyzed (E):	NR	NR				
	No analyzed (S):	NR	NR				

Table 65. Patient flow through trials—haloperidol versus clozapine (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Kane et al. 2001 ⁹⁵	Classification	FGA	SGA				
	Medication	Haloperidol	Clozapine				
	Dosage	5–16mg/d	12.5–800mg/d				
	No screened:	NR					
	No randomized:	34	37				
	No completed:	12	24				
	No analyzed (E):	11	23				
	No analyzed (S):	34	37				
Kleiser et al. 1994 ¹⁰³	Classification	FGA	SGA				
	Medication	Haloperidol	Clozapine				
	Dosage	16mg/d	350mg/d				
	No screened:	NR					
	No randomized:	18	18				
	No completed:	17	17				
	No analyzed (E):	17	17				
	No analyzed (S):	17	17				
Krakowski et al. 2006 ¹⁰⁵	Classification	FGA	SGA	SGA			
	Medication	Haloperidol	Clozapine	Olanzapine			
	Dosage	10–30mg/d	200–800mg/d	10–35mg/d			
	No screened:	134					
	No randomized:	36	37	37			
	No completed:	20	24	26			
	No analyzed (E):	36	37	37			
	No analyzed (S):	36	37	37			
Rosenheck et al. 1997 ¹²⁶	Classification	FGA	SGA				
	Medication	Haloperidol	Clozapine				
	Dosage	5–30mg/d	100–900mg/d				
	No screened:	423					
	No randomized:	218	205				
	No completed:	61	117				
	No analyzed (E):	218	205				
	No analyzed (S):	218	205				

Table 65. Patient flow through trials—haloperidol versus clozapine (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Volakva et al. 2002 ¹⁴⁵	Classification	FGA	SGA	SGA	SGA		
	Medication	Haloperidol	Clozapine	Olanzapine	Risperidone		
	Dosage	10–30mg/d	200–800mg/d	10–40mg/d	4–16mg/d		
	No screened:	NR					
	No randomized:	37	40	39	41		
	No completed:	21	22	26	22		
	No analyzed (E):	37	40	39	41		
	No analyzed (S):	37	40	39	41		

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 66. Patient flow through trials—haloperidol versus olanzapine

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Altamura et al. 2002⁴³	Classification	FGA	SGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	10–20mg/d	10–20mg/d				
	No screened:	NR					
	No randomized:	15	13				
	No completed:	8	13				
	No analyzed (E):	11	13				
	No analyzed (S):	11	13				
Alvarez–Jimenez et al. 2006¹⁴²	Classification	FGA	SGA	SGA			
	Medication	Haloperidol	Olanzapine	Risperidone			
	Dosage	3–9mg/d	5–20mg/d	3–6mg/d			
	No screened:	NR					
	No randomized:	20	17	24			
	No completed:	20	17	24			
	No analyzed (E):	20	17	24			
	No analyzed (S):	20	17	24			
Beasley et al. 1996⁴⁹	Classification	FGA	SGA	SGA	SGA		
	Medication	Haloperidol	Olanzapine	Olanzapine	Olanzapine		
	Dosage	10–20mg/d	2.5–7.5mg/d	7.5–12.5mg/d	12.5–17.5mg/d		
	No screened:	335					
	No randomized:	69	65	64	69		
	No completed:	30	30	30	34		
	No analyzed (E):	18	16	19	27		
	No analyzed (S):	69	65	64	69		
Beasley et al. 1997⁵⁰	Classification	FGA	SGA	SGA	SGA	SGA	
	Medication	Haloperidol	Olanzapine	Olanzapine	Olanzapine	Olanzapine	
	Dosage	15±5mg/d	1.0mg/d	5±2.5mg/d	10±2.5mg/d	15±2.5mg/d	
	No screened:	NR					
	No randomized:	81	88	87	86	89	
	No completed:	43	48	48	53	55	
	No analyzed (E):	79	83	85	83	85	
	No analyzed (S):	81	88	87	86	89	

Table 66. Patient flow through trials–haloperidol versus olanzapine (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Bernardo et al. 2001⁵¹	Classification	FGA	SGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	10mg/d	10mg/d				
	No screened:	NR					
	No randomized:	13	14				
	No completed:	NR	NR				
	No analyzed (E):	13	14				
	No analyzed (S):	13	14				
Boulay et al. 2007⁵⁴	Classification	FGA	SGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	2.5–20mg/d	2.5–20mg/d				
	No screened:	NR					
	No randomized:	13	14				
	No completed:	8	14				
	No analyzed (E):	11	14				
	No analyzed (S):	11	14				
Breier et al. 2002⁵⁶	Classification	FGA	SGA	SGA	SGA	SGA	
	Medication	Haloperidol	Olanzapine	Olanzapine	Olanzapine	Olanzapine	
	Dosage	7.5mg	2.5mg	5.0mg	7.5mg	10.0mg	
	No screened:	NR					
	No randomized:	40	48	45	46	46	
	No completed:	40	48	43	46	46	
	No analyzed (E):	40	48	43	46	46	
	No analyzed (S):	40	48	43	46	46	
Buchanan et al. 2005⁵⁸	Classification	FGA	SGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	10–30mg/d	10–30mg/d				
	No screened:	68					
	No randomized:	34	29				
	No completed:	31	26				
	No analyzed (E):	34	29				
	No analyzed (S):	34	29				

Table 66. Patient flow through trials—haloperidol versus olanzapine (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Citrome et al. 2001⁶²	Classification	FGA	SGA	SGA	SGA		
	Medication	Haloperidol	Clozapine	Olanzapine	Risperidone		
	Dosage	10–30mg/d	200–800mg/d	10–40mg/d	4–16mg/d		
	No screened:	NR					
	No randomized:	37	40	39	41		
	No completed:	27	32	30	28		
	No analyzed (E):	37	40	39	41		
	No analyzed (S):	37	40	39	41		
Crespo–Facorro et al. 2006⁷¹	Classification	FGA	SGA	SGA			
	Medication	Haloperidol	Olanzapine	Risperidone			
	Dosage	3–9mg/d	5–20mg/d	3–6mg/d			
	No screened:	202					
	No randomized:	56	55	61			
	No completed:	55	53	57			
	No analyzed (E):	56	55	61			
	No analyzed (S):	56	55	61			
Davidson et al. 2009⁷⁵	Classification	FGA	SGA	SGA	SGA		
	Medication	Haloperidol	Olanzapine	Quetiapine	Ziprasidone		
	Dosage	1–4mg/d	5–20mg/d	200–750mg/d	40–160mg/d		
	No screened:	NR					
	No randomized:	103	104	105	82		
	No completed:	52	60	74	45		
	No analyzed (E):	52	60	74	45		
	No analyzed (S):	52	60	74	45		
de Haan et al. 2003⁷⁸	Classification	FGA	SGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	2.5mg/d	7.5mg/d				
	No screened:	NR					
	No randomized:	12	12				
	No completed:	10	9				
	No analyzed (E):	10	9				
	No analyzed (S):	10	9				

Table 66. Patient flow through trials—haloperidol versus olanzapine (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Goldman et al. 2004⁸⁴	Classification	FGA	SGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	5–20mg/d	5–20mg/d				
	No screened:	NR					
	No randomized:	5	5				
	No completed:	2	5				
	No analyzed (E):	5	5				
Ishigooka et al. 2001⁸⁸	No analyzed (S):	5	5				
	Classification	FGA	SGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	4–12mg/d	5–15mg/d				
	No screened:	NR					
	No randomized:	89	93				
	No completed:	59	75				
Kahn et al. 2008⁹¹	No analyzed (E):	78	80				
	No analyzed (S):	84	90				
	Classification	FGA	SGA	SGA	SGA		
	Medication	Haloperidol	Olanzapine	Quetiapine	Ziprasidone		
	Dosage	1–4mg/d	5–20mg/d	200–750mg/d	40–16mg/d		
	No screened:	1047					
	No randomized:	103	105	104	82		
Keefe et al. 2006¹⁰¹	No completed:	68	82	70	53		
	No analyzed (E):	103	105	104	82		
	No analyzed (S):	103	105	104	82		
	Classification	FGA	SGA	SGA			
	Medication	Haloperidol	Olanzapine	Risperidone			
	Dosage	2–19mg/d	5–20mg/d	2–10mg/d			
	No screened:	414					
	No randomized:	97	159	158			
	No completed:	27	64	54			
	No analyzed (E):	94	153	148			
	No analyzed (S):	97	159	158			

Table 66. Patient flow through trials–haloperidol versus olanzapine (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Kim et al. 2010 ¹⁰²	Classification	FGA	SGA	SGA	SGA		
	Medication	Haloperidol	Aripiprazole	Olanzapine	Risperidone		
	Dosage	15.9+/-7.1mg/d	21.7+/-5.5mg/d	15.9+/-4.3mg/d	4.8+/-2.9mg/d		
	No screened:	NR					
	No randomized:	35	31	32	41		
	No completed:	NR	NR	NR	NR		
	No analyzed (E):	NR	NR	NR	NR		
	No analyzed (S):	NR	NR	NR	NR		
Kongsakon et al. 2006 ¹⁰⁴	Classification	FGA	SGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	5–20mg	5–20mg				
	No screened:	440					
	No randomized:	132	144				
	No completed:	94	113				
	No analyzed (E):	123	139				
	No analyzed (S):	124	139				
Krakowski et al. 2006 ¹⁰⁵	Classification	FGA	SGA	SGA			
	Medication	Haloperidol	Clozapine	Olanzapine			
	Dosage	10–30mg/d	200–800mg/d	10–35mg/d			
	No screened:	134					
	No randomized:	36	37	37			
	No completed:	20	24	26			
	No analyzed (E):	36	37	37			
	No analyzed (S):	36	37	37			
Lahti et al. 2009 ¹⁰⁶	Classification	FGA	SGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	10–20mg/d	12.5–25mg/d				
	No screened:	37					
	No randomized:	14	18				
	No completed:	12	17				
	No analyzed (E):	12	17				
	No analyzed (S):	12	17				

Table 66. Patient flow through trials—haloperidol versus olanzapine (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Lieberman et al. 2003 ¹⁰⁸	Classification	FGA	SGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	2–20mg/d	5–20mg/d				
	No screened:	263					
	No randomized:	132	131				
	No completed:	71	89				
	No analyzed (E):	132	131				
	No analyzed (S):	132	131				
Lindenmayer et al. 2007 ¹¹⁰	Classification	FGA	SGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	5–20mg/d	5–20mg/d				
	No screened:	36					
	No randomized:	19	16				
	No completed:	19	16				
	No analyzed (E):	16	15				
	No analyzed (S):	16	15				
McCue et al. 2006 ⁷³	Classification	FGA	SGA	SGA	SGA	SGA	SGA
	Medication	Haloperidol	Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone
	Dosage	4–30mg	10–45mg	5–40mg	50–1200mg	2–9mg	40–240mg
	No screened:	584					
	No randomized:	61	63	62	58	65	59
	No completed:	53	49	50	50	55	45
	No analyzed (E):	57	53	50	52	57	50
	No analyzed (S):	57	53	50	52	57	50
Purdon et al. 2000 ¹²⁴	Classification	FGA	SGA	SGA			
	Medication	Haloperidol	Olanzapine	Risperidone			
	Dosage	5–20mg/d	5–20mg/d	2–6mg/d			
	No screened:	NR					
	No randomized:	23	21	21			
	No completed:	9	12	7			
	No analyzed (E):	23	21	21			
	No analyzed (S):	23	21	21			

Table 66. Patient flow through trials–haloperidol versus olanzapine (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Rosenheck et al. 2003¹²⁷	Classification	FGA	SGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	5–20mg/d	5–20mg/d				
	No screened:	4386					
	No randomized:	150	159				
	No completed:	64	68				
	No analyzed (E):	150	159				
	No analyzed (S):	150	159				
Saddichha et al. 2008¹²⁹	Classification	FGA	SGA	SGA			
	Medication	Haloperidol	Olanzapine	Risperidone			
	Dosage	13.4+/-3.6mg/d	16.5+/-4.6mg/d	4.4+/-1.2mg/d			
	No screened:	NR					
	No randomized:	NR	NR	NR			
	No completed:	31	35	33			
	No analyzed (E):	31	35	33			
	No analyzed (S):	NR	NR				
Sayers et al. 2005¹³⁰	Classification	FGA	SGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	10–20 mg/d	10–20mg/d				
	No screened:	170					
	No randomized:	12	12				
	No completed:	7	7				
	No analyzed (E):	12	12				
	No analyzed (S):	12	12				
Sergi et al. 2007¹³⁴	Classification	FGA	SGA	SGA			
	Medication	Haloperidol	Olanzapine	Risperidone			
	Dosage	8mg/d	15mg/d	4mg/d			
	No screened:	NR					
	No randomized:	20	40	40			
	No completed:	12	22	25			
	No analyzed (E):	13	28	32			
	No analyzed (S):	13	28	32			

Table 66. Patient flow through trials—haloperidol versus olanzapine (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Smelson et al. 2006 ¹³⁶	Classification	FGA	SGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	5–20mg/d	5–20mg/d				
	No screened:	NR					
	No randomized:	15	16				
	No completed:	10	8				
	No analyzed (E):	15	16				
	No analyzed (S):	NR	NR				
Smith et al. 2001 ¹³⁷	Classification	FGA	SGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	5–40mg/d	5–20mg/d				
	No screened:	NR					
	No randomized:	NR	NR				
	No completed:	13	16				
	No analyzed (E):	13	16				
	No analyzed (S):	NR	NR				
Tollefson et al. 1997 ¹⁴¹	Classification	FGA	SGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	5–20mg/d	5–20mg/d				
	No screened:	2223					
	No randomized:	660	1336				
	No completed:	309	888				
	No analyzed (E):	660	1336				
	No analyzed (S):	660	1336				
Volakva et al. 2002 ¹⁴⁵	Classification	FGA	SGA	SGA	SGA		
	Medication	Haloperidol	Clozapine	Olanzapine	Risperidone		
	Dosage	10–30mg/d	200–800mg/d	10–40mg/d	4–16mg/d		
	No screened:	NR					
	No randomized:	37	40	39	41		
	No completed:	21	22	26	22		
	No analyzed (E):	37	40	39	41		
	No analyzed (S):	37	40	39	41		

Table 66. Patient flow through trials—haloperidol versus olanzapine (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Wright et al. 2001¹⁴⁷	Classification	FGA	SGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	7.5mg	10mg				
	No screened:	311					
	No randomized:	126	131				
	No completed:	126	131				
	No analyzed (E):	126	131				
Wynn et al. 2007¹⁴⁸	No analyzed (S):	126	131				
	Classification	FGA	SGA	SGA			
	Medication	Haloperidol	Olanzapine	Risperidone			
	Dosage	8mg/d	15mg/d	4mg/d			
	No screened:	100					
	No randomized:	11	21	19			
	No completed:	7	16	14			
	No analyzed (E):	11	21	19			
	No analyzed (S):	7	16	14			

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 67. Patient flow through trials—haloperidol versus quetiapine

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Arvanitis et al. 1997⁴⁶	Classification	FGA	SGA	SGA	SGA	SGA	SGA
	Medication	Haloperidol	Quetiapine	Quetiapine	Quetiapine	Quetiapine	Quetiapine
	Dosage	12mg/d	75mg/d	150mg/d	300mg/d	600mg/d	750mg/d
	No screened:	402					
	No randomized:	52	53	48	52	51	54
	No completed:	18	17	21	24	27	26
	No analyzed (E):	50	52	48	51	51	53
	No analyzed (S):	52	53	48	52	51	54
Atmaca et al. 2002⁴⁷	Classification	FGA	SGA				
	Medication	Haloperidol	Quetiapine				
	Dosage	10mg/d	600mg/d				
	No screened:	NR					
	No randomized:	17	18				
	No completed:	17	18				
	No analyzed (E):	17	18				
	No analyzed (S):	17	18				
Copolov et al. 2000⁶⁸	Classification	FGA	SGA				
	Medication	Haloperidol	Quetiapine				
	Dosage	1–16mg/d	50–800mg/d				
	No screened:	NR					
	No randomized:	227	221				
	No completed:	147	152				
	No analyzed (E):	218	213				
	No analyzed (S):	227	221				
Davidson et al. 2009⁷⁵	Classification	FGA	SGA	SGA	SGA		
	Medication	Haloperidol	Olanzapine	Quetiapine	Ziprasidone		
	Dosage	1–4mg/d	5–20mg/d	200–750mg/d	40–160mg/d		
	No screened:	NR					
	No randomized:	103	104	105	82		
	No completed:	52	60	74	45		
	No analyzed (E):	52	60	74	45		
	No analyzed (S):	52	60	74	45		

Table 67. Patient flow through trials—haloperidol versus quetiapine (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Emsley et al. 2000⁷⁹	Classification	FGA	SGA				
	Medication	Haloperidol	Quetiapine				
	Dosage	5–20mg/d	600mg/d				
	No screened:	365					
	No randomized:	145	143				
	No completed:	135	127				
	No analyzed (E):	141	140				
	No analyzed (S):	141	140				
Emsley et al. 2005⁸⁰	Classification	FGA	SGA				
	Medication	Haloperidol	Quetiapine				
	Dosage	5–20mg	100–800mg				
	No screened:	47					
	No randomized:	23	22				
	No completed:	15	12				
	No analyzed (E):	23	22				
	No analyzed (S):	23	22				
Glick et al. 2005⁶⁵	Classification	FGA	SGA				
	Medication	Haloperidol	Quetiapine				
	Dosage	200mg/wk	500mg/d				
	No screened:	NR					
	No randomized:	14	21				
	No completed:	5	7				
	No analyzed (E):	7	15				
	No analyzed (S):	9	16				
Kahn et al. 2008⁹¹	Classification	FGA	SGA	SGA	SGA		
	Medication	Haloperidol	Olanzapine	Quetiapine	Ziprasidone		
	Dosage	1–4mg/d	5–20mg/d	200–750mg/d	40–16mg/d		
	No screened:	1047					
	No randomized:	103	105	104	82		
	No completed:	68	82	70	53		
	No analyzed (E):	103	105	104	82		
	No analyzed (S):	103	105	104	82		

Table 67. Patient flow through trials–haloperidol versus quetiapine (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
McCue et al. 2006⁷³	Classification	FGA	SGA	SGA	SGA	SGA	SGA
	Medication	Haloperidol	Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone
	Dosage	4–30mg	10–45mg	5–40mg	50–1200mg	2–9mg	40–240mg
	No screened:	584					
	No randomized:	61	63	62	58	65	59
	No completed:	53	49	50	50	55	45
	No analyzed (E):	57	53	50	52	57	50
	No analyzed (S):	57	53	50	52	57	50
Purdon et al. 2001¹²³	Classification	FGA	SGA				
	Medication	Haloperidol	Quetiapine				
	Dosage	10–20mg/d	300–600mg/d				
	No screened:	NR					
	No randomized:	12	13				
	No completed:	3	9				
	No analyzed (E):	12	13				
	No analyzed (S):	12	13				
Velligan et al. 2002¹⁴³	Classification	FGA	SGA	SGA			
	Medication	Haloperidol	Quetiapine	Quetiapine			
	Dosage	12mg/d	300mg/d	600mg/d			
	No screened:	301					
	No randomized:	NR	NR	NR			
	No completed:	15	17	26			
	No analyzed (E):	15	17	26			
	No analyzed (S):	15	17	26			

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 68. Patient flow through trials—haloperidol versus risperidone

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Apiquian et al. 2008⁴⁵	Classification	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	2mg/d	1mg/d				
	No screened:	NR					
	No randomized:	10	10				
	No completed:	6	9				
	No analyzed (E):	6	9				
	No analyzed (S):	6	9				
Blin et al. 1996⁵²	Classification	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	4–12mg/d	4–12mg/d				
	No screened:	NR					
	No randomized:	20	21				
	No completed:	14	17				
	No analyzed (E):	20	21				
	No analyzed (S):	20	21				
Borison et al. 1992⁵³	Classification	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	4–20mg/d	2–10mg/d				
	No screened:	NR					
	No randomized:	12	12				
	No completed:	NR	NR				
	No analyzed (E):	NR	NR				
	No analyzed (S):	NR	NR				
Cavallaro et al. 2001⁵⁹	Classification	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	2.5–10mg/d	2.5–10mg/d				
	No screened:	NR					
	No randomized:	16	17				
	No completed:	9	10				
	No analyzed (E):	14	15				
	No analyzed (S):	14	15				

Table 68. Patient flow through trials—haloperidol versus risperidone (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Ceskova et al. 1993⁶⁰	Classification	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	2–20mg/d	2–20mg/d				
	No screened:	NR					
	No randomized:	31	31				
	No completed:	28	31				
	No analyzed (E):	28	31				
	No analyzed (S):	28	31				
Chouinard et al. 1993⁶¹	Classification	FGA	SGA	SGA	SGA	SGA	
	Medication	Haloperidol	Risperidone	Risperidone	Risperidone	Risperidone	
	Dosage	20mg/d	2mg/d	6mg/d	10mg/d	16mg/d	
	No screened:	NR					
	No randomized:	21	24	22	22	24	
	No completed:	8	7	17	14	18	
	No analyzed (E):	21	24	22	22	24	
	No analyzed (S):	21	24	22	22	24	
Citrome et al. 2001⁶²	Classification	FGA	SGA	SGA	SGA		
	Medication	Haloperidol	Clozapine	Olanzapine	Risperidone		
	Dosage	10–30mg/d	200–800mg/d	10–40mg/d	4–16mg/d		
	No screened:	NR					
	No randomized:	37	40	39	41		
	No completed:	27	32	30	28		
	No analyzed (E):	37	40	39	41		
	No analyzed (S):	37	40	39	41		
Claus et al. 1992⁶⁴	Classification	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	1–10mg/d	1–10mg/d				
	No screened:	NR					
	No randomized:	21	21				
	No completed:	16	20				
	No analyzed (E):	21	21				
	No analyzed (S):	21	21				

Table 68. Patient flow through trials—haloperidol versus risperidone (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Crespo–Facorro et al. 2006⁷¹	Classification	FGA	SGA	SGA			
	Medication	Haloperidol	Olanzapine	Risperidone			
	Dosage	3–9mg/d	5–20mg/d	3–6mg/d			
	No screened:	202					
	No randomized:	56	55	61			
	No completed:	55	53	57			
	No analyzed (E):	56	55	61			
	No analyzed (S):	56	55	61			
Csernansky et al. 2002⁷²	Classification	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	5–20mg/d	2–8mg/d				
	No screened:	NR					
	No randomized:	188	177				
	No completed:	89	99				
	No analyzed (E):	188	177				
	No analyzed (S):	187	173				
de Sena et al. 2003⁷⁷	Classification	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	5–17mg/d	1–6mg/d				
	No screened:	NR					
	No randomized:	13	20				
	No completed:	12	18				
	No analyzed (E):	12	18				
	No analyzed (S):	NR	NR				
Emsley et al. 1999⁸¹	Classification	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	2–10mg/d	2–10mg/d				
	No screened:	NR					
	No randomized:	84	99				
	No completed:	58	79				
	No analyzed (E):	84	98				
	No analyzed (S):	84	98				

Table 68. Patient flow through trials—haloperidol versus risperidone (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Fakra et al. 2008 ⁸²	Classification	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	NR	NR				
	No screened:	NR					
	No randomized:	15	15				
	No completed:	14	11				
	No analyzed (E):	14	11				
	No analyzed (S):	14	11				
Heck et al. 2000 ⁸⁵	Classification	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	3–24mg/d	2–16mg/d				
	No screened:	NR					
	No randomized:	37	40				
	No completed:	22	25				
	No analyzed (E):	37	40				
	No analyzed (S):	37	40				
Kee et al. 1998 ⁹⁹	Classification	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	15mg/d	6mg/d				
	No screened:	NR					
	No randomized:	10	10				
	No completed:	9	9				
	No analyzed (E):	9	9				
	No analyzed (S):	9	9				
Keefe et al. 2003 ¹⁰⁰	Classification	FGA	SGA	SGA			
	Medication	Haloperidol	Olanzapine	Risperidone			
	Dosage	2.5–10.0mg/d	2.5–10.0mg/d	2.0–8.0mg/d			
	No screened:	49					
	No randomized:	4	7	5			
	No completed:	4	7	5			
	No analyzed (E):	4	7	5			
	No analyzed (S):	NR	NR	NR			

Table 68. Patient flow through trials—haloperidol versus risperidone (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Keefe et al. 2006 ¹⁰¹	Classification	FGA	SGA	SGA			
	Medication	Haloperidol	Olanzapine	Risperidone			
	Dosage	2–19mg/d	5–20mg/d	2–10mg/d			
	No screened:	414					
	No randomized:	97	159	158			
	No completed:	27	64	54			
	No analyzed (E):	94	153	148			
	No analyzed (S):	97	159	158			
Kim et al. 2010 ¹⁰²	Classification	FGA	SGA	SGA	SGA		
	Medication	Haloperidol	Aripiprazole	Olanzapine	Risperidone		
	Dosage	15.9+/-7.1mg/d	21.7+/-5.5mg/d	15.9+/-4.3mg/d	4.8+/-2.9mg/d		
	No screened:	NR					
	No randomized:	35	31	32	41		
	No completed:	NR	NR	NR	NR		
	No analyzed (E):	NR	NR	NR	NR		
	No analyzed (S):	NR	NR	NR	NR		
Lee et al. 2007 ¹⁰⁷	Classification	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	7.6+/-2.6mg/d	4.1+/-0.8mg/d				
	No screened:	68					
	No randomized:	10	10				
	No completed:	10	10				
	No analyzed (E):	10	10				
	No analyzed (S):	10	10				
Lim et al. 2010 ¹⁵¹	Classification	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	5–15mg	2–6mg				
	No screened:	144					
	No randomized:	62	62				
	No completed:	62	62				
	No analyzed (E):	62	62				
	No analyzed (S):	62	62				

Table 68. Patient flow through trials—haloperidol versus risperidone (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Liu et al. 2000¹¹¹	Classification	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	NR	NR				
	No screened:	56					
	No randomized:	28	28				
	No completed:	19	21				
	No analyzed (E):	19	19				
	No analyzed (S):	19	19				
Marder et al. 1994¹¹⁴	Classification	FGA	SGA	SGA	SGA	SGA	
	Medication	Haloperidol	Risperidone	Risperidone	Risperidone	Risperidone	
	Dosage	20mg/d	2mg/d	6mg/d	10mg/d	16mg/d	
	No screened:	388					
	No randomized:	66	63	64	65	64	
	No completed:	28	29	35	34	36	
	No analyzed (E):	64	63	63	63	61	
	No analyzed (S):	66	63	64	65	64	
Marder et al. 2003¹¹³	Classification	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	2mg TID for the first week; then 6mg HS	2mg TID for the first week; then 6mg HS				
	No screened:	110					
	No randomized:	30	33				
	No completed:	11	18				
	No analyzed (E):	11	18				
	No analyzed (S):	30	33				
McCue et al. 2006⁷³	Classification	FGA	SGA	SGA	SGA	SGA	SGA
	Medication	Haloperidol	Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone
	Dosage	4–30mg	10–45mg	5–40mg	50–1200mg	2–9mg	40–240mg
	No screened:	584					
	No randomized:	61	63	62	58	65	59
	No completed:	53	49	50	50	55	45
	No analyzed (E):	57	53	50	52	57	50
	No analyzed (S):	57	53	50	52	57	50

Table 68. Patient flow through trials—haloperidol versus risperidone (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Min et al. 1993¹¹⁷	Classification	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	2.5–5mg/d	2.5–5mg/d				
	No screened:	35					
	No randomized:	19	16				
	No completed:	19	13				
	No analyzed (E):	19	16				
	No analyzed (S):	19	16				
Moller et al. 2008¹¹⁸	Classification	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	2–8mg/d	2–8mg/d				
	No screened:	1372					
	No randomized:	148	148				
	No completed:	67	88				
	No analyzed (E):	146	143				
	No analyzed (S):	146	143				
Peuskens et al. 1995¹²⁰	Classification	FGA	SGA	SGA	SGA	SGA	SGA
	Medication	Haloperidol	Risperidone	Risperidone	Risperidone	Risperidone	Risperidone
	Dosage	10mg/d	1mg/d	4mg/d	8mg/d	12mg/d	16mg/d
	No screened:	1362					
	No randomized:	226	229	227	230	226	224
	No completed:	163	171	182	174	164	165
	No analyzed (E):	223	226	227	228	225	223
	No analyzed (S):	225	226	227	228	225	224
Purdon et al. 2000¹²⁴	Classification	FGA	SGA	SGA			
	Medication	Haloperidol	Olanzapine	Risperidone			
	Dosage	5–20mg/d	5–20mg/d	2–6mg/d			
	No screened:	NR					
	No randomized:	23	21	21			
	No completed:	9	12	7			
	No analyzed (E):	23	21	21			
	No analyzed (S):	23	21	21			

Table 68. Patient flow through trials–haloperidol versus risperidone (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Remillard et al. 2008 ¹²⁵	Classification	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	2–40mg/d	2–6mg/d				
	No screened:	NR					
	No randomized:	14	14				
	No completed:	14	14				
	No analyzed (E):	14	14				
	No analyzed (S):	NR	NR				
Schooler et al. 2005 ¹³²	Classification	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	1–8mg/d	1–8mg/d				
	No screened:	NR					
	No randomized:	277	278				
	No completed:	176	161				
	No analyzed (E):	267	266				
	No analyzed (S):	276	278				
Sergi et al. 2007 ¹³⁴	Classification	FGA	SGA	SGA			
	Medication	Haloperidol	Olanzapine	Risperidone			
	Dosage	8mg/d	15mg/d	4mg/d			
	No screened:	NR					
	No randomized:	20	40	40			
	No completed:	12	22	25			
	No analyzed (E):	13	28	32			
	No analyzed (S):	13	28	32			
Shrivastava et al. 2000 ¹³⁵	Classification	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	5–15mg/d	2mg/d				
	No screened:	NR					
	No randomized:	NR	NR				
	No completed:	50	50				
	No analyzed (E):	50	50				
	No analyzed (S):	NR	NR				

Table 68. Patient flow through trials—haloperidol versus risperidone (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Tamrakar et al. 2006 ¹³⁹	Classification	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	10–20mg/d	4–6mg/d				
	No screened:	NR					
	No randomized:	18	18				
	No completed:	18	18				
	No analyzed (E):	18	18				
Volakva et al. 2002 ¹⁴⁵	No analyzed (S):	18	18				
	Classification	FGA	SGA	SGA	SGA		
	Medication	Haloperidol	Clozapine	Olanzapine	Risperidone		
	Dosage	10–30mg/d	200–800mg/d	10–40mg/d	4–16mg/d		
	No screened:	NR					
	No randomized:	37	40	39	41		
	No completed:	21	22	26	22		
Wirshing et al. 1999 ¹⁴⁶	No analyzed (E):	37	40	39	41		
	No analyzed (S):	37	40	39	41		
	Classification	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	15mg/d	6mg/d				
	No screened:	NR					
	No randomized:	33	34				
Wynn et al. 2007 ¹⁴⁸	No completed:	28	28				
	No analyzed (E):	32	33				
	No analyzed (S):	32	33				
	Classification	FGA	SGA	SGA			
	Medication	Haloperidol	Olanzapine	Risperidone			
	Dosage	8mg/d	15mg/d	4mg/d			
	No screened:	100					
	No randomized:	11	21	19			
	No completed:	7	16	14			
	No analyzed (E):	11	21	19			
	No analyzed (S):	7	16	14			

Table 68. Patient flow through trials—haloperidol versus risperidone (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Yen et al. 2004 ¹⁴⁹	Classification	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	4–20mg/d	2–12mg/d				
	No screened:	41					
	No randomized:	20	21				
	No completed:	13	14				
	No analyzed (E):	20	21				
	No analyzed (S):	20	21				
Zhang et al. 2001 ¹⁵⁰	Classification	FGA	SGA				
	Medication	Haloperidol	Risperidone				
	Dosage	6mg/d	20mg/d				
	No screened:	NR					
	No randomized:	37	41				
	No completed:	33	40				
	No analyzed (E):	37	41				
	No analyzed (S):	37	41				

d = day; E = efficacy; FGA = first-generation antipsychotic; HS = half strength; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic; TID = three times daily

Table 69. Patient flow through trials—haloperidol versus ziprasidone

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Brook et al. 2005⁵⁷	Classification	FGA	SGA				
	Medication	Haloperidol	Ziprasidone				
	Dosage	IM: 2.5–10mg/d; Oral: 5–20mg/d	IM: 10–40mg/d; Oral: 40–80mg/d				
	No screened:	621					
	No randomized:	138	429				
	No completed:	91	292				
	No analyzed (E):	138	429				
	No analyzed (S):	138	429				
Corripio et al. 2005⁶⁹	Classification	FGA	SGA				
	Medication	Haloperidol	Ziprasidone				
	Dosage	5–20mg/d	10–40mg/d				
	No screened:	NR					
	No randomized:	10	10				
	No completed:	10	10				
	No analyzed (E):	10	10				
	No analyzed (S):	10	10				
Davidson et al. 2009⁷⁵	Classification	FGA	SGA	SGA	SGA		
	Medication	Haloperidol	Olanzapine	Quetiapine	Ziprasidone		
	Dosage	1–4mg/d	5–20mg/d	200–750mg/d	40–160mg/d		
	No screened:	NR					
	No randomized:	103	104	105	82		
	No completed:	52	60	74	45		
	No analyzed (E):	52	60	74	45		
	No analyzed (S):	52	60	74	45		
Goff et al. 1998⁸³	Classification	FGA	SGA	SGA	SGA	SGA	
	Medication	Haloperidol	Ziprasidone	Ziprasidone	Ziprasidone	Ziprasidone	
	Dosage	15mg/d	4mg/d	10mg/d	40mg/d	160mg/d	
	No screened:	NR					
	No randomized:	17	19	17	17	20	
	No completed:	9	9	6	8	12	
	No analyzed (E):	17	19	17	17	20	
	No analyzed (S):	17	19	17	17	20	

Table 69. Patient flow through trials—haloperidol versus ziprasidone (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Hirsch et al. 2002⁸⁶	Classification	FGA	SGA				
	Medication	Haloperidol	Ziprasidone				
	Dosage	5–15mg/d	80–160mg/d				
	No screened:	363					
	No randomized:	153	148				
	No completed:	64	66				
	No analyzed (E):	117	110				
	No analyzed (S):	117	110				
Kahn et al. 2008⁹¹	Classification	FGA	SGA	SGA	SGA		
	Medication	Haloperidol	Olanzapine	Quetiapine	Ziprasidone		
	Dosage	1–4mg/d	5–20mg/d	200–750mg/d	40–16mg/d		
	No screened:	1047					
	No randomized:	103	105	104	82		
	No completed:	68	82	70	53		
	No analyzed (E):	103	105	104	82		
	No analyzed (S):	103	105	104	82		
McCue et al. 2006⁷³	Classification	FGA	SGA	SGA	SGA	SGA	SGA
	Medication	Haloperidol	Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone
	Dosage	4–30mg	10–45mg	5–40mg	50–1200mg	2–9mg	40–240mg
	No screened:	584					
	No randomized:	61	63	62	58	65	59
	No completed:	53	49	50	50	55	45
	No analyzed (E):	57	53	50	52	57	50
	No analyzed (S):	57	53	50	52	57	50
Miceli et al. 2010¹¹⁶	Classification	FGA	SGA				
	Medication	Haloperidol	Ziprasidone				
	Dosage	7.5–10mg	20–30mg				
	No screened:	87					
	No randomized:	27	31				
	No completed:	24	25				
	No analyzed (E):	27	31				
	No analyzed (S):	27	31				

Table 69. Patient flow through trials—haloperidol versus ziprasidone (continued)

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Potkin et al. 2009 ¹²²	Classification	FGA	SGA	SGA			
	Medication	Haloperidol	Ziprasidone	Ziprasidone			
	Dosage	5–20mg/d	80–120mg/d	80–160mg/d			
	No screened:	NR					
	No randomized:	151	221	227			
	No completed:	16	28	25			
	No analyzed (E):	47	67	72			
	No analyzed (S):	47	67	72			

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 70. Patient flow through trials—perphenazine versus aripiprazole

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Kane et al. 2007 ⁹³	Classification	FGA	SGA				
	Medication	Perphenazine	Aripiprazole				
	Dosage	8–64mg/d	15–30mg/d				
	No screened:	512					
	No randomized:	146	154				
	No completed:	115	110				
	No analyzed (E):	144	150				
	No analyzed (S):	144	150				

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 71. Patient flow through trials—perphenazine versus olanzapine

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Ascher–Svanum et al. 2008¹³¹	Classification	FGA	SGA				
	Medication	Perphenazine	Olanzapine				
	Dosage	NR	NR				
	No screened:	NR					
	No randomized:	48	229				
	No completed:	48	222				
	No analyzed (E):	48	222				
	No analyzed (S):	NR	NR				
Lieberman et al. 2005²³	Classification	FGA	SGA	SGA	SGA	SGA	
	Medication	Perphenazine	Olanzapine	Quetiapine	Risperidone	Ziprasidone	
	Dosage	8–32mg/d	7.5–30mg/d	200–800mg/d	1.5–6.0mg/d	40–160mg/d	
	No screened:	1894					
	No randomized:	261	336	337	341	185	
	No completed:	65	120	60	88	38	
	No analyzed (E):	257	330	329	333	183	
	No analyzed (S):	261	336	337	341	185	

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 72. Patient flow through trials—perphenazine versus quetiapine

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Lieberman et al. 2005²³	Classification	FGA	SGA	SGA	SGA	SGA	
	Medication	Perphenazine	Olanzapine	Quetiapine	Risperidone	Ziprasidone	
	Dosage	8–32mg/d	7.5–30mg/d	200–800mg/d	1.5–6.0mg/d	40–160mg/d	
	No screened:	1894					
	No randomized:	261	336	337	341	185	
	No completed:	65	120	60	88	38	
	No analyzed (E):	257	330	329	333	183	
	No analyzed (S):	261	336	337	341	185	

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 73. Patient flow through trials—perphenazine versus risperidone

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Ascher-Svanum et al. 2008¹³¹	Classification	FGA	SGA				
	Medication	Perphenazine	Risperidone				
	Dosage	NR	NR				
	No screened:	NR					
	No randomized:	48	221				
	No completed:	48	217				
	No analyzed (E):	48	217				
	No analyzed (S):	NR	NR				
Lieberman et al. 2005²³	Classification	FGA	SGA	SGA	SGA	SGA	
	Medication	Perphenazine	Olanzapine	Quetiapine	Risperidone	Ziprasidone	
	Dosage	8–32mg/d	7.5–30mg/d	200–800mg/d	1.5–6.0mg/d	40–160mg/d	
	No screened:	1894					
	No randomized:	261	336	337	341	185	
	No completed:	65	120	60	88	38	
	No analyzed (E):	257	330	329	333	183	
	No analyzed (S):	261	336	337	341	185	

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 74. Patient flow through trials—trifluoperazine versus clozapine

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Rinieris et al. 1980¹⁵⁷	Classification	FGA	FGA	SGA			
	Medication	Chlorpromazine	Trifluoperazine	Clozapine			
	Dosage	50–100mg	2.5–5mg	50–100mg			
	No screened:	NR					
	No randomized:	16	20	5			
	No completed:	10	9	5			
	No analyzed (E):	10	9	5			
	No analyzed (S):	10	9	5			

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

B) Bipolar Disorder

Table 75. Patient flow through trials—chlorpromazine versus clozapine

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Barbini et al. 1997 ⁴⁸	Classification	FGA	FGA				
	Medication	Chlorpromazine	Clozapine				
	Dosage	2mg/kg/d	25mg/d				
	No screened:	NR					
	No randomized:	15	15				
	No completed:	12	15				
	No analyzed (E):	12	15				
	No analyzed (S):	12	15				

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 76. Patient flow through trials—haloperidol versus aripiprazole

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Vieta et al. 2005 ³²	Classification	FGA	FGA				
	Medication	Haloperidol	Aripiprazole				
	Dosage	10-15mg/d	15-30mg/d				
	No screened:	NR					
	No randomized:	172	175				
	No completed:	50	89				
	No analyzed (E):	164	174				
	No analyzed (S):	169	175				
Young et al. 2009 ³³	Classification	FGA	FGA				
	Medication	Haloperidol	Aripiprazole				
	Dosage	5-10mg/d	15-30mg/d				
	No screened:	NR					
	No randomized:	165	167				
	No completed:	95	95				
	No analyzed (E):	161	166				
	No analyzed (S):	165	166				

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 77. Patient flow through trials–haloperidol versus olanzapine

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Moreno et al. 2007¹¹⁹	Classification	FGA	FGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	3-15mg/d	5-20mg/d				
	No screened:	19					
	No randomized:	5	7				
	No completed:	5	7				
	No analyzed (E):	5	7				
	No analyzed (S):	5	7				
Tohen et al. 2003¹⁴⁰	Classification	FGA	FGA				
	Medication	Haloperidol	Olanzapine				
	Dosage	3-15mg/d	5-20mg/d				
	No screened:	498					
	No randomized:	219	234				
	No completed:	116	140				
	No analyzed (E):	219	234				
	No analyzed (S):	219	234				

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 78. Patient flow through trials–haloperidol versus quetiapine

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
McIntyre et al. 2005¹¹⁵	Classification	FGA	FGA				
	Medication	Haloperidol	Quetiapine				
	Dosage	2-8mg/d	100-800mg/d				
	No screened:	NR					
	No randomized:	99	102				
	No completed:	54	55				
	No analyzed (E):	98	101				
	No analyzed (S):	98	101				

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

Table 79. Patient flow through trials—haloperidol versus risperidone

		Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Janicak et al. 2001⁹⁰	Classification	FGA	FGA				
	Medication	Haloperidol	Risperidone				
	Dosage	2-10mg/d	1-5mg/d				
	No screened:	62					
	No randomized:	32	30				
	No completed:	13	12				
	No analyzed (E):	32	30				
	No analyzed (S):	32	30				
Sachs et al. 2002¹²⁸	Classification	FGA	FGA				
	Medication	Haloperidol	Risperidone				
	Dosage	4-12 mg/d	2-6 mg/d				
	No screened:	156					
	No randomized:	53	52				
	No completed:	25	34				
	No analyzed (E):	53	52				
	No analyzed (S):	53	52				
Segal et al. 1998¹³³	Classification	FGA	FGA				
	Medication	Haloperidol	Risperidone				
	Dosage	10mg/d	6mg/d				
	No screened:	NR					
	No randomized:	15	15				
	No completed:	12	13				
	No analyzed (E):	15	15				
	No analyzed (S):	15	15				
Smulevich et al. 2005¹³⁸	Classification	FGA	FGA				
	Medication	Haloperidol	Risperidone				
	Dosage	2-12mg/d	1-6mg/d				
	No screened:	NR					
	No randomized:	144	154				
	No completed:	56	77				
	No analyzed (E):	144	153				
	No analyzed (S):	144	153				

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

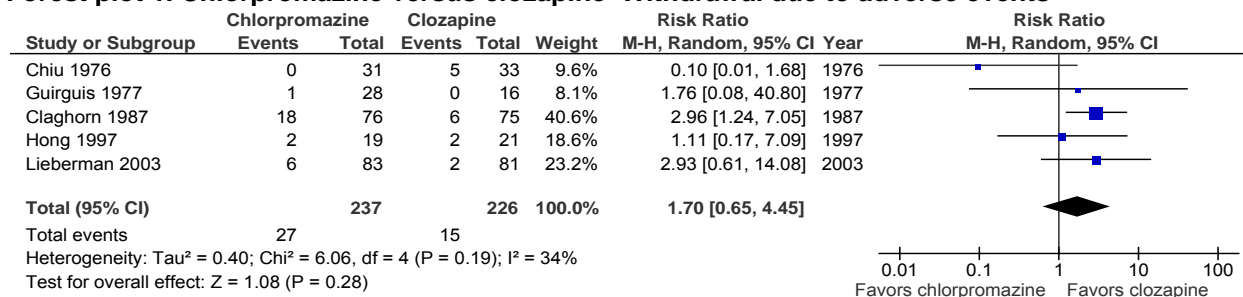
Table 80. Patient flow through trials–haloperidol versus ziprasidone

	Intervention #1	Intervention #2	Intervention #3	Intervention #4	Intervention #5	Intervention #6
Vieta et al. 2010 ¹⁴⁴	Classification	FGA	FGA			
	Medication	Haloperidol	Ziprasidone			
	Dosage	4-30mg/d	40-160mg/d			
	No screened:	540				
	No randomized:	172	178			
	No completed:	78	73			
	No analyzed (E):	171	178			
	No analyzed (S):	171	178			

d = day; E = efficacy; FGA = first-generation antipsychotic; mg = milligram; No = number; NR = not reported; S = safety; SGA = second-generation antipsychotic

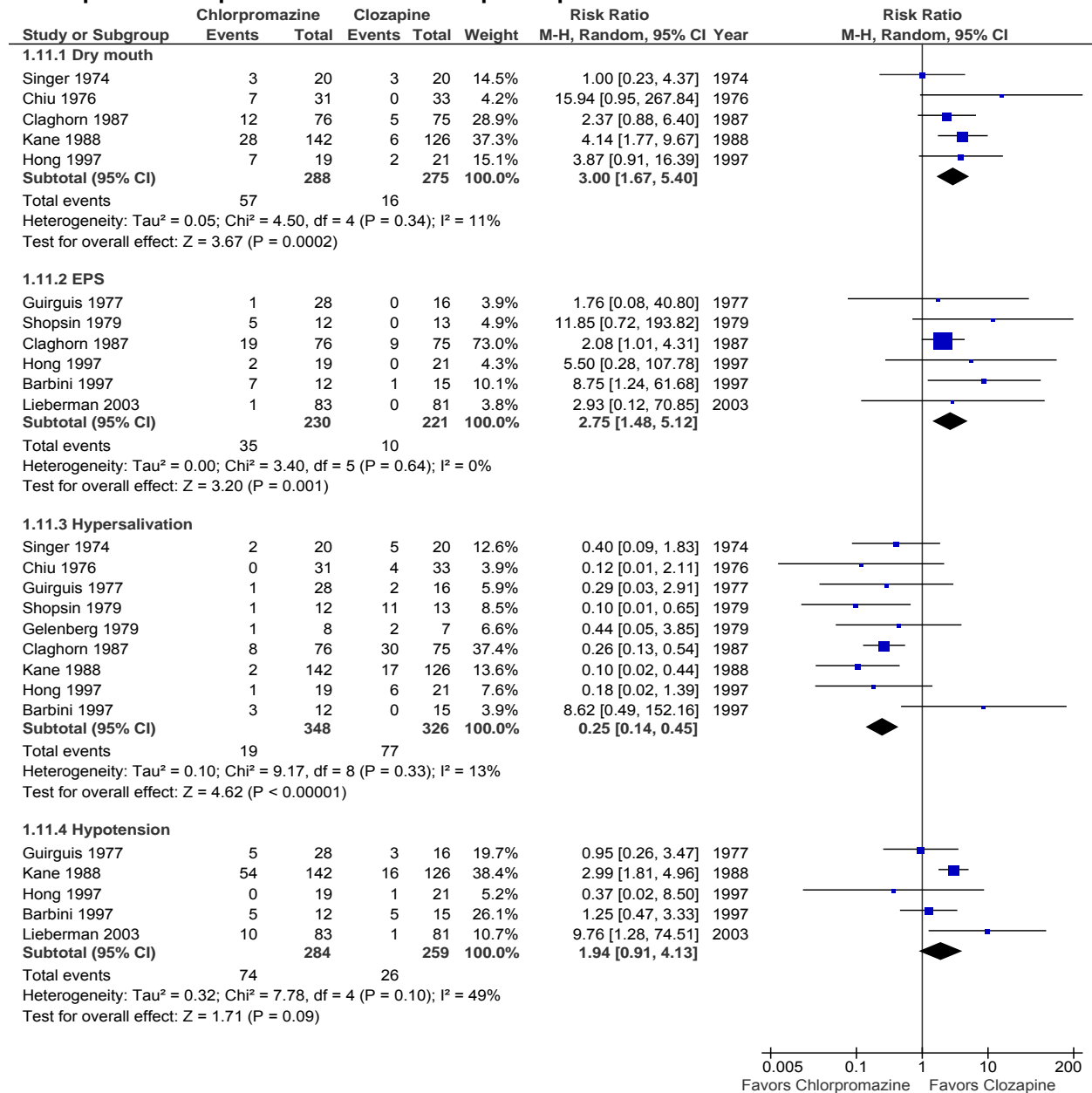
Appendix J. Forest Plots for Adverse Events

Forest plot 1. Chlorpromazine versus clozapine—Withdrawal due to adverse events



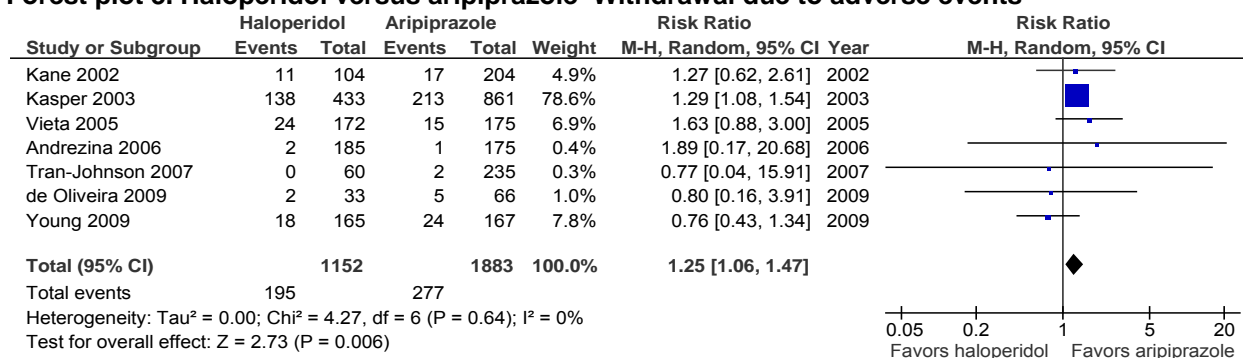
CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; M-H = Mantel-Haenszel

Forest plot 2. Chlorpromazine versus clozapine—Specific adverse events



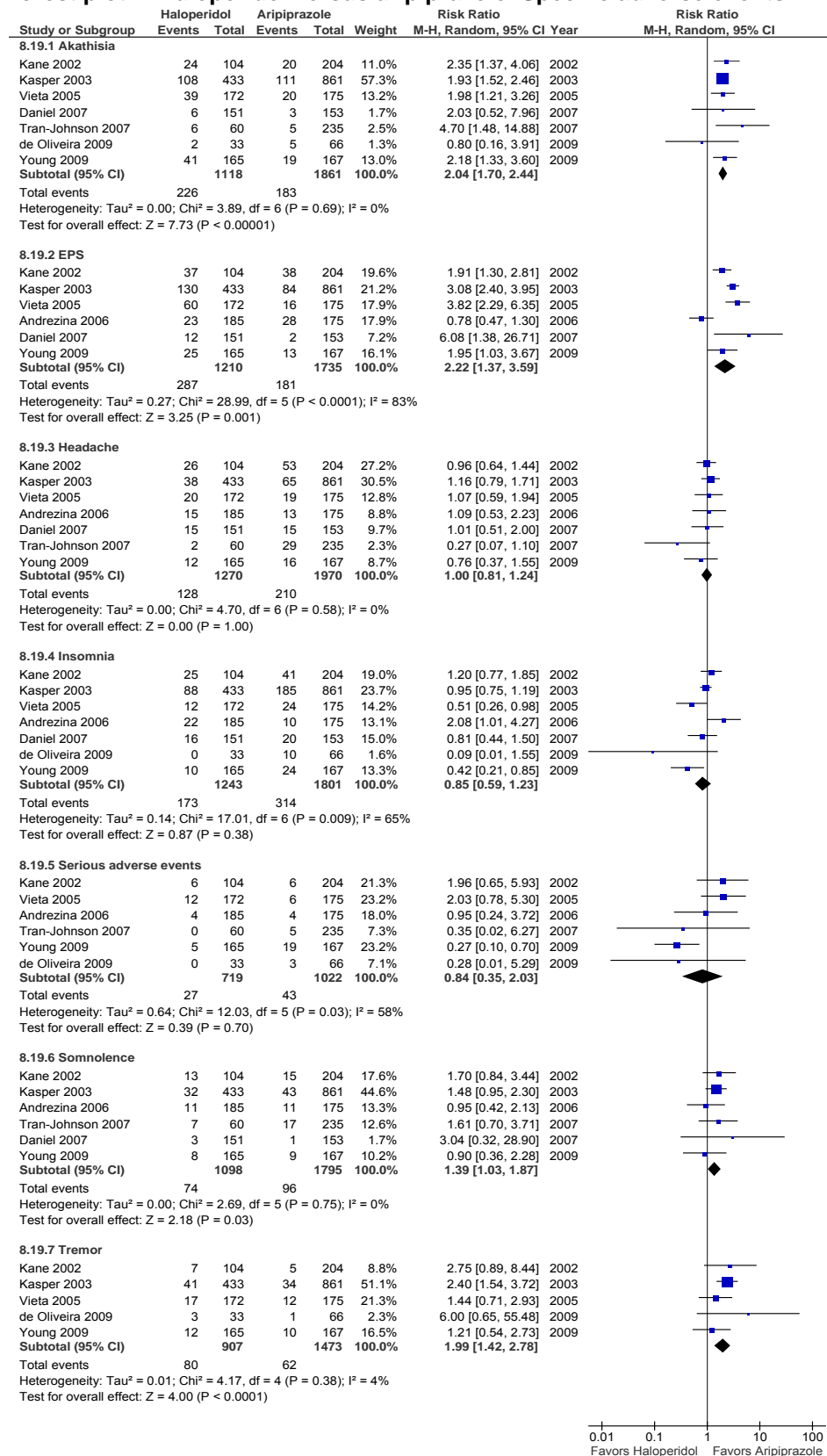
CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; M-H = Mantel-Haenszel

Forest plot 3. Haloperidol versus aripiprazole–Withdrawal due to adverse events



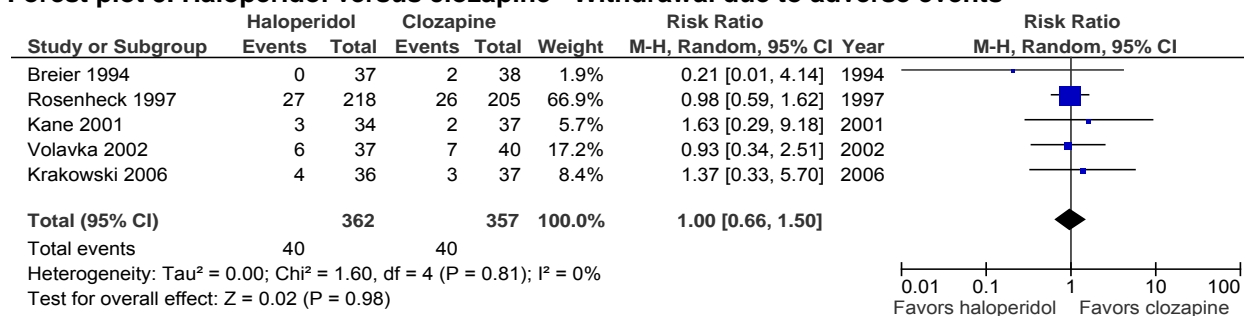
CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; M-H = Mantel-Haenszel

Forest plot 4. Haloperidol versus aripiprazole–Specific adverse events



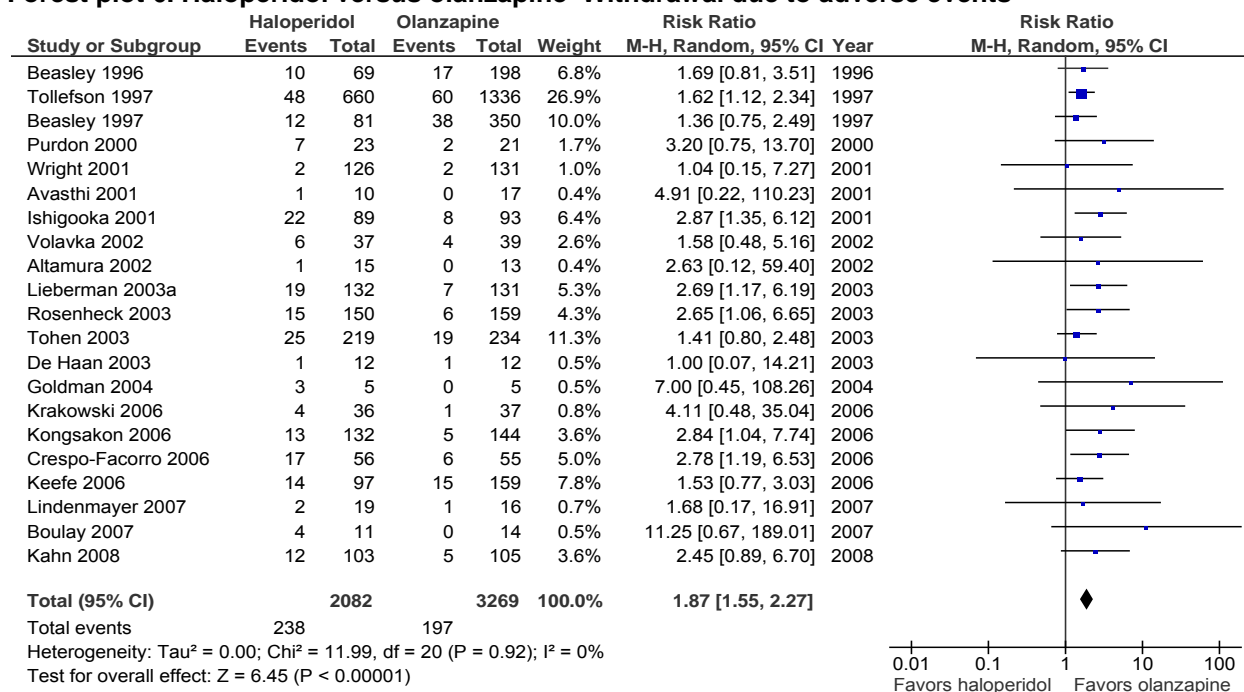
CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; M-H = Mantel-Haenszel

Forest plot 5. Haloperidol versus clozapine– Withdrawal due to adverse events



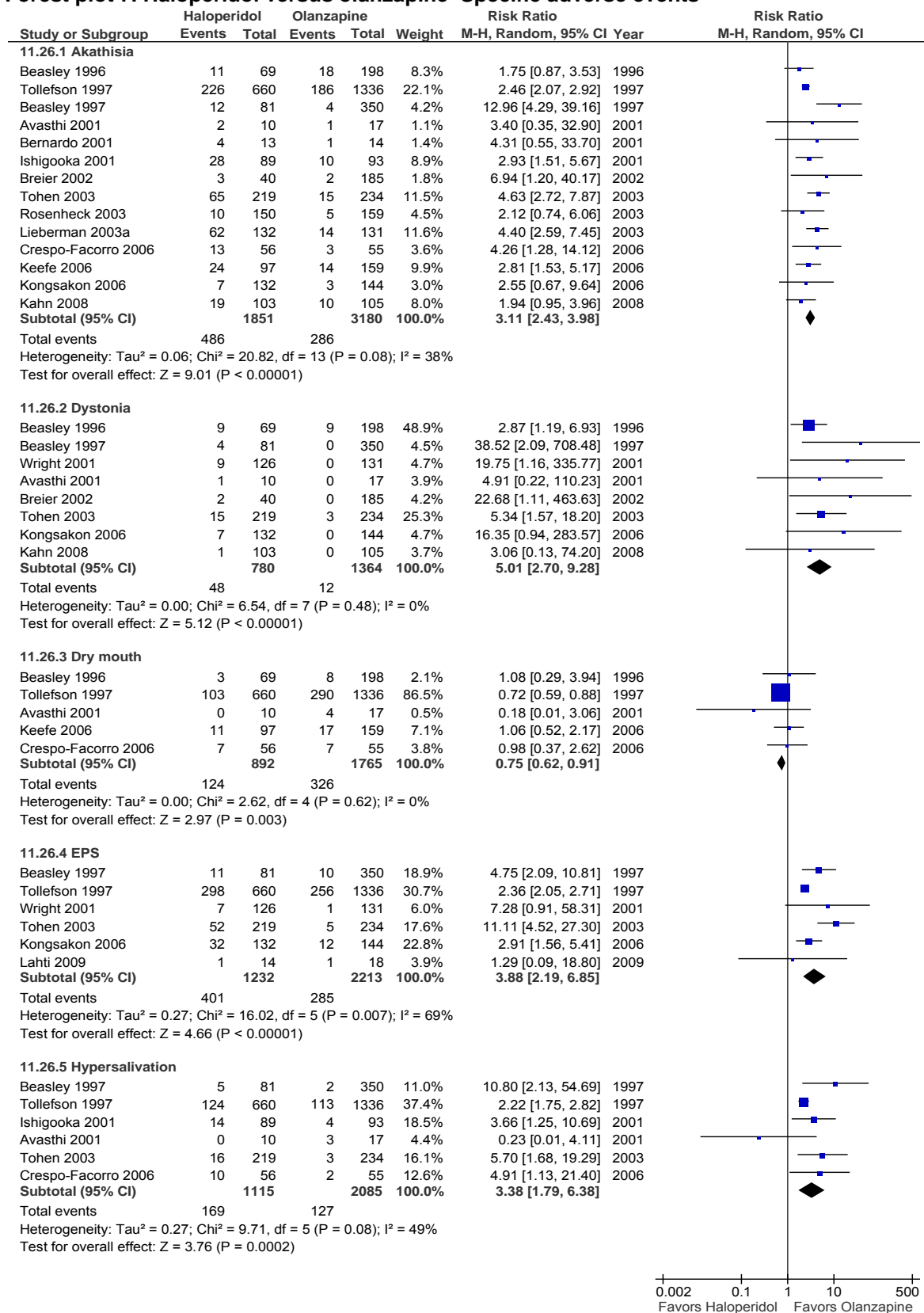
CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; M-H = Mantel-Haenszel

Forest plot 6. Haloperidol versus olanzapine–Withdrawal due to adverse events



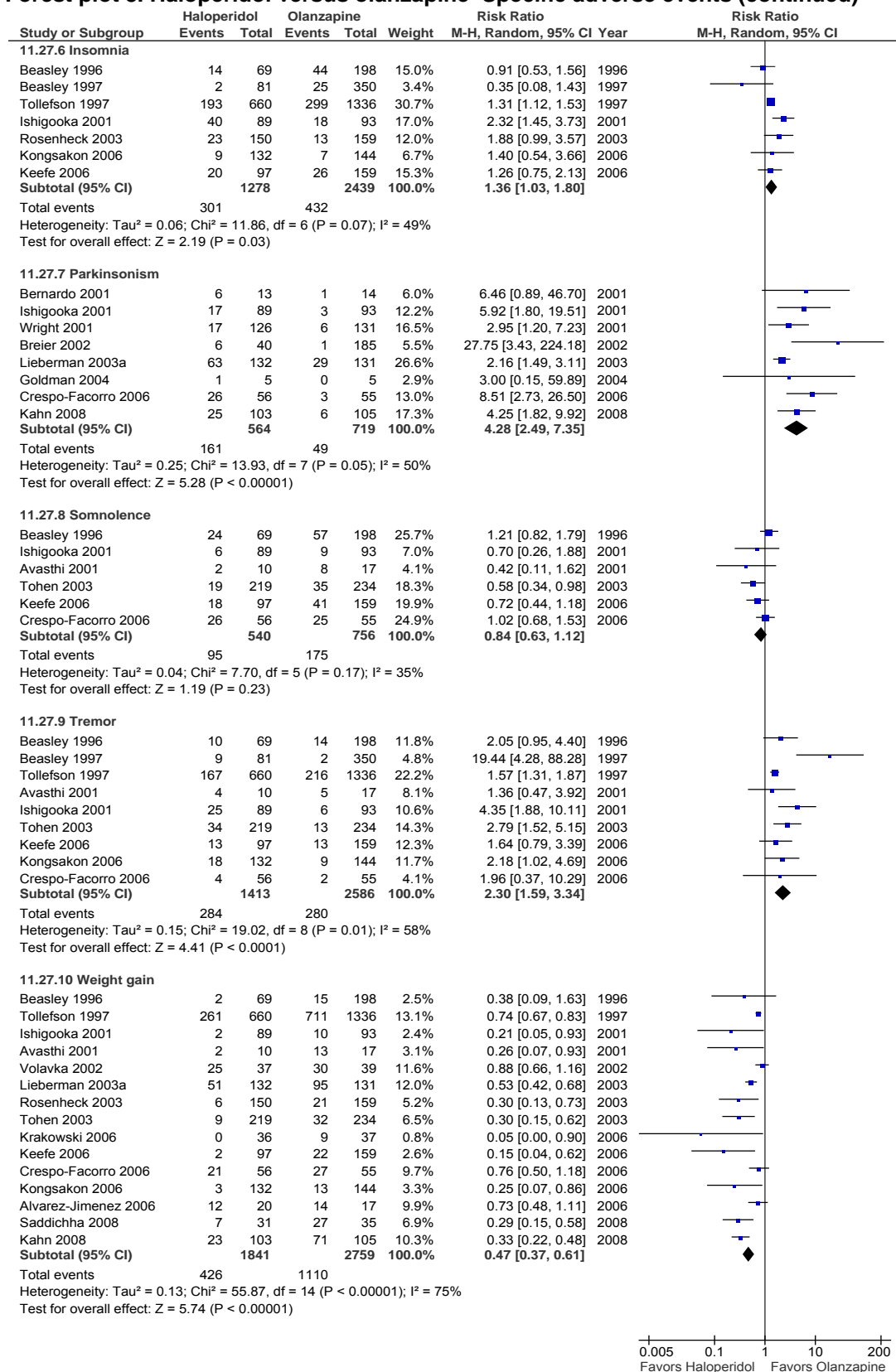
CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; M-H = Mantel-Haenszel

Forest plot 7. Haloperidol versus olanzapine—Specific adverse events



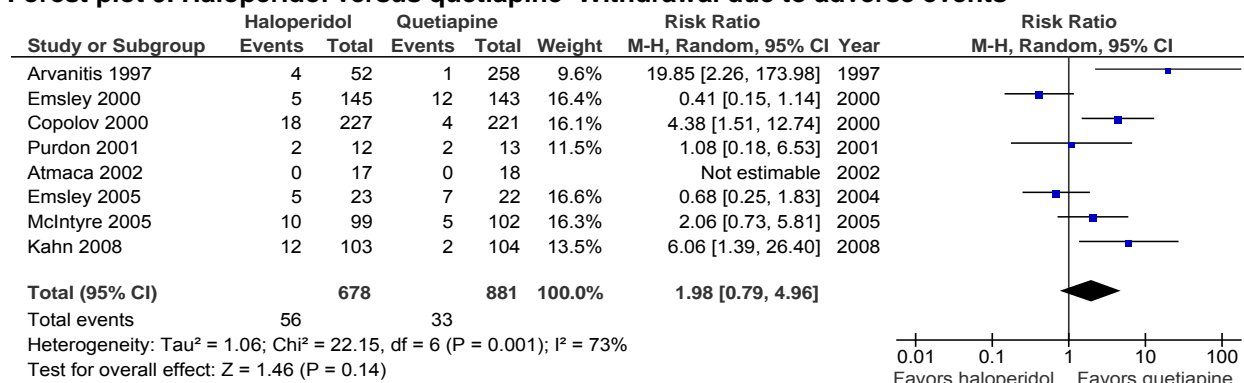
CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; M-H = Mantel-Haenszel

Forest plot 8. Haloperidol versus olanzapine—Specific adverse events (continued)



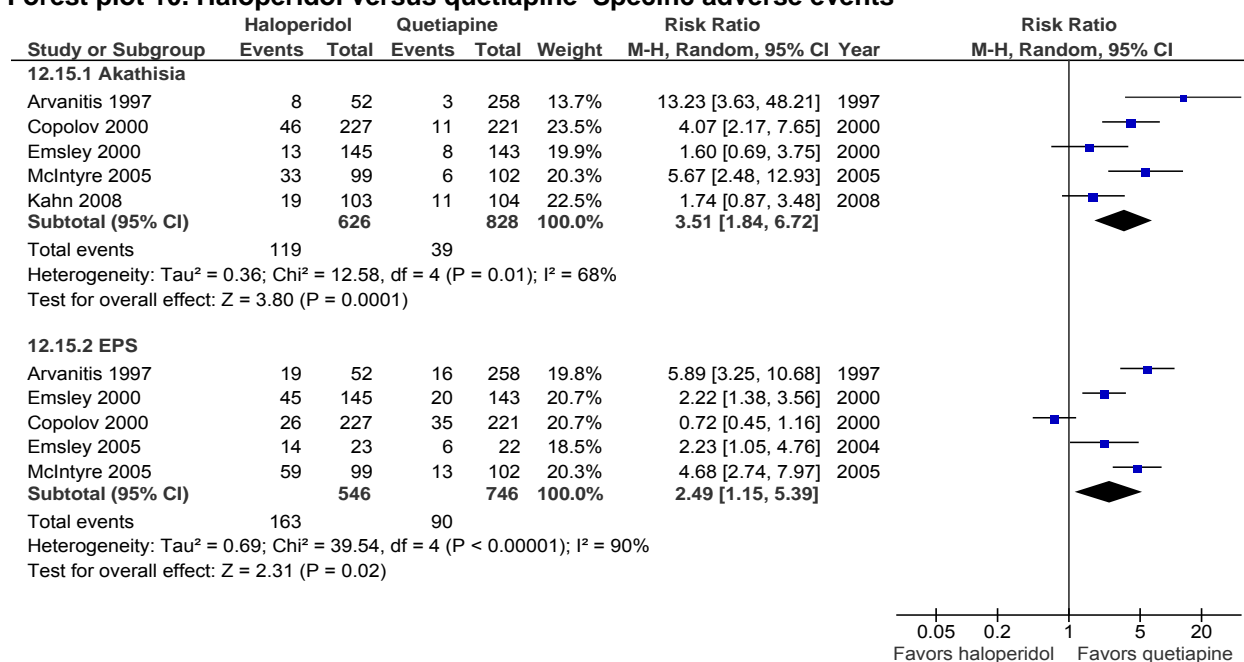
CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; M-H = Mantel-Haenszel

Forest plot 9. Haloperidol versus quetiapine–Withdrawal due to adverse events



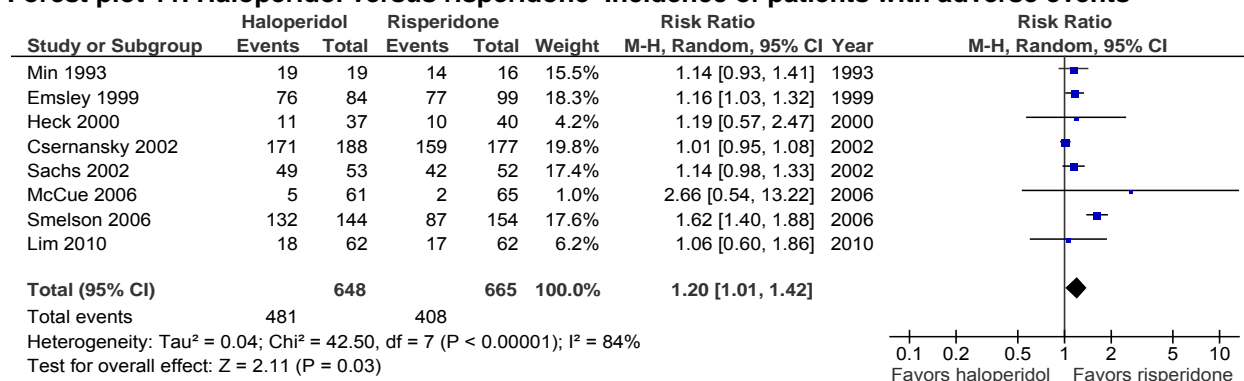
CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; M-H = Mantel-Haenszel

Forest plot 10. Haloperidol versus quetiapine–Specific adverse events



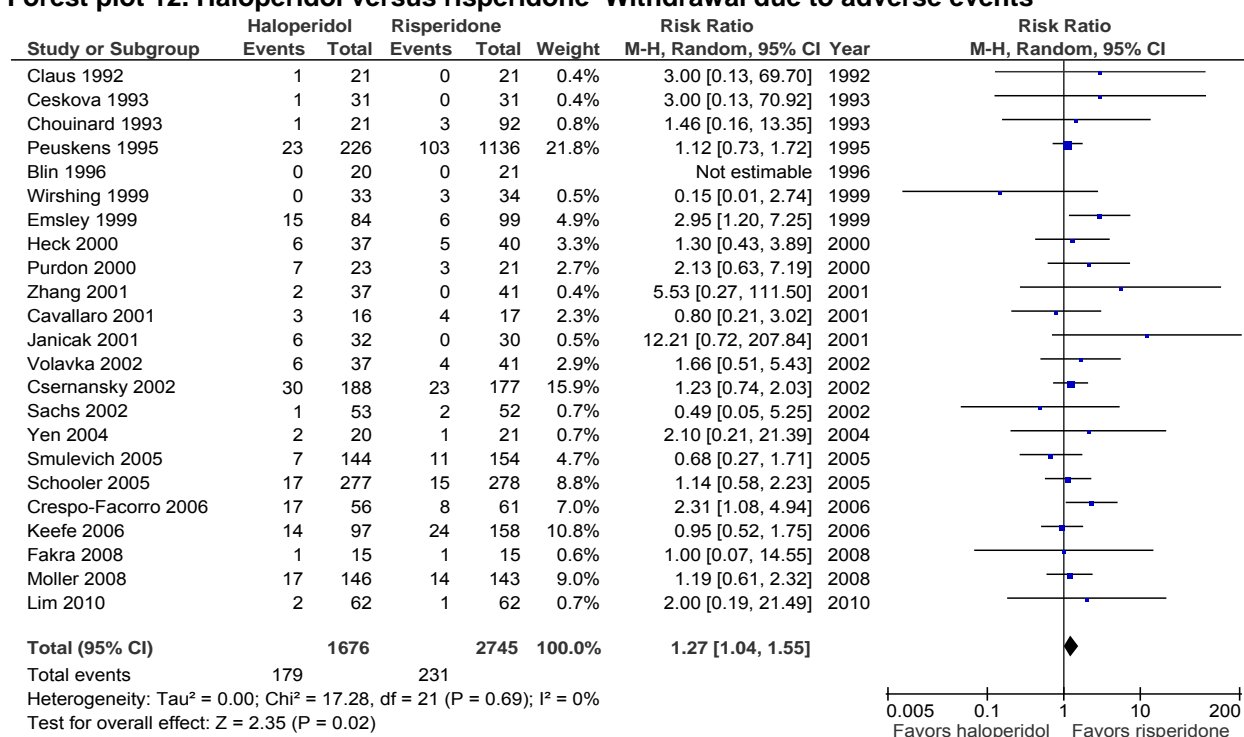
CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; M-H = Mantel-Haenszel

Forest plot 11. Haloperidol versus risperidone—Incidence of patients with adverse events



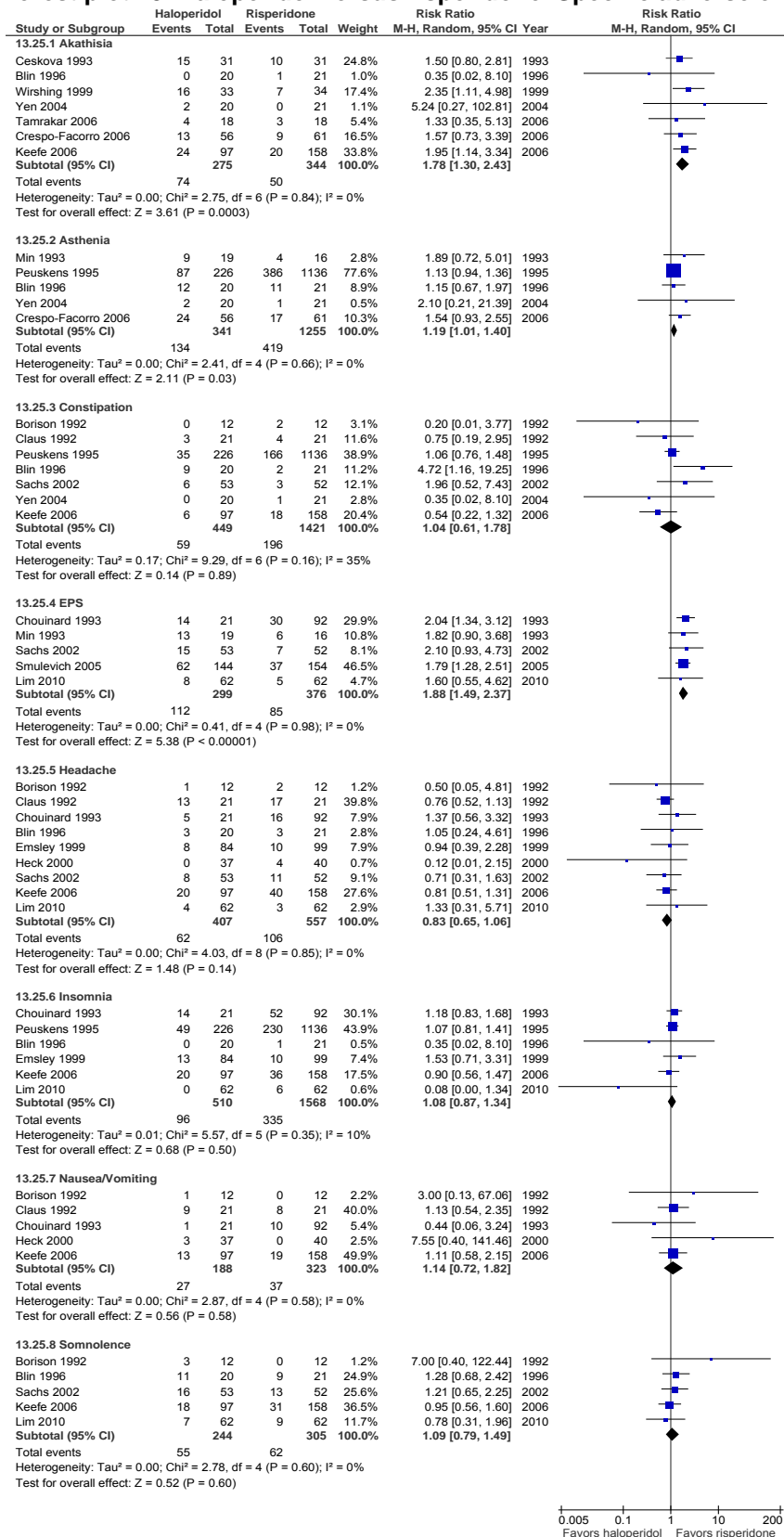
CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; M-H = Mantel-Haenszel

Forest plot 12. Haloperidol versus risperidone—Withdrawal due to adverse events



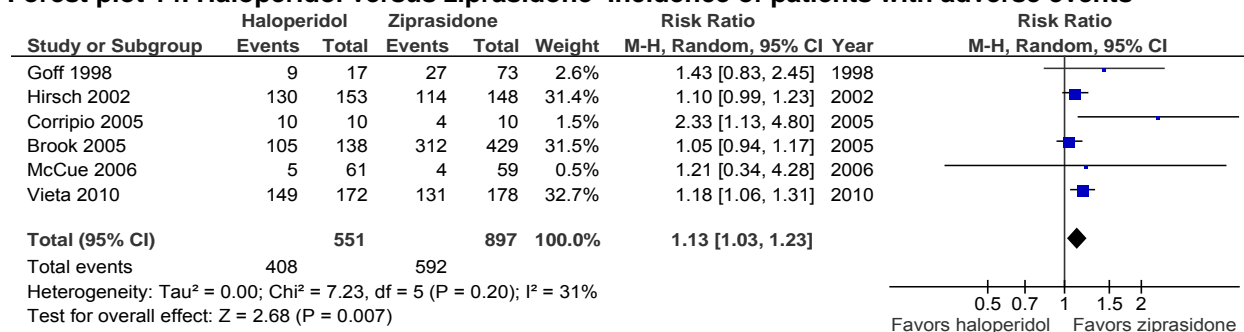
CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; M-H = Mantel-Haenszel

Forest plot 13. Haloperidol versus risperidone—Specific adverse events



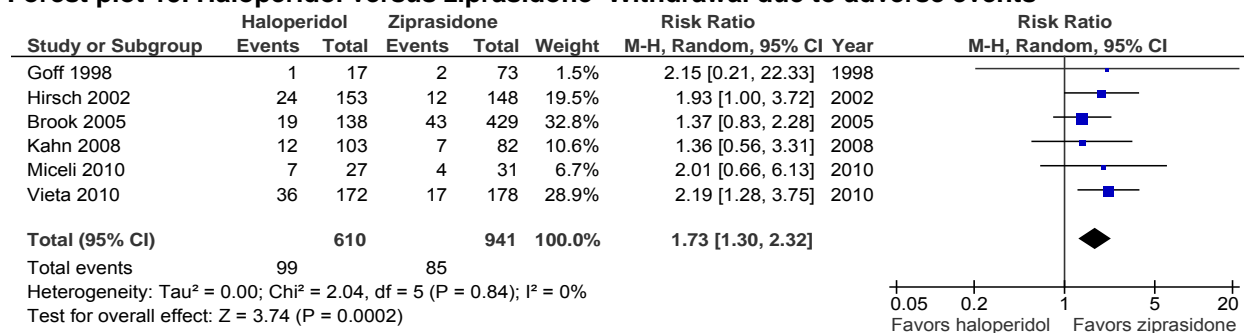
CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; M-H = Mantel-Haenszel

Forest plot 14. Haloperidol versus ziprasidone—Incidence of patients with adverse events



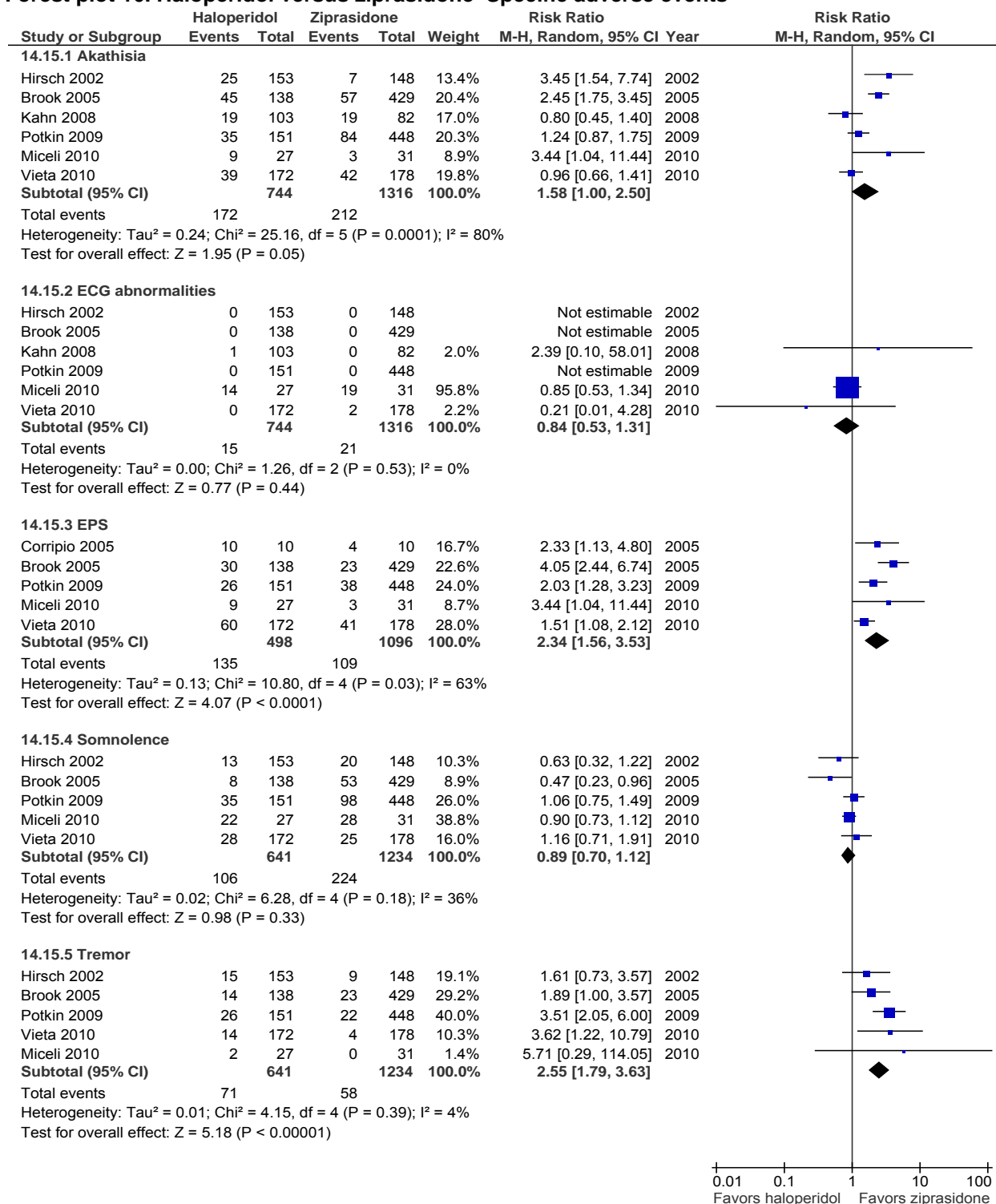
CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; M-H = Mantel-Haenszel

Forest plot 15. Haloperidol versus ziprasidone—Withdrawal due to adverse events



CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; M-H = Mantel-Haenszel

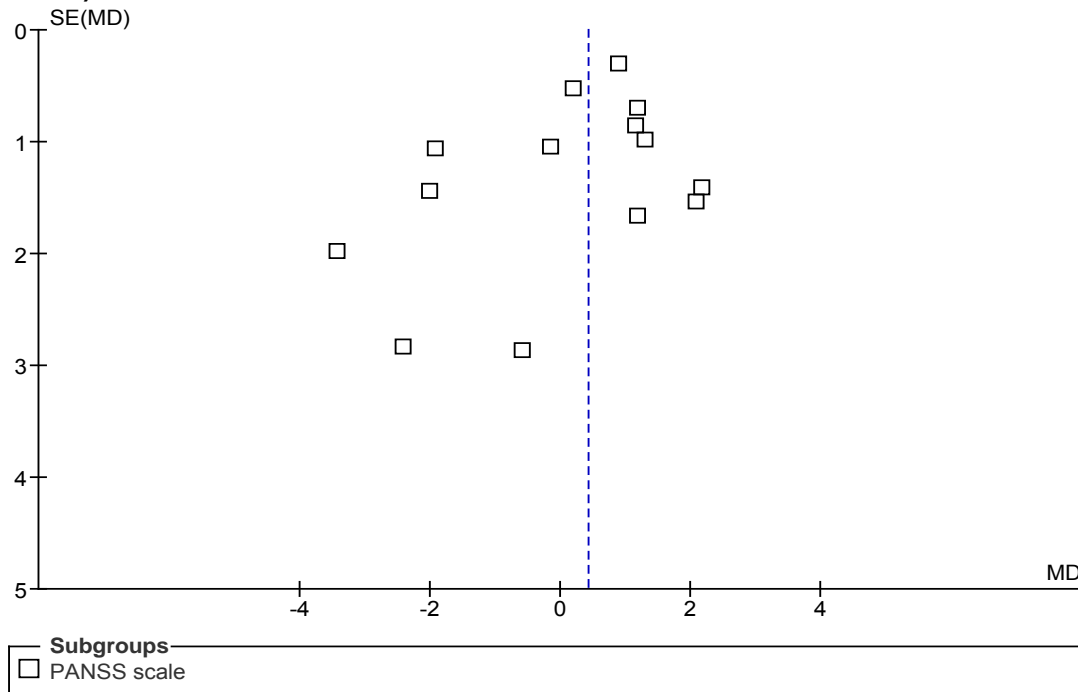
Forest plot 16. Haloperidol versus ziprasidone–Specific adverse events



CI = confidence intervals; df = degrees of freedom; I^2 = I-squared; IV = inverse variance; M-H = Mantel-Haenszel

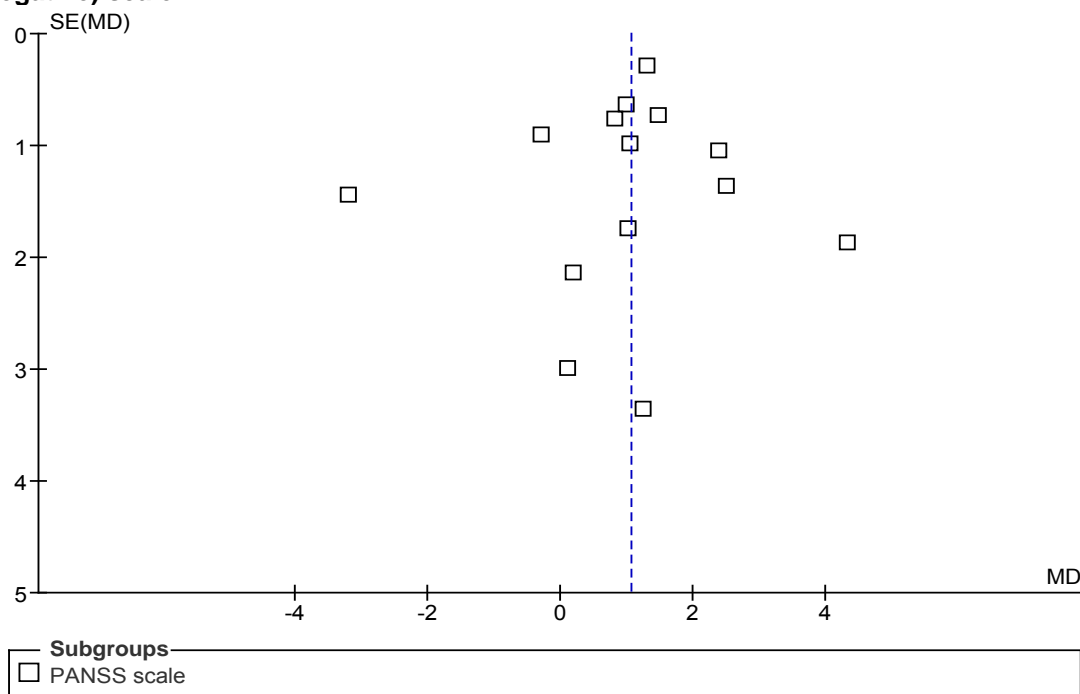
Appendix K. Funnel Plots

Funnel plot 1. Haloperidol versus olanzapine–Core symptoms (Sz)–Positive symptoms–PANSS (positive) scale



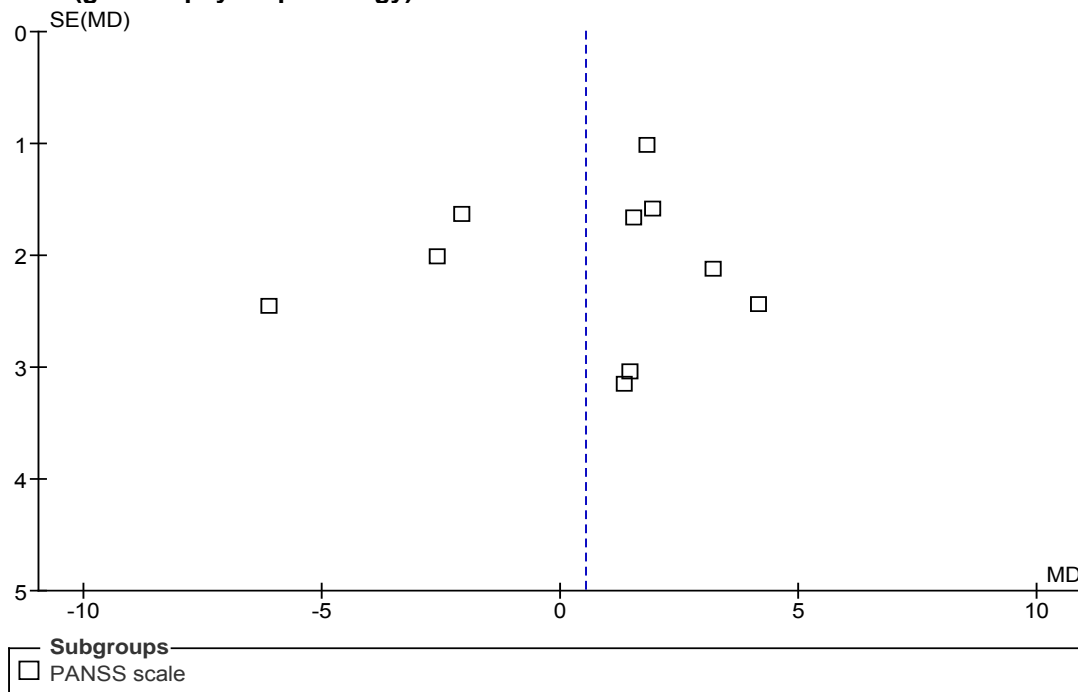
PANSS = Positive and Negative Syndrome Scale; MD = Mean Difference; SE = Standard Error; Sz = schizophrenia
Begg and Mazumdar rank correlation: $p = 0.19$; Egger's regression intercept: $p = 0.17$

Funnel plot 2. Haloperidol versus olanzapine–Core symptoms (Sz)–Negative symptoms–PANSS (negative) scale



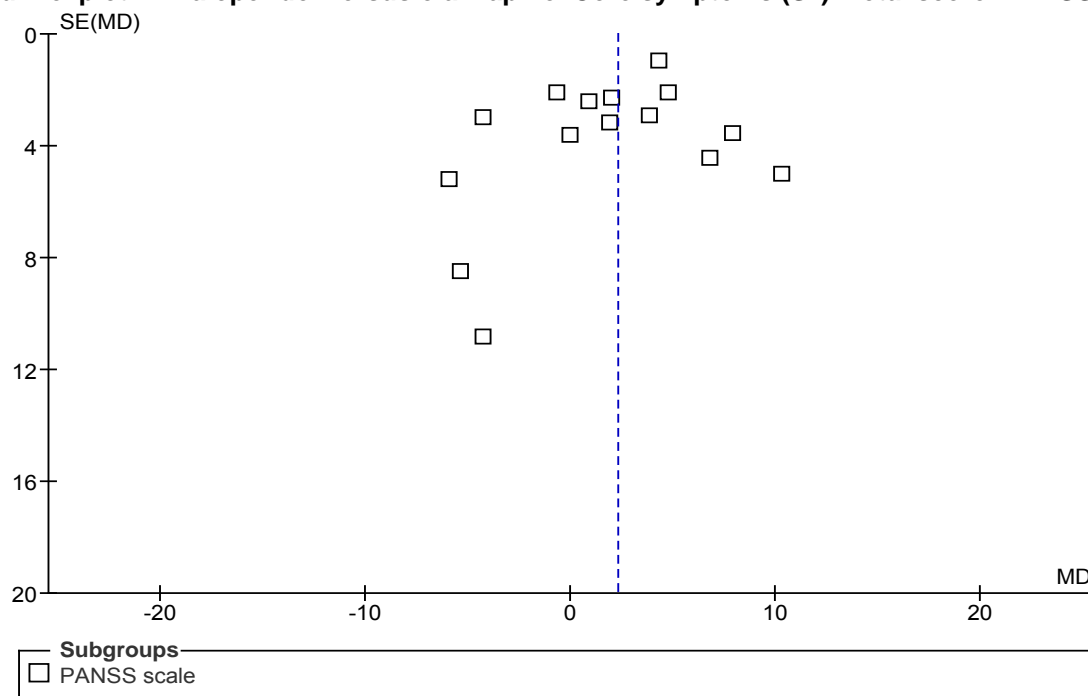
PANSS = Positive and Negative Syndrome Scale; MD = Mean Difference; SE = Standard Error; Sz = schizophrenia
 Begg and Mazumdar rank correlation: $p = 1.00$; Egger's regression intercept: $p = 0.64$

Funnel plot 3. Haloperidol versus olanzapine—Core symptoms (Sz)—General psychopathology—PANSS (general psychopathology) scale



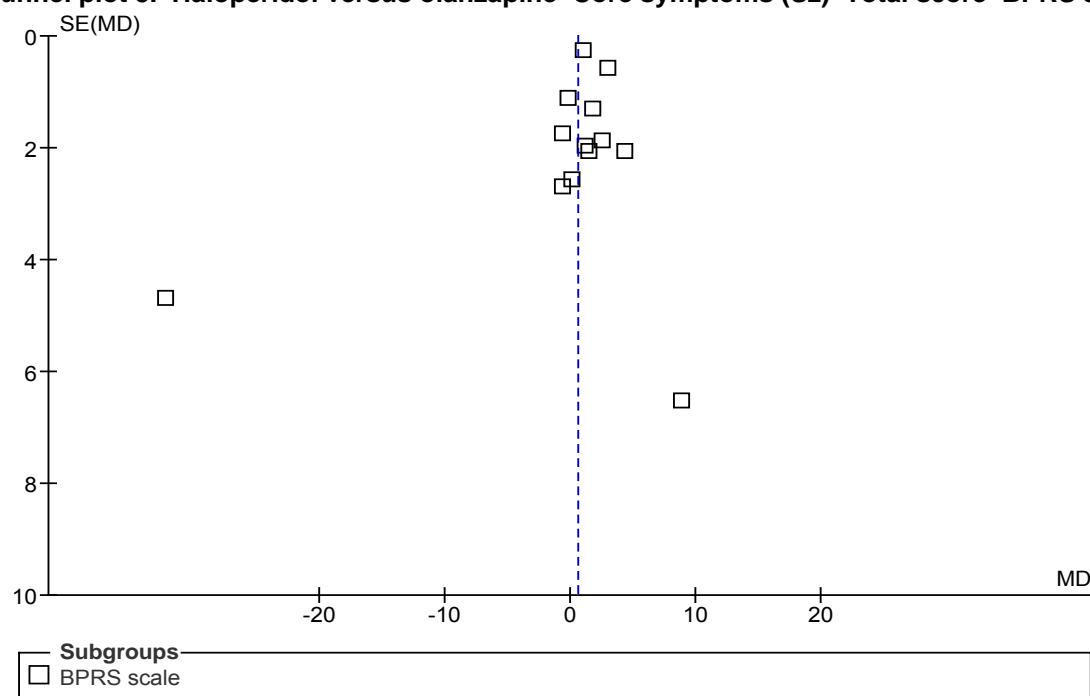
PANSS = Positive and Negative Syndrome Scale; MD = Mean Difference; SE = Standard Error; Sz = schizophrenia
 Begg and Mazumdar rank correlation: $p = 0.59$; Egger's regression intercept: $p = 0.55$

Funnel plot 4. Haloperidol versus olanzapine–Core symptoms (Sz)–Total score–PANSS scale



PANSS = Positive and Negative Syndrome Scale; MD = Mean Difference; SE = Standard Error; Sz = schizophrenia
 Begg and Mazumdar rank correlation: $p = 0.55$; Egger's regression intercept: $p = 0.24$

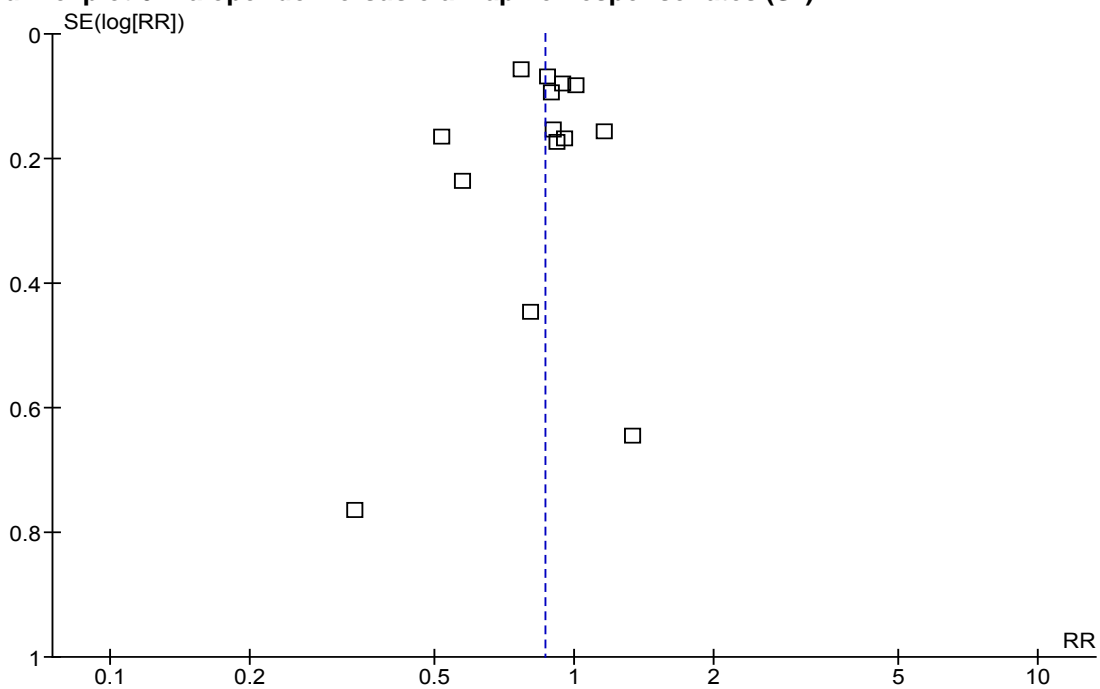
Funnel plot 5. Haloperidol versus olanzapine—Core symptoms (Sz)—Total score—BPRS scale



BPRS = Brief Psychiatric Rating Scale; MD = Mean Difference; SE = Standard Error; Sz = schizophrenia

Begg and Mazumdar rank correlation: $p = 0.86$; Egger's regression intercept: $p = 0.49$

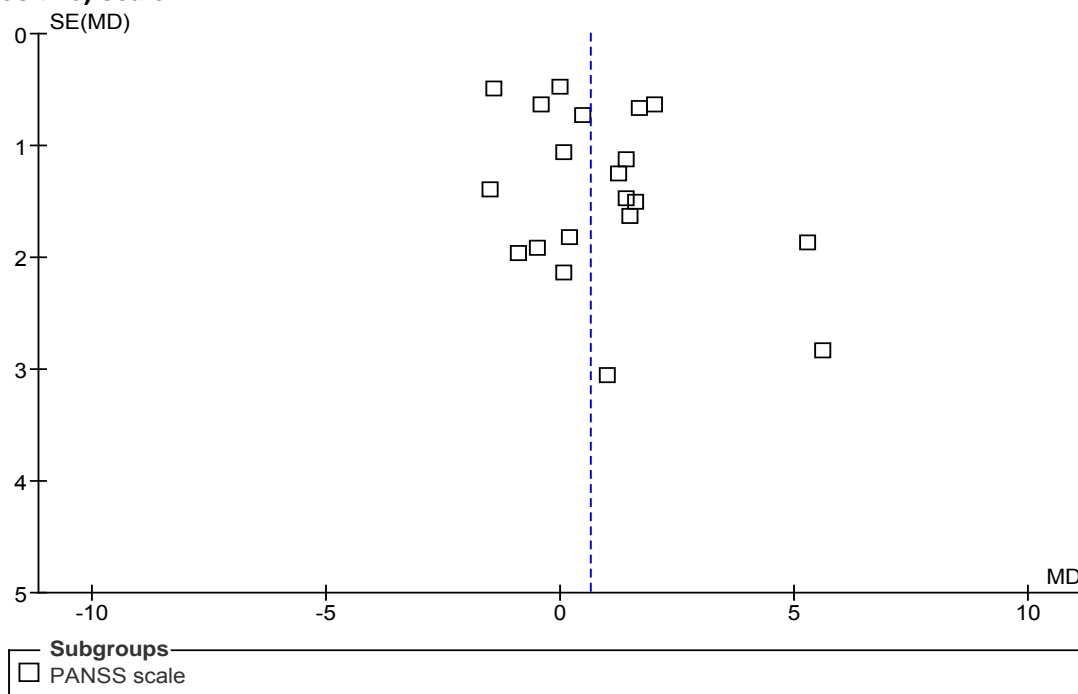
Funnel plot 6. Haloperidol versus olanzapine—response rates (Sz)



Log = Log Scale; RR = Relative Risk; SE = Standard Error; Sz = schizophrenia

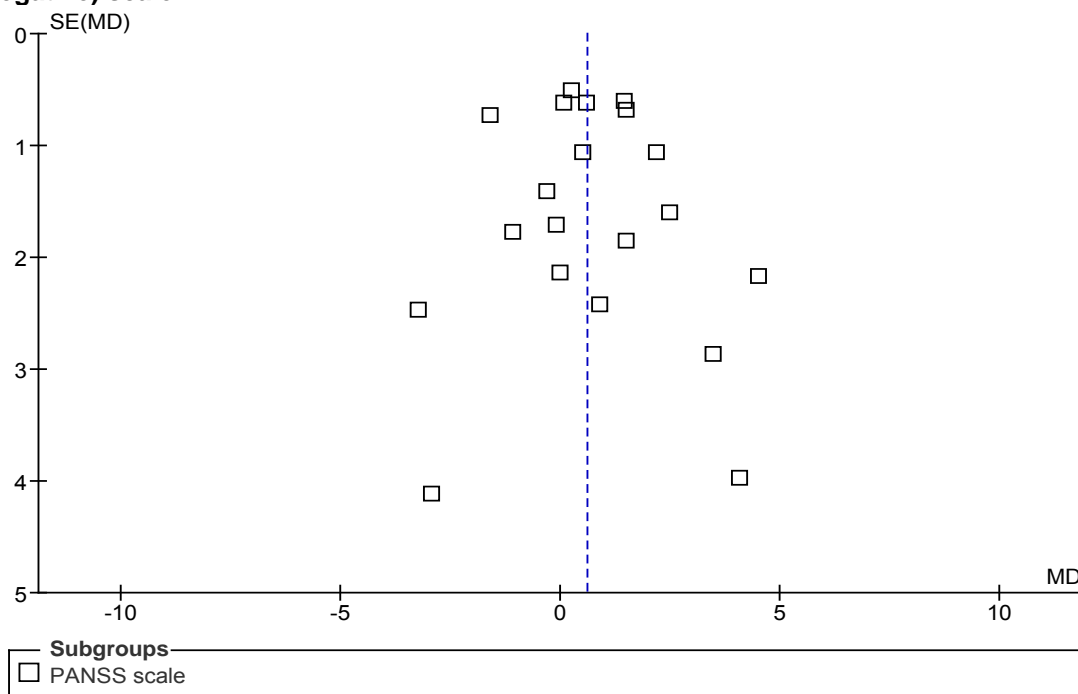
Begg and Mazumdar rank correlation: $p = 0.74$; Egger's regression intercept: $p = 0.74$

Funnel plot 7. Haloperidol versus risperidone–Core symptoms (Sz)–positive score–PANSS (positive) scale



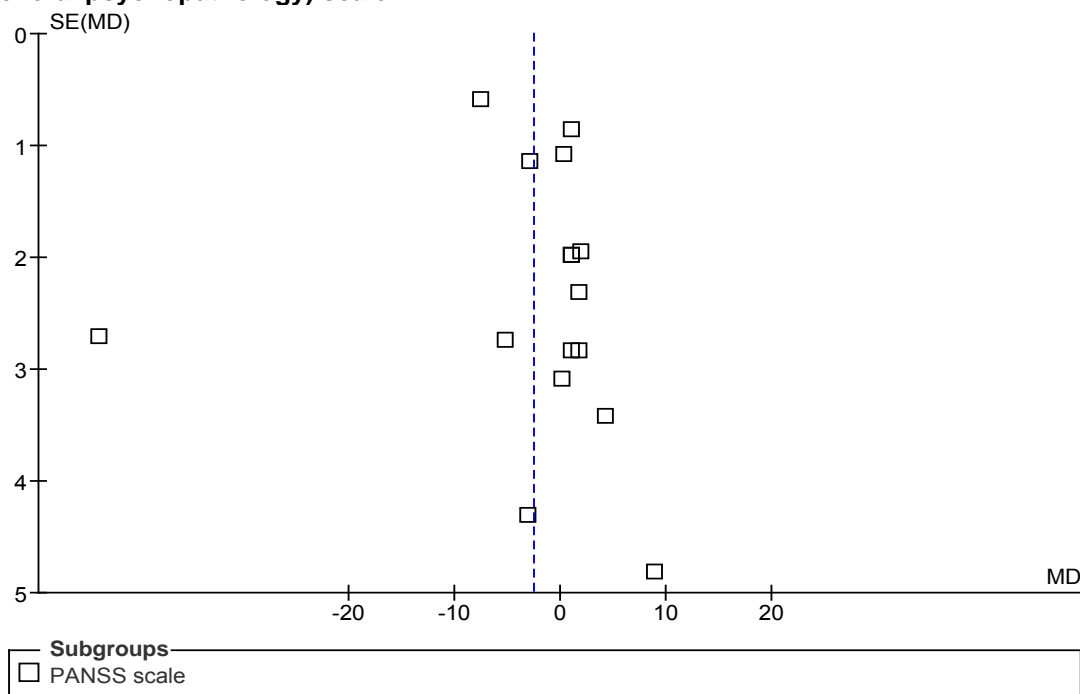
PANSS = Positive and Negative Syndrome Scale; MD = Mean Difference; SE = Standard Error; Sz = schizophrenia
 Begg and Mazumdar rank correlation: $p = 0.63$; Egger's regression intercept: $p = 0.11$

Funnel plot 8. Haloperidol versus risperidone–Core symptoms (Sz)–negative score–PANSS (negative) scale



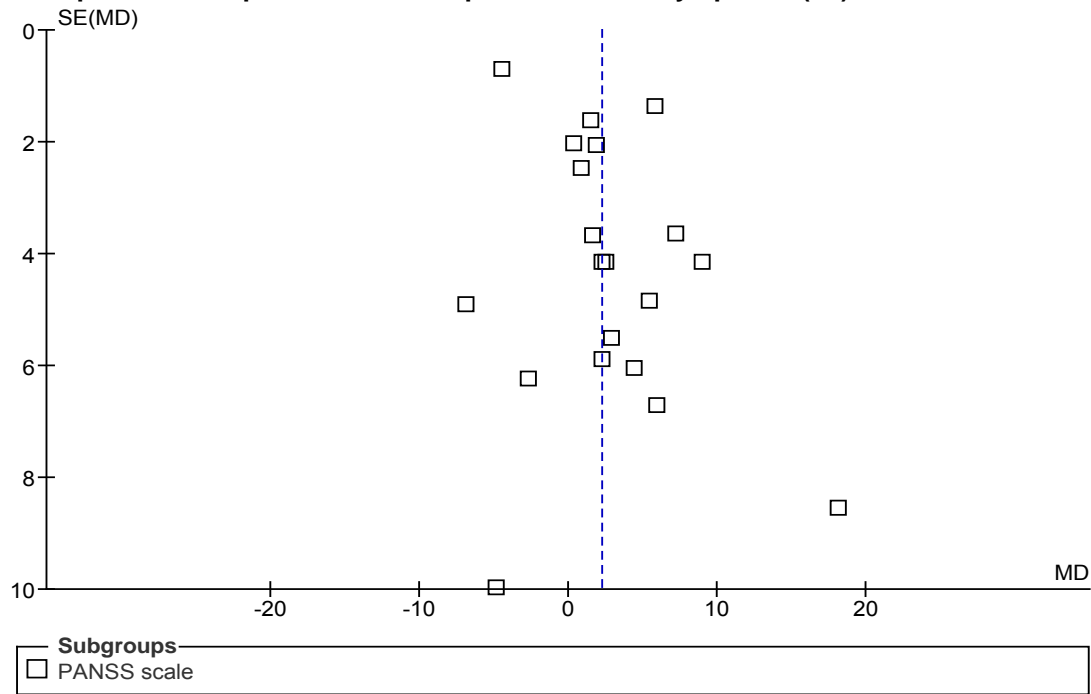
PANSS = Positive and Negative Syndrome Scale; MD = Mean Difference; SE = Standard Error; Sz = schizophrenia
 Begg and Mazumdar rank correlation: $p = 0.97$; Egger's regression intercept: $p = 0.69$

Funnel plot 9. Haloperidol versus risperidone–Core symptoms (Sz)–General symptoms–PANSS (general psychopathology) scale



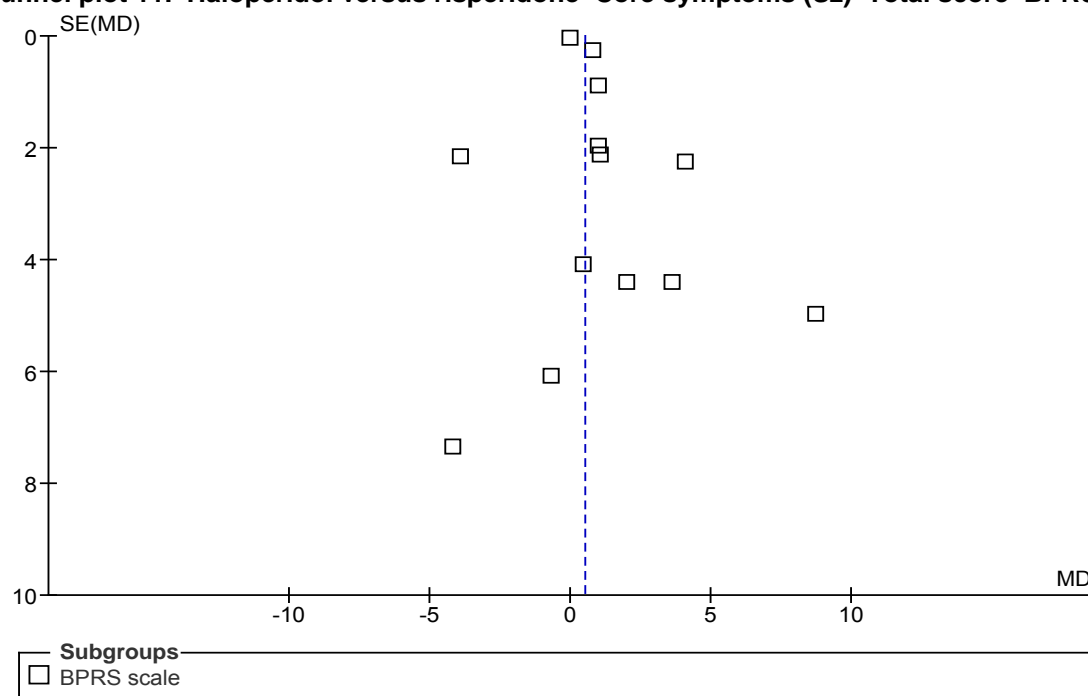
PANSS = Positive and Negative Syndrome Scale; MD = Mean Difference; SE = Standard Error; Sz = schizophrenia
 Begg and Mazumdar rank correlation: $p = 0.26$; Egger's regression intercept: $p = 0.61$

Funnel plot 10. Haloperidol versus risperidone—Core symptoms (Sz)—Total score—PANSS scale



PANSS = Positive and Negative Syndrome Scale; MD = Mean Difference; SE = Standard Error; Sz = schizophrenia
 Begg and Mazumdar rank correlation: $p = 0.35$; Egger's regression intercept: $p = 0.01$

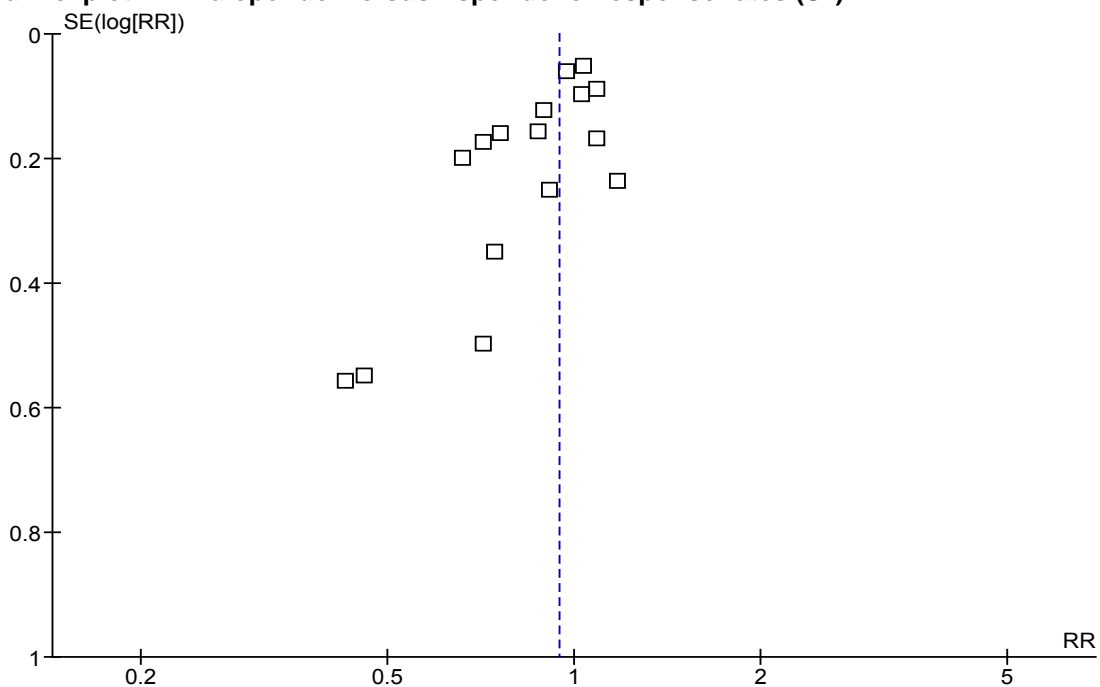
Funnel plot 11. Haloperidol versus risperidone—Core symptoms (Sz)—Total score—BPRS scale



BPRS = Brief Psychiatric Rating Scale; MD = Mean Difference; SE = Standard Error; Sz = schizophrenia

Begg and Mazumdar rank correlation: $p = 0.50$; Egger's regression intercept: $p = 0.14$

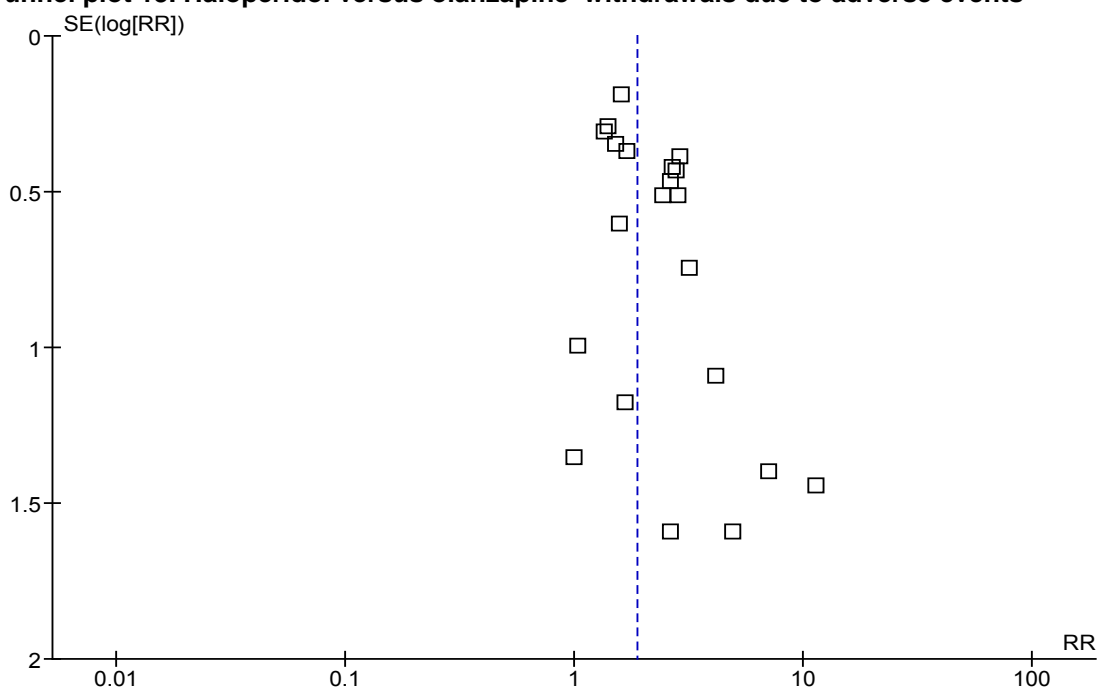
Funnel plot 12. Haloperidol versus risperidone—response rates (Sz)



Log = Log Scale; RR = Relative Risk; SE = Standard Error; Sz = schizophrenia

Begg and Mazumdar rank correlation: $p = 0.03$; Egger's regression intercept: $p = 0.006$

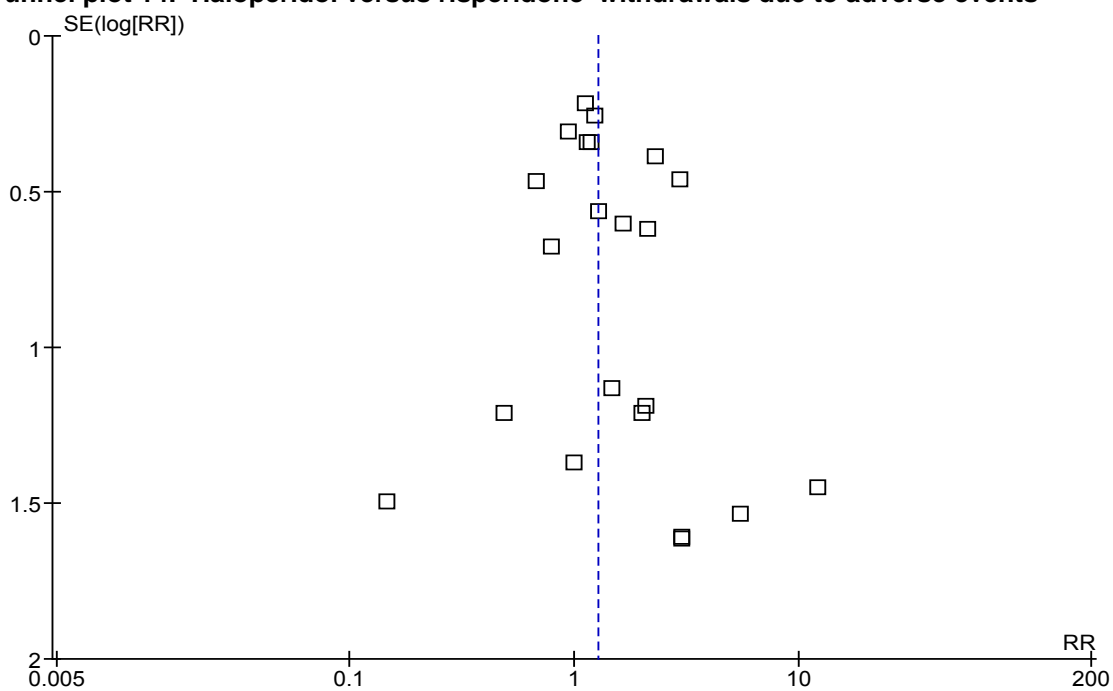
Funnel plot 13. Haloperidol versus olanzapine—withdrawals due to adverse events



Log = Log Scale; RR = Relative Risk; SE = Standard Error

Begg and Mazumdar rank correlation: $p = 0.17$; Egger's regression intercept: $p = 0.02$

Funnel plot 14. Haloperidol versus risperidone—withdrawals due to adverse events



Log = Log Scale; RR = Relative Risk; SE = Standard Error

Begg and Mazumdar rank correlation: $p = 0.26$; Egger's regression intercept: $p = 0.28$

Appendix L. Subscales, Composite Outcomes, and Functional Capacity

A) Schizophrenia and Related Psychoses

Table 81. Evidence summary table: chlorpromazine versus clozapine

Outcome	Studies	Participants	Effect Estimate	I ²	Favors
Positive symptoms					
BPRS - cluster of four key items ⁹⁴	1	268	3.00 (1.91, 4.09)	NE	clozapine
BPRS - hostility subscale ^{63,109,154,158}	4	355	0.25 (-0.43, 0.94)	43%	ND
BPRS - psychotic subscale ¹⁵²	1	64	0.11 (-0.26, 0.48)	NE	ND
NOSIE - Irritability subscale ¹⁵²	1	64	0.59 (0.26, 0.92)	NE	clozapine
NOSIE - Volitional Lack/Hallucination subscale ¹⁵²	1	64	-0.09 (-0.60, 0.42)	NE	ND
Negative symptoms					
BPRS - Anergia subscale ^{63,109,154,160}	4	374	0.30 (-0.65, 1.25)	0%	ND
NOSIE - Depression subscale ¹⁵²	1	64	0.81 (0.36, 1.26)	NE	clozapine
SANS - Affective blunting subscale ¹⁰⁹	1	164	1.20 (0.00, 2.40)	NE	ND
SANS - Alogia subscale ¹⁰⁹	1	164	0.30 (-0.46, 1.06)	NE	ND
SANS - Apathy subscale ¹⁰⁹	1	164	-0.10 (-0.87, 0.67)	NE	ND
SANS - Avolition subscale ¹⁰⁹	1	164	0.50 (-0.66, 1.66)	NE	ND
SANS - Disturbance of attention subscale ¹⁰⁹	1	164	0.10 (-0.22, 0.42)	NE	ND
General psychopathology					
BPRS - Agitation/Activation ^{63,109}	2	315	-0.17 (-0.71, 0.37)	77%	ND
BPRS - Anxiety/Depression subscale ^{63,152}	2	215	0.07 (-0.45, 0.60)	70%	ND
BPRS - Thought Disorder ^{63,109,154,160}	4	374	0.26 (-0.27, 0.78)	32%	ND
NOSIE - Autistic ¹⁵²	1	64	0.39 (-0.12, 0.90)	NE	ND
NOSIE - Social competence ^{152,160}	2	108	0.36 (-1.10, 1.82)	89%	ND
NOSIE - Social interest ^{152,160}	2	108	-0.17 (-1.43, 1.10)	67%	ND

Note: bolded results are statistically significant; BPRS = Brief Psychiatric Rating Scale; I² = I-squared; ND = no difference; NE = not estimable; NOSIE = Nurses' Observation Scale for Inpatient Evaluation; SANS = Scale for the Assessment of Negative Symptoms

Table 82. Evidence summary table: chlorpromazine versus olanzapine

Outcome	Studies	Participants	Effect Estimate	I ²	Favors
Positive symptoms					
BPRS - cluster of four key items ⁶⁶	1	84	1.30 (-0.28, 2.88)	NE	ND
BPRS - hostility subscale ⁶⁶	1	84	0.20 (-1.43, 1.83)	NE	ND
Negative symptoms					
BPRS - anergia ⁶⁶	1	84	0.60 (-1.05, 2.25)	NE	ND
General psychopathology					
BPRS - activation ⁶⁶	1	84	0.40 (-1.10, 1.90)	NE	ND
BPRS - anxiety/depression ⁶⁶	1	84	1.30 (-0.37, 2.97)	NE	ND

BPRS = Brief Psychiatric Rating Scale; I² = I-squared; ND = no difference; NE = not estimable

Table 83. Evidence summary table: fluphenazine versus olanzapine

Outcome	Studies	Participants	Effect Estimate	I ²	Favors
General psychopathology					
PANSS - mood subscale ⁸⁹	1	60	1.60 (-0.32, 3.52)	NE	ND
Functional capacity					
Auditory verbal learning (# words recalled) ¹¹²	1	18	2.30 (-1.73, 6.33)	NE	ND
Finger tapping test dominant hand ¹¹²	1	18	34.70 (-38.87, 108.27)	NE	ND
Finger tapping test non-dominant hand ¹¹²	1	18	47.10 (-13.64, 107.84)	NE	ND
LSEQ awakening score ⁸⁹	1	60	-2.70 (-9.76, 4.36)	NE	ND
LSEQ behavior following wakefulness ⁸⁹	1	60	-6.60 (-13.50, 0.30)	NE	ND
LSEQ getting to sleep ⁸⁹	1	60	-6.10 (-15.37, 3.17)	NE	ND
LSEQ quality of sleep ⁸⁹	1	60	-4.40 (-13.59, 4.79)	NE	ND
Serial digital learning ¹¹²	1	18	-2.30 (-9.72, 5.12)	NE	ND
SNST color task (# of errors) ¹¹²	1	18	-0.40 (-2.83, 2.03)	NE	ND
SNST color task (# of words) ¹¹²	1	18	-4.50 (-50.60, 41.60)	NE	ND
SNST word task (# of errors) ¹¹²	1	18	-1.80 (-4.97, 1.37)	NE	ND
SNST word task (# of words) ¹¹²	1	18	6.80 (-24.02, 37.62)	NE	ND
WAIS overall function ¹¹²	1	18	0.70 (-16.08, 17.48)	NE	ND
WCST total correct ¹¹²	1	18	-0.50 (-27.56, 26.56)	NE	ND

I² = I-squared; LSEQ = Listening Self-Efficacy Questionnaire; ND = no difference; NE = not estimable; PANSS = Positive and negative symptom scale; SNST = Stroop Neuropsychological Screening Test; WAIS = Wechsler Adult Intelligence Scale; WCST = Wisconsin Card Sorting Test

Table 84. Evidence summary table: fluphenazine versus quetiapine

Outcome	Studies	Participants	Effect Estimate	I ²	Favors
Positive symptoms					
BPRS - hostility subscale ⁶⁷	1	25	0.79 (-2.37, 3.95)	NE	ND
General psychopathology					
BPRS - activation ⁶⁷	1	25	-0.33 (-2.89, 2.23)	NE	ND
BPRS - anxiety/depression ⁶⁷	1	25	0.13 (-3.39, 3.65)	NE	ND

BPRS = Brief Psychiatric Rating Scale; I² = I-squared; ND = no difference; NE = not estimable

Table 85. Evidence summary table: fluphenazine versus risperidone

Outcome	Studies	Participants	Effect Estimate	I ²	Favors
Positive symptoms					
BPRS - hostility subscale ⁶⁷	1	26	0.92 (-2.12, 3.96)	NE	ND
General psychopathology					
BPRS - Activation subscale ⁶⁷	1	26	0.00 (-2.62, 2.62)	NE	ND
BPRS - Anxiety/depression subscale ⁶⁷	1	26	1.07 (-3.21, 5.35)	NE	ND

BPRS = Brief Psychiatric Rating Scale; I² = I-squared; ND = no difference; NE = not estimable

Table 86. Evidence summary table: haloperidol versus asenapine

Outcome	Studies	Participants	Effect Estimate	I ²	Favors
Positive symptoms					
PANSS - hostility/excitement subscale ⁹⁷	1	335	-0.70 (-1.54, 0.14)	NE	ND
General psychopathology					
PANSS - anxiety/depression subscale ⁹⁷	1	335	0.26 (-0.51, 1.04)	NE	ND
PANSS - disorganized thought subscale ⁹⁷	1	335	0.01 (-0.95, 0.97)	NE	ND

I² = I-squared; ND = no difference; NE = not estimable; PANSS = Positive and Negative Syndrome Scale

Table 87. Evidence summary table: haloperidol versus clozapine

Outcome	Studies	Participants	Effect Estimate	I ²	Favors
Positive symptoms					
BPRS - hostile/suspiciousness subscale ⁹⁵	1	71	1.40 (0.29, 2.51)	NE	clozapine
BPRS - psychosis cluster subscale ⁹⁵	1	71	2.70 (0.48, 4.92)	NE	clozapine
PANSS - hostility subscale ⁶²	1	77	0.71 (0.07, 1.35)	NE	clozapine
PANSS - excitement factor ¹⁴⁵	1	77	-0.60 (-1.20, 0.00)	NE	ND
PANSS - positive factor ¹⁴⁵	1	77	0.06 (-0.38, 0.50)	NE	ND
Negative symptoms					
PANSS - negative factor ¹⁴⁵	1	77	-0.41 (-0.80, -0.02)	NE	haloperidol
SANS - affective flattening subscale ⁹⁵	1	71	-0.30 (-0.84, 0.24)	NE	ND
SANS - alogia subscale ⁹⁵	1	71	0.10 (-0.44, 0.64)	NE	ND
SANS - anhedonia/sociality subscale ⁹⁵	1	71	-0.30 (-0.89, 0.29)	NE	ND
SANS - avolition/apathy subscale ⁹⁵	1	71	0.20 (-0.36, 0.76)	NE	ND
General psychopathology					
BPRS - activation ⁹⁵	1	71	0.60 (-0.26, 1.46)	NE	ND
BPRS - anergia ⁹⁵	1	71	-0.70 (-2.55, 1.15)	NE	ND
BPRS - anxiety/depression ⁹⁵	1	71	1.10 (-0.65, 2.85)	NE	ND
BPRS - thought disorder ⁹⁵	1	71	0.30 (-1.68, 2.28)	NE	ND
PANSS - cognitive factor ¹⁴⁵	1	77	-0.03 (-0.36, 0.30)	NE	ND
PANSS - depression/anxiety factor ¹⁴⁵	1	77	-0.05 (-0.46, 0.36)	NE	ND
Functional capacity					
Block Design ^{55,105}	2	148	-0.89 (-2.44, 0.67)	80%	ND
Cat. Fluency ⁵⁵	1	75	-11.50 (-17.71, -5.29)	NE	clozapine
Declarative verbal learning and memory - Neurocognitive testing ¹⁴⁵	1	77	0.06 (-0.40, 0.52)	NE	ND
Disorientation ¹⁰⁵	1	73	0.19 (-0.28, 0.66)	NE	ND
Executive function ¹⁰⁵	1	73	0.15 (-0.12, 0.42)	NE	ND
GCI ¹⁰⁵	1	73	-0.07 (-0.35, 0.21)	NE	ND
General intelligence ¹⁰³	1	34	-9.00 (-17.87, -0.13)	NE	clozapine
Judgment of Lines ⁵⁵	1	75	-5.00 (-11.96, 1.96)	NE	ND
Memory: Figural ⁵⁵	1	75	0.17 (-0.67, 1.01)	NE	ND
Memory: Logical ⁵⁵	1	75	5.80 (-2.67, 14.27)	NE	ND
Memory: Verbal pairs ⁵⁵	1	75	-0.60 (-2.94, 1.74)	NE	ND
Memory: Visual pairs ⁵⁵	1	75	-0.90 (-3.09, 1.29)	NE	ND
Memory: Visual Reprod. ⁵⁵	1	75	-0.80 (-4.70, 3.10)	NE	ND
Motor function ¹⁰⁵	1	73	-0.29 (-0.60, 0.02)	NE	ND
Neurocognitive Global Score ¹⁴⁵	1	77	-0.19 (-0.43, 0.05)	NE	ND
Neurocognitive testing - General executive and perceptual organization ¹⁴⁵	1	77	-0.19 (-0.46, 0.08)	NE	ND
Neurocognitive testing - Processing speed and attention ¹⁴⁵	1	77	-0.29 (-0.74, 0.16)	NE	ND
Neurocognitive testing - Simple motor Functioning ¹⁴⁵	1	77	-0.55 (-1.00, -0.10)	NE	clozapine
Mooney Faces ⁵⁵	1	75	-0.80 (-1.70, 0.10)	NE	ND
MMSE ⁵⁵	1	75	-1.14 (-3.56, 1.28)	NE	ND
Poor attention ¹⁰⁵	1	75	0.21 (-0.25, 0.67)	NE	ND
Stroop ⁵⁵	1	75	-1.00 (-5.08, 3.08)	NE	ND
Syndrome short test ¹⁰³	1	34	-28.70 (-31.51, -25.89)	NE	clozapine
Trail Making Test A ¹⁰⁵	1	73	-0.27 (-0.78, 0.24)	NE	ND
Trail Making Test B ⁵⁵	1	75	0.00 (-0.10, 0.10)	NE	ND

Table 87. Evidence summary table: haloperidol versus clozapine (continued)

Outcome	Studies	Participants	Effect Estimate	I ²	Favors
Verbal fluency ⁵⁵	1	75	-1.50 (-7.42, 4.42)	NE	ND
Verbal Memory ¹⁰⁵	1	73	0.01 (-0.44, 0.46)	NE	ND
Visual Memory ¹⁰⁵	1	73	0.23 (-0.36, 0.82)	NE	ND
WCST ⁵⁵	1	75	0.40 (-8.02, 8.82)	NE	ND

BPRS = Brief Psychiatric Rating Scale; GCI = General Cognitive Index; I² = I-squared; MMSE = Mini-Mental State Examination; ND = no difference; NE = not estimable; PANSS = Positive and Negative Syndrome Scale; SANS = Scale for the Assessment of Negative Symptoms; WCST = Wisconsin Card Sorting Test

Table 88. Evidence summary table: haloperidol versus olanzapine

Outcome	Studies	Participants	Effect Estimate	I ²	Favors
Positive symptoms					
BPRS - anxiety ¹⁵⁹	1	27	1.40 (-0.54, 3.34)	NE	ND
BPRS - hostility subscale ⁸⁸	1	182	1.75 (1.04, 2.46)	NE	olanzapine
PANSS - hostility subscale ⁶²	1	76	0.71 (-0.02, 1.44)	NE	ND
PANSS - PEC ^{56,147}	2	482	0.07 (-1.54, 1.67)	69%	ND
PANSS - excitement factor ¹⁴⁵	1	76	-0.25 (-0.81, 0.31)	NE	ND
PANSS - positive factor ¹⁴⁵	1	76	-0.21 (-0.66, 0.24)	NE	ND
Negative symptoms					
BPRS - activation ⁸⁸	1	182	0.74 (-0.19, 1.67)	NE	ND
BPRS - anergia ⁸⁸	1	182	0.33 (-0.60, 1.26)	NE	ND
PANSS - negative factor ¹⁴⁵	1	76	-0.37 (-0.74, 0.00)	NE	ND
SANS - Affective flattening subscale ¹⁵⁹	1	27	0.38 (-0.48, 1.24)	NE	ND
SANS - Alogia subscale ¹⁵⁹	1	27	0.08 (-0.84, 1.00)	NE	ND
SANS - Anhedonia subscale ¹⁵⁹	1	27	0.76 (-0.49, 2.01)	NE	ND
SANS - Attention subscale ¹⁵⁹	1	27	0.77 (-0.41, 1.95)	NE	ND
SANS - Avolition subscale ¹⁵⁹	1	27	0.07 (-0.94, 1.08)	NE	ND
SANS - composite ⁴⁹	1	267	2.93 (-1.35, 7.21)	NE	ND
General psychopathology					
BPRS - Psychosis ¹⁰⁶	1	32	-1.10 (-2.59, 0.39)	NE	ND
BPRS - anxiety/depression ⁸⁸	1	182	0.72 (-0.28, 1.72)	NE	ND
PANSS - Cognitive factor ¹⁴⁵	1	76	-0.26 (-0.57, 0.05)	NE	ND
PANSS - Depression/anxiety factor ¹⁴⁵	1	76	-0.19 (-0.56, 0.18)	NE	ND
BPRS - thought disorder ⁸⁸	1	182	0.25 (-0.72, 1.22)	NE	ND
Subjective well-being - emotional regulation subscale ⁷⁸	1	24	1.70 (-1.07, 4.47)	NE	ND
Subjective well-being - mental functioning subscale ⁷⁸	1	24	0.80 (-2.92, 4.52)	NE	ND
Subjective well-being - physical functioning subscale ⁷⁸	1	24	1.80 (-0.62, 4.22)	NE	ND
Subjective well-being - self-control subscale ⁷⁸	1	24	3.20 (0.75, 5.65)	NE	olanzapine
Functional capacity					
Attention Span ¹²⁴	1	44	-0.22 (-0.59, 0.15)	NE	ND
Block Design ¹⁰⁵	1	73	-0.61 (-1.15, -0.07)	NE	olanzapine
Brief test of attention (correct responses) ⁷¹	1	111	-0.76 (-1.88, 0.36)	NE	ND
COWAT, category/semantic ¹¹⁰	1	35	-5.13 (-10.50, 0.24)	NE	ND
continuous performance test (correct responses) ⁷¹	1	111	-2.78 (-7.30, 1.74)	NE	ND
Cognitive composite score ⁷⁵	1	208	-0.10 (-0.28, 0.08)	NE	ND
COWAT ^{71,110,124,134}	4	250	-2.64 (-8.48, 3.19)	78%	ND
CRT ⁵⁴	1	25	-50.00 (-163.48, 63.48)	NE	ND
CVLT ¹³⁴	1	60	4.60 (-1.91, 11.11)	NE	ND
D2 Test of Attention ⁵⁴	1	25	-1.71 (-37.40, 33.98)	NE	ND
Declarative verbal learning and memory ¹⁴⁵	1	76	-0.34 (-0.74, 0.06)	NE	ND
Design List Learning ¹²⁴	1	44	-4.68 (-9.30, -0.06)	NE	olanzapine
Digit Span ¹²⁴	1	44	-0.70 (-2.80, 1.40)	NE	ND
Digit Span Backward ⁵⁴	1	25	0.82 (-0.82, 2.46)	NE	ND
Digit Span Distractibility Test ⁵⁴	1	25	7.99 (-13.85, 29.83)	NE	ND
Digit Symbol Subtest ¹²⁴	1	44	-4.20 (-9.76, 1.36)	NE	ND
Discrimination of self-generated words ¹⁰¹	1	256	0.07 (-0.06, 0.20)	NE	ND
Disorientation ¹⁰⁵	1	73	-0.41 (-0.87, 0.05)	NE	ND
Distractibility task, no. correct ¹¹⁰	1	35	-2.33 (-7.97, 3.31)	NE	ND

Table 88. Evidence summary table: haloperidol versus olanzapine (continued)

Outcome	Studies	Participants	Effect Estimate	I ²	Favors
DSC CPT ¹³⁴	1	60	0.05 (-0.01, 0.11)	NE	ND
DSC ¹³⁴	1	60	2.60 (-4.01, 9.21)	NE	ND
Executive function ¹⁰⁵	1	73	-0.03 (-0.29, 0.23)	NE	ND
Executive Skills ¹²⁴	1	44	-0.33 (-0.96, 0.30)	NE	ND
Fagerstrom Tolerance Questionnaire ¹⁰²	1	67	2.60 (1.52, 3.68)	NE	haloperidol
Finger Tapping ^{54,124}	2	69	-4.02 (-10.66, 2.62)	36%	ND
Finger tapping left, no. taps ¹¹⁰	1	35	-8.43 (-16.57, -0.29)	NE	ND
Finger tapping right, no. taps ¹¹⁰	1	35	-7.59 (-18.35, 3.17)	NE	ND
Finger tapping test (mean taps/10 ses) ⁷¹	1	111	0.27 (-3.15, 3.69)	NE	ND
GCI ¹⁰⁵	1	73	-0.49 (-0.77, -0.21)	NE	olanzapine
General executive and perceptual organization - Neurocognitive testing ¹⁴⁵	1	76	-0.45 (-0.76, -0.14)	NE	olanzapine
GPT ¹³⁴	1	60	-14.80 (-42.36, 12.76)	NE	ND
Pegboard ^{54,71,75,124}	4	388	3.14 (-2.03, 8.31)	76%	ND
Hooper Visual Organization Test ¹²⁴	1	44	-0.85 (-1.84, 0.14)	NE	ND
Immediate Recall ¹²⁴	1	44	-0.63 (-1.03, -0.23)	NE	olanzapine
IOWA gambling ⁷¹	1	111	-16.02 (-31.31, -0.73)	NE	olanzapine
Level of Functioning Scale ⁵⁸	1	63	0.00 (-2.87, 2.87)	NE	ND
LNS ^{54,110,134}	3	120	0.56 (-1.99, 3.11)	63%	ND
memory: Z mean score ¹²⁷	1	309	-0.19 (-0.39, 0.01)	NE	ND
MMSE ¹⁰⁵	1	73	-3.89 (-6.32, -1.46)	NE	olanzapine
Motor function ^{105,124,127,145}	4	502	-0.39 (-0.76, -0.02)	74%	olanzapine
neurocognitive composite score ^{101,108,145}	3	595	-0.06 (-0.44, 0.32)	86%	ND
Nonverbal Fluency ¹²⁴	1	44	-3.40 (-6.52, -0.28)	NE	olanzapine
Nonverbal Fluency and Construction ¹²⁴	1	44	-0.66 (-1.36, 0.04)	NE	ND
Peabody Picture Vocabulary Test ¹²⁴	1	44	-2.68 (-9.54, 4.18)	NE	ND
Poor attention ¹⁰⁵	1	73	-0.59 (-1.05, -0.13)	NE	olanzapine
Processing speed and attention ¹⁴⁵	1	76	-0.49 (-0.87, -0.11)	NE	olanzapine
Rey auditory verbal learning (# words recalled) ⁷¹	1	111	-3.09 (-7.35, 1.17)	NE	ND
Rey auditory verbal learning LTR (# words recalled from list after delay) ⁷¹	1	111	-1.40 (-2.69, -0.11)	NE	olanzapine
Rey complex figure test (long term recall) ⁷¹	1	111	0.10 (-2.60, 2.80)	NE	ND
Rey Auditory Verbal Learning Test, recognition form ^{75,110}	2	243	-0.20 (-0.35, -0.06)	0%	olanzapine
Rey Auditory Verbal Learning Test, sum of trials 1-5 ¹¹⁰	1	35	-19.61 (-28.53, -10.69)	NE	olanzapine
Rey-Taylor Complex Figure Copy ¹²⁴	1	44	-1.92 (-5.53, 1.69)	NE	ND
Rey-Taylor Complex Figure Immediate Recall ¹²⁴	1	44	-0.08 (-3.89, 3.73)	NE	ND
Similarities Subtest ¹²⁴	1	44	0.50 (-1.47, 2.47)	NE	ND
SRT ^{54,124}	2	69	-2.98 (-8.21, 2.24)	0%	ND
Stoop ⁵⁴	1	25	0.22 (-4.48, 4.92)	NE	ND
Trail Making Test A ^{75,105,110}	3	316	-0.38 (-1.17, 0.41)	79%	ND
Trail Making Test B ^{71,75,110,124}	4	398	8.79 (-6.26, 23.85)	66%	ND
Unweighted Neurocognitive Composite Score based on Z score (change score) ¹⁰⁸	1	263	0.16 (0.04, 0.28)	NE	haloperidol
VCCQ-intensity score ¹³⁶	1	31	-5.90 (-12.36, 0.56)	NE	ND
VCCQ-mood score ¹³⁶	1	31	8.20 (-1.79, 18.19)	NE	ND
VCCQ-sick ¹³⁶	1	31	11.20 (0.85, 21.55)	NE	haloperidol
Verbal STM ⁵⁴	1	25	-4.22 (-11.62, 3.18)	NE	ND

Table 88. Evidence summary table: haloperidol versus olanzapine (continued)

Outcome	Studies	Participants	Effect Estimate	I ²	Favors
Verbal Memory ¹⁰⁵	1	73	-0.82 (-1.26, -0.38)	NE	Olanzapine
Verbal Fluency and Reasoning ¹²⁴	1	44	-0.32 (-0.61, -0.03)	NE	olanzapine
Verbal List Learning ¹²⁴	1	44	-8.52 (-14.18, -2.86)	NE	olanzapine
Visual Memory Span Backward ⁵⁴	1	25	0.11 (-1.64, 1.86)	NE	ND
Visual Memory Span Forward ⁵⁴	1	25	0.54 (-1.11, 2.19)	NE	ND
Visual Memory ¹⁰⁵	1	73	0.21 (-0.37, 0.79)	NE	ND
Visual Digit Coding Task ¹¹⁰	1	35	-10.57 (-17.24, -3.90)	NE	olanzapine
Visual Reproduction ¹²⁴	1	44	-0.90 (-2.78, 0.98)	NE	ND
Visual Span ¹²⁴	1	44	-0.78 (-2.70, 1.14)	NE	ND
WAIS III backwards digits (total score) ⁷¹	1	111	0.41 (-0.34, 1.16)	NE	ND
WAIS III digit symbol (total score) ^{71,75}	2	319	-0.29 (-0.83, 0.24)	28%	ND
WCST ¹³⁴	1	60	0.80 (-0.15, 1.75)	NE	ND
VCCQ-energy score ¹³⁶	1	31	11.50 (3.69, 19.31)	NE	haloperidol
WCS Test total errors ¹³⁷	1	29	9.32 (2.63, 16.01)	NE	haloperidol
WCST, perseverative errors ^{110,124}	2	79	0.05 (-0.07, 0.17)	0%	ND
Social relatedness/ functioning					
Subjective well-being, social functioning subscale ⁷⁸	1	24	-0.90 (-4.23, 2.43)	NE	ND

Note: bolded results are statistically significant; BPRS = Brief Psychiatric Rating Scale; COWA = Controlled Oral Word Association; COWAT = Controlled Oral Word Association Test; CRT = Clinical Global Impressions; CVLT = California Verbal Learning Test; DS CPT = Degraded Stimuli–Continuous Performance Test; DSC = Degraded Stimuli–Continuous; GCI = General Cognitive Index; GPT = Grooved Pegboard Test; I² = I-squared; LNS = Letter–Number Sequencing; ND = no difference; NE = not estimable; PANSS = Positive and Negative Syndrome Scale; SANS = Scale for the Assessment of Negative Symptoms; SRT = Simple Reaction Time; STM = short-term memory; VCCQ = Voris Cocaine Craving Questionnaire; WAIS = Wechsler Adult; Intelligence Scale; WCST = Wisconsin Card Sorting Test

Table 89. Evidence summary table: haloperidol versus quetiapine

Outcome	Studies	Participants	Effect Estimate	I ²	Favors
Positive symptoms					
BPRS - elated mood subscale ⁷⁹	1	288	0.53 (-0.17, 1.23)	NE	ND
Negative symptoms					
PANSS - Depressive subscale ⁷⁹	1	288	1.06 (0.32, 1.80)	NE	quetiapine
Functional capacity					
Cognition - Attention Span ¹²³	1	25	-0.20 (-0.68, 0.28)	NE	ND
Cognition - Executive skills/visuomotor tracking ¹²³	1	25	0.10 (-0.42, 0.62)	NE	ND
Cognition - General ¹²³	1	25	-0.10 (-0.49, 0.29)	NE	ND
Cognition - Immediate recall ¹²³	1	25	-0.20 (-0.67, 0.27)	NE	ND
Cognition - Motor speed/dexterity ¹²³	1	25	0.10 (-1.04, 1.24)	NE	ND
Cognition - Verbal reasoning/fluency ¹²³	1	25	-0.20 (-0.58, 0.18)	NE	ND
Cognition - Visuospatial fluency/construction ¹²³	1	25	-0.60 (-1.29, 0.09)	NE	ND
Cognitive - composite score ⁷⁵	1	207	-0.14 (-0.33, 0.05)	NE	ND
Cognitive - Summary Score ¹⁴³	1	58	-0.11 (-0.61, 0.39)	NE	ND
Complex Figure Copy Test ¹²³	1	25	-1.30 (-3.09, 0.49)	NE	ND
Complex Figure Recall Test ¹²³	1	25	1.00 (0.10, 1.90)	NE	haloperidol
Design Learning Test ¹²³	1	25	-0.40 (-1.35, 0.55)	NE	ND
Finger Tapping ¹²³	1	25	-0.40 (-1.56, 0.76)	NE	ND
Grooved Pegboard ^{75,123}	2	232	-0.02 (-0.25, 0.21)	0%	ND
Hopkins Verbal Learning ¹⁴³	1	58	-1.52 (-5.84, 2.80)	NE	ND
Nonverbal fluency ¹²³	1	25	-0.10 (-0.46, 0.26)	NE	ND
Paragraph Recall ¹⁴³	1	58	-0.72 (-3.05, 1.60)	NE	ND
Rey Auditory Verbal Learning Test ⁷⁵	1	207	0.00 (-0.26, 0.26)	NE	ND
Story Recall Test ¹²³	1	25	-1.00 (-1.91, -0.09)	NE	
Stroop Color-Word ¹⁴³	1	58	-2.57 (-13.52, 8.37)	NE	ND
Symbol Digit ¹⁴³	1	58	1.14 (-7.55, 9.83)	NE	ND
Trail Making Test A ⁷⁵	1	207	-0.04 (-0.22, 0.14)	NE	ND
Trail Making Test B ^{75,123}	2	232	-0.12 (-0.24, -0.01)	0%	quetiapine
Trails B-A ¹⁴³	1	58	-1.00 (-33.10, 31.10)	NE	ND
Verbal Fluency ^{123,143}	2	83	-0.42 (-1.02, 0.17)	0%	ND
Verbal Learning Test ¹²³	1	25	0.00 (-0.91, 0.91)	NE	ND
Visual Organization Test ¹²³	1	25	0.00 (-0.48, 0.48)	NE	ND
WAIS-III Digit Symbol ⁷⁵	1	207	-0.26 (-0.46, -0.06)	NE	ND
WAIS-R Digit Symbol Test ¹²³	1	25	0.00 (-0.36, 0.36)	NE	ND
WAIS-R Similarities ¹²³	1	25	-0.30 (-0.77, 0.17)	NE	ND
WCST (perseverations) ¹²³	1	25	0.50 (-0.53, 1.53)	NE	ND
WMS Digit Span ¹²³	1	25	-0.10 (-0.53, 0.33)	NE	ND
WMS Visual Reproduction ¹²³	1	25	-0.10 (-1.44, 1.24)	NE	ND
WMS Visual Span ¹²³	1	25	-0.50 (-1.23, 0.23)	NE	ND

Note: bolded results are statistically significant; BPRS = Brief Psychiatric Rating Scale; PANSS = Positive and Negative Syndrome Scale; WAIS = Wechsler Adult Intelligence Scale; WCST = Wisconsin Card Sorting Test; WMS = Wechsler Memory Scale

Table 90. Evidence summary table: haloperidol versus risperidone

Outcome	Studies	Participants	Effect Estimate	I ²	Favors
Positive symptoms					
BPRS - Hostility/suspiciousness subscale ¹¹³	1	63	0.05 (-0.13, 0.23)	NE	ND
PANSS-derived BPRS - activity subscale ¹²⁰	1	1362	0.30 (-0.11, 0.71)	NE	ND
PANSS-derived BPRS - hostility subscale ¹²⁰	1	1362	0.08 (-0.38, 0.54)	NE	ND
PANSS - hostility subscale ^{62,72}	2	443	0.47 (-0.13, 1.06)	0%	ND
PANSS - excitement factor ¹⁴⁵	1	78	-0.15 (-0.73, 0.43)	NE	ND
PANSS - positive factor ¹⁴⁵	1	78	0.03 (-0.38, 0.44)	NE	ND
PANSS - Uncontrolled hostility/excitement MADRS ¹¹⁸	1	289	-0.70 (-1.18, -0.22)	NE	haloperidol
SCL-90-R - Anger/hostility subscale ¹¹³	1	63	0.22 (0.04, 0.40)	NE	risperidone
SCL-90-R - Obsessive/compulsive subscale ¹¹³	1	63	0.35 (0.13, 0.57)	NE	risperidone
SCL-90-R - Paranoid ideation subscale ¹¹³	1	63	0.16 (-0.16, 0.48)	NE	ND
SCL-90-R - Psychoticism subscale ¹¹³	1	63	0.17 (-0.09, 0.43)	NE	ND
Negative symptoms					
BPRS - emotional withdrawal subscale ¹¹³	1	63	0.00 (-0.17, 0.17)	NE	ND
CDS-S - depression subscale ⁴⁵	1	20	2.30 (-0.42, 5.02)	NE	ND
PANSS - 5-factor solution ¹¹⁸	1	289	-1.40 (-2.93, 0.13)	NE	ND
PANSS - negative factor ¹⁴⁵	1	78	-0.14 (-0.53, 0.25)	NE	ND
PANSS-derived BPRS - Anergia ¹²⁰	1	1362	0.36 (-0.12, 0.84)	NE	ND
SANS - Affective Flattening ¹¹³	1	63	-0.02 (-0.35, 0.31)	NE	ND
SANS - Alogia ¹¹³	1	63	-0.01 (-0.29, 0.27)	NE	ND
SANS - Anhedonia ¹¹³	1	63	0.11 (-0.24, 0.46)	NE	ND
SANS - Attentional impairment score ¹¹⁸	1	289	-0.20 (-0.47, 0.07)	NE	ND
SANS - Avolition ¹¹³	1	63	0.06 (-0.26, 0.38)	NE	ND
SANS - Global ¹¹³	1	63	0.04 (-0.21, 0.29)	NE	ND
SCL-90 - Depression subscale ¹¹³	1	63	0.46 (0.22, 0.70)	NE	risperidone
General psychopathology					
BPRS - Factor I ⁶⁰	1	62	-0.52 (-0.84, -0.20)	NE	haloperidol
BPRS - anxiety/depression subscale ^{113,117}	2	98	0.18 (-0.13, 0.49)	51%	ND
BPRS - Factor II ⁶⁰	1	62	-0.17 (-0.46, 0.12)	NE	ND
BPRS - Factor III ⁶⁰	1	62	-0.11 (-0.51, 0.29)	NE	ND
BPRS - Factor IV ⁶⁰	1	62	-0.09 (-0.22, 0.04)	NE	ND
BPRS - Factor V ⁶⁰	1	62	-0.13 (-0.45, 0.19)	NE	ND
BPRS - Thought disturbances subscale ^{113,117}	2	98	-0.10 (-0.33, 0.12)	0%	ND
PANSS - anxiety/depression subscale ^{72,118,145}	3	732	0.25 (-0.26, 0.77)	50%	ND
PANSS - Cognitive subscale ¹⁴⁵	1	78	-0.13 (-0.42, 0.16)	NE	ND
PANSS - disorganized thought subscale ^{72,118}	2	654	-0.25 (-2.91, 2.41)	93%	ND
PANSS-derived BPRS - Anxiety/depression subscale ¹²⁰	1	1362	0.33 (-0.15, 0.81)	NE	ND
PANSS-derived BPRS - Thought disturbances subscale ¹²⁰	1	1362	-0.06 (-0.62, 0.50)	NE	ND

Table 90. Evidence summary table: haloperidol versus risperidone (continued)

Outcome	Studies	Participants	Effect Estimate	I ²	Favors
Total score					
SCL-9-R - Anxiety subscale ¹¹³	1	63	0.35 (0.13, 0.57)	NE	risperidone
SCL-90-R - Interpersonal sensitivity subscale ¹¹³	1	63	0.33 (0.05, 0.61)	NE	risperidone
SCL-90-R - Phobic Anxiety subscale ¹¹³	1	63	0.33 (0.09, 0.57)	NE	risperidone
SCL-90-R - Somatization subscale ¹¹³	1	63	0.21 (-0.01, 0.43)	NE	ND
Functional capacity					
Attention Span ¹²⁴	1	44	0.08 (-0.24, 0.40)	NE	ND
Brief test of attention (correct responses) ⁷¹	1	117	-0.51 (-1.54, 0.52)	NE	ND
Continuous performance test (correct responses) ⁷¹	1	117	-2.45 (-6.83, 1.93)	NE	ND
COWAT ^{71,124,132,134}	4	776	-0.95 (-4.20, 2.31)	62%	ND
CVLT ¹³⁴	1	60	6.20 (-0.31, 12.71)	NE	ND
Design List Learning ¹²⁴	1	44	-3.78 (-9.34, 1.78)	NE	ND
Digit Span ¹²⁴	1	44	0.20 (-1.42, 1.82)	NE	ND
Digit Symbol Subtest ¹²⁴	1	44	0.20 (-4.34, 4.74)	NE	ND
Discrimination of self-generated words ¹⁰⁰	1	9	-0.01 (-0.12, 0.10)	NE	ND
DS CPT ¹³⁴	1	60	-0.01 (-0.06, 0.04)	NE	ND
DSC ¹³⁴	1	60	0.40 (-6.41, 7.21)	NE	ND
Early night ⁴⁵	1	20	244.45 (-49.52, 538.42)	NE	ND
Executive Skills ¹²⁴	1	44	0.11 (-0.51, 0.73)	NE	ND
Fagerstrom Tolerance Questionnaire ¹⁰²	1	76	1.90 (0.94, 2.86)	NE	haloperidol
Finger Tapping ^{71,124}	2	161	0.44 (-6.66, 7.54)	65%	ND
GAF ¹¹⁸	1	289	-2.20 (-5.64, 1.24)	NE	ND
GPT ¹³⁴	1	60	-1.40 (-25.41, 22.61)	NE	ND
Grooved Pegboard ^{71,124}	2	161	-0.48 (-17.58, 16.61)	64%	ND
Hooper Visual Organization Test ¹²⁴	1	44	0.38 (-0.47, 1.23)	NE	ND
Immediate Recall ¹²⁴	1	44	-0.22 (-0.58, 0.14)	NE	ND
IOWA gambling ⁷¹	1	117	-11.99 (-26.45, 2.47)	NE	ND
Late night ⁴⁵	1	20	88.89 (-1.54, 179.32)	NE	ND
LNS ¹³⁴	1	60	0.20 (-2.40, 2.80)	NE	ND
Maze tasks CM velocity ¹⁰⁷	1	20	-41.70 (-81.21, -2.19)	NE	risperidone
Maze tasks SM velocity ¹⁰⁷	1	20	-48.00 (-94.88, -1.12)	NE	risperidone
Morning ⁴⁵	1	20	-200.00 (-561.65, 161.65)	NE	ND
Motor Skills ¹²⁴	1	44	-0.48 (-1.10, 0.14)	NE	ND
Neurocognitive composite score ¹⁰¹	1	255	-0.06 (-0.27, 0.15)	NE	ND
Neurocognitive Global Score ¹⁴⁵	1	78	-0.46 (-0.73, -0.19)	NE	risperidone
Neurocognitive testing - Declarative verbal learning and memory ¹⁴⁵	1	78	-0.66 (-1.08, -0.24)	NE	risperidone
Neurocognitive testing - General executive and perceptual organization ¹⁴⁵	1	78	-0.44 (-0.77, -0.11)	NE	risperidone
Neurocognitive testing - Simple motor Functioning ¹⁴⁵	1	78	-0.24 (-0.72, 0.24)	NE	ND
Nonverbal Fluency ¹²⁴	1	44	-3.60 (-6.17, -1.03)	NE	risperidone
Nonverbal Fluency and Construction ¹²⁴	1	44	0.24 (-0.24, 0.72)	NE	ND
Peabody Picture Vocabulary Test ¹²⁴	1	44	1.02 (-4.41, 6.45)	NE	ND
Perception of emotion ⁹⁹	1	18	-6.93 (-10.32, -3.54)	NE	risperidone

Table 90. Evidence summary table: haloperidol versus risperidone (continued)

Outcome	Studies	Participants	Effect Estimate	I ²	Favors
Neurocognitive testing - Processing speed and attention ¹⁴⁵	1	78	-0.21 (-0.63, 0.21)	NE	ND
Processing speed: WAIS-R Digit Symbol age-corrected score ¹³²	1	555	-0.35 (-0.67, -0.03)	NE	risperidone
Rey auditory verbal learning (# words recalled) ⁷¹	1	117	-1.26 (-5.18, 2.66)	NE	ND
Rey auditory verbal learning LTR (# words recalled from list after delay) ⁷¹	1	117	-0.98 (-2.36, 0.40)	NE	ND
Rey complex figure test (long term recall) ⁷¹	1	117	-0.46 (-2.97, 2.05)	NE	ND
Rey Verbal Learning Test: trials 1-5 ¹³²	1	555	-1.47 (-3.08, 0.14)	NE	ND
Rey-Taylor Complex Figure Copy ¹²⁴	1	44	2.31 (-0.36, 4.98)	NE	ND
Rey-Taylor Complex Figure Immediate Recall ¹²⁴	1	44	-0.08 (-4.15, 3.99)	NE	ND
RVLT: Long-delay free recall ¹³²	1	555	-0.63 (-1.12, -0.14)	NE	risperidone
RVLT: Recognition discriminability ¹³²	1	555	-0.78 (-2.85, 1.29)	NE	ND
Similarities Subtest ¹²⁴	1	44	-0.65 (-2.11, 0.81)	NE	ND
Sleep time (hrs) ⁴⁵	1	20	-0.46 (-2.22, 1.30)	NE	ND
SRM 5 s ¹⁴⁶	1	67	1.60 (-0.20, 3.40)	NE	ND
SRM 15 s ¹⁴⁶	1	67	1.50 (-0.20, 3.20)	NE	ND
Story Recall Test ¹²⁴	1	44	-2.45 (-7.44, 2.54)	NE	ND
SWM 5 s ¹⁴⁶	1	67	-1.50 (-4.69, 1.69)	NE	ND
SWM 15s ¹⁴⁶	1	67	-2.90 (-5.92, 0.12)	NE	ND
Trail Making Test B ^{71,124}	2	161	2.64 (-9.02, 14.30)	0%	ND
Verbal Fluency and Reasoning ¹²⁴	1	44	-0.30 (-0.49, -0.11)	NE	risperidone
Verbal List Learning ¹²⁴	1	44	-2.27 (-7.50, 2.96)	NE	ND
Vigilance: Continuous Performance Test d' total ¹³²	1	555	0.08 (-0.01, 0.17)	NE	ND
Visual Reproduction ¹²⁴	1	44	0.45 (-1.33, 2.23)	NE	ND
Visual Span ¹²⁴	1	44	0.47 (-1.31, 2.25)	NE	ND
Waking bouts ⁴⁵	1	20	7.26 (-1.46, 15.98)	NE	ND
WAIS III backwards digits (total score) ⁷¹	1	117	-0.07 (-0.84, 0.70)	NE	ND
WAIS III digit symbol (total score) ⁷¹	1	117	-0.30 (-1.42, 0.82)	NE	ND
WCST Categories ^{107,132,134}	3	635	-0.21 (-0.84, 0.41)	37%	ND
WCST Nonperseverative errors ¹⁰⁷	1	20	19.10 (-10.11, 48.31)	NE	ND
WCST Perseverative errors ^{107,124,132}	3	619	0.58 (-2.92, 4.08)	12%	ND
WCST Perseverative responses ¹⁰⁷	1	20	5.10 (-16.83, 27.03)	NE	ND
WMS_RVR: Delayed recall total ¹³²	1	555	-0.81 (-2.15, 0.53)	NE	ND
WMS_RVR: Immediate recall total score ¹³²	1	555	-0.05 (-1.07, 0.97)	NE	ND
Functional deterioration					
Deterioration (Csernasky criterion) ¹¹⁸	1	289	0.87 (0.46, 1.64)	NE	haloperidol
Marked clinical deterioration ¹¹⁸	1	289	0.84 (0.29, 2.44)	NE	haloperidol

Table 90. Evidence summary table: haloperidol versus risperidone (continued)

Outcome	Studies	Participants	Effect Estimate	I ²	Favors
Social relatedness/functioning					
Improvement ¹³⁵	1	100	0.65 (0.45, 0.93)*	NE	risperidone
Social Adjustment Scale II-Instrumental role ¹¹³	1	63	-0.01 (-0.55, 0.53)	NE	ND
Social Adjustment Scale II-Intimate relationship ¹¹³	1	63	0.47 (0.01, 0.93)	NE	haloperidol
Social Adjustment Scale II-Overall Social functioning ¹¹³	1	63	0.18 (-0.18, 0.54)	NE	ND
Social Adjustment Scale II-Sense of wellbeing ¹¹³	1	63	0.12 (-0.20, 0.44)	NE	ND
Social Adjustment Scale II - Total Social relatedness/functioning ¹¹³	1	63	0.05 (-0.25, 0.35)	NE	ND
Social Adjustment Scale II-Social/leisure ¹¹³	1	63	-0.06 (-0.42, 0.30)	NE	ND
SOFAS ¹¹⁸	1	289	-1.80 (-5.14, 1.54)	NE	ND
Total score ¹¹⁸	1	289	-1.10 (-4.45, 2.25)	NE	ND
Facial Emotion Identification Test ¹³⁴	1	60	-0.50 (-2.26, 1.26)	NE	ND
Half profile nonverbal sensitivity ¹³⁴	1	60	5.20 (0.45, 9.95)	NE	haloperidol
Interpersonal Perception Task - 15 ¹³⁴	1	60	0.30 (-0.62, 1.22)	NE	ND
Voice Emotion Identification Test ¹³⁴	1	60	0.50 (-1.51, 2.51)	NE	ND

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; ND = no difference; 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; RVLT = 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 91. Evidence summary table: haloperidol versus ziprasidone

Outcome	Studies	Participants	Effect Estimate	I ²	Favors
Functional capacity					
Cognitive composite score ^{/5}	1	185	-0.08 (-0.28, 0.12)	NE	ND
Purdue Pegboard Test ^{/5}	1	185	0.30 (0.05, 0.55)	NE	haloperidol
RVLT ^{/5}	1	185	-0.24 (-0.48, 0.00)	NE	ND
Trail Making Test A ^{/5}	1	185	-0.06 (-0.27, 0.15)	NE	ND
Trail Making Test B ^{/5}	1	185	-0.19 (-0.39, 0.01)	NE	ND
WAIS-III Digit Symbol ^{/5}	1	185	-0.19 (-0.41, 0.03)	NE	ND

Note: bold = statistically significant; * = binary outcome; I² = I-squared; ND = no difference; NE = not estimable; RVLT = Rey's Auditory Verbal Learning Test; WAIS = Wechsler Adult Intelligence Scale

B) Bipolar Disorder

Table 92. Evidence summary table: haloperidol versus aripiprazole

Outcome	Studies	Participants	Effect Estimate	I ²	Favors
Positive symptoms					
PANSS - Hostility subscale ³³	1	332	-0.50 (-1.09, 0.09)	NE	ND
Mood-Mania					
CGI-BP - Mania subscale ^{32,33}	2	679	0.13 (-0.17, 0.43)	44%	ND
Mood-Depression					
CGI-BP - Depression subscale ^{32,33}	2	679	0.01 (-0.16, 0.18)	0%	ND
General psychopathology					
PANSS - cognitive subscale ³³	1	332	-0.70 (-1.81, 0.41)	NE	ND

Note: bold = statistically significant; * = binary outcome; CGI—BP = Clinical Global Impressions—Bipolar; I² = I-squared; ND = no difference; NE = not estimable; PANSS = Positive and Negative Symptom Scale

Table 93. Evidence summary table: haloperidol versus risperidone

Outcome	Studies	Participants	Effect Estimate	I ²	Favors
Positive symptoms					
PANSS - hostility subscale ⁹⁰	1	62	0.70 (-1.35, 2.75)	NE	ND
Mood-Mania					
CARS-M - Mania subscale ⁹⁰	1	62	4.00 (-1.66, 9.66)	NE	ND
Mood-Depression					
HAM-D - core depression ⁹⁰	1	62	1.70 (-1.13, 4.53)	NE	ND
HAM-D - Secondary symptoms ⁹⁰	1	62	1.00 (-0.62, 2.62)	NE	ND
HAM-D - sleep disturbance ⁹⁰	1	62	1.80 (0.20, 3.40)	NE	olanzapine
HAM-D - Somatic symptoms ⁹⁰	1	62	0.70 (-0.44, 1.84)	NE	ND
General psychopathology					
PANSS - anxiety/depression subscale ⁹⁰	1	62	-0.30 (-2.64, 2.04)	NE	ND
PANSS - disorganized thought subscale ⁹⁰	1	62	0.10 (-2.31, 2.51)	NE	ND

Note: bold = statistically significant; * = binary outcome; CARS-M = Clinician-Administered Rating Scale for Mania; HAM-D = Hamilton Rating Scale for Depression; I² = I-squared; ND = no difference; NE = not estimable; PANSS = Positive and Negative Symptom Scale

Appendix M. Subgroup and Sensitivity Analyses

Table 94. Subgroup and sensitivity analyses: chlorpromazine vs. clozapine – Total Score (BPRS)

Total Symptoms (BPRS)	Studies	Participants	Effect Estimate	I ²	Favors
OVERALL POOLED RESULTS	6	535	8.40 (5.92, 10.88)	20%	clozapine
Race					
Asian	2	80	4.73 (-0.39,9.85)	0%	ND
Mixed	4	455	9.57 (7.36,11.8)	0%	clozapine
First time vs. other					
Previous episodes	4	474	9.63 (7.40,11.86)	0%	clozapine
Mixed first and previous episodes	2	61	4.77 (-0.17,9.71)	0%	ND
Treatment resistance					
Treatment resistant	2	308	10.22 (7.12,13.33)	10%	clozapine
Mixed	4	227	6.96 (3.94,9.97)	0%	clozapine
Duration of followup					
>6weeks	3	191	6.70 (3.55, 9.84)	0%	clozapine
≤6weeks	3	304	10.32 (7.66, 12.98)	0%	clozapine
Dosage of FGA (chlorpromazine)					
Up to 1800mg/d	4	474	9.63 (7.40,11.9)	0%	clozapine
Maximum 100 and 600mg/d	2	61	4.77 (-0.17,9.71)	0%	ND
Source of funding					
Industry funding	2	283	11.1 (8.13,14.0)	0%	clozapine
No industry funding reported	4	252	6.72 (3.89, 9.54)	0%	clozapine
Risk of bias					
Unclear	4	363	8.23 (3.82, 12.6)	45%	clozapine
High	2	172	7.59 (4.20, 11.0)	0%	clozapine
Imputations					
Data imputed	3	206	6.77 (2.39, 11.15)	20%	clozapine
No data imputed	3	329	9.70 (7.03, 12.37)	5%	clozapine

Significant results are in bold. BPRS = Brief Psychiatric Rating Scale; d = day; FGA = first generation antipsychotic; I² = I-squared; mg = milligrams; ND = no difference

Table 95. Subgroup and sensitivity analyses: haloperidol vs. aripiprazole – Response rates

Response Rates	Studies	Participants	Effect Estimate	I ²	Favors
OVERALL POOLED RESULTS	6	2175	1.01 (0.76, 1.34)	83%	ND
Disorder subtypes					
Schizoaffective included	3	531	0.93 (0.41, 2.11)	87%	ND
Mixed or schizoaffective disorder excluded	2	1654	0.94 (0.75, 1.16)	74%	ND
Co-morbid drug/alcohol use					
Excluded	3	767	0.89 (0.57, 1.38)	64%	ND
Mixed	2	1418	1.13 (0.62, 2.06)	94%	ND
First time vs. other					
Mixed first and previous episodes	4	891	1.06 (0.72, 1.57)	79%	ND
Multiple episodes only	1	1294	0.85 (0.75, 0.96)	NE	aripiprazole
Treatment resistance					
Treatment resistant excluded	3	1778	1.10 (0.80, 1.51)	89%	ND
Mixed	2	108	0.35 (0.03, 3.93)	69%	ND
Duration of followup					
>6weeks	2	1393	0.37 (0.04, 3.76)	68%	ND
≤6weeks	3	792	1.12 (0.80, 1.57)	80%	ND
Dosage of FGA (haloperidol)					
<15mg/d	4	2061	0.90 (0.73, 1.11)	60%	ND
Up to 30mg/d	1	124	1.55 (1.20, 2.00)	NE	haloperidol
Dosage of SGA (aripiprazole)					
Up to 30mg/d	4	2061	0.90 (0.73, 1.11)	60%	ND
>30mg/d	1	124	1.55 (1.20, 2.00)	NE	haloperidol
Source of funding					
Industry funding	4	2061	0.90 (0.73, 1.11)	60%	ND
No industry funding reported	1	124	1.55 (1.20, 2.00)	NE	haloperidol
Risk of bias					
Unclear	3	1654	0.94 (0.75, 1.16)	74%	ND
High	2	531	0.93 (0.41, 2.11)	87%	ND

Significant results are in bold. d = day; FGA = first generation antipsychotic; I² = I-squared; ND = no difference; NE = not estimable; mg = milligrams; SGA = second generation antipsychotic

Table 96. Subgroup and sensitivity analyses: haloperidol vs. olanzapine - Positive symptoms (PANSS Scale)

Total Symptoms	Studies	Participants	Effect Estimate	I ²	Favors
OVERALL POOLED RESULTS	14	3742	0.43 (-0.22, 1.08)	36%	ND
Disorder subtypes					
Schizoaffective disorder	1	76	1.20 (-2.07, 4.47)	NE	ND
Mixed	13	3666	0.38 (-0.30, 1.07)	41%	ND
Co-morbid drug/alcohol use					
Excluded	4	527	-0.44 (-2.75, 1.87)	51%	ND
Included only	1	31	-2.00 (-4.82, 0.82)	NE	ND
Mixed	9	3184	0.70 (0.15, 1.26)	17%	olanzapine
Treatment resistance					
Treatment resistant	5	2207	0.26 (-1.26, 1.78)	53%	ND
No treatment resistance	1	44	2.18 (-0.59, 4.95)	NE	ND
Mixed	8	1491	0.32 (-0.51, 1.15)	30%	ND
Duration of followup					
≤6 weeks	2	58	-2.08 (-4.59, 0.43)	0%	ND
>6 weeks and <6 months	7	694	0.21 (-1.19, 1.62)	48%	ND
≥6 months	5	2990	0.77 (0.30, 1.24)	0%	olanzapine
Dosage of FGA (haloperidol)					
≤20mg/d	12	3593	0.62 (0.03, 1.21)	23%	olanzapine
Upper limit >20mg/d	2	149	-0.62 (-3.62, 2.38)	60%	ND
Dosage of SGA (olanzapine)					
≤20mg/d	12	3593	0.62 (0.03, 1.21)	23%	olanzapine
>20mg/d	2	149	-0.62 (-3.62, 2.38)	60%	ND
Source of funding					
Industry funding	13	3560	0.33 (-0.38, 1.05)	40%	ND
No industry funding reported	1	182	1.15 (-0.55, 2.85)	NE	ND
Risk of bias					
Unclear	11	1688	0.45 (-0.36, 1.25)	36%	ND
High	3	2054	-0.12 (-2.21, 1.98)	51%	ND
Race					
Other	13	3466	0.34 (-0.36, 1.04)	39%	ND
Asian	1	276	1.30 (-0.65, 3.25)	NE	ND
Data analysis					
Imputed data	2	336	-0.66 (-2.68, 1.36)	68%	ND
No imputed data	12	3406	0.74 (0.11, 1.37)	17%	olanzapine

Significant results are in bold. d = day; FGA = first generation antipsychotic; I² = I-squared; mg = milligrams; ND = no difference; NE = not estimable; PANSS = Positive and Negative Syndrome Scale; SGA = second generation antipsychotic

Table 97. Subgroup and sensitivity analyses: haloperidol vs. olanzapine – Negative symptoms (PANSS Scale)

Total Symptoms	Studies	Participants	Effect Estimate	I ²	Favors
OVERALL POOLED RESULTS	14	3742	1.06 (0.46, 1.67)	27%	olanzapine
Disorder subtypes					
Schizoaffective disorder specifically included	1	76	2.50 (-0.18, 5.18)	NE	ND
Mixed	13	3666	0.99 (0.37, 1.62)	29%	olanzapine
Co-morbid drug/alcohol use					
Excluded	4	527	0.88 (-0.63, 2.39)	0%	ND
Included only	1	31	-3.20 (-6.03, -0.37)	NE	haloperidol
Mixed	9	3184	1.27 (0.82, 1.72)	2%	olanzapine
Treatment resistance					
Treatment resistant	5	2207	1.28 (0.11, 2.44)	40%	olanzapine
Mixed	8	1491	0.90 (-0.02, 1.81)	35%	ND
No treatment resistance	1	44	1.02 (-2.39, 4.43)	NE	ND
Duration of followup					
≤6 weeks	2	58	-1.87 (-5.12, 1.39)	42%	ND
>6 weeks and <6 months	7	694	1.37 (0.25, 2.50)	25%	olanzapine
≥6 months	5	2990	1.26 (0.79, 1.73)	0%	olanzapine
Dosage of FGA (haloperidol)					
≤20mg/d	12	3593	1.13 (0.51, 1.75)	24%	olanzapine
Upper limit >20mg/d	2	149	0.92 (-1.78, 3.62)	65%	ND
Dosage of SGA (olanzapine)					
≤20mg/d	12	3593	1.13 (0.51, 1.75)	24%	olanzapine
>20mg/d	2	149	0.92 (-1.78, 3.62)	65%	ND
Source of funding					
Industry funding	13	3560	1.08 (0.40, 1.76)	32%	olanzapine
No industry funding reported	1	182	0.82 (-0.69, 2.33)	NE	ND
Risk of bias					
Unclear	11	1688	1.18 (0.58, 1.78)	0%	olanzapine
High	3	2054	-0.33 (-3.82, 3.16)	79%	ND
Race					
Other	13	3466	0.97 (0.34, 1.59)	27%	olanzapine
Asian	1	276	2.40 (0.35, 4.45)	NE	olanzapine
Data analysis					
Imputed data	2	336	0.69 (-1.04, 2.41)	56%	ND
No imputed data	12	3406	1.14 (0.45, 1.83)	28%	olanzapine

Significant results are in bold. d = day; FGA = first generation antipsychotic; I² = I-squared; mg = milligrams; ND = no difference; NE = not estimable; PANSS = Positive and Negative Syndrome Scale; SGA = second generation antipsychotic

Table 98. Subgroup and sensitivity analyses: haloperidol vs. olanzapine – General psychopathology (PANSS Scale)

Total Symptoms	Studies	Participants	Effect Estimate	I ²	Favors
OVERALL POOLED RESULTS	10	1187	0.53 (-1.20, 2.25)	52%	ND
Disorder subtypes					
Schizoaffective disorder	1	76	3.20 (-0.95, 7.35)	NE	ND
Mixed	9	1111	0.24 (-1.60, 2.08)	54%	ND
Co-morbid drug/alcohol use					
Excluded	3	500	0.02 (-2.77, 2.81)	25%	ND
Included only	1	31	-6.10 (-10.90, -1.30)	NE	haloperidol
Mixed	6	656	1.50 (-0.12, 3.12)	25%	ND
Treatment resistance					
Treatment resistant	3	184	1.49 (-2.58, 5.56)	68%	ND
Mixed	6	959	0.05 (-2.23, 2.32)	60%	ND
No treatment resistance	1	44	1.35 (-4.82, 7.52)	NE	ND
Duration of followup					
≤6 weeks	1	31	-6.10 (-10.90, -1.30)	NE	haloperidol
>6 weeks and <6 months	6	418	0.79 (-1.48, 3.05)	47%	ND
≥6 months	3	738	1.71 (0.08, 3.35)	0%	olanzapine
Dosage of FGA (haloperidol)					
≤20mg/d	8	1038	0.60 (-1.35, 2.55)	51%	ND
Upper limit >20mg/d	2	149	0.40 (-4.73, 5.54)	74%	ND
Dosage of SGA (olanzapine)					
≤20mg/d	8	1038	0.60 (-1.35, 2.55)	51%	ND
>20mg/d	2	149	0.40 (-4.73, 5.54)	74%	ND
Source of funding					
Industry funding	9	1005	0.32 (-1.64, 2.27)	56%	ND
No industry funding reported	1	182	1.93 (-1.17, 5.03)	NE	ND
Risk of bias					
Unclear	8	1129	1.08 (-0.43, 2.58)	33%	ND
High	2	58	-2.54 (-9.93, 4.85)	73%	ND
Data analysis					
Imputed data	8	851	0.65 (-1.56, 2.86)	52%	ND
No imputed data	2	336	0.10 (-3.67, 3.87)	75%	ND

Significant results are in bold. d = day; FGA = first generation antipsychotic; I² = I-squared; mg = milligrams; ND = no difference; NE = not estimable; PANSS = Positive and Negative Syndrome Scale; SGA = second generation antipsychotic

Table 99. Subgroup and sensitivity analyses: haloperidol vs. olanzapine – Total scores (PANSS Scale)

Total Symptoms	Studies	Participants	Effect Estimate	I ²	Favors
OVERALL POOLED RESULTS	15	4209	2.31 (0.44, 4.18)	37%	olanzapine
Disorder subtypes					
Paranoid schizophrenia	1	28	-0.65 (-4.77, 3.47)	NE	ND
Schizoaffective disorder	3	593	2.13 (-0.91, 5.17)	0%	ND
Mixed	11	3588	2.65 (0.17, 5.12)	42%	olanzapine
Co-morbid drug/alcohol use					
Excluded	3	483	-0.73 (-5.83, 4.38)	0%	ND
Mixed	12	3726	2.71 (0.75, 4.67)	40%	olanzapine
Treatment resistance					
Treatment resistant	6	2231	2.54 (-2.21, 7.29)	56%	ND
Mixed	8	1770	2.25 (0.00, 4.50)	23%	ND
No treatment resistance	1	208	0.90 (-3.81, 5.61)	NE	ND
Duration of followup					
≤6 weeks	2	51	-4.88 (-17.94, 8.18)	0%	ND
>6 weeks and <6 months	7	695	2.26 (-1.85, 6.37)	61%	ND
≥6 months	6	3463	3.47 (1.99, 4.94)	0%	olanzapine
Dosage of FGA (haloperidol)					
≤20mg/d	13	4060	2.74 (1.02, 4.46)	23%	olanzapine
>20mg/d	2	149	0.79 (-10.00, 11.58)	77%	ND
Dosage of SGA (olanzapine)					
≤20mg/d	13	4060	2.74 (1.02, 4.46)	23%	olanzapine
Upper limit >20mg/d	2	149	0.79 (-10.00, 11.58)	77%	ND
Source of funding					
Industry funding	13	4003	2.21 (0.15, 4.26)	45%	olanzapine
No industry funding reported	2	206	3.34 (-2.21, 8.90)	0%	ND
Risk of bias					
Unclear	13	2005	2.01 (-0.30, 4.33)	35%	ND
High	2	2204	3.30 (0.27, 6.34)	41%	olanzapine
Race					
Other	14	3933	2.01 (0.13, 3.89)	36%	olanzapine
Asian	1	276	7.90 (0.96, 14.84)	NE	olanzapine
Data analysis					
Imputed data	3	364	-1.50 (-4.54, 1.54)	0%	ND
No imputed data	12	3845	3.68 (2.17, 5.18)	5%	olanzapine

Significant results are in bold. d = day; FGA = first generation antipsychotic; I² = I-squared; mg = milligrams; ND = no difference; NE = not estimable; PANSS = Positive and Negative Syndrome Scale; SGA = second generation antipsychotic

Table 100. Subgroup and sensitivity analyses: haloperidol vs. olanzapine – Total scores (BPRS Scale)

Total Symptoms	Studies	Participants	Effect Estimate	I ²	Favors
OVERALL POOLED RESULTS	13	4014	0.59 (-1.10, 2.28)	82%	ND
Disorder subtypes					
Paranoid schizophrenia	1	28	8.85 (-3.92, 21.62)	NE	ND
Schizoaffective disorder	2	182	0.99 (-2.19, 4.17)	0%	ND
Mixed	10	3804	0.33 (-1.56, 2.22)	86%	ND
Co-morbid drug/alcohol use					
Excluded	6	1124	-2.37 (-6.19, 1.44)	90%	ND
Mixed	7	2890	2.05 (0.55, 3.55)	36%	olanzapine
Treatment resistance					
Treatment resistant	4	2205	-5.50 (-14.1, 3.07)	95%	ND
Mixed	9	1809	1.10 (0.62, 1.58)	0%	olanzapine
Duration of followup					
≤6 weeks	6	771	-2.00 (-5.42, 1.42)	90%	ND
>6 weeks and <6 months	4	549	2.86 (0.50, 5.22)	0%	olanzapine
≥6 months	3	2694	1.63 (-0.72, 3.97)	55%	ND
Dosage of FGA (haloperidol)					
≤20mg/d	11	3832	0.49 (-1.38, 2.37)	85%	ND
>20mg/d	2	182	0.99 (-2.19, 4.17)	0%	ND
Dosage of SGA (olanzapine)					
≤20mg/d	10	3800	0.55 (-1.41, 2.52)	86%	ND
Upper limit >20mg/d	3	214	0.57 (-2.16, 3.30)	0%	ND
Source of funding					
Industry funding	9	3570	-0.42 (-3.48, 2.64)	88%	ND
No industry funding reported	4	444	1.12 (0.61, 1.63)	0%	olanzapine
Risk of bias					
Unclear	9	1725	-0.84 (-4.35, 2.67)	86%	ND
High	4	2289	1.78 (0.36, 3.21)	66%	olanzapine
Race					
Other	12	3738	0.28 (-1.48, 2.04)	83%	ND
Asian	1	276	4.40 (0.33, 8.47)	NE	olanzapine

Significant results are in bold. BPRS = Brief Psychiatric Rating Scale; d = day; FGA = first generation antipsychotic; I² = I-squared; mg = milligrams; ND = no difference; NE = not estimable; SGA = second generation antipsychotic

Table 101. Subgroup and sensitivity analyses: haloperidol vs. olanzapine – Total scores (CGI–S Scale)

Total Symptoms	Studies	Participants	Effect Estimate	I ²	Favors
OVERALL POOLED RESULTS	8	3564	0.14 (-0.05, 0.33)	89%	ND
Disorder subtypes					
Schizoaffective disorder	2	271	0.20 (-0.35, 0.75)	34%	ND
Mixed	6	3293	0.13 (-0.08, 0.34)	92%	ND
Co-morbid drug/alcohol use					
Excluded	5	1097	0.03 (-0.13, 0.20)	61%	ND
Mixed	3	2467	0.28 (0.19, 0.38)	0%	olanzapine
Treatment resistance					
Treatment resistant	2	2059	0.24 (0.01, 0.47)	32%	olanzapine
Mixed	5	1297	0.07 (-0.10, 0.24)	71%	ND
No treatment resistance	1	208	0.60 (-0.23, 1.43)	NE	ND
Duration of followup					
≤6 weeks	2	336	-0.06 (-0.19, 0.06)	47%	ND
>6 weeks and <6 months	1	63	0.00 (-0.47, 0.47)	NE	ND
≥6 months	5	3165	0.26 (0.16, 0.37)	7%	olanzapine
Dosage of FGA (haloperidol)					
≤20mg/d	7	3501	0.15 (-0.05, 0.36)	90%	ND
Upper limit >20mg/d	1	63	0.00 (-0.47, 0.47)	NE	ND
Dosage of SGA (olanzapine)					
≤20mg/d	7	3501	0.15 (-0.05, 0.36)	90%	ND
>20mg/d	1	63	0.00 (-0.47, 0.47)	NE	ND
Source of funding					
Industry funding	7	3453	0.20 (0.07, 0.32)	33%	olanzapine
No industry funding reported	1	111	-0.10 (-0.14, -0.06)	NE	haloperidol
Risk of bias					
Unclear	4	1186	0.13 (-0.01, 0.27)	11%	ND
High	4	2378	0.13 (-0.19, 0.45)	94%	ND
Data analysis					
Imputed data	1	263	0.17 (-0.08, 0.42)	NE	ND
No imputed data	7	3301	0.13 (-0.08, 0.35)	90%	ND

Significant results are in bold. CGI–S = Clinical Global Impression–Severity; FGA = first generation antipsychotic; I² = I-squared; mg = milligrams; ND = no difference; NE = not estimable; SGA = second generation antipsychotic

Table 102. Subgroup and sensitivity analyses: haloperidol vs. olanzapine – Response rates

Total Symptoms	Studies	Participants	Effect Estimate	I ²	Favors
OVERALL POOLED RESULTS	14	4099	0.86 (0.78, 0.96)	55%	olanzapine
Disorder subtypes					
Schizoaffective disorder	2	327	0.73 (0.33, 1.63)	95%	ND
Mixed	12	3772	0.87 (0.80, 0.95)	26%	olanzapine
Co-morbid drug/alcohol use					
Only	1	24	1.33 (0.38, 4.72)	NE	ND
Excluded	2	378	1.02 (0.79, 1.32)	29%	ND
Mixed	11	3697	0.84 (0.75, 0.94)	61%	olanzapine
Treatment resistance					
Treatment resistant	5	2247	0.81 (0.62, 1.04)	70%	ND
Mixed	8	1644	0.92 (0.85, 0.99)	0%	olanzapine
No treatment resistance	1	208	0.52 (0.37, 0.72)	NE	olanzapine
Duration of followup					
≤6 weeks	4	519	0.96 (0.87, 1.07)	0%	ND
>6 weeks and <6 months	5	590	0.83 (0.68, 1.01)	22%	ND
≥6 months	5	2990	0.83 (0.68, 1.01)	74%	ND
Dosage of FGA (haloperidol)					
≤20mg/d	12	3907	0.86 (0.78, 0.96)	48%	olanzapine
>20mg/d	2	192	0.79 (0.42, 1.47)	85%	ND
Dosage of SGA (olanzapine)					
≤20mg/d	11	3875	0.86 (0.77, 0.96)	53%	olanzapine
Upper limit >20mg/d	3	224	0.80 (0.50, 1.29)	70%	ND
Source of funding					
Industry funding	9	3631	0.83 (0.73, 0.95)	66%	olanzapine
No industry funding reported	5	468	0.97 (0.85, 1.11)	0%	ND
Risk of bias					
Unclear	9	1641	0.91 (0.83, 0.99)	7%	olanzapine
High	5	2458	0.81 (0.64, 1.02)	78%	ND
Race					
Other	13	3823	0.86 (0.76, 0.97)	59%	olanzapine
Asian	1	276	0.87 (0.76, 1.00)	NE	ND
Data analysis					
Imputed data	3	360	0.80 (0.56, 1.13)	42%	ND
No imputed data	11	3739	0.87 (0.78, 0.98)	61%	olanzapine

Significant results are in bold. d = day; FGA = first generation antipsychotic; I² = I-squared; mg = milligrams; ND = no difference; NE = not estimable; SGA = second generation antipsychotic

Table 103. Subgroup and sensitivity analyses: haloperidol vs. quetiapine – Negative symptoms (PANSS)*

Negative Symptoms	Studies	Participants	Effect Estimate	I ²	Favors
OVERALL POOLED RESULTS	4	393	1.36 (-0.41, 3.13)	76%	ND
Disorder subtypes					
Schizoaffective disorder	1	45	-1.20 (-4.49, 2.09)	NE	ND
Mixed	3	348	1.87 (0.09, 3.65)	77%	quetiapine
Co-morbid drug/alcohol use					
Excluded	1	25	3.10 (-1.60, 7.80)	NE	ND
Mixed	3	368	1.12 (-0.86, 3.10)	83%	ND
Treatment resistance					
Treatment resistant	1	288	0.61 (-0.57, 1.79)	NE	ND
Mixed	3	105	1.65 (-0.93, 4.23)	61%	ND
Duration of followup					
≤6 months	2	323	1.70 (-0.34, 3.75)	88%	ND
>6 months	2	70	0.61 (-3.55, 4.77)	54%	ND
Dosage of FGA (haloperidol)					
≤20mg/d	4	393	1.36 (-0.41, 3.13)	76%	ND
Upper limit >20mg/d	0	0	NE	NE	NE
Dosage of SGA (quetiapine)					
Lower range ≤250mg/d	1	45	-1.20 (-4.49, 2.09)	NE	ND
Lower range >250mg/d	3	348	1.87 (0.09, 3.65)	77%	quetiapine
Risk of bias					
Unclear	3	358	0.53 (-0.81, 1.87)	10%	ND
High	1	35	2.70 (1.92, 3.48)	NE	quetiapine

*All studies were industry-funded. Significant results are in bold. d = day; FGA = first generation antipsychotic; I² = I-squared; mg = milligrams; ND = no difference; NE = not estimable; PANSS = Positive and Negative Syndrome Scale; SGA = second generation antipsychotic

Table 104. Subgroup and sensitivity analyses: haloperidol vs. quetiapine – response rates*

Total Symptoms	Studies	Participants	Effect Estimate	I ²	Favors
OVERALL POOLED RESULTS	6	1421	0.99 (0.76, 1.30)	77%	ND
Disorder subtypes					
Schizoaffective disorder	1	45	0.64 (0.21, 1.96)	NE	ND
Mixed	5	1376	1.01 (0.77, 1.34)	81%	ND
Co-morbid drug/alcohol use					
Excluded	1	123	1.62 (1.24, 2.11)	NE	haloperidol
Mixed	5	1298	0.90 (0.73, 1.10)	47%	ND
Treatment resistance					
Treatment resistant	2	411	1.08 (0.49, 2.41)	95%	ND
Mixed	4	1010	1.00 (0.85, 1.17)	6%	ND
Duration of followup					
≤6 months	3	881	1.22 (0.93, 1.61)	71%	ND
>6 months	3	540	0.74 (0.60, 0.91)	0%	quetiapine
Dosage of FGA (haloperidol)					
≤20mg/d	5	1298	0.90 (0.73, 1.10)	47%	ND
Upper limit >20mg/d	1	123	1.62 (1.24, 2.11)	NE	haloperidol
Dosage of SGA (quetiapine)					
Lower range ≤250mg/d	5	1133	1.08 (0.82, 1.42)	69%	ND
Lower range >250mg/d	1	288	0.73 (0.56, 0.94)	NE	quetiapine
Risk of bias					
Unclear	3	663	0.85 (0.62, 1.15)	44%	ND
High	3	778	1.12 (0.76, 1.64)	83%	ND

*All studies were industry-funded. Significant results are in bold. d = day; FGA = first generation antipsychotic; I² = I-squared; mg = milligrams; ND = no difference; NE = not estimable; SGA = second generation antipsychotic

Table 105. Subgroup and sensitivity analyses: haloperidol vs. risperidone – Positive symptoms (PANSS Scale)

Total Symptoms	Studies	Participants	Effect Estimate	I ²	Favors
OVERALL POOLED RESULTS	20	4043	0.64 (-0.06, 1.34)	53%	ND
Disorder subtypes					
Schizoaffective disorder	4	1181	0.64 (-0.55, 1.83)	47%	ND
Schizoaffective excluded	2	363	2.70 (-1.10, 6.50)	47%	ND
Mixed	14	2499	0.48 (-0.42, 1.38)	57%	ND
Co-morbid drug/alcohol use					
Excluded	14	3210	0.46 (-0.42, 1.34)	58%	ND
Mixed	6	833	1.24 (0.44, 2.03)	0%	risperidone
First vs. multiple episodes					
Mixed first and multiple episodes	12	1876	1.04 (0.21, 1.86)	30%	risperidone
Multiple episodes only	7	1984	0.10 (-1.17, 1.36)	70%	ND
First episode only	1	183	0.10 (-1.98, 2.18)	NE	ND
Treatment resistance					
No treatment resistant	4	881	0.32 (-1.44, 2.08)	80%	ND
Treatment resistant	2	156	-0.00 (-3.04, 3.03)	56%	ND
Mixed	14	3006	0.84 (0.07, 1.60)	36%	risperidone
Duration of followup					
≤6 weeks	3	260	1.07 (-1.51, 3.64)	41%	ND
>6 weeks and <6 months	10	2147	0.26 (-0.44, 0.96)	0%	ND
≥6 months	7	1636	0.91 (-0.39, 2.21)	81%	ND
Dosage of FGA (haloperidol)					
≤20mg/d	17	3881	0.48 (-0.21, 1.17)	51%	ND
Upper limit >20mg/d	2	106	3.28 (-0.33, 6.89)	58%	ND
Dosage of SGA (risperidone)					
Lower limit <4mg/d	15	3754	0.68 (-0.08, 1.45)	59%	ND
Upper range >6mg/d	13	3394	-0.01 (-0.67, 0.64)	29%	ND
Source of funding					
Industry funding	10	2091	0.68 (-0.38, 1.74)	66%	ND
No industry funding	11	2317	0.85 (0.02, 1.67)	34%	risperidone
Risk of bias					
Unclear	15	3488	0.46 (-0.34, 1.26)	55%	ND
High	5	555	1.52 (0.57, 2.47)	0%	risperidone
Race					
Other	15	3813	0.74 (-0.06, 1.54)	63%	ND
Asian	5	230	0.18 (-1.32, 1.67)	0%	ND
Data analysis					
Imputed data	3	1439	0.01 (-0.89, 0.90)	0%	ND
No imputed data	17	2604	0.77 (-0.05, 1.60)	60%	ND

Significant results are in bold. d = day; FGA = first generation antipsychotic; I² = I-squared; mg = milligrams; ND = no difference; NE = not estimable; PANSS = Positive and Negative Syndrome Scale; SGA = second generation antipsychotic

Table 106. Subgroup and sensitivity analyses: haloperidol vs. risperidone – Negative symptoms (PANSS Scale)

Total Symptoms	Studies	Participants	Effect Estimate	I ²	Favors
OVERALL POOLED RESULTS	20	4043	0.60 (0.01, 1.20)	30%	risperidone
Disorder subtypes					
Schizoaffective disorder	4	1181	0.88 (0.12, 1.64)	0%	risperidone
Schizoaffective excluded	2	363	2.36 (0.39, 4.32)	0%	risperidone
Mixed	14	2499	0.32 (-0.51, 1.16)	35%	ND
Co-morbid drug/alcohol use					
Excluded	14	3210	0.52 (-0.22, 1.26)	31%	ND
Mixed	6	833	0.77 (-0.37, 1.91)	37%	ND
First vs. multiple episodes					
Mixed first and multiple episodes	13	2059	0.88 (0.30, 1.47)	0%	risperidone
Multiple episodes only	7	1984	0.05 (-1.19, 1.29)	57%	ND
Treatment resistance					
No treatment resistant	4	881	-0.04 (-1.78, 1.70)	73%	ND
Treatment resistant	2	156	1.00 (-1.74, 3.73)	41%	ND
Mixed	14	3006	0.71 (0.15, 1.27)	3%	risperidone
Duration of followup					
≤6 weeks	3	260	1.05 (-0.84, 2.95)	0%	ND
>6 weeks and <6 months	10	2147	0.54 (-0.21, 1.29)	0%	ND
≥6 months	7	1636	0.54 (-0.49, 1.57)	65%	ND
Dosage of FGA (haloperidol)					
≤20mg/d	18	3937	0.56 (-0.03, 1.15)	28%	ND
Upper limit >20mg/d	2	106	1.82 (-2.85, 6.49)	71%	ND
Dosage of SGA (risperidone)					
Lower limit <4mg/d	15	3754	0.53 (-0.13, 1.19)	40%	ND
Upper range >6mg/d	10	3283	0.26 (-0.45, 0.96)	38%	ND
Source of funding					
Industry funding	10	2091	0.43 (-0.54, 1.41)	56%	ND
No industry funding not reported	10	1952	0.76 (0.08, 1.45)	0%	risperidone
Risk of bias					
Unclear	15	3488	0.39 (-0.30, 1.08)	35%	ND
High	5	555	1.47 (0.44, 2.51)	0%	risperidone
Race					
Other	15	3813	0.60 (-0.08, 1.28)	43%	ND
Asian	5	230	0.78 (-1.03, 2.59)	0%	ND
Data analysis					
Imputed data	3	1439	-0.40 (-2.38, 1.58)	18%	ND
No imputed data	17	2604	0.74 (0.08, 1.41)	32%	risperidone

Significant results are in bold. d = day; FGA = first generation antipsychotic; I² = I-squared; mg = milligrams; ND = no difference; NE = not estimable; PANSS = Positive and Negative Syndrome Scale; SGA = second generation antipsychotic

Table 107. Subgroup and sensitivity analyses: haloperidol vs. risperidone – General symptoms (PANSS Scale)

Total Symptoms	Studies	Participants	Effect Estimate	I²	Favors
OVERALL POOLED RESULTS	16	3073	-2.54 (-6.39, 1.32)	96%	ND
Disorder subtypes					
Schizoaffective disorder	3	816	0.60 (-1.08, 2.27)	0%	ND
Schizoaffective excluded	1	41	8.90 (-0.51, 18.31)	NE	ND
Mixed	12	2216	-4.18 (-9.09, 0.72)	96%	ND
Co-morbid drug/alcohol use					
Excluded	12	2817	0.31 (-1.18, 1.80)	43%	ND
Mixed	4	256	-12.2 (-26.8, 2.51)	99%	ND
First vs. multiple episodes					
Mixed first and multiple episodes	8	906	-4.07 (-14.33, 6.19)	97%	ND
Multiple episodes only	7	1984	-1.24 (-5.05, 2.57)	93%	ND
First episode only	1	41	8.90 (-0.51, 18.31)	NE	ND
Treatment resistance					
No treatment resistant	3	516	-1.13 (-3.95, 1.70)	42%	ND
Treatment resistant	2	156	1.51 (-1.22, 4.23)	0%	ND
Mixed	11	2401	-3.82 (-9.26, 1.61)	97%	ND
Duration of followup					
≤6 weeks	3	260	-11.31 (-44.1, 21.5)	99%	ND
>6 weeks and <6 months	9	1825	0.98 (-0.25, 2.20)	0%	ND
≥6 months	4	988	-2.76 (-7.19, 1.68)	94%	ND
Dosage of FGA (haloperidol)					
≤20mg/d	13	2995	-2.79 (-6.84, 1.27)	96%	ND
Upper limit >20mg/d	1	78	1.10 (-2.78, 4.98)	NE	ND
Dosage of SGA (risperidone)					
Lower limit <4mg/d	11	2784	-0.36 (-3.30, 2.58)	91%	ND
Upper range >6mg/d	9	2704	0.62 (-0.90, 2.14)	43%	ND
Source of funding					
Industry funding	6	1121	-0.16 (-2.05, 1.73)	37%	ND
No industry funding reported	10	1952	-4.41 (-10.45, 1.63)	97%	ND
Risk of bias					
Unclear	12	2840	0.52 (-0.75, 1.78)	28%	ND
High	4	233	-13.6 (-28.5, 1.41)	98%	ND
Race					
Other	11	2843	-3.44 (-8.34, 1.45)	97%	ND
Asian	5	230	0.01 (-2.83, 2.84)	33%	ND
Data analysis					
Imputed data	3	1439	0.99 (-0.60, 2.58)	0%	ND
No imputed data	13	1634	-3.07 (-7.73, 1.59)	96%	ND

Significant results are in bold. d = day; FGA = first generation antipsychotic; I² = I-squared; mg = milligrams; ND = no difference; NE = not estimable; PANSS = Positive and Negative Syndrome Scale; SGA = second generation antipsychotic

Table 108. Subgroup and sensitivity analyses: haloperidol vs. risperidone – Total score (PANSS Scale)

Total Symptoms	Studies	Participants	Effect Estimate	I ²	Favors
OVERALL POOLED RESULTS	20	4021	2.23 (-0.37, 4.83)	75%	ND
Disorder subtypes					
Schizoaffective disorder	4	1181	3.08 (-0.19, 6.34)	45%	ND
Schizoaffective excluded	2	363	9.93 (0.77, 19.09)	27%	risperidone
Mixed	14	2477	1.04 (-1.82, 3.90)	65%	ND
Co-morbid drug/alcohol use					
Excluded	14	3188	2.56 (0.65, 4.47)	18%	risperidone
Mixed	6	833	1.95 (-3.14, 7.04)	82%	ND
First vs. multiple episodes					
Mixed first and multiple episodes	12	1854	3.78 (1.37, 6.18)	32%	risperidone
Multiple episodes only	7	1984	-0.56 (-3.98, 2.86)	65%	ND
First episode only	1	183	1.60 (-5.61, 8.81)	NE	ND
Treatment resistance					
No treatment resistant	3	837	3.53 (-0.06, 7.13)	46%	ND
Treatment resistant	2	156	2.52 (-3.99, 9.02)	0%	ND
Mixed	15	3028	1.89 (-1.10, 4.89)	71%	ND
Duration of followup					
≤6 weeks	4	280	5.89 (-0.00, 11.79)	30%	ND
>6 weeks and <6 months	10	2147	2.01 (-0.30, 4.32)	0%	ND
≥6 months	6	1594	1.06 (-3.29, 5.42)	90%	ND
Dosage of FGA (haloperidol)					
≤20mg/d	19	3943	2.23 (-0.46, 4.93)	76%	ND
Upper limit >20mg/d	1	78	2.30 (-5.85, 10.45)	NE	ND
Dosage of SGA (risperidone)					
Lower limit <4mg/d	14	3702	1.83 (-1.14, 4.79)	79%	ND
Upper range >6mg/d	12	3646	2.95 (1.19, 4.70)	20%	risperidone
Source of funding					
Industry funding	9	2049	3.11 (1.23, 5.00)	13%	risperidone
No industry funding reported	11	1972	1.67 (-2.15, 5.49)	71%	ND
Risk of bias					
Unclear	13	3416	2.72 (1.17, 4.27)	5%	risperidone
High	7	605	1.91 (-3.47, 7.29)	77%	ND
Race					
Other	15	3791	2.56 (-0.37, 5.48)	81%	ND
Asian	5	230	0.76 (-4.40, 5.92)	6%	ND
Data analysis					
Imputed data	3	1439	1.11 (-1.91, 4.13)	0%	ND
No imputed data	17	2582	2.66 (-0.31, 5.63)	79%	ND

Significant results are in bold. d = day; FGA = first generation antipsychotic; I² = I-squared; mg = milligrams; ND = no difference; NE = not estimable; PANSS = Positive and Negative Syndrome Scale; SGA = second generation antipsychotic

Table 109. Subgroup and sensitivity analyses: haloperidol vs. risperidone – Total score (BPRS)

Total Symptoms	Studies	Participants	Effect Estimate	I ²	Favors
OVERALL POOLED RESULTS	13	2592	0.51 (-0.17, 1.20)	44%	ND
Disorder subtypes					
Schizoaffective disorder	2	209	1.05 (-1.78, 3.87)	0%	ND
Schizoaffective excluded	2	363	4.88 (0.88, 8.89)	0%	risperidone
Mixed	9	1920	0.34 (-0.29, 0.98)	46%	ND
Co-morbid drug/alcohol use					
Excluded	7	1875	0.84 (0.36, 1.32)	0%	risperidone
Mixed	6	717	0.23 (-1.44, 1.90)	29%	ND
First vs. multiple episodes					
Mixed first and multiple episodes	7	805	0.98 (-1.14, 3.10)	41%	ND
Multiple episodes only	5	1604	0.00 (-0.11, 0.11)	0%	ND
First episode only	1	183	1.10 (-3.07, 5.27)	NE	ND
Treatment resistance					
No treatment resistant	1	183	1.10 (-3.07, 5.27)	NE	ND
Treatment resistant	2	193	1.17 (-2.35, 4.68)	0%	ND
Mixed	10	2216	0.49 (-0.28, 1.27)	57%	ND
Duration of followup					
≤6 weeks	5	491	0.82 (0.32, 1.32)	0%	risperidone
>6 weeks and <6 months	6	1961	0.80 (-1.63, 3.23)	33%	ND
≥6 months	1	63	0.00 (-0.11, 0.11)	NE	ND
Dosage of FGA (haloperidol)					
≤20mg/d	11	2389	0.52 (-0.23, 1.27)	53%	ND
Upper limit >20mg/d	2	203	0.91 (-2.57, 4.38)	0%	ND
Dosage of SGA (risperidone)					
Lower limit <4mg/d	10	2421	0.80 (0.33, 1.28)	0%	risperidone
Upper range >6mg/d	9	2310	1.01 (-0.74, 2.75)	22%	ND
Source of funding					
Industry funding	6	666	0.00 (-0.11, 0.11)	0%	ND
No industry funding reported	7	1926	0.71 (-0.29, 1.71)	18%	ND
Risk of bias					
Unclear	10	2027	0.01 (-0.19, 0.21)	0%	ND
High	3	565	0.95 (0.04, 1.85)	7%	risperidone
Race					
Other	12	2557	0.53 (-0.18, 1.24)	49%	ND
Asian	1	35	-0.70 (-12.6, 11.2)	NE	ND
Data analysis					
Imputed data	5	1565	0.93 (-0.74, 2.60)	0%	ND
No imputed data	8	1027	0.49 (-0.36, 1.35)	65%	ND

Significant results are in bold. BPRS = Brief Psychiatric Rating Scale; d = day; FGA = first generation antipsychotic; I² = I-squared; mg = milligrams; ND = no difference; NE = not estimable; SGA = second generation antipsychotic

Table 110. Subgroup and sensitivity analyses: haloperidol vs. risperidone – Total score (CGI-S)

Total Symptoms	Studies	Participants	Effect Estimate	I²	Favors
OVERALL POOLED RESULTS	8	2346	0.03 (-0.17, 0.23)	63%	ND
Disorder subtypes					
Schizoaffective excluded	2	363	0.52 (-0.41, 1.46)	75%	ND
Mixed	6	1983	-0.10 (-0.24, 0.05)	30%	ND
Co-morbid drug/alcohol use					
Excluded	6	1957	0.01 (-0.23, 0.24)	66%	ND
Mixed	2	389	0.13 (-0.18, 0.45)	0%	ND
First vs. multiple episodes					
Mixed first and multiple episodes	4	593	0.13 (-0.25, 0.50)	78%	ND
Multiple episodes only	4	1753	0.01 (-0.19, 0.21)	0%	ND
Treatment resistance					
No treatment resistant	1	289	-0.10 (-0.40, 0.20)	NE	ND
Treatment resistant	1	67	0.20 (-0.72, 1.12)	NE	ND
Mixed	6	1990	0.07 (-0.19, 0.34)	72%	ND
Duration of followup					
≤6 weeks	2	158	0.37 (-0.89, 1.64)	88%	ND
>6 weeks and <6 months	5	1899	0.11 (-0.08, 0.30)	0%	ND
≥6 months	1	289	-0.10 (-0.40, 0.20)	NE	ND
Dosage of SGA (risperidone)					
Lower limit <4mg/d	6	2238	-0.05 (-0.22, 0.11)	50%	ND
Upper range >6mg/d	5	2127	0.11 (-0.11, 0.34)	39%	ND
Source of funding					
Industry funding	4	791	0.03 (-0.17, 0.23)	0%	ND
No industry funding reported	4	1555	0.07 (-0.31, 0.45)	76%	ND
Risk of bias					
Unclear	6	1907	0.10 (-0.14, 0.35)	28%	ND
High	2	439	-0.08 (-0.39, 0.23)	73%	ND
Race					
Other	7	2311	0.04 (-0.17, 0.26)	68%	ND
Asian	1	35	-0.30 (-1.58, 0.98)	NE	ND
Data analysis					
Imputed data	3	1464	0.09 (-0.17, 0.35)	0%	ND
No imputed data	5	882	0.03 (-0.23, 0.29)	71%	ND

Significant results are in bold. CGI-S = Clinical Global Impression–Severity; d = day; FGA = first generation antipsychotic; I² = I-squared; mg = milligrams; ND = no difference; NE = not estimable; SGA = second generation antipsychotic

Table 111. Subgroup and sensitivity analyses: haloperidol vs. risperidone – Response rates

Total Symptoms	Studies	Participants	Effect Estimate	I²	Favors
OVERALL POOLED RESULTS	16	3453	0.94 (0.87, 1.02)	29%	ND
Disorder subtypes					
Schizoaffective included	3	864	1.03 (0.95, 1.12)	0%	ND
Schizoaffective excluded	2	363	0.78 (0.56, 1.07)	42%	ND
Mixed	11	2226	0.93 (0.83, 1.03)	16%	ND
Co-morbid drug/alcohol use					
Excluded	10	1586	0.97 (0.91, 1.05)	0%	ND
Mixed	6	913	0.86 (0.68, 1.10)	66%	ND
First vs. multiple episodes					
Mixed first and multiple episodes	8	1553	0.93 (0.81, 1.07)	48%	ND
Multiple episodes only	7	1717	0.95 (0.84, 1.07)	14%	ND
First episodes only	1	183	0.89 (0.70, 1.14)	NE	ND
Treatment resistance					
No treatment resistant	1	183	0.89 (0.70, 1.14)	NE	ND
Treatment resistant	3	271	0.82 (0.52, 1.29)	75%	ND
Mixed	12	2999	0.96 (0.88, 1.04)	18%	ND
Duration of followup					
≤6 weeks	6	524	0.97 (0.85, 1.11)	16%	ND
>6 weeks and <6 months	7	2019	0.86 (0.72, 1.03)	33%	ND
≥6 months	3	910	0.98 (0.85, 1.13)	48%	ND
Dosage of FGA (haloperidol)					
≤20mg/d	15	3327	0.93 (0.85, 1.01)	26%	ND
Upper limit >20mg/d	1	126	1.09 (0.91, 1.29)	NE	ND
Dosage of SGA (risperidone)					
Lower limit <4mg/d	13	3267	0.97 (0.90, 1.05)	21%	ND
Upper range >6mg/d	11	3056	0.94 (0.86, 1.03)	31%	ND
Source of funding					
Industry funding	8	1411	0.79 (0.63, 1.00)	53%	ND
No industry funding	8	2042	0.98 (0.91, 1.06)	0%	ND
Risk of bias					
Unclear	12	2788	0.93 (0.84, 1.01)	20%	ND
High	4	665	0.99 (0.82, 1.19)	56%	ND
Race					
Other	14	3340	0.96 (0.88, 1.04)	25%	ND
Asian	2	113	0.90 (0.55, 1.46)	65%	ND
Data analysis					
Imputed data	5	1530	0.92 (0.71, 1.18)	23%	ND
No imputed data	11	1923	0.94 (0.85, 1.03)	38%	ND

Significant results are in bold. d = day; FGA = first generation antipsychotic; I² = I-squared; mg = milligrams; ND = no difference; NE = not estimable; SGA = second generation antipsychotic

Table 112. Subgroup and sensitivity analyses: haloperidol vs. ziprasidone – Response rates

Total Symptoms	Studies	Participants	Effect Estimate	I ²	Favors
OVERALL POOLED RESULTS	6	1283	0.98 (0.74, 1.30)	80%	ND
Co-morbid drug/alcohol use					
Excluded	3	677	1.03 (0.92, 1.15)	0%	ND
Mixed	3	606	0.90 (0.49, 1.62)	91%	ND
Treatment resistance					
Treatment resistant	1	120	1.54 (1.19, 2.00)	NE	ziprasidone
No treatment resistance	3	1053	0.79 (0.56, 1.13)	84%	ND
Mixed	2	110	1.21 (0.74, 1.98)	0%	ND
Mixed and treatment resistant	3	230	1.46 (1.16, 1.84)	0%	ziprasidone
Duration of followup					
≤6 weeks	4	797	1.22 (0.91, 1.62)	66%	ND
>6 months	2	486	0.68 (0.54, 0.85)	0%	haloperidol
Dosage of FGA (haloperidol)					
≤20mg/d	5	1163	0.87 (0.66, 1.15)	70%	ND
Upper limit >20mg/d	1	120	1.54 (1.19, 2.00)	NE	ziprasidone
Dosage of SGA (ziprasidone)					
Lower limit <120mg/d	6	1283	0.98 (0.74, 1.30)	80%	ND
Upper range >160mg/d	1	120	1.54 (1.19, 2.00)	NE	ziprasidone
Risk of bias					
Unclear	1	120	1.54 (1.19, 2.00)	NE	ziprasidone
High	5	1163	0.87 (0.66, 1.15)	70%	ND
Source of funding					
Industry-funded	4	1073	0.82 (0.59, 1.12)	76%	ND
Funding not reported	2	210	1.50 (1.19, 1.91)	0%	ziprasidone
Imputed Data					
Data imputed	3	958	0.93 (0.66, 1.31)	77%	ND
Data not imputed	3	325	1.02 (0.53, 1.97)	86%	ND

Significant results are in bold. d = day; FGA = first generation antipsychotic; I² = I-squared; mg = milligrams; ND = no difference; NE = not estimable; SGA = second generation antipsychotic

Appendix N. Summary Tables of Adverse Events

Chlorpromazine Versus Clozapine

Table 113. Evidence summary table: chlorpromazine versus clozapine – general adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Mortality ^{109,156}	2	214	0.98 (0.10, 9.19)	0%	ND
Withdrawals due to AE ^{63,87,109,152,160}	5	463	1.70 (0.65, 4.45)	34%	ND

AE = adverse event; I² = I-squared; ND = no difference

Table 114. Evidence summary table: chlorpromazine versus clozapine – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Behavior and psychosis					
Agitation ¹⁵³	1	41	6.68 (0.37, 121.71)	NE	ND
Depression ¹⁵²	1	64	9.56 (0.54, 170.62)	NE	ND
Paranoia (increasing) ¹⁵⁴	1	15	0.30 (0.01, 6.29)	NE	ND
BMI and weight					
Weight gain (>5%) ⁸⁷	1	40	2.21 (0.79, 6.18)	NE	ND
Weight loss ⁸⁷	1	40	2.21 (0.22, 22.47)	NE	ND
Cardiovascular					
Abnormal ECG ^{154,160}	2	59	0.81 (0.39, 1.68)	0%	ND
Cardiotoxic effects ¹⁵³	1	41	NE	NE	ND
Hypertension ^{94,160}	2	312	0.39 (0.17, 0.90)	0%	chlorpromazine
Hypotension ^{48,87,94,109,160}	5	543	1.94 (0.91, 4.13)	49%	ND
Orthostatic hypotension ^{153,158,160}	3	110	0.61 (0.12, 3.09)	0%	ND
Tachycardia ^{87,94}	2	308	0.66 (0.37, 1.20)	0%	ND
Cholinergic and anticholinergic					
Dry mouth ^{63,87,94,152,161}	5	563	3.00 (1.67, 5.40)	11%	clozapine
Hypersalivation ^{48,63,87,94,152,154,158,160,161}	9	674	0.25 (0.14, 0.45)	13%	chlorpromazine
Ileus ¹⁰⁹	1	164	2.93 (0.12, 70.85)	NE	ND
CNS					
Dizziness ^{94,160,161}	3	352	0.62 (0.21, 1.87)	50%	ND
Drowsiness ^{94,152,153,160,161}	5	457	0.75 (0.58, 0.97)	0%	chlorpromazine
Sedation ^{48,63,87}	3	218	1.07 (0.69, 1.64)	0%	ND
Seizure ^{63,87,153}	3	232	2.91 (0.31, 27.28)	0%	ND
Slurred speech ¹⁶⁰	1	44	1.76 (0.08, 40.80)	NE	ND
Dermatology					
Dermatitis ¹⁰⁹	1	164	2.93 (0.12, 70.85)	NE	ND
Dermatologic problem ⁸⁷	1	40	5.50 (0.28, 107.78)	NE	ND
Exanthema or eczema ¹⁵³	1	41	8.59 (0.49, 150.00)	NE	ND
Endocrine (prolactin - thyroid)					
Hyperprolactinemia ⁶³	1	151	4.94 (0.24, 101.10)	NE	ND
EPS					
Akathisia ^{63,87,154}	3	206	0.99 (0.37, 2.67)	0%	ND
Dystonia ^{63,154}	2	166	3.64 (0.43, 31.19)	0%	ND
EPS ^{48,63,87,109,158,160}	6	451	2.75 (1.48, 5.12)	0%	clozapine
Oculogyric crisis ¹⁵⁴	1	15	2.67 (0.13, 56.63)	NE	ND
Parkinsonism ^{153,154}	2	56	2.67 (0.13, 56.63)	NE	ND
Rigidity ^{63,152,160}	3	259	0.76 (0.10, 6.07)	58%	ND
Staggering ¹⁶⁰	1	44	0.57 (0.04, 8.53)	NE	ND
Tardive dyskinesia (deterioration) ⁸⁷	1	40	3.30 (0.14, 76.46)	NE	ND

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Tremor ^{152,160,161}	3	148	0.74 (0.28, 1.94)	7%	ND

Table 114. Evidence summary table: chlorpromazine versus clozapine – specific adverse events (continued)

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Genito-urinary					
Impotence ⁶³	1	151	2.96 (0.12, 71.55)	NE	ND
GI					
Abdominal cramps ¹⁶⁰	1	44	1.76 (0.08, 40.80)	NE	ND
Constipation ^{63,94,109,152}	4	647	0.69 (0.44, 1.09)	0%	ND
Diarrhea ¹⁶⁰	1	44	0.38 (0.07, 2.04)	NE	ND
Heartburn ¹⁶⁰	1	44	1.76 (0.08, 40.80)	NE	ND
Nausea/vomiting ^{87,94,160}	3	352	1.06 (0.55, 2.04)	0%	ND
Hematology					
Agranulocytosis ^{63,94}	2	419	NE	NE	ND
Blood cell count (abnormal) ¹⁵⁴	1	15	NE	NE	ND
Neutropenia ¹⁰⁹	1	164	2.93 (0.12, 70.85)	NE	ND
Platelet count (elevated) ¹⁵⁴	1	15	0.07 (0.00, 1.03)	NE	ND
Leukocytopenia ^{48,63,87,94}	4	486	0.71 (0.18, 2.76)	55%	ND
Hepato-biliary					
Hepatic enzymes (elevated) ^{87,94}	2	308	0.79 (0.11, 5.71)	33%	ND
Jaundice ⁸⁷	1	40	3.30 (0.14, 76.46)	NE	ND
Sleep					
Deep sleep ¹⁵³	1	41	0.32 (0.01, 7.38)	NE	ND
Sleep disturbances ¹⁵³	1	41	6.68 (0.37, 121.71)	NE	ND
Respiratory and airway					
Cough ¹⁶⁰	1	44	0.20 (0.01, 4.53)	NE	ND
Systemic AE					
Fall (accident) ⁸⁷	1	40	0.22 (0.01, 4.31)	NE	ND
Fever/Chills ^{94,160}	2	312	0.35 (0.15, 0.83)	0%	chlorpromazine
Headache ^{94,160}	2	312	0.86 (0.43, 1.71)	0%	ND
Hyperthermia ^{109,154,160}	3	223	0.23 (0.05, 1.20)	0%	ND
Tension ¹⁶⁰	1	44	2.93 (0.15, 57.52)	NE	ND

Significant results are in bold; AE = adverse event; BMI = body mass index; CNS = central nervous system; ECG = electrocardiogram; EPS = extrapyramidal symptoms/syndrome; GI = gastrointestinal; I² = I-squared; ND = no difference; NE = not estimable

Chlorpromazine Versus Olanzapine

Table 115. Evidence summary table: chlorpromazine versus olanzapine – general adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Withdrawals due to adverse events ⁶⁶	1	84	6.00 (0.75, 47.71)	NE	ND

AE = adverse event; I² = I-squared; ND = no difference; NE = not estimable

Table 116. Evidence summary table: chlorpromazine versus olanzapine – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Cardiovascular					
Orthostatic hypotension ⁶⁶	1	84	7.50 (2.90, 19.42)	NE	olanzapine
Tachycardia ⁶⁶	1	84	7.00 (0.90, 54.44)	NE	ND
Cholinergic and anticholinergic					
Dry mouth ⁶⁶	1	84	1.94 (1.27, 2.97)	NE	olanzapine
CNS					
Dizziness ⁶⁶	1	84	1.17 (0.43, 3.18)	NE	ND
Drowsiness/lethargy ⁶⁶	1	84	1.47 (0.89, 2.41)	NE	ND
Slurred speech ⁶⁶	1	84	9.00 (0.50, 162.10)	NE	ND
Unsteady gait ⁶⁶	1	84	15.00 (2.07, 108.48)	NE	olanzapine
EPS					
EPS ⁶⁶	1	84	1.75 (0.99, 3.08)	NE	ND
GI					
Constipation ⁶⁶	1	84	2.60 (1.02, 6.65)	NE	olanzapine
Dyspepsia/heartburn ⁶⁶	1	84	2.25 (0.75, 6.74)	NE	ND
Nausea/vomiting ⁶⁶	1	84	1.00 (0.31, 3.20)	NE	ND
Gentio-urinary					
Dysuria ⁶⁶	1	84	9.00 (0.50, 162.10)	NE	ND
Ophthalmology					
Blurred vision ⁶⁶	1	84	1.25 (0.36, 4.33)	NE	ND
Sleep					
Insomnia ⁶⁶	1	84	0.33 (0.07, 1.56)	NE	ND
Systemic AE					
Headache ⁶⁶	1	84	0.67 (0.30, 1.46)	NE	ND

Note: Bold = statistically significant; AE = adverse event; EPS = extrapyramidal symptoms/syndrome; GI = gastrointestinal; I² = I-squared; ND = no difference; NE = not estimable

Chlorpromazine Versus Quetiapine

Table 117. Evidence summary table: chlorpromazine versus quetiapine – general adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Severe AEs ¹²¹	1	201	1.31 (0.92, 1.86)	NE	ND
Withdrawals due to AEs ¹²¹	1	201	2.27 (0.72, 7.14)	NE	ND

AE = adverse event; I² = I-squared; ND = no difference; NE = not estimable

Table 118. Evidence summary table: chlorpromazine versus quetiapine – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Behavior and psychosis					
Agitation ¹²¹	1	201	2.02 (0.79, 5.17)	NE	ND
Anxiety ¹²¹	1	201	1.35 (0.48, 3.74)	NE	ND
Nervousness ¹²¹	1	201	2.53 (0.50, 12.71)	NE	ND
BMI and weight					
Weight gain ¹²¹	1	201	0.67 (0.40, 1.14)	NE	ND
Cardiovascular					
Hypotension ¹²¹	1	201	2.36 (0.63, 8.86)	NE	ND
Orthostatic hypotension ¹²¹	1	201	3.64 (1.40, 9.42)	NE	quetiapine
Tachycardia ¹²¹	1	201	1.01 (0.34, 3.03)	NE	ND
Cholinergic and anticholinergic					
Dry mouth ¹²¹	1	201	0.76 (0.27, 2.10)	NE	ND
CNS					
Dizziness ¹²¹	1	201	2.53 (0.50, 12.71)	NE	ND
Somnolence ¹²¹	1	201	1.15 (0.60, 2.24)	NE	ND
EPS					
Akathasia ¹²¹	1	201	1.52 (0.44, 5.21)	NE	ND
Hypertonia ¹²¹	1	201	0.51 (0.13, 1.96)	NE	ND
Tremor ¹²¹	1	201	0.51 (0.13, 1.96)	NE	ND
GI					
Constipation ¹²¹	1	201	4.04 (0.88, 18.56)	NE	ND
Hepato-biliary					
Elevated ALT ¹²¹	1	201	1.01 (0.30, 3.38)	NE	ND
Sleep					
Insomnia ¹²¹	1	201	1.62 (0.77, 3.39)	NE	ND
Systemic AE					
Headache ¹²¹	1	201	1.62 (0.55, 4.77)	NE	ND

Significant results are in bold; AE = adverse event; ALT = alanine transaminase; BMI = body mass index; CNS = central nervous system; EPS = extrapyramidal symptoms/syndrome; GI = gastrointestinal; I² = I-squared; ND = no difference; NE = not estimable

Chlorpromazine Versus Ziprasidone

Table 119. Evidence summary table: chlorpromazine versus ziprasidone – general adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Mortality ⁹⁶	1	306	NE	NE	ND
Withdrawals due to AEs ⁹⁶	1	306	1.32 (0.47, 3.70)	NE	ND

AE = adverse events; I² = I-squared; ND = no difference; NE = not estimable

Table 120. Evidence summary table: chlorpromazine versus ziprasidone – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
BMI and weight					
Weight gain ⁹⁶	1	306	3.29 (0.92, 11.72)	NE	ND
Weight loss ⁹⁶	1	306	0.19 (0.06, 0.62)	NE	chlorpromazine
Cardiovascular					
ECG abnormalities ⁹⁶	1	306	NE	NE	ND
Orthostatic hypotension ⁹⁶	1	306	2.63 (0.71, 9.73)	NE	ND
CNS					
Dizziness ⁹⁶	1	306	2.08 (0.97, 4.46)	NE	ND
Somnolence ⁹⁶	1	306	1.50 (0.99, 2.26)	NE	ND
Endocrine (prolactin - thyroid)					
Amenorrhea ⁹⁶	1	306	3.95 (0.45, 34.92)	NE	ND
EPS					
Akathisia ⁹⁶	1	306	1.43 (0.63, 3.24)	NE	ND
EPS ⁹⁶	1	306	1.09 (0.79, 1.49)	NE	ND
Tardive dyskinesia ⁹⁶	1	306	1.21 (0.61, 2.44)	NE	ND
Tremor ⁹⁶	1	306	0.42 (0.17, 1.07)	NE	ND
Genital, urinary, and breast					
Male sexual dysfunction ⁹⁶	1	306	0.42 (0.11, 1.61)	NE	ND
GI					
Vomiting ⁹⁶	1	306	0.74 (0.26, 2.08)	NE	ND

Significant results are in bold; BMI = body mass index; CNS = central nervous system; ECG = electrocardiogram EPS = extrapyramidal symptoms/syndrome; GI = gastrointestinal; I² = I-squared; ND = no difference; NE = not estimable

Fluphenazine Versus Olanzapine

Table 121. Evidence summary table: fluphenazine versus olanzapine – general adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Incidence of patients with AEs ⁸⁹	1	60	9.00 (0.51, 160.17)	NE	ND
Withdrawals due to AEs ⁸⁹	1	60	0.74 (0.51, 1.07)	NE	ND

AE = adverse event; I² = I-squared; ND = no difference; NE = not estimable

Table 122. Evidence summary table: fluphenazine versus olanzapine – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
BMI and weight					
Weight gain ⁸⁹	1	60	0.09 (0.01, 1.57)	NE	ND
CNS					
Stupor ⁸⁹	1	60	3.00 (0.13, 70.83)	NE	ND
EPS					
Akathisia ⁸⁹	1	60	0.33 (0.10, 1.11)	NE	ND
Dyskinesia ⁸⁹	1	60	0.25 (0.03, 2.11)	NE	ND
Dyskinetic symptoms ⁸⁹	1	60	2.00 (0.19, 20.90)	NE	ND
Hypertonia ⁸⁹	1	60	0.33 (0.04, 3.03)	NE	ND
Parkinsonism ⁸⁹	1	60	1.20 (0.41, 3.51)	NE	ND
Tremor ⁸⁹	1	60	1.50 (0.27, 8.34)	NE	ND
Sleep					
Insomnia ⁸⁹	1	60	0.08 (0.00, 1.31)	NE	ND

AE = adverse event; BMI = body mass index; CNS = central nervous system; EPS = extrapyramidal symptoms/syndrome; I² = I-squared; ND = no difference; NE = not estimable

Fluphenazine Versus Quetiapine

Table 123. Evidence summary table: fluphenazine versus quetiapine – general adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Withdrawals due to adverse events ⁶⁷	1	25	0.19 (0.01, 3.52)	NE	ND

AE = adverse event; I² = I-squared; ND = no difference; NE = not estimable

Table 124. Evidence summary table: fluphenazine versus quetiapine – persistence and reversibility of adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Amenorrhea resolved by end of study ⁶⁷	1	25	NE	NE	ND
Gynecomastia resolved by end of study ⁶⁷	1	25	2.79 (0.12, 62.48)	NE	ND

I² = I-squared; ND = no difference; NE = not estimable

Table 125. Evidence summary table: fluphenazine versus quetiapine – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Behavior and psychosis					
Anxiety ⁶⁷	1	25	0.92 (0.06, 13.18)	NE	ND
Cardiovascular					
ECG abnormalities ⁶⁷	1	25	0.31 (0.01, 6.94)	NE	ND
Orthostatic hypotension ⁶⁷	1	25	1.85 (0.19, 17.84)	NE	ND
Cholinergic and anticholinergic					
Dry mouth ⁶⁷	1	25	0.46 (0.10, 2.08)	NE	ND
CNS					
Dizziness ⁶⁷	1	25	0.92 (0.06, 13.18)	NE	ND
Lethargy ⁶⁷	1	25	1.38 (0.28, 6.91)	NE	ND
Somnolence ⁶⁷	1	25	1.23 (0.34, 4.40)	NE	ND
Endocrine (prolactin - thyroid)					
Amenorrhea ⁶⁷	1	25	NE	NE	ND
Galactorrhea ⁶⁷	1	25	NE	NE	ND
EPS					
Tremor ⁶⁷	1	25	0.31 (0.01, 6.94)	NE	ND
Genital, urinary, and breast					
Gynecomastia ⁶⁷	1	25	2.79 (0.12, 62.48)	NE	ND
Urinary hesitancy ⁶⁷	1	25	0.92 (0.15, 5.56)	NE	ND
Urinary frequency ⁶⁷	1	25	0.31 (0.01, 6.94)	NE	ND
GI					
Constipation ⁶⁷	1	25	0.92 (0.29, 2.89)	NE	ND
Diarrhea ⁶⁷	1	25	0.19 (0.01, 3.52)	NE	ND
Dyspepsia/heartburn ⁶⁷	1	25	2.77 (0.33, 23.14)	NE	ND
Increased appetite ⁶⁷	1	25	0.62 (0.12, 3.07)	NE	ND
Nausea/vomiting ⁶⁷	1	25	1.85 (0.19, 17.84)	NE	ND
Ophthalmology					
Blurry vision ⁶⁷	1	25	0.92 (0.15, 5.56)	NE	ND
Sleep					
Insomnia ⁶⁷	1	25	1.54 (0.46, 5.09)	NE	ND
Systemic AE					
Headache ⁶⁷	1	25	0.92 (0.35, 2.41)	NE	ND

AE = adverse event; CNS = central nervous system; EPS = extrapyramidal symptoms/syndrome; GI = gastrointestinal; I² = I-squared; ND = no difference; NE = not estimable

Fluphenazine Versus Risperidone

Table 126. Evidence summary table: fluphenazine versus risperidone – general adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Withdrawals due to adverse events ⁶⁷	1	26	NE	NE	ND

I² = I-squared; ND = no difference; NE = not estimable

Table 127. Evidence summary table: fluphenazine versus risperidone – persistence and reversibility of adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Amenorrhea resolved by end of study ⁶⁷	1	26	0.33 (0.01, 7.50)	NE	ND
Gynecomastia resolved by end of study ⁶⁷	1	26	1.00 (0.07, 14.34)	NE	ND

I² = I-squared; ND = no difference; NE = not estimable

Table 128. Evidence summary table: fluphenazine versus risperidone – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Behavior and psychosis					
Anxiety ^{6/7}	1	26	0.50 (0.05, 4.86)	NE	ND
Cardiovascular					
ECG abnormalities ^{6/7}	1	26	NE	NE	ND
Orthostatic hypotension ^{6/7}	1	26	0.40 (0.09, 1.70)	NE	ND
Cholinergic and anticholinergic					
Dry mouth ^{6/7}	1	26	1.00 (0.16, 6.07)	NE	ND
CNS					
Dizziness ^{6/7}	1	26	0.33 (0.04, 2.80)	NE	ND
Lethargy ^{6/7}	1	26	0.75 (0.21, 2.71)	NE	ND
Somnolence ^{6/7}	1	26	0.80 (0.28, 2.32)	NE	ND
Endocrine (prolactin - thyroid)					
Amenorrhea ^{6/7}	1	26	0.20 (0.01, 3.80)	NE	ND
Galactorrhea ^{6/7}	1	26	0.33 (0.01, 7.50)	NE	ND
EPS					
Tremor ^{6/7}	1	26	NE	NE	ND
Genital, urinary, and breast					
Gynecomastia ^{6/7}	1	26	1.00 (0.07, 14.34)	NE	ND
Urinary hesitancy ^{6/7}	1	26	5.00 (0.26, 95.02)	NE	ND
Urinary frequency ^{6/7}	1	26	0.33 (0.01, 7.50)	NE	ND
GI					
Constipation ^{6/7}	1	26	9.00 (0.53, 151.94)	NE	ND
Diarrhea ^{6/7}	1	26	0.20 (0.01, 3.80)	NE	ND
Dyspepsia ^{6/7}	1	26	3.00 (0.36, 25.21)	NE	ND
Increased appetite ^{6/7}	1	26	0.67 (0.13, 3.35)	NE	ND
Nausea ^{6/7}	1	26	0.67 (0.13, 3.35)	NE	ND
Ophthalmology					
Blurry vision ^{6/7}	1	26	1.00 (0.16, 6.07)	NE	ND
Sleep					
Insomnia ^{6/7}	1	26	1.67 (0.50, 5.57)	NE	ND
Systemic AE					
Headache ^{6/7}	1	26	0.71 (0.30, 1.67)	NE	ND

AE = adverse event; CNS = central nervous system; ECG = electrocardiogram; EPS = extrapyramidal symptoms/syndrome; GI = gastrointestinal; I² = I-squared; ND = no difference; NE = not estimable

Haloperidol Versus Aripiprazole

Table 129. Evidence summary table: haloperidol versus aripiprazole – general adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Incidence of patients with AEs ^{31,73,98}	3	1713	1.11 (1.06, 1.17)	0%	aripiprazole
Mortality ^{31,44}	2	655	0.77 (0.04, 15.91)	NE	ND
Serious AEs ^{31-33,44,76,92}	6	1741	0.84 (0.35, 2.03)	58%	ND
Withdrawals due to AEs ^{31-33,44,76,92,98}	7	3035	1.25 (1.06, 1.47)	0%	aripiprazole

AE = adverse event; I² = I-squared; ND = no difference; NE = not estimable

Table 130. Evidence summary table: haloperidol versus aripiprazole – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Behavior and psychosis					
Agitation ^{31,44,74,98}	4	2253	1.09 (0.80, 1.48)	0%	ND
Anxiety ^{33,74,92,98}	4	2238	0.93 (0.73, 1.19)	0%	ND
Depression ^{32,33}	2	679	0.85 (0.26, 2.76)	82%	ND
Deterioration ⁷³	1	124	0.34 (0.01, 8.29)	NE	ND
Mania ³³	1	332	0.20 (0.05, 0.91)	NE	haloperidol
Psychosis ⁹⁸	1	1294	0.89 (0.69, 1.15)	NE	ND
BMI and weight					
Weight gain ^{33,92,98}	3	1934	1.03 (0.54, 1.96)	53%	ND
Cardiovascular					
ECG abnormalities ^{31,32,92}	3	950	1.33 (0.42, 4.19)	36%	ND
Orthostatic hypotension ⁹²	1	308	0.22 (0.03, 1.70)	NE	ND
Tachycardia ³¹	1	295	1.57 (0.51, 4.82)	NE	ND
CNS					
Dizziness ^{31,44,92}	3	963	0.53 (0.31, 0.90)	0%	haloperidol
Seizure ³¹	1	295	1.29 (0.05, 31.27)	NE	ND
Somnolence ^{31,33,44,74,92,98}	6	2893	1.39 (1.03, 1.87)	0%	aripiprazole
Dermatology					
Injection site reaction ^{31,44}	2	655	0.36 (0.09, 1.45)	0%	ND
Endocrine (prolactin - thyroid)					
Hyperprolactinemia ^{32,33}	2	679	3.67 (2.16, 6.24)	70%	aripiprazole
EPS					
Akathisia ^{31-33,74,76,92,98}	7	2979	2.04 (1.70, 2.44)	0%	aripiprazole
Asthenia ⁹²	1	308	1.09 (0.37, 3.17)	NE	ND
Dystonia ³¹	1	295	7.83 (1.47, 41.76)	NE	aripiprazole
EPS ^{32,33,44,74,92,98}	6	2945	2.22 (1.37, 3.59)	83%	aripiprazole
Hypertonia ⁹²	1	308	0.59 (0.17, 2.09)	NE	ND
Rigidity ³³	1	332	8.10 (1.89, 34.66)	NE	aripiprazole
Tremor ^{32,33,76,92,98}	5	2380	1.99 (1.42, 2.78)	4%	aripiprazole
GI					
Abdominal pain ⁹²	1	308	0.78 (0.31, 1.96)	NE	ND
Diarrhea ⁷⁴	1	304	1.01 (0.26, 3.98)	NE	ND
Dyspepsia ⁷⁴	1	304	9.12 (1.17, 71.10)	NE	aripiprazole
Nausea/Vomiting ^{31,44,74,92}	4	1267	0.49 (0.28, 0.85)	0%	haloperidol
Hepato-biliary					
Liver Damage ³²	1	347	3.05 (0.13, 74.41)	NE	ND
Ophthalmology					
Blurred vision ⁹²	1	308	5.23 (1.42, 19.30)	NE	aripiprazole
Sleep					
Insomnia ^{32,33,44,74,76,92,98}	7	3044	0.85 (0.59, 1.23)	65%	ND
Systemic AE					
Headache ^{31-33,44,74,92,98}	7	3240	1.00 (0.81, 1.24)	0%	ND

Significant results are in bold; AE = adverse event; BMI = body mass index; CNS = central nervous system; EPS = extrapyramidal symptoms/syndrome; GI = gastrointestinal; I² = I-squared; ND = no difference; NE = not estimable

Haloperidol Versus Asenapine

Table 131. Evidence summary table: haloperidol versus asenapine – general adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Incidence of patients with adverse events ⁹⁷	1	335	1.09 (0.96, 1.25)	NE	ND
Serious adverse events ⁹⁷	1	335	0.96 (0.42, 2.17)	NE	ND
Withdrawals due to adverse events ⁹⁷	1	335	1.53 (0.74, 3.16)	NE	ND

I^2 = I-squared; ND = no difference; NE = not estimable

Table 132. Evidence summary table: haloperidol versus asenapine – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Behavior and psychosis					
Agitation ⁹⁷	1	335	1.01 (0.47, 2.20)	NE	ND
Anxiety ⁹⁷	1	335	1.12 (0.45, 2.76)	NE	ND
Worse psychotic symptoms ⁹⁷	1	335	1.28 (0.54, 3.03)	NE	ND
BMI and weight					
Weight gain ⁹⁷	1	335	0.96 (0.33, 2.73)	NE	ND
Weight loss ⁹⁷	1	335	0.27 (0.01, 5.22)	NE	ND
CNS					
Oral hypoesthesia ⁹⁷	1	335	0.04 (0.00, 0.69)	NE	haloperidol
Sedation ⁹⁷	1	335	0.59 (0.20, 1.76)	NE	ND
Somnolence ⁹⁷	1	335	0.21 (0.05, 0.90)	NE	haloperidol
Endocrine (prolactin - thyroid)					
Abnormal Fasting glucose ⁹⁷	1	335	1.91 (0.39, 9.33)	NE	ND
Hyperprolactinemia ⁹⁷	1	335	2.30 (1.02, 5.15)	NE	asenapine
EPS					
Akathisia ⁹⁷	1	335	1.71 (0.93, 3.16)	NE	ND
Dystonia ⁹⁷	1	335	3.51 (1.33, 9.24)	NE	asenapine
EPS ⁹⁷	1	335	2.07 (1.40, 3.07)	NE	asenapine
Parkinsonism ⁹⁷	1	335	1.91 (0.99, 3.68)	NE	ND
Rigidity ⁹⁷	1	335	2.19 (0.81, 5.88)	NE	ND
GI					
Nausea/Vomiting ⁹⁷	1	335	0.48 (0.10, 2.22)	NE	ND
Sleep					
Insomnia ⁹⁷	1	335	0.75 (0.44, 1.27)	NE	ND
Systemic AE					
Headache ⁹⁷	1	335	0.64 (0.24, 1.71)	NE	ND

Significant results are in bold; AE = adverse event; BMI = body mass index; CNS = central nervous system; EPS = extrapyramidal symptoms/syndrome; GI = gastrointestinal; I² = I-squared; ND = no difference; NE = not estimable

Haloperidol Versus Clozapine

Table 133. Evidence summary table: haloperidol versus clozapine – general adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Incidence of patients with adverse events ¹²⁶	1	423	0.81 (0.49, 1.34)	NE	ND
Mortality (Cohort) ¹⁶³	1	49625	1.98 (1.30, 3.00)	NE	clozapine
Withdrawals due to adverse events ^{55,95,105,126,145}	5	719	1.00 (0.66, 1.50)	0%	ND

Significant results are in bold; AE = adverse event; I² = I-squared; ND = no difference; NE = not estimable

Table 134. Evidence summary table: haloperidol versus clozapine – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Behavior and psychosis					
Clinical deterioration conducive to termination ¹⁴⁵	1	77	3.24 (0.70, 15.08)	NE	ND
Irritability ¹⁵⁵	1	88	3.21 (1.26, 8.15)	NE	clozapine
Overt aggression ¹⁴⁵	1	77	1.66 (1.03, 2.66)	NE	clozapine
BMI and weight					
Weight gain ^{105,145}	2	150	0.34 (0.01, 7.76)	80%	ND
Cardiovascular					
Hypertension ⁵⁵	1	75	2.57 (0.53, 12.42)	NE	ND
Hypertensive episodes ¹⁴⁵	1	77	0.22 (0.01, 4.35)	NE	ND
Intrathoracic oppression ¹⁵⁵	1	88	0.29 (0.06, 1.27)	NE	ND
Orthostatic hypotension ¹⁵⁵	1	88	0.48 (0.18, 1.24)	NE	ND
Palpitation ¹⁵⁵	1	88	0.29 (0.06, 1.27)	NE	ND
Cholinergic and anticholinergic					
Dry mouth ^{55,155}	2	163	2.81 (1.61, 4.92)	0%	clozapine
Hypersalivation ⁵⁵	1	75	0.23 (0.12, 0.46)	NE	haloperidol
CNS					
Dizziness ^{55,155}	2	163	0.84 (0.18, 3.95)	90%	ND
Drowsiness ¹⁵⁵	1	88	0.72 (0.40, 1.30)	NE	ND
Dysarthria ¹⁵⁵	1	88	1.72 (0.30, 9.79)	NE	ND
Sedation ⁵⁵	1	75	0.67 (0.39, 1.14)	NE	ND
Seizures ¹⁴⁵	1	77	0.12 (0.01, 2.15)	NE	ND
Seizures conducive to termination ¹⁴⁵	1	77	0.22 (0.01, 4.35)	NE	ND
Dermatology					
Pruritus ¹⁵⁵	1	88	0.23 (0.01, 4.63)	NE	ND
Rash ¹⁵⁵	1	88	0.23 (0.01, 4.63)	NE	ND
Endocrine (prolactin - thyroid)					
Abnormal menstruation ¹⁵⁵	1	88	3.44 (0.37, 31.79)	NE	ND
EPS					
Hyperkinesia ¹⁵⁵	1	88	2.01 (1.13, 3.56)	NE	clozapine
Hypertonia ¹⁵⁵	1	88	1.59 (0.89, 2.83)	NE	ND
Tardive Dyskinesia (Cohort) ¹⁶²	1	333	34.50 (2.07, 573.55)	NE	clozapine
Genital, urinary, and breast					
Enuresis ⁵⁵	1	75	0.15 (0.01, 2.74)	NE	ND
GI					
Constipation ^{55,155}	2	163	1.10 (0.62, 1.95)	0%	ND
Diarrhea ^{55,155}	2	163	0.75 (0.22, 2.55)	0%	ND
Loss of Appetite ¹⁵⁵	1	88	1.02 (0.43, 2.40)	NE	ND
Nausea/Vomiting ^{55,155}	2	163	0.44 (0.21, 0.93)	17%	haloperidol
Other GI ¹⁵⁵	1	88	0.46 (0.09, 2.24)	NE	ND
Hematology					
Agranulocytosis ^{126,145}	2	500	0.21 (0.02, 1.85)	0%	ND
Bruising ⁵⁵	1	75	NE	NE	ND
Hematological problems conducive to termination ¹⁴⁵	1	77	0.15 (0.01, 2.89)	NE	ND
Leukopenia ¹²⁶	1	423	0.47 (0.09, 2.54)	NE	ND
Neutropenia ^{126,145}	2	500	0.97 (0.41, 2.30)	0%	ND
Metabolic					
Abnormal Glucose levels ¹⁰⁵	1	73	0.05 (0.00, 0.80)	NE	haloperidol
Hypercholesterolemia ¹⁰⁵	1	73	0.08 (0.00, 1.35)	NE	ND
Hypertriglyceridemia ¹⁰⁵	1	73	0.39 (0.11, 1.34)	NE	ND
Metabolic syndrome (emergent) ¹⁰⁵	1	73	0.27 (0.10, 0.75)	NE	haloperidol
Ophthalmology					
Ophthalmic disturbances ¹⁵⁵	1	88	3.44 (0.37, 31.79)	NE	ND

Table 134. Evidence summary table: haloperidol versus clozapine – specific adverse events (continued)

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Respiratory and airway					
Cough ¹⁵⁵	1	88	0.57 (0.11, 2.97)	NE	ND
Nasal congestion ¹⁵⁵	1	88	0.23 (0.03, 1.88)	NE	ND
Sore throat ⁵⁵	1	75	1.37 (0.33, 5.70)	NE	ND
Sleep					
Insomnia ¹⁵⁵	1	88	3.44 (1.51, 7.84)	NE	clozapine
Systemic AE					
Headache ¹⁵⁵	1	88	0.53 (0.24, 1.18)	NE	ND
Fever ^{55,155}	2	163	0.65 (0.36, 1.15)	0%	ND
Intercurrent illnesses conducive to termination ¹⁴⁵	1	77	0.36 (0.04, 3.31)	NE	ND
Malaise ⁵⁵	1	75	0.51 (0.23, 1.13)	NE	ND
Sweating ¹⁵⁵	1	88	0.13 (0.02, 0.96)	NE	ND
Weakness ¹⁵⁵	1	88	0.51 (0.17, 1.53)	NE	ND

Significant results are in bold; AE = adverse event; BMI = body mass index; CNS = central nervous system; EPS = extrapyramidal symptoms/syndrome; GI = gastrointestinal; I² = I-squared; ND = no difference; NE = not estimable

Haloperidol Versus Olanzapine

Table 135. Evidence summary table: haloperidol versus olanzapine – general adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Incidence of patients with adverse events ⁷³	1	119	10.47 (0.59, 185.18)	NE	ND
Persistence and reversibility of AE ⁸⁸	1	182	3.48 (0.99, 12.24)	NE	ND
Serious AEs ^{91,104,147}	3	741	1.41 (0.32, 6.21)	54%	ND
Withdrawals due to adverse events ^{43,49,50,54,71,78,84,88,91,101,104,105,108,110,124,127,140,141,145,147,159}	21	5351	1.87 (1.55, 2.27)	0%	olanzapine

Significant results are in bold; AE = adverse event; I² = I-squared; ND = no difference; NE = not estimable

Table 136. Evidence summary table: haloperidol versus olanzapine – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Behavior and psychosis					
Abnormal thinking ¹⁰¹	1	256	0.98 (0.37, 2.62)	NE	ND
Accommodation disturbance ¹⁵⁹	1	27	8.18 (0.43, 155.12)	NE	ND
Agitation ^{49,101}	2	523	1.25 (0.85, 1.85)	0%	ND
Anorexia ⁸⁸	1	182	3.66 (1.25, 10.69)	NE	olanzapine
Anxiety ^{49,88,101,147}	4	962	1.27 (0.90, 1.79)	0%	ND
Appetite (decreased) ¹⁴¹	1	1996	1.56 (1.25, 1.96)	NE	olanzapine
Appetite (excessive) ¹⁴¹	1	1996	0.51 (0.41, 0.64)	NE	haloperidol
Behavioral deterioration ^{73,84}	2	129	0.76 (0.05, 11.55)	39%	ND
Conversion symptoms ¹⁴¹	1	1996	2.34 (1.12, 4.88)	NE	olanzapine
Depression ¹⁰¹	1	256	0.64 (0.34, 1.23)	NE	ND
Excitement ⁸⁸	1	182	1.04 (0.54, 2.01)	NE	ND
Hallucinations ^{84,101}	2	266	1.06 (0.53, 2.11)	0%	ND
Nervousness ^{49,101}	2	523	1.45 (1.00, 2.11)	0%	ND
Overt aggression/violent behavior ^{49,110,145}	3	378	1.22 (0.54, 2.73)	52%	ND
Paranoia ¹⁰¹	1	256	1.64 (0.71, 3.79)	NE	ND
Personality disorder ⁴⁹	1	267	0.51 (0.15, 1.68)	NE	ND
Suicidal ideation ¹¹⁰	1	35	0.84 (0.06, 12.42)	NE	ND
Suicide ⁸⁸	1	182	3.13 (0.13, 75.92)	NE	ND
suicide (attempt) ⁸⁸	1	182	3.13 (0.13, 75.92)	NE	ND
BMI and weight					
Overweight/Obese ^{91,129}	2	274	0.35 (0.21, 0.58)	0%	haloperidol
Weight gain ^{49,71,88,91,101,104,105,108,127,129,140-142,145,159}	15	4600	0.47 (0.37, 0.61)	75%	haloperidol
Weight loss ^{88,141}	2	2178	2.43 (0.74, 7.99)	46%	ND
Cardiovascular					
ECG abnormalities ^{56,91}	2	433	0.34 (0.04, 3.21)	NE	ND
Hypertensive episodes ¹⁴⁵	1	76	NE	NE	ND
Hypotension ⁵⁶	1	225	0.30 (0.02, 5.19)	NE	ND
Palpitations ¹⁴¹	1	1996	1.48 (1.09, 2.02)	NE	olanzapine
Cholinergic and anticholinergic					
Dry mouth ^{49,71,101,141,159}	5	2657	0.75 (0.62, 0.91)	0%	haloperidol
Hypersalivation ^{50,71,88,140,141,159}	6	3200	3.38 (1.79, 6.38)	49%	olanzapine
CNS					
Asthenia ^{49,71,159}	3	405	1.43 (1.00, 2.05)	0%	ND
Concentration difficulty ⁷¹	1	111	3.93 (0.87, 17.68)	NE	ND
Dizziness ^{49,101,140}	3	976	0.69 (0.22, 2.20)	76%	ND
Drowsiness ¹⁴¹	1	1996	1.19 (1.02, 1.38)	NE	olanzapine
Seizures ¹⁴⁵	1	76	NE	NE	ND
Somnolence ^{49,71,88,101,140,159}	6	1296	0.84 (0.63, 1.12)	35%	ND
Gait abnormalities ⁸⁸	1	182	8.36 (1.98, 35.32)	NE	olanzapine
Heaviness in extremities ¹⁴¹	1	1996	1.40 (1.11, 1.77)	NE	olanzapine
Hypokinesia ^{71,140,141,159}	4	2587	3.01 (1.88, 4.82)	7%	olanzapine
Hypotonia ¹⁴¹	1	1996	1.68 (1.03, 2.72)	NE	olanzapine
Dermatology					
Maculopapular rash ¹⁴⁷	1	257	0.35 (0.01, 8.43)	NE	ND
Endocrine (prolactin - thyroid)					
Amenorrhea ⁷¹	1	111	4.91 (0.24, 100.05)	NE	ND
Hot flashes ¹⁴¹	1	1996	1.62 (1.06, 2.49)	NE	olanzapine
Hyperprolactinemia ^{50,91,108}	3	902	NR	97%	ND

Table 136. Evidence summary table: haloperidol versus olanzapine – specific adverse events (continued)

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
EPS					
Akathisia ^{49-51,56,71,88,91,101,104,108,127,140,141,159}	14	5031	3.11 (2.43, 3.98)	38%	olanzapine
Ataxia ¹⁴¹	1	1996	1.84 (1.01, 3.35)	NE	olanzapine
Bradykinesia ⁸⁸	1	182	8.36 (1.98, 35.32)	NE	olanzapine
Dyskinesia ^{50,91,140,141}	4	3088	3.55 (2.01, 6.27)	10%	olanzapine
Dystonia ^{49,50,56,91,104,140,147,159}	8	2144	5.01 (2.70, 9.28)	0%	olanzapine
EPS ^{50,104,106,140,141,147}	6	3445	3.88 (2.19, 6.85)	69%	olanzapine
Hypertonia ^{49,50,140,141}	4	3147	2.54 (1.65, 3.91)	55%	olanzapine
Neuroleptic malignant syndrome ¹⁴⁷	1	257	3.12 (0.13, 75.83)	NE	ND
Parkinsonism ^{51,56,71,84,88,91,108,147}	8	1283	4.28 (2.49, 7.35)	50%	olanzapine
Rigidity ^{71,159}	2	138	10.65 (2.08, 54.50)	0%	olanzapine
Tardive dyskinesia ¹⁴⁰	1	453	11.75 (0.65, 211.26)	NE	ND
Tremor ^{49,50,71,88,101,104,140,141,159}	9	3999	2.30 (1.59, 3.34)	58%	olanzapine
Genital, urinary, and breast					
Difficult micturition ¹⁴¹	1	1996	1.68 (1.11, 2.54)	NE	olanzapine
Ejaculatory dysfunction ⁷¹	1	111	4.91 (0.24, 100.05)	NE	ND
Erectile dysfunction ⁷¹	1	111	4.91 (0.59, 40.69)	NE	ND
Micturition disturbances ¹⁵⁹	1	27	3.40 (0.35, 32.90)	NE	ND
GI					
Constipation ^{49,101,159}	3	550	1.06 (0.43, 2.63)	23%	ND
Diarrhea ¹⁰¹	1	256	1.64 (0.84, 3.20)	NE	ND
Dyspepsia ⁴⁹	1	267	1.32 (0.68, 2.54)	NE	ND
Nausea/Vomiting ^{49,88,101,141,141}	5	4697	1.43 (1.06, 1.92)	34%	olanzapine
Hematology					
Agranulocytosis ^{141,145}	2	2072	NE	NE	ND
Eosinophilia ⁵⁰	1	431	0.19 (0.01, 3.13)	NE	ND
Hematological problems conducive to termination ¹⁴⁵	1	76	NE	NE	ND
Neutropenia ¹⁴⁵	1	76	3.16 (0.13, 75.16)	NE	ND
Hepato-biliary					
Elevated ALT ⁵⁰	1	431	0.14 (0.02, 1.04)	NE	ND
Increased gGT ⁵⁰	1	431	0.33 (0.02, 5.79)	NE	ND
SGOT abnormality ¹⁰⁸	1	263	0.41 (0.28, 0.58)	NE	haloperidol
SGPT abnormality ^{49,108}	2	530	0.46 (0.35, 0.62)	0%	haloperidol
Metabolic					
Diabetes ¹²⁹	1	66	0.85 (0.21, 3.49)	NE	ND
Hypercholesterolemia ^{91,105}	2	281	0.43 (0.26, 0.72)	0%	haloperidol
Hyperglycemia ^{91,105}	2	281	0.28 (0.12, 0.66)	0%	haloperidol
Hypertriglyceridemia ^{91,105}	2	281	0.53 (0.30, 0.92)	0%	haloperidol
HDL (low) ⁹¹	1	208	0.38 (0.16, 0.94)	NE	haloperidol
Metabolic syndrome ^{105,129}	2	139	0.38 (0.06, 2.51)	63%	ND
Ophthalmology					
Blurred vision ¹⁴¹	1	1996	1.40 (1.10, 1.78)	NE	olanzapine
Respiratory and airway					
Rhinitis ^{49,101}	2	523	1.44 (0.90, 2.33)	0%	ND
Sleep					
Early awakening ¹⁴¹	1	1996	1.49 (1.24, 1.79)	NE	olanzapine
Increased dreams/nightmares ¹⁴¹	1	1996	1.31 (1.05, 1.63)	NE	olanzapine
Insomnia ^{49,50,88,101,104,127,141}	7	3717	1.36 (1.03, 1.80)	49%	olanzapine

Table 136. Evidence summary table: haloperidol versus olanzapine – specific adverse events (continued)

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Systemic AE					
Chills ¹⁴¹	1	1996	1.74 (1.19, 2.52)	NE	olanzapine
Fever ¹⁴⁰	1	453	0.05 (0.00, 0.86)	NE	haloperidol
Headache ^{49,50,101}	3	954	1.19 (0.85, 1.65)	0%	ND
Infection ¹⁴⁰	1	453	0.27 (0.08, 0.93)	NE	haloperidol
Increased perspiration ¹⁴¹	1	1996	1.91 (1.44, 2.54)	NE	olanzapine
Injury ⁴⁹	1	267	0.86 (0.24, 3.04)	NE	ND
Intercurrent illnesses conducive to termination ¹⁴⁵	1	76	1.05 (0.07, 16.24)	NE	ND
Malaise ⁸⁸	1	182	0.94 (0.40, 2.21)	NE	ND
Pain ^{49,101}	2	523	0.81 (0.44, 1.50)	22%	ND
Tension ¹⁵⁹	1	27	14.73 (0.87, 248.02)	NE	ND

Significant results are in bold; AE = adverse event; ALT = alanine transaminase; BMI = body mass index; CNS = central nervous system; ECG = electrocardiogram; EPS = extrapyramidal symptoms/syndrome; gGT = serum gamma-glutamyl transferase; GI = gastrointestinal; HDL = high density lipoprotein; I² = I-squared; ND = no difference; NE = not estimable; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase

Haloperidol Versus Quetiapine

Table 137. Evidence summary table: haloperidol versus quetiapine – general adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Incidence of patients with AEs ^{68,73,79}	3	859	1.08 (0.93, 1.25)	25%	ND
Serious AEs ⁹¹	1	207	1.68 (0.41, 6.86)	NE	ND
Withdrawals due to AEs ^{46,47,68,79,80,91,115,123}	8	1559	1.98 (0.79, 4.96)	73%	ND

AE = adverse event; I² = I-squared; ND = no difference NE = not estimable

Table 138. Evidence summary table: haloperidol versus quetiapine – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Behavior and psychosis					
Agitation ^{46,68,115,123}	4	984	0.83 (0.51, 1.36)	0%	ND
Anxiety ⁶⁸	1	448	1.86 (0.92, 3.76)	NE	ND
Asthenia ⁶⁸	1	448	0.29 (0.12, 0.71)	NE	haloperidol
Depression ¹¹⁵	1	201	2.75 (0.75, 10.06)	NE	ND
Deterioration ⁷³	1	123	NE	NE	ND
Fatigue ¹²³	1	25	0.36 (0.02, 8.05)	NE	ND
Irritability ¹²³	1	25	3.23 (0.14, 72.46)	NE	ND
BMI and weight					
Overweight ⁹¹	1	207	0.65 (0.37, 1.14)	NE	ND
Weight gain ^{46,91,123}	3	542	0.59 (0.39, 0.89)	0%	haloperidol
Cardiovascular					
ECG abnormalities ^{46,91}	2	517	0.50 (0.05, 5.48)	NE	ND
Orthostatic hypotension ^{46,68,115}	3	959	0.49 (0.25, 0.94)	0%	haloperidol
Cholinergic and anticholinergic					
Dry mouth ^{68,115,123}	3	674	0.32 (0.15, 0.65)	0%	haloperidol
Hypersalivation ^{68,123}	2	473	1.88 (0.22, 16.18)	50%	ND
CNS					
Dizziness ^{46,68}	2	758	0.68 (0.36, 1.28)	0%	ND
Drowsiness ¹²³	1	25	0.36 (0.02, 8.05)	NE	ND
Sedation ¹²³	1	25	3.23 (0.14, 72.46)	NE	ND
Somnolence ^{46,68,115,123}	4	984	0.57 (0.39, 0.84)	0%	haloperidol
Dermatology					
Dry skin/rash ¹²³	1	25	3.23 (0.14, 72.46)	NE	ND
Endocrine (prolactin - thyroid)					
Amenorrhea/Menstrual cycle irregularities ¹²³	1	25	0.36 (0.02, 8.05)	NE	ND
Cold flashes ¹²³	1	25	0.36 (0.02, 8.05)	NE	ND
Galactorrhea ⁴⁷	1	35	5.28 (0.27, 102.58)	NE	ND
Hyperprolactinemia ^{68,79,91}	3	943	2.24 (1.04, 4.80)	89%	quetiapine
Thyroid function test abnormalities ⁶⁸	1	448	0.05 (0.00, 0.79)	NE	haloperidol
EPS					
Akathisia ^{46,68,79,91,115}	5	1454	3.51 (1.84, 6.72)	68%	quetiapine
Akinesia ⁶⁸	1	448	2.92 (0.12, 71.32)	NE	ND
Cogwheel rigidity ⁶⁸	1	448	2.92 (0.12, 71.32)	NE	ND
Dyskinesia ⁹¹	1	207	5.05 (0.25, 103.88)	NE	ND
Dystonia ^{46,68,91}	3	965	3.94 (0.79, 19.70)	29%	ND
EPS ^{46,68,79,80,115}	5	1292	NR	90%	ND
Fine tremors ¹²³	1	25	0.36 (0.02, 8.05)	NE	ND
Hypertonia ^{68,79}	2	736	2.05 (0.82, 5.10)	60%	ND
Involuntary movement (jaw) ¹²³	1	25	0.36 (0.02, 8.05)	NE	ND
Neck rigidity ⁶⁸	1	448	2.92 (0.12, 71.32)	NE	ND
Oculogyric crisis ⁶⁸	1	448	6.82 (0.35, 131.19)	NE	ND
Parkinsonism ^{46,91}	2	517	4.04 (1.97, 8.26)	53%	quetiapine
Stiffness ¹²³	1	25	3.23 (0.14, 72.46)	NE	ND
Tardive dyskinesia ⁶⁵	1	35	NE	NE	ND
Tremor ^{68,115}	2	649	3.80 (2.12, 6.81)	0%	quetiapine
Twitch in the extremities ¹²³	1	25	0.36 (0.02, 8.05)	NE	ND
GI					
Constipation ^{46,68}	2	758	0.45 (0.22, 0.93)	0%	haloperidol
Dyspepsia ⁴⁶	1	310	0.99 (0.35, 2.78)	NE	ND
Hematology					
Agranulocytosis ⁴⁶	1	310	NE	NE	ND
Leucopenia ⁶⁸	1	448	0.32 (0.03, 3.10)	NE	ND

Table 138. Evidence summary table: haloperidol versus quetiapine – specific adverse events (continued)

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Hepato-biliary					
Elevated liver transaminases ⁶⁸	1	448	0.14 (0.02, 1.12)	NE	ND
Metabolic					
HDL (low) ⁹¹	1	207	0.76 (0.27, 2.11)	NE	ND
Hypercholesterolemia ⁹¹	1	207	1.24 (0.63, 2.45)	NE	ND
Hyperglycemia ⁹¹	1	207	0.67 (0.25, 1.82)	NE	ND
Hypertriglyceridemia ⁹¹	1	207	1.19 (0.56, 2.54)	NE	ND
Ophthalmology					
Blurred vision ¹²³	1	25	3.23 (0.14, 72.46)	NE	ND
Sleep					
Insomnia ^{46,68,115,123}	4	984	1.12 (0.71, 1.76)	29%	ND
Systemic AE					
Headache ^{46,68,115,123}	4	984	1.31 (0.86, 1.98)	5%	ND

Significant results are in bold; AE = adverse event; BMI = body mass index; CNS = central nervous system; ECG = electrocardiogram; EPS = extrapyramidal symptoms/syndrome; GI = gastrointestinal; HDL = high density lipoprotein; I² = I-squared; ND = no difference; NE = not estimable

Haloperidol Versus Risperidone

Table 139. Evidence summary table: haloperidol versus risperidone – general adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
AE resolved spontaneously by 24hrs ¹⁵¹	1	124	1.06 (0.60, 1.86)	NE	ND
Incidence of patients with AEs ^{72,73,81,85,117,128,136,151}	8	1313	1.20 (1.01, 1.42)	84%	risperidone
Mortality (Cohort) ¹⁶³	1	63352	1.70 (1.31, 2.20)	NE	risperidone
Serious AEs ⁵²	1	41	NE	NE	ND
Withdrawals due to AEs ^{52,59-61,64,71,72,81,82,85,90,101,118,120,124,128,132,138,145,146,149-151}	23	4421	1.27 (1.04, 1.55)	0%	risperidone

Significant results are in bold; AE = adverse event; I² = I-squared; ND = no difference; NE = not estimable

Table 140. Evidence summary table: haloperidol versus risperidone – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Behavior and psychosis					
Abnormal thinking ¹⁰¹	1	255	0.61 (0.25, 1.51)	NE	ND
Accommodation disturbances ^{120,149}	2	1403	1.37 (0.99, 1.89)	0%	ND
Agitation ^{61,72,81,101}	4	916	1.30 (0.96, 1.76)	7%	ND
Anxiety ^{61,81,101}	3	551	0.95 (0.67, 1.34)	67%	ND
Asthenia ^{52,71,117,120,149}	5	1596	1.20 (1.02, 1.41)	0%	risperidone
Concentration difficulty ^{64,71,117,120}	4	1556	1.18 (0.97, 1.43)	65%	ND
Decreased appetite ⁶⁴	1	42	0.55 (0.25, 1.20)	NE	ND
Depression ^{101,118}	2	544	0.63 (0.34, 1.16)	0%	ND
Deterioration ⁷³	1	126	NE	NE	ND
Drug overdose ¹¹⁸	1	289	0.33 (0.01, 7.95)	NE	ND
Decreased sexual desire ^{120,149}	2	1403	1.07 (0.72, 1.59)	0%	ND
Fatigue ^{60,64}	2	104	1.00 (0.63, 1.60)	0%	ND
Hallucination ¹⁰¹	1	255	1.00 (0.49, 2.02)	NE	ND
Increased appetite ⁶⁴	1	42	1.20 (0.43, 3.33)	NE	ND
Manic reaction ¹²⁸	1	105	6.87 (0.36, 129.81)	NE	ND
Nervousness ¹⁰¹	1	255	1.20 (0.68, 2.14)	NE	ND
Paranoia ¹⁰¹	1	255	1.16 (0.54, 2.52)	NE	ND
Sexual disturbances ⁵²	1	41	0.35 (0.02, 8.10)	NE	ND
BMI and weight					
Weight gain ¹⁰¹	1	255	0.19 (0.05, 0.81)	NE	haloperidol
Cardiovascular					
ECG abnormalities ¹²⁸	1	105	1.31 (0.31, 5.56)	NE	ND
Hypotension ⁶¹	1	113	1.41 (0.06, 33.44)	NE	ND
Orthostatic tachycardia ⁶¹	1	113	0.60 (0.03, 11.27)	NE	ND
Orthostatic hypotension ^{52,61,64}	3	196	0.76 (0.39, 1.48)	0%	ND
Palpitation ^{52,64}	2	83	1.18 (0.44, 3.13)	0%	ND
Cholinergic and anticholinergic					
Decreased salivation ⁷¹	1	117	2.54 (0.69, 9.35)	NE	ND
Dry mouth ^{52,60,64,101}	4	400	1.44 (0.89, 2.33)	0%	ND
Hypersalivation ⁸⁵	1	77	0.15 (0.01, 2.89)	NE	ND
CNS					
Dizziness ^{101,128,151}	3	484	1.20 (0.72, 1.99)	22%	ND
Sedation ⁶⁴	1	42	0.87 (0.56, 1.33)	NE	ND
Somnolence ^{52,53,101,128,151}	5	549	1.09 (0.79, 1.50)	0%	ND
Vertigo ^{52,64}	2	83	0.56 (0.23, 1.38)	63%	ND
Endocrine (prolactin - thyroid)					
Amenorrhea ^{64,71,120,149}	4	1562	1.17 (0.80, 1.71)	0%	ND
Galactorrhea ¹³²	1	555	0.08 (0.00, 1.36)	NE	ND
EPS					
Akathisia ^{52,60,71,101,139,146,149}	7	619	1.79 (1.31, 2.44)	0%	risperidone
Dystonia ^{60,139,149}	3	139	1.01 (0.41, 2.50)	19%	ND
EPS ^{61,117,128,138,151}	5	675	1.86 (1.46, 2.36)	0%	risperidone
Oculogyric crisis ⁸⁵	1	77	0.15 (0.01, 2.89)	NE	ND
Tremor ^{52,85,101,128}	4	478	2.09 (1.23, 3.53)	0%	risperidone
Genital, urinary, and breast					
Breast tension ⁶⁴	1	42	4.00 (0.49, 32.87)	NE	ND
Dry vagina ¹⁴⁹	1	41	0.53 (0.11, 2.56)	NE	ND
Ejaculatory dysfunction ^{64,71,120,149}	4	1562	0.68 (0.43, 1.07)	0%	ND
Erectile dysfunction ^{64,71,120}	3	1521	1.19 (0.83, 1.70)	18%	ND
Gynecomastia ¹³²	1	555	0.14 (0.01, 2.76)	NE	ND
Micturition disturbances ⁵²	1	41	NE	NE	ND

Table 140. Evidence summary table: haloperidol versus risperidone – specific adverse events (continued)

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
GI					
Constipation ^{52,53,64,101,120,128,149}	7	1870	1.04 (0.78, 1.38)	35%	ND
Diarrhea ¹⁰¹	1	255	1.36 (0.72, 2.57)	NE	ND
Dyspepsia ¹²⁸	1	105	0.98 (0.42, 2.27)	NE	ND
Nausea/Vomiting ^{53,61,64,85,101}	5	511	1.17 (0.74, 1.87)	0%	ND
Hematology					
Agranulocytosis ¹⁴⁵	1	78	NE	NE	ND
Ophthalmology					
Blurred vision ^{60,64}	2	104	0.47 (0.17, 1.30)	40%	ND
Respiratory and airway					
Rhinitis ¹⁰¹	1	255	1.00 (0.60, 1.67)	NE	ND
Sleep					
Insomnia ^{52,61,81,101,120,151}	6	2078	1.03 (0.85, 1.26)	10%	ND
Sleep disorder ^{52,85}	2	118	2.47 (0.90, 6.76)	33%	ND
Systemic AE					
Headache ^{52,53,61,64,81,85,101,128,151}	9	964	0.83 (0.63, 1.08)	0%	ND
Increased sweating ^{52,64}	2	83	1.54 (0.59, 3.99)	41%	ND
Infection ⁵³	1	24	7.00 (0.40, 122.44)	NE	ND
Pain ¹⁰¹	1	255	0.48 (0.21, 1.06)	NE	ND

Significant results are in bold; AE = adverse event; BMI = body mass index; CNS = central nervous system; ECG = electrocardiogram; EPS = extrapyramidal symptoms/syndrome; GI = gastrointestinal; I² = I-squared; ND = no difference; NE = not estimable

Haloperidol Versus Ziprasidone

Table 141. Evidence summary table: haloperidol versus ziprasidone – general adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Incidence of patients with AEs ^{57,69,73,83,86,144}	6	1448	1.13 (1.03, 1.23)	31%	ziprasidone
Mortality ^{116,144}	2	408	3.10 (0.13, 75.68)	NE	ND
Serious AEs ^{57,86,91,144}	4	1403	1.02 (0.60, 1.75)	0%	ND
Withdrawals due to AEs ^{57,83,86,91,116,144}	6	1551	1.73 (1.30, 2.32)	0%	ziprasidone

Significant results are in bold; AE = adverse event; I² = I-squared; ND = no difference; NE = not estimable

Table 142. Evidence summary table: haloperidol versus ziprasidone – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Behavior and psychosis					
Agitation ^{86,116}	2	359	1.05 (0.66, 1.68)	0%	ND
Anxiety ^{86,116,144}	3	709	1.42 (0.77, 2.61)	15%	ND
Asthenia ^{86,116}	2	359	0.63 (0.29, 1.35)	0%	ND
Depression ^{86,144}	2	651	1.52 (0.84, 2.76)	0%	ND
Deterioration ⁷³	1	120	2.90 (0.12, 69.87)	NE	ND
Hallucinations ⁸⁶	1	301	1.29 (0.56, 2.97)	NE	ND
BMI and weight					
Overweight ⁹¹	1	185	0.91 (0.47, 1.75)	NE	ND
Weight gain ^{91,144}	2	535	0.86 (0.45, 1.67)	47%	ND
Weight loss ¹⁴⁴	1	350	0.23 (0.05, 1.05)	NE	ND
Cardiovascular					
Cardiovascular AEs ¹¹⁶	1	58	NE	NE	ND
ECG abnormalities ^{57,86,91,116,122,144}	6	2060	0.84 (0.53, 1.31)	0%	ND
Hypertension ¹¹⁶	1	58	3.43 (0.15, 80.83)	NE	ND
Hypotension ¹¹⁶	1	58	0.57 (0.06, 5.99)	NE	ND

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Syncope ¹¹⁶	1	58	NE	NE	ND

Table 143. Evidence summary table: haloperidol versus ziprasidone – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Cholinergic and anticholinergic					
Dry mouth ^{86,116}	2	359	1.20 (0.38, 3.84)	29%	ND
CNS					
Dizziness ^{86,116,144}	3	709	1.19 (0.43, 3.34)	55%	ND
Hypokinesia ¹⁴⁴	1	350	6.21 (1.41, 27.34)	NE	ziprasidone
Hypotonia ¹⁴⁴	1	350	5.86 (1.75, 19.65)	NE	ziprasidone
Somnolence ^{57,86,116,122,144}	5	1875	0.89 (0.70, 1.12)	36%	ND
Dermatology					
Injection-site pain ¹¹⁶	1	58	0.57 (0.06, 5.99)	NE	ND
Endocrine (prolactin - thyroid)					
Hyperprolactinemia ^{57,91}	2	752	1.53 (0.46, 5.05)	89%	ND
EPS					
Akathisia ^{57,86,91,116,122,144}	6	2060	1.58 (1.00, 2.50)	80%	ND
Dyskinesia ⁹¹	1	185	3.99 (0.19, 81.98)	NE	ND
Dystonia ^{57,91,144}	3	1102	2.19 (1.34, 3.60)	15%	ziprasidone
EPS ^{57,69,116,122,144}	5	1594	2.34 (1.56, 3.53)	63%	ziprasidone
Hypertonía ^{57,86,116}	3	926	2.45 (1.52, 3.94)	0%	ziprasidone
Movement disorder ⁸⁶	1	301	2.73 (1.77, 4.19)	NE	ziprasidone
Parkinsonism ⁹¹	1	185	1.81 (0.95, 3.46)	NE	ND
Psychosis ⁸⁶	1	301	0.48 (0.15, 1.57)	NE	ND
Tardive dyskinesia ⁸⁶	1	301	4.84 (0.23, 99.93)	NE	ND
Tremor ^{57,86,116,122,144}	5	1875	2.55 (1.79, 3.63)	4%	ziprasidone
GI					
Dyspepsia ¹⁴⁴	1	350	0.38 (0.12, 1.16)	NE	ND
Nausea/Vomiting ^{86,116}	2	359	0.55 (0.27, 1.11)	0%	ND
Metabolic					
HDL (low) ⁹¹	1	185	0.96 (0.30, 3.02)	NE	ND
Hypercholesterolemia ⁹¹	1	185	0.75 (0.40, 1.39)	NE	ND
Hyperglycemia ⁹¹	1	185	0.68 (0.24, 1.95)	NE	ND
Hypertriglyceridemia ⁹¹	1	185	1.03 (0.48, 2.24)	NE	ND
Ophthalmology					
Abnormal vision ¹¹⁶	1	58	5.71 (0.29, 114.05)	NE	ND
Sleep					
Insomnia ^{57,86,116,122}	4	1525	0.81 (0.63, 1.04)	0%	ND
Systemic AE					
Headache ^{86,116,144}	3	709	0.49 (0.11, 2.18)	82%	ND
Malaise ¹¹⁶	1	58	0.38 (0.04, 3.47)	NE	ND
Sweating ¹¹⁶	1	58	5.71 (0.29, 114.05)	NE	ND

Significant results are in bold; AE = adverse event; BMI = body mass index; CN = central nervous system; ECG = electrocardiogram; EPS = extrapyramidal symptoms/syndrome; GI = gastrointestinal; HDL = high density lipoprotein; I² = I-squared; ND = no difference; NE = not estimable

Perphenazine Versus Aripiprazole

Table 144. Evidence summary table: perphenazine versus aripiprazole – general adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Serious AEs ⁹³	1	300	0.79 (0.49, 1.28)	NE	ND
Withdrawals due to AEs ⁹³	1	300	0.53 (0.27, 1.05)	NE	ND

AE = adverse event; I² = I-squared; ND = no difference; NE = not estimable

Table 145. Evidence summary table: perphenazine versus aripiprazole – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Behavior and psychosis					
Agitation ⁹³	1	300	1.01 (0.61, 1.69)	NE	ND
Anxiety ⁹³	1	300	1.19 (0.63, 2.24)	NE	ND
Dizziness ⁹³	1	300	5.27 (1.18, 23.66)	NE	aripiprazole
Psychosis ⁹³	1	300	0.82 (0.42, 1.59)	NE	ND
Cardiovascular					
ECG abnormalities ⁹³	1	300	15.82 (2.12, 118.27)	NE	aripiprazole
CNS					
Somnolence ⁹³	1	300	2.64 (0.85, 8.22)	NE	ND
Endocrine (prolactin - thyroid)					
Hyperprolactinemia ⁹³	1	300	13.89 (6.25, 30.86)	NE	aripiprazole
EPS					
Akathisia ⁹³	1	300	2.29 (0.89, 5.85)	NE	ND
EPS ⁹³	1	300	1.90 (0.65, 5.53)	NE	ND
GI					
Dyspepsia ⁹³	1	300	0.59 (0.27, 1.30)	NE	ND
Metabolic					
Abnormal total creatinine phosphokinase value ⁹³	1	300	0.62 (0.25, 1.52)	NE	ND
Increased creatinine phosphokinase ⁹³	1	300	0.47 (0.15, 1.49)	NE	ND
Sleep					
Insomnia ⁹³	1	300	0.86 (0.56, 1.31)	NE	ND
Systemic AE					
Headache ⁹³	1	300	0.55 (0.29, 1.03)	NE	ND
Injury ⁹³	1	300	4.75 (1.04, 21.60)	NE	aripiprazole

Significant results are in bold; AE = adverse event; CNS = central nervous system; ECG = electrocardiogram; EPS = extrapyramidal symptoms/syndrome; I² = I-squared; ND = no difference; NE = not estimable

Perphenazine Versus Olanzapine

Table 146. Evidence summary table: perphenazine versus olanzapine – general adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Incidence of patients with AEs ²³	1	597	0.93 (0.83, 1.04)	NE	ND
Serious AEs ²³	1	597	1.17 (0.72, 1.88)	NE	ND
Withdrawals due to AEs ²³	1	597	0.83 (0.58, 1.19)	NE	ND

AE = adverse event; I² = I-squared; ND = no difference; NE = not estimable

Table 147. Evidence summary table: perphenazine versus olanzapine – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Behavior and psychosis					
Suicide attempt ²³	1	597	0.64 (0.06, 7.06)	NE	ND
Suicidal ideation ²³	1	597	3.86 (0.40, 36.91)	NE	ND
BMI and weight					
Weight gain ²³	1	597	0.41 (0.28, 0.60)	NE	perphenazine
Cardiovascular					
ECG abnormalities ²³	1	597	6.43 (0.31, 133.39)	NE	ND
Hypertension ²³	1	597	0.85 (0.51, 1.40)	NE	ND
Orthostatic hypotension ²³	1	597	1.20 (0.75, 1.95)	NE	ND
Endocrine (prolactin - thyroid)					
Menstrual irregularities ²³	1	597	0.82 (0.32, 2.08)	NE	ND
EPS					
AIMS global severity score ≥ 2 ²³	1	597	1.65 (1.07, 2.54)	NE	olanzapine
BARS global score ≥ 3 ²³	1	597	1.37 (0.69, 2.73)	NE	ND
Dystonia ²³	1	597	1.29 (0.08, 20.48)	NE	ND
SAS mean score ≥ 1 ²³	1	597	0.84 (0.45, 1.58)	NE	ND
Genital, urinary, and breast					
Gynecomastia/galactorrhea ²³	1	597	0.74 (0.22, 2.49)	NE	ND
Incontinence, nocturia ²³	1	597	0.43 (0.17, 1.07)	NE	ND
Metabolic					
Diabetes ²³	1	597	0.81 (0.45, 1.45)	NE	ND
Metabolic syndrome ²³	1	597	0.88 (0.63, 1.21)	NE	ND
Ophthalmology					
Cataracts ²³	1	597	0.43 (0.04, 4.10)	NE	ND
Sleep					
Hypersomnia ²³	1	597	0.92 (0.71, 1.18)	NE	ND
Insomnia ²³	1	597	1.54 (1.12, 2.13)	NE	olanzapine

Significant results are in bold; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; BMI = body mass index; ECG = electrocardiogram; EPS = extrapyramidal symptoms/syndrome; I² = I-squared; ND = no difference; NE = not estimable; SAS = Simpson Angus Scale

Perphenazine Versus Quetiapine

Table 148. Evidence summary table: perphenazine versus quetiapine – general adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Incidence of patients with AEs ²³	1	598	1.00 (0.89, 1.12)	NE	ND
Serious AEs ²³	1	598	1.17 (0.73, 1.88)	NE	ND
Withdrawals due to AEs ²³	1	598	1.05 (0.72, 1.55)	NE	ND

AE = adverse event; I² = I-squared; ND = no difference; NE = not estimable

Table 149. Evidence summary table: perphenazine versus quetiapine – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Behavior and psychosis					
Suicidal ideation ²³	1	598	1.94 (0.33, 11.51)	NE	ND
Suicide attempt ²³	1	598	1.29 (0.08, 20.55)	NE	ND
BMI and weight					
Weight gain ²³	1	598	0.76 (0.50, 1.17)	NE	ND
Cardiovascular					
ECG abnormalities ²³	1	598	0.43 (0.09, 2.12)	NE	ND
Hypertension ²³	1	598	0.80 (0.49, 1.32)	NE	ND
Orthostatic hypotension ²³	1	598	0.99 (0.62, 1.55)	NE	ND
Cholinergic and anticholinergic					
Anticholinergic side-effects ²³	1	598	0.70 (0.53, 0.93)	NE	perphenazine
Endocrine (prolactin - thyroid)					
Menstrual irregularities ²³	1	598	1.81 (0.58, 5.63)	NE	ND
EPS					
AIMS global severity score ≥ 2 ²³	1	598	1.76 (1.13, 2.75)	NE	quetiapine
BARS global score ≥ 3 ²³	1	598	1.29 (0.66, 2.53)	NE	ND
Dystonia ²³	1	598	1.29 (0.08, 20.55)	NE	ND
SAS mean score ≥ 1 ²³	1	598	1.61 (0.77, 3.39)	NE	ND
Genital, urinary, and breast					
Gynecomastia/ galactorrhea ²³	1	598	0.86 (0.25, 3.02)	NE	ND
Incontinence/nocturia ²³	1	598	0.52 (0.20, 1.31)	NE	ND
Metabolic					
Diabetes ²³	1	598	1.57 (0.79, 3.12)	NE	ND
Metabolic syndrome ²³	1	598	1.19 (0.84, 1.70)	NE	ND
Ophthalmology					
Cataracts ²³	1	598	1.29 (0.08, 20.55)	NE	ND
Sleep					
Hypersomnia ²³	1	598	0.93 (0.72, 1.19)	NE	ND
Insomnia ²³	1	598	1.37 (1.01, 1.87)	NE	ND

Significant results are in bold; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; BMI = body mass index; ECG = electrocardiogram; EPS = extrapyramidal symptoms/syndrome; I² = I-squared; ND = no difference; NE = not estimable; SAS = Simpson Angus Scale

Perphenazine Versus Risperidone

Table 150. Evidence summary table: perphenazine versus risperidone – general adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Incidence of patients with AEs ²³	1	602	0.96 (0.85, 1.07)	NE	ND
Serious AEs ²³	1	602	1.15 (0.72, 1.84)	NE	ND
Withdrawals due to AEs ²³	1	602	1.54 (1.00, 2.36)	NE	ND

AE = adverse event; I² = I-squared; ND = no difference; NE = not estimable

Table 151. Evidence summary table: perphenazine versus risperidone – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Behavior and psychosis					
Suicidal ideation ²³	1	602	0.98 (0.22, 4.34)	NE	ND
Suicide attempt ²³	1	602	0.65 (0.06, 7.17)	NE	ND
BMI and weight					
Weight gain ²³	1	602	0.90 (0.58, 1.41)	NE	ND
Cardiovascular					
ECG abnormalities ²³	1	602	0.37 (0.08, 1.78)	NE	ND
Hypertension ²³	1	602	0.94 (0.56, 1.57)	NE	ND
Orthostatic hypotension ²³	1	602	1.02 (0.65, 1.62)	NE	ND
Cholinergic and anticholinergic					
Anticholinergic side-effects ²³	1	602	0.89 (0.66, 1.19)	NE	ND
Endocrine (prolactin - thyroid)					
Menstrual irregularities ²³	1	602	0.57 (0.24, 1.37)	NE	ND
EPS					
AIMS global severity score ≥ 2 ²³	1	602	1.41 (0.93, 2.13)	NE	ND
BARS global score ≥ 3 ²³	1	602	1.05 (0.55, 1.98)	NE	ND
Dystonia ²³	1	602	0.65 (0.06, 7.17)	NE	ND
SAS mean score ≥ 1 ²³	1	602	0.85 (0.45, 1.60)	NE	ND
Genital, urinary, and breast					
Gynecomastia/ galactorrhea ²³	1	602	0.37 (0.12, 1.12)	NE	ND
Incontinence/ nocturia ²³	1	602	0.31 (0.13, 0.75)	NE	perphenazine
Metabolic					
Diabetes ²³	1	602	1.06 (0.57, 1.96)	NE	ND
Metabolic syndrome ²³	1	602	1.42 (0.98, 2.06)	NE	ND
Ophthalmology					
Cataracts ²³	1	602	0.65 (0.06, 7.17)	NE	ND
Sleep					
Hypersomnia ²³	1	602	1.01 (0.78, 1.30)	NE	ND
Insomnia ²³	1	602	1.04 (0.79, 1.37)	NE	ND

Significant results are in bold; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; BMI = body mass index; ECG = electrocardiogram; EPS = extrapyramidal symptoms/syndrome; I² = I-squared; ND = no difference; NE = not estimable; SAS = Simpson Angus Scale

Perphenazine Versus Ziprasidone

Table 152. Evidence summary table: perphenazine versus ziprasidone – general adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Incidence of patients with AEs ²³	1	446	1.01 (0.88, 1.16)	NE	ND
Serious AEs ²³	1	446	1.08 (0.63, 1.87)	NE	ND
Withdrawals due to AEs ²³	1	446	1.01 (0.65, 1.58)	NE	ND

AE = adverse event; I² = I-squared; ND = no difference; NE = not estimable

Table 153. Evidence summary table: perphenazine versus ziprasidone – specific adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Behavior and psychosis					
Suicidal ideation ²³	1	446	1.06 (0.18, 6.30)	NE	ND
Suicide attempt ²³	1	446	0.71 (0.04, 11.26)	NE	ND
BMI and weight					
Weight gain ²³	1	446	1.71 (0.90, 3.27)	NE	ND
Cardiovascular					
ECG abnormalities ²³	1	446	0.71 (0.10, 4.99)	NE	ND
Hypertension ²³	1	446	0.65 (0.38, 1.11)	NE	ND
Orthostatic hypotension ²³	1	446	0.86 (0.52, 1.42)	NE	ND
Cholinergic and anticholinergic					
Anticholinergic side-effects ²³	1	446	1.09 (0.76, 1.58)	NE	ND
Endocrine (prolactin - thyroid)					
Menstrual irregularities ²³	1	446	0.62 (0.23, 1.68)	NE	ND
EPS					
AIMS global severity score ≥ 2 ²³	1	446	1.61 (0.96, 2.72)	NE	ND
BARS global score ≥ 3 ²³	1	446	0.81 (0.41, 1.62)	NE	ND
Dystonia ²³	1	446	0.24 (0.02, 2.25)	NE	ND
SAS mean score ≥ 1 ²³	1	446	1.77 (0.70, 4.48)	NE	ND
Genital, urinary, and breast					
Gynecomastia/ galactorrhea ²³	1	446	0.47 (0.14, 1.65)	NE	ND
Incontinence/ nocturia ²³	1	446	0.43 (0.16, 1.15)	NE	ND
Metabolic					
Diabetes ²³	1	446	1.00 (0.49, 2.05)	NE	ND
Metabolic syndrome ²³	1	446	1.51 (0.96, 2.39)	NE	ND
Ophthalmology					
Cataracts ²³	1	446	2.13 (0.09, 51.99)	NE	ND
Sleep					
Hypersomnia ²³	1	446	1.17 (0.85, 1.60)	NE	ND
Insomnia ²³	1	446	0.84 (0.62, 1.13)	NE	ND

AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; BMI = body mass index; ECG = electrocardiogram; EPS = extrapyramidal symptoms/syndrome; I² = I-squared; ND = no difference; NE = not estimable; SAS = Simpson Angus Scale

Thioridazine versus Clozapine

Table 154. Evidence summary table: thioridazine versus clozapine – general adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Mortality (Cohort) ¹⁶³	1	32280	2.12 (1.38, 3.26)	NE	clozapine

I² = I-squared; NE = not estimable

Thioridazine versus Risperidone

Table 155. Evidence summary table: thioridazine versus risperidone – general adverse events

Outcome	Studies	Participants	Effect Estimate	I ²	Less with
Mortality (Cohort) ¹⁶³	1	46007	1.82 (1.37, 2.40)	NE	risperidone

I² = I-squared; NE = not estimable

Appendix O. First-Generation and Second-Generation FDA-Approved and Available Antipsychotics

Table O–1. First-generation antipsychotics included in the CER

Generic name	Trade names(s)	Mode of administration	Recommended dose	Frequency
Chlorpromazine	Chlorpromazine hydrochloride Chlorpromazine hydrochloride	Oral IM/IV	200-600 mg/day	1-4 times
Droperidol	Inapsine	IM/IV	Initial 2.5 mg/dose	increase by 1.25 mg as needed
Fluphenazine	Fluphenazine decanoate Fluphenazine hydrochloride	Oral IM	2.5-10 mg/day 2.5-10 mg/dose	3-4 times every 6 to 8 hour
Haloperidol	Haloperidol Haldol Haloperidol decanoate	Oral Tablets Solution IM (as lactate)	4-12 mg/day	1-2 times 2-3 times Every hour if needed
Loxapine	Loxapine, Loxapine succinate	Oral	60-100 mg/day	2-4 times
Perphenazine	Perphenazine	Oral (non-hospitalized) Oral (hospitalized)	12-18 mg/day; 16-64 mg/day	3 times 2-4 times
Pimozide	ORAP	Oral	7-10 mg/day	1-3 times
Prochlorperazine	Compro Prochlorperazine Prochlorperazine edisylate Prochlorperazine maleate	Oral IM IV	15-40 mg/day 15-40 mg/day 7.5-40 mg/day	3-4 times 3-4 times 3-4 times
Thioridazine	Thioridazine hydrochloride D/C: Thioridazine hydrochloride intensol, Mellaril, Mellaril-S	Oral	150-300 mg/day	2-3 times
Thiothixene	Navane Thiothixene D/C : Thiothixene hydrochloride, Thiothixene hydrochloride intensol	Oral	6-30 mg/day	2-3 times
Trifluoperazine	Trifluoperazine hydrochloride	Oral (non-hospitalized)	1-2 mg	2 times/day

D/C = discontinued according to FDA site; IM = intramuscular; IV = intravenous; mg = milligrams

Table O–2. Second-generation antipsychotics included in the CER

Generic name	Brand names(s)	Mode of administration	Recommended dose	Frequency
Aripiprazole	Abilify	Tablet Solution Orally disintegrating tablet Injection	10-15mg/day; Max 30mg/day	QD ≥2 hour between doses
Asenapine	Saphouris	Orally disintegrating tablet	Schizophrenia 5mg; BD 10mg	2 times/day 2 times/day
Clozapine	Clozapine Clozaril	Tablet Orally disintegrating tablet	300-450 mg/day	1-3 times/day
Iloperidone	Fanapt	Tablet	12-24mg/day	2 times/day
Olanzapine	Olanzapine Zyprexa, Zyprexa Zydis	Tablet Orally disintegrating tablet IM injection	Schizophrenia, 10mg/day; BD I 10-15mg/day	QD QD
Lurasidone	Latuda	Tablet	40-80mg/day	1-2 times/day
Paliperidone	Invega	Tablet extended release	6mg/day	QD in the AM
Quetiapine	Invega sustenna Quetiapine fumarate Seroquel Seroquel XR	IM injection Tablet Sustained release tablets	39-234 mg/day Schizophrenia, 150-750mg/day; BD (mania), 400-800mg/day; BD (depression), 300mg/day; BD (maintenance), 400-800mg/day	2 times/day 2 times/day 2 times/day 2 times/day QD at bedtime 2 times/day
Risperidone	Risperidone, Risperdal,	Tablet Solution Orally disintegrating tablet	Schizophrenia, 4-8mg/day; BD (mania), 1-6mg/day	1-2 times/day
Ziprasidone	Risperdal consta Ziprasidone hydrochloride Geodon	IM injection Capsules IM injection	25 mg/day Schizophrenia, up to 80mg; BD (manic/mixed, maintenance), 40-80mg; Agitation associated with Schizophrenia (IM), up to max 40mg/day	2 times/day 2 times/day 10mg may be injected q2 hour

BD = bipolar disease; IM = intramuscular; mg = milligrams; QD = every day; q2 = every two hours

Table O–3. First-generation antipsychotics: FDA status

Drug	FDA status	Indications	Age group approved for	Black box Warnings
Chlorpromazine	Approved 1974	Schizophrenia BP (mania) Hyperactivity Uncontrolled hiccups, nausea and vomiting	Adults Children (1-12 yrs)	Patients with cardiovascular disease or hx of seizures
Droperidol	Approved 1988	Antiemetic Acute psychosis	Adults Children (2-12 yrs) as antiemetic, no data on pediatric psychosis	QT prolongation (dose related) Torsades de pointes
Fluphenazine	Approved 1960	Schizophrenia BD (mania)	Adults Children >12yrs Not recommended for use in children under 12 yrs	Possible increased mortality in elderly with dementia-related psychosis Not approved for the treatment of dementia-related behavior problems.
Haloperidol	Approved 1986	Schizophrenia Tourette's Disorder	Adults Safety and effectiveness in pediatric patients <18 yrs have not been established	Increased mortality in elderly with dementia-related psychosis
Loxapine	Approved 1975	Schizophrenia	Adults Safety and effectiveness in pediatric patients <16 have not been established	Increased mortality in elderly with dementia-related psychosis
Perphenazine	Approved 1965	Schizophrenia	Adults Safety and effectiveness in pediatric patients have not been established	Increased mortality in elderly with dementia-related psychosis Children, adolescents, and young adults taking antidepressants are at increased risk of suicidal thinking

Table O–3. First-generation antipsychotics: FDA status (continued)

Drug	FDA status	Indications	Age group approved for	Black box Warnings
Pimozide	Approved 1984	Tourette's Disorder	Children and adults 8-53 yrs. Limited evidence in children <12 yrs Use and safety have not been evaluated in other childhood disorders, ORAP is not recommended for use in any condition other than Tourette's Disorder	Use of pimozide in tx of Tourette's Disorder involves different risk/benefit considerations than tx of other conditions. A decision to use ORAP should take into consideration Tardive Dyskinesia Neuroleptic Malignant Syndrome (NMS) Sudden, unexpected deaths in conditions other than Tourette's Disorder. May have tumorigenic potential.
Thiothixene	Approved 1967	Schizophrenia	Adults Safety and effectiveness in pediatric patients <12 years have not been established	Increased mortality in elderly with dementia-related psychosis
Trifluoperazine	Approved 1959	Schizophrenia	Adults and children (6-12 yrs)	Increased mortality in elderly patients with dementia-related psychosis
Prochlorperazine	Approved 1956	Schizophrenia Severe nausea and vomiting	Adults and children Children >2 yrs and >20 pounds	May cause tardive dyskinesia
Thioridazine	Approved 1962	Schizophrenia	Adults and children	Life-threatening pro-arrhythmic effect

BD = bipolar disease; IM = intramuscular; tx = treatment; yrs = years

Table O–4. Second-generation antipsychotics: FDA status

Drug	FDA status	Indications	Age group approved for	Black box warnings
Aripiprazole	Approved 2002	Schizophrenia	Adults & adolescents (13-17 yrs)	Increased mortality in elderly with dementia-related psychosis
	Approved 2004	BD(L) (manic/mixed) monotherapy or adjunctive to lithium or valproate	Adults & pediatrics (10-17 yrs)	Children, adolescents, and young adults taking antidepressants are at increased risk of suicidal thinking & behavior
	Approved 2007	Adjunctive tx of major depressive disorder	Adults Children (6-17 yrs) Adults with agitation associated with Schizophrenia or BD(L) (manic/mixed)	Leukopenia, Neutropenia, Agranulocytosis Not approved for behavior problems in older adults with dementia.
	Approved 2009	Autistic Disorder, Injection		
Aripiprazole	Approved 2002	Schizophrenia	Adults and adolescents (13-17 yrs)	Increased mortality in elderly with dementia-related psychosis
	Approved 2004	BD(L) (manic/mixed) monotherapy or adjunctive to lithium or valproate	Adults and pediatrics (10-17 yrs)	Children, adolescents, and young adults taking antidepressants are at increased risk of suicidal thinking and behavior
	Approved 2007	Adjunctive tx of major depressive disorder	Adults	Not approved for behavior problems in older adults with dementia.
		Injection	Adults with agitation associated with Schizophrenia or BD(L) (manic/mixed)	
Asenapine	Approved 2009	Acute Schizophrenia BD I (manic/mixed)	Adults Adults Pediatric use: safety & effectiveness not established in patients <18 yrs	Increased mortality in elderly with dementia-related psychosis
Clozapine,	Approved 1989	Treatment resistant Schizophrenia	Adults	1. agranulocytosis
	Approved 2002	Reduce the risk of suicidal behavior in younger schizophrenics.	Pediatric use: safety & effectiveness not established in patients <18 yrs	2. seizures 3. myocarditis 4. cardiovascular and respiratory effects, (respiratory and/or cardiac arrest). 5. increased mortality in elderly patients with dementia-related psychosis
Iloperidone	Approved 2009	Acute Schizophrenia	Adults	Increased mortality in elderly with dementia-related psychosis Not approved for patients with dementia-related psychosis.

BD = bipolar disease; tx = treatment; yrs = years

Table O–4. Second-generation antipsychotics: FDA status (continued)

Drug	FDA status	Indications	Age group approved for	Black box warnings
Lurasidone	Approved 2010	Schizophrenia	Adults	Increased mortality in elderly with dementia-related psychosis
Olanzapine	Approved 1996	Schizophrenia & BD(L) (manic/mixed)	Adults	Increased mortality in elderly with dementia-related psychosis Not approved for patients with dementia-related psychosis.
	Approved 2003: combined w fluoxetine	BD (depressive)	Adolescents (13-17 yrs), Schizophrenia & BD (manic/mixed)	
	Approved 2004 Approved 2009: combined w fluoxetine	BD(L) long-term tx Tx resistant depression	Pediatric use: safety & effectiveness not established in patients <13 yrs	
Paliperidone	Approved 2006	Schizophrenia Schizoaffective disorder	Adult Pediatric use: safety & effectiveness not established in patients <18 yrs	Increased mortality in elderly with dementia-related psychosis
Quetiapine	Approved 1997	Schizophrenia	Adults & adolescents (13-17 yrs) Adults, children & adolescents (10-17 yrs)	Increased mortality in elderly with dementia-related psychosis Increased risk of suicidal thinking and behavior Not approved for patients with dementia-related psychosis
	Approved 2004	BD (acute manic)	Adults	
	Approved 2008	BD (depression) BD (maintenance)	Adults	
Risperidone	Approved 1993	Schizophrenia	Adults & adolescents (13-17 yrs) Adults & adolescents (10-17 years)	Increased mortality in elderly with dementia-related psychosis
	Approved 2007	BD (manic/mixed)	Children (5-16 yrs)	
	Approved 2003	Irritability associated with autism		
Ziprasidone	Approved 2001	Schizophrenia BD (manic/mixed) BD (maintenance)	Adults Adults Adults Pediatric use: safety & effectiveness not established in patients <18 yrs	Increased mortality in elderly with dementia-related psychosis