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

This continuing education monograph examines the results of a comparative effectiveness review to compare individual first-generation antipsychotics with individual second-generation antipsychotics 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.
INTRODUCTION

In response to a request from the public about antipsychotics used to treat schizophrenia and bipolar disorder in adults (U.S. Food and Drug Administration-approved indications), a comparative effectiveness review (CER) was undertaken to examine what is known about the comparative effectiveness, benefits, and adverse effects of these drugs. CERs are comprehensive systematic reviews of the literature that usually compare two or more types of treatment, such as different drugs or adding a second drug to usual care for the same disease. The literature included in this review was identified in searches for trials and studies that explicitly compared first-generation with second-generation antipsychotics for the approved indications of schizophrenia and bipolar disorder in adults ages 18–64. Searches were conducted for studies published through July 2011.

Studies of antipsychotics used in treating dementia, an off-label indication, were not included in the review. The systematic review included 114 clinical studies of schizophrenia and 12 studies of bipolar disorder published up to July 2011. The full report of research evidence is available at the Agency for Healthcare Research and Quality’s Effective Healthcare website (http://effectivehealthcare.ahrq.gov). This monograph is a summary of the full report. It is provided to inform discussions of options with patients and their caregivers and to assist in decision making along with consideration of a patient’s values and preferences. Reviews of evidence should not be construed to represent clinical recommendations or guidelines.

LEARNING OBJECTIVES

✓ Use evidence for comparative benefit or lack of benefit to support treatment of first- and second-generation antipsychotics when determining treatment for patients with schizophrenia or bipolar disorder.

✓ Compare and contrast the adverse effects of first- and second-generation antipsychotics as used in treatment of patients with schizophrenia or bipolar disorder.

✓ Identify current gaps in the knowledge and evidence base.

WHAT’S INSIDE

- Background to antipsychotics.
- Introduction to schizophrenia and bipolar disorder.
- Methodology of the CER.
- Key Questions addressed.
- Results of the CER.
- Conclusions about the comparative benefits and harms of first generation versus second generation antipsychotics.
- What to discuss with patients and caregivers.

AHRQ COMPARATIVE EFFECTIVENESS REVIEW PROCESS

The Agency for Healthcare Research and Quality (AHRQ) consider topics for systematic review that are nominated through a public process, including submissions from health care professionals, professional organizations, the private sector, policymakers, members of the public, and others. A systematic review of all relevant clinical studies is conducted by independent researchers, funded by the Agency, to synthesize the evidence in a report in order to summarize what is known and not known about the clinical issue. The research questions and the results of the report are subject to expert input and peer review, and are posted for public comment. The results of these reviews are then compiled into Clinician Research Summaries and Consumer Research Summaries for use in decision making and in discussions with patients.
**BACKGROUND**

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.²³

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 (see Figure 1).⁴ 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.⁴

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 (see Table 1). The major differences between these three FGAs are their potency (low to high, respectively) and side-effect profiles.

### Table 1. First Generation Antipsychotics Approved in the U.S.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>Thorazine</td>
</tr>
<tr>
<td>Droperidol</td>
<td>Inapsine</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>Permitil, Proltin</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Haldol</td>
</tr>
<tr>
<td>Loxapine</td>
<td>Loxitane</td>
</tr>
<tr>
<td>Perphenazine²</td>
<td>Trilafon</td>
</tr>
<tr>
<td>Pimozide</td>
<td>Orap</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>Compazine</td>
</tr>
<tr>
<td>Thoridazine⁴</td>
<td>Mellaril</td>
</tr>
<tr>
<td>Thiothixene</td>
<td>Navane</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>Stelazine</td>
</tr>
</tbody>
</table>

*Included in the review.

† Most frequently prescribed FGAs as of 2012.

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 (see Table 2).⁵

Individuals taking an antipsychotic may stop taking their medication for a number of reasons, including side effects and lack of improvement in their symptoms.⁶ As a result, ongoing evaluations of drug efficacy and models of patient decision making are essential.
Schizophrenia and Related Psychoses

Schizophrenia is a heterogeneous syndrome that includes disturbances in language, perception, cognition, social relatedness, and volition. Schizophrenia is characterized by positive symptoms (i.e., delusions and hallucinations), negative symptoms (i.e., passive or apathetic social withdrawal and blunted affect) and general psychopathology (i.e., preoccupation, lack of insight, and motor retardation) (see Figure 2). Onset of symptoms typically occurs in late adolescence or early adulthood, with approximately 0.4 to 0.6 percent of the population affected worldwide. 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 (if any) to the drug and its side-effect profile.

In the treatment of schizophrenia, FGAs act on the dopaminergic system by blocking the dopamine type 2 (D2) receptors. 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). Although these antipsychotics are effective against the positive symptoms of schizophrenia, they have been considered to be ineffective in treating negative symptoms. Such symptoms particularly play a critical role in producing the severe social and vocational disabilities experienced by many patients with schizophrenia.

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. SGAs have also been associated with metabolic side effects (e.g., elevated lipids and development of type II diabetes mellitus), 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.

### Table 2. Second Generation Antipsychotics Approved in the US

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>Abilify</td>
</tr>
<tr>
<td>Asenapine</td>
<td>Saphris</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Clozaril</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>Fanapt</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>Latuda</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Zyprexa</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>Invega</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Seroquel</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Risperdal</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Geodon</td>
</tr>
<tr>
<td>Olanzapine plus fluoxetine</td>
<td>Symbax</td>
</tr>
</tbody>
</table>

† Most frequently prescribed SGAs as of 2012.
‡ Combination therapy

### Figure 2. Symptoms Associated with Schizophrenia

**Positive Symptoms**
- Delusions
- Hallucinations

**Negative Symptoms**
- Passive/apathetic social withdrawal
- Blunted affect

**General Psychopathology**
- Preoccupation
- Lack of insight
- Motor retardation
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) (see Table 3). 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 of 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).

<table>
<thead>
<tr>
<th>Table 3. Scales Assessing Core Symptoms of Schizophrenia</th>
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<tbody>
<tr>
<td><strong>Scale</strong></td>
</tr>
<tr>
<td>BPRS</td>
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<td></td>
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<tr>
<td>CGI</td>
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<td>PANSS</td>
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<td>SANS</td>
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<td>SAPS</td>
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</table>

BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impression; PANSS, Positive and Negative Symptom Scale; SANS, Scale for the Assessment of Negative Symptoms SAPS, Scale for the Assessment of Positive Symptoms
Bipolar Disorder

Bipolar disorder is characterized by severe fluctuations in mood, activity, thought, and behavior. Bipolar I disorder involves one or more episodes of mania or mixed mood, which are associated with a variety of symptoms as seen in Figure 3. 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. The APA (2002) recommends the following treatment plan: 1) polytherapy (lithium or valproate in conjunction with an antipsychotic) for severe manic or mixed episodes; and 2) monotherapy (lithium, valproate, or an antipsychotic) for less ill patients. The APA recommendations state that SGAs are preferred over FGAs because of their side-effect profile.

Table 4. Core Illness Symptom Measurement Scales for Bipolar Disorder

<table>
<thead>
<tr>
<th>Scale</th>
<th>Description</th>
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<tbody>
<tr>
<td>CGI-BP</td>
<td>Rates severity of manic and depressive episodes</td>
</tr>
<tr>
<td>GAS</td>
<td>Single-item scale</td>
</tr>
<tr>
<td>YMRS</td>
<td>11-item scale</td>
</tr>
</tbody>
</table>

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) (see Table 4). CGI–BP was developed for rating the severity of manic and depressive episodes and the degree of change from the immediately preceding phase and from the worst phase of illness. GAS is a single-item scale for evaluating overall patient functioning (i.e., 1 (sickest person) to 100 (healthiest person) divided into 10 equal intervals). The YMRS scale is an 11-item, multiple-choice, diagnostic questionnaire for psychiatrists to measure the severity of manic episodes. Items include elevated mood, increased motor activity, sexual interest, sleep, irritability, speech (rate and amount), thought disorder, thought content, aggressive behavior, appearance, and insight.
The following 5 Key Questions were investigated in the report:

**Key Question 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.

**Key Question 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.

**Key Question 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?

AEs included:
a) Overall adverse events.
b) Specific adverse events:
   i. **Major:** mortality, cerebrovascular disease–related events, development of diabetes mellitus, diabetic ketoacidosis, neuroleptic malignant syndrome, seizures, tardive dyskinesia, cardiomyopathies and cardiac arrhythmias, agranulocytosis, suicide-related behaviors, and death by suicide.
   ii. **General:** extrapyramidal symptoms, 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.

The full systematic review on the effects of FGAs compared with SGAs on core symptoms, functional outcomes, healthcare utilization, adverse events, and other outcomes can be found on the Agency for Healthcare Research and Quality’s Effective Healthcare Website.¹

Available at: [http://www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov)
Key Question 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.

Key Question 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.

INCLUSION CRITERIA

Studies that evaluated the participants, interventions, comparators, and outcomes as listed in Table 5, were included for review. The focus of the report was 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. Studies which included pediatric or geriatric populations were not included in this systematic review. Interventions or comparators (FGAs or SGAs) which had not received approval from the FDA at the time of the systematic review were also not included.

Table 5. Inclusion Criteria for the Systematic Review

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
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</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Adults (age 18 to 64 years) with schizophrenia or related psychoses or bipolar disorder</td>
</tr>
<tr>
<td>Interventions</td>
<td>Any currently available FDA-approved FGA (See Table 1)</td>
</tr>
<tr>
<td>Comparators</td>
<td>Any currently available FDA-approved SGA (See Table 2)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Outcomes listed in the KQ; cohort studies must report on ≥1 SAE</td>
</tr>
<tr>
<td>Timing</td>
<td>All followup periods for trials; cohort studies ≥2 years followup</td>
</tr>
<tr>
<td>Setting</td>
<td>All settings</td>
</tr>
</tbody>
</table>

FDA, Food and Drug Administration; FGA, first-generation antipsychotic; KQ, Key Question; SAE, serious adverse event; SGA, second-generation antipsychotic
STRENGTH OF EVIDENCE

Throughout this monograph, strength-of-evidence ratings are assigned to findings of the systematic review. Strength of evidence is typically assigned to reviews of medical treatments after assessing four domains: risk of bias, consistency, directness, and precision. Available evidence for each Key Question was assessed for each of these four domains; these assessments were then used to assign the overall strength of evidence for each Key Question, as recommended in the AHRQ Methods Guide. Table 6 provides the ratings and corresponding definitions.

A “High” strength of evidence grade is assigned if further research is very unlikely to change the confidence in the estimate of effect, based on consistent findings from low risk of bias studies that directly address the populations and outcomes of interest and provide precise estimates of effects. A “Moderate” grade is assigned if further research may change the confidence in the estimate of effect and may change the estimate, due to methodological limitations, imprecision, indirectness, or inconsistency. A “Low” strength of evidence grade is assigned if further research is likely to change the confidence in the estimate of effect and is likely to change the estimate. And an “Insufficient” grade is assigned if evidence either is unavailable or does not permit estimation of an effect.

Table 6. Strength of Evidence Ratings

<table>
<thead>
<tr>
<th>Grade</th>
<th>Rating</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>🌟🌟🌟🌟🌟</td>
<td>Further research is very unlikely to change the confidence in the estimate of effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>🌟🌟🌟🌟</td>
<td>Further research may change the confidence in the estimate of effect and may change the estimate.</td>
</tr>
<tr>
<td>Low</td>
<td>🌟🌟🌟</td>
<td>Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.</td>
</tr>
<tr>
<td>Insufficient</td>
<td>🌟🌟</td>
<td>Evidence either is unavailable or does not permit estimation of an effect.</td>
</tr>
</tbody>
</table>

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 randomized controlled trials (RCTs), 2 nonrandomized controlled trials, and 2 retrospective cohort studies. The studies were published between 1974 and 2010. The majority of studies were multicenter (56 percent) and involved inpatients (50 percent), and 46 percent of studies were conducted in North America. The number of participants in the studies ranged from 10 to 95,632. The average age of study participants ranged from 21 to 50 years. The length of follow-up ranged from <1 day to 22 years. Seventy percent of studies had some form of support from the pharmaceutical industry. Included studies are listed at the end of this monograph.

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.

Other complementary reports investigating different SGAs, the off-label use of antipsychotics, and FGAs versus SGAs in the pediatric population can be found on the Agency for Healthcare Research and Quality’s Effective Healthcare Website.

Available at: http://www.effectivehealthcare.ahrq.gov
Key Question 1. Core Illness Symptoms

The findings for core illness symptoms are presented for schizophrenia and schizophrenia-related disorders in Table 7 and bipolar disorder in Table 8. Comparisons and outcomes for which there was insufficient strength of evidence to draw a conclusion (e.g., evidence from single trials) are not displayed in the tables. The strength of 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.

Schizophrenia or Schizophrenia-Related Psychoses

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 strength of evidence).

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 strength of evidence was low for positive outcomes, global ratings, and total scores; the strength of evidence was insufficient for general psychopathology. Aripiprazole showed benefits for negative symptoms (moderate strength of evidence).

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 strength of evidence). 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 strength of evidence); one study showed benefits for clozapine on the Clinical Global Impression–Improvement (CGI–I) and Clinical Global Impression–Severity (CGI–S) scales (insufficient strength of evidence).

Twenty-seven studies provided data on core illness symptoms for haloperidol versus olanzapine. No differences were found for positive symptoms (low strength of evidence). Olanzapine was favored for negative symptoms (moderate strength of evidence). 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 strength of evidence 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 strength of evidence 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 strength of evidence across outcomes ranged from insufficient to moderate.
Table 7. Summary of the Strength of Evidence for Core Illness Symptoms in Schizophrenia or Schizophrenia-Related Psychoses

<table>
<thead>
<tr>
<th>Comparison</th>
<th>SoE</th>
<th>Summary (Number of Studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive Symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol vs. aripiprazole</td>
<td>○○○</td>
<td>No significant difference for PANSS (2 RCTs).</td>
</tr>
<tr>
<td>Haloperidol vs. clozapine</td>
<td>○○○</td>
<td>No significant difference for PANSS (2 RCTs).</td>
</tr>
<tr>
<td>Haloperidol vs. olanzapine</td>
<td>○○○</td>
<td>No difference for PANSS (14 RCTs) or SAPS (2 RCTs).</td>
</tr>
<tr>
<td>Haloperidol vs. quetiapine</td>
<td>○○○</td>
<td>No significant difference for PANSS (4 RCTs).</td>
</tr>
<tr>
<td>Haloperidol vs. risperidone</td>
<td>○○○</td>
<td>No difference for PANSS (20 RCTs) or SAPS (2 RCTs).</td>
</tr>
<tr>
<td><strong>Negative Symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol vs. aripiprazole</td>
<td>○●○</td>
<td>Significant difference favoring aripiprazole for PANSS (3 RCTs).</td>
</tr>
<tr>
<td>Haloperidol vs. clozapine</td>
<td>○○○</td>
<td>No significant difference for PANSS (2 RCTs) or SANS (2 RCTs).</td>
</tr>
<tr>
<td>Haloperidol vs. olanzapine</td>
<td>○●○</td>
<td>Significant difference favoring olanzapine for PANSS (14 RCTs)</td>
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<tr>
<td></td>
<td></td>
<td>and SANS (5 RCTs).</td>
</tr>
<tr>
<td>Haloperidol vs. quetiapine</td>
<td>○○○</td>
<td>No significant difference for PANSS (4 RCTs).</td>
</tr>
<tr>
<td>Haloperidol vs. risperidone</td>
<td>○○○</td>
<td>Significant difference favoring risperidone for SANS (moderate SoE, 4 RCTs). No significant difference for PANSS (low SoE, 20 RCTs).</td>
</tr>
<tr>
<td>Haloperidol vs. ziprasidone</td>
<td>○○○</td>
<td>No significant difference for PANSS (2 RCTs).</td>
</tr>
<tr>
<td><strong>General Psychopathology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol vs. clozapine</td>
<td>○○○</td>
<td>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).</td>
</tr>
<tr>
<td>Haloperidol vs. olanzapine</td>
<td>○○○</td>
<td>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).</td>
</tr>
<tr>
<td>Haloperidol vs. quetiapine</td>
<td>○○○</td>
<td>No significant difference for CDS–S (2 RCTs) or PANSS (4 RCTs).</td>
</tr>
<tr>
<td><strong>Global Ratings and Total Scores</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine vs. clozapine</td>
<td>○○○</td>
<td>Significant difference favoring clozapine for BPRS (6 RCTs).</td>
</tr>
<tr>
<td>Haloperidol vs. aripiprazole</td>
<td>○○○</td>
<td>No significant difference for BPRS (3 RCTs) or CGI–S (5 RCTs).</td>
</tr>
<tr>
<td>Haloperidol vs. clozapine</td>
<td>○○○</td>
<td>No difference for BPRS (4 RCTs) or PANSS (3 RCTs).</td>
</tr>
<tr>
<td>Haloperidol vs. olanzapine</td>
<td>○○○</td>
<td>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).</td>
</tr>
<tr>
<td>Haloperidol vs. quetiapine</td>
<td>○○○</td>
<td>No difference for BPRS (13 RCTs), CGI–I (3 RCTs), CGI–S (8 RCTs), or PANSS (20 RCTs).</td>
</tr>
<tr>
<td>Haloperidol vs. risperidone</td>
<td>○○○</td>
<td>No significant difference for BPRS (4 RCTs), CGI–S (4 RCTs), GAF (3 RCTs), or PANSS (4 RCTs).</td>
</tr>
</tbody>
</table>

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; 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.
Thirty-one studies provided data on core illness symptoms for haloperidol versus risperidone. There were no differences for positive symptoms (low strength of evidence). Risperidone was favored for negative symptoms based on the Scale for the Assessment of Negative Symptoms (SANS) (moderate strength of evidence); in contrast, no difference for negative symptoms was found based on PANSS (low strength of evidence). No differences were found for any of the six measures used to assess general psychopathology (low to insufficient strength of evidence). 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 strength of evidence).

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 strength of evidence). No studies provided data on positive symptoms.

**Bipolar Disorder**

A total of 12 studies included patients with bipolar disorder. A summary of the findings are displayed in Table 8. 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 strength of evidence). 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 strength of evidence). 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 strength of evidence). Single studies compared chlorpromazine versus clozapine and haloperidol versus quetiapine and ziprasidone (insufficient strength of evidence).

**Table 8. Summary of the Strength of Evidence for Core Illness Symptoms in Bipolar Disorder**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>SoE</th>
<th>Summary (Number of Studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mood (Mania)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol vs. aripiprazole</td>
<td>⬤ ● ●</td>
<td>No significant difference in YMRS (2 RCTs).</td>
</tr>
<tr>
<td>Haloperidol vs. olanzapine</td>
<td>⬤ ● ●</td>
<td>No significant difference in YMRS (2 RCTs).</td>
</tr>
<tr>
<td>Haloperidol vs. risperidone</td>
<td>⬤ ● ●</td>
<td>No significant difference in YMRS (3 RCTs).</td>
</tr>
<tr>
<td><strong>Mood (Depression)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol vs. aripiprazole</td>
<td>⬤ ● ●</td>
<td>No significant difference in MADRS (2 RCTs).</td>
</tr>
<tr>
<td><strong>Global Ratings and Total Scores</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol vs. aripiprazole</td>
<td>⬤ ● ●</td>
<td>No significant difference in CGI–BP (2 RCTs).</td>
</tr>
</tbody>
</table>

CGI-BP, Clinical Global Impression–Bipolar version; MADRS, Montgomery-Asberg Depression Rating Scale; SoE, strength of evidence; YMRS, Young Mania Rating Scale
Key Question 2. Functional Outcomes and Health Care System Utilization

Schizophrenia or Schizophrenia-Related Psychoses

Results for functional outcomes were available from nine head-to-head comparisons in studies of patients with schizophrenia or schizophrenia-related psychoses. A summary of the evidence can be found in Table 9. 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.

Table 9. Summary of Evidence for Functional Outcomes and Health Care System Utilization for Schizophrenia or Schizophrenia-Related Psychoses

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Summary (Number of Studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Functional Outcomes</strong></td>
<td></td>
</tr>
<tr>
<td>Fluphenazine vs. quetiapine</td>
<td>No significant difference for sexual dysfunction or improvement on treatment (1 RCT).</td>
</tr>
<tr>
<td>Fluphenazine vs. risperidone</td>
<td>No significant difference for sexual dysfunction or improvement on treatment (1 RCT).</td>
</tr>
<tr>
<td>Haloperidol vs. olanzapine</td>
<td>No significant difference for positive urine cocaine toxicology (1 RCT) or sexual dysfunction (1 RCT).</td>
</tr>
<tr>
<td>Haloperidol vs. quetiapine</td>
<td>No significant difference for sexual dysfunction (1 RCT).</td>
</tr>
<tr>
<td>Haloperidol vs. risperidone</td>
<td>No significant difference for economic independence (1 RCT) or attitude regarding drugs (1 RCT).</td>
</tr>
<tr>
<td>Haloperidol vs. ziprasidone</td>
<td>No difference for sexual dysfunction (1 RCT).</td>
</tr>
<tr>
<td>Perphenazine vs. quetiapine</td>
<td>No significant difference in patients with paid employment (1 RCT).</td>
</tr>
<tr>
<td>Perphenazine vs. risperidone</td>
<td>No significant difference in patients with paid employment (1 RCT).</td>
</tr>
<tr>
<td>Perphenazine vs. ziprasidone</td>
<td>No significant difference in patients with paid employment (1 RCT).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Health Care System Use</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine vs. clozapine</td>
<td>No significant difference in rates of hospitalization or rehospitalization (1 RCT).</td>
</tr>
<tr>
<td>Haloperidol vs. clozapine</td>
<td>No significant difference in mean hospital bed days (1 RCT).</td>
</tr>
<tr>
<td>Haloperidol vs. olanzapine</td>
<td>No significant difference in mean hospital bed days or rates of hospitalization or rehospitalization (1 RCT).</td>
</tr>
<tr>
<td>Haloperidol vs. quetiapine</td>
<td>No significant difference in rates of hospitalization or rehospitalization (1 RCT).</td>
</tr>
<tr>
<td>Haloperidol vs. risperidone</td>
<td>No significant difference in rates of hospitalization or rehospitalization (3 RCTs).</td>
</tr>
<tr>
<td>Haloperidol vs. ziprasidone</td>
<td>No significant difference in rates of hospitalization or rehospitalization (2 RCTs).</td>
</tr>
<tr>
<td>Perphenazine vs. olanzapine</td>
<td>No significant difference in rates of hospitalization or rehospitalization (1 RCT).</td>
</tr>
<tr>
<td>Perphenazine vs. quetiapine</td>
<td>No significant difference in rates of hospitalization or rehospitalization (1 RCT).</td>
</tr>
<tr>
<td>Perphenazine vs. risperidone</td>
<td>No significant difference in rates of hospitalization or rehospitalization (1 RCT).</td>
</tr>
<tr>
<td>Perphenazine vs. ziprasidone</td>
<td>No significant difference in rates of hospitalization or rehospitalization (1 RCT).</td>
</tr>
</tbody>
</table>

RCT, randomized controlled trial
**Bipolar Disorder**

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. No study evaluated health care system utilization among people with bipolar disorder.

**KQ3. Medication-Associated Adverse Events and Safety**

The findings for the adverse events that were deemed most clinically important are summarized in Table 10. The strength of 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 strength of evidence for these comparisons was low; suggesting that further research may change the results and change our confidence in the results.

Data were also recorded for general measures of adverse events and specific adverse events by physiological system (e.g., cardiovascular, endocrine); these outcomes were not assessed for strength of evidence. For general measures of adverse events, significant differences were found in the incidence of patients with adverse events and withdrawals due to adverse events for several comparisons. Most often, the comparison included haloperidol, and the risk was consistently higher for the FGA. The most frequently reported adverse events with significant differences were in the category of extrapyramidal symptoms, and they most often involved a comparison with haloperidol. In the vast majority of cases, the SGA had the preferred adverse event profile for extrapyramidal symptoms.

Due to the relatively short follow-up of the included studies, persistence and reversibility of adverse events was not examined. Study follow-up periods averaged 8 weeks. It is unclear whether adverse event persistence and reversibility of several significant adverse events could be reasonably examined during this time period (e.g., metabolic conditions, body mass index or weight, and cardiovascular measures).

**Table 10. Summary of the Strength of Evidence for Medication-Associated Adverse Events and Safety**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>SoE</th>
<th>Summary (Number of Studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine vs. clozapine</td>
<td>⬤  ⬤  ⬤</td>
<td>No significant difference (2 RCTs, length of f/u: 52 and 208 wks)</td>
</tr>
<tr>
<td>Haloperidol vs. aripiprazole</td>
<td>⬤  ⬤  ⬤</td>
<td>No significant difference (2 RCTs, length of f/u: 24 hrs for both)</td>
</tr>
<tr>
<td><strong>Metabolic Syndrome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol vs. olanzapine</td>
<td>⬤  ⬤  ⬤</td>
<td>No significant difference (2 RCTs, length of f/u: 6 and 12 wks)</td>
</tr>
</tbody>
</table>

f/u, follow-up; RCT, randomized controlled trial; SoE, strength of evidence
Key Question 4. Other Outcomes

Schizophrenia or Schizophrenia-related Psychoses

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).

Bipolar Disorder

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.

KQ5. Subgroups

Schizophrenia or Schizophrenia-Related Psychoses

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.

Bipolar Disorder

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.

CONCLUSIONS

This monograph provides a summary of the evidence on the comparative effectiveness and safety of individual FDA-approved FGAs compared with individual FDA-approved SGAs as reported in a comparative effectiveness review commissioned by the Agency for Healthcare Research and Quality. The full report provides extensive details in terms of study characteristics and methodological features, which may help inform individual treatment decisions.

Few differences were found in comparisons of the FGA haloperidol with the SGAs. Clinical significance, defined as at least a 20 percent difference between interventions on an individual scale, was rarely found. Numerous studies provided data on core illness symptoms; however, many different scales were used to assess outcomes, which limited the quantitative pooling of data. The strength of evidence 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.

The systematic review included cohort studies with a minimum follow-up of 2 years in order to identify the adverse events of most clinical importance, including diabetes mellitus, mortality, tardive dyskinesia, and major metabolic syndrome (i.e., a group of risk factors that increase risk of heart disease and other health problems). Only two studies with long-term follow-up were identified; hence, evidence on these important adverse events is limited and urgently needed. A variety of adverse events associated with numerous physiological systems were reported. The adverse events most often reported involved extrapyramidal symptoms, 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.

**Comparative Effectiveness of FGAs and SGAs in Adults With Schizophrenia**

When compared with haloperidol, olanzapine may provide clinically significant, greater improvement in negative symptoms (PANSS; SANS), total scores (PANSS), and measures of general psychopathology (HAM-D; MADRS). ●●○

When compared with haloperidol, risperidone yields lower relapse rates and olanzapine provides better response and remission rates. (Strength of Evidence Not Rated)

Positive symptoms include hallucinations and delusions. Negative symptoms include social withdrawal, apathy, and blunted affect.

HAM-D, Hamilton Depression Scale; MADRS, Montgomery-Asberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; SANS, Scale for the Assessment of Negative Symptoms

**Comparative Effectiveness of FGAs and SGAs in Adults With Bipolar Disorder**

No statistically significant differences in symptoms of mania, depression, or global impressions of bipolar disorder were noted in comparisons of patients treated with haloperidol or aripiprazole. ● ○ ○

No statistically significant difference in total score for mania assessment was found when patients treated with haloperidol were compared with those treated with olanzapine or risperidone. ● ○ ○

Haloperidol produced lower relapse rates than aripiprazole and provided better response rates than ziprasidone. (Strength of Evidence Not Rated)
Comparative Adverse Effects of FGAs and SGAs

For most comparisons, the evidence about the adverse events of greatest clinical importance (diabetes mellitus, tardive dyskinesia, metabolic syndrome, and mortality) is insufficient to permit conclusions about differences in risk between FGAs and SGAs. Study durations may be inadequate to reveal differences reported from longer term clinical experience. ○ ○ ○

Diabetes Mellitus and Metabolic Syndrome

No statistically significant difference in risk of metabolic syndrome is found in comparisons of olanzapine and haloperidol. ● ○ ○

Mortality

There are no significant differences in risk of mortality in comparisons of chlorpromazine and clozapine or between haloperidol and aripiprazole. ● ○ ○

NOTE: This report focused specifically on adults age 18-64.

Other Findings

Functional and Other Outcomes

The variety of functional measures assessed across the studies prevents analysis and firm conclusions about comparative effectiveness for patient functioning (e.g., sleep characteristics, memory, verbal fluency, attention, neurocognitive testing).

Outcome Modifiers

In treatment of schizophrenia, the most commonly performed subgroup analysis was for the effect of race on treatment resistance. No notable differences from the overall findings were found for subgroups.

For bipolar disorder, subgroup analysis was by disorder subtype. For bipolar 1 disorder, haloperidol was found to be more effective than ziprasidone for core illness symptoms (Young Mania Rating Scale and total score).

Gaps in Knowledge

- Older adults, minorities, patients with comorbid substance abuse, and the most seriously ill patients were under-represented in the studies, which were highly selective in patient enrollment. Thus the studies reported here are more likely to show consistency of benefit and reduced risk of adverse effects.
- The evidence about the influence of drug dose, formulation (e.g., long-acting injectable forms), polypharmacy, patient age, and comorbidities is inadequate to inform decision making.
- A consensus is needed on outcomes that demonstrate patient functioning and well-being by using treatment goals that are important to patients.
- More head-to-head trials are needed to compare currently approved FGAs and SGAs for treating bipolar disorder.
- More studies are needed to evaluate long-term (2 years or more) effectiveness.
WHAT TO DISCUSS WITH PATIENTS

There are a variety of topics patients and providers should discuss when deciding if an antipsychotic medication is appropriate.

Patient and providers may want to consider whether a medication’s ability to help is worth the risk of a serious side effect. Patients should be made aware that not every person responds in the same way to each medicine and thus it may require trying several medicines before finding the most effective one.

Patients will want to consider the possible benefits of taking an antipsychotic medicine; which antipsychotic medicine might work best; the possible side effects; the risk of a serious side effect; what to look out for in side effects so treatment can be administered or the medication can be changed; patient values and preferences regarding treatment; and the cost of medication.

Issues you should discuss with your patients and their caregivers regarding antipsychotic medications include the items listed below.

- The potential benefits of antipsychotics
- The risks of adverse effects, including irreversible extrapyramidal symptoms, when antipsychotics are used
- The effect of medications on other medical conditions and possible interactions with other medications
- The trade-offs between benefits and adverse effects
- The roles antipsychotics may play as part of a broader treatment regimen
- The importance of taking their medicine consistently and not discontinuing it without medical advice
- Patient and caregiver preferences and values regarding treatment

FIGURE 4. RESOURCE FOR PATIENTS

Antipsychotic Medicines for Treating Schizophrenia and Bipolar Disorder is a free companion to this monograph. It can help adults talk with their health care professionals about antipsychotic medications for schizophrenia and bipolar disorder.
First Generation Versus Second Generation Antipsychotics in Adults: Comparative Effectiveness is provided to inform discussions with patients of options and to assist in decision making along with consideration of a patient's values and preferences.

ORDERING INFORMATION

For electronic copies of Antipsychotic Medicines for Treating Schizophrenia and Bipolar Disorder, the Clinician Research Summary and the full comparative effectiveness review on antipsychotics visit www.effectivehealthcare.ahrq.gov/antipsychotics-adult.cfm. To order free print copies, call the AHRQ Publications Clearinghouse at 800-358-9295.

SOURCE

The information in this summary is based on First-Generation Versus Second-Generation Antipsychotics in Adults: Comparative Effectiveness, Comparative Effectiveness Review No. 63, prepared by the University of Alberta Evidence-based Practice Center under Contract No. HHSA 290-2007-10021 for the Agency for Healthcare Research and Quality, August 2012. Available at www.effectivehealthcare.ahrq.gov/antipsychotics-adult.cfm.
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