Effective Health Care Program

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

Research Focus for Clinicians

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 systematic review was undertaken to examine what is known about the comparative effectiveness, benefits, and adverse effects of these drugs. 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 www.effectivehealthcare.ahrq.gov/antipsychotics-adult.cfm. This is a summary of the full report. It is provided to inform discussions of options with patients and their caregivers and to assist in decisionmaking along with consideration of a patient's values and preferences. Reviews of evidence should not be construed to represent clinical recommendations or guidelines.

Background

Antipsychotics can be organized into two classes—based on the timeline of their development, their pharmacology, and their adverse effects profiles—either as first-generation (FGA) or second-generation (SGA) or as typical or atypical. Although FGAs successfully treat symptoms, they are associated with significant adverse effects (e.g., dry mouth, sedation, extrapyramidal symptoms, and tardive dyskinesia), some of which are irreversible. The SGAs, developed in response to the difficulties of managing adverse effects, are not as strongly associated with neuromotor side effects but are associated with elevated risks of dyslipidemia, significant weight gain, metabolic syndrome, and diabetes mellitus. Individuals taking antipsychotics of either class may discontinue use due to adverse effects, lack of improvement in symptoms, or both. A synthesis of the evidence from the clinical literature that directly compares the FGAs and SGAs may inform treatment choices that balance benefits and adverse effects for adults with psychosis, mania, or bipolar disorder.

Conclusions

Few clinically important differences are found between FGAs and SGAs in core illness symptoms or response and remission rates in treating schizophrenia or bipolar disorder. No class effects for either benefits or adverse effects of antipsychotics can be assumed based on the evidence to date. Differences between the antipsychotic drugs may be clinically meaningful for individual patients.

The evidence base about comparative effectiveness and safety is inadequate for informed decisionmaking because of sparse data, imprecise effect estimates, and concerns about study usefulness (high risk of bias, wide variety of outcome measures).

For treatment of schizophrenia, most head-to-head evaluations compared haloperidol with the SGAs and found no statistically or clinically significant differences. Only olanzapine demonstrated a clinically significant advantage over haloperidol in improving negative symptoms, total scores, and the general psychopathology of schizophrenia. For mania and mixed episodes of bipolar disorder, limited evidence of low strength suggests similar benefits from haloperidol and aripiprazole for mania, depression, and global scores, and olanzapine and risperidone are similar to haloperidol in effect on mania symptoms.

There is little evidence from head-to-head comparisons of FGAs and SGAs to estimate differences in risk for the most clinically important adverse effects: mortality, diabetes mellitus, tardive dyskinesia, and metabolic syndrome. Clinical studies are still lacking to describe comparative long-term efficacy and safety, optimal dosage and duration of treatment, and risks and benefits in patient subpopulations.

Clinical Bottom Line

Comparative Effectiveness of FGAs and SGAs in Adults With Schizophrenia

- Few differences are 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. See Table 1 for a description of comparative effectiveness studies, results, and strengths of evidence.

(Continued on next page)

Strength of Evidence Scale

High:	●●●	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate:	●●○	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low:	●○○	Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
Insufficient:	○○○	Evidence either is unavailable or does not permit a conclusion.

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Clinical Bottom Line *(Continued)*

Comparative Effectiveness of FGAs and SGAs in Adults With Schizophrenia *(Continued)*	Comparative Effectiveness of FGAs and SGAs in Adults With Bipolar Disorder
■ When compared with haloperidol (Haldol®), olanzapine (Zyprexa®) 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)	**Studies 6 to 12 weeks in duration evaluated patients with mania or mixed episodes, with these outcomes:** ■ 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. ●○○ ■ In bipolar disorder, haloperidol produced lower relapse rates than aripiprazole and provided better response rates than ziprasidone. (Strength of Evidence Not Rated)

Positive symptoms = hallucinations and delusions. Negative symptoms = 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

Table 1. Comparative Effectiveness Trials of FGAs and SGAs in Treating the Core Illness Symptoms of Schizophrenia

A summary of the comparisons evaluated in the systematic review is presented in the table below. Comparisons that were statistically significant but not clinically significant are noted in the footnotes. Unless indicated, no statistically significant difference was found in the analysis, or the evidence was insufficient to permit conclusions. Only olanzapine demonstrated a clinically significant, greater benefit in comparisons with haloperidol.

SGAs*	FGAs*			
	Chlorpromazine	Fluphenazine	Haloperidol	Perphenazine[†]
Aripiprazole			8[1]	1**
Clozapine	12[2]		11[††]	
Olanzapine	1**	2**	35[3]	2**
Quetiapine	1**	1**	11[4]	1**
Risperidone		1**	39[5]	2**
Ziprasidone	1**		9[††]	1**

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

Abbreviations: ABS = Agitated Behavior Scale; ACES = Agitation-Calmness Evaluation Scale; BPRS = Brief Psychiatric Rating Scale; CDS-S = Calgary Depression Scale of Schizophrenia; CGI-I = Clinical Global Impression–Improvement; HAM-A = Hamilton Anxiety Scale; HAM-D = Hamilton Depression Scale; MADRS = Montgomery-Asberg Depression Rating Scale; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; YMRS = Young Mania Rating Scale

  * Comparisons not shown in this table are: asenapine versus haloperidol (1 RCT); clozapine versus trifluoperazine and thoridazine (1 RCT each); risperidone versus thoridazine (1 RCT). The evidence from these studies is insufficient to permit conclusions.

  [†] The perphenazine comparisons include the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) trial.

** Evidence was insufficient to permit conclusions from these comparisons.

[††] Comparisons found either no statistically significant difference (●○○) or insufficient evidence.

  [1] A statistically significant greater improvement with aripiprazole for negative symptoms by PANSS (3 RCTs). ●●○

  [2] A statistically significant greater improvement with clozapine for global ratings and total scores by BPRS (6 RCTs). ●●○

  [3] A clinically significant greater benefit with olanzapine for negative symptoms by PANSS (14 RCTs) and SANS (5 RCTs), for general psychopathology by HAM-D (3 RCTs) and MADRS (6 RCTs), and global ratings and total scores (CGI-S, 7 RCTs; PANSS, 14 RCTs) ●●○. No statistically significant difference in general psychopathology or global ratings and total scores is noted by other instruments in multiple RCTs (ABS, 2 RCTs; ACES, 2 RCTs; CDS-S, 3 RCTs; HAM-A, 2 RCTs; PANSS, 10 RCTs) ●○○.

  [4] A statistically significant greater improvement with haloperidol for global ratings and total scores on CGI-S (4 RCTs) ●○○. No statistically significant difference was found for BPRS (4 RCTs), CGI-I (3 RCTs), or PANSS (6 RCTs) ●○○.

  [5] A statistically significant greater improvement with risperidone for negative symptoms by SANS (4 RCTs). ●●○

Clinical Bottom Line *(Continued)*

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. ●○○
- Antipsychotics elevate mortality risk for elderly patients; however, the evidence examined for this report was insufficient to permit conclusions about differences in mortality risks between SGAs and FGAs in patient subgroups, including the elderly.

Positive symptoms = hallucinations and delusions. Negative symptoms = 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

Other Report 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 decisionmaking.
- 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.
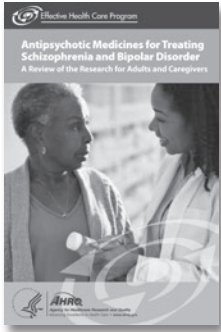
What To Discuss With Your Patients
- The potential benefits of antipsychotics
- The risks of adverse effects, including irreversible extrapyramidal symptoms, when antipsychotics are used
- The effect of medications on other medical conditions and possible interactions with other medications
- The trade-offs 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

Resource for Patients

For electronic copies of *Antipsychotic Medicines for Treating Schizophrenia and Bipolar Disorder, A Review of the Research for Adults and Caregivers* is a free companion to this clinician research summary. It covers:

- A description of the symptoms of schizophrenia and bipolar disorder
  - A description of antipsychotic medicines
  - The evidence about how the likelihood of short-term and long-term benefits compares between the antipsychotic drugs
  - The associated adverse effects and the evidence about the comparative risks for adverse effects of the antipsychotic drugs

Ordering Information

For electronic copies of *Antipsychotic Medicines for Treating Schizophrenia and Bipolar Disorder, A Review of the Research for Adults and Caregivers*, this clinician research summary, and the full systematic review, visit www.effectivehealthcare.ahrq.gov/antipsychotics-adult.cfm. To order free print copies, call the AHRQ Publications Clearinghouse at 800-358-9295.

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