First-Generation Versus Second-Generation Antipsychotics in Adults: Comparative Effectiveness [Internet].

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.

Table 1

List of antipsychotics included in the comparative effectiveness review.

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.

Schizophrenia and Related Psychoses

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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 symptoms[20] 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 results[25] 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

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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

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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.

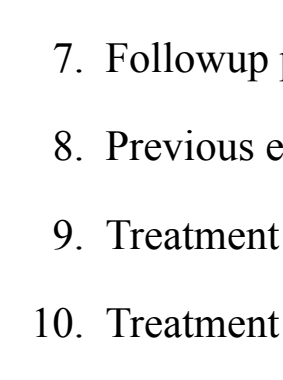

Figure 1

Analytic framework for the comparative effectiveness of FGAs and SGAs. FGA = first-generation antipsychotic; KQ = Key Question; SGA = second-generation antipsychotic

Bookshelf ID: NBK107237