



Effective Health Care Program

Treatments for Schizophrenia in Adults: A Systematic Review

Evidence Summary

Condition and Treatment Strategies

Schizophrenia is a chronic mental health condition that most often presents in early adulthood and can lead to disabling outcomes. The most recent version of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 5th edition, (DSM-5),¹ defines schizophrenia as: the presence of two or more of the five core symptoms (delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms), with at least one of the symptoms being delusions, hallucinations, or disorganized speech, and the presence of symptoms for at least 6 months. Differential diagnosis is broad, and includes delineation from mood disorders (bipolar disorder or major depressive disorder) with psychotic features and substance/medication-induced psychotic disorders. The course of schizophrenia varies. Approximately 20 percent of individuals may experience significant improvement including, in some cases, full recovery; however, the majority tend to experience some degree of social and occupational difficulty as well as need for daily living supports.² That said, more recent research and practice has focused on early intervention with first episode psychosis, demonstrating promise toward improving outcomes sooner and reducing longer-term disability.^{3,4}

Purpose of Review

To evaluate treatments for schizophrenia.

Key Messages

- Olanzapine, aripiprazole, risperidone, quetiapine, and ziprasidone were similar in function, quality of life, mortality, and overall adverse events. Core illness symptoms were better with olanzapine and risperidone than aripiprazole, quetiapine, and ziprasidone, and with paliperidone than lurasidone and iloperidone.
- Haloperidol had similar benefits but more adverse events than olanzapine and risperidone.
- Psychosocial treatments improved outcomes versus usual care: assertive community care (core illness symptoms, function), cognitive behavioral therapy (core illness symptoms, function, quality of life), cognitive remediation (core illness symptoms), family interventions (core illness symptoms, function, relapse), illness self-management (core illness symptoms), psychoeducation (core illness symptoms, function, relapse), social skills training (core illness symptoms, function), and supported employment (core illness symptoms, employment).



Antipsychotic medications and nonpharmacological treatments are typically used together when treating individuals with schizophrenia. Both pharmacological and nonpharmacological treatments for schizophrenia can result in meaningful improvements in a variety of outcome areas, including psychiatric symptoms, functioning (e.g., employment, social), service utilization (e.g., hospitalization, crisis services), legal system involvement, quality of life, self-harm and aggressive behaviors, treatment engagement and retention, and co occurring substance abuse. Ideally, improvements in symptoms translate to long-term, clinically relevant, positive changes in other outcome areas, with limited and manageable adverse effects.

Older, first-generation antipsychotics (FGAs), such as haloperidol, have proven efficacy but adverse effects, such as extrapyramidal symptoms and in some cases tardive dyskinesia, often limit long-term adherence. Second-generation antipsychotics (SGAs), beginning with clozapine, were introduced as having equal or better efficacy, particularly with negative symptoms, and lower risk of extrapyramidal symptoms and tardive dyskinesia. SGAs have potentially serious adverse effects (e.g., cardiovascular and endocrinologic effects) that make their overall risk/benefit profile less clear-cut than anticipated.

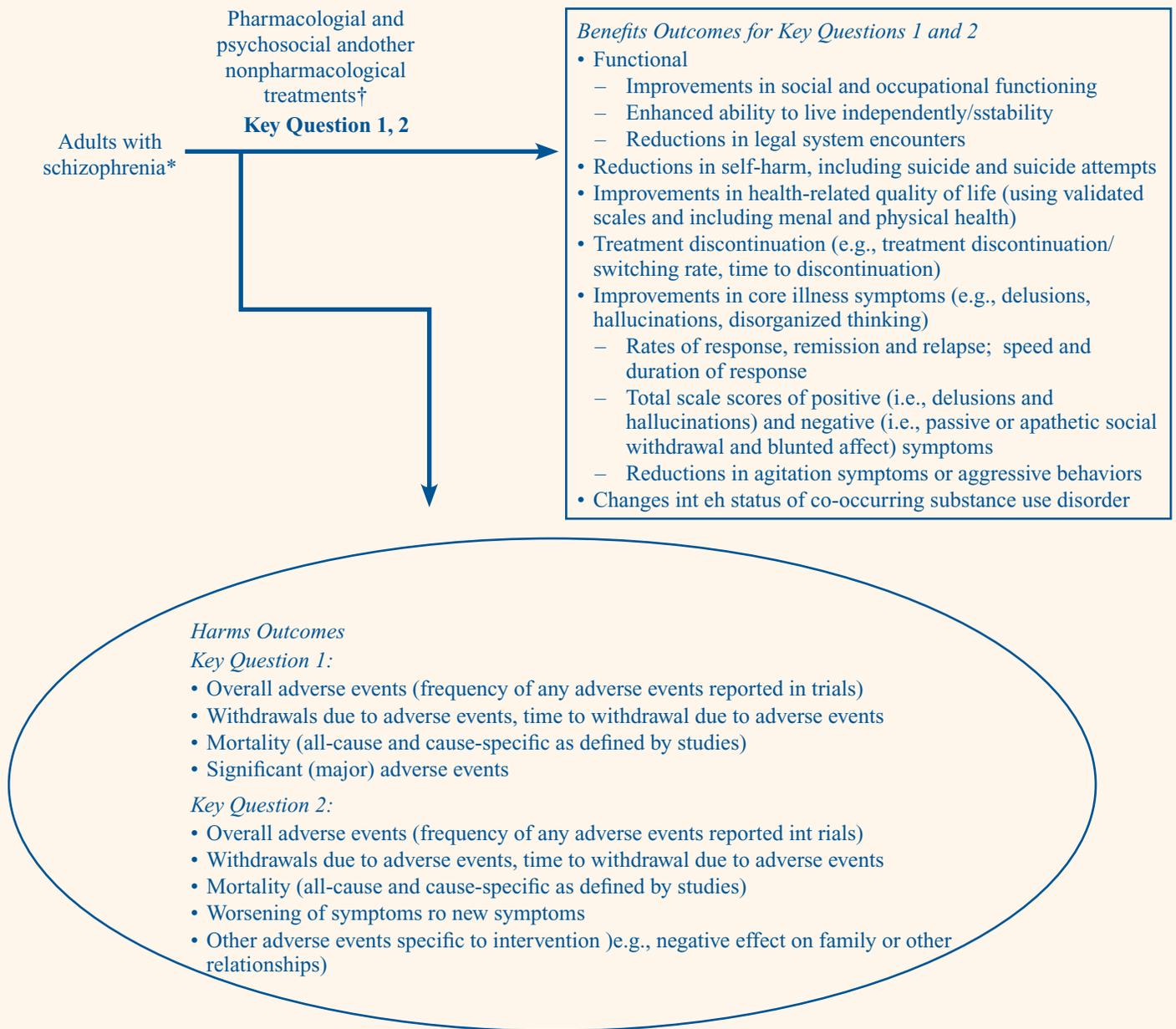
Although there are a large number of treatments for schizophrenia, it is not clear whether they afford long-term benefits on employment and social relationships and increase the likelihood of recovery, or what the most effective duration of treatment is. Equally important in selecting among competing interventions for a specific patient is consideration of patient-level characteristics that may affect the outcomes across a diverse group of possible interventions.

Scope and Key Questions

Scope of the Review

This systematic review provides a comprehensive review of current evidence that can help in determining how to treat individuals with schizophrenia. The review synthesizes evidence on pharmacological treatments compared with each other and the general effectiveness of psychosocial and other nonpharmacological strategies compared with usual care for treating individuals with schizophrenia, and highlights areas of controversy and areas for future research. The analytic framework (Figure A) illustrates the population, interventions, and outcomes considered. Due to a very large body of research literature, the review has been focused in several ways (see Methods).

Figure A. Analytic framework



* Adults with a diagnosis of schizophrenia, including those with co-occurring substance use disorders, and including those experiencing a first episode of schizophrenia (including those with schizophreniform disorder).

1. Pharmacological treatments:

- At least 90 percent of patients must have been diagnosed with schizophrenia.
- For studies specifically on harms of antipsychotic drugs, populations can be mixed-diagnoses, as the harms are not diagnosis-specific

2. Psychosocial and other nonpharmacological treatments: 50 percent of patients must have been diagnosed with a schizophrenia spectrum disorder diagnosis (i.e., schizophrenia, schizoaffective disorder, or schizophreniform disorder)

† Pharmacological treatments include US Food and Drug Administration-approved second-generation and selected first-generation antipsychotics. Psychosocial and other nonpharmacological treatments include: assertive community treatment, cognitive adaptive training, cognitive behavioral therapy, cognitive remediation/training, co-occurring substance use and schizophrenia interventions, early interventions for first episode psychosis, family interventions, intensive case management, illness self-management training, psychoeducation, social skills training, supported employment, and supportive therapy.

Key Questions

- 1a. What are the comparative benefits and harms of pharmacological treatments for adults with schizophrenia?
- 1b. How do the benefits and harms of pharmacological treatments for adults with schizophrenia vary by patient characteristics?^a
- 2a. What are the benefits and harms of psychosocial and other nonpharmacological treatments for adults with schizophrenia?
- 2b. How do the benefits and harms of psychosocial and other nonpharmacological treatments for adults with schizophrenia vary by patient characteristics?^a

Methods

The methods for this systematic review follow the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*⁵ and are reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) checklist.⁶ The scope of the report was developed with consultation with a group of key informants. The details of the inclusion criteria, including the prioritized list of outcomes, were developed with input from a group of technical experts. See the full report and the review protocol (<http://effectivehealthcare.ahrq.gov/index.cfm>) for additional details on methods.

Literature Search Strategy and Inclusion Criteria

A research librarian searched Ovid MEDLINE[®], the Cochrane Library, and PsycINFO[®]. For Key Question 1, recent high-quality systematic reviews were used as the starting point, such that our searches began in 2011 for FGA versus SGA drugs and in 2013 for SGA versus SGA drugs. For Key Question 2, search dates were not restricted. Searches were conducted through February 1, 2017. Other standard search methods were also applied. Only English-language articles were included. A summary of the eligibility criteria and review methods are described below, and further details are in the full report.

^a Patient characteristics include age, sex, race, ethnicity, socioeconomic status, time since illness onset, prior treatment history, co-occurring psychiatric disorders, pregnancy, etc.

^b “Older” SGAs; approved up through 2001 and included in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trials.

Key Eligibility Criteria

Population(s): Adults with a diagnosis of schizophrenia

Interventions:

- Key Question 1: Antipsychotic medications
 - First-generation antipsychotic drugs (FGAs)
 - ♦ Fluphenazine (Prolixin[®], Permitil[®])
 - ♦ Haloperidol (Haldol[®])
 - ♦ Perphenazine (Trilafon[®])
 - Second-generation antipsychotic drugs (SGAs)
 - ♦ Aripiprazole (Abilify[®], Aristada[™])
 - ♦ Asenapine (Saphris[®]),
 - ♦ Brexpiprazole (Rexulti[®])
 - ♦ Cariprazine (Vraylar[™])
 - ♦ Clozapine^b (Clozaril[®], Fazaclor[®] ODT, Versacloz[™])
 - ♦ Iloperidone (Fanapt[®])
 - ♦ Lurasidone (Latuda[®])
 - ♦ Olanzapine^b (Zyprexa[®], Zyprexa Zydis[®]),
 - ♦ Olanzapine Pamoate (Zyprexa[®] Relprevv[™])
 - ♦ Paliperidone^b (Invega[®]) and Paliperidone palmitate (Invega[®] Sustenna[®], Invega Trinza[™])
 - Oral paliperidone is marketed only as an extended-release product, and will be noted as paliperidone in the report because there is no immediate-release formulation.
 - ♦ Quetiapine^b (Seroquel[®], Seroquel XR[®])
 - The extended-release formulation is noted as quetiapine ER in this report; the immediate-release formulation is not noted by a suffix to be consistent with the other immediate release formulations of SGAs.
 - ♦ Risperidone^b (Risperdal[®], Risperdal[®] M-TAB[®] ODT (oral dissolving tablet), Risperdal[®] Consta[®])
 - ♦ Ziprasidone^b (Geodon[®])

- Key Question 2: Psychosocial and other nonpharmacological interventions^c
 - Assertive community treatment
 - Cognitive adaptive training
 - Cognitive behavioral therapy
 - Cognitive remediation/training
 - Co-occurring substance use and schizophrenia interventions
 - Early interventions for first episode psychosis
 - Family interventions
 - Intensive case management
 - Illness self-management training
 - Psychoeducation
 - Social skills training
 - Supported employment
 - Supportive therapy
- For each Key Question, eight outcomes were prioritized as most important.
 - Key Question 1: Functional outcomes, quality of life, response and/or remission rate, mortality, reductions in self-harm, overall/any adverse events, improvements in core illness symptoms, and withdrawal due to adverse events.
 - Key Question 2: Functional outcomes (including social, occupational and other types of function), quality of life, reductions in self-harm, response and/or remission rate, improvements in core illness symptoms, treatment discontinuation (for any reason; may be reported as loss to followup or leaving study early), relapse rate, and adverse events.
 - ♦ Rehospitalization was not included as an outcome because: (1) there is important variation in the indications for and length of psychiatric hospitalizations across time, in different localities, and with different financial contexts, and (2) there is important variation across trials in how rehospitalization is measured/evaluated, which may confound study interpretation. However, it was reported in addition to the prioritized outcomes for assertive community treatment because it is the target of this intervention for patients with a history of frequent hospitalization.

Comparators:

- Key Question 1: Head-to-head comparisons: FGAs versus SGAs, and SGAs versus SGAs.
- Key Question 2: Usual care/standard care/treatment as usual/waitlist, as defined in the trials.
 - Usual care can consist of elements of medication treatment, medication management, case management, rehabilitation services, and psychotherapy. Both groups (treatment and usual care) received usual care, including drug treatment throughout the study.
 - Evidence with active controls (other interventions with expected benefit, or attention controls which have minimal or no benefit but similar patient participation time) was considered where the evidence base with usual care comparisons for a given intervention is too small to draw conclusions (i.e., one or two trials, no systematic reviews).

Outcomes for each question (see also outcomes in Figure A):

We limited the outcomes to those that are patient centered health outcomes (rather than intermediate outcomes), which were arranged according to their priority from the perspective of the patient, their family, and their clinicians. We considered advice from our experts in selecting and prioritizing this list of outcomes.

Timing:

- Minimum duration of followup: 12 weeks.

Settings:

- United States-relevant, such as countries listed as “high” or “very high” on the United Nations International Human Development Index (HDI), and applicable to United States practices.
- Excluded: inpatient setting.

Study designs:

- Recent, comprehensive, good- or fair-quality systematic reviews, as well as randomized controlled trials (RCTs) published since the systematic reviews.
- Sample size of >50 for Key Question 2.

^c Limited to the most commonly used interventions relevant to U.S. practices.

Study Inclusion Decisions

Two independent reviewers assessed study eligibility and extracted data from included studies, with discrepancies resolved by consensus and involvement of a third reviewer, if necessary. Only English-language articles were included. We included trials with study populations of mostly outpatients and duration of at least 12 weeks, and systematic reviews that assessed the comparisons in Key Questions 1 and 2 that were deemed to be good or fair quality (see below). Whenever possible, systematic reviews were used as the primary evidence, with trials not included in reviews also fully evaluated and synthesized with the review evidence.

Risk of Bias Assessment of Individual Studies

Two investigators independently rated the risk of bias (quality) of each included study based on predefined criteria. Disagreements were resolved by consensus. Randomized controlled trials were evaluated with criteria developed by the Drug Effectiveness Review Project.⁷ The quality of systematic reviews was assessed using the Assessing the Methodological Quality of Systematic Reviews quality (AMSTAR)-rating instrument.⁸ These methods were used in accordance with the approach recommended in the chapter, “Assessing the Risk of Bias of Individual Studies When Comparing Medical Interventions” in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.⁵ Studies were rated as “good,” “fair,” or “poor.”

Data Synthesis

We synthesized results by summarizing study characteristics and investigating whether there were important differences in the distribution in characteristics that modified the treatment effects. Synthesis focused on the better-quality studies. Meta-analyses were conducted when studies were homogeneous enough to provide a meaningful combined estimate. We conducted pairwise meta-analyses, using the DerSimonian and Laird random-effects model. Statistical heterogeneity was assessed using the I^2 statistic or the Q-statistic chi-square. Network meta-analyses were conducted using a Bayesian hierarchical model.

Strength of the Body of Evidence

The strength of evidence (SOE) for each prioritized outcome was assessed by two reviewers using the approach described in the *Methods Guide for Effectiveness and*

Comparative Effectiveness Reviews.^{5,9} We assigned an SOE grade of High, Moderate, Low, or Insufficient for the body of evidence for each outcome, based on evaluation of four domains: study limitations, consistency, directness, and precision. High, Moderate and Low ratings reflect our confidence in the accuracy and validity of the findings and whether future studies might alter these findings (magnitude or direction). We gave a rating of insufficient when we were unable to draw conclusions due to serious inconsistency, serious methodological limitations, or sparseness of evidence.

Peer Review and Public Commentary

Experts in treatments for schizophrenia were invited to provide external peer review of this systematic review; the Agency for Healthcare Research and Quality (AHRQ) and an associate editor also provided comments. In addition, the draft report was posted on the AHRQ Web site for 4 weeks to elicit public comment. We addressed the reviewer comments and revised the text as appropriate.

Results Summary

Summary of Results of Literature Searches

For Key Question 1 on the benefits and harms of pharmacological interventions for schizophrenia, we reviewed 698 titles and abstracts and included one systematic review of 138 trials and 24 additional trials for SGAs versus SGAs, and one systematic review of 111 trials and five additional trials for FGAs versus SGAs. Some studies included comparisons of both intervention areas (SGA vs. SGA and SGA vs. FGA). The majority of new trials (71%) were fair quality, with 21 percent rated poor quality and 8 percent good quality.

For Key Question 2 on the benefits and harms of psychosocial and other nonpharmacological interventions for schizophrenia, we reviewed 2,766 titles and abstracts and included 13 systematic reviews of 271 trials and 32 additional trials. The included studies investigated 13 main intervention areas. Of these new trials, 20 were fair quality, four were good quality, and three were poor quality.

For each intervention area, we reported on the available evidence for prioritized outcomes, as described in the Methods section. Prioritized outcomes for which the evidence was insufficient or unavailable are not included in the Results Summary.

Summary of Results by Key Question

Key Question 1: Comparative Evidence Regarding Antipsychotic Drugs

The findings on antipsychotic drugs came from one systematic review of 138 trials (N=47,189) and 24 additional trials (N=6,672) for SGAs versus SGAs, and one systematic review of 111 trials (N=118,503) and five additional trials (N=1,055) for FGAs versus SGAs. In our review, we examined the prioritized outcomes: measures of functional abilities, quality of life, response and/or remission, mortality, self-harm, core illness symptoms, overall adverse events, and withdrawal from treatment due to adverse events. Overall, no drug intervention had high-strength evidence for any outcome of interest, but we found moderate-strength evidence for some outcomes. The evidence is divided into SGA versus SGA and FGA versus SGA according to traditional categorization of the drugs used in the two systematic reviews, although the drugs could be considered as one group with variations in effects associated with individual drugs.

Second-Generation Antipsychotics Versus Second-Generation Antipsychotics

We found the most evidence about the older SGAs (clozapine, risperidone, olanzapine, quetiapine, and ziprasidone). We also found some evidence on the most commonly reported outcomes (e.g., core illness symptom improvement) for oral aripiprazole and paliperidone. Evidence for the newer drugs (asenapine, brexpiprazole, cariprazine, iloperidone, lurasidone, paliperidone, and long-acting injection [LAI] formulations of aripiprazole and paliperidone) is limited, with few studies, none finding a newer drug superior to an older SGA or each other on any outcome. Similarly, quetiapine and ziprasidone (older SGAs) were not found superior to any other SGA on any outcome.

Benefits Outcomes

Although functional outcomes were prioritized as most important, few studies of SGA versus SGA reported these outcomes. Very few differences were found among the older SGAs regarding effects on social, occupational, or global functioning (low SOE). A single study found risperidone LAI to result in greater improvements in social function over 24 months compared with quetiapine. None of the studies of the newer SGAs reported on any type of functional outcomes. Findings on quality of life showed that there was no difference between olanzapine and risperidone or ziprasidone (moderate SOE); olanzapine or risperidone oral or LAI and quetiapine; or oral aripiprazole

and aripiprazole monthly LAI (low SOE) in studies with up to 2 years of followup.

Symptom response and remission are dichotomous outcomes, which are measured as response or no response, remission or no remission. By definition, response and remission are outcomes that are meant to reflect clinically relevant improvement in core illness symptoms. However, response was defined in varying ways in the trials, although the most common definition was 20 percent improvement on a core illness symptoms scale, such as the Positive and Negative Symptoms Scale (PANSS). A network meta-analysis of 46 head-to-head trials found that olanzapine and risperidone were significantly more likely to result in response than quetiapine (low SOE). Other comparisons and meta-regressions examining the influence of study duration, dose-level, populations (either treatment-resistant or first-episode status), and category of response definition did not result in any statistically significant differences between the SGAs (low SOE). Remission was reported too infrequently to assess comparatively, except in the group of studies on patients with a first episode of schizophrenia.

Improvement in core illness symptoms is a continuous outcome measured as the mean change in symptoms using a scale. A published network meta-analysis of 212 trials found that clozapine was superior to other oral SGAs except for olanzapine in improving core illness symptoms (low SOE). Olanzapine and risperidone were not significantly different compared with each other, and both were superior to the other SGAs, except for paliperidone and clozapine (low SOE). Paliperidone also improved core illness symptoms more than lurasidone and iloperidone (low SOE). This analysis found that all of the drugs included were superior to placebo. In treatment-resistant patients, olanzapine improved core illness symptoms more than quetiapine. These findings are based on two published network meta-analyses (low SOE).

While infrequent, self-harm, including suicide, is a major cause of death among individuals with schizophrenia that antipsychotics, along with other interventions, are intended to help prevent. Although clozapine is often reserved for treatment-resistant patients, due to the serious adverse event profile and required monitoring, evidence supports its superiority over the other SGAs (primarily the older ones) in preventing self-harm (suicide-related outcomes) in both patients at risk for suicide-related outcomes (versus olanzapine) and in patients with unknown or mixed risk for these outcomes (versus olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole) (low SOE).

Harms Outcomes

Although SGAs have somewhat differing adverse event profiles, the evidence indicates no difference in the overall risk for adverse events between asenapine and olanzapine (moderate SOE). Differences were also not found between quetiapine extended release (ER) versus quetiapine and risperidone; risperidone versus clozapine and aripiprazole; olanzapine versus paliperidone; risperidone LAI versus paliperidone and paliperidone palmitate monthly LAI; and aripiprazole versus aripiprazole monthly LAI (all low SOE). Given the variation in specific adverse event profiles across the SGAs, withdrawals due to adverse events is an outcome measure that has the advantage of measuring the seriousness and tolerability of adverse events experienced, including those that might be treated with another drug or dose reduction. Our network meta-analysis of 90 trials indicates that risperidone LAI had significantly lower risk of withdrawal due to adverse events than five other SGAs: clozapine, lurasidone, quetiapine ER, risperidone and ziprasidone (low SOE). Olanzapine had lower risk than five other SGAs: clozapine, lurasidone, quetiapine, risperidone, and ziprasidone (low SOE). Aripiprazole had lower risk than two SGAs: clozapine and ziprasidone, and cariprazine and iloperidone had lower risk of withdrawal due to adverse events than clozapine (low SOE). Comparative evidence on extrapyramidal symptoms, cardiovascular events, diabetes, weight gain, metabolic syndrome, and sexual function is summarized in the full report. Although these were secondary outcomes in this report, in general the evidence is not able to identify differences between drugs studied in cardiovascular adverse events, metabolic syndrome, and sexual function. Risk of diabetes and weight gain is greater with olanzapine, with increased risk of weight gain also found with clozapine and quetiapine. Findings on extrapyramidal symptoms are more mixed.

All-cause mortality is a rare event, but it is still an important outcome to evaluate as SGAs continue to be developed, approved, and marketed, and particularly as all SGAs carry an FDA Boxed Warning against their use in older patients with dementia due to increased risk of mortality. The mortality rate is low in SGA trials and cohort studies (0 to 1.17%), and there were no differences in mortality rates between olanzapine and risperidone or asenapine, risperidone and quetiapine, or paliperidone palmitate monthly LAI and risperidone LAI. There were also no differences in cardiovascular mortality among risperidone, olanzapine, and quetiapine (low SOE). Comparative evidence on the risk of cardiovascular or all-cause mortality was not available for the other SGA drugs.

Subgroups

There are few differences among the SGAs in effects on several important outcomes, but in some cases the superior drug has serious adverse effects (e.g., clozapine's risk of agranulocytosis [severe neutropenia] and olanzapine's risk of weight gain and new onset diabetes). Therefore, it is especially important to consider how patient characteristics may affect outcomes. Evidence in subgroups was low strength.

In patients experiencing their first episode of schizophrenia, response and remission were not significantly different among olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole, or paliperidone. Most studies also reported no difference in improvement in core illness symptoms, measured by symptoms scales, except that core illness symptoms were more improved with paliperidone than ziprasidone or aripiprazole, but response rates did not differ significantly. Response rates with olanzapine and risperidone were similar in patients with first-episode schizophrenia compared with patients with multiple previous episodes. These findings did not differ according to the duration of study, the specific drugs compared, in women, or whether or not studies were blinded. Evidence on SGA treatment discontinuation was more limited, with conflicting findings from five trials. An included systematic review reports that the incidence of clinically important weight gain is significant in first-episode patients, who have little previous exposure to antipsychotics, but differences among the SGA drugs has not been shown. These studies did not find a difference in benefits outcomes between risperidone and olanzapine over the first 3 years of treatment, but they found that that risperidone had higher risk of some specific adverse events (worsening akathisia, sexual dysfunction, and amenorrhea). Aripiprazole had either lower rates of or longer time to discontinuation due to adverse events than ziprasidone or quetiapine. Core illness symptoms were improved more with paliperidone than ziprasidone or aripiprazole, but response rates did not differ significantly.

In treatment-resistant patients (most commonly defined as having received an adequate course of at least two prior antipsychotics without achieving symptom response), a network meta-analysis of 40 trials indicated that olanzapine resulted in greater improvement in core illness symptoms, although the difference in mean change (-6 points) in the PANSS may not meet minimal clinically important difference criteria (-11.5 points for more severe symptoms), depending on the severity of the patient's symptoms at baseline. A network meta-analysis of negative symptoms also found olanzapine significantly

better than the other older SGAs, whereas response rates and all-cause discontinuations indicated no significant differences among the older SGAs. Clozapine had fewer discontinuations due to lack of efficacy than risperidone and quetiapine.

The evidence on other subgroups of patients is limited. Analysis of age subgroups did not find differences for comparisons of olanzapine with risperidone. Women had greater improvements than men in core illness symptoms with clozapine and in quality of life with olanzapine. Improvement in core illness symptoms was similar in Asian patients, compared with overall study populations for comparisons of aripiprazole and paliperidone with olanzapine, quetiapine, and risperidone. Among illicit drug users, differences between older SGAs were not found in rate or time to drug discontinuation. Response rates with olanzapine and risperidone were similar in patients with a history of cannabis use disorders and in those without such history.

First-Generation Antipsychotics Versus Second-Generation Antipsychotics

Although the SGAs were initially marketed as having multiple advantages over the FGAs, there has been concern that the evidence on first-generation versus second-generation antipsychotics was biased toward the SGAs in various ways (e.g., using higher than typical doses of the first-generation drugs). The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial included one FGA along with five SGAs to test this theory. The trial found perphenazine to be noninferior to the other drugs, with the exception of olanzapine. However, the CATIE trial did not resolve the questions around the use of FGAs in current practice. The findings of the comprehensive systematic review of FGAs versus SGAs published in 2012 are not substantially changed with the additional consideration of five newer studies (2 good quality, 2 fair quality, and 1 poor quality). The 111 trials included in the previously published systematic review were rated as mainly fair quality (70 studies), with 41 rated as poor quality, and none rated as good quality. The FGA evidence was largely about haloperidol, with 108 studies, and only 7 of perphenazine and 4 of fluphenazine. The most common comparisons were risperidone (37 trials) and olanzapine (34 trials) versus haloperidol.

Benefits Outcomes

Quality of life, a highly prioritized outcome, was not different between the FGAs and SGAs, quetiapine and risperidone (low SOE), and olanzapine (moderate SOE). Only ziprasidone was found better than haloperidol (low

SOE). Evidence on functional outcomes was insufficient to draw conclusions. Risperidone is not different from haloperidol in response rates (moderate SOE). Symptom response and remission were better with olanzapine than haloperidol, but no differences were found in response between haloperidol and aripiprazole, quetiapine and ziprasidone, or in remission between haloperidol and ziprasidone (low SOE).

Comparative evidence on core illness symptoms is only available for haloperidol versus older SGAs. Core illness symptoms were improved significantly more with olanzapine and risperidone than haloperidol (moderate SOE), but evidence on other comparisons did not show significant differences (low SOE). Olanzapine improved negative symptoms significantly more than haloperidol (moderate SOE), and risperidone and aripiprazole improved negative symptoms significantly more than haloperidol (low SOE).

Harms Outcomes

Overall rates of patients reporting adverse events were 11 to 20 percent higher with haloperidol versus aripiprazole (moderate SOE), risperidone, and ziprasidone (low SOE). Similarly, evidence indicates a higher rate of withdrawal from study (and treatment) due to adverse events with haloperidol versus aripiprazole, olanzapine, risperidone, and ziprasidone (moderate SOE). There were no differences in withdrawal due to adverse events between haloperidol and clozapine or quetiapine (low SOE).

Subgroups

Evidence comparing FGAs to SGAs in population subgroups is fairly limited, with unclear implications. In general, differences in outcomes were not found between FGAs and SGAs in patients with a first episode of schizophrenia. In treatment-resistant patients the effects on total core illness symptoms and negative symptoms mirrored the findings in the overall population. Response and core illness symptom improvement was similar in Asian populations and the overall study populations. In patients with co-occurring substance use disorder, core illness symptoms were improved more with olanzapine than haloperidol, but not with risperidone.

Key Question 2: Evidence on Psychosocial and Other Nonpharmacological Interventions

The studies included in our review reported that psychosocial and other nonpharmacological interventions were administered in addition to usual care, which typically includes treatment with antipsychotics, but could include other treatments. Therefore, the studies that

make up the evidence base for this question compared (a) psychosocial and other nonpharmacological interventions plus usual care with (b) usual care alone. With usual care as the comparator, we did not include studies that provided direct evidence about head-to-head comparisons and therefore do not consider this a comparative effectiveness review. The evidence base is comprised of 13 systematic reviews (11 good quality, 2 fair quality) that included 271 trials (N=25,050) relevant to this report. In addition, we included 27 trials that were not included in these reviews (N=6,404). Of these new trials, 4 were good, 20 were fair, and 3 were poor quality. Overall, no psychosocial intervention had high-strength evidence for any outcome of interest, but we found moderate-strength evidence for some outcomes.

Benefit Outcomes

Patients receiving assertive community treatment were more likely to be living independently and to be employed, and they were less likely to be homeless or to discontinue treatment compared with patients assigned to usual care (moderate SOE). There were no significant differences in the degree of improvement in core illness symptoms or social functioning, and there were no differences in arrests, imprisonment, or police contacts compared with usual care (low SOE).

Cognitive behavioral therapy (CBT) resulted in improvements in global function and quality of life (low SOE), and overall core illness symptoms (moderate SOE) compared with usual care during treatment and with up to 6 months of followup. In studies with longer-term followup after CBT ended, these differences were not significant, although there were few studies with a usual care control group. Low-strength evidence suggests that improvement in negative symptoms was not different between CBT and usual care.

Cognitive remediation resulted in small positive effects on social, occupational, and global function, core illness symptoms (low SOE), and negative symptoms (moderate SOE) compared with usual care over 15 to 16 weeks of treatment.

Supported employment, specifically the individual placement and support model intervention, resulted in significantly better employment outcomes over 2 years compared with usual care. More patients gained either employment (competitive or any job), had more hours worked, were employed longer, and earned more money than those receiving usual care. Evidence with comparisons with other vocational training confirmed these findings.

Family interventions resulted in significantly lower relapse rates than usual care with up to 24 months treatment and at 5 years post-treatment followup; differences in relapse rates were not found from 25 to 36 months. Family interventions improved core illness symptoms, including negative symptoms. Unemployment, independent living, social functioning, or reduction in self-harm were not found to be different between groups (low SOE, except for reduced relapse from 7 to 12 months [moderate SOE]).

Intensive case management was not found to improve global function, quality of life, or core illness symptoms more than usual care.

Illness self-management training interventions reduced symptom severity (moderate SOE) and relapse rates (low SOE). No significant difference was found for negative symptoms (low SOE). Fidelity to intervention was associated with better effects.

Psychoeducation had a greater effect than usual care on global function at 1 year and resulted in lower relapse rates at 9 to 18 months (moderate SOE).

Social skills training improved social function at 6 months, 1 year, and 2 years, compared with usual care. Core illness symptoms and negative symptoms were also improved more with social skills training than usual care.

Supportive therapy was not significantly different from usual care in improving global or social function (low SOE).

Subgroups

Clinical Subgroups

Early team-based multi-component treatment programs for patients with first episode psychosis resulted in significant improvements in global function with up to 2 years of treatment compared with usual care, but there were no significant differences in housing status (moderate SOE). Quality of life was improved and participants in team-based multi-component treatment programs were less likely to relapse (moderate SOE), but there was no difference in total PANSS scores or rates of self-harm compared with usual care (low SOE).

In patients with **co-occurring substance use disorder**, there was low-strength evidence that assertive community treatment was not different from usual care in function, mortality, and substance use.

Demographic Subgroups

We found limited subgroup analyses across all psychosocial and nonpharmacological interventions to identify potential patient characteristics that might predict outcomes. Limited evidence on social skills training from one trial of a mixed population (about 50% diagnosed with schizophrenia or schizoaffective disorder) suggested that the intervention may be more effective in men than women for improving social function and core illness symptoms.

Harms Outcomes

Four trials and seven systematic reviews assessed or reported any type of harms associated with psychosocial or other nondrug interventions. The few that did (e.g., studies of family interventions) resulted in insufficient evidence.

Discussion

Key Findings and Strength of Evidence

This systematic review evaluated the evidence on treatments for schizophrenia, comparing drug

treatments with each other and psychosocial and other nonpharmacological interventions with usual care. The purpose was to inform clinicians, patients and their families, and guideline authors with the ultimate goal of improving patient care. In the summary of the key findings and strength of evidence tables (Tables A, B, and C), we do not include findings where the evidence was insufficient to draw conclusions. (The full report presents additional detail on the findings.) There were no instances of high-strength evidence. This was primarily due to specific intervention comparisons having only fair-quality trials with few studies contributing evidence for a particular outcome, leaving moderate- and low-strength evidence. Tables showing the summary results for each drug, indicating magnitude, direction, and strength of evidence for an effect across all seven prioritized, patient-important, outcomes are included in Appendix I of the full report.

Table A. Summary of key findings and strength of evidence for Key Question 1: SGA versus SGA*

Outcome	Moderate Strength of Evidence	Low Strength of Evidence
Function: Improvements in Social Function		<ul style="list-style-type: none">• Risperidone LAI significantly better than quetiapine in social function over 24 months• No difference between paliperidone palmitate LAI (monthly) and risperidone LAI (every 2 weeks)
Function: Improvements in Occupational Function		<ul style="list-style-type: none">• No significant differences between risperidone, olanzapine, quetiapine, and ziprasidone at 18 months (CATIE)
Function: Improvements in Global Functioning		<ul style="list-style-type: none">• Global functioning was not different between olanzapine and either risperidone or quetiapine
Improvements in Quality of Life	<ul style="list-style-type: none">• Olanzapine was not found significantly different than risperidone or ziprasidone	With up to 2 years of followup: <ul style="list-style-type: none">• Olanzapine and risperidone were not found different from quetiapine• Risperidone LAI was not found different from quetiapine• Oral aripiprazole was not found different from aripiprazole monthly LAI
Response		<ul style="list-style-type: none">• Significantly more likely with olanzapine and risperidone than quetiapine based on a network meta-analysis of 46 trials

Table A. Summary of key findings and strength of evidence for Key Question 1: SGA versus SGA* (continued)

Outcome	Moderate Strength of Evidence	Low Strength of Evidence
Mortality		No difference between: <ul style="list-style-type: none"> • Asenapine and olanzapine • Quetiapine and risperidone • Paliperidone palmitate LAI (monthly) and risperidone LAI • Risperidone, olanzapine, and quetiapine (including cardiovascular mortality)
Self-Harm	<ul style="list-style-type: none"> • Clozapine was found superior to olanzapine in preventing significant suicide attempts or hospitalization to prevent suicide in high-risk patients 	<ul style="list-style-type: none"> • Clozapine was associated with lower risk of suicide or suicide attempts than olanzapine, quetiapine, and ziprasidone in unselected patients
Core Illness Symptoms: Improvements in Total Scale Scores		<ul style="list-style-type: none"> • Clozapine improved core illness symptoms more than the other SGAs, except for olanzapine • Olanzapine and risperidone improved core illness symptoms more than the other SGAs, except for each other and paliperidone • Paliperidone improved core illness symptoms more than lurasidone and iloperidone • In treatment-resistant patients, olanzapine improved core illness symptoms more than quetiapine
Overall Adverse Events	<ul style="list-style-type: none"> • No significant difference in overall adverse events between olanzapine and asenapine 	<ul style="list-style-type: none"> • No differences between: Quetiapine ER vs. quetiapine and risperidone; risperidone vs. clozapine and aripiprazole; olanzapine vs. paliperidone; risperidone LAI vs. paliperidone and paliperidone palmitate monthly LAI; and aripiprazole vs. aripiprazole monthly LAI
Withdrawal Due to Adverse Events		Based on a network meta-analysis of 90 trials: <ul style="list-style-type: none"> • Risperidone LAI had significantly lower risk than clozapine, lurasidone, quetiapine ER, risperidone, and ziprasidone • Olanzapine had lower risk than clozapine, lurasidone, quetiapine, risperidone, and ziprasidone • Aripiprazole had lower risk than clozapine and ziprasidone • Cariprazine and Iloperidone had lower risk than clozapine

CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness; ER = extended release; IR = immediate release; LAI = long-acting injectable; SGA = second-generation antipsychotic

*No interventions met high strength of evidence criteria for any outcome

Table B. Summary of key findings and strength of evidence for Key Question 1: FGA versus SGA*

Outcome	Moderate Strength of Evidence	Low Strength of Evidence
Quality of Life	<ul style="list-style-type: none"> No differences between haloperidol and olanzapine 	<ul style="list-style-type: none"> Quality of life was better with ziprasidone than haloperidol No differences between perphenazine and olanzapine, quetiapine, risperidone, or ziprasidone
Response/Remission	<ul style="list-style-type: none"> No difference in response rates between haloperidol and risperidone 	<ul style="list-style-type: none"> Response was better with olanzapine than haloperidol No difference in response between haloperidol and aripiprazole, quetiapine, and ziprasidone Remission was greater with olanzapine than with haloperidol No difference in remission rates between haloperidol and ziprasidone
Core Illness Symptoms: Improvements in Total Scale Scores	<ul style="list-style-type: none"> Olanzapine and risperidone improved PANSS total more than haloperidol 	<ul style="list-style-type: none"> No differences in total PANSS, BPRS, CGI-S, and CGI-I scores for other FGA vs. SGA comparisons
Core Illness Symptoms: Improvements in Negative Scale Scores	<ul style="list-style-type: none"> Olanzapine was more effective than haloperidol at improving negative symptoms based on SANS scores 	<ul style="list-style-type: none"> SGAs had significant, but small, improvements in PANSS negative subscale scores over haloperidol (aripiprazole, olanzapine, and risperidone) No differences in PANSS negative or SANS scores for other FGA vs. SGA comparisons
Overall Adverse Events	<ul style="list-style-type: none"> Overall adverse event rates favored SGAs when comparing haloperidol with aripiprazole 	<ul style="list-style-type: none"> Overall adverse event rates favored SGAs when comparing haloperidol with risperidone and ziprasidone
Withdrawal Due to Adverse Events	<ul style="list-style-type: none"> Withdrawals due to adverse events were significantly higher with haloperidol use compared with aripiprazole, olanzapine, risperidone, and ziprasidone 	<ul style="list-style-type: none"> No differences in withdrawal due to adverse events between haloperidol and clozapine or quetiapine

BPRS = Brief Psychiatric Rating Scale; CI = confidence interval; CGI-S = Clinical Global Impressions-Severity scale; CGI-I = Clinical Global Impressions-Improvement scale; FGA = first-generation antipsychotic; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; RR = risk ratio; SANS = Scale for Assessment of Negative Symptoms; SGA = second-generation antipsychotic

*No interventions met high strength of evidence criteria for any outcome

Table C. Summary of key findings and strength of evidence for Key Question 2: nonpharmacological interventions versus usual care*

Outcome	Moderate Strength of Evidence	Low Strength of Evidence
Function: Improvements in Global Function	<ul style="list-style-type: none"> • CBT: benefit over usual care over 6 months; not during 6 to 12 months of treatment • Early team-based multi-component treatment programs for first-episode psychosis: Beneficial with treatment duration up to 2 years • Psychoeducation x 3 months; beneficial at 1-year followup 	<ul style="list-style-type: none"> • Social skills training: Beneficial at end of treatment (6 months to 2 years treatment duration) versus usual care • Cognitive remediation resulted in a small positive effect on social, occupational, living situation, and global function versus usual care, based on six RCTs (effect sizes ranged from 0.16 to 0.40) • ICM: Not different from usual care • Supportive therapy: Not different from usual care
Function: Improvements in Social Function	<ul style="list-style-type: none"> • CBT: Benefit over usual care over 6 months; not during 6 to 12 months treatment • Early team-based multi-component treatment programs for first-episode psychosis: Beneficial with treatment duration up to 2 years 	<ul style="list-style-type: none"> • ACT: Not different from usual care in social function or criminal justice system events • ICM: Not different from usual care in rate of imprisonment • Family Intervention: Not different from usual care
Function: Improvements in Occupational Function	<ul style="list-style-type: none"> • ACT: beneficial versus usual care with intervention duration up to 2 years • Supported employment, using the individual placement and support (IPS) model is beneficial versus usual care with intervention duration up to 2 years (more patients employed, worked more, for longer, and earned more) 	<ul style="list-style-type: none"> • Family Interventions: Not different from usual care
Function: Improvements in Living Situation	<ul style="list-style-type: none"> • ACT: beneficial with treatment duration up to 2 years 	<ul style="list-style-type: none"> • Family Interventions: Not different from usual care
Improvements in Quality of Life		<ul style="list-style-type: none"> • CBT: Benefit over usual care over 6 months treatment; difference not found with longer followup versus usual care (up to 18 months followup) • Early team-based multi-component treatment programs for first-episode psychosis: Beneficial with treatment duration up to 2 years
Core Illness Symptoms: Improvements in Total Scale Scores	<ul style="list-style-type: none"> • CBT: Benefit over usual care during treatment (8 weeks to 5 years); effect not maintained after treatment end • Illness self-management: Benefit over usual care during treatment (12-48 sessions) 	<ul style="list-style-type: none"> • Cognitive remediation: Small improvements in core illness symptoms versus usual care, based on 2 trials • Early team-based multi-component treatment programs for first-episode psychosis: Not different from usual care • Family Interventions: Improved core illness symptoms • ICM: Not different from usual care • Social skills training: Greater improvement than with usual care during 6 months and 2 years of treatment • ACT: Not different from usual care

Table C. Summary of key findings and strength of evidence for Key Question 2: nonpharmacological interventions versus usual care* (continued)

Outcome	Moderate Strength of Evidence	Low Strength of Evidence
Core Illness Symptoms: Improvements in Negative Scale Scores	<ul style="list-style-type: none"> • Cognitive remediation: Beneficial compared with usual care (1 SR of 18 RCTs, effect size -0.36, 95% CI -0.52 to -0.20). 	<ul style="list-style-type: none"> • CBT: Not different from usual care (treatment duration 8 weeks to 5 years) • Illness self-management: Not different from usual care (treatment duration 16-48 sessions) • Social skills training: Greater improvement than with usual care during 6 months and 2 years of treatment • Family interventions: Improved negative symptoms based on 3 RCTs
Improvements in Rates of Relapse	<ul style="list-style-type: none"> • Early team-based multi-component treatment programs for first-episode psychosis: Lower relapse rate than usual care with treatment duration up to 2 years • Psychoeducation x 3 months; lower relapse rate than usual care at 9 to 18 months of followup • Family Interventions: Lower relapse rates than usual care from 7 to 12 months 	<ul style="list-style-type: none"> • Family interventions: Lower than usual care 0 to 6 months, 13 to 24 months, 5 years; not different from usual care at 25 to 36 months • Illness self-management: Lower relapse with >10 sessions, not different from usual care with ≤10 sessions

ACT = assertive community treatment; CBT = cognitive behavioral therapy; ICM = intensive case management; IPS = individual placement and support; PANSS = Positive and Negative Syndrome Scale

*No interventions met high strength of evidence criteria for any outcome

Findings in Relationship to What Is Already Known

With regard to drug therapy, the findings of our review are generally consistent with prior systematic reviews that make comparisons among the SGAs and between SGAs and FGAs.¹⁰⁻¹⁵ Although we incorporated the most relevant of these systematic reviews in our report, our findings differ to some extent from previous reviews because we consider outcomes prioritized with input from technical experts, incorporate newer evidence and the most recently approved drugs, and include three updated network meta-analyses. For example, in comparing SGAs, our network meta-analyses of response, withdrawal due to adverse events, and all-cause treatment discontinuation of treatment incorporate evidence on brexpiprazole and cariprazine, the two most recently approved oral drugs, and all of the long-acting injection SGAs, whereas the previously published network meta-analyses are limited to older oral drugs, included drugs not approved in the United States, and did not control for important potential effect modifiers.^{10,11,13,15-18} Therefore, there are no existing reviews that cover the same scope as this report.

Our review is consistent with other reviews in the findings on the older SGAs. Clozapine, risperidone, and olanzapine have the most consistent evidence of superiority for specific outcomes (e.g., symptom improvement, response, self-harm, all-cause treatment discontinuations, and time to discontinuation), or populations (first-episode and treatment-resistant).^{14,17,19-21} Other findings in this review are new, such as the finding that risperidone LAI and olanzapine result in significantly lower withdrawals due to adverse events than most other SGAs. Previous reviews did not assess key effectiveness outcomes, such as function, quality of life, and mortality.

A single comprehensive review on FGAs versus SGAs is available and serves as the basis of our review of FGAs versus SGAs, with nine new trials included.^{22,23} Our findings are generally consistent with this review, which concluded that there were few differences of clinical importance for effectiveness outcomes, and that evidence on patient-important outcomes and adverse events were not well-studied. In adding new evidence, we found moderate-strength evidence of specific SGAs resulting in better symptom improvement (olanzapine and risperidone) and lower rates of overall adverse events (aripiprazole) and

withdrawal due to adverse events (aripiprazole, olanzapine, risperidone, and ziprasidone) than haloperidol.

For the psychosocial interventions, our findings are consistent with some prior review findings and discordant with others. Key reasons for differing findings can be attributed to study eligibility criteria, outcomes included, inclusion of additional, newer studies, and review methodology. For example, we included trials with a usual care comparison group and excluded studies with sample sizes <50 patients and studies conducted in countries that were not United States-relevant (primarily studies conducted in China for certain interventions). Each of these criterion eliminated studies that were included in some other reviews.

The decision to focus our review of psychosocial interventions on comparisons with usual care was made as part of a set of decisions required to reduce the scope of the project. After identifying a large body of evidence for Key Question 2, we determined that the funding and timeline required a reduction in scope. We first decided to use systematic reviews as the primary evidence, with subsequently published trials included as well. Examining those, we saw a large amount of heterogeneity in how control groups were defined and handled. In some reviews, all controls were lumped together, while in others “active” and usual care controls were assessed separately. Controls described as “active” varied widely, from competing interventions to attention controls, and these were not handled consistently across reviews. Interventions categorized as “active” in one review were evaluated separately as “passive” in another review. Many, however, reviewed usual care comparisons separately or exclusively. Therefore, within the systematic reviews, usual care was the most commonly reported comparison group. In the end we included well over 200 studies of the 12 psychosocial interventions that made comparisons with usual care. The implications of this choice certainly have been contemplated in the literature before²⁴⁻²⁷ with no clear conclusion, although some have found little difference in analyses limiting to usual care comparisons and those including other comparisons.²⁴ The potential bias introduced by this decision depends on the usual care actually received by patients in the control group. For example, if no difference was found between an intervention and usual care controls, it could be attributed to better usual care; but where a difference was found it could be due to the intervention, lower quality usual care, or a combination of factors. In addition, the magnitude of difference could be affected. The difference in usual care received could occur at the patient level, at the study level, or at the body of evidence level for a given intervention.

The decision to eliminate studies conducted in China mainly affected the body of studies for family psychoeducation interventions. In this case, both a prior Cochrane review²⁸ and our own analysis indicate that the studies from China very likely overestimate treatment effects, which is consistent with the findings of other researchers in other clinical areas. Our decision to exclude rehospitalization as one of the prioritized outcomes was made after considering input from our technical expert panel, reflecting the lack of confidence that the findings are meaningful across time and different health care systems or settings. While studies of a few interventions regularly report this outcome, primarily as a proxy for relapse, we found that only assertive community treatment formally targets reducing rehospitalization. Hence, we reported rehospitalization as an outcome only for that intervention in the full report.

The other potential reasons for differences are to be expected—our searches are more recent, adding new evidence that could alter the prior findings, and we used the most up-to-date systematic review methodology, including assessing the strength of the body of evidence. Our finding that the strength of evidence for psychosocial interventions was moderate or low is consistent with our findings for antipsychotic drugs and with numerous reviews across other populations and interventions. This system of assessing the strength of evidence helps to make clear where future studies could alter findings, either in direction or magnitude, inform future research, and identify outcomes for which a given intervention is not effective. It does not, however, determine whether the intervention is useful or not in a broader sense, since the ratings are made on an outcome-by-outcome basis.

Below we summarize our findings in the context of key prior reviews for selected interventions for which differences in findings may be of particular interest. The Schizophrenia Patient Outcomes Research Team (PORT) 2009 publication is a highly regarded resource that assessed evidence and made recommendations on using several psychosocial interventions, and we discuss their findings as well as individual reviews of these specific interventions.²⁹

Cognitive Behavioral Therapy

Overall, our findings on CBT are consistent with prior findings, except that we found additional outcomes where CBT showed benefit over usual care and we did not find strong evidence regarding duration of effects. Consistent with other reviews, we found CBT to be effective at improving core illness symptoms with treatment durations of 8 weeks to 5 years and additionally for outcomes other

than symptoms (e.g., functional outcomes), even when those outcomes were not the focus of the CBT.²⁹⁻³¹ With respect to the durability of these effects after CBT ends, there is less clarity. A 2011 meta-analysis found that the effects on symptoms were greater at followup than at the end of treatment, but only with comparisons to a diverse group of comparators, and with no specified duration of followup. Their findings for CBT compared with usual care are not statistically significant, so are similar to ours.³² Results related to durability of treatment from individual trials with longer post-treatment followup have been mixed. One trial³³ of 9 months of CBT versus befriending found sustained benefit on overall and negative symptoms at 5-year followup with CBT, while a second trial³⁴ of 6 months of intensive CBT versus leisure activities found no difference between groups in negative symptoms after 5 years. Both studies had methodological limitations, which makes generalizable interpretation of these results difficult.

CBT in schizophrenia typically targets positive symptoms, with few studies targeting negative symptoms specifically.^{30,35} Our findings regarding negative symptoms, based on two good-quality systematic reviews,^{24,36} are somewhat in contrast with a 2008 review by Wykes et al. that found CBT associated with significant improvements in negative symptoms.³⁰ The Velthorst 2015 review found that studies published prior to 2003 reported larger and more positive effect sizes than studies published later. All three reviews found higher study quality to be associated with lower effect sizes, resulting in a nonsignificant effect on negative symptoms in favor of CBT.

Cognitive Remediation

Although the direct focus of cognitive remediation is on improving cognitive functioning, an outcome that is outside the scope of our review, there is some evidence that improvements in cognition can lead to improved global functioning.³⁷ Our review found that cognitive remediation improved functional outcomes, overall symptoms, and negative symptoms. Our findings differ from the conclusions of the 2009 PORT publication, which determined that the evidence base was inadequate to make recommendations, primarily due to a paucity of good-quality trials. Our findings are based on more than 39 trials included in two good-quality systematic reviews.²⁹

Family Interventions

Previous systematic reviews³⁸ and other reviews³⁹ and the 2009 PORT publication²⁹ report findings similar to our review. The 2001 systematic review by Pitschel-Walz and colleagues found that both short- and long-term family

interventions are superior to usual care in prevention of relapse.³⁸ They also found that the effect remained regardless of the length of the followup period, but that the type of intervention (psychoeducation or therapeutic) made little difference in treatment effect (both better than usual care). These results are largely consistent with our findings. The Dixon update on family psychoeducation³⁹ concludes that family psychoeducation should be included as part of best practice guidelines for schizophrenia. The 2009 PORT publication recommends that family interventions should last between 6 and 9 months to reduce rates of relapse and hospitalization.⁴⁰ Similarly, we found the strongest evidence for interventions lasting 7 to 12 months. In addition, we found that the number of sessions was more predictive of reduction in relapse than was duration of treatment. The two studies with family interventions consisting of 10 or fewer sessions at 7 to 12 months were not different from usual care on risk of relapse. Pooled estimates for relapse in trials of 11 to 20 sessions, 21 to 50 sessions, and greater than 50 sessions were all statistically superior to treatment as usual. One difference between our review and some others is that we excluded trials conducted in China as we are not confident that the findings from Chinese studies are applicable to the United States population. Our review, and two other reviews, conducted sensitivity analyses (two analyses, one including the Chinese studies and a second excluding them) and found pooled effect estimates were reduced when Chinese studies were excluded.^{41,42}

Social Skills Training

Our inclusion criteria were considerably stricter than those of other recent reviews^{43,44} in that we limited to larger trials (N>50) with longer duration (>12 weeks) that utilized a usual care control group. Still, our findings for function, one of the primary targets of social skills training, were consistent with other reviews that found significant improvements in measures of function with social skills training.⁴³⁻⁴⁵ Our findings for relapse, another target of social skills training, were also consistent with other reviews^{43,45} that found social skills training reduced relapse; however, our estimates did not reach statistical significance, likely due to the low number of events and because the analysis in the other reviews included rehospitalizations as a surrogate for relapse. Our review also found social skills training significantly reduced negative symptoms, a finding that is consistent with one of these other reviews.⁴³ The addition of new trials provided information on additional outcomes or durations of followup, but did not change the prior findings. In 2009, the PORT publication reported that evidence for skills

training supported benefits in community functioning, but that the studies were not adequate to show positive effects on symptoms or relapse.²⁹ Our findings are consistent with these findings.

Supported Employment

Our findings on supported employment are consistent with other reviews, such as the 2009 PORT recommendations and a review by Marshall, et al.^{29,46} We found that supported employment, specifically the individual placement and support model intervention, resulted in significantly better employment outcomes over 2 years compared with usual care. More patients either gained employment (competitive or any job), had more hours worked, were employed longer, or earned more money than those receiving usual care. Because we found only one trial that met our criteria for inclusion in this review, we included a review and a study that included other comparison groups besides usual care.^{47,48} In using this evidence, our findings are similar to PORT and Marshall, with the exception that our strength of evidence rating is moderate, while the Marshall rating is high. Our lower strength of evidence rating is due to our comparison group, i.e., usual care, where Marshall did not specify a comparison group. We note also, that the good quality Cochrane review⁴⁷ that we included rated the evidence as very low quality according to the Grading of Recommendations, Assessment, Development, and Evaluation working group (GRADE)⁴⁹⁻⁵⁵ criteria for multiple reasons, including large amounts of missing data due to higher dropout rates in the control groups, skewed data for some outcomes, and concerns over the lack of blinding of outcome assessors.

Applicability

The applicability of the evidence in this review is limited to adult outpatients in United States-relevant settings. Applicability specific to the Key Questions is summarized in terms of the populations, interventions, comparisons, outcomes, timing, and study designs/settings (PICOTS).

Key Question 1: Comparative Effectiveness of Pharmacological Treatments

Populations

Findings are applicable to adults (mean age 25 to 50 years), with mainly moderate and moderate-to-severe disease. There is heterogeneity in the relative predominance of specific symptoms of patients enrolled. For comparisons of SGAs, there is fairly robust evidence on first-episode patients, but less on treatment-resistant

patients. The evidence is not clearly applicable to adolescents, older adults, patients with severe disease, or patients with multiple comorbidities.

Interventions/Comparisons

For the SGAs versus each other, the majority of the evidence is relevant to comparisons of the older SGAs, with very little evidence regarding drugs approved in the last 10 years. For the FGAs versus the SGAs, the evidence is almost entirely applicable to comparisons of the older SGAs and haloperidol. The evidence is less applicable to newer SGAs (i.e., brexpiprazole, cariprazine, iloperidone, lurasidone, and LAIs of paliperidone and aripiprazole). Evidence on clozapine may be less generalizable due to the potential effects of the required monitoring, which in essence insures adherence to treatment and may provide nonspecific support, encouragement, and even structure to the daily or weekly schedule through consistent interaction with a provider.

Outcomes

For the SGAs versus each other, there is evidence for all of the prioritized outcomes; however, again the majority of the evidence on effectiveness (long-term health outcomes) is mainly limited to the older drugs. The newer drugs primarily have evidence only for symptom-based outcomes and adverse events. For FGAs versus SGAs, the outcomes are more limited, with little good evidence on effectiveness outcomes. The evidence is less applicable to long-term outcomes, such as function, long-term quality of life, self-harm, and mortality, particularly for the comparison of FGAs versus SGAs and newer SGAs.

Timing

For all of the drug interventions, whereas the range of study durations was less than 1 day to 22 years, more studies were short term (6 to 12 weeks) than longer term (1 to 2 years). The evidence is not applicable to long-term followup (greater than 2 years).

Setting

For SGAs versus each other, the evidence applies only to outpatients. In the systematic review we included on FGAs versus SGAs, almost half the studies were in inpatients.

Key Question 2: Psychosocial and Other Nonpharmacological Interventions

Similar to the issues noted in Key Question 1, the evidence base is limited in part by the scope identified for this review. For example, for Key Question 2 we added criteria that studies had to have at least 50 percent of patients

diagnosed with schizophrenia, to reflect the fact that many of these interventions are aimed at patients with serious mental illness, as a group, rather than at specific diagnoses. Similar to our limiting FGAs to only the three drugs most commonly used today, we limited the Key Question 2 interventions also to those that are used commonly in clinical practice. We also limited to studies with a comparator of usual care across the 13 interventions included. Thus, this is not a traditional comparison of two active interventions.

Populations

Findings are applicable to adults ranging in age from 16 to 80 years (adolescents to older adults), mostly with a diagnosis of schizophrenia or a related disorder. The specific characteristics of patients varied somewhat by intervention category. For example, supportive therapy is most applicable to middle-aged men with schizophrenia and related conditions who were experiencing long-standing hallucinations and/or delusions. The evidence is not clearly applicable to patients with treatment resistance, or multiple comorbidities. Across the interventions it is not clear what level of disease severity was addressed.

Interventions/Comparisons

The evidence in this review, by design, applies only to the comparisons with usual care, and the 13 intervention categories identified here. The evidence is not applicable to comparative effectiveness questions. For some interventions, such as family interventions and supportive therapy, a key limitation of the ability to understand the applicability of the evidence is varying or unclear definitions and descriptions of the elements of interventions and poor reporting of intervention and usual care details. As a result, specific description of the intervention applicability is limited. The evidence is less applicable to variations of these interventions, or emerging interventions.

Outcomes

The evidence is applicable only to a select group of outcomes that vary by intervention. Not all prioritized outcomes were reported consistently across studies. The evidence generally does not apply to long-term effectiveness outcomes that were highly prioritized (e.g., function, quality of life, mortality). For some interventions, outcomes reported were common, standard outcomes used in assessing individuals with schizophrenia, whereas for others there was wide variety and introduction of unique outcome measures.

Timing

Most of the interventions do not have evidence that is applicable to long-term followup (greater than 2 years).

Setting

The settings were mostly applicable to the United States, as evidence clearly not applicable was excluded from our review. The evidence is not exclusively applicable to the outpatient setting. Although the criteria for this review stipulated an outpatient setting, several of the systematic reviews used to provide evidence for Key Question 2 included inpatient studies as well, limiting the applicability based on setting.

Research Recommendations

Based on the research gaps and limitations identified in this review (see the full report for a more extensive discussion of limitations of the review and of the evidence base), we recommend the following:

Pharmacological Interventions

Trials should:

- Involve multiple newer SGA drugs (approved in the last 10 years), in comparison with one of the older SGAs (e.g., clozapine, olanzapine, risperidone LAI) and haloperidol and compare fluphenazine and perphenazine with both older and newer SGAs.
- Ensure comparable dosing with the best dosing titration methods for all drugs included.
- Measure key health outcomes, using agreed-upon direct measures. For example, measuring functional outcomes using not only valid and reliable scales, but also actual measures of patient functioning. These measures need to be agreed upon by clinical and research experts and then used consistently across trials.
- Study durations must reflect real-life practice. Minimum study duration should be 1 year, with 3- to 5-year followup in order to measure the durability of effects, and truly long-term outcomes, including harms (e.g., metabolic changes and tardive dyskinesia). Long-term harms are not assessable in short-term studies, and relying on observational evidence has limitations.
- The concept of recovery should be incorporated into study designs, with testing of duration of effect and discontinuation of drug treatment following remission.
- Enroll subjects who reflect real populations. Studies exclusively of older patients, with multiple

comorbidities and concomitant medications, and patients with severe disease, including treatment-resistance are needed. To better study other subgroups, such as minorities and women, specification and planning of subgroup analyses a priori and use of randomization methods that insure adequate distribution of these characteristics are needed to examine differences.

- Inpatients need to be studied separately from outpatients. Future reviews should evaluate treatments for inpatients.

Psychosocial and Other Nonpharmacological Interventions

The issues may vary by the specific intervention, but below are several key recommendations:

- Trials should have adequate sample sizes to address important health outcomes, rather than intermediate or surrogate outcomes and should adhere to the current standards for reporting, such as the Consolidated Standards of Reporting Trials (CONSORT) criteria.⁵⁶
- Studies need to be conducted in broader, but better-defined populations, with either separate studies of subpopulations or large enough sample sizes to allow meaningful subgroup analysis.
 - Future studies might consider using the National Institutes of Mental Health Research Domain Criteria⁵⁷ approach to categorizing patients.
 - Future reviews should evaluate treatments for inpatients.
- Interventions should be clearly defined and described, including required components. Some interventions, such as cognitive remediation, have used expert groups to refine definitions and required components of interventions. Measurements of fidelity to the intervention model should be undertaken where possible.
- Trials need to evaluate and report patient-important health outcomes such as function, quality of life, self-harm, and *adverse effects* using standardized and easily interpretable methods. Studies should identify what constitutes clinically meaningful change in scale scores.
- Studies are needed to address the heterogeneity in usual care control groups. Usual care is highly variable; so studies using a usual care control group must report on the specific services and treatments received and standardize the comparison or control for attention effects.

- Studies should measure both intensity and duration of intervention required to achieve the best result and the duration of effect in relation to these.
- Additional well-designed long-term studies are needed. The long-term benefits versus risks and costs of treatments remain unclear, particular for individuals whose illness is resistant or only partially responsive to treatment.
- Future systematic review research should:
 - Include an evaluation of comparative effectiveness of psychosocial interventions compared with each other. Emerging methods of evaluating complex interventions may be helpful in such future studies.^{58,59}
 - Include other nonpharmacological, device-based somatic treatments, such as electroconvulsive therapy and transcranial magnetic stimulation.
 - Organize the evidence according to the patient characteristics that the intervention focuses on.

Conclusions

The majority of the comparative evidence on pharmacotherapy to treat schizophrenia relates to the older SGAs (mainly clozapine, olanzapine, risperidone, quetiapine, and ziprasidone), with some evidence on paliperidone and aripiprazole, and the LAIs of risperidone, aripiprazole, and paliperidone. There is very little comparative evidence on newer SGAs (drugs approved in the last 10 years: asenapine, brexpiprazole, cariprazine, iloperidone, and lurasidone). Although there are some differences among the older SGAs on specific outcomes, no single drug was superior on multiple high-priority outcomes. However, clozapine, olanzapine, and risperidone oral and LAI did have superiority on more outcomes than other SGAs and quetiapine and ziprasidone were not superior to other SGAs on any outcome. No evidence found a newer SGA superior to older SGAs on any outcome. Evidence on FGAs versus SGAs indicates that olanzapine, risperidone, ziprasidone, and aripiprazole were similar to haloperidol on some outcomes of benefit, and were superior on overall adverse events and withdrawal due to adverse events.

In comparison with usual care, most of the psychosocial interventions to treat schizophrenia reviewed were more effective in improving two or more outcomes, including nontargeted but patient-important outcomes. Various functional outcomes were improved more with assertive community treatment, CBT, psychoeducation, social

skills training, supported employment, and early team-based multi-component treatment programs for patients with first-episode psychosis than with usual care. Quality of life was improved more with CBT and early team-based multi-component treatment programs for first-episode psychosis than usual care. Core illness symptoms were improved with assertive community treatment, CBT, cognitive remediation, illness self-management, psychoeducation, social skills training, and early team-based multi-component treatment programs for patients with first-episode psychosis. Relapse was reduced with psychoeducation, illness self-management, family interventions, and early team-based multi-component treatment programs for patients with first-episode psychosis. Self-harm, response and/or remission, and adverse events were rarely reported.

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Full Report

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