

# Treatments for Schizophrenia in Adults: A Systematic Review



## **Treatments for Schizophrenia in Adults: A Systematic Review**

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## Key Messages

### **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 asenapine, 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).

This report is based on research conducted by the Pacific Northwest Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2015-00009-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

**None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.**

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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## Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see [www.effectivehealthcare.ahrq.gov/reference/purpose.cfm](http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm).

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site ([www.effectivehealthcare.ahrq.gov](http://www.effectivehealthcare.ahrq.gov)) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

If you have comments on this evidence report, they may be sent by mail to the Task Order Officers named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to [epc@ahrq.hhs.gov](mailto:epc@ahrq.hhs.gov).

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## Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

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Peer Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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# Treatments for Schizophrenia in Adults: A Systematic Review

## Structured Abstract

**Objectives.** This systematic review (SR) provides evidence on pharmacological and psychosocial treatments for schizophrenia.

**Data sources.** MEDLINE<sup>®</sup>, the Cochrane Library databases, PsycINFO<sup>®</sup>, and included studies through February 2017.

**Study selection.** We included studies comparing second-generation antipsychotics (SGA) with each other or with a first-generation antipsychotic (FGA) and studies comparing psychosocial interventions with usual care in adults with schizophrenia.

**Data extraction.** We extracted study design, year, setting, country, sample size, eligibility criteria, population, clinical and intervention characteristics, results, and funding source.

**Results.** We included 1 SR of 138 trials (N=47,189) and 24 trials (N=6,672) for SGAs versus SGAs, 1 SR of 111 trials (N=118,503) and 5 trials (N=1,055) for FGAs versus SGAs, and 13 SRs of 271 trials (N=25,050) and 27 trials (n=6,404) for psychosocial interventions. Trials were mostly fair quality and strength of evidence was low or moderate. For drug therapy, the majority of the head-to-head evidence was on older SGAs, with sparse data on SGAs approved in the last 10 years (asenapine, lurasidone, iloperidone, cariprazine, brexpiprazole) and recent long-acting injection (LAI) formulations of aripiprazole and paliperidone. Older SGAs were similar in measures of function, quality of life, mortality, and overall adverse events, except that risperidone LAI had better social function than quetiapine. Core illness symptoms were improved more with olanzapine and risperidone than asenapine, quetiapine, and ziprasidone, and more with paliperidone than lurasidone and iloperidone; all were superior to placebo. Risperidone LAI and olanzapine had less withdrawal due to adverse events. Compared with olanzapine and risperidone, haloperidol, the most studied FGA, had similar improvement in core illness symptoms, negative symptoms, symptom response, and remission but greater incidence of adverse event outcomes. In comparison with usual care, most psychosocial interventions reviewed were more effective in improving intervention-targeted outcomes, including core illness symptoms. Various functional outcomes were improved more with assertive community treatment, cognitive behavioral therapy, family interventions, psychoeducation, social skills training, supported employment, and early interventions for first episode psychosis (FEP) than with usual care. Quality of life was improved more with cognitive behavioral therapy and early interventions for FEP than usual care. Relapse was reduced with family interventions, psychoeducation, illness self-management, family interventions, and early interventions for FEP.

**Conclusions.** Most comparative evidence on pharmacotherapy relates to the older drugs, with clozapine, olanzapine, and risperidone superior on more outcomes than other SGAs. Older SGAs were similar to haloperidol on benefit outcomes but had fewer adverse event outcomes. Most psychosocial interventions improved functional outcomes, quality of life, and core illness symptoms, and several reduced relapse compared with usual care.

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# 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),<sup>1</sup> 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.<sup>2</sup> 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.<sup>3,4</sup>

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.

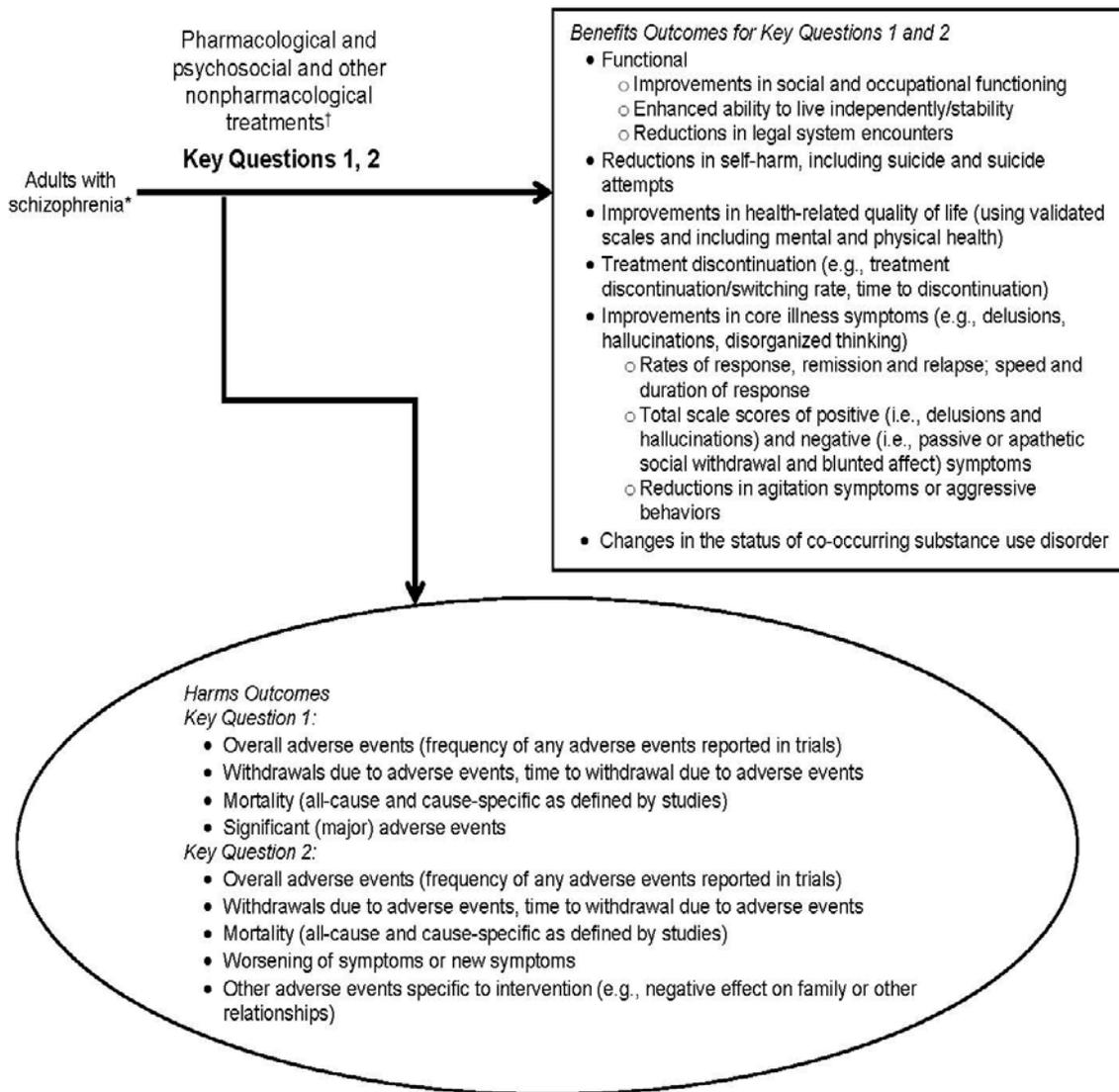
## Scope and Key Questions

### 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:

a. At least 90 percent of patients must have been diagnosed with schizophrenia.

b. 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?<sup>a</sup>
- 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?<sup>a</sup>

## Methods

The methods for this systematic review follow the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*<sup>5</sup> and are reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) checklist.<sup>6</sup> 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<sup>®</sup>, the Cochrane Library, and PsycINFO<sup>®</sup>. 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.

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

## Key Eligibility Criteria

**Population(s):** Adults with a diagnosis of schizophrenia

**Interventions:**

- Key Question 1: Antipsychotic medications
  - First-generation antipsychotic drugs (FGAs)
    - Fluphenazine (Prolixin<sup>®</sup>, Permitil<sup>®</sup>)
    - Haloperidol (Haldol<sup>®</sup>)
    - Perphenazine (Trilafon<sup>®</sup>)
  - Second-generation antipsychotic drugs (SGAs)
    - Aripiprazole (Abilify<sup>®</sup>, Aristada<sup>™</sup>)
    - Asenapine (Saphris<sup>®</sup>),
    - Brexpiprazole (Rexulti<sup>®</sup>)
    - Cariprazine (Vraylar<sup>™</sup>)
    - Clozapine<sup>b</sup> (Clozaril<sup>®</sup>, Fazaclo<sup>®</sup> ODT, Versacloz<sup>™</sup>)
    - Iloperidone (Fanapt<sup>®</sup>)
    - Lurasidone (Latuda<sup>®</sup>)
    - Olanzapine<sup>b</sup> (Zyprexa<sup>®</sup>, Zyprexa Zydis<sup>®</sup>),
    - Olanzapine Pamoate (Zyprexa<sup>®</sup> Relprevv<sup>™</sup>)
    - Paliperidone<sup>b</sup> (Invega<sup>®</sup>) and Paliperidone palmitate (Invega<sup>®</sup> Sustenna<sup>®</sup>, Invega Trinza<sup>™</sup>)
      - 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<sup>b</sup> (Seroquel<sup>®</sup>, Seroquel XR<sup>®</sup>)
      - 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<sup>b</sup> (Risperdal<sup>®</sup>, Risperdal<sup>®</sup> M-TAB<sup>®</sup> ODT (oral dissolving tablet), Risperdal<sup>®</sup> Consta<sup>®</sup>)
    - Ziprasidone<sup>b</sup> (Geodon<sup>®</sup>)
- Key Question 2: Psychosocial and other nonpharmacological interventions<sup>c</sup>
  - 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

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

<sup>c</sup>Limited to the most commonly used interventions relevant to U.S. practices.

- Psychoeducation
- Social skills training
- Supported employment
- Supportive therapy

**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.

- 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.

**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.

## 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.<sup>7</sup> The quality of systematic reviews was assessed using the Assessing the Methodological Quality of Systematic Reviews quality (AMSTAR)-rating instrument.<sup>8</sup> 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*.<sup>5</sup> 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*.<sup>5,9</sup> 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"> <li>• Risperidone LAI significantly better than quetiapine in social function over 24 months</li> <li>• No difference between paliperidone palmitate LAI (monthly) and risperidone LAI (every 2 weeks)</li> </ul>
Function: Improvements in Occupational Function		<ul style="list-style-type: none"> <li>• No significant differences between risperidone, olanzapine, quetiapine, and ziprasidone at 18 months (CATIE)</li> </ul>
Function: Improvements in Global Functioning		<ul style="list-style-type: none"> <li>• Global functioning was not different between olanzapine and either risperidone or quetiapine</li> </ul>
Improvements in Quality of Life	<ul style="list-style-type: none"> <li>• Olanzapine was not found significantly different than risperidone or ziprasidone</li> </ul>	<p>With up to 2 years of followup:</p> <ul style="list-style-type: none"> <li>• Olanzapine and risperidone were not found different from quetiapine</li> <li>• Risperidone LAI was not found different from quetiapine</li> <li>• Oral aripiprazole was not found different from aripiprazole monthly LAI</li> </ul>
Response		<ul style="list-style-type: none"> <li>• Significantly more likely with olanzapine and risperidone than quetiapine based on a network meta-analysis of 46 trials</li> </ul>
Mortality		<p>No difference between:</p> <ul style="list-style-type: none"> <li>• Asenapine and olanzapine</li> <li>• Quetiapine and risperidone</li> <li>• Paliperidone palmitate LAI (monthly) and risperidone LAI</li> <li>• Risperidone, olanzapine, and quetiapine (including cardiovascular mortality)</li> </ul>
Self-Harm	<ul style="list-style-type: none"> <li>• Clozapine was found superior to olanzapine in preventing significant suicide attempts or hospitalization to prevent suicide in high-risk patients</li> </ul>	<ul style="list-style-type: none"> <li>• Clozapine was associated with lower risk of suicide or suicide attempts than olanzapine, quetiapine, and ziprasidone in unselected patients</li> </ul>
Core Illness Symptoms: Improvements in Total Scale Scores		<ul style="list-style-type: none"> <li>• Clozapine improved core illness symptoms more than the other SGAs, except for olanzapine</li> <li>• Olanzapine and risperidone improved core illness symptoms more than the other SGAs, except for each other and paliperidone</li> <li>• Paliperidone improved core illness symptoms more than lurasidone and iloperidone</li> <li>• In treatment-resistant patients, olanzapine improved core illness symptoms more than quetiapine</li> </ul>
Overall Adverse Events	<ul style="list-style-type: none"> <li>• No significant difference in overall adverse events between olanzapine and asenapine</li> </ul>	<ul style="list-style-type: none"> <li>• 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</li> </ul>

Outcome	Moderate Strength of Evidence	Low Strength of Evidence
Withdrawal Due to Adverse Events		<p>Based on a network meta-analysis of 90 trials:</p> <ul style="list-style-type: none"> <li>• Risperidone LAI had significantly lower risk than clozapine, lurasidone, quetiapine ER, risperidone, and ziprasidone</li> <li>• Olanzapine had lower risk than clozapine, lurasidone, quetiapine, risperidone, and ziprasidone</li> <li>• Aripiprazole had lower risk than clozapine and ziprasidone</li> <li>• Cariprazine and lloperidone had lower risk than clozapine</li> </ul>

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

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"> <li>• CBT: benefit over usual care over 6 months; not during 6 to 12 months of treatment</li> <li>• Early team-based multi-component treatment programs for first-episode psychosis: Beneficial with treatment duration up to 2 years</li> <li>• Psychoeducation x 3 months; beneficial at 1-year followup</li> </ul>	<ul style="list-style-type: none"> <li>• Social skills training: Beneficial at end of treatment (6 months to 2 years treatment duration) versus usual care</li> <li>• 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)</li> <li>• ICM: Not different from usual care</li> <li>• Supportive therapy: Not different from usual care</li> </ul>
Function: Improvements in Social Function	<ul style="list-style-type: none"> <li>• CBT: Benefit over usual care over 6 months; not during 6 to 12 months treatment</li> <li>• Early team-based multi-component treatment programs for first-episode psychosis: Beneficial with treatment duration up to 2 years</li> </ul>	<ul style="list-style-type: none"> <li>• ACT: Not different from usual care in social function or criminal justice system events</li> <li>• ICM: Not different from usual care in rate of imprisonment</li> <li>• Family Intervention: Not different from usual care</li> </ul>
Function: Improvements in Occupational Function	<ul style="list-style-type: none"> <li>• ACT: beneficial versus usual care with intervention duration up to 2 years</li> <li>• 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)</li> </ul>	<ul style="list-style-type: none"> <li>• Family Interventions: Not different from usual care</li> </ul>
Function: Improvements in Living Situation	<ul style="list-style-type: none"> <li>• ACT: beneficial with treatment duration up to 2 years</li> </ul>	<ul style="list-style-type: none"> <li>• Family Interventions: Not different from usual care</li> </ul>
Improvements in Quality of Life		<ul style="list-style-type: none"> <li>• CBT: Benefit over usual care over 6 months treatment; difference not found with longer followup versus usual care (up to 18 months followup)</li> <li>• Early team-based multi-component treatment programs for first-episode psychosis: Beneficial with treatment duration up to 2 years</li> </ul>
Core Illness Symptoms: Improvements in Total Scale Scores	<ul style="list-style-type: none"> <li>• CBT: Benefit over usual care during treatment (8 weeks to 5 years); effect not maintained after treatment end</li> <li>• Illness self-management: Benefit over usual care during treatment (12-48 sessions)</li> </ul>	<ul style="list-style-type: none"> <li>• Cognitive remediation: Small improvements in core illness symptoms versus usual care, based on 2 trials</li> <li>• Early team-based multi-component treatment programs for first-episode psychosis: Not different from usual care</li> <li>• Family Interventions: Improved core illness symptoms</li> <li>• ICM: Not different from usual care</li> <li>• Social skills training: Greater improvement than with usual care during 6 months and 2 years of treatment</li> <li>• ACT: Not different from usual care</li> </ul>

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

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.<sup>10-15</sup> 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.<sup>10,11,13,15-18</sup>

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).<sup>14,17,19-21</sup> 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.<sup>22,23</sup> 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 before<sup>24-27</sup> with no clear conclusion, although some have found little difference in analyses limiting to usual care comparisons and those including other comparisons.<sup>24</sup> 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 review<sup>28</sup> 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.<sup>29</sup>

## **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.<sup>29-31</sup> 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.<sup>32</sup> Results related to durability of treatment from individual trials with longer post-treatment followup have been mixed. One trial<sup>33</sup> of 9 months of CBT versus befriending found sustained benefit on overall and negative symptoms at 5-year followup with CBT, while a second trial<sup>34</sup> 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.<sup>30,35</sup> Our findings regarding negative symptoms, based on two good-quality systematic reviews,<sup>24,36</sup> are somewhat in contrast with a 2008 review by Wykes et al. that found CBT associated with significant improvements in negative symptoms.<sup>30</sup> 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.<sup>37</sup> 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.<sup>29</sup>

## **Family Interventions**

Previous systematic reviews<sup>38</sup> and other reviews<sup>39</sup> and the 2009 PORT publication<sup>29</sup> 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.<sup>38</sup> 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 psychoeducation<sup>39</sup> 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.<sup>40</sup> 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.<sup>41,42</sup>

## **Social Skills Training**

Our inclusion criteria were considerably stricter than those of other recent reviews<sup>43,44</sup> 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.<sup>43-45</sup> Our findings for relapse, another target of social skills training, were also consistent with other reviews<sup>43,45</sup> 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.<sup>43</sup> 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.<sup>29</sup> 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.<sup>29,46</sup> 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.<sup>47,48</sup> 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 review<sup>47</sup> that we included rated the evidence as very low quality according to the Grading of Recommendations, Assessment, Development, and Evaluation working group (GRADE)<sup>49-55</sup> 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.<sup>56</sup>
- 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 Criteria<sup>57</sup> 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.<sup>58,59</sup>
  - 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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# Introduction

## Background

### Condition

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),<sup>1</sup> has continued the trend of clarifying and simplifying the diagnostic criteria for schizophrenia from the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition (DSM-III) through DSM-IV without changing the defined patient population among the editions.<sup>2</sup> Currently, DSM-5 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); at least one of the symptoms being delusions, hallucinations, or disorganized speech; and, symptoms being present for at least 6 months. Lifetime prevalence is approximately 0.3 to 0.7 percent, with onset most commonly between late adolescence through the third decade.<sup>3</sup> 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;<sup>4</sup> however, the majority tend to experience some degree of social and occupational difficulty as well as need for daily living supports. 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.<sup>5,6</sup>

### Treatment Strategies

Antipsychotic medications (primarily effective via dopaminergic antagonism) and nonpharmacological treatments are typically used together when treating individuals with schizophrenia. Both approaches 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. While pivotal trials of antipsychotic efficacy are limited to measurement of symptom reduction, measurement of other important recovery-oriented outcomes that reflect improvement in social and occupational functioning are necessary to describe benefits of treatments on overall quality of life and functional ability.

Historically, the wide array of antipsychotic drug treatments has had uncertain impact on long-term patient-centered outcomes, such as the ability to have consistent employment and successful interpersonal relationships, as well as maintenance in independent living, and includes serious concerns about adverse effects (e.g., tardive dyskinesia, weight gain, diabetes, and dyslipidemia) for some treatments. Many patients prescribed an antipsychotic discontinue it. Discontinuation rates and time to discontinuation vary by treatment and patient characteristics.

Older, first-generation antipsychotics (FGAs), such as haloperidol, have proven efficacy but adverse effects such as extrapyramidal symptoms (EPS) 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, specifically potentially better effects on negative symptoms, and the hope of fewer EPS and lower risk of tardive dyskinesia. But SGAs also have potentially serious adverse effects (e.g., cardiovascular and endocrinologic adverse 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 improve the likelihood of recovery, and the most effective duration of treatment is unclear. Equally important in selecting among competing interventions for a specific patient is consideration of patient-level characteristics that may affect the outcomes (including age, duration of symptoms, severity, and other psychiatric or medical comorbidities) across a diverse group of possible interventions. For example, treatment of negative symptoms (e.g., diminished emotional response and lack of interest) may differ from treatment of positive symptoms (e.g., hallucinations and delusions). Most psychosocial interventions have specific targets for the patient population and outcome measure. Patients and providers are also interested in other patient-centered health outcomes.

While the success of any given treatment depends on the balance of benefit and harm, specific treatment considerations will vary across the lifespan. Treating patients aggressively early in the disease is thought to improve long-term outcomes although overly aggressive treatments, particularly drug treatments, may result in adverse effects. Additionally, substance abuse (e.g., tobacco, alcohol, illicit drugs) may begin early on for individuals with schizophrenia, and in these patients successful treatment of schizophrenia involves consideration of this comorbidity as well.<sup>7-10</sup> The metabolic effects related to both the disease and drug treatments are concerning across age groups, starting in adolescence or early adulthood.<sup>11</sup> Epidemiologic studies have found an association with obesity, elevated lipids, and shorter lifespan, and several antipsychotic drugs are known to increase these risks.<sup>12-18</sup> Older patients may have increased risk of mortality<sup>19-22</sup> and require antipsychotic dosing changes with age.<sup>23,24</sup> Across all age groups, primary goals include diminishing core illness symptoms and reducing relapses of acute psychosis; however, physical health comorbidities can present challenges requiring modification of the treatment plan.

## **Scope and Key Questions**

### **Scope of the Review**

In this systematic review, we evaluate the current evidence to inform treatment options for individuals with schizophrenia. The review synthesizes evidence on the comparative effectiveness of pharmacological treatments and the effectiveness of common psychosocial and other nonpharmacological treatment strategies for individuals with schizophrenia, points out areas of controversy, and highlights future research needed.

Due to a very large number of studies and interventions, the scope of the review focuses on specific types of evidence. For pharmacological interventions, we limited to the most commonly used FGA drugs (fluphenazine, haloperidol, and perphenazine), but included all United States Food and Drug Administration (FDA)-approved SGA drugs. For the pharmacological interventions, the focus was on comparative evidence, directly comparing drugs to each other. This decision was based in part on the availability of sufficient evidence on general efficacy of

the drugs to treat schizophrenia in the form of studies used to gain FDA approval, that is, placebo-controlled trials. For psychosocial and nonpharmacological interventions, we limited to the most commonly-used interventions relevant to United States practices. In doing this, we excluded single studies of unique interventions, and studies conducted in countries with cultural, social, and health care environments that are very different from the United States. We limited to studies comparing a psychosocial or other nonpharmacological intervention to “usual care” as a common comparator. This decision was made largely due to the heterogeneity of interventions and comparators across studies, the existence of many studies comparing these interventions to usual care, and to provide a common comparator across the interventions.

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 the outcomes. We did not include two outcomes that are sometimes evaluated. First, we excluded rehospitalization, 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. For assertive community treatment, where decreasing rehospitalization is the target of the intervention, we included rehospitalization as an outcome. Second, we excluded changes in neurocognitive test results, as these were viewed as an intermediate outcome. Instead, we have prioritized measures of functioning that include neurocognition as part of a set of broader patient-centered health outcomes. The Analytic Framework for the review appears in Figure 1.

## Key Questions

1a. What are the comparative benefits and harms of pharmacological treatments for adults with schizophrenia?

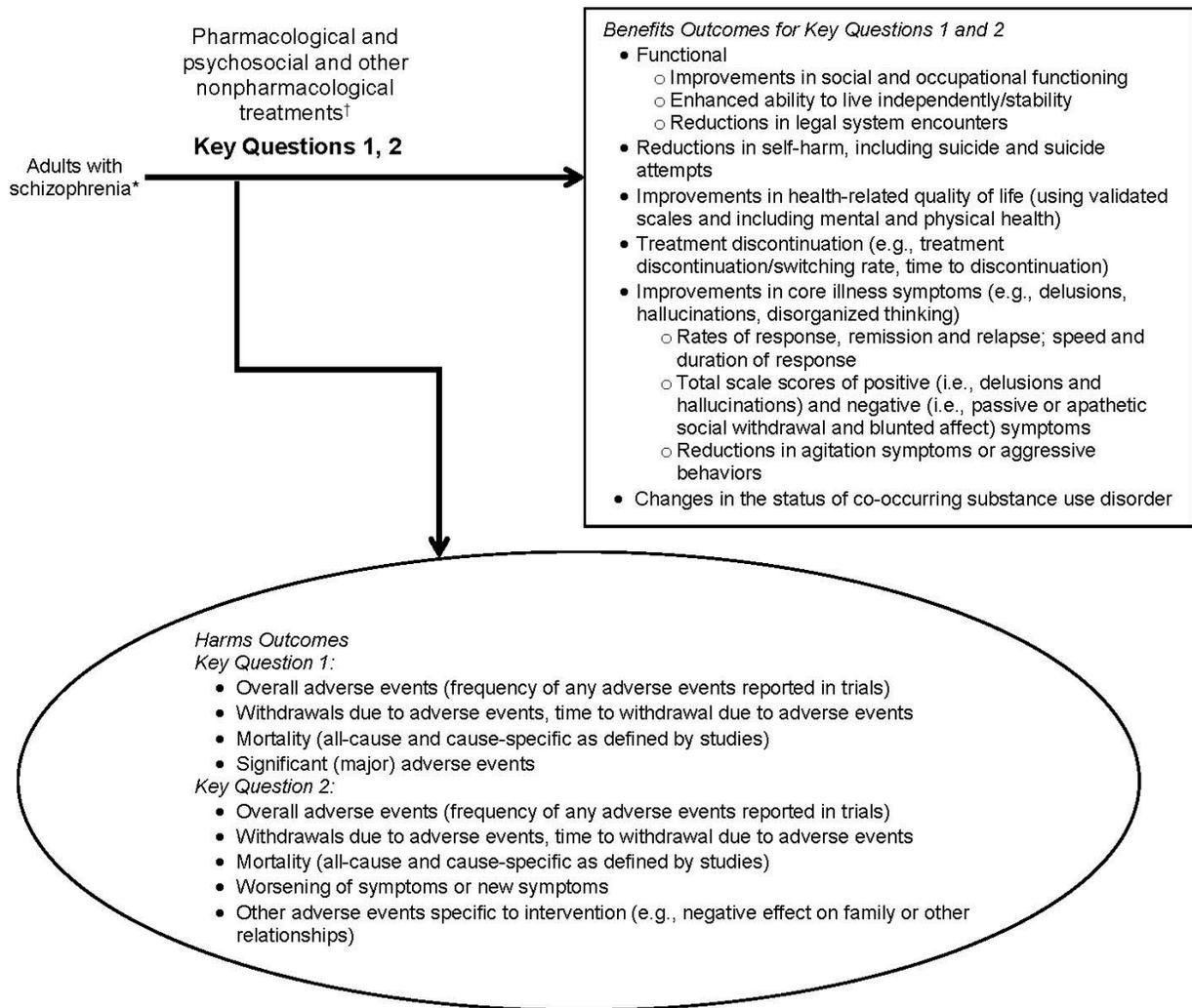
1b. How do the benefits and harms of pharmacological treatments for adults with schizophrenia vary by patient characteristics?<sup>a</sup>

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?<sup>a</sup>

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

**Figure 1. 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:

a. At least 90 percent of patients must have been diagnosed with schizophrenia.

b. 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.

## Methods

The methods for this systematic review follow the Agency for Healthcare Research & Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.<sup>25,26</sup> See the review protocol (<http://effectivehealthcare.ahrq.gov/index.cfm>) for full details.

### Topic Refinement and Review Protocol

Initially a panel of key informants gave input on the key questions to be examined; these key questions were posted on AHRQ's Effective Health Care (EHC) Web site for public comment in May 2016 for 3 weeks and revised in response to comments. We then drafted a protocol for the systematic review and recruited a panel of technical experts to provide high-level content and methodological expertise throughout the development of the review. The finalized protocol is posted on the EHC Web site at <http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2279>. The International Prospective Register of Systematic Reviews (PROSPERO) registration is PROSPERO 2016:CRD42016048403.

### Literature Search Strategy

**Publication date range.** For Key Question 1 on pharmacological interventions, recent high-quality systematic reviews directly addressing large portions of the key questions in the current review have been published and were used as the starting point for the review.<sup>27-29</sup> Based on the search dates in these reviews, searches for trials and systematic reviews began in 2011 for first generation antipsychotic (FGA) versus second generation antipsychotic (SGA) drugs and in 2013 for SGA versus SGA drugs. Starting the searches in January of 2011 and 2013, respectively, allows for multiple months of overlap of the new search dates with the search dates in the prior reviews.

For Key Question 2 on nonpharmacological interventions, search dates were not restricted. Within these searches we first identified the most recent, good-quality systematic reviews for particular interventions. Any trials identified in our searches that were published since the search dates in these reviews were also included to update the included reviews.

Library searches were updated through February 1, 2017 during which the draft report was posted for public comment and peer review to capture any new publications. Literature identified during the updated search, or through other methods described below, was assessed by following the same process of dual review as all other trials considered for inclusion in the report.

**Literature databases.** A research librarian searched Ovid MEDLINE<sup>®</sup>, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and PsycINFO<sup>®</sup> to capture published literature (Appendix A.).

**Scientific information packets.** The AHRQ Evidence-based Practice Center (EPC) Scientific Resource Center sent email notification to relevant stakeholders about the opportunity to submit scientific information packets (SIPs) via the EHC Web site for the pharmaceutical interventions listed in Key Question 1.

**Hand searching.** Reference lists of included articles were reviewed for includable literature.

**Grey literature.** Searches for grey (unpublished) literature include the SIPs submitted for pharmacological interventions and the ClinicalTrials.gov trial registry to identify trials that have been completed but not yet published.

## Inclusion and Exclusion Criteria

### Population(s):

- Adults with a diagnosis of schizophrenia, including those with co-occurring substance use disorders (SUDs), and including those experiencing a first episode of schizophrenia (including those with schizophreniform disorder)
  - Key Question 1:
    - 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
  - Key Question 2:
    - 50 percent of patients must have been diagnosed with a schizophrenia spectrum disorder (i.e., schizophrenia, schizoaffective disorder, or schizophreniform disorder).<sup>30</sup>

### Interventions:

- Key Question 1: Antipsychotic medications
  - Key first-generation antipsychotic drugs
    - Fluphenazine (Prolixin<sup>®</sup>, Permitil<sup>®</sup>)
    - Haloperidol (Haldol<sup>®</sup>)
    - Perphenazine (Trilafon<sup>®</sup>)
  - Second-generation antipsychotic drugs
    - Aripiprazole (Abilify<sup>®</sup>, Aristada<sup>™</sup>)
    - Asenapine (Saphris<sup>®</sup>),
    - Brexpiprazole (Rexulti<sup>®</sup>)
    - Cariprazine (Vraylar<sup>™</sup>)
    - Clozapine<sup>b</sup> (Clozaril<sup>®</sup>, Fazaclor<sup>®</sup> oral dissolving tablet [ODT], Versacloz<sup>™</sup>)
    - Iloperidone (Fanapt<sup>®</sup>)
    - Lurasidone (Latuda<sup>®</sup>)
    - Olanzapine<sup>b</sup> (Zyprexa<sup>®</sup>, Zyprexa Zydis<sup>®</sup>), Olanzapine Pamoate (Zyprexa<sup>®</sup> Relprevv<sup>™</sup>)
    - Paliperidone<sup>b</sup> (Invega<sup>®</sup>) and Paliperidone palmitate (Invega<sup>®</sup> Sustenna<sup>®</sup>, Invega Trinza<sup>™</sup>)
      - 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.

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

- Quetiapine<sup>b</sup> (Seroquel<sup>®</sup>, Seroquel XR<sup>®</sup>)
  - The extended release formulation is noted as quetiapine extended release (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<sup>b</sup> (Risperdal<sup>®</sup>, Risperdal<sup>®</sup> M-TAB<sup>®</sup> ODT, Risperdal<sup>®</sup> Consta<sup>®</sup>)
- Ziprasidone<sup>b</sup> (Geodon<sup>®</sup>)

Excluded: Short-acting injectable drugs, as they are generally only used in emergent, acute conditions and on a short-term basis (hours to days)

- Key Question 2: Psychosocial and other nonpharmacological interventions<sup>c</sup>
  - Assertive community treatment
  - Cognitive adaptive training
  - Cognitive behavioral therapy
  - Cognitive remediation/training
  - Co-occurring substance use and schizophrenia interventions (reported in Key Question 2b)
  - Early interventions for first episode psychosis (reported in Key Question 2b)
  - Family interventions
  - Intensive case management
  - Illness self-management training
  - Psychoeducation
  - Social skills training
  - Supported employment
  - Supportive therapy

**Comparators:**

- Key Question 1:
  - Head-to-head comparisons: three FGAs (listed above) and all FDA-approved SGAs
    - Exclude: FGA versus FGA drug comparisons
- Key Question 2:
  - Antipsychotic drugs (alone)
  - 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. We assumed that randomization would balance the specific elements of usual care interventions between treatment and control arms within each randomized controlled trial (RCT). Both groups (treatment and usual care) received usual care, including drug treatment throughout the study.

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

<sup>c</sup>Limited to the most commonly-used interventions relevant to United States practices.

- 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:<sup>d</sup>**

- Benefits outcomes
  - Key Questions 1 and 2
    - Functional
      - Improvements in social and occupational/educational functioning
      - Enhanced level of independent or stable living situation
      - Reductions in legal system encounters
      - Global functioning
    - Reductions in self-harm, including suicide and suicide attempts
    - Improvements in health-related quality of life (using validated scales and including mental and physical health)
    - Treatment discontinuation (e.g., treatment discontinuation/switching rate, time to discontinuation for any reason including lack of efficacy or intolerable adverse effects)
    - Improvements in core illness symptoms (e.g., delusions, hallucinations, disorganized thinking)
      - Rates of response, remission, and relapse; speed and duration of response
      - Total scale scores of positive (i.e., delusions and hallucinations) and negative (i.e., passive or apathetic social withdrawal and blunted affect) symptoms
      - Reductions in agitation symptoms or aggressive behaviors
    - Changes in the status of co-occurring SUD (Key Question 2b).
- Exclusions:
  - 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.
  - Neurocognitive testing is an intermediate outcome, rather than a patient-centered health outcome, and is excluded in favor of improvements in functioning that reflect cognition.

<sup>d</sup> Intervention patient-outcome targets are highlighted in the results; most are included among the prioritized outcomes listed above.

- Harms outcomes
  - Key Question 1
    - Overall adverse events (frequency of any adverse events reported in trials)
    - Withdrawals due to adverse events, time to withdrawal due to adverse events
    - Mortality (all-cause and cause-specific as defined by studies)
    - Significant (major) adverse events (e.g., life threatening, results in long-term morbidity, or require medical intervention to treat, such as cerebrovascular or cardiovascular disease and related events, development of diabetes mellitus, diabetic ketoacidosis, neuroleptic malignant syndrome, seizures, extrapyramidal symptoms (EPS), tardive dyskinesia, clinically important weight changes, dyslipidemia, incidence and severity of sexual dysfunction, galactorrhea, amenorrhea, orthostatic hypotension, and agranulocytosis/severe neutropenia)
  - Key Question 2
    - Overall adverse events (frequency of any adverse events reported in trials)
    - Withdrawals due to adverse events, time to withdrawal due to adverse events
    - Mortality (all-cause and cause-specific as defined by trials)
    - Outcomes reported as adverse events related to the intervention, such as:
      - New or worsening symptoms (e.g., anxiety or depression) using validated scales
      - Negative effect on family or other relationships.

**Timing:**

- Minimum duration of followup: 12 weeks.

**Settings:**

- United States-relevant, for example 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:**

- Key Questions 1 and 2:
  - Best-evidence approach:<sup>31</sup>
    - Recent, comprehensive, good- or fair-quality systematic reviews to be used as primary evidence, as well as RCTs published since the systematic reviews
      - For benefits of any included intervention, systematic reviews of RCTs will be included
      - For harms of any included intervention, systematic reviews of observational trials to evaluate harms will be included in addition to reviews of trials
      - Note: We included some systematic reviews that included a portion of trials with inpatients, otherwise, most evidence would have had to be excluded. However, we did not include individual trials that included inpatients.
    - If no systematic reviews available for particular interventions, RCTs will be included

- Key Question 2: Studies must have a sample size of >50.

## Study Selection

The pre-established criteria (described above) was used to determine eligibility for inclusion and exclusion of abstracts in accordance with the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.<sup>26</sup> All citations deemed appropriate for inclusion by at least one of the reviewers was retrieved; excluded abstracts were dual reviewed. Each full-text article was independently reviewed for eligibility by at least two team members. Any disagreements were resolved by consensus.

A list of included studies is available in Appendix B, and a list of excluded studies with reasons for exclusion is available in Appendix C.

## Data Extraction

After studies were selected for inclusion, the following data was abstracted into predetermined table templates: study design, year, setting, country, sample size, eligibility criteria, population and clinical characteristics, intervention characteristics, and results relevant to each key question, as well as other information (e.g., funding source). When results were reported as scale scores, we included the scale abbreviation in our tables; full names of scales used, score ranges, and direction of effect are available in Appendix D. Abstracted information that is relevant for assessing applicability included the number of patients randomized relative to the number of patients enrolled, use of run-in or wash-out periods (for drug studies), and characteristics of the population, intervention, and care settings. All study data has been verified for accuracy and completeness by a second team member. Data extraction tables are available in Appendix E.

## Quality Assessment of Individual Studies

The quality of individual controlled trials and systematic reviews were assessed by using clearly predefined criteria. RCTs were evaluated with appropriate criteria and methods developed by the Drug Effectiveness Review Project (DERP).<sup>32</sup> Systematic reviews were assessed using the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) quality-rating instrument.<sup>33</sup> These criteria and methods were used in conjunction 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*.<sup>26</sup> Studies were rated as “good,” “fair,” or “poor.” Observational studies that were included in systematic reviews included in this review must have been assessed for quality or risk of bias using a design-appropriate tool.

Studies rated “good” quality were considered to have the least risk of bias, and their results will be considered valid. Good-quality studies include clear descriptions of the population, setting, interventions, and comparison groups; a valid method for allocation of patients to treatment; low dropout rates and clear reporting of dropouts; appropriate means for preventing bias; and appropriate measurement of outcomes.

Studies rated “fair” quality were susceptible to some bias, although not enough to invalidate the results. These studies may not meet all the criteria for a rating of good quality, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess

limitations and potential problems. The fair-quality category is broad, and studies with this rating will vary in their strengths and weaknesses.

Studies rated “poor” quality have significant flaws that imply biases of various types that may invalidate the results. They will have a serious or “fatal” flaw in design, analysis, or reporting; large amounts of missing information; discrepancies in reporting; or serious problems in the delivery of the intervention. The results of these studies will be as likely to reflect flaws in the study as the true difference between the compared interventions. We will not exclude studies rated as being poor in quality *a priori*, but poor-quality studies will be considered to be less reliable than higher-quality studies when synthesizing the evidence, particularly if discrepancies between studies are present (see strength of evidence [SOE] rating system below).

This approach to evaluating the internal validity of studies is similar to the “risk of bias” method, although the direction of the scale for ratings is inverse to the good, fair, and poor ratings used here. Specifically, low, moderate, or high risk of bias correlates with good, fair, and poor quality, respectively. Each study was dual-reviewed for quality by two team members. Any disagreements were resolved by consensus. Quality assessment tables are available in Appendix F.

## Data Synthesis

We constructed evidence tables identifying the study characteristics (as discussed above), results for outcomes of interest, and quality ratings for all included studies, and, when appropriate, summary tables to highlight the main findings. Good- and fair-quality systematic reviews and trials were the focus of the results for each key question. Results from systematic reviews were presented first, followed by synthesis of the findings from trials not included in the reviews. To the extent possible, meta-analyses in included systematic reviews were updated with data from trials not included in the reviews. For the remainder of the included trials (those not included in the included systematic reviews and with evidence not conducive to meta-analysis), we summarized the trials’ findings in the context of the included systematic review findings; we identified both consistent and discordant findings and evaluated reasons for any discordant findings.

Qualitative data was summarized as ranges and descriptive analysis, and interpretation of the results was provided. We compiled and summarized study characteristics and investigated whether there were important differences in the distribution in characteristics that modified the treatment effects.

Meta-analyses were conducted to summarize data and obtain more precise estimates on outcomes for which studies were homogeneous enough to provide a meaningful combined estimate. To determine whether meta-analysis could be meaningfully performed, we considered the quality of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes. We examined the possibility for conducting network meta-analyses to provide estimates of comparative effect across the interventions for specific outcomes, according to key question.

We conducted pairwise meta-analyses to calculate relative risks for dichotomous outcomes. For continuous outcomes, we used endpoint scores where baseline scores were similar between groups (within study), and changed scores where they were the only data provided. We used standard deviations where reported and performed calculations when standard errors or 95% confidence intervals (CIs) were reported instead. We used the DerSimonian and Laird random-effects model with Review Manager Version 5.3 software,<sup>34</sup> StatsDirect, version 3.0.167,<sup>35</sup> or

Stata 14.<sup>36</sup> Statistical heterogeneity was assessed using the  $I^2$  statistic for three or more studies and the Q-statistic chi square test where only two studies could be pooled.

Network meta-analyses were conducted for key effectiveness binary outcomes with adequate data to support a network using a Bayesian hierarchical model for exploratory purpose.<sup>37,38</sup> The appropriateness of combining direct and indirect evidence and the consistency of the network was assessed by using the loop-specific approach to examine inconsistency separately in every closed loop of a network, the node-splitting method and overall comparison of consistency and inconsistency models.<sup>39,40</sup> Inconsistency was explored if detected. We used vague priors in the Bayesian model, and posterior inference was based on Markov Chain Monte Carlo (MCMC) Sampling using two chains. Trace plot and the Gelman-Rubin statistic, as modified by Brooks and Gelman (1998) was used to check convergence of Markov Chains.<sup>41</sup> Posterior point and interval estimates of model parameters were obtained based on 200,000 MCMC iterations thinned at every 100<sup>th</sup> value after initial burn-in of 200,000 iterations (i.e., 2000 iterations per chain). Comparative effectiveness was measured by using odds ratio (OR), and estimated by controlling for variation in study duration, dose levels (low, medium, and high), and whether studies enrolled patients with a first episode of schizophrenia or whose symptoms were resistant to prior treatment in all models. For Response, the Bayesian model also included assessment of the definition of response, grouped into three categories: 20 percent improvement in Positive and Negative Syndrome Scale (PANSS); other scales (i.e., Clinical Global Impression - Improvement scale [CGI-I]) or thresholds; and combined 20 percent improvement in PANSS and other measures. Controlling the study-level variables also allowed us to evaluate whether the drug effectiveness varied by these variables. The construction of network plot and evaluation of inconsistency was done using Stata/SE 14.1 (StataCorp LP, College Station, TX 77845), and the Bayesian model was implemented using OpenBUGS 3.2.3 (<http://www.openbugs.net/w/FrontPage>). Forest plots for pooled analyses and matrixes of results for network analyses are available in Appendix G.

## Strength of the Body of Evidence

The SOE for each key outcome per intervention area was assessed by using the approach described in the AHRQ EPC Methods Guide.<sup>26,42</sup> Key outcomes were clinical, patient-centered (i.e., health outcomes) and were selected based on input from the Technical Expert Panel (TEP), a panel of experts convened to review the appropriateness and relevance of the report at the scoping phase. The prioritized outcomes are listed below, per intervention area.

### Pharmacological interventions:

1. Functional outcomes (e.g., social, occupational)
2. Health-related quality of life (including physical)
3. Rates of response and/or remission
4. Mortality (all-cause and/or specific)
5. Reductions in self-harm, suicide, and suicide attempts
6. Improvements in core illness symptoms scale score changes
7. Overall/any adverse events (rate or proportion)
8. Withdrawal due to adverse events

### **Psychosocial and other nonpharmacological interventions:**

1. Functional (e.g., social, occupational)
2. Health-related quality of life
3. Reductions in self-harm, suicide, and suicide attempts
4. Rates of response and/or remission
5. Improvements in core illness symptoms scale score changes
6. Treatment discontinuation (typically reported as the number of patients lost to followup or leaving study early)
7. Rates of relapse
8. Outcomes reported as adverse events related to the intervention

SOE was initially assessed by one researcher, and to ensure consistency and validity of the evaluation, a senior reviewer reviewed the grades and any disagreements were resolved through consensus. SOE was based on the following domains<sup>e</sup>:

1. Study limitations (low, medium, or high level of study limitations based on the quality/risk of bias of individual studies)
2. Consistency (consistent, inconsistent, or unknown/not applicable)
3. Directness (direct or indirect)
4. Precision (precise or imprecise)

The SOE was assigned an overall grade of high, moderate, low, or insufficient according to a four-level scale by evaluating and weighing the combined results of the above domains:

**High** — We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable (i.e., another study would not change the conclusions).

**Moderate** — We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.

**Low** — We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.

**Insufficient** — We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

The details of the SOE are available in Appendix H. If the entire body of evidence was deemed insufficient for an intervention category, we presented tables of the main study characteristics and quality, descriptive summary of findings, funding source and reasons for being deemed insufficient. These bodies of evidence did not undergo further synthesis.

<sup>e</sup> Reporting bias is also a domain listed in the AHRQ EPC Methods guidance on SOE, but as none of the included reviews assessed this domain we were unable to fully assess this item. If obvious problems with reporting bias were found, they are noted under the study limitations domain.

Similarly, the evidence for subgroups in Key Questions 1b and 2b was only assessed for SOE if an intervention was studied in a specific subgroup, but subgroup analyses of the larger evidence base were not assessed as they represent hypothesis generating research and would not meet the criteria for SOE.

## **Applicability**

Applicability was assessed according to the approach described in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.<sup>26</sup> We used the population, intervention, comparison, outcomes, timing, study design/setting (PICOTS) framework to consider the applicability of the evidence base for each key question and intervention area, for example examining the characteristics of the patient populations (e.g., age, severity and duration of illness).

## **Peer Review and Public Commentary**

Experts in treatments for schizophrenia were invited to provide external peer review of this systematic review; 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

## Results of Literature Searches

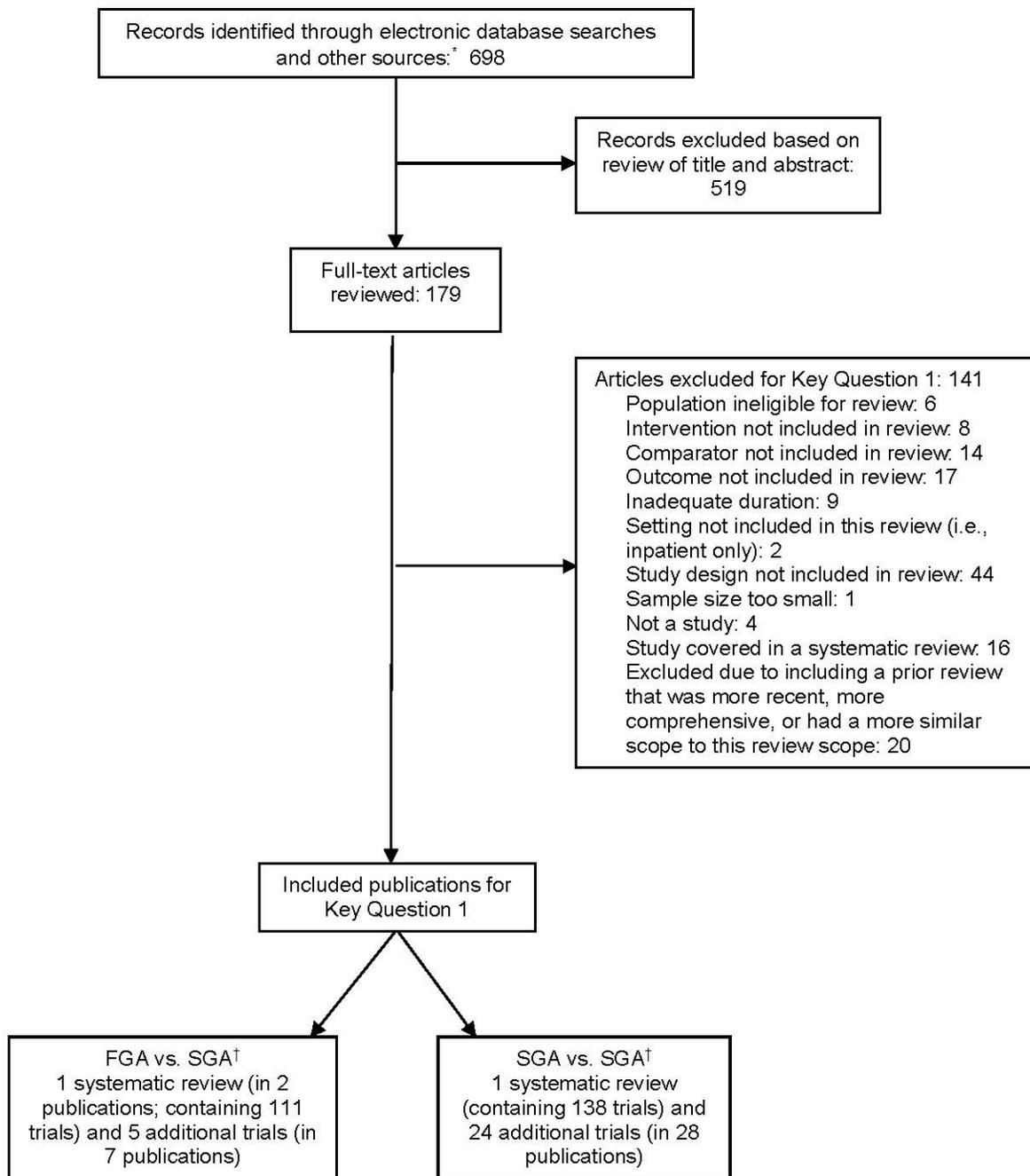
For Key Question 1 on the benefits and harms of pharmacological interventions for schizophrenia, we reviewed 698 titles and abstracts and included one systematic review<sup>29</sup> of 138 trials (N=47,189) and 24 additional trials<sup>43-66</sup> (N=6,672) for second-generation antipsychotics (SGAs) versus other SGAs, and one systematic review of 111 trials<sup>27,28</sup> (N=118,503) and five additional trials<sup>57,67-70</sup> (N=1,055) for first-generation antipsychotics (FGAs) versus SGAs. There was significant overlap of studies between the two sections.

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 (N=25,050) and 27 additional trials (n=6,404) across 13 main intervention areas: assertive community treatment (1 systematic review<sup>71</sup> and 1 trial<sup>72</sup>), cognitive adaptive training (CAT; 3 trials<sup>73-76</sup>), cognitive-behavioral therapy (CBT; 3 systematic reviews<sup>77-79</sup> and 5 trials<sup>76,80-83</sup>), cognitive remediation/training (2 systematic reviews<sup>84,85</sup> and 4 trials),<sup>86-90</sup> family interventions (1 systematic review<sup>91</sup> and 6 trials<sup>92-97</sup>), intensive case management (ICM; 1 systematic review<sup>98</sup> and 1 trial<sup>99</sup>), illness self-management and recovery (1 systematic review<sup>100</sup> and 1 trial<sup>101</sup>), psychoeducation (1 systematic review<sup>102</sup>), social skills training (3 trials<sup>97,103-105</sup>), supported employment (1 systematic review<sup>106</sup> and 2 trials<sup>107-109</sup>) supportive therapy (1 systematic review<sup>110</sup>), early interventions for first episode psychosis (4 trials<sup>111-119</sup>), and co-occurring substance use disorders (SUDs) and schizophrenia (1 systematic review<sup>120</sup>). For each intervention area, we reported on the available evidence for prioritized, patient centered, outcomes, as described in the Methods. Prioritized outcomes for which there was no evidence available are not included in the Results. Direct comparisons were to usual care, which may include pharmacologic as well as other nonpharmacologic treatments.

The literature flow diagrams are shown in Figures 2 and 3. Tables 1–4 show the main characteristics of the included studies for the systematic reviews and trials for Key Questions 1 and 2 by intervention area. Detailed evidence tables of included studies are available in Appendix E, and details on quality assessment are available in Appendix F.

As described in the methods, for Key Question 2 we excluded unique psychosocial and nonpharmacological interventions, as well as interventions that are not commonly used in the United States (see Appendix C).

**Figure 2. Key Question 1 literature flow diagram**

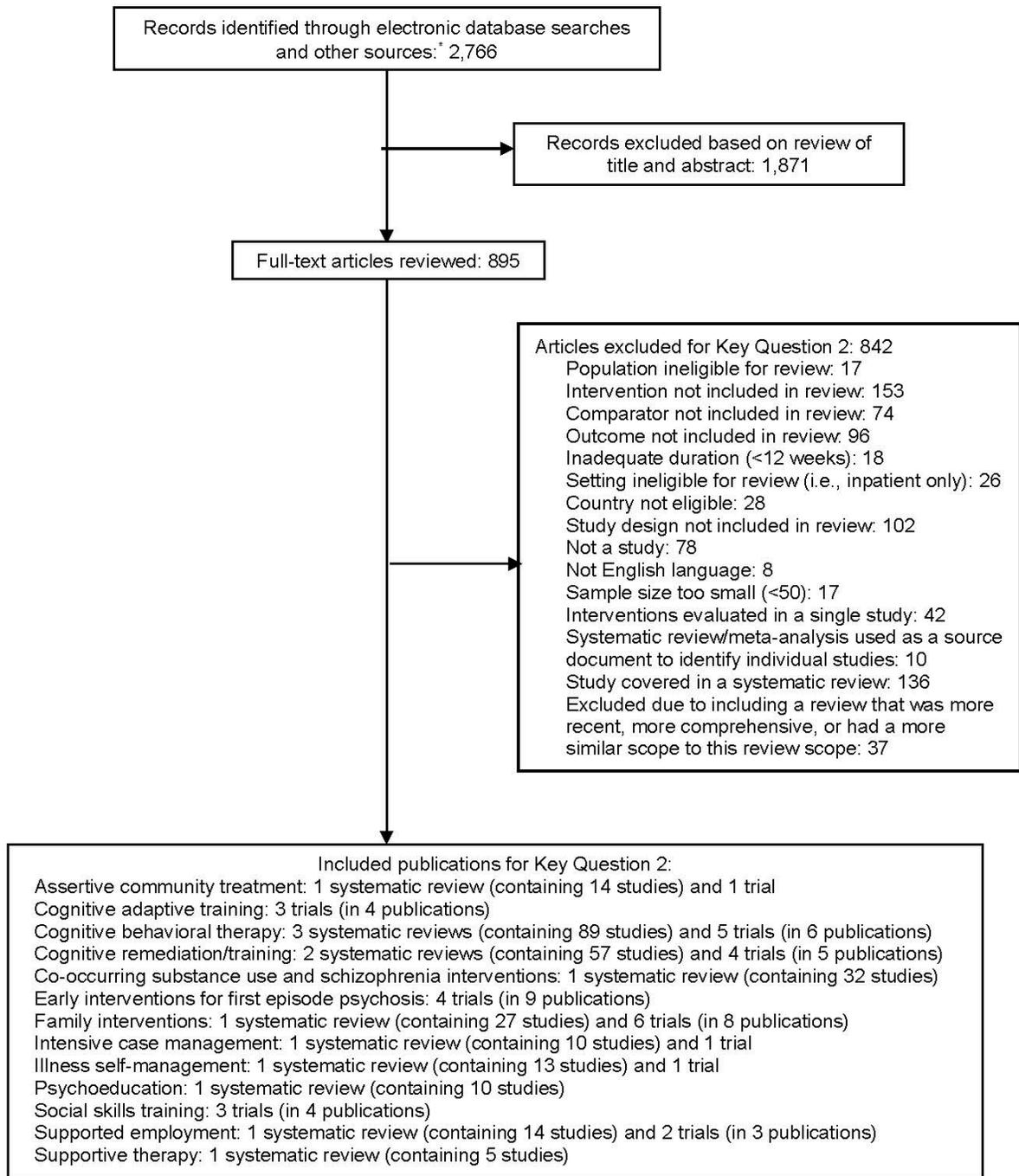


FGA = first-generation antipsychotic; SGA = second-generation antipsychotic

\* Other sources include prior reports, references lists, referrals from experts, and grey literature.

† Some studies were included for both FGA vs. SGA and SGA vs. SGA sections.

**Figure 2. Key Question 2 literature flow diagram**



\*Other sources include prior reports, reference lists, referrals from experts, and grey literature.

**Table 1. Characteristics of included systematic reviews for Key Question 1**

Study Characteristic	FGA Versus SGA	SGA Versus SGA
Study quality (number of SRs)	Good (1)	Good (1)
Number of included studies	113 (111 RCTs and 2 observational studies)	169 (138 RCTs and 31 observational studies)
Sample size	118,503	138 RCTs (N=47,189) 31 observational studies (N=602,547)
Duration of Intervention (range)	<1 day-22 years (median 8 weeks)	6-104 weeks

FGA = first-generation antipsychotic; RCT = randomized controlled trial; SGA = second-generation antipsychotic; SR = systematic review

**Table 2. Characteristics of new included trials for Key Question 1**

Study Characteristic	Category	FGA Versus SGA	SGA Versus SGA
Study quality	Good	2	2
	Fair	2	17
	Poor	1	5
Sample size	Total	1,055	6,672
Duration of intervention / followup	Range	12 weeks-3 years	6 weeks-3 years
Location	U.S. only	1	3
	Other	4	21

FGA = first-generation antipsychotic; SGA = second-generation antipsychotic

**Table 3. Characteristics of included systematic reviews for Key Question 2**

Study Characteristic	ACT	CBT	Cognitive Remediation/ Training	Co-occurring Substance Use Disorder	Family	ICM	Illness Self-Management	Psycho-education	Supported Employment	Supportive Therapy
Study quality (number of SRs)	Good (1)	Good (3)	Good (2)	Good (1)	Fair (1)	Good (1)	Fair (1)	Good (1)	Good (1)	Good (1)
Number of included studies	14	89	57	32	27	10	13	10	14	5
Sample size	2,281	7,154	2,885	3,165	2,297	1,652	1,404	1,125	2,265	822
Duration of intervention	Not reported	8 weeks-5 years	2 weeks-2 years	1 month-3 years	6 weeks-3 years	Not reported	7-49 sessions, 45-90 minutes each	1-18 months	12 – 24 months	7 months-1 year
Duration of followup	1 month-2 years	8 weeks-5 years	2 weeks-2 years	1 month-3 years	6 weeks-8 years	1 month-4 years	Up to 24 months post-treatment	2 months-5 years	2 years	7 months-2 years

ACT = assertive community treatment; CBT = cognitive behavioral therapy; ICM = intensive case management; SR = systematic review

**Table 4. Characteristics of included trials for Key Question 2**

Study Characteristic	Category	Overall	ACT	CBT	Cognitive Remediation/ Training	Early Interventions for First Episode	Family	ICM	Illness Self-Management	Social Skills Training	Supported Employment
Study quality and number of trials	Good	4	0	1	1	1	1	0	0	0	0
	Fair	20	1	4	3	2	3	1	1	3	2
	Poor	3	0	0	0	1	2	0	0	0	0
Sample size	Total	6,404	118	823	341	2,363	562	77	210	433	1477
Duration of intervention	Range	8 weeks-2 years	1 year	8 weeks-9 months	12 weeks-6 months	1-2 years	6-12 months	18 months	8 months	6 months-2 years	2 years
Duration of followup	Range	6 months-3 years	2 years	24 weeks-2 years	6 months-1 year	1-10 years	1-2 years	3 years	8 months	6 months-3 years	2 years
Location	U.S.	8	0	2	1	1	2	0	0	1	2
	Other	18	1	3	3	3	4	1	1	2	0

ACT = assertive community treatment; CBT = cognitive-behavioral therapy; ICM = intensive case management

# Key Question 1a. Comparative Benefits and Harms of Pharmacological Treatments for Adults With Schizophrenia

## Second-Generation Antipsychotic Versus Second-Generation Antipsychotic

### Key Points

- The comparative evidence on SGAs came from one good-quality systematic review that included 138 head-to-head randomized controlled trials (RCTs) (N=47,189), 31 observational studies (N=602,547), and 24 newer RCTs (N=6,672). The studies were mostly fair quality.
- SGAs did not differ in effects on social, occupational, or global functioning.
  - No difference in social functioning was found between paliperidone palmitate monthly long-acting injection (LAI) and risperidone bi-weekly LAI (Personal and Social Performance [PSP] scale mean change from baseline 16.8 and 18.6, respectively; least squares mean [LSM] difference 0.5, 95% confidence interval [CI] -2.14 to 3.12) based on one RCT (N=452) (strength of evidence [SOE]: low).
  - A single study (N=666) found risperidone LAI to result in greater improvements in social function over 24 months compared with quetiapine (change at endpoint 6.6 vs. 1.1;  $p<0.0001$ ) (SOE: low).
  - Although both groups improved significantly from baseline, risperidone LAI resulted in greater improvements than quetiapine on the Social and Occupational Functioning Assessment Scale (SOFAS) at 6 months (6.1 vs. 2.7,  $p=0.02$ ) and 12 months (9.5 vs. 6.1;  $p=0.009$ ) (SOE: low).
  - Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Phase 1 found no significant differences in rates of employment between risperidone, olanzapine, quetiapine, perphenazine, and ziprasidone at 18 months (SOE: low)
  - Global functioning was not different (based on the Global Assessment of Functioning [GAF] scale) between olanzapine and either risperidone (four cohort studies; weighted mean difference [WMD] 0.61, 95% CI -1.78 to 2.99) or quetiapine (two RCTs; WMD 1.14, 95% CI -4.75 to 7.02) (SOE: low).
- Older SGAs (clozapine, risperidone oral and LAI, olanzapine, quetiapine, and ziprasidone) were not found different from one another on a variety of quality of life measures, although small but significant improvements were seen from baseline.
  - Olanzapine was not found significantly different than risperidone (two RCTs; moderate SOE), ziprasidone (two RCTs; moderate SOE), or quetiapine (one RCT; low SOE) at 12 months using the Heinrich Carpenter Quality of Life Scale (QLS) (change in scores ranged from 0.09 to 0.26).
  - Risperidone was not found significantly different from quetiapine or ziprasidone at 12 months using the QLS scale (one RCT each; range of change in scores 0.19 to 0.26) (SOE: low). Risperidone LAI was not found different from quetiapine on the 12-Item Short Form Health Survey (SF-12) or Schizophrenia Quality of Life Scale –Revision 4 (SQLS-R4) at 24 months (SOE: low).

- Response was significantly more likely with olanzapine (odds ratio [OR] 1.71, 95% CI 1.11 to 2.68) and risperidone (OR 1.41, 95% CI 1.01 to 2.00) than quetiapine, based on a network meta-analysis of 46 head-to-head RCTs (SOE: low)
  - The rate of response in individual study arms ranged from 20 to 80 percent.
  - Meta-regression examining the influence of study duration, dose-level, population (either treatment-resistant or first-episode status), and category of response definition did not result in any significant findings.
  - Due to few studies, the findings for newer SGAs (e.g., the 3-month paliperidone palmitate LAI, lurasidone, iloperidone, brexpiprazole, and cariprazine) should be interpreted with caution.
- All-cause mortality was not different between the SGAs in incidental reports in RCTs or retrospective cohort studies, but evidence was not available for the newest SGAs.
  - With mortality rates of 0 to 1.17 percent, significant differences in mortality were not found in two RCTs (4 to 24 months duration) of asenapine with olanzapine (relative risk [RR] 2.49, 95% CI 0.54 to 11.5), quetiapine and risperidone (RR 3.24, 95% CI 0.72 to 14.6), and two RCTs (also 4 to 24 months duration) of paliperidone palmitate monthly LAI versus risperidone LAI (RR 1.26, 95% CI 0.21 to 7.49) (SOE: low).
  - Retrospective cohort studies found no significant difference in the risk of all-cause (one study, N=48,595) or cardiovascular mortality (two studies, N=55,582) between risperidone, olanzapine, and quetiapine (SOE: low).
- Clozapine was found superior to olanzapine in preventing significant suicide attempts or hospitalization to prevent suicide (hazard ratio [HR] 0.76, 95% CI 0.58 to 0.97) and Clinical Global Impression of Severity-Suicidality Scale (CGI-SS) ratings of “much worse” or “very much worse” (HR 0.78, 95% CI 0.61 to 0.99); number needed to treat [NNT] of 12) among patients at high risk (SOE: low). Observational studies confirm these findings in broader populations.
- There were no significant differences between the SGAs in the proportions of patients reporting overall adverse events, based on 72 RCTs and 31 drug comparisons.
- Clozapine was found to improve core illness symptoms significantly more than the other SGAs, except for olanzapine (network meta-analysis of 212 RCTs; standard mean differences [SMDs] on Positive and Negative Syndrome Scale [PANSS] or Brief Psychiatric Rating Scale [BPRS]). All of the SGAs were superior to placebo (SMDs -0.33 to -0.88) (SOE: low).
- Olanzapine and risperidone were found to result in similar core illness symptom improvements, which were greater in these drugs than in the other SGAs, except for paliperidone (SMDs -0.13 to -0.26) (SOE: low). Paliperidone was found to improve core illness symptoms more than lurasidone and iloperidone (SMDs -0.17) (SOE: low).
- In a separate network analysis of 40 RCTs of clozapine, risperidone, olanzapine, quetiapine, and ziprasidone in patients who were resistant to treatment, the only significant difference was that the mean change in the PANSS was greater with olanzapine than quetiapine (SMD -0.29, 95% CI -0.56 to -0.13) (SOE: low).
- Based on a network meta-analysis of 90 head-to-head RCTs withdrawal due to adverse events were significantly lower with four SGAs compared with the others (SOE: low).
  - Risperidone LAI had significantly lower risk than clozapine (OR 0.27, 95% CI 0.10 to 0.71); lurasidone (OR 0.39, 95% CI 0.18 to 0.84); quetiapine extended

- release (ER) (OR 0.43, 95% CI 0.22 to 0.81); risperidone (OR 0.50, 95% CI 0.25 to 0.99); and ziprasidone (OR 0.40, 95% CI 0.20 to 0.82)
- Olanzapine had lower risk than clozapine (OR 0.39, 95% CI 0.19 to 0.79); lurasidone (OR 0.57, 95% CI 0.34 to 0.94); quetiapine (OR 0.62, 95% CI 0.44 to 0.87); risperidone (OR 0.72, 95% CI 0.55 to 0.96); and ziprasidone (OR 0.58, 95% CI 0.41 to 0.82)
- Aripiprazole had lower risk than ziprasidone (OR 0.64, 95% CI 0.44 to 0.94) and clozapine (OR 0.43, 95% CI 0.21 to 0.88)
- Cariprazine (OR 0.40, 95% CI 0.17 to 0.95) and iloperidone (OR 0.34, 95% CI 0.13 to 0.91) had lower risk than clozapine
- Meta-regression examining the influence of study duration, dose level, and either treatment-resistant or first-episode status did not result in any significant findings.
- There are fewer data available for the newer drugs; results for these drugs should be interpreted with caution.

## Detailed Synthesis

### Description of Included Studies

A recent large, good-quality systematic review compared the benefits and harms of SGAs, including oral and LAI drugs (Appendix Tables E-1 and F-1).<sup>29</sup> The review included 138 RCTs of at least 6 weeks duration, including 47,189 patients with schizophrenia or related psychosis (includes 3 trials of adolescents with 315 patients). Of these, 17.5 percent were rated as poor quality, and 9 percent as good quality. Reasons for trials being rated as poor quality were unclear methods of randomization and/or allocation concealment, lack of blinding of outcome assessors and incomplete reporting of outcome data or high attrition (missing data). Patients enrolled in the included trials of adults not experiencing a first episode of schizophrenia had a mean age of 39 years, and in trials of adults with a first episode the mean age was 26 years. These trials made comparisons of the older SGAs (clozapine, risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole) with few studies or only placebo-controlled trials of newer SGAs (iloperidone, lurasidone, paliperidone, and the LAI products). The duration of followup among the included studies ranged widely from 6 weeks to 3 years, with most being 8 to 12 weeks. The review also included 31 observational studies (cohort and case-control) with at least 6 months of followup to evaluate harms and selected effectiveness outcomes (e.g., functioning, employment). These studies included 602,547 patients, mostly diagnosed with schizophrenia or related psychosis. Twenty-one percent of these studies were rated poor quality, and 5 percent were good quality. Reasons for observational studies being rated as poor quality were potentially biased selection of patients, unclear description of methods for ascertaining exposure or outcomes, and lack of blinding of, or inadequate, control for confounding. Mean doses reported for the observational studies tended to be lower than those used in the trials noted above. Mean doses of olanzapine in particular were 10 to 12 mg daily in the observational studies, whereas across 54 trials reporting a mean olanzapine dose, the mean was 17 mg daily. For risperidone, the observational studies reported doses of 3 to 4 mg daily, whereas the mean across 55 trials was 5.7 mg daily.<sup>29</sup> Evidence on dosing of other SGAs was limited. The reasons for this apparent difference in dosing between the observational studies and trials were not clear, primarily because data on patient characteristics were poorly reported in the observational studies. A number of these studies were poor quality for a variety of reasons, but primarily unclear population selection

criteria and methods (potential for biased selection), lack of blinding outcome assessors, short durations of followup, small sample sizes, and little or no statistical analysis of potential confounding factors.<sup>29</sup>

Since the inclusion dates of the systematic review above, we have included 24 newer RCTs directly comparing SGAs<sup>43-66</sup> (Appendix Tables E-2 and F-2). The comparisons in these newer trials included seven studies of a LAI drug; four of oral versus LAI of the same drugs (aripiprazole and risperidone, two studies each), and three comparing different LAI formulations or drugs (aripiprazole and paliperidone monthly injections, risperidone 2-week and paliperidone monthly, and paliperidone monthly and 3-month injections). Additionally, there were eight new trials comparing aripiprazole to other SGAs, including brexpiprazole, olanzapine, paliperidone, quetiapine, risperidone and ziprasidone; three new trials comparing either immediate or extended-release quetiapine to risperidone; one trial of olanzapine and ziprasidone, and two of cariprazine and risperidone. The duration of treatment in these studies was six to 52 weeks, median 28 weeks with six being 52 weeks long. Mean age of patients in these trials was 36 years. Five trials (21%) were deemed to be poor quality, based on unclear reporting on randomization and concealment of allocation procedures, lack of blinding of outcome assessors, some differences in prognostic factors at baseline, and high attrition combined with unclear handling of missing data.<sup>44,53,58,60,64</sup> Two trials were good quality<sup>56,61</sup> and the rest were fair quality.

In comparing SGAs with each other (and to one FGA), the CATIE trial, a large, federally funded effectiveness trial with three phases, is a major contribution to the evidence base, and deserves introduction.<sup>121-125</sup> In Phase 1 patients were randomized to olanzapine, quetiapine, risperidone, ziprasidone, or perphenazine (however, patients with tardive dyskinesia at baseline were not randomized to perphenazine; this group=Phase 1A). Ziprasidone was added to the trial partway through enrollment, after it received FDA approval. As a result, the numbers of patients randomized to ziprasidone were fewer (183 vs. 329 to 333 in other SGA groups), limiting statistical power. The mean modal dose of each SGA was within the typical dosing range for each drug.<sup>29</sup> The study was planned to enroll patients from a broad range of settings, excluding patients with treatment resistance. However, the large number of study sites at major academic centers drew criticism that the results may not be generalizable to other setting. The study was funded by the National Institute of Mental Health and is a good-quality study.

In Phase 1B those patients who were randomized to perphenazine in Phase 1 but discontinued the drug prior to 18 months were then randomized to one of the four SGAs. In Phase 2E patients who discontinued the originally assigned drug in Phase 1 due to inadequate efficacy were randomized to open-label clozapine or to a blinded trial of olanzapine, risperidone, or quetiapine. In Phase 2T patients who discontinued the originally assigned drug in Phase 1 due to poor tolerability were randomized to ziprasidone or one of olanzapine, risperidone, or quetiapine with no one receiving the same drug assigned in Phase 1 during Phase 2. It has been noted, however, that some patients who discontinued drug during Phase 1 due to lack of efficacy opted to be enrolled in Phase 2T. Fifty-eight percent (184 of 318) of those enrolling had discontinued treatment in Phase 1 due to lack of efficacy, most likely due to patients wanting to avoid randomization to clozapine. The authors noted “patients who were assigned to olanzapine during Phase 2 had the lowest rates of Phase 1 discontinuation because of intolerable side effects and the lowest rates of discontinuation due to weight gain or metabolic side effects.” In Phase 3, 270 patients who discontinued the Phase 2 drug (or discontinued Phase 1 drug and did not wish to be rerandomized to another treatment) were offered enrollment in an open-label treatment chosen by the patient, clinician, and research staff from among nine treatments: aripiprazole,

clozapine, fluphenazine decanoate, olanzapine, perphenazine, quetiapine, risperidone, ziprasidone, or two of these combined.<sup>125</sup> In addition to the results from the main analyses of each of these phases, numerous subgroup analyses and modeling studies have been published using data from this study.

The primary outcome measure in CATIE, all-cause treatment discontinuation, was selected for two reasons: first, because it was a discrete, common outcome that is easily understood; and second, because it encompassed lack of efficacy and/or intolerable side effects. Although this was an important outcome measure, it was an indirect measure of effectiveness and there appeared to be lack of agreement about its value to patients.<sup>126-128</sup> Direct measures of effectiveness would include ability to work and to maintain successful social relationships. Hence, this outcome was not prioritized in the current review.

## Findings

### Function

#### Social Function

Across five RCTs (four included in the systematic review) and one observational study, assessments of social function resulted in mixed findings and insufficient evidence for the comparison of the older SGAs (clozapine, olanzapine, risperidone and quetiapine; Appendix Tables E-1 and E-2).<sup>29,50</sup> Two fair-quality, open-label randomized trials with 12 months of followup came to different conclusions comparing olanzapine and risperidone, using different scales. In the first trial (N=108) no significant differences were seen between olanzapine and risperidone based on the Role Functioning Scale (RFS) or the Social Adjustment Scale (SAS) – Severely Mentally Ill version.<sup>129</sup> In contrast, in the second trial (N=235), improvement on the Social Function Scale (SFS) was greater with olanzapine (+7.75) than risperidone (-0.92;  $p=0.0028$ ) after controlling for baseline scores.<sup>130</sup> These changes from baseline are very small, given the range of the scale (0 to 226). Data were not presented in a way that would allow pooling these findings, and the difference may be attributable to differences in patient characteristics. In the study finding a significant difference, patients had predominantly negative symptoms and SFS scores correlated with improvements in negative symptoms. In the study not finding a significant difference, patients had two or more psychiatric hospitalizations in the past 12 months and were known to be nonadherent to treatments. A large (N=10,972) prospective cohort study reported 84.6 percent of patients taking olanzapine to be socially active (self-report) at 6 months.<sup>131</sup> This was significantly more than with risperidone (82.4%, OR 1.27, 95% CI 1.05 to 1.54) or quetiapine (78.9%, OR 1.67, 95% CI 1.29 to 2.16). Clozapine was not found significantly different from olanzapine (81.6%; OR 1.25, 95% CI 0.87 to 1.80). Evidence on comparisons of older SGAs on social functioning is insufficient to draw conclusions. Three short-term (8- and 10-week) trials found no differences in various social function scales (Social Skills Performance Assessment [SSPA], the Penn Emotional Acuity Test [PEAT], and the SFS) between risperidone and either quetiapine or clozapine.<sup>132-134</sup>

For newer SGAs, the review found that evidence from a pooled analysis of patient-level data from three, 6-week placebo-controlled trials of paliperidone and a small group assigned to olanzapine was insufficient to draw conclusions.<sup>135</sup> Although the publication states that there were no significant differences on the PSP scale, statistical results were not reported and reporting of baseline characteristic of the olanzapine group were inadequately reported.

For the comparison of paliperidone palmitate monthly LAI and risperidone biweekly LAI, the review found low strength evidence that there is no difference in improvements in social functioning. This finding is based on a single fair-quality trial conducted in China (N=452) that found no difference at 13 weeks on the clinician rated PSP scale (mean change from baseline 16.8 with paliperidone and 18.6 with risperidone; LSM difference 0.5 [95% CI -2.14 to 3.12]).<sup>136</sup> Since the review, another very small (N=30) fair-quality 6-month trial of paliperidone palmitate LAI and risperidone LAI, conducted in Japan, found paliperidone palmitate to result in a significant improvement if SFS scores compared with risperidone (14.60 vs. -1.64; p=0.038).<sup>50,137</sup> The study also assessed functional capacity using the San Diego Performance Based Skills Assessment- Brief (UPSA-B) tool, but found no difference between groups on this measure. This study should be interpreted cautiously due to the very small sample size.

A secondary publication from a trial of risperidone LAI and quetiapine that was originally included in the systematic review reported on social function using the SOFAS scale.<sup>138</sup> Although both groups improved significantly from baseline, risperidone LAI resulted in greater improvements in SOFA at 6 months (6.1 vs. 2.7; p=0.02), 12 months (9.5 vs. 6.1; p=0.009), and endpoint (6.6 vs. 1.1; p<0.0001). This evidence was low strength.

A single fair-quality trial of cariprazine and risperidone (N=456) that enrolled patients with stable schizophrenia and predominantly negative symptoms found no difference between the drugs on the SAS after 26 weeks of treatment.<sup>56</sup>

### **Employment and Residential Status**

The systematic review included two RCTs and three observational studies that reported employment outcomes with the older SGAs (olanzapine, risperidone, quetiapine and ziprasidone) and found low strength evidence of no differences between the drugs (Appendix Table E-1).<sup>29</sup> Results from Phase 1 of the CATIE study (N=1,121) did not indicate differences in employment at 18 months followup among olanzapine, quetiapine, risperidone, or ziprasidone.<sup>139</sup> The threshold for “employment” was low—1 day in the last 30 days or an average of 1 hour a week over the last 30 days, with a mean of 18 percent reporting employment. The other smaller 12-month, open-label trial (N=235) only reported on the subscale occupation/employment item of the SFS, and found olanzapine to result in an improvement while risperidone resulted in a decrease in score (p=0.0024).<sup>130</sup> Three observational studies did not show significant differences in employment outcomes between older SGAs.<sup>140-142</sup>

One fair-quality trial, comparing quetiapine with risperidone (N=771), assessed combined occupational and residential status using a “modified vocational status index” and a “modified location code index”.<sup>55</sup> They defined “real functional improvement” as better status in both at 12 months than at baseline, and stable status if the status for both was unchanged from baseline. Using these definitions, they found that 3.8 and 3.1 percent, respectively, had real improved status, and that 75.5 and 75.3 percent had stable status, with no significant differences between groups. This evidence is insufficient to draw conclusions due to imprecision, unknown consistency, and study limitations.

### **Global Assessment of Functioning**

The systematic review found that several studies have reported on the comparative effects of older SGAs using the GAF scale (score 0 to 100), but that very small differences (<4 points) were found favoring olanzapine compared with risperidone, quetiapine, and ziprasidone in three trials, otherwise differences were not found among drugs in nine studies (Appendix Table E-1).<sup>29</sup>

Such small differences are unlikely to have clinical importance as the minimal clinically important difference has been suggested to be 10 points.<sup>143</sup>

In the review, four observational studies reported on GAF scores in patients taking olanzapine and risperidone with followup of 6 months to 2 years. The pooled estimate of change from baseline in these studies was not significant (pooled WMD 0.61, 95% CI -1.78 to 2.99;  $I^2=43\%$ ). The range in change of score from baseline was 6.0 to 18.34 with olanzapine and 6.0 to 16.13 with risperidone. In comparing olanzapine and quetiapine, the pooled estimate for difference in change in GAF score was not significant (2 RCTs, N=363; pooled WMD 1.14, 95% CI -4.75 to 7.02;  $Q=3.99$ ,  $df=1$ ;  $p=0.045$ ). One of these studies found a small but significant difference, favoring olanzapine in patients with predominantly negative symptoms. This difference was correlated with improvements in negative symptoms (difference of 3.8 points;  $p=0.007$ ).<sup>144</sup> The evidence for indicating no difference in global function between olanzapine and risperidone or quetiapine was low strength. Evidence on comparisons of quetiapine and risperidone (one RCT), olanzapine and ziprasidone (one RCT), and clozapine and multiple other antipsychotics (one retrospective cohort study, one RCT) was insufficient to draw conclusions due to study limitations, unknown consistency and imprecision.

### Quality of Life

Quality of life is a major consideration for choice of antipsychotic medication and is affected by both effectiveness and adverse events. There are multiple methods of measuring quality of life, many of which are intended for use in any population, such as the EuroQol five dimensions questionnaire (EQ-5D) or 36-Item Short Form Health Survey (SF-36), whereas a few are specifically designed for people with schizophrenia, such as the QLS. These methods measure different aspects of quality of life, and the data have been reported with too much variation to allow statistical pooling (e.g., not reporting standard deviations or standard errors, not reporting total scale scores, reporting endpoint only). The systematic review included five RCTs (N=3,443), including the CATIE trial, and five prospective cohort studies (N=5,728). Since then three additional trials of SGAs have reported quality of life.<sup>49,54,55,138</sup> Using specific and nonspecific tools, 14 studies evaluated quality of life with seven oral and two injectable SGAs, with the majority finding no statistical or clinically meaningful differences (Appendix Tables E-1 and E-2).

Comparisons of olanzapine with risperidone and ziprasidone resulted in moderate-strength evidence of no significant difference in quality of life at 6 and 12 months. Low-strength evidence (due to smaller sample sizes) of no difference was found for comparisons of olanzapine with quetiapine, risperidone compared with quetiapine, and oral aripiprazole and aripiprazole monthly LAI. Evidence for the comparisons of olanzapine and asenapine, quetiapine ER and risperidone, and monthly LAIs of aripiprazole and paliperidone palmitate was insufficient to draw conclusions due to methodological limitations, unknown consistency (single trials), and imprecision in estimates (inadequate sample sizes). A secondary publication from a trial of risperidone LAI and quetiapine that was originally included in the systematic review reported on quality of life using the SF-12 physical and mental components and the SQLF-R4.<sup>138</sup> Although both groups improved significantly from baseline, there was not a significant difference between groups at end point (24 months). This evidence was low strength.

The observational studies included in the systematic review support these findings for olanzapine, risperidone, and quetiapine with two exceptions. First, in the European Schizophrenia Outpatient Health Outcome (SOHO) study (N=919) whereas there were no differences in quality of life based on the EQ-5D at 6 or 36 months in the overall group, in the

subgroup who were treatment-naïve at entry, patients taking olanzapine had significantly higher scores at 6 months than risperidone (adjusted mean difference 3.73, 95% CI -1.48 to 5.97).<sup>145</sup> In another prospective cohort study (N=903; 612 with schizophrenia), olanzapine oral dissolving tablet (ODT) was found to have greater improvement on the Psychological General Well-being Index (scale scores 0 to 110) at 12 months than standard oral olanzapine (22.3 vs. 12.2,  $p<0.001$ ).<sup>146</sup> Because these are single observational studies, this evidence is insufficient to draw conclusions but may be useful in planning future RCTs.

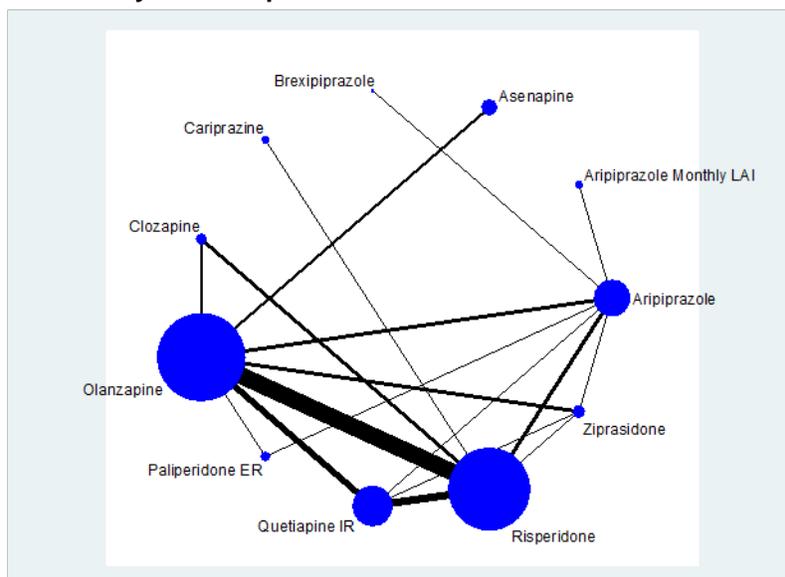
## Response and Remission

Response rates varied somewhat across trials due to differences in patient populations, timing of measurement, and definition of response (Appendix Tables E-1 and E-2). The most common definition of response was  $\geq 20$  percent improvement on the PANSS. Other definitions included the Kane criteria (improvement of  $\geq 20\%$  on BPRS and either Clinical Global Impression – Severity scale (CGI-S)  $\leq 3$  or BPRS  $\leq 35$ );<sup>147</sup> 30, 40, and 50 percent improvements in PANSS or BPRS; and  $\leq 3$  on all PANSS items and  $\leq 3$  on the CGI-S. Across the trials, significant differences in response rates were very rare, and generally were not confirmed in other trials, if available. Remission was rarely reported in these RCTs.

We conducted a network meta-analysis of response rates, controlling for duration of study, category of dose (low, mid-level, high), treatment status (first-episode and treatment-resistant) and definition of response (Figure 4). We grouped the response definition into three categories:  $>20$  percent improvement on PANSS or BPRS scale, definition based on a scale with any threshold (20%, 30% 40%, etc.) and composite definitions and subjective definitions (e.g., Kane criteria plus one other element like hospitalization). Forty-six trials (40 two-arm studies and six three-arm studies; N=12,536),<sup>43,46,47,51,55,59,130,132-135,148-182</sup> including 10 oral drugs (aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone) and aripiprazole monthly LAI were eligible for the analysis. Trials of the LAIs of paliperidone palmitate (monthly or 3-month formulations) and risperidone did not have a comparator drug in common with anything else in the network, and could not be included. Aripiprazole 4 to 6 week LAI, iloperidone, and lurasidone had no response data in head-to-head trials and could also not be included. The network analysis found only two significant differences between the drugs; both olanzapine (OR 1.71, 95% CI 1.11 to 2.68) and risperidone (OR 1.41, 95% CI 1.01 to 2.00) were significantly more likely to result in response than quetiapine. The rate of response in individual study arms ranged from 20 to 80 percent (data not shown, available upon request). The matrix of results for response can be found in Appendix G-1. Multiple methods were used to assess the model for inconsistency. Although the data available to test for inconsistency was limited, inconsistency in the model was not found. Taking this lack of inconsistency into account, and considering the indirectness of comparisons in the network, and the limited evidence for some comparisons, we found the results of the network meta-analysis to be low-strength evidence. Meta-regression examining the influence of study duration, dose-level, population (either treatment-resistant or first-episode status), and category of response definition did not result in any significant findings. There are fewer data available for the newer drugs; particularly all of the LAI drugs (e.g., the 3-month paliperidone palmitate injection), lurasidone, iloperidone, brexpiprazole, and cariprazine. Results for these drugs should be interpreted with caution.

A fair-quality published network analysis of patients with treatment-resistant symptoms assessed response.<sup>183</sup> Significant differences were not found in comparisons of clozapine, risperidone, olanzapine quetiapine, and ziprasidone.

**Figure 3. Network meta-analysis of response rates in trials of SGAs**



ER = extended-release; IR = immediate-release; LAI = long-acting injection; SGAs = second-generation antipsychotic

Legend: Circles represent relative numbers of studies including each drug. Line thickness represents number of studies making specific comparison for this outcome.

## Mortality

In April 2005, the United States Food and Drug Administration (FDA) issued a public health advisory regarding increased risk of all-cause mortality associated with the use of all SGAs in elderly patients with dementia-related psychosis ([www.fda.gov/cder/drug/advisory/antipsychotics.htm](http://www.fda.gov/cder/drug/advisory/antipsychotics.htm)). Evidence on the risk of death associated with the SGAs specifically in patients with schizophrenia is limited by the lack of RCTs with adequate duration, sample sizes, and broadness of eligibility criteria as well as the lack of specific methodology for identifying and categorizing cases. Evaluating the incidental reports of mortality in RCTs included in the systematic review indicates that over 4 months to 2 years of treatment the rate of all-cause deaths was 0 to 1.17 percent in trials of quetiapine compared with quetiapine ER (one RCT), quetiapine immediate-release or ER versus risperidone (three RCTs), asenapine versus olanzapine (two RCTs), paliperidone versus risperidone LAI (one RCT), paliperidone monthly LAI versus risperidone LAI (one RCT), paliperidone 3-month versus monthly LAIs (one RCT), and brexpiprazole versus aripiprazole (one RCT) (Appendix Tables E-1 and E-2).<sup>43,55,136,154,175,184-188</sup> None of the comparisons were significant. For comparisons of asenapine with olanzapine (RR 2.49, 95% CI 0.54 to 11.5), quetiapine and risperidone (RR 3.24, 95% CI 0.72 to 14.6), and paliperidone palmitate monthly LAI versus risperidone LAI (RR 1.26, 95% CI 0.21 to 7.49), there was low-strength evidence of no difference in mortality over 4 to 24 months, but the evidence for the other comparisons is insufficient to draw conclusions.

The systematic review included three observational studies to address the risk of mortality with SGAs in patients with schizophrenia (Table 5). Only older SGAs were included in these studies. There was low-strength evidence of no significant difference in the risk of all-cause or cardiovascular mortality between risperidone and olanzapine or quetiapine (Appendix H). Evidence on the association of clozapine, risperidone, olanzapine and quetiapine and all-cause

mortality versus no treatment is insufficient to draw conclusions due to the risk of bias of the study designs, and the lack of confirmatory studies (i.e., unknown consistency). Similarly, the evidence on cardiovascular mortality with risperidone compared with clozapine is insufficient. This study reported no differences in an analysis of older (starting drug at age 55 or older) versus younger patients, and found no association, however the mortality rates were very similar between drugs in the younger group (e.g., 2.7% and 2.8%) but the absolute difference was larger in the older group (e.g., 16.0% clozapine and 5.7% risperidone); the very small sample size in the older group may have prevented finding a significant difference.

**Table 5. Mortality in retrospective cohort studies of SGAs**

Study, Year	Study Population N, Mean Age (Quality)	Drugs and Comparison	All-Cause Mortality (95% CI)	Cardiovascular Mortality
Pasternak, 2014 <sup>189</sup>	Starting SGA N=48,595 39 years (Good)	Risperidone versus olanzapine, or quetiapine 1 year followup	Risperidone versus: Olanzapine HR 1.09, (0.79 - 1.49) Quetiapine HR 0.75, (0.53 -1.07)	Risperidone versus: Olanzapine HR 0.99 (0.37 - 2.67) Quetiapine HR 0.76 (0.25 - 2.28)
Kiviniemi, 2013 <sup>190</sup>	First episode N=6,987 39 years (Good)	Clozapine, risperidone, olanzapine and quetiapine versus no treatment a 5 years followup	Clozapine OR 0.35 (0.21 - 0.58) Quetiapine OR 0.46 (0.30 - 0.72) Risperidone OR 1.0 (0.75 - 1.43) Olanzapine OR 0.73 (0.54 - 1.00)	Risperidone OR 0.82 (0.41-1.66) Clozapine OR 0.23 (0.05 -.02) Olanzapine OR 0.89 (0.46-1.72) Quetiapine OR 0.72 (0.30-1.73)
Kelly, 2010 <sup>191</sup>	Starting SGA N=1686 40 years (Fair)	Clozapine versus risperidone 10 years followup	NR	4.8% and 2.5%; RR 1.39 (0.61 to 2.53)

CI = confidence interval; HR = hazard ratio; OR = odds ratio; RR = risk ratio; SGA = second-generation antipsychotic

## Reduction in Self-Harm

The best evidence on comparative effectiveness of SGAs in preventing suicide and suicide-related behaviors comes from the good-quality InterSePT trial<sup>192</sup> of clozapine and olanzapine, that was included in the systematic review (Appendix Table E-1).<sup>29</sup> This pragmatic, open-label RCT (N=980) of patients with schizophrenia or schizoaffective disorder who were at high risk of suicide behaviors was conducted in 11 countries and had the specific aim of assessing suicidal behaviors over 2 years. Clozapine was found superior to olanzapine in preventing significant suicide attempts or hospitalization to prevent suicide (HR 0.76, 95% CI 0.58 to 0.97) and CGI-SS ratings of “much worse” or “very much worse” (HR 0.78, 95% CI 0.61 to 0.99). Additional analyses that controlled for drug treatment, prior suicide attempts, active substance or alcohol misuse, country, sex, and age also found clozapine superior (HR 0.74, 95% CI 0.57 to 0.96), and indicated that the olanzapine group had significantly higher rates of using antidepressants, anxiolytics and rescue interventions to prevent suicide. The Kaplan-Meier life-table estimates indicated a significant reduction in the 2-year event rate in the clozapine group (p=0.02) with a NNT of 12. There was not a significant difference in suicide deaths (5 for clozapine and 3 for olanzapine). The strength of this evidence is moderate for serious attempts/hospitalizations and deaths, moderate for worsening of CGI-SS.

There were no other trials of SGAs that reported suicidal attempts, suicide deaths or other self-harm as a primary outcome measure, using explicit methods for ascertaining the outcome.

Six fair-quality trials reported suicide-related outcomes as adverse events, all with very low event rates and no clear differences between treatments. Studies that did not prespecify or report methods were used for ascertaining and verifying the outcomes are open to misclassification and missing events. Patients were not selected for the trial based on risk for suicidal behavior, and there were no apparent differences between study groups in baseline severity of illness. A 52-week fair-quality efficacy trial of asenapine compared with olanzapine (N=1,225) reported 1.8 and 2.3 percent suicides attempts, respectively.<sup>187</sup> A 13-week trial of risperidone LAI compared with paliperidone palmitate monthly LAI (N=452) reported that there were three suicidal behavior-related adverse events in the risperidone group (1.4%) and none in the paliperidone palmitate injection group (0%), with one suicide death in a patient with no prior history of suicidal behavior (0.5%).<sup>136</sup> A 24-month trial of risperidone and quetiapine (N=1,098) initially designed to assess risk of ocular adverse events, reported two suicide deaths in the quetiapine group (0.34%) and one in the risperidone group (0.2%).<sup>184</sup> Similarly, a 12-month trial of quetiapine ER and risperidone (N=798) reported a single death in the risperidone group (0.25%).<sup>55</sup> In a RCT of asenapine and olanzapine, conducted at sites around the world, results were reported according to the hemisphere of study site. In the Eastern hemisphere results, there was one suicide death in each group (0.41% and 0.42%),<sup>154</sup> and none in the Western hemisphere analysis. This evidence is insufficient to draw conclusions due to lack of confirmatory studies, study limitations (i.e., ascertainment techniques), and small numbers of events (imprecision).

The systematic review also included four observational studies that used adequate ascertainment methods to assess the risk of suicide or suicide attempts in patients taking SGAs (not limited to those at high risk). Low-strength evidence from two retrospective cohort studies (combined N=16,584) found clozapine to be associated with lower risk of death by suicide. At 6 months, compared with no treatment, the risk with clozapine was OR 0.29, 95% CI 0.14 to 0.63. Risperidone, olanzapine, and quetiapine were not different from no treatment.<sup>190</sup> In the other study, patients with schizophrenia newly starting on clozapine had a lower rate of suicide at 1 - year (1.1%) than the other drugs studied or than the 6 months prior to treatment (2.2%).<sup>193</sup> Rates for the other drugs studied were risperidone 51 (2.1%), aripiprazole 13 (2.2%), risperidone LAI 26 (2.4%), quetiapine 49 (3.1%), olanzapine 57 (3.5%), and ziprasidone 17 (3.7%).

The other two studies, one assessing risk of suicide attempts in the fair-quality European SOHO prospective cohort study (N=10,204) of olanzapine, risperidone, quetiapine, and clozapine and the other assessing the risk of suicide attempts or death by suicide with aripiprazole compared with older SGAs provide only insufficient evidence due to methodological limitations of the study designs and lack of confirmatory studies for the specific outcomes and comparisons.

### **Improvement in Core Illness Symptoms**

Three good-quality network meta-analyses compared several of the SGAs with each other on improvements in core illness symptoms.<sup>183,194</sup> A network analysis published in 2013 included 212 head-to-head and placebo-controlled trials of 15 oral antipsychotics (both FGAs and SGAs).<sup>194</sup> Cariprazine was not included, and the analysis includes drugs not available in the United States. This analysis pooled changes in the PANSS or BPRS, using SMDs. Clozapine was found significantly superior to all the other drugs in the network, except olanzapine, on this measure with SMDs ranging from -0.32 to -0.55 (small to medium differences). Olanzapine and risperidone were superior to the other drugs, except for each other and paliperidone, with effect sizes ranging from -0.13 to -0.26 (generally small differences). Using only indirect comparisons in the network, paliperidone was found superior to lurasidone and iloperidone, with SMDs of -0.17 (a small difference). All other comparisons were not significant, but all of the drugs in the

network were found superior to placebo (SMDs -0.33 to -0.88). The network did not include injectable drugs, and it is possible that some of these findings would change, particularly for newer drugs, with new head-to-head studies. This evidence was low strength.

An analysis of six oral SGAs (clozapine, risperidone, olanzapine, quetiapine, and ziprasidone) in 40 RCTs of patients with treatment-resistant schizophrenia found that the mean change in the PANSS was greater with olanzapine than quetiapine (SMD -0.29, 95% CI -0.56 to -0.13).<sup>183</sup> The authors noted that this corresponds to a difference in points on the PANSS of -6.08 (scale scores range from 30 to 210; 180 possible points). There is some evidence that in patients with more severe disease a minimal clinically important difference on the PANSS is 11.5 points, indicating that a difference of six points may not be clinically important, although statistically significant.<sup>195</sup> The newer oral drugs (aripiprazole, iloperidone, lurasidone, asenapine, cariprazine, brexpiprazole) were not included. This was low-strength evidence.

A single fair-quality 6-week trial of brexpiprazole and aripiprazole (N=97) found that both drugs improved symptoms using the PANSS scale (-22.9 vs. -19.4 from baseline mean of 93.7;  $p < 0.0001$  for each drug vs. baseline).<sup>43</sup> Comparisons across the drugs were not made, although the absolute difference was very small. This study was not included in published network meta-analyses, and alone this evidence is insufficient.

## Overall Adverse Events

We identified 64 RCTs, making 34 comparisons of SGAs that reported the numbers of patients reporting an adverse event during the study by group.<sup>45-47,49-51,54-56,61,123,125,133,136,148,150,151,154,155,161,163,167,169,171,172,174-178,184,186-188,196-227</sup>

The majority of the trials did not find significant differences between the drugs compared. The rates of patients reporting adverse events varied widely across the studies, although the majority was above 60 percent for all SGAs, and the variability does not correlate with duration of study or mean or range of doses.

There was moderate-strength evidence of no significant difference in overall adverse event reporting between asenapine and olanzapine (five RCTs; N=2189)<sup>154,176,187,223</sup>, and quetiapine and risperidone (seven RCTs; N=3,254; Table 6).<sup>123,133,169,171,172,184,186</sup>

Similarly, the following comparisons had two to three RCTs each (6 weeks to 12 month; N=7810) that again found no significant differences in proportions of patients reporting adverse events: Quetiapine 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. This was low-strength evidence for these comparisons.

Single trials (3 weeks to 2 years; N=6700) of oral aripiprazole versus brexpiprazole, olanzapine, paliperidone, and risperidone LAI; ziprasidone versus clozapine, risperidone, iloperidone and lurasidone; risperidone versus asenapine, cariprazine and risperidone and risperidone LAI; clozapine versus quetiapine, quetiapine versus risperidone LAI; olanzapine versus olanzapine LAI and lurasidone; aripiprazole monthly LAI versus paliperidone; and paliperidone palmitate monthly LAI versus 3-monthly LAI found similar rates of overall adverse events with no significant differences. This evidence is insufficient to draw conclusions due to lack of confirmatory studies and imprecision for each comparison's estimate of effect.

**Table 6. Overall adverse events in trials of SGAs versus SGAs**

SGA Comparison Number Studies/Number Patients	Percentage of Patients Reporting Adverse Events	Pooled Relative Risk
Asenapine vs. olanzapine 5 RCTs (4 publications); N=2189) <sup>154,176,187,225</sup>	Asenapine 68% to 82% Olanzapine 69% to 82%	1.00 (95% CI 0.96 to 1.05); I <sup>2</sup> 9%
Quetiapine vs. risperidone 7 RCTs (N=3254) <sup>123,133,169,171,172,184,186</sup>	Quetiapine 67% to 93% Risperidone 42% to 88%	1.04 (95% CI 0.97 to 1.12); I <sup>2</sup> 56%
Clozapine vs. olanzapine (N=182) <sup>169,214</sup>	Clozapine 77% to 91% Olanzapine 73% to 77%	RR 1.15 (95% CI 1.00 to 1.33); I <sup>2</sup> 0%
Risperidone vs. olanzapine 5 RCTs (N=873) <sup>123,149,163,169,171</sup>	Risperidone 42% to 71% Olanzapine 47% to 74%	RR 1.02 (95% CI 0.81 to 1.29); I <sup>2</sup> =77%
Olanzapine vs. ziprasidone 5 RCTs (N=1097; 6 weeks to 6 months durations) <sup>161,167,178,197,226</sup>	Olanzapine 30% to 94% Ziprasidone 28% to 92%	RR 1.00 (95% CI 0.86 to 1.16); I <sup>2</sup> =80%
Olanzapine vs. quetiapine 3 RCTs (N=448) <sup>123,169,171</sup>	Olanzapine 47% to 74% Quetiapine 60% to 68%	RR 0.90 (95% CI 0.74 to 1.11); I <sup>2</sup> =30%

CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness; CI = confidence interval; RCT = randomized controlled trial; RR = risk ratio; SGA = second-generation antipsychotic

### Withdrawals Due to Adverse Events

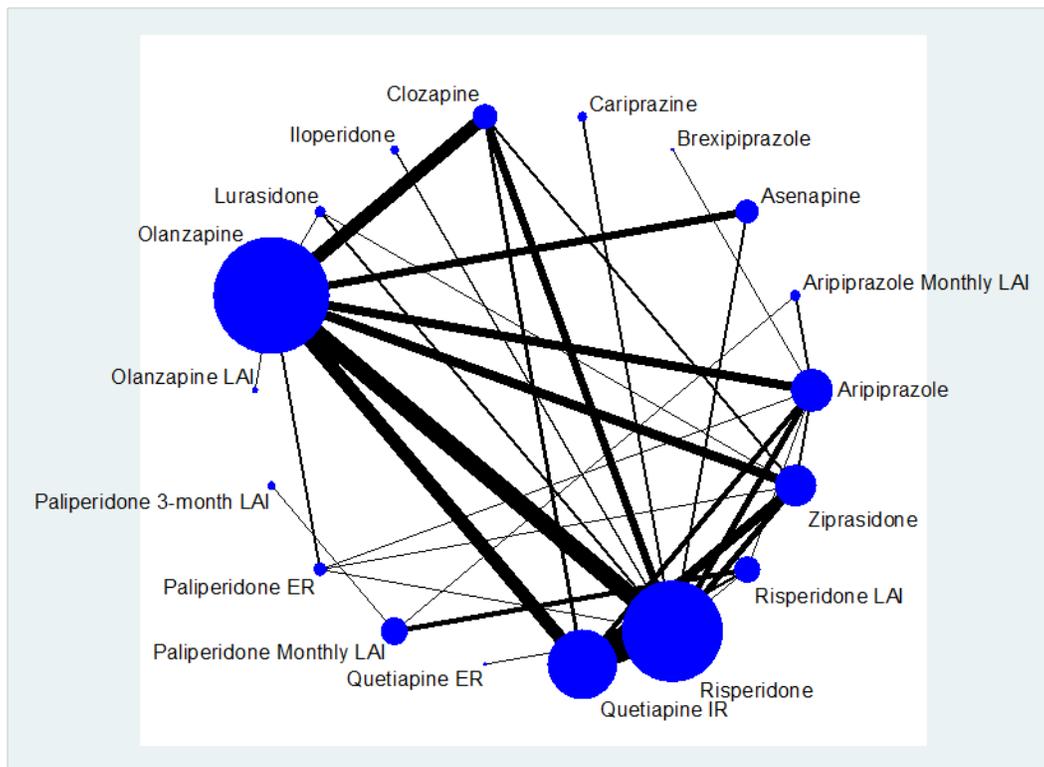
Adverse events that are intolerable lead to discontinuation from studies, although some may take longer to result in discontinuation. Such discontinuations take into account the patient's evaluation of the degree to which the adverse event is tolerable. The CATIE trials included these discontinuations as a secondary outcome measure and found significant differences among the drugs. In CATIE Phase 1, discontinuations due to adverse events were highest among patients taking olanzapine (primarily due to weight gain or other metabolic effects, 18%) and lowest among those taking risperidone (10%;  $p=0.04$  across groups). Time to discontinuation for adverse events did not differ among the groups. In Phases 1B, 2T, and 2E, differences were not seen between groups for rate of discontinuations or time to discontinuation due to adverse events (intolerability).

A network meta-analysis assessed discontinuation rates due to adverse events using data from 90 head-to-head trials of greater than 6-weeks duration (77 two arm studies, 8 three arm studies, 3 four arm studies and 2 five arm studies; N=29,678).<sup>43,45-47,49-51,54-57,59,61,63,66,121-124,132-134,136,144,148,150-156,158,160,161,163-166,168-172,175-178,180,184,186-188,192,197,200,202,204-206,209,211,213,214,216,218-221,223,224,226-243</sup> (Figure 5). This analysis used direct and indirect comparisons based on the head-to-head trials and found that risperidone LAI had significantly lower risk of withdrawals due to adverse events than clozapine (OR 0.27, 95% CI 0.10 to 0.71); lurasidone (OR 0.39, 95% CI 0.18 to 0.84); quetiapine ER (OR 0.43, 95% CI 0.22 to 0.81); risperidone (OR 0.50, 95% CI 0.25 to 0.99); and ziprasidone (OR 0.40, 95% CI 0.20 to 0.82). Olanzapine had lower risk than clozapine (OR 0.39, 95% CI 0.19 to 0.79); lurasidone (OR 0.57, 95% CI 0.34 to 0.94); quetiapine (OR 0.62, 95% CI 0.44 to 0.87); risperidone (OR 0.72, 95% CI 0.55 to 0.96); and ziprasidone (OR 0.58, 95% CI 0.41 to 0.82). Aripiprazole had lower risk than clozapine (OR 0.43, 95% CI 0.21 to 0.88) and ziprasidone (OR 0.64, 95% CI 0.44 to 0.94). Cariprazine (OR 0.40, 95% CI 0.17 to 0.95) and iloperidone (OR 0.34, 95% CI 0.13 to 0.91) had lower risk than clozapine. The matrix of results for withdrawals can be found in Appendix G-2. Multiple methods were used to assess the model for inconsistency, and although the data available to test for inconsistency was limited, inconsistency was not found.

Meta-regression examining the influence of study duration, dose-level, and either treatment-resistant or first-episode status did not result in any significant findings. There are fewer data available for the newer drugs; particularly all of the LAI drugs (e.g., the 3-month paliperidone

palmitate injection), lurasidone, iloperidone, brexpiprazole, and cariprazine. Results for these drugs should be interpreted with caution.

**Figure 4. Network meta-analysis of withdrawals due to adverse events in trials of SGAs**



ER = extended-release; IR = immediate-release; LAI = long-acting injection; SGAs = second-generation antipsychotic

Legend: Circles represent relative numbers of studies including each drug. Line thickness represents number of studies making specific comparison for this outcome.

### Other Outcomes

There were several outcomes that were important to the evaluation of the evidence on SGAs, but that were lower priority and were not rated for their SOE. However, the Drug Effectiveness Review Project (DERP) systematic review<sup>29</sup> included evidence synthesis on these outcomes, which is summarized below; complete details can be found in the review report.

### Relapse

The systematic review found that the evidence on relapse suffers from methodological issues that could affect the findings, mainly lack of blinding, high dropout rates, and that no two studies used the same definition of relapse.<sup>29</sup> Evidence on the comparison of olanzapine with risperidone and quetiapine was inconsistent, and conclusions of differences could not be drawn. Comparisons of risperidone and quetiapine to each other or to clozapine and lurasidone were based on very few studies but generally did not indicate significant differences. Single studies found risperidone LAI had lower relapse rates than oral risperidone (5% to 18% vs. 33% to 50% at 1 year;  $p < 0.01$ ) or quetiapine (16.5% vs. 31.3%;  $p < 0.0001$  at 1 year). No differences in relapse rates were found for comparisons of lurasidone and quetiapine ER or risperidone; aripiprazole LAI or risperidone LAI, or oral olanzapine and oral aripiprazole; or risperidone and quetiapine ER.

## Drug Discontinuation and Time to Discontinuation

The rate of drug discontinuation and time to discontinuation were summary values representing the net effect of the two main causes of discontinuations: lack of efficacy and adverse events. Patients who withdraw from a study are also counted as having discontinued the study treatment drug. Based on a network analysis of 111 studies (95 two-arm studies, 11 three-arm studies, three four-arm studies, and two five-arm studies; N=32,096), there were several significant findings (the matrix of results for discontinuation can be found in Appendix G-3).<sup>43,45-47,49-51,54-57,59,61,63,66,121-124,132-134,136,144,148,150-156,158,160,161,163-166,168-172,175-178,180,184,186-</sup>

188,192,197,200,202,204-206,209,211,213,214,216,218-221,223,224,226-243 Olanzapine and clozapine had significantly lower discontinuation rates than asenapine, cariprazine, iloperidone, lurasidone, olanzapine LAI, quetiapine, risperidone, and ziprasidone (ORs range from 0.42 for clozapine vs. iloperidone to 0.69 for clozapine vs. risperidone). Clozapine was found to also have lower risk than paliperidone palmitate monthly LAI (OR 0.56, 95% CI 0.33 to 0.96) and olanzapine had lower risk than paliperidone (OR 0.67, 95% CI 0.50 to 0.89). Quetiapine ER had lower risk of discontinuing study than iloperidone, olanzapine LAI, or quetiapine (ORs 0.26 to 0.35), and both risperidone and aripiprazole had lower risk than iloperidone or quetiapine (ORs 0.61 to 0.77). Both risperidone and aripiprazole monthly LAI had lower risk than iloperidone (ORs 0.52 and 0.62, respectively). Few studies of newer drugs exist, suggesting that these findings should be interpreted cautiously. Meta-regression examining the influence of study duration, dose level, and either treatment-resistant or first-episode status did not result in any significant findings.

Olanzapine was found to have longer time to discontinuation than quetiapine, risperidone, and ziprasidone (4 months longer based on trial data; 46 to 66 days longer based on observational data). Based on a single small trial, Phase 2E of the CATIE study, clozapine may have longer time to discontinuation (10.5 months) than olanzapine (2.7 months), risperidone (2.8 months) or quetiapine (3.3 months). Evidence did not differentiate aripiprazole, olanzapine, risperidone and quetiapine or ziprasidone and olanzapine or risperidone. A single fair-quality retrospective study found risperidone LAI to have significantly longer duration of treatment than aripiprazole, clozapine, olanzapine, quetiapine, or ziprasidone (79 to 120 days longer). These findings need confirmation.

## Cardiac and Cardiovascular Risk

The DERP systematic review<sup>29</sup> included evidence synthesis on these outcomes, although the evidence on cardiovascular risks is limited largely to observational studies of the older SGAs.

**Coronary heart disease.** A large, good-quality retrospective cohort study found no significant differences in the risk of cardiovascular death, acute coronary syndrome or ischemic stroke between risperidone and olanzapine or quetiapine in patients age 18 to 64 years within the first year of starting the drug. Based on data from CATIE, the estimated 10-year risk of coronary heart disease was increased with olanzapine compared with risperidone, and the highest risk increases occurred among those with higher baseline risk.

**Myocarditis and cardiomyopathy.** A large adverse event database study found that clozapine was significantly associated with myocarditis or cardiomyopathy, whereas olanzapine, quetiapine, and risperidone were not. Limited evidence suggested an increased risk of cardiac arrest and arrhythmia with risperidone compared with clozapine. Comparisons of second-generation to conventional antipsychotics showed lower odds of cardiomyopathy or coronary heart disease with aripiprazole, and increased odds of hypertension with ziprasidone.

**Diabetes mellitus and ketoacidosis.** The systematic review reported that evidence on diabetes mellitus and ketoacidosis was limited, and the studies did not control for several important potentially confounding factors such as weight or family history of diabetes.<sup>29</sup> The absolute increase in risk was not clear based on this evidence. In children and adolescents, the risk of diabetes increased with antipsychotic exposure based on one good-quality systematic review of observational studies when compared with healthy controls (OR 2.58, 95% CI 1.56 to 4.24) or nonexposed psychiatric controls (OR 2.09, 95% CI 1.50 to 52.90). In children and adolescents, treatment with aripiprazole was associated with increased risk of diabetes when compared with risperidone based on one large observational study (OR 1.58, 95% CI 1.21 to 2.07). In adults, observational evidence indicated an increased risk of new-onset diabetes with olanzapine compared with risperidone (OR 1.16, 95% CI 1.03 to 1.31). Limited evidence did not consistently support a significant difference between clozapine and risperidone or between quetiapine and olanzapine, risperidone, or clozapine.

Diabetic ketoacidosis was significantly increased with olanzapine compared with risperidone (OR 3.5, 95% CI 1.7 to 7.9) in a single study; a second study found no difference in a composite outcome of diabetic ketoacidosis, hyperglycemia, or hyperglycemic hyperosmolar state between risperidone and olanzapine, regardless of age group, but a significantly lower risk with quetiapine compared with risperidone in older patients (adjusted HR 0.69, 95% CI 0.53 to 0.90).

**Tardive dyskinesia.** Comparative observational evidence suggested a significantly increased risk of new-onset tardive dyskinesia with risperidone compared with olanzapine (OR 1.70, 95% CI 1.35 to 2.14). Similar increases were not seen with clozapine or quetiapine. Rates of new-onset tardive dyskinesia were low overall: 3 percent with risperidone and 1 to 2 percent for others.

### **Extrapyramidal Symptoms**

The systematic review reported that the best evidence suggested that the rates of patients experiencing extrapyramidal side effects (prevalent or incident), measures of severity of symptoms were mostly not different among the drugs, although use of anticholinergic medications did differ in some comparisons.<sup>29</sup> Differences found, mainly in single studies, are summarized in Table 7.

**Table 7. Extrapyramidal symptoms: significant differences in trials of SGAs**

Primary SGA Comparison	Findings
Risperidone	Quetiapine and ziprasidone had lower use of anticholinergic medications to treat EPS and lower rates of withdrawal due to EPS than risperidone.
	EPS adverse events were more frequent with risperidone LAI than with oral olanzapine or quetiapine
	A single fair-quality trial suggested that aripiprazole may cause worse akathisia in early weeks of treatment but not with longer treatment.
	Differences were not found between risperidone and cariprazine over 6 weeks on EPS outcomes in a fair-quality trial.
Ziprasidone	Ziprasidone was associated with lower risk of withdrawal due to EPS adverse events than quetiapine, but quetiapine had lower use of anticholinergic medications to treat EPS.
	EPS adverse events were significantly more frequent with ziprasidone (9%) than with iloperidone (3%) in a fair-quality 3-week trial.
Olanzapine	Based on the CATIE trial, quetiapine had lower risk of patients using anticholinergic medications than olanzapine.
	Evidence suggested that paliperidone and asenapine cause more EPS adverse events and worse severity of symptoms than olanzapine, and that asenapine results in more patients using an anticholinergic medication (6% vs. 2%).
Long-Acting Injections	Aripiprazole monthly LAI resulted in greater incidence of EPS adverse events (RR 1.88, 95% CI 1.26 to 2.81) and worse akathisia symptoms (+0.06 vs. -0.05 on a 0 to 5 scale; p=0.0184) than oral aripiprazole in a short-term study, but differences were not found in a year-long study.
	Differences in EPS adverse events were not found in a 28-week trial of aripiprazole and paliperidone palmitate monthly injections, or in a network meta-analysis comparing the monthly and 4- to 6-week injections of aripiprazole.

CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness; CI = confidence interval; EPS = extrapyramidal symptoms; IR = immediate-release; LAI = long-acting injection; RR = risk ratio; SGA = second-generation antipsychotic

Source: McDonagh, 2013<sup>29</sup>

## Weight Gain

The systematic review reported that the rate of clinically important weight gain (defined as a 7% or more increase from baseline) in clinical trials was greater with olanzapine than with aripiprazole (RR 2.31), asenapine (RR 2.59), clozapine (RR 1.71), quetiapine (RR 1.82), risperidone (RR 1.81), and particularly ziprasidone (RR 5.76) across 3.7 to 24 months.<sup>29</sup> The analysis of risk of important weight gain for olanzapine compared with risperidone appeared to vary by duration of study, whereas the others did not. The RR of 1.81 represents studies of 6 to 7 months duration, whereas the CATIE Phase 1 results indicated much higher risk (RR 7.49, 95% CI 4.25 to 13.33) at 18 months.

The review reports that single studies of olanzapine compared with olanzapine ER, olanzapine ODT, and paliperidone palmitate injection did not find significant differences in risk of weight gain.<sup>29</sup> Data for other SGAs compared with olanzapine were insufficient. Observational evidence generally agreed with trial evidence, but resulted in somewhat lower estimates of increased risk with olanzapine. Risperidone was found to have greater risk of weight gain (in single studies) compared with aripiprazole (12% vs. 3%; p=0.018), or cariprazine (calculated RR 1.98, 95% CI 1.03 to 3.80 for any dose cariprazine vs. risperidone). There was not a significant difference in the proportion of patients with weight gain between paliperidone and aripiprazole at 6 months in a single study. An open-label RCT of medication-naïve patients with first-episode schizophrenia (not included in the review) found aripiprazole to result in greater absolute weight gain and more patients with  $\geq 7$  percent gain than with ziprasidone or quetiapine.<sup>244</sup>

## Metabolic Syndrome

The systematic review found that olanzapine had a significantly greater risk of metabolic syndrome than risperidone with followup of 6 weeks to 3 months (pooled OR 1.60, 95% CI 1.10 to 2.21,  $I^2=0\%$ ).<sup>29</sup> Olanzapine also had significantly greater risk of metabolic syndrome than aripiprazole (Evidence-based Practice Center [EPC] pooled OR 2.50, 95% CI 1.32 to 4.76;  $I^2=0\%$ ) with followup of 3.5 to 12 months. Evidence for other comparisons was too limited to draw conclusions.

## Sexual Function

Evidence on the comparative effect of SGAs on sexual function reported in the systematic review<sup>29</sup> was inconsistent or limited by single-study bodies of evidence, inadequate sample sizes or lack of explicit methodology to measure symptoms. Based on four very small trials, evidence on risperidone compared with quetiapine was inconclusive. A single study comparing risperidone and quetiapine ER (N=798) found significantly more men had sexual adverse effects at 6 months (13% vs. 6%;  $p<0.05$ ), but the difference was not significant at 12 months. Individual trials found no significant differences between olanzapine and paliperidone, risperidone, or ziprasidone or between risperidone and paliperidone or aripiprazole.

## Agranulocytosis (Severe Neutropenia)

Although the incidence of agranulocytosis and neutropenia are known serious adverse events with clozapine that require regular monitoring, evidence on the risk with other SGAs is very limited and does not indicate a serious concern with the other drugs currently available.<sup>29</sup>

# First-Generation Antipsychotic Versus Second-Generation Antipsychotic

## Key Points

- Evidence comparing FGA versus SGA is available from a good-quality systematic review (111 RCTs and two cohort studies; N=118,503) and five RCTs (N=1,055) not included in the systematic review.
- There was little evidence of a differential effect between FGAs and SGAs in quality of life outcomes using various measures based on a good-quality systematic review, with one trial comparing haloperidol with ziprasidone finding a positive effect favoring ziprasidone (effect estimate -12.12, 95% CI -22.06 to -2.17) and no difference between groups reported in another trial (SOE: low)
  - There were no differences between haloperidol and olanzapine (SOE: moderate), or perphenazine and olanzapine, quetiapine, risperidone, or ziprasidone (SOE: low).
- For response and remission, olanzapine was found superior to haloperidol.
  - Pooled results from 14 RCTs comparing haloperidol with olanzapine found a significant effect on response rate favoring olanzapine (N=4,099; RR 0.86, 95% CI 0.78 to 0.96) (SOE: low). Three trials comparing haloperidol with olanzapine found a significant difference in remission rates favoring olanzapine (RR 0.64, 95% CI 0.45 to 0.94) (SOE: low).

- There was no difference in response rates between haloperidol and aripiprazole (five RCTs, N=2,185; RR 1.01; 95% CI 0.76 to 1.34), quetiapine (six RCTs, N=1,421; RR 0.99, 95% CI 0.76 to 1.30), risperidone (16 RCTs, N=3,452; RR 0.94, 95% CI 0.87 to 1.02), and ziprasidone (six RCTs, N=1,283; RR 0.98, 95% CI 0.74 to 1.30) (SOE: moderate for haloperidol versus risperidone; low for other comparisons).
- There was no difference in remission rates between haloperidol and ziprasidone based on three trials (RR 0.89, 95% CI 0.71 to 1.12) (SOE: low).
- Reductions in core illness symptoms were greater with older SGAs than with haloperidol
  - There were significant difference in total PANSS between haloperidol and olanzapine (15 RCTs, N=4,209; mean difference [MD] 2.31, 95% CI 0.44 to 4.18) and risperidone (21 RCTs, N=4,020; MD 3.24, 95% CI 1.62 to 4.86), both favoring the SGA over haloperidol (SOE: moderate).
  - There were no differences in total PANSS, BPRS, CGI-S, and Clinical Global Impression - Improvement scale (CGI-I) scores for other FGA versus SGA comparisons (SOE: low).
- SGAs improved negative symptoms more than haloperidol
  - Olanzapine was more effective than haloperidol at improving negative symptoms based on Scale for Assessment of Negative Symptoms (SANS) scores (five RCTs, N=535; MD 2.56, 95% CI 0.94 to 4.18) (SOE: moderate).
  - Using the negative symptoms subscale of the PANSS scale, MDs (although small) between haloperidol and aripiprazole (three RCTs, N=1,701; MD 0.80, 95% CI 0.14 to 1.46), olanzapine (14 RCTs, N=3,742; MD 1.06, 95% CI 0.46 to 1.67), and risperidone (22 RCTs, N=4,142; MD 0.80, 95% CI 0.14 to 1.46) all favored the SGA (SOE: low).
  - There were no differences in negative PANSS or SANS scores for other FGA versus SGA comparisons (SOE: low).
- Overall adverse event rates were lower with SGAs when comparing haloperidol with aripiprazole (three RCTs, N=1,713; RR 1.11; 95 % CI 1.06 to 1.17), risperidone (eight RCTs, N=1,313; RR 1.20, 95% CI 1.01 to 1.42), and ziprasidone (six RCTs, N=1,448, RR 1.13, 95% CI 1.03 to 1.23) (SOE: moderate).
- Withdrawals due to adverse events were significantly higher with haloperidol than with SGAs: compared with aripiprazole (eight RCTs, N=3,232; RR 1.25, 95% CI 1.07 to 1.47), olanzapine (24 RCTs, N=5,708; RR 1.89; 95% CI 1.57 to 2.27), risperidone (25 RCTs, N=4,581; RR 1.32; 95% CI 1.09 to 1.60), and ziprasidone (seven RCTs, N=1,597; RR 1.68, 95% CI 1.26 to 2.23) (SOE: moderate).

## Detailed Synthesis

### Description of Included Studies

A recent large, good-quality systematic review compared the benefits and harms of FGAs versus SGAs (Appendix Table E-1).<sup>27,28</sup> The review included 111 RCTs and 2 cohort studies conducted in people with schizophrenia or related psychosis (n=118,503). Patients enrolled in the included studies had a mean age of 37 years; half of the included studies were conducted in inpatient populations. The included studies compared: oral fluphenazine with olanzapine (two RCTs), quetiapine (one RCT) and risperidone (one RCT); haloperidol with aripiprazole (eight

RCTs), asenapine (one RCT), clozapine (10 RCTs, one cohort study), olanzapine (34 RCTs, one cohort study), paliperidone (one RCT), quetiapine (10 RCTs, one cohort study), risperidone (37 RCTs, one nonrandomized trial, one cohort study) and ziprasidone (eight RCTs, one nonrandomized trial); and perphenazine with aripiprazole (one RCT), olanzapine (two RCTs), quetiapine (one RCT), risperidone (two RCTs) and ziprasidone (one RCT). No studies compared a FGA with brexpiprazole, cariprazine, iloperidone, or lurasidone. Doses of FGAs and SGAs varied widely among the studies included in the systematic review. For FGAs, doses of fluphenazine ranged from 6 to 21 milligrams per day (mg/day), haloperidol ranged from 1 to 30 mg/day and perphenazine ranged from 8 to 64 mg/day. SGA doses ranged from 1 to 45 mg/day for aripiprazole, 5 to 10 mg/day for asenapine, 200 to 800 mg/day for clozapine, 1 to 40 mg/day for olanzapine, 200 to 1200 mg/day for quetiapine, 1 to 6 mg/day for risperidone and 4 to 240 mg/day for ziprasidone. The duration of followup among the included studies ranged widely from less than 1 day to 22 years, although median followup was eight weeks. None of the included studies were rated as having low risk of bias. Reasons for unclear or high risk of bias among the studies were unclear methods of randomization and/or allocation concealment, unclear or lack of blinding of outcome assessors and incomplete reporting of outcome data (Appendix Table F-1).

We also included five additional trials not in the systematic review comparing FGAs with SGAs (N=1,055; Appendix Table E-2).<sup>57,67-70</sup> These trials enrolled between 78 and 300 participants, mean age ranged from 26 to 45 years and the proportion of female participants ranged from 25 to 42 percent. Race was reported in one trial, enrolling predominantly black patients (57%); this was also the only trial conducted in the United States.<sup>70</sup> Two trials limited enrollment to participants with first-episode psychosis.<sup>67,69</sup> The FGA used in all of the trials was haloperidol, compared with olanzapine (three RCTs), quetiapine (two RCTs), aripiprazole, risperidone and ziprasidone (one RCT each). Two trials were rated good quality,<sup>68,70</sup> one was rated poor quality,<sup>69</sup> and the others were rated fair quality (Appendix Table F-2). The primary limitation in the fair-quality trials was lack of blinding of clinicians and patients.

## Findings

### Function

Outcomes related to function were rarely reported in the systematic review, with no significant differences between FGAs and SGAs for any measure of function (Appendix Table E-1).<sup>28</sup> No significant differences were found in global function, based on GAF score, between haloperidol and olanzapine (one RCT, N=208; effect estimate -4.00; 95% CI -13.70 to 5.70), quetiapine (one RCT, N=207; effect estimate 0.20, 95% CI -9.60 to 9.80), or ziprasidone (two RCTs, one non-RCT, N=1,085; effect estimate 0.30, 95% CI -1.58 to 2.19;  $I^2=0\%$ ), or in encounters with the legal system (one RCT, N=31; RR 3.20, 95% CI 0.76 to 13.46). There were also no differences in proportion of patients with paid employment for comparisons of perphenazine versus olanzapine (N=597; RR 1.29; 95% CI 0.70 to 2.38), quetiapine (N=598; RR 1.75; 95% CI 0.90 to 3.43), risperidone (N=602; RR 1.38; 95% CI 0.74 to 2.57) and ziprasidone (N=446; RR 1.22; 95% CI 0.60 to 2.51) based on one trial each. The number of patients with economic independence was also not different in one trial of haloperidol versus risperidone (N=100; RR 0.94; 95% CI 0.68 to 1.29). This SOE was insufficient due to limited evidence for each comparison.

## Quality of Life

The systematic review found little evidence of a differential effect between FGAs and SGAs in quality of life outcomes (Appendix Table E-1).<sup>28</sup> One trial comparing haloperidol with ziprasidone found a positive effect on QLS score favoring ziprasidone (N=599; effect estimate -12.12, 95% CI -22.06 to -2.17). There was no difference between haloperidol and ziprasidone in one other trial based on the Manchester Short Assessment of Quality of Life (MANSA) score (N=185; effect estimate -0.10, 95% CI -1.48 to 1.28). This was low SOE. There was no difference in quality of life outcomes in trials comparing haloperidol with olanzapine (five RCTs, N=816; effect sizes ranged from -3.62 to 0). This SOE was moderate. There was also no difference for haloperidol versus quetiapine (one RCT, N=207; effect estimate 0.00, 95% CI -1.38 to 1.38) and risperidone (two RCTs, N=352; effect estimates ranged from -0.10 to 0.10) using various quality of life measures; this evidence was of insufficient strength. Based on one trial each, no significant differences in quality of life measures were found when comparing perphenazine with aripiprazole (N=300; RR 4.74, 95% CI 2.58 to 8.69), olanzapine (N=597; effect estimate 0.00; 95% CI -0.16 to 0.16), quetiapine (N=598; effect estimate 0.10, 95% CI -0.07 to 0.27), risperidone (N=602; effect estimate -0.07, 95% CI -0.24 to 0.10), or ziprasidone (N=446; effect estimate -0.07, 95% CI -0.27 to 0.13). Due to limited evidence and the heterogeneity of measures used to assess quality of life, this SOE was low to insufficient (for perphenazine versus aripiprazole).

## Response and Remission

### Response

Evidence on response rate was mixed in the systematic review and heterogeneity was moderate to high for most risk estimates (Appendix Table E-1).<sup>28</sup> Pooled results from 14 RCTs comparing haloperidol with olanzapine found a significant effect favoring olanzapine (N=4,099; RR 0.86, 95% CI 0.78 to 0.96;  $I^2=55\%$ ). However, the review found no difference in response rates between haloperidol and aripiprazole (five RCTs, N=2,185; RR 1.01, 95% CI 0.76 to 1.34;  $I^2=83\%$ ), quetiapine (six RCTs, N=1,421; RR 0.99; 95% CI 0.76 to 1.30;  $I^2=77\%$ ), risperidone (16 RCTs, N=3,452; RR 0.94, 95% CI 0.87 to 1.02;  $I^2=29\%$ ) and ziprasidone (six RCTs, N=1,283; RR 0.98, 95% CI 0.74 to 1.30;  $I^2=80\%$ ). This was low to moderate (for haloperidol versus risperidone) SOE. There was no difference between groups for other comparisons, including fluphenazine versus olanzapine, quetiapine and risperidone and for perphenazine versus aripiprazole based on one trial each. This evidence was insufficient for all comparisons.

### Remission

Pooled evidence from three trials comparing haloperidol with olanzapine found a significant difference in remission rates favoring olanzapine (RR 0.64; 95% CI 0.45 to 0.94) with moderate heterogeneity ( $I^2=54\%$ ).<sup>28</sup> Evidence from a trial not included in the systematic review was consistent, though not significant, finding a greater number of patients taking olanzapine experienced remission compared with the haloperidol group 33% versus 25%;  $p=0.5$ .<sup>67</sup> This was low SOE. There were no differences between haloperidol and clozapine (one RCT, N=71; RR 0.16, 95% CI 0.02 to 1.20), quetiapine (one RCT, N=207; RR 0.72, 95% CI 0.41 to 1.25), risperidone (two RCTs, N=179; RR 0.84, 95% CI 0.56 to 1.24;  $I^2=0\%$ ), or ziprasidone (three RCTs, N=1,085; RR 0.89, 95% CI 0.71 to 1.12;  $I^2=12\%$ ). This was low (for ziprasidone) and insufficient (for clozapine, quetiapine and risperidone) SOE.

## **Mortality**

The systematic review did not include any trials of outpatients reporting mortality rates.<sup>28</sup> One retrospective cohort study was included, reporting higher risk of mortality in patients taking haloperidol versus clozapine or risperidone. These results are difficult to interpret, as patient characteristics such as age were not reported in patients taking antipsychotic medications, and the controls in the study were taking antipsychotic medications for reasons other than schizophrenia or other psychotic disorders.<sup>245</sup>

## **Reduction in Self-Harm**

Most RCTs excluded patients at risk for suicide. In trials of haloperidol versus olanzapine (N=182) and perphenazine versus olanzapine (N=597) there were no differences in incidence of attempted suicide (RR 3.13, 95% CI 0.13 to 76; and 0.64, 95% CI 0.06 to 7.06) or suicide deaths (RR 3.13, 95% CI 0.13 to 76; and 3.86, 95% CI 0.40 to 37).<sup>28</sup> One trial not included in the systematic review reported no difference between LAI paliperidone and LAI haloperidol in incidence of suicidal or homicidal ideation (RR 1.10, 95% CI 0.63 to 1.89).<sup>70</sup> This was insufficient SOE.

## **Improvement in Core Illness Symptoms**

The systematic review assessed total and negative symptoms based on a number of scale measures, including total PANSS, BPRS, CGI-S and CGI-I for total symptoms and PANSS and SANS for negative symptoms (Appendix Table E-1).<sup>27,28</sup> Comparative evidence was only available for haloperidol versus SGAs. The review did not combine results across different scales.

## **Total Symptoms**

### **PANSS**

Based on pooled analysis, there were significant difference in total PANSS between haloperidol and olanzapine (15 RCTs, N=4,209; MD 2.31, 95% CI 0.44 to 4.18) and risperidone (21 RCTs, N=4,020; MD 3.24, 95% CI 1.62 to 4.86), both favoring the SGA over haloperidol. This was moderate SOE, and the differences are small enough to possibly not meet a minimal clinically important difference threshold. There were no differences between haloperidol and clozapine (four RCTs, N=607; MD 2.69, 95% CI -1.28 to 6.65), quetiapine (five RCTs, N=1,013; MD 0.31, 95% CI -2.34 to 2.96) and ziprasidone (four RCTs, N=1,105; MD 1.22, 95% CI -0.62 to 3.07). This evidence was low strength.

### **BPRS**

There were no differences in BPRS scores between haloperidol and aripiprazole (three RCTs, N=779; MD -0.01, 95% CI -2.82 to 2.81), clozapine (four RCTs, N=268; MD 2.16, 95% CI -0.56 to 4.87), olanzapine (13 RCTs, N=4,014; MD 0.19, 95% CI -2.09 to 2.47), quetiapine (four RCTs, N=756; MD 1.23, 95% CI -0.50 to 2.96), risperidone (14 RCTs, N=2,659; MD 0.67, 95% CI -0.53 to 1.88) and ziprasidone (four RCTs, N=1,143; MD 0.24, 95% CI -0.57 to 1.06). This was low-strength evidence.

### **CGI-S**

CGI-S scores, as a measure of illness severity, were marginally better with olanzapine (MD 0.16, 95% CI 0.01 to 0.31) when compared with haloperidol, and better with haloperidol

when compared with quetiapine (MD -0.23, 95% CI -0.42 to -0.04) based on analysis of eight (N=3,564) and four (N=1,253) trials each. Though these estimates were significant, they were considered not clinically meaningful.<sup>27</sup> The SOE was moderate for both comparisons. MD in scores for haloperidol and aripiprazole (five RCTs, N=1,366; -0.03, 95% -0.20 to 0.14) risperidone (eight RCTs, N=2,348; 0.07, 95% CI -0.11 to 0.25) and ziprasidone (four RCTs, N=1,143; -0.00, 95% CI -0.26 to 0.26) was not significantly different between groups, with low SOE for all comparisons.

### **CGI-I**

There was no difference in CGI-I scores, as a measure of improvement since beginning treatment, between haloperidol and olanzapine (two RCTs, N=281; MD 0.11, 95% -0.30 to 0.51), quetiapine (three RCTs, N=623; MD 0.02, 95 % CI -0.24 to 0.27) and risperidone (three RCTs, N=657; -0.02, 95 % CI -0.39 to 0.36) based on pooled analysis. This was low SOE.

### **Negative Symptoms**

#### **PANSS Negative**

There was moderate-strength evidence that some SGAs were more effective than haloperidol at improving PANSS negative symptom scores. Analysis of MD in score between haloperidol and aripiprazole (three RCTs, N=1,701; 0.80, 95% CI 0.14 to 1.46), olanzapine (14 RCTs, N=3,742; 1.06, 95% CI 0.46 to 1.67), and risperidone (22 RCTs, N=4,142; 0.80, 95% CI 0.14 to 1.46) all favored the SGA. Evidence was not able to identify a difference in PANSS negative symptoms scores when comparing haloperidol and clozapine (three RCTs, N=184; MD 0.28, 95% CI -0.96 to 1.51), quetiapine (three RCTs, N=358; MD 0.53, 95% CI -0.81 to 1.87) and ziprasidone (two RCTs, N=900; MD 0.56, 95% CI -0.30 to 1.42). This evidence is low strength, primarily due to the small sample sizes. Whether significant or not, the differences found were very small.

#### **SANS**

Olanzapine was found to be more effective than haloperidol at improving SANS scores based on analysis of five RCTs (N=535; MD 2.56, 95% CI 0.94 to 4.18). The SOE was moderate. Evidence was not able to identify a difference between haloperidol and clozapine (two RCTs, N=157; MD 0.94, 95% CI -2.60 to 4.48) or risperidone (4 RCTs, N=508; MD 0.30, 95% CI -2.79 to 3.38). This was low-strength evidence.

### **Overall Adverse Events**

Overall adverse event rates were reported for each FGA and select SGAs (Appendix Table E-1).<sup>28</sup> When compared with haloperidol, there were significant differences favoring aripiprazole (three RCTs, N=1,713; RR 1.11, 95% CI 1.06 to 1.17;  $I^2=0\%$ ), risperidone (eight RCTs, N=1,313; RR 1.20, 95% CI 1.01 to 1.42;  $I^2=84\%$ ), and ziprasidone (six RCTs, N=1,448; RR 1.13, 95 % CI 1.03 to 1.23;  $I^2=31\%$ ). Due to limited evidence and heterogeneity for the risperidone and ziprasidone comparisons, SOE is low. No significant differences overall adverse event rates for other comparisons, primarily based on single studies, comparing: fluphenazine with olanzapine (one RCT, N=60; RR 9.00, 95% CI 0.51 to 160); haloperidol with asenapine (one RCT, N=335; RR 1.09, 95% CI 0.96 to 1.25), clozapine (one RCT, N=423; RR 0.81, 95% CI 0.49 to 1.34), olanzapine (one RCT, N=119; RR 10.47, 95% 0.59 to 185), or quetiapine (three RCTs, N=859; RR 1.08, 95% CI 0.93 to 1.25;  $I^2=25\%$ ); perphenazine with olanzapine (one RCT,

N=597; RR 0.93, 95% CI 0.83 to 1.04), quetiapine (one RCT, N=598; RR 1.00, 95% CI 0.89 to 1.12), risperidone (one RCT, N=602; RR 0.96, 95% CI 0.85 to 1.07), or ziprasidone (one RCT, N=446; RR 1.01; 95% CI 0.88 to 1.16). SOE for all of these comparisons was insufficient.

### **Withdrawal Due to Adverse Events**

Evidence on withdrawals due to adverse events comes from the systematic review<sup>28</sup> and four additional RCTs<sup>57,67-69</sup> not included in the systematic review (Appendix Tables E-1 and E-2). When comparing haloperidol with specific SGAs, withdrawals due to adverse events were significantly higher with haloperidol use compared with aripiprazole (eight RCTs, N=3,232; RR 1.25, 1.07 to 1.47;  $I^2=0\%$ ; Appendix G-4), olanzapine (24 RCTs, N=5,708; RR 1.89, 95% 1.57 to 2.27;  $I^2=0\%$ ; Appendix G-5), risperidone (25 RCTs, N=4,581; RR 1.32, 95 % CI 1.09 to 1.60;  $I^2=0\%$ ; Appendix G-6), and ziprasidone (seven RCTs, N=1,597; RR 1.68, 95% 1.26 to 2.23;  $I^2=0\%$ ; Appendix G-7). This was moderate SOE. There is low SOE of no difference in withdrawal due to adverse events when comparing haloperidol and clozapine (5 RCTs, N=719; RR 1.00, 95% CI 0.66 to 1.50;  $I^2=0\%$ ) or quetiapine (10 RCTs, N=1,759; RR 1.97, 95% CI 0.96 to 4.01;  $I^2=62\%$ ; Appendix G-8). Based on single studies for each comparison, there was no significant differences when comparing: haloperidol to asenapine (N=335; RR 1.53, 95% 0.74 to 3.16); fluphenazine to olanzapine (N=60; RR 0.74, 95% CI 0.51 to 1.07) or quetiapine (N=25; RR 0.19, 95% CI 0.01 to 3.52); or perphenazine to aripiprazole (N=300; RR 0.53, 95% CI 0.27 to 1.05), olanzapine (N=597; RR 0.83, 95% CI 0.58 to 1.19), quetiapine (N=598; RR 1.05, 95% CI 0.72 to 1.55), risperidone (N=602; RR 1.54, 95% CI 1.00 to 2.36), or ziprasidone (N=446; RR 1.01, 95% CI 0.65 to 1.58). SOE for these comparisons was insufficient.

## **Key Question 1b. Variation of Benefits and Harms of Pharmacological Treatments for Adults With Schizophrenia by Patient Characteristics**

### **Second-Generation Antipsychotic Versus Second-Generation Antipsychotic**

#### **Key Points**

- Evidence on SGAs versus each other in population subgroups was limited.
- In 17 trials in patients with first-episode psychosis evidence did not indicate significant differences between oral olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole, or paliperidone in rates of response or remission.
  - Most studies also reported no difference in core illness symptom measures. These findings did not differ according to the duration of study, the specific drugs compared, in adolescents or women, or whether or not studies were blinded.
  - Evidence on study medication discontinuation was more limited, with conflicting findings from five trials. Olanzapine was not found to have fewer discontinuations and longer time to discontinuation consistently across the studies.
  - Single-trial evidence suggests that fewer patients taking aripiprazole discontinue medication than ziprasidone or quetiapine but patients receiving aripiprazole had more weight gain than those receiving ziprasidone.

- In treatment-resistant patients, network meta-analyses indicated a small benefit with olanzapine over other older SGAs in core illness symptom improvement, negative symptoms, whereas response rates and all-cause treatment discontinuations were not different. Clozapine had fewer discontinuations due to lack of efficacy.
- In subgroups based on age and sex:
  - Subgroup analyses did not find differences based on age between olanzapine and risperidone in symptom measures, quality of life, or persistence (>60 years or 50 to 65 years vs. younger populations).
  - Subgroup analyses indicated that women improved more than men on the CGI scale with clozapine and the EQ-5D visual analog scale score with olanzapine, compared with men.
  - Women and younger patients (<40 years) were at higher risk of new onset diabetes than older, male patients with olanzapine and risperidone compared with FGAs.
- Asian patients: Comparisons of aripiprazole and paliperidone with olanzapine, and quetiapine and risperidone in Asian patients were similar to the overall conclusions for these comparisons.
- In subgroups based on comorbidities and concomitant drug use:
  - Users of illicit drugs did not have different findings on any outcome compared with the overall study population in CATIE Phase 1 (olanzapine, risperidone, quetiapine and ziprasidone).
  - Response rates were also similar for olanzapine and risperidone in patients with first-episode schizophrenia and a history of cannabis use disorders.

## Detailed Synthesis

### Description of Included Studies

Very limited direct comparative evidence addressed SGAs used for the treatment of schizophrenia in subgroups of the population. Five studies assessed the impact of age,<sup>163,240,246-248</sup> two assessed the impact of race,<sup>249,250</sup> and three evaluated the impact of SGAs in patients with comorbid substance use or alcohol use disorders.<sup>251-253</sup> Most trials did not report ethnicity of enrolled patients and although three trials reported that a substantial number of patients were of African ancestry, none stratified results to examine differences in response or adverse events.<sup>152,192,254</sup> Three trials assessed the effects of these drugs on depressive symptoms, but the patients were not selected for the trial based on depressive symptoms.<sup>255-257</sup> The results of these trials were discussed above.

In a subgroup analysis, 100 patients who had been randomly assigned to aripiprazole or risperidone were tested for the rs2514218 genotype. The authors then correlated symptom response and adverse events with genotype status. They found that “homozygotes for the risk (C) allele at rs2514218 had significantly greater reduction in positive symptoms during 12 weeks of treatment compared to the T allele carriers. In the aripiprazole group, C/C homozygotes also reported more akathisia than the T allele carriers, whereas in the risperidone group, male T allele carriers demonstrated greater prolactin elevations compared to male C/C homozygotes.”<sup>258</sup> These findings suggest further development of genotyping may help with selection of SGA medications, but is preliminary at this point.

## Findings

### Clinical Subgroups

#### First-Episode Schizophrenia

The systematic review identified 17 trials (in 22 publications) of oral SGAs in patients experiencing their first episode of symptoms of schizophrenia.<sup>29</sup> The studies were mainly fair quality (12 of 17), with nine open label trials (Table 8). Six trials had at least 12 months of followup and sample sizes ranged from 50 to 498. One trial included only women. And the mean age of patients was early 20s to late 30s.

Differences among the SGAs on at least one outcome were found in five of 12 fair-quality trials. Olanzapine was found to have lower risk and longer time to all-cause treatment discontinuation than risperidone (one of three RCTs), quetiapine (two of two RCTs), and ziprasidone (one of three RCTs), but differences in other benefit outcomes were not found. One trial that did not find differences in benefit outcomes at 1 year also found no differences at 3 years of followup. This trial also reported that patients taking risperidone had higher incidence of increasing severity of akathisia, sexual dysfunction (in men) and amenorrhea, whereas more patients reported daytime drowsiness with olanzapine. In a single study, aripiprazole was found to have lower risk of all-cause treatment discontinuation than quetiapine or ziprasidone, lower risk of discontinuing due to adverse events than ziprasidone, longer time to discontinuing than quetiapine, and greater risk of important weight gain than ziprasidone, but differences in other benefit outcomes were not found. A single trial found that core illness symptoms (based on the PANSS) were better with paliperidone than ziprasidone or aripiprazole, but that response rates did not differ significantly.

**Table 8. Studies of SGAs in patients treated for first episode of schizophrenia**

Study	N Duration Blinding	Comparison	Results
Crespo-Facorro, 2011 <sup>67</sup>	N=174 1 year with 3 year followup Open	Olanzapine vs. Risperidone	NSD relapse, time to relapse or remission at 1 year NSD Symptoms or global functioning (1 and 3 years) NSD in discontinuation for any reason (1 and 3 years). NSD % reporting weight gain, change in EPS or new parkinsonism (3 years) NSD % akathisia, but increase in severity greater with risperidone vs. olanzapine (p=0.042). Daytime drowsiness greater with olanzapine Sexual dysfunction in men and amenorrhea in women greater with risperidone.
Crespo-Facorro, 2006 <sup>159</sup>	N=182 6 weeks Open	Olanzapine vs. Risperidone	NSD symptoms
Robinson, 2006 <sup>173</sup>	N=112 16 weeks Open	Olanzapine vs. Risperidone	NSD response, negative symptoms
McEvoy, 2007 <sup>169</sup> (CAFÉ study)	N=400 1 year DB	Olanzapine vs. Quetiapine vs. Risperidone	NSD in all-cause treatment discontinuations and core illness symptoms
Li, 2012 <sup>167</sup>	N=80 6 weeks Open	Olanzapine vs. Ziprasidone	NSD symptoms

Study	N Duration Blinding	Comparison	Results
Kahn, 2008 <sup>231,259</sup> (EUFEST study)	N=498 12 months Open	Olanzapine vs. Quetiapine vs. Ziprasidone	NSD response or remission. NSD all-cause treatment discontinuations for ziprasidone vs. quetiapine and olanzapine Quetiapine results in significantly higher risk of discontinuation than olanzapine. (OR 2.41, 95% CI 1.31 to 4.45)
San, 2012 <sup>68</sup>	N=114 12 months Open	Olanzapine vs. Quetiapine vs. Risperidone vs. Ziprasidone	All-cause treatment discontinuation lower with olanzapine (40%) than quetiapine (56.5%), risperidone (64%), or ziprasidone (80%). Mean time to discontinuation significantly longer with olanzapine (260 days) than the other drugs (range 142 days ziprasidone to 206 days risperidone; p=0.005).
Liu, 2014 <sup>52</sup>	N=80 12 months Open Women	Quetiapine vs. Risperidone	NSD Core illness symptoms at 9 and 12 months (lower with risperidone at 3 and 6 months).
Gafoor, 2010 <sup>260</sup>	N=72 12 weeks SB	Quetiapine vs. Risperidone	NSD all-cause treatment discontinuation, time to discontinuation, symptoms
Robinson, 2015 <sup>59</sup>	N=209 12 weeks DB	Aripiprazole vs. Risperidone	NSD in response, core illness symptoms
Crespo-Facorro, 2013 <sup>261</sup>	N=249 12 months Open	Aripiprazole vs. Ziprasidone vs. Quetiapine	NSD relapse or remission, core illness symptoms, adverse events, EPS, akathisia Treatment discontinuation: Quetiapine 82.3%, ziprasidone 66.1%, aripiprazole 43.6% (p<0.001) Time to D/C (mean days): Quetiapine 77.24, ziprasidone 129.88, aripiprazole 106.71 (p<0.001) D/C due to adverse events: Quetiapine 11.3%, ziprasidone 29%, aripiprazole 10.3% (p=0.005) ≥ 7% weight gain: Aripiprazole vs. ziprasidone: 45.6% vs.23.5% (p=0.02)
Zhang, 2012 <sup>242</sup>	N=254 52 weeks Open	Paliperidone vs. Ziprasidone vs. Aripiprazole	Core illness symptoms significantly lower with paliperidone than ziprasidone or aripiprazole at 13, 26 and 52 weeks NSD response rate

CGI = Clinical Global Impressions scale; CGI-S = Clinical Global Impressions-Severity scale; CI = confidence interval; N = sample size; NSD = no significant difference; OR = odds ratio; PANSS = Positive and Negative Syndrome Scale; SGA = second-generation antipsychotic; SS = statistically significant

### Treatment-Resistant Patients

Treatment resistance, defined as at least two adequate trials of an antipsychotic medication with failure to respond, is a challenge in approximately 20 to 30 percent of patients with schizophrenia.<sup>262</sup> Although clozapine has been considered the treatment of choice, comparisons to other SGAs are needed since clozapine has a serious adverse event profile, the need for regular laboratory monitoring, and not all patients respond.

An analysis of six oral SGAs (clozapine, risperidone, olanzapine, quetiapine, and ziprasidone) in 40 RCTS of patients with treatment-resistant schizophrenia found that the mean change in the PANSS was greater with olanzapine than quetiapine (SMD -0.29, 95% CI -0.56 to -0.13).<sup>183</sup> The authors note that this corresponds to a difference in points on the PANSS of -6.08 (scale scores range from 30 to 210; 180 possible points). There is some evidence that in patients with more severe disease a minimal clinically important difference on the PANSS is 11.5 points,

indicating that a difference of six points may not be clinically important, although statistically significant.<sup>195</sup> The newer oral drugs (aripiprazole, iloperidone, lurasidone, asenapine, cariprazine, brexpiprazole) were not included. This was low-strength evidence.

There are three systematic reviews published since 2013 that address the comparative benefits and harms of SGAs for treatment-resistant patients.<sup>183,263,264</sup> The most recent and comprehensive of these uses network meta-analysis of 40 RCTS to analyze clozapine, risperidone, olanzapine, quetiapine, and ziprasidone (as well as three FGAs and an SGA not available in the United States).<sup>183</sup> The newer oral drugs (aripiprazole, iloperidone, lurasidone, asenapine, cariprazine, brexpiprazole) and injectable SGAs were not included. The mean change in the PANSS was greater with olanzapine than quetiapine (SMD -0.29, 95% CI -0.56 to -0.13).<sup>183</sup> The authors note that this corresponds to a difference in points on the PANSS of -6.08 (scale scores range from 30 to 210; 180 possible points). There is some evidence that in patients with more severe disease a minimal clinically important difference on the PANSS is 11.5 points, indicating that a difference of six points may not be clinically important, although statistically significant.<sup>195</sup> Network analysis of negative symptoms found olanzapine significantly better than the other SGAs (and two FGAs), whereas response rates and all-cause treatment discontinuations indicated no significant differences among the SGAs (although SGAs were better than haloperidol). Analysis of discontinuations due to lack of efficacy showed clozapine to be better than risperidone and quetiapine (and two FGAs). One of the other two reviews compared only olanzapine and clozapine, and had consistent findings (no differences on discontinuation rates or improvement in PANSS total scores; clozapine superior on positive and negative symptoms).<sup>263</sup> The third review evaluated strategies when clozapine fails, but was not able to come to a conclusion on adjunctive drug therapy including adding a second SGA.<sup>264</sup>

### **Special Populations**

**Age.** Two fair-quality studies were specifically designed to compare the effects of olanzapine with risperidone in older patients ( $\geq 60$  years) with schizophrenia or schizoaffective disorder.<sup>163,240,265</sup> In an 8-week trial, no between-group differences were found in response rates (20% improvement on PANSS) or change in PANSS, CGI, or Hamilton Depression Scale (HAM-D) scores. In a smaller study (N=66), during the initial 6 months of followup there were no significant differences in efficacy outcomes (BPRS, SANS, Montgomery-Asberg Depression Scale [MADRS]) between the drugs. However, patients taking olanzapine were seen to have better quality of life at 6 months as assessed using the World Health Organization Quality of Life tool ( $p=0.040$  for overall quality of life,  $p=0.031$  for satisfaction with health), with better physical health and social relationships. Differences were not seen on the psychological or environmental domains. These outcomes are similar to outcomes found in younger populations, reported above.

Post hoc subgroup analyses of the Tran trial, which compared olanzapine with risperidone, reported outcomes for the subgroup of patients 50 to 65 years old.<sup>181,247,266</sup> Out of a total study population of 339 patients, 39 were between 50 and 65 years old. The split between sexes was not evenly distributed across the two drug groups. The risperidone group was 42 percent male, whereas the olanzapine group was 70 percent male. Another difference at baseline was the duration of the current episode, a mean of 61 days in the olanzapine group and 120 days in the risperidone group (although not significant). The mean modal dose in the olanzapine group was 18 mg (within midrange) and in the risperidone group 8 mg (above midrange). In general, because the size of the subgroup was small and the age range covered only up to 65 years, the implications of the findings of this subanalysis for older patients with schizophrenia were

difficult to interpret. However, the analysis did indicate that results were probably not different in this older population.

A retrospective study from the US Department of Veterans Affairs database, conducted to evaluate the risk of new onset diabetes among new users of SGAs, found a differential effect with analysis by age.<sup>246</sup> Higher risk was found with olanzapine ( $p=0.05$ ) and risperidone ( $p=0.03$ ) for patients less than 45 years old, whereas the risk with quetiapine in this group was not significant.

**Race.** A retrospective study of Texas Medicaid claims data analyzing the mean number of days patients continued to take their prescribed SGA drug found that patients who were Mexican American or African American had significantly fewer days on drug than white patients, although the difference in days was small (18 and 19, respectively).<sup>250</sup> The analysis did not indicate a difference among these groups when stratified by which SGA they were taking (olanzapine or risperidone).

Subgroup analyses of a 26-week trial of aripiprazole and olanzapine ( $N=314$ ) evaluated the risk of metabolic syndrome in white patients and black or Hispanic patients. In comparing the drugs, the results across the subgroups were similar to the overall findings (that aripiprazole resulted in lower risk), although the point estimate was lower for white patients than for black and Hispanic patients and the comparison for the smaller black/Hispanic group did not reach significance.<sup>267</sup> The ORs were 0.33 (95% CI 0.19 to 0.55) for all patients, 0.20 (95% CI 0.10 to 0.41) for white patients, and 0.53 (95% CI 0.25 to 1.12) for black and Hispanic patients. Analyses of effects of ethnicity within each drug group found that white patients had lower risk than black and Hispanic patients taking aripiprazole, but that there was no difference between these groups among patients taking olanzapine.

Aripiprazole's effect in Japanese patients, compared with other drugs, was evaluated in meta-analyses using both published and unpublished information in a good-quality systematic review.<sup>268</sup> Although the overall analysis combined results from multiple different comparator drugs in a simple way (i.e., not an indirect comparison or network meta-analysis), the publication also reported pair-wise comparisons for aripiprazole compared with risperidone, olanzapine and quetiapine, based on a single study that included all four drugs.<sup>230</sup> This study found no differences between the drugs on the PANSS total scores or subscale scores, but did find aripiprazole to result in a higher risk of discontinuation due to lack of efficacy compared with olanzapine (OR 6.25, 95% CI 1.14 to 34.12) and risperidone (OR 4.52, 95% CI 1.30 to 15.73), but no difference compared with quetiapine (OR 0.68, 95% CI 0.20 to 2.30). The confidence intervals are wide, as these results are based on a single, small ( $N=80$ ), 8-week study and the results should be interpreted with caution. Future studies could overturn these findings. These results are consistent with the findings of all trials comparing these drugs. Another trial, reported above in Key Questions 1 and 2, included 455 Japanese, Taiwanese, Malaysian and Filipino patients randomized to oral or aripiprazole LAI, finding the injectable drug to be noninferior to the oral drug in "non-exacerbation of psychotic symptoms/non-relapse" as the primary outcome measure.<sup>49</sup> There were no significant differences on secondary outcomes as well, including extrapyramidal adverse events.

Two trials compared aripiprazole and risperidone in Asian patients; one in Taiwan<sup>155</sup> and one in mainland China.<sup>51,193</sup> Both studies found no significant differences in efficacy outcomes at 4 and 6 weeks, consistent with the findings of the overall analysis in Key Question 1 above. These studies come to different conclusions on extrapyramidal symptoms (EPS)-related adverse events,

with the small 4-week study conducted in Taiwan (N=83) reporting more EPS adverse events, particularly akathisia with aripiprazole,<sup>155</sup> and the larger 6-week study conducted in China (N=279) reporting no differences between the drugs on EPS outcomes. A third study, conducted in North America in patients with first-episode schizophrenia, found aripiprazole to be significantly associated with higher akathisia scores on the Barnes Akathisia Scale in the early months of the trial, but not at 12 months.<sup>59</sup> Other measures, Parkinsonism and EPS severity, were not found different when akathisia was not considered part of EPS. Based on these studies, it is not clear that there is a difference in effects, benefits or harms, of aripiprazole and risperidone in Asian patients.

A fair-quality systematic review evaluated paliperidone and paliperidone palmitate monthly LAI in Chinese patients with schizophrenia.<sup>269</sup> The review included 53 studies of the oral paliperidone and 9 of the injection that were conducted in China, including pharmacokinetic studies, single-arm studies, and studies with olanzapine, quetiapine, risperidone or aripiprazole. The review concludes that few differences were found between the drugs and that the findings are consistent with study results in non-Asian patients.

**Sex.** Analysis of differences in effect by sex in the European SOHO study found that compared with women, men had lower odds of response (based on the CGI scale; OR 0.56, 95% CI 0.34 to 0.93) with clozapine and smaller improvement in quality of life (based on EQ-5D visual analog score; OR -1.52, 95% CI -2.53 to -0.50).<sup>248</sup> Risperidone did not result in any differences between men and women.

### Substance Use

In a post-hoc analysis of the CATIE Phase 1 trial data, outcomes were compared between users and nonusers of illicit substances.<sup>252</sup> Based on the primary outcome measure of overall discontinuation (rate and time to), the results were consistent with the overall trial results for those who were nonusers (olanzapine superior to quetiapine and risperidone, ziprasidone not significantly different). However, significant differences were not found for any of the comparisons among users of illicit drugs. Further analyses compared olanzapine to the combined group of antipsychotic drugs in the trial and were not useful for the purposes of this report.

A subgroup analysis from a fair-quality trial of 49 patients with first-episode schizophrenia and a lifetime history of cannabis use disorders found no significant difference between olanzapine and risperidone in rate of response at 16 weeks, defined as (1) mild or better on all the Schedule for Affective Disorders and Schizophrenia – Change Version with Psychosis and Disorganization (SADS-C + PD) items severity of delusions, severity of hallucinations, impaired understandability, derailment, illogical thinking, and bizarre behavior; and (2) a concurrent rating of very much improved or much improved on the CGI (45% vs. 54%; p=0.68).<sup>270</sup> These results were consistent with results for the trial population as a whole (N=112).<sup>173</sup>

Three additional studies addressed substance misuse subgroups, but we rated them poor-quality and they did not contribute to our overall conclusions.<sup>251,253</sup> A small study of 29 patients with comorbid schizophrenia and cocaine or marijuana abuse or dependence that compared olanzapine with risperidone was rated poor-quality based on unclear randomization and allocation concealment procedures with resulting imbalances in baseline characteristics among the groups, unclear analyses, and differential discontinuation.<sup>253</sup> A small cohort study (N=67) of patients with comorbid alcohol use disorder that compared rehospitalization rates with risperidone or clozapine was rated poor-quality due to unclear methods of patient selection. Nine percent of patients were removed from analysis because they discontinued drug due to adverse

events and potentially important differences at baseline were not controlled for in analyses.<sup>251</sup> We also gave a poor-quality rating to a randomized trial of 139 patients with schizophrenia and nicotine dependence because of unclear methods of randomization, allocation concealment, and blinding and unclear reporting about attrition and completeness of the analysis dataset.<sup>271</sup>

### **Obesity**

An exploratory analysis of treatment effect across baseline body mass index categories (normal:  $<25 \text{ kg/m}^2$ ; overweight:  $\geq 25$  to  $<30 \text{ kg/m}^2$ ; obese:  $\geq 30 \text{ kg/m}^2$ ) from a 53-week, fair-quality RCT of 749 patients found that the difference in mean change in PANSS total score indicated noninferiority for paliperidone palmitate injection 63.5 mg (mean dose) compared with risperidone long-acting injectable 32.4 mg (mean dose) for the normal and overweight subgroup (difference in least-squared means  $-0.5$ , 95% CI  $-4.01$  to  $+3.08$ ), but not for the obese subgroup ( $-7.5$ , 95% CI  $-12.1$  to  $-2.82$ ).<sup>188</sup> The findings of this study may be affected by the rate of dose initiation and location of injections used for paliperidone palmitate injection, which was lower than currently recommended.

## **First-Generation Antipsychotic Versus Second-Generation Antipsychotic**

### **Key Points**

- In patients with a first episode of schizophrenia, the evidence comparing FGAs to SGAs is less robust than SGAs versus SGAs, but did not find significant differences between the drugs.
- In treatment-resistant patients, response was significantly better with ziprasidone than haloperidol (N=120; RR 1.54, 95% CI 1.19 to 2.00), whereas there was no significant effect in nontreatment-resistant patients. Negative symptoms were significantly reduced with olanzapine versus haloperidol (N=2,207; MD 1.28, 95% CI 0.11 to 2.44, whereas in mixed populations the difference was not significant.
- There was not a clear impact of dose on response or core illness symptom improvement based on subgroup analyses of aripiprazole, olanzapine, quetiapine, and risperidone versus haloperidol.
- Asian patients: Although response rates were similar between Asian and non-Asian subgroups, core illness symptoms were significantly improved in Asian patients with olanzapine versus haloperidol (one RCT; MD 4.40; 95% CI 0.33 to 8.47), and not in other races.
- In patients with co-occurring SUD, core illness symptoms improved significantly more with olanzapine than haloperidol, whereas the subgroup of studies excluding these patients showed no difference. With risperidone, the results were opposite: there was no significant difference in studies that included patients with SUD, whereas risperidone was better than haloperidol in studies that excluded such patients.

## Detailed Synthesis

### Description of Included Studies

The 2012 systematic review reported a number of subgroup analyses according to demographic and clinical patient characteristics. Analyses for which there was a difference between patient groups are reported below.<sup>28</sup>

### Findings

#### Clinical Subgroups

##### First-Episode Schizophrenia

There was no difference between groups in total PANSS score in studies of haloperidol versus risperidone in patients with first-episode psychosis (one RCT, N=183; MD 1.60, 95% CI -5.61 to 8.81) and those with multiple psychotic episodes (seven RCTs, N=1,984; MD -0.56, 95% CI -3.98 to 2.86;  $I^2=65\%$ ).<sup>28</sup> For other comparisons, outcomes were significantly better for the SGA only for the subgroup that included multiple episodes (Appendix Table E-1).

##### Treatment-Resistant Schizophrenia

Analysis of studies of haloperidol versus olanzapine stratifying results according to treatment resistance found mixed and unclear effects on total symptom scores (Appendix Table E-1).<sup>28</sup> Using BPRS as a measure, a mixed population treatment and nontreatment-resistant patients fared better with olanzapine than haloperidol (nine RCTs, N=1,809; MD 1.10, 95% CI 0.62 to 1.58;  $I^2=0\%$ ), whereas in the treatment-resistant only populations there was no difference between the drugs, (four RCTs, N=2,205; MD -5.50, 95% CI -14.1 to 3.07) although heterogeneity was so high as to render this estimate unreliable ( $I^2=95\%$ ). Using CGI-S as a measure, in treatment-resistant patients olanzapine resulted in a significant benefit (two RCTs, N=2,059; MD 0.24, 95% CI 0.01 to 0.47;  $I^2=32\%$ ), although the difference is so small (0.24 on a 0 to 7 scale) that clinical relevance is unlikely. The analysis of mixed populations showed no significant benefit (five RCTs, N=1,297; MD 0.07, 95% CI -0.10 to 0.24;  $I^2=71\%$ ).

Negative symptoms were reduced with olanzapine use in treatment-resistant patients based on five trials (N=2,207; MD 1.28, 95% CI 0.11 to 2.44;  $I^2=40\%$ ) with no significant effect in patients with no treatment resistance based on one small trial (N=44; MD 1.02, 95% CI -2.39 to 4.43; Appendix Table E-1).

Treatment-resistant patients taking ziprasidone were twice as likely to respond to treatment versus haloperidol based on one trial (N=120; RR 1.54, 95% CI 1.19 to 2.00) whereas no such effect was found in three trials of patients without treatment resistance (N=1,053; RR 0.79, 95% CI 0.56 to 1.13; Appendix Table E-1).

##### Impact of Dose

Analyses according to FGA dose were limited to studies comparing haloperidol with aripiprazole, olanzapine, quetiapine and ziprasidone with response being the only outcome available for all comparisons (Appendix Table E-1).<sup>28</sup> The subgroup analyses divided the haloperidol dosing into <20 mg/day and >20 mg/day. The findings are not consistent across the SGAs, and not consistent with the theory that lower doses of FGAs would have better results. The findings of the overall and lower-haloperidol dose subgroup analyses were consistent; olanzapine was significantly better. The higher-haloperidol dose subgroup analysis

was not significantly different, but there were only two studies, limiting the statistical power to find a difference, and the relative risk was similar to the other analyses. For aripiprazole and quetiapine, again the overall and lower-haloperidol dose analyses were similar (no difference in these cases), but the higher-haloperidol dose subgroup analyses showed the FGA to be better. With ziprasidone, finally, the lower-dose haloperidol subgroup analysis showed ziprasidone superior, whereas the other analyses found no difference. This evidence is difficult to interpret in due to high heterogeneity and the small numbers of studies using higher doses of haloperidol (1-2 studies of the higher doses for each comparison).

## Special Populations

### Race

When comparing haloperidol and olanzapine, total BPRS scores were significantly better in the olanzapine group when stratified according to Asian race (one RCT; MD 4.40; 95% CI 0.33 to 8.47) but not significant in a subgroup of studies in other races (12 RCTs; MD 0.28; 95% CI -1.48 to 2.04). For the same comparison, response rates were similar for Asian (one RCT; RR 0.87; 95% CI 0.76 to 1.00) versus other races (13 RCTs; RR 0.86; 95% CI 0.76 to 0.97) favoring olanzapine, although the estimate was significant for other races but not Asians (Appendix Table E-1).<sup>28</sup>

### Substance Use

Evidence on the comparative effectiveness of haloperidol versus SGAs on core illness total symptom scores in patients with co-occurring SUD were mixed (Appendix Table E-1).<sup>28</sup> Although the systematic review did not have data to evaluate only a subgroup of patients with SUD, in studies of mixed populations olanzapine had significantly better total PANSS (12 RCTs, N=3,726; MD 2.71, 95% CI 0.75 to 4.67;  $I^2=40\%$ ), BRPS (seven RCTs, N=2,890; MD 2.05; 95% CI 0.55 to 3.55;  $I^2=90\%$ ) and CGI-S (three RCTs, N=2,467; MD 0.28, 95% CI 0.19 to 0.38;  $I^2=0\%$ ) scores than haloperidol. In studies that excluded people with SUD the difference was not significant, possibly due to smaller sample sizes (PANSS: three RCTs, N=483; MD -0.73, 95% CI -5.83 to 4.38;  $I^2=0\%$ ; BPRS: six RCTs, N=1,124; MD -2.37, 95% CI -6.19 to 1.44;  $I^2=36\%$ ; and CGI-S: five RCTs, N=1,097; MD 0.30, 95% CI -0.13 to 0.20). Conversely, risperidone use resulted in better symptom scores in the studies that excluded those with SUD based on total PANSS (14 RCTs, N=3,188; MD 2.56, 95% CI 0.65 to 4.47;  $I^2=18\%$ ) and BPRS (seven RCTs, N=1,875; MD 0.84, 95% CI 0.36 to 1.32;  $I^2=0\%$ ), whereas there was no significant effect in studies of mixed populations (six RCTs, N=833; MD 1.95, 95% CI -3.14 to 7.04;  $I^2=82\%$ ; and six RCTs, N=717; MD 0.23, 95% CI -1.44 to 1.90;  $I^2=29\%$ ).

Haloperidol use resulted in significantly better negative symptom scores in patients with co-occurring SUD based on one small (N=31) RCT versus olanzapine (MD -3.20, 95% CI -6.03 to -0.37), whereas in nine trials (N=3,184) enrolling a mixed population, olanzapine use resulted in better negative symptom scores compared with haloperidol (MD 1.27, 95% CI 0.82 to 1.72;  $I^2=2\%$ ).

## Key Question 2a. Benefits and Harms of Psychosocial and Other Nonpharmacological Treatments for Adults With Schizophrenia Compared With Usual Care

### Assertive Community Treatment Versus Usual Care

#### Key Points

- Evidence on assertive community treatment comes from one good-quality systematic review (14 RCTs; N=2,281) and one other RCT (N=118) not included in the review. The primary outcome target of this intervention is reduction in rehospitalization (not a prioritized outcome for this review).
- Assertive community treatment did not improve social function more than usual care, based on pooled analysis of three studies (MD 0.03; 95% CI -0.28 to 0.34); an additional trial also found no difference (SOE: low).
- Compared with usual care, there were no significant differences in arrests (two trials, total N=604; OR 1.17, 95% CI 0.60 to 2.29), imprisonment (four trials, total N=471; OR 1.19, 95% CI 0.70 to 2.01), or police contacts (two trials, total N=149; OR 0.76, 95% CI 0.32 to 1.79) with assertive community treatment (SOE: low).
- Assertive community treatment resulted in a lower likelihood of *not* living independently (four trials; OR 0.52, 95% CI 0.35 to 0.79), being homeless (four trials, OR 0.20, 95% CI 0.09 to 0.47) and being unemployed (three trials; OR 0.46, 95% CI 0.21 to 0.99) compared with usual care (SOE: moderate).
- Core illness symptoms improved to a similar degree in both assertive community treatment and usual care groups (three trials, MD -0.14; 95% CI -0.36 to 0.08). (SOE: moderate).
- Assertive community treatment reduced the likelihood of patients being admitted to a hospital, compared with usual care (N=six RCTs; OR 0.59, 95% CI 0.41 to 0.85,  $I^2=73\%$ ).

#### Detailed Synthesis

##### Description of Included Studies

A good-quality systematic review of 14 RCTs (N=2,281) assessed assertive community treatment compared with usual care (Appendix Tables E-3 and F-3).<sup>71</sup> The review defines assertive community treatment as a multi-disciplinary team-based approach to caring for patients with severe mental illness who are described as reluctant and uncooperative. The care is provided through “assertive outreach,” offering services at home or work, with team members sharing responsibility for patients. Key goals of assertive community treatment are to maintain the patient’s contact with services, reduce the incidence and duration of hospitalizations, and improve social functioning and quality of life.<sup>71</sup> A more recent review that combined evidence for assertive community treatment and intensive case management was not used, as we considered these to be distinct interventions.<sup>272</sup> However, all of the trials of assertive community treatment included in the newer review are included here. The earlier systematic review included

trials of interventions explicitly described as assertive community treatment, assertive case management, or PACT (Program of Assertive Community Treatment), or as being based on acknowledged models of assertive community treatment. Participants in the included trials had been diagnosed with schizophrenia or schizophrenia-like disorders, bipolar disorder, or depression with psychotic features. Most studies used eligibility criteria aimed at enrolling patients with frequent hospitalizations over the past 2 to 5 years, or recently hospitalized patients, but not all. Mean age ranged from 29 to 48 years. Among trials reporting other patient demographics, the proportion of female participants ranged from 0 to 56 percent and blacks were 18 to 72 percent of included populations. Quality of included studies ranged from fair to good; poor-quality studies were excluded, and the review notes that one of the flaws in the evidence based is the lack of measurements of program fidelity. Study duration ranged from 6 months to 2 years.

We identified one additional fair-quality RCT (N=118) of assertive community treatment, conducted in the Netherlands and published since the systematic review described above that enrolled participants with severe mental illness, including schizophrenia-spectrum or psychotic disorders (75%), bipolar disorder (4%), major depressive disorder (14%), and other mental illness (7%).<sup>72</sup> (Appendix Table E-4). The mean age was 42 years, 31 percent were females; duration of illness was about 8 years; ethnicity was not reported and patients were followed for 15 to 24 months. This study measured fidelity to the assertive community treatment program using the Dartmouth Assertive Community Treatment Scale (DACT), and found that the study treatment achieved scores ranging from 3.8 to 4.1 on a scale of 1 to 5.

## **Findings**

### **Function**

#### **Social Function**

Based on a systematic review of three RCTs and one additional trial not included in the RCT, there was low-strength evidence that assertive community treatment does not improve social function more than usual care after 1 to 2 years. The systematic review of assertive community treatment found no significant effect on social function, based on pooled analysis of three trials (N=206) using different measures of social function (MD 0.03; 95% CI -0.28 to 0.34;  $I^2=7%$ ; Appendix Table E-3).<sup>71</sup> Using the SFS scale, the additional RCT (N=118) found no impact of assertive community treatment compared with usual care at 12 months followup.<sup>72</sup> (Appendix Table E-4). The SOE for function was low due to study limitations and imprecision.

#### **Legal System Encounters**

The systematic review reported no significant differences in arrests (two trials, total N=604; OR 1.17, 95% CI 0.60 to 2.29;  $I^2=0%$ ), imprisonment (four trials, total N=471; OR 1.19, 95% CI 0.70 to 2.01;  $I^2=27%$ ), or police contacts (two trials, total N=149; OR 0.76, 95% CI 0.32 to 1.79;  $I^2=84%$ ; Appendix Table E-3). This was low-strength evidence due to study limitations and imprecision.

#### **Living Situation**

The systematic review reported that assertive community treatment patients were less likely to not be living independently (i.e., more likely to be living independently) at the end of the trials compared with those receiving usual care (three trials, total N=362; OR 0.46, 95% CI 0.29 to

0.74;  $I^2=0\%$ ) (Appendix Table E-3). The additional trial reported that the change in the number of days in “sheltered homes” was not different between assertive community treatment and usual care.<sup>72</sup> In our analysis, assertive community treatment resulted in a lower likelihood of not living independently (four trials; OR 0.52, 95% CI 0.35 to 0.79; Appendix G-9) compared with usual care. This SOE is moderate.

The review also found that patients assigned to assertive community treatment were less likely to be homeless during or at the end of study compared to patients assigned to usual care (three trials, total N=374; OR 0.24, 95% CI 0.11 to 0.51;  $I^2=52\%$ ). The additional study (N=118) also found a reduction in homelessness in the assertive community treatment group. Combining this evidence, the pooled odds ratio is 0.20 (95% CI 0.09 to 0.47; Appendix G-10). This was low-strength evidence due to the small numbers of events, leading to imprecise estimates.

### **Employment**

The systematic review reported significantly less unemployment in the assertive community treatment group compared to the usual care group based on two trials (total N=604; OR 0.31, 95% CI 0.19 to 0.50;  $I^2=34\%$ ). In our analysis, assertive community treatment resulted in a lower likelihood of being unemployed (three trials; OR 0.46, 95% CI 0.21 to 0.99; Appendix G-11) compared with usual care. The strength of this evidence is moderate.

### **Health-Related Quality of Life**

Only one trial included in the systematic review reported quality of life, finding assertive community treatment associated with a significant but very small difference in quality of life score relative to usual care (MD -0.52, 95% CI -0.99 to -0.05; Appendix Table E-3). The additional trial also reported quality of life, using the MANSA scale, but found no impact with assertive community treatment relative to usual care. This evidence is insufficient due to study limitations, inconsistency between the trials, and imprecision.

### **Improvement in Core Illness Symptoms**

The systematic review combined a wide range of symptom measures, including the BPRS, Brief Symptom Inventory, and Colorado Symptom Index and reported no significant differences between groups in symptoms based on three trials (N=255; MD -0.14; 95% CI -0.36 to 0.08) (Appendix Table E-3).<sup>71</sup>

The other RCT (N=118) not included in the systematic review reported total symptom scores using the BPRS symptom scale and found that, whereas symptoms improved in both assertive community treatment and usual care groups over time, there was no difference between interventions at 1 year (Appendix Table E-4).<sup>72</sup> This was moderate SOE.

### **Treatment Discontinuation**

The systematic review reported significantly less loss to followup with assertive community treatment compared to usual care based on 10 trials (total N=1,597; OR 0.51, 95% CI 0.40 to 0.65;  $I^2=0\%$ ) (Appendix Table E-3). The RCT reported the number of patients who were “out-of-care” during the last 12 months of the study, and found assertive community treatment to result in significantly lower rates (OR 0.10, 95% CI 0.03 to 0.33).<sup>72</sup> In our analysis, fewer patients receiving assertive community treatment were lost to followup (discontinued treatment) than those in usual care (12 trials; OR 0.51, 95% CI 0.41 to 0.63; Appendix G-12). This was moderate SOE.

## Other Outcomes

**Rehospitalization.** The systematic review found that assertive community treatment reduced the likelihood of patients being admitted to a hospital, compared with usual care (OR 0.59, 95% CI 0.41 to 0.85,  $I^2=73\%$ ).<sup>71</sup> The statistical heterogeneity was high in this analysis, and examination of the forest plot reveals that inclusion criteria and country of study may have influenced these findings – specifically, those studies enrolling a broader population, not limited to those with a history of frequent hospitalizations, had a smaller and not significant effect. The review also found that the duration of hospitalizations was reduced for those receiving assertive community treatment compared with usual care, in seven of eight trials reporting this outcome but was statistically significant in five. The data were reported in varying ways, such that a mean or range of difference in duration was not clear, and the authors of the review note that not all the data were analyzed correctly.

The additional RCT that was not included in this review did not find that assertive community treatment significantly reduced inpatient days per month or the number of admissions per month.<sup>72</sup> This difference in findings may be related to the setting, which was the Netherlands, whereas all of the studies finding a significant difference in the review were conducted in the United States. None of the studies of assertive community treatment that were excluded from this review (Appendix C) were excluded solely because they reported hospitalization as an outcome.

## Cognitive Adaptation Training Versus Usual Care

### Key Points

- Evidence from three RCTs of cognitive adaptation training was insufficient due to the limited number of studies and participants.

### Detailed Synthesis

We identified three RCTs (in four publications) comparing cognitive adaptive training with usual care (Appendix Table E-5).<sup>73-76</sup> Due to the limited number of studies and participants, we were not able to reliably rate the SOE for this intervention. However, among the three trials, all found that cognitive adaptation training led to greater improvements in function (based on various scale measures) relative to usual care, and one trial found cognitive adaptation training reduced risk of relapse.

## Cognitive Behavioral Therapy Versus Usual Care

### Key Points

- Three good-quality systematic reviews (9 to 50 trials each; N=895 to 3,947) and five RCTs (N=66 to 422) provided evidence for cognitive behavioral therapy (CBT). Most trials were designed to assess the effect of CBT on symptoms.
- CBT resulted in consistent improved short-term global function based on GAF and other measures, compared with usual care. Differences were not seen in long-term followup (>1 year; seven RCTs) (SOE: moderate and low, respectively).
- Social and occupational function was better with CBT than usual care in trials of  $\leq 6$  months duration (three trials; MD on SOFAS 9.11; 95% CI 6.31 to 11.91); evidence on longer-term effects was inconsistent (SOE: low).

- CBT improved quality of life more than usual care in the short term (12 to 24 weeks followup) based on two trials. Differences were not seen with longer followup (18 to 24 months; two trials) (SOE: low).
- CBT had a greater effect than usual care on overall core illness symptoms based on one good-quality systematic review of 34 trials (SMD -0.33, 95% CI -0.47 to -0.19) (SOE: moderate).
- Based on two systematic reviews, there is no meaningful difference in negative symptom improvement with CBT compared with usual care (SOE: low).

## Detailed Synthesis

### Description of Included Studies

We identified three good-quality systematic reviews<sup>77-79</sup> comparing CBT with usual care (Appendix Tables E-6 and F-3). The systematic reviews included nine to 50 RCTs each (N=895 to 3,947) and followup among the included studies ranged widely from 8 weeks to 5 years. Studies of both individual and group CBT were included and combined in all three reviews, though one review conducted separate analyses for individual and group CBT.<sup>79</sup> In all three reviews, the majority of included studies were focused on the use of CBT to control positive symptoms and were not necessarily designed to address other outcomes. Control groups among the trials included in the reviews varied. In addition to usual care, other controls included waitlists and nonactive interventions such as befriending and psychosocial interventions designed to control for the nonspecific effects of psychotherapy. Patient demographics were not well reported in the reviews. Participants in the included studies ranged from 18 to 65 years in one review<sup>78</sup> and 22 to 40 years in another. Duration of illness also varied, from 6 months to 30 years across all studies. The proportion of female participants also varied widely, from 8 to 67 percent. Two reviews<sup>77,78</sup> included studies conducted in people with schizophrenia, schizoaffective disorder and/or psychosis, while the third included studies conducted exclusively in people with schizophrenia.<sup>79</sup> Though two of the reviews were recently published,<sup>77,79</sup> the third, a Cochrane review, was last updated in 2010.<sup>78</sup>

The three systematic reviews were all rated good quality, however, they have some important limitations regarding applicability to our review. Presumably all three reviews included some inpatient studies, though this was only reported in one of the reviews, which included 11 (of 30) studies that enrolled exclusively inpatients or mixed inpatient and outpatient populations.<sup>79</sup> The reviews all noted that there was considerable variability among the CBT interventions, and the specific methods and timing of treatment delivery were not always clearly described. Finally, studies included in these reviews utilized a wide range of outcome measures and scales, making meaningful synthesis and judgment regarding clinical applicability challenging.

Literature searches identified five additional RCTs not included in the systematic reviews (Appendix Table E-7).<sup>76,80-83</sup> Searches identified one trial<sup>95</sup> of family-based CBT, which is included in the Family Interventions section. The number of patients enrolled in these trials ranged from 66 to 422. Mean age ranged from 30 to 47 years, and the proportion of female patients ranged from 14 to 54 percent. In four trials reporting race, white patients predominated in two trials, while blacks were the majority in the one and Hispanics were the majority in the other.<sup>76,80-82</sup> Baseline symptom severity varied among the trials based on study inclusion criteria and baseline measures. Three trials enrolled patients with persistent and ongoing symptoms and/or risk of relapse.<sup>76,80,82</sup> Baseline symptom scores (total PANSS) were 76 and 82 in two

trials,<sup>80,81</sup> approximately corresponding to moderate illness.<sup>273</sup> At baseline, patients ranged from minimal to serious functional impairment, based on three trials using various measures.<sup>76,80,82</sup> The mean duration of illness, reported in three trials, ranged from 15 to 20 years in two trials,<sup>81,83</sup> while a third study reported time elapsed since first contact with services of  $\geq 10$  years for about half of the participants.<sup>80</sup>

As with RCTs included in the above systematic reviews, the additional RCTs that met our inclusion criteria varied with regard to modality (group vs. individual), duration (brief vs. longer-term), and treatment target (e.g., role functioning, symptoms, and medication adherence). Studies were inconsistent in reporting therapist qualifications to provide CBT and few addressed fidelity. In four trials, CBT was delivered in individual sessions,<sup>76,80,82,83</sup> and one trial<sup>81</sup> used a combination of individual and group CBT as part of a manualized intervention targeting occupational functioning. Both brief and longer-term CBT interventions were included, with duration of CBT ranging from 8 weeks to 9 months. Four trials included post-treatment followup ranging from 4 to 19 months; total followup in these studies ranged from 6 to 24 months.<sup>76,80,82</sup> One trial was rated good quality<sup>80</sup> and the remaining four were rated fair quality (Appendix Table F-4).<sup>76,81-83</sup> Methodological limitations in the fair-quality trials included unclear group allocation concealment and high attrition rates.

As the two more recent systematic reviews<sup>77,79</sup> only assessed the effect of CBT on total and/or negative symptoms, we reviewed the included studies of both reviews for reporting of other outcomes of interest. Based on this review, we identified seven additional RCTs reporting function, relapse, and/or quality of life.<sup>93,274-279</sup> We acknowledge that many of these studies were not specifically designed to assess these outcome measures, but we included evidence on these secondary outcomes when reported. Study characteristics, symptom outcomes and risk of bias assessments are presented in the existing good-quality systematic reviews, and we abstracted additional information only on relevant outcomes.

## Findings

### Global Function

#### Short Term

The effects of CBT on short-term ( $\leq 6$  months since CBT initiation) function was reported in four RCTs<sup>83,274,278,279</sup> and one systematic review<sup>78</sup> that included two RCTs<sup>280,281</sup> reporting functional outcomes (Table 9). Results from the single study that focused on global function found a higher proportion of CBT patients had normal functioning after 6 months treatment versus usual care patients (28% vs. 14%, RR 2.21, 95% CI 1.25 to 3.93).<sup>279</sup>

In total, six trials reported a common measure of global function (GAF score), that when pooled found delivery of CBT resulted in significantly improved function regardless of CBT focus or treatment modality (MD 5.35, 95% CI 1.05 to 9.65,  $I^2=77\%$ ) (Appendix G-13).<sup>83,274,278,280,281</sup> The single study of group CBT (focused on positive symptoms) is also the only study that did not find a positive effect of CBT on short-term function.<sup>274</sup> Removing this study from the pooled analysis resulted in a pooled MD of 6.62 (95% CI 4.47 to 8.78), and eliminated statistical heterogeneity ( $I^2=0\%$ ). This SOE is moderate.

#### Medium Term

The effect of CBT on medium term function ( $>6$  months to 1 year since CBT initiation) was reported in one RCT of group CBT versus usual care focused on positive symptoms, reporting no

difference between CBT and usual care in Global Assessment Scale (GAS) scores (Table 9).<sup>274</sup> However, it should be noted that this trial evaluated the effect of a group-delivered CBT primarily intended to target positive symptoms of psychosis with functioning assessed as a secondary outcome. This SOE is insufficient to draw conclusions.

### **Long Term**

The single trial designed to assess long-term global function reported better adjusted mean GAS scores in the CBT group after 18 months treatment (58.3 vs. 47.9;  $p=0.03$ ; Table 9).<sup>276</sup> Patients enrolled in this study had chronic schizophrenia (mean duration of illness was >15 years) and were low-functioning at baseline. Two other trials not specifically focused on function reported no significant difference between CBT and usual care at 6-months and 1-year post-treatment followup.<sup>76,279</sup> A systematic review pooled three RCTs and found no statistically significant difference in GAF between CBT and usual care (MD 4.20; 95% CI -0.63 to 9.03) (Appendix Table E-6).<sup>78</sup>

## **Social and Occupational Function**

### **Short Term**

The effects of CBT on short-term ( $\leq 6$  months since CBT initiation) social and/or occupational function were reported in two RCTs<sup>83,282</sup> (Table 9). Improvement in function was the CBT focus in one of the trials, which found significant improvement GAF, SFS and SOFAS.<sup>83</sup> Significant improvement in SOFAS was also found when results from both trials were pooled (MD 9.11; 95% CI 6.31 to 11.91; Appendix G-13). One other trial found a significantly higher proportion of study participants in the CBT group had normal function, based on an SFS score within 95 percent of a normal population, when compared with usual care (RR 2.21; 95% CI 1.25 to 3.93).<sup>279</sup> This SOE is low.

### **Medium Term**

A trial of 6 months of vocational-focused CBT (both group and individual sessions) found a significant effect favoring CBT for hours worked and Work Behavior Inventory (WBI) score.<sup>81</sup> This evidence is insufficient to draw conclusions due to lack of corroborating evidence. There was no clear effect of CBT on medium term social and combined social and/or occupational function (>6 months to 1 year since CBT initiation) based on one additional RCT (Table 9).<sup>93</sup> Neither trial identified functional improvement as the primary outcome. In one of the trials, SOFAS scores were assessed at the conclusion of 12-20 sessions over 9 months of individual CBT aimed at preventing relapse, finding no difference between CBT and usual care groups.<sup>93</sup> This SOE is low.

### **Long Term**

Three trials<sup>78,82,279</sup> with long-term post-treatment followup (9 to 18 months after treatment cessation) did not find sustained benefits in social and/or occupational function, though none of these studies were designed to assess functional outcomes and one study<sup>279</sup> used a novel cotherapy approach to CBT (Table 9; Appendix Table E-6). This evidence is low strength.

### **Basic Living Skills**

A single trial reported the effect of CBT on measures of basic living skills after 6 months treatment and followup, found improvement in basic living skills, based on the Independent Living Skills Survey (ILSS), (Table 9).<sup>275</sup> This evidence is insufficient to draw conclusions.

### **Overall Findings on Functional Outcomes**

Although many trials reported functional outcomes, few were specifically designed to assess measures of function as a primary outcome (Table 9). Short-term, individual CBT (treatment  $\leq$  6 months) consistently resulted in greater functional improvements versus usual care, even if function was not the primary focus of CBT. Studies that employed CBT targeted at improving functioning consistently led to functional improvements. Longer-term effects of CBT focused on functioning were less consistent with CBT focused on other outcomes (e.g., positive symptoms) or with lengthy post-treatment followup, suggesting that CBT was more effective for primary treatment targets than other targets of interest.

Evidence of differences between individual and group CBT and functional outcomes was limited. Only one trial utilized a group CBT approach (directed at improving positive symptoms) finding no difference between CBT and usual care in functional outcomes.<sup>274</sup> One trial that included both individual and group CBT focused on vocational outcomes found significantly better outcomes with CBT.<sup>81</sup>

**Table 9. Functional outcomes in randomized controlled trials of cognitive behavioral therapy versus usual care**

<b>Timing of Assessment</b>	<b>Outcome</b>	<b>Author, Year</b>	<b>Study Characteristics Intervention/Control CBT Focus/Primary Outcome Total N Duration of Treatment Duration of Followup</b>	<b>CBT Versus Usual Care Results</b>	<b>CBT Versus Usual Care Effect</b>
<b>Short Term (≤6 months)</b>	<b>Global Function</b>	van der Gaag 2011 <sup>279</sup>	CBT vs. usual care Global function N=216 Treatment: 6 months Followup: 18 months	<u>6-month outcomes</u> Participants with normal functioning; 28% (31/109) vs. 14% (14/97); RR 2.21 (95% CI 1.25 to 3.93)	Favors CBT
	<b>Global Function</b>	Barrowclough 2006 <sup>274</sup>	Group CBT vs. usual care Positive symptoms N=113 Treatment: 6 months Followup: 12 months	<u>6-month outcomes</u> GAF – Disability mean score (N=54 vs. 45): 38.11 vs. 39.98; mean difference -1.87 (95% CI -5.47 to 1.73)	No difference
	<b>Global Function</b>	Lincoln 2012 <sup>278</sup>	CBT vs. waitlist Positive symptoms N=80 Treatment: 4 months Followup: 4 months	GAF mean score: 54.5 vs. 47.0; mean difference 7.50 (95% CI 1.80 to 13.20)	Favors CBT
	<b>Global and Social/ Occupational Function</b>	Zimmer 2007 <sup>83</sup>	Integrated psychological CBT vs. usual care Social function N=66 Treatment: 12 weeks Followup: 12 weeks	GAF mean score: 39.50 vs. 33.81; mean difference 5.69 (95% CI 2.05 to 10.97) SOFAS mean score: 43.25 vs. 34.14; mean difference 9.11 (95% CI 6.31 to 11.91) SAS mean score: 1.86 vs. 2.27; p=0.04	All scales favor CBT
<b>Medium Term (6-12 months)</b>	<b>Global Function</b>	Barrowclough 2006 <sup>274</sup>	Group CBT vs. usual care Positive symptoms N=113 Treatment: 6 months Followup: 12 months	<u>12-month outcomes</u> GAF – Disability mean score (N=52 vs. 46): 39.04 vs. 40.74; mean difference -1.70 (95% CI -6.00 to 2.60)	No difference
	<b>Social/ Occupational Function</b>	Garety 2008 <sup>93</sup>	CBT vs. usual care Relapse N=273 Treatment: 12 months Followup: 24 months	<u>12-month outcomes</u> SOFAS, treatment effect: 2.77 (95% CI -1.02 to 6.55)	No difference

<b>Timing of Assessment</b>	<b>Outcome</b>	<b>Author, Year</b>	<b>Study Characteristics Intervention/Control CBT Focus/Primary Outcome Total N Duration of Treatment Duration of Followup</b>	<b>CBT Versus Usual Care Results</b>	<b>CBT Versus Usual Care Effect</b>
	<b>Occupational function</b>	Lysaker 2009 <sup>81</sup>	Indianapolis Vocational Intervention Program (group and individual sessions) vs. social support Employment N=100 Treatment: 26 weeks Followup: 26 weeks	Mean total hours worked: 360.86 vs. 228.82; p<0.01 Mean number of weeks at least 1 hour worked: 18.64 vs. 14.46; p<0.05 Mean WBI: 113.34 vs. 105.43; p<0.05	Favors CBT
	<b>Basic Living Skills</b>	Granholm 2005 <sup>275</sup>	CBT + social skills training vs. usual care Social function N=76 Treatment: 6 months Followup: 6 months	ILSS marginal mean score: 0.72 vs. 0.67; p<0.05	ILSS: favors CBT
<b>Long Term (&gt;1 year)</b>	<b>Global Function</b>	Grant 2012 <sup>276</sup>	CBT vs. usual care Global function N=60 Treatment: 18 months Followup: 18 months	GAS adjusted mean score 58.3 vs. 47.9; p=0.03	Favors CBT
	<b>Global Function</b>	van der Gaag 2011 <sup>279</sup>	CBT vs. usual care Global function N=216 Treatment: 6 months Followup: 18 months	<u>18-month outcomes</u> Participants with normal functioning (based on SFS score 95% of normal population); 38% (39/109) vs. 26% (25/97); RR 1.39 (95% CI 0.79 to 1.27)	No difference
	<b>Global Function</b>	Velligan 2015b <sup>76</sup>	CBT vs. usual care Positive symptoms and global function N=85 Treatment: 9 months Followup: 15 months	Normatively reported a nonsignificant treatment effect on function with CBT	No difference
	<b>Social/Occupational Function</b>	Garety 2008 <sup>93</sup>	CBT vs. usual care Relapse and positive function N=273 Treatment: 12 months Followup: 24 months	<u>24-month outcomes</u> SOFAS, treatment effect: 2.42 (95% CI -1.42 to 6.26)	No difference

<b>Timing of Assessment</b>	<b>Outcome</b>	<b>Author, Year</b>	<b>Study Characteristics Intervention/Control CBT Focus/Primary Outcome Total N Duration of Treatment Duration of Followup</b>	<b>CBT Versus Usual Care Results</b>	<b>CBT Versus Usual Care Effect</b>
	<b>Occupational function</b>	Malik 2009 <sup>82</sup>	Brief CBT vs. usual care Relapse N=422 Treatment: 5 months Followup: 2 years	Proportion of patients with occupational recovery: 10% (21/205) vs. 14% (17/125); RR 0.75 (95% CI 0.41 to 1.37)	No difference

CBT = cognitive behavioral therapy; CI = confidence interval; GAF = Global Assessment of Functioning; GAS = Global Assessment Scale; ILSS = Independent Living Skills Survey; MCID = minimally clinical important difference; NS = not significant; RR = relative risk; SFS = Social Functioning Scale; SOFAS = Social and Occupational Functioning Assessment Scale; WBI = Work Behavior Inventory

## Health-Related Quality of Life

Quality of life is challenging to assess in people with schizophrenia, and the reliability of such assessments is tied to clinical factors, including the patient's level of insight.<sup>283</sup> Only one small study (N=66) included in this review assessed quality of life as a primary outcome,<sup>83</sup> while three other trials (N=66 to 273) reported on the effect of CBT on quality of life as a tertiary outcome (Appendix Table E-7).<sup>80,93,279</sup> All four trials employed an individual CBT approach. Patient populations were similar across the four trials, but duration of treatment ranged from 8 weeks to 1 year. Quality of life was assessed using different scales, and measured at time points ranging from the cessation of treatment to 1 year after treatment cessation. CBT was associated with better quality of life than usual care in two trials<sup>80,83</sup> with short-term followup (12 weeks and 24 weeks), including the single trial designed to assess quality of life.<sup>83</sup> The two trials with quality of life assessments up to 1 year after cessation of treatment (total followup 18 and 24 months), found no difference between CBT and usual care.<sup>93,279</sup> This evidence is low strength.

## Reduction in Self-Harm

No studies reviewed evaluated the effect of CBT on self-harm as a primary outcome. A single trial, included in one systematic review, reported incidental suicide, finding no difference in risk between CBT and nonactive psychological therapies (3% [2/78] versus 4% [3/79]; RR 0.68, 95% CI 0.12 to 3.93).<sup>284</sup> An additional trial, not included in any of the systematic reviews, found no difference between CBT and usual care in suicide attempts (3% [2/73] versus 5% [4/77]; RR 0.53, 95% CI 0.12 to 2.79) or serious violent incidents (3% [2/73] versus 1% [1/77]; RR 2.11, 95% CI 0.20 to 23).<sup>80</sup> This evidence is insufficient to draw conclusions.

## Improvement in Core Illness Symptoms

### Overall Symptoms

A recent systematic review of 34 RCTs found CBT more effective than usual care at improving overall symptoms (SMD -0.33, 95% CI -0.47 to -0.19;  $I^2=68%$  [a negative estimate favors CBT]; Appendix Table E-6) based on a number of scales (PANSS, BPRS, Comprehensive Psychopathology Rating Scale [CPRS] and the Hopkins Psychiatric Rating Scale).<sup>77</sup> As noted above, the majority of the included studies in this review were designed to address positive symptoms. The review combined studies of both individual and group CBT, and brief and longer duration CBT, but did not stratify results according to treatment modality or duration. Limiting the analysis to 20 trials in which outcome assessors were blinded to intervention group greatly reduced the effect size (-0.15). Although it remained significant (95% CI -0.27 to -0.03), it is unclear that this difference is clinically meaningful. One trial not included in the systematic review found similar improvements in total PANSS with CBT (Appendix Table E-7).<sup>80</sup> This evidence is moderate.

### Negative Symptoms

The effect of CBT on negative symptoms, based on PANSS-negative subscale, BPRS-negative subscale and SANS scales, was mixed based on two reviews. Study inclusion criteria for the two reviews differed slightly in that the Jauhar review included any study of CBT that reported symptom outcomes (positive, negative or overall) regardless of the CBT focus and the Velthorst review only included studies of CBT specifically targeted at either positive or negative symptom reduction. It should be noted that, of the 30 RCTs included in the Velthorst review,

only two studies identified negative symptoms as the primary treatment target. The Jauhar review found a small, marginally significant effect in favor of CBT (34 trials; SMD -0.13, 95% CI -0.25 to -0.01;  $I^2=48%$  [a negative estimate favors CBT]),<sup>77</sup> while the Velthorst review found no difference between CBT and usual care based on 28 trials (SMD 0.09, 95% CI -0.03 to 0.21;  $I^2=63%$  [a positive estimate favors CBT]).<sup>79</sup> Pooled results from the two trials that specifically targeted negative symptoms as a primary outcome resulted in an improved (but not significant) effect size favoring CBT: SMD 0.16, 95% CI -0.10 to 0.41. Estimates from this review were consistent when trials were limited to those that enrolled outpatients (10 trials; SMD 0.12, 95% CI -0.08 to 0.31). Estimates were also similar when stratified according to short-term (3-6 months after treatment; 13 trials; SMD 0.21, 95% CI -0.05 to 0.46) and long-term (9-12 months after treatment; 10 trials; SMD 0.01, 95% CI -0.02 to 0.18) treatment effects. The same review found individual (SMD 0.21, 95% CI 0.05 to 0.37) more effective than group CBT (SMD -0.17, 95% CI -0.44 to 0.09.) Trials published more recently (since 2009) and higher-quality trials reported smaller effect sizes (Appendix Table E-6).

Because the difference found in the Jauhar review was so small and the Velthorst review found consistent results with multiple sensitivity analyses, we find low strength evidence for negative symptom improvement.

### Treatment Discontinuation

In addition to one outpatient study included in the systematic reviews,<sup>285</sup> we identified 11 other RCTs not included in the systematic review reporting on the proportion of patients remaining in treatment.<sup>76,80,82,83,93,274-279</sup> Treatment duration among the trials ranged from 8 weeks to 18 months. When pooled (Appendix G-14), there was no difference between CBT and usual care (86% vs. 82%; RR 1.02, 95% CI 0.95 to 1.10). The risk of discontinuing treatment was not affected by the intended duration of treatment;  $\leq 6$  months or  $>6$  months did not affect the risk estimates (RR 1.07, 95% CI 0.97 to 1.17 versus RR 0.98, 95% CI 0.88 to 1.09). This was low strength evidence. One other study reported that the mean number of sessions attended was higher for employment-focused CBT compared with general social support (17.34 vs. 12.78 sessions;  $p<0.05$ ).<sup>81</sup>

### Relapse

We identified five RCTs (in six publications) reporting relapse rates in patients receiving CBT or usual care in the outpatient setting.<sup>82,93,274,277,286,287</sup> One of these trials<sup>286,287</sup> had been included in a good-quality systematic review that pooled data on inpatients with data on outpatients.<sup>78</sup> In these five trials (N=1,013) duration of treatment ranged widely, from 10 weeks to 2 years. In all of the trials, relapse prevention was a focus of the CBT intervention. Relapse was variably defined among these trials, though all but one included hospitalization as a criterion for relapse (Appendix Table E-7). When results from these five trials were pooled, there was no difference in relapse rate (29% vs. 30%; RR 0.93, 95% CI 0.61 to 1.42), though heterogeneity was high ( $I^2=73%$ ; Appendix G-15). When the analysis was limited to three trials<sup>82,277,286,287</sup> that used only hospitalization as criteria for defining relapse, there was a significant effect in favor of CBT and statistical heterogeneity was eliminated (RR 0.70, 95% CI 0.54 to 0.91;  $I^2=0%$ ).

In subgroup of two trials that used criteria related to increasing symptoms and/or hospitalization as criteria for relapse, neither found a significant difference between CBT and usual care.<sup>93,274</sup> Due to the inconsistency of these risk estimates, this evidence is insufficient to draw conclusions. As with other bodies of evidence in this report, the reasons likely lie in the variability in definition of relapse.

## Harms

Harms of treatment were infrequently reported in trials of CBT; only one trial identified harms of treatment a priori as an outcome of interest.<sup>80</sup> This trial found no difference between CBT and usual care in incidence of mortality (no deaths in either group). This evidence is insufficient to draw conclusions.

## Cognitive Remediation/Training Versus Usual Care

### Key Points

- Two good-quality systematic reviews and one good- and three fair-quality trials (N=56 to 156) provided evidence for cognitive remediation. The reviews stratified results for studies with usual care comparators.
- Compared with usual care, cognitive remediation resulted in a small positive effect on social, occupational, living situation, and global function, based six RCTs (effect sizes ranged from 0.16 to 0.40) (SOE: low).
- Cognitive remediation resulted in small improvements in core illness symptoms, based on two trials (N=153, SMD -0.62 (95% CI -1.01 to -0.24) (SOE: low).
- Negative symptoms were significantly improved with cognitive remediation compared to usual care based on a good-quality systematic review of 18 RCTs (SOE: moderate).

### Detailed Synthesis

#### Description of Included Studies

Studies of cognitive remediation focus on improving cognitive function. Two good-quality systematic reviews of 39 (Wykes 2011, N=2,104) and 18 (Cella 2017, N=781) trials reported on the effect of cognitive remediation versus active or passive (usual care) controls, with subgroup analyses of studies with usual care comparisons (Appendix Tables E-8 and F-3).<sup>84,85</sup> Studies were included based on cognitive remediation as defined by the Cognitive Remediation Experts Workshop<sup>288</sup> or based on standard cognitive remediation principles. Inclusion criteria in the Wykes review<sup>84</sup> required that at least 70 percent of the study population had a diagnosis of schizophrenia, while the Cella review used a 75 percent threshold.<sup>85</sup>

In the Wykes review, 19 studies were conducted in inpatient, 18 in outpatient, and 2 in mixed in and outpatient populations. Mean age across all studies was 36 years (range 18-49; one other study enrolled adolescents); men made up 67 percent of the study populations. Baseline symptom severity, reported in 26 trials, was characterized as mild to moderate. The review included trials that reported cognitive (outside the scope of our review) or functional outcomes, including 31 studies of individual and nine studies of group cognitive remediation. The review's inclusion criteria required a usual care control group, although an active comparator was also included in most studies. Separate analyses according to control group were conducted for measures of function. Cognitive remediation was delivered using drill and practice methods in 21 trials, and drill plus strategy in 19 trials. The mean number of sessions per week was 2.2 (range 0.6 to five), for a mean total of 32 hours (range four to 130) over 17 weeks (range 2 to 104 weeks). Study quality among the included studies ranged from poor to fair. The review noted that inadequate method of randomization and allocation concealment, and lack of treatment fidelity were frequent contributors to diminished study quality.

The Cella review provided few details about the 18 included studies comparing cognitive remediation with usual care.<sup>85</sup> The mean age across all studies was 35 years, and men made up 71 percent of the population. Baseline symptom severity, treatment setting (inpatient or outpatient), and description of cognitive remediation delivery were not reported. Seven studies had treatment duration  $\geq 12$  weeks. Negative symptoms were primarily assessed using the PANSS negative subscale, although BPRS and SANS were also used. As with the Wykes review, studies with both passive (usual care) and active control groups were included in the review, but sub-group analyses were conducted according to control group. The studies were judged to have medium to high risk of bias.

We identified four other RCTs (in five publications) of cognitive remediation not included in one or both systematic reviews above (Appendix Table E-9).<sup>86-90</sup> The trials enrolled between 56 and 156 participants, mean age ranged from 31 to 41 years and  $<60$  percent of participants were female across all studies. Whites comprised 60 percent of the population in the only study reporting race.<sup>89</sup> Three of the trials required a diagnosis of schizophrenia for study inclusion,<sup>86-88,90</sup> and in the fourth trial<sup>89</sup> the vast majority (97%) of the study population had a diagnosis of schizophrenia or schizoaffective disorder. Duration of illness ranged from 10 to 18 years. All four trials provided biweekly, group-based cognitive remediation; duration of treatment ranged from 4 to 6 months. The trials used both computer-based and manual cognitive remediation, often in combination. One study was rated good quality,<sup>86,90</sup> and the other three were rated fair quality due to unclear method of randomization or allocation concealment and lack of intention to treat analysis (Appendix Table F-4).

## Findings

### Function

When limiting analyses to three trials that used a passive control group (usual care), the Wykes systematic review of cognitive remediation found a small positive effect that was not statistically significant (effect size 0.16, 95% CI -0.16 to 0.49). This lack of significance may be due to the paucity of evidence rather than a true reflection of the effect of cognitive remediation on function. For context, when the analysis included 19 trials with either usual care or active control groups (N=1,036) a larger, significant, effect size was found (effect size 0.42; 95% CI 0.21 to 0.62; Appendix Table E-8), and the effect was sustained in 12 trials that provided post-treatment followup (6 to 24 months; effect size 0.37; 95% CI 0.11 to 0.66).<sup>84</sup> These analyses combined 16 different measures of social, occupational, living situation and global function, and used the effect size measure to standardize across the assessments of function.

Results from three other RCTs, not included in the systematic review, also reported on functional outcomes.<sup>87-89</sup> The trials used different measures of function at different timepoints, but all found delivery of cognitive remediation improved function relative to usual care, although results were not always significant (Appendix Table E-9). For example, one study found significantly better global function after 15 weeks of cognitive remediation therapy versus usual care based on GAF score (SMD 0.56; 95% CI 0.34 to 0.88),<sup>88</sup> while the difference between groups was similar in magnitude, though not significant, in another study measuring function and disability with the Life Skills Profile (LSP) after 16 weeks of treatment (SMD 0.41; 95% CI -0.10 to 0.91).<sup>87</sup> Combined, this evidence is low strength.

## Health-Related Quality of Life

One study reported on the effect of cognitive remediation on quality of life (Appendix Table E-9).<sup>89</sup> There was no difference in Subjective Quality of Life (QOLI) scores after 12 weeks of treatment (effect estimate, adjusted for group and time 0.52;  $p=0.17$ ), but QOLI score was significantly better in the cognitive remediation group at 3-months post-treatment followup (effect estimate, adjusted for group and time 1.15;  $p=0.002$ ). This evidence is insufficient due to study limitations, lack of confirmatory trials, and imprecision.

## Improvement in Core Illness Symptoms

### Overall Symptoms

Results were mixed in two RCTs ( $N=153$ ), not included in either of the systematic reviews, reporting total symptom scores (Appendix Table E-9). In one trial comparing 6 months of cognitive remediation to usual care, improvements in total PANSS were greater in the cognitive remediation group at the end of treatment (SMD -0.90; 95% CI -1.50 to -0.31) and at 1-year followup (SMD -0.68; 95% CI -1.26 to -0.09).<sup>86</sup> The other study did not find the difference to be statistically significant at 16 (SMD -0.42; 95% CI -0.92 to 0.09) and 40 weeks (SMD -0.04; 95% CI -0.54 to 0.46).<sup>87</sup> Pooling these provides a combined point SMD of -0.62 (95% CI -1.01 to -0.24).

The Wykes systematic review combined a wide range of symptom measures, including the Scale for Assessment of Positive Symptoms (SAPS), SANS, PANSS and BPRS, among others (Appendix Table E-8). The review found that cognitive remediation improved symptoms, based on 20 trials (effect size 0.18; 95% CI 0.03 to 0.32).<sup>84</sup> Symptom improvement was not sustained following treatment removal (8 RCTs, effect size 0.17, 95% CI -0.03 to 0.48). The review did not report results for the subgroup of studies utilizing a passive control group, but the effect sizes for the four studies reporting symptom effects versus usual care ranged from 0.05 to 0.45. Combined, this evidence is low strength.

### Negative Symptoms

The Cella systematic review (18 RCTs;  $N=781$ ) conducted a network meta-analysis on the effect of cognitive remediation versus usual care on negative symptoms.<sup>85</sup> The review found cognitive remediation led to significant improvement in negative symptoms, with an effect size of -0.36 (95% CI -0.52 to -0.20; a negative effect size favors cognitive remediation). These results were consistent when compared to all control interventions (usual care alone and usual care plus an active treatment, excluding three outliers; effect size -0.30, 95% CI -0.36 to -0.22) and at post-treatment followup (effect size -0.36, 95% CI -0.51 to -0.21). One other RCT not included in the systematic review and focused on executive function and metacognition, also found negative symptoms, based on PANSS-negative scores, were significantly improved after 4 months treatment (effect size 0.36, 95% CI 0.01 to 0.70).<sup>87</sup> There was no difference between groups at 6 month post-treatment followup.

### Treatment Discontinuation

Treatment discontinuation was not different between cognitive remediation and usual care groups in two RCTs not included in the systematic review (Appendix Table E-9). Relative risk was 1.01 (95% CI 0.91 to 1.12) in one trial, and the other trial normatively reported no difference between groups in the proportion of patients able to maintain treatment ( $p=0.08$ ).<sup>87,88</sup> The Cella systematic review found no difference between cognitive remediation and usual care in the

proportion of patients discontinuing treatment (21 trials; RR 0.82, 95% CI 0.67 to 1.01; Appendix Table E-8), but did not conduct subgroup analyses of only trials comparing to usual care.<sup>85</sup> This was moderate strength evidence.

## Family Interventions Versus Usual Care

### Key Points

- Trials of family interventions differ in type of interventions included, methods of intervention delivery, number of treatment sessions, duration of intervention, level of patient participation, and target of the intervention. Most family interventions are targeted at reducing relapse.
- One fair-quality systematic review provided evidence from 27 trials (N=2,297); six trials not in the systematic review were also included (N=562).
- Family interventions did not affect social function, including employment and housing situation, more than usual care at 1 year (SOE: low).
- Suicide rates were similar in family intervention participants and those who received usual care, but events were few (SOE: low).
- Improvement in core illness symptoms was found with family intervention compared with usual care (four RCTs, N=223, SMD -0.46, 95% CI -0.73 to -0.20) compared with usual care (SOE: low).
- Family interventions resulted in significantly lower relapse rates than usual care when measured at:
  - 0 to 6 months (three RCTs; N=244, 23% vs. 37%, RR 0.62, 95% CI 0.41 to 0.92)
  - 7-12 months (19 RCTs; N=1118, 30% vs. 44%, RR 0.67; 95% CI 0.54 to 0.83)
  - 13-24 months (nine RCTs; N=517; 49% vs. 61%; RR 0.75, 95% CI 0.58 to 0.99)
  - 5 years post-treatment (two RCTs; N=140, 78% vs. 94%, RR 0.82; 95% CI 0.72 to 0.94)
  - Evidence was not adequate to show a difference for 25 to 36 months (SOE: moderate for 7-12 months, low for all others)
  - Evidence suggests that relapse is lower with >10 treatment sessions.

### Detailed Synthesis

#### Description of Included Studies

One fair-quality Cochrane systematic review included 53 trials that enrolled patients with schizophrenia and/or schizoaffective disorder (Appendix Table E-10).<sup>91</sup> Approximately half of the included trials were conducted in China. As applicability to United States populations was a concern, we excluded these studies and, where necessary, performed our own analyses using the remaining 27 studies (N=2,297). We also included six additional trials (in eight publications, N=562) that were not included in the systematic review.<sup>92-97,289,290</sup> and pooled results where appropriate. Including all evidence, participant age ranged from 15 to 65 years, and the proportion of men to women was 66.5 to 33.5 percent, although six trials did not report gender distribution. Length of treatment ranged from 6 weeks to 3 years and consisted of any family-oriented psychosocial intervention that required at least five sessions compared with usual care. One trial met all quality criteria.<sup>93</sup> Relatively few trials reported methods of randomization and allocation concealment or reported blinded outcome assessors. Study attrition and reasons for

attrition were also infrequently reported. Information on harms was rare. Most studies were small in size with fewer than 100 participants.

In addition to duration of treatment, trials of family intervention are heterogeneous in what is actually included in the family intervention (Appendix Tables E-11 and E-12). In some instances psychoeducation is included but may consist of one or two brief education sessions or several entire days. Psychoeducation may be the sole part of the intervention or, more frequently, part of a package that may include motivational interviewing, behavioral family therapy, support groups, communication training, stress management, goal setting, and development of social networks. Families may experience the intervention as a single family or in multiple family groups. The patient may be present for some sessions and not others. The target of the intervention may be to prevent relapse (most often) or hospitalization, promote treatment or medication adherence, or improve social or global function, for example. In pooled analyses of trials with relapse as an outcome, we have stratified these trials by number of treatment sessions, duration of treatment, and an estimate of the degree psychoeducation is included in the family intervention, in order to explore the degree to which each factor may influence patient relapse.

## **Findings**

### **Function**

#### **Social Functioning**

One small study (N=69) reported patient change scores from baseline on the SFS.<sup>95</sup> This trial provided 6 months of treatment and assessed social functioning at 6 months and 12 months. Family intervention included motivational interviewing, individual cognitive behavior therapy, along with a family intervention based on carer's needs. This trial provide insufficient evidence of no difference in social function between family intervention and usual care at either 12 or 24 months (p>0.05).

#### **Unemployment**

Four trials provided low-strength evidence of no difference in unemployment with family interventions compared with usual care after 6-12 months of followup (N=230; 75% vs. 66%; RR 1.09; 95% CI 0.91 to 1.29, I<sup>2</sup>=0%; Appendix G-16).<sup>91</sup> Although unemployment rates at 2 years (N=51; 69% vs. 52%; RR 1.33; 95% CI 0.84 to 2.10) and at 3 years of followup (N=99; 82% vs. 69%; RR 1.19; 95% CI 0.92 to 1.55) were also not different between family intervention and usual care, the evidence is insufficient to draw conclusions due to methodological limitations, lack of confirmatory trials, and imprecision.

#### **Unable To Live Independently**

Based on three RCTs, there was low-strength evidence of no differences between family interventions and usual care in the inability to live independently at 1 year (N=164; 57% vs. 63%; RR 0.83; 95% CI 0.66 to 1.03).<sup>91</sup> A single trial included in the included systematic review reported independent living at 3 years post intervention (N=99; 54% vs. 66%; RR 0.82; 95% CI 0.59 to 1.14), but this evidence is insufficient. On small trial (N=97) reported data from 63 participants (65%) at a 5-year followup of a 15-month intervention and found family intervention associated with living fewer months in an institution for psychiatric patients (10.87 months vs. 21.18 months, p=0.04) compared with usual care.<sup>291</sup> Evidence at 5 years was considered

insufficient from which to draw meaningful conclusions regarding the effect of family intervention in ability to live independently.

### **Health-Related Quality of Life**

One study (N=50) reported mean endpoint change in quality of life scores based on the Heinrichs QLS scale (21-item scale, high score=good).<sup>91</sup> An additional study (N=55) reported that a 9-month family intervention improved overall quality of life based on the EuroQol scale by 7.38 points over treatment as usual at 24 months but this difference was not statistically significant (-7.38, 95% CI -22.07 to 7.31).<sup>93</sup> Values on the EuroQol were not reported prior to the 24-month followup. Evidence was considered insufficient to draw meaningful conclusions on the effect of family interventions versus usual care on quality of life.

### **Reduction in Self-Harm**

There was low-strength evidence, from six trials, of no difference in risk of suicide for participants who received family interventions compared with usual care, but events were few (N=314, 4% vs. 6%, RR 0.85; 95% CI 0.24 to 3.02,  $I^2=23%$ ; Appendix G-17).<sup>91</sup>

### **Improvement in Core Illness Symptoms**

#### **Overall Symptoms**

Combining the scores on the BPRS from three trials (N=190).<sup>91,96</sup> with PANSS scores from one trial<sup>93</sup> (N=55) provided low strength evidence of improvement in core illness symptoms with family interventions (four RCTs, N=223, SMD -0.46, 95% CI -0.73 to -0.20,  $I^2=0%$ ; Appendix G-18).<sup>91,93,96</sup> The data from one small trial (N=64) could not be pooled with the other trials, but reported a significant improvement with family intervention in an analysis of covariance ( $p=0.017$ ).<sup>95</sup>

#### **Negative Symptoms**

Three trials (N=163)<sup>92,93,96</sup> also reported scores on the negative subscale of the BPRS, the PANSS, and the Modified Scale for the Assessment of Negative Symptoms. A pooled analysis found lower risk of negative symptoms with family intervention (SMD -0.38, 95% CI -0.69 to -0.07; Appendix G-19).

### **Treatment Discontinuation**

Six trials provided low strength evidence of no difference between family intervention and usual care on leaving the study early between 3 and 6 months (N=504; 13% vs. 14%; RR 0.86; 95% CI 0.51 to 1.45,  $I^2=19%$ ; Appendix G-20).<sup>91</sup> However, between 7 and 12 months participants receiving usual care were more likely to leave the study early when compared with participants receiving a family intervention (13 RCTs; N=953, 24% vs. 26%, RR 0.77; 95% CI 0.64 to 0.93,  $I^2=0%$ ; Appendix G-21)<sup>91,93,94,97</sup> based on low-strength evidence. Results for leaving the study early were not different between 13 months and 2 years (six RCTs, N=362, 22% vs. 27%, RR 0.82, 95% CI 0.57 to 1.16,  $I^2=0%$ ),<sup>91</sup> based on low-strength evidence. Evidence was insufficient to determine the benefit of family therapy compared with usual care on study departures between 25 and 36 months and after 3 years.

## Relapse

Consistent with the included systematic review,<sup>91</sup> we considered participants missing data for relapse as having relapsed. Three trials provided low-strength evidence of lower risk of relapse between 0 and 6 months with family interventions compared with usual care, (N=244, 23% vs. 37%, RR 0.62; 95% CI 0.41 to 0.92,  $I^2=0\%$ , Appendix G-22).<sup>91,290</sup> In the trial with a greater number of sessions (11 to 20) relapse rates were slightly lower than in the two trials with a family intervention of 0 to 10 sessions (RR 0.51 vs. RR 0.69).

Nineteen trials (N=1118) provided moderate-strength evidence of lower risk of relapse between 7 and 12 months with family interventions compared with usual care (30% vs. 44%, RR 0.67; 95% CI 0.54 to 0.83;  $I^2=44\%$ ; Appendix G-23).<sup>91,93,96,97,290</sup> As above, studies with greater number of sessions (i.e., greater than 10) were more likely to favor family intervention, while duration of the intervention (Appendix G-24) favored trials up to 12 months, and trials including psychoeducation (Appendix G-25) as all or part of the treatment package were slightly less likely to show a treatment effect (RR 0.78; 95% CI 0.60 to 1.02).

The SOE was considered low for relapse rates beyond 12 months. Relapse rates at 13 to 24 months also favored family intervention (nine RCTs; N=517; 49% vs. 61%; RR 0.75, 95% CI 0.58 to 0.99;  $I^2=57\%$ ; Appendix G-26).<sup>91</sup> There were no difference in the statistical significance of the treatment effect based on number of sessions within the family intervention or the duration of the intervention (Appendix G-27). Almost all trials included psychoeducation. For 25 to 36 months, there was low-strength evidence of no difference between family intervention and usual care on relapse rates (two RCTs; N=147; 79% vs. 73%; RR 1.05; 95% CI 0.79 to 1.39;  $I^2=45\%$ ; Appendix G-28).

Two small studies (N=140) provided relapse data at 5 years followup (after 15 months of intervention).<sup>91,289</sup> Pooled analysis provided low-strength evidence that the benefit of family interventions on the risk of relapse may be retained at 5 years (78% vs. 94%, RR 0.82; 95% CI 0.72 to 0.94,  $I^2=0\%$ ; Appendix G-29). One small, study (N=63) provided data at 8 years and found no difference in risk of relapse between family intervention and usual care (81% vs. 94%, RR 0.86; 95% CI 0.71 to 1.05).<sup>91</sup> This evidence at 8 years is insufficient for which to draw conclusions.

## Harms

One small study (N=51) provided insufficient evidence on measures of family burden to determine whether family interventions reduce family burden when compared with usual care.<sup>91</sup>

There was insufficient evidence of no difference in nonsuicide mortality based on three trials (N=113, 3% vs. 4%, RR 0.96; 95% CI 0.17 to 5.33,  $I^2=0\%$ ; Appendix G-30).<sup>91</sup>

## Intensive Case Management Versus Usual Care

### Key Points

- ICM was assessed in one good-quality systematic review (10 trials; N=1,652) and one RCT (N=77).
- ICM was not different to usual care in improvements in social function, based on pooled analysis of three trials (MD 0.46; 95% CI -0.34 to 1.26) (SOE: low).
- There was no difference in rates of imprisonment with ICM versus usual care, based on pooled analysis of five trials (OR 0.90, 95% CI 0.45 to 1.82) (SOE: low).
- ICM did not improve quality of life more than usual care in two trials (SOE: low).

- ICM did not improve core illness symptoms more than usual care, based on pooled analysis of two trials (MD, 0.46; 95% CI -3.67 to 4.60). One subsequent trial also reported no difference in symptoms using a different scale (SOE: low).

## Detailed Synthesis

### Description of Included Studies

A good-quality systematic review of 10 trials (N=1,652) assessed ICM compared with usual care (Appendix Tables E-13 and F-3).<sup>98</sup> Another review that combined evidence for assertive community treatment and ICM was not used, as we considered these to be distinct interventions.<sup>272</sup> However, all of the studies included in the second review are included here. Included studies enrolled patients with schizophrenia or schizophrenia-like disorders, bipolar disorder, or depression with psychotic features. Mean age of participants enrolled in the studies ranged from 35 to 49 years, 0 to 59 percent were female, and 0 to 91 percent were nonwhite. Included interventions were explicitly described as case management; studies (or arms of studies) of assertive community treatment and home-based care were excluded. Study quality of included trials ranged from fair to good; poor-quality studies were excluded.

We identified one other RCT of ICM published since the systematic review described above (Appendix Tables E-14 and F-4).<sup>99</sup> The fair-quality study (N=77) enrolled participants with a mean age of 37 years, and the proportion of female participants was 53 percent; race/ethnicity was not reported. The trial enrolled Swedish patients with diagnosed mental illness and serious functional impairment. Patients were followed for 3 years.

## Findings

### Function

#### Global and Social Function

The systematic review of ICM found no significant effect on social function, based on pooled analysis of three trials (N=197) (MD 0.46, 95% CI -0.34 to 0.1.26;  $I^2=48%$ ; Appendix Table E-13).<sup>98</sup>

One trial published since the systematic review also reported on functional outcomes.<sup>99</sup> Consistent with the findings of the systematic review, the study reported no difference between groups in function assessed using the Strauss Carpenter scale (Appendix Table E-14). The SOE for this comparison is low due to study limitations and imprecision.

#### Encounters With the Legal System

The systematic review reported no significant differences in imprisonment based on five trials (N=757; OR 0.90, 95% CI 0.45 to 1.82;  $I^2=0%$ ).<sup>98</sup> This was low-strength evidence due to study limitations and imprecision.

#### Health-Related Quality of Life

The systematic review of ICM identified two trials reporting quality of life (Appendix Table E-13).<sup>98</sup> ICM was not associated with differences in quality of life scores on the Quality of Life Scale (MD, 0.09, 95% CI -0.23 to 0.42). One subsequent trial,<sup>99</sup> which assessed quality of life using the Lancashire Quality of Life Profile, also found no difference between groups in quality of life. This evidence is low strength due to study limitations and imprecision.

## Improvement in Core Illness Symptoms

The systematic review reported no significant differences between groups in symptoms based on BPRS scores (two trials; N=126; MD, 0.46; 95% CI -3.67 to 4.60).<sup>98</sup> One subsequent trial assessed symptoms using the Hopkins Symptom Check List and also reported no difference between groups (Appendix Table E-14).<sup>99</sup> This evidence is low strength due to study limitations and imprecision.

## Treatment Discontinuation

The systematic review reported significantly less loss to followup with ICM compared to usual care based on seven trials (N=1,210; OR 0.70, 95% CI 0.54 to 0.90;  $I^2=36\%$ ; Appendix Table E-13).<sup>98</sup> The addition of data from the single study published since the systematic review did not substantially alter these results (eight trials; N=1,287; OR 0.71, 95% CI 0.54 to 0.95;  $I^2=11\%$ ; Appendix G-32). This was moderate-strength evidence.

## Illness Self-Management and Recovery Versus Usual Care

### Key Points

- One fair-quality systematic review provided evidence from 13 trials (N=1,404); one other trial not included in the review provided additional evidence.
- Participants receiving a self-management education intervention were significantly more likely to demonstrate a reduction in severity of symptoms based on the BPRS (five RCTs, WMD -4.19, 95% CI -5.84 to -2.54) (SOE: moderate), but no change in negative symptoms based PANSS – negative subscale (SOE: low).
- Patients receiving more than 10 self-management intervention sessions had a greater reduction in the likelihood of experiencing relapse compared with usual care (OR 0.41; 95% CI 0.21 to 0.79), whereas those receiving 10 or fewer sessions had a smaller, nonsignificant, reduction in the risk of relapse (OR 0.67, 95% CI 0.39 to 1.15) (SOE: low).

## Detailed Synthesis

### Description of Included Studies

Illness self-management training programs are designed to improve knowledge, management of symptoms, social and occupational functioning, with a primary goal of reducing the risk of relapse by focusing on medication management, recognizing signs or relapse, and developing a relapse prevention plan and coping skills for persistent symptoms. Given these, the primary target of this intervention is reducing the risk of relapse.

We identified one fair-quality systematic review<sup>100</sup> that examined the effect of self-management education interventions compared with usual care, which was not clearly defined (Appendix Tables E-15 and F-3). This review included 13 trials (N=1404; range 23 to 125) with three trials from United States populations (N=211). Only three to five trials (N=257 to 534) reported results for each outcome of interest. The proportion of female participants ranged from 27 to 58 percent in 12 trials; one study enrolled exclusively male participants. Mean age ranged from 30 to 40 years. All interventions were delivered in a group setting and the number of intervention sessions ranged from 7 to 48 sessions lasting 45 minutes to 90 minutes each. Duration of followup ranged from the time of treatment cessation to 24 months post-treatment.

We included one other fair-quality RCT comparing a specific illness self-management training program for schizophrenia, the Illness Management and Recovery program compared with usual care.<sup>101</sup> This Israeli study included 210 people with severe mental illness and measured efficacy using the Coping Efficacy Scale and the Illness Management and Recovery scale. The percentage of participants with schizophrenia was 80 and 89 percent in the intervention and control groups, respectively. Fidelity to the program was measured via the Illness Management and Recovery Fidelity scale after 4 to 5 months and ranged from 2.66 to 4.77 (means) on a scale of 1 to 5. There were no significant differences between groups in any of the sociodemographic variables (Appendix Tables E-16 and F-4).

## **Findings**

### **Function**

Functional outcomes were reported in 10 RCTs included in the systematic review,<sup>100</sup> and the single RCT that was published after the review,<sup>101</sup> but none of the trials used the same method to measure the outcomes. Overall, five trials found benefit with self-management interventions on global, social, and occupational outcomes whereas the other six trials did not. This evidence is insufficient to draw conclusions.

### **Improvement in Core Illness Symptoms**

#### **Overall Symptoms (BPRS)**

The systematic review<sup>100</sup> reported the effect of self-management education interventions on psychiatric symptoms (Appendix Table E-15). Five trials (N=409) reported mean data for psychiatric symptoms using the BPRS, with meta-analysis of these data demonstrating that participants in the intervention group were significantly more likely to demonstrate a reduction in the severity of symptoms (WMD -4.19, 95% CI -5.84 to -2.54). A measure of statistical heterogeneity was not reported, and it is not clear that a difference of 4.19 points is clinically meaningful. This evidence was moderate strength. A meta-analysis of 3 of 13 trials (N=257) showed a significant reduction in the severity of positive symptoms (WMD -2.12, 95% CI -3.04 to -1.20) as measured by the PANSS, but total scores were not assessed.

#### **Negative Symptoms (PANSS-Negative)**

The effect of self-management education on negative symptoms, based on PANSS - Negative symptoms subscale, was reported in one systematic review that included three RCTs for this outcome (N=257).<sup>100</sup> Results demonstrate a significant reduction in severity of negative symptoms reported favoring the intervention group (WMD -4.01, 95% CI -5.23 to -2.79; Appendix Table E-15). This evidence was low strength due to study limitations and imprecision.

#### **Relapse**

The systematic review included five trials (N=534) that reported outcome data on relapse and stratified the analysis by the number of self-management education sessions (Appendix Table E-15).<sup>100</sup> Three trials had more than 10 sessions and two trials had less than 10 sessions. Patients receiving more than 10 sessions were 59 percent less likely to experience relapse than those receiving usual care (OR 0.41, 95% CI 0.21 to 0.79) whereas those receiving 10 sessions or less were 33 percent less likely to experience relapse than those receiving usual care (OR 0.67, 95% CI 0.39-1.15). This was low-strength evidence.

## Other Outcomes

The fair-quality RCT published after the systematic review included the Illness Management and Recovery Scale as the primary outcome measure (Appendix Table E-16).<sup>101</sup> The scale is a composite scale, measuring personal goals, knowledge of mental illness, involvement with significant others, functioning, symptoms, stress, coping, relapse prevention, hospitalization, medication, and use of drugs and alcohol (range to 5; higher scores better). The intervention resulted in significantly greater improvement on this scale, although the absolute improvements were small (0.18 vs. 0.03;  $p < 0.01$ ). The study also reported the Coping Efficacy Scale, which assesses symptoms, substance use and sleep problems experienced, strategies used to cope, and the patient's assessment of the efficacy of these strategies, with scores ranging from 1 to 5. On this scale, the intervention also resulted in small but statistically significant improvements compared with usual care (final scores 3.25 versus 3.09;  $p < 0.05$ ). In post hoc analyses, this study found better results with higher intervention fidelity scores.

## Patient Psychoeducation (Individual or Group) Versus Usual Care

### Key Points

- One good-quality systematic review provided evidence from 10 trials (N=1,125).
- Psychoeducation had a greater effect than usual care on global functional outcomes at 1 year of followup based on one good-quality systematic review of three trials (MD -5.23, 95% CI -8.76 to -1.71) (SOE: low).
- Psychoeducation had a greater effect than usual care on relapse rates (with or without readmission) at 9 to 18 months of followup based on one good-quality systematic review of six trials (RR 0.80, 95% CI 0.70 to 0.92) (SOE: moderate).

### Detailed Synthesis

#### Description of Included Studies

We identified one good-quality systematic review<sup>102</sup> comparing formalized psychoeducation to usual care (Appendix Tables E-17 and F-3). This review included 10 RCTs (total N=1,125), eight of which included stabilized outpatients, with duration of followup as long as 5 years. Subjects among the included studies had various diagnoses, including schizophrenia, schizophreniform disorder, schizoaffective disorder, and schizotypal disorder (with inclusion of individuals with multiple diagnoses). Studies were conducted primarily in North America and northern Europe (with 15% of subjects from the United States). Psychoeducational interventions were diverse, including variations of brief, usual length, individual, and group techniques. Usual care was also diversely defined, including elements of medication management, psychosocial rehabilitation, and supportive psychotherapy.

Psychoeducation itself is related to the informed consent process, which is an integral part of usual management of any illness. This could be hypothesized to account for some difficulty in observing differences in outcomes between psychoeducation and usual care. Heterogeneity in study designs further complicates the synthesis of available data into overall assessments of the effect of psychoeducation.

## Findings

### Function

Functional outcomes at 1 year of followup as measured by use of either the GAF or GAS scales in three trials were pooled, showing a significant beneficial effect of psychoeducation (MD -5.23, 95% CI -8.76 to -1.71;  $I^2=79\%$ ).<sup>102</sup> Nevertheless, the SOE for this effect was low related to study limitations mentioned above and small number of observations. Individual trials reported the GAS or GAF at the end of treatment, 6 months, 18 months, and 2 and 5 years after treatment, but this evidence was insufficient to draw conclusions due to study limitations, lack of confirmatory studies, and small sample sizes. Within this evidence, two RCTs suggested the possibility of improved functional outcomes with psychoeducation; one study finding a significant benefit of psychoeducation at 2 years, but not 5 years of followup, and the other finding improvement in psychosocial functioning immediately after the intervention, with no observable difference at 6 or 18 months of followup using the SAS scale (Appendix Table E-17).

### Health-Related Quality of Life

Although a single small RCT (N=114) observed a nonsignificant finding of improved quality of life as measured by Heinrich's Scale at the end of treatment and at 3 months, the SOE evidence was insufficient due to study limitations and small number of observations and inability to assess consistency in this single RCT.<sup>102</sup>

### Improvement in Core Illness Symptoms

Differences in BPRS total scores were compared in two RCTs (one observing a small but nonsignificant benefit, one showing no effect), with overall SOE insufficient related to study design, imprecision, and unknown consistency.<sup>102</sup>

### Relapse

A combined relapse and readmission analysis was conducted in the systematic review in order to increase the amount of extractable data (Appendix Table E-17). Based on six trials (N=720), psychoeducation had a greater effect than usual care on relapse rates (with or without readmission) at 9 to 18 months of followup (RR 0.80, 95% CI 0.70 to 0.92;  $I^2=54\%$ )<sup>102</sup> SOE for this finding is moderate. Other analyses of the available RCTs restricted to relapse without readmission showed no significant effects of psychoeducation, and had low SOE related to study methodologies and lack of precision. One group included in this SR<sup>292</sup> has reported data suggesting benefit from psychoeducation in reducing readmission rates after 7 years of followup.

### Harms

Potential harms that might be related to a psychoeducation intervention that were analyzed in the systematic review<sup>102</sup> included death and all-cause dropouts of subjects exposed to the psychoeducation intervention (Appendix Table E-17). Only two RCTs reported on deaths, with no indication that deaths varied between groups, but the SOE was low primarily related to imprecision and the infrequency of death during the trials. No difference was detected in rates of subjects who left trials or were lost to followup in eight trials (RR 1.13, 95% CI 0.89 to 1.44;  $I^2=15\%$ )

# Social Skills Training Versus Usual Care

## Key Points

- Three fair-quality RCTs (N=384) provided evidence for social skills training.
- Global function was significantly better in patients receiving 6 months (SMD on the GAF scale 1.60, 95% CI 1.19 to 2.02) and 1 year (SMD 2.02; 95% CI 1.53 to 2.52) of social skills training. Social function was significantly better in patients receiving 2 years (SMD on The Multnomah Community Ability Scale (MCAS) 0.65, 95% CI 0.36 to 0.95) of social skills training in three trials (SOE: low).
- In patients with schizophrenia, symptoms, based on the PANSS, improved more with social skills training at 6 months (SMD -1.50, 95% CI -1.92 to -1.09) and 2 years (SMD -0.81, 95% CI -1.22 to -0.40) (SOE: low).
- Negative symptoms were consistently and significantly improved with social skills training relative to usual care in three trials (SMD range -0.45 to -1.30) (SOE: low).

## Detailed Synthesis

### Description of Included Studies

We identified two systematic reviews of social skills training (Kurtz 2008<sup>293</sup> and Almerie 2015<sup>294</sup>), however both were subsequently excluded due to the inclusion of a high number of inpatients and short-term studies (i.e., less than 12 weeks duration), and/or studies that used an active control group with no separate analysis according to active or passive controls. Although these reviews did not meet our inclusion criteria, for contextual purposes we have included the findings from the Kurtz review below for function, negative symptoms and relapse. We did not report results from the Almerie review due to the inclusion of a high proportion of studies conducted in China, which have been shown to overestimate treatment effects and are of questionable relevance to United States clinical practice.<sup>295</sup>

Review of the reference lists of these reviews and literature searches identified three RCTs (in 4 publications) meeting inclusion criteria comparing social skills training and usual care (Appendix Table E-18).<sup>97,103-105</sup> One other RCT of cognitive behavioral social skills training is included in the CBT section of this report.<sup>275</sup>

The three RCTs of social skills training enrolled between 98 and 183 study participants. In these trials, social skills training consisted weekly sessions (ranging from 24 weeks to 1 year; total followup 6 month to 3 years) of specific, progressive intervention modules that generally included management of symptoms and medication, improving social and family relationships, and increasing functional skills such as money management, among others. In all three trials, social skills training was specifically focused on improving psychosocial function and reducing relapse and need for hospitalization. One study was conducted in the United States,<sup>103,104</sup> and the other two were conducted in Mexico.<sup>97,105</sup> Mean age was about 30 years in two trials.<sup>97,105</sup> In the other study, which specifically enrolled older adults, the mean age was 60 years.<sup>103,104</sup> In the same study, more than half of study participants were female, and >80 percent were white. In the other two trials, women made up about 30 percent of participants and race was not reported.<sup>97,105</sup> Two trials required a diagnosis of schizophrenia for study inclusion, but in the other, only about 55 percent of participants had schizophrenia or schizoaffective disorder. Duration of illness was 8 and 9 years in two trials,<sup>97,105</sup> and not reported in the other. All three trials were rated fair quality (Appendix Table F-4). Methodological limitations among the studies were inadequate

reporting of methods of randomization and allocation concealment, dissimilarities of baseline groups (one study) and no intention to treat analysis (two studies).

## Findings

### Function

Functional improvement is a primary focus of social skills training. All three trials reported significant improvements functional outcomes with social skills training, based on different measures (Appendix Table E-18).<sup>97,103-105</sup> Since functional outcomes were reported in various ways in the trials, we converted scale scores to SMDs here for comparison purposes. In two trials, GAF scores were significantly better in social skills training groups compared with usual care after 6 months (N=119; SMD 1.60, 95% CI 1.19 to 2.02)<sup>105</sup> and 1 year of treatment (N=98; SMD 2.02, 95% CI 1.53 to 2.52).<sup>97</sup> The third study, which included a mix of patients with schizophrenia and mood disorders, reported improvement in function based on MCAS score after 2 years of social skills training (N=183; SMD 0.65, 95% CI 0.36 to 0.95) but these results were not sustained at 3 years followup (1 year after treatment was stopped; SMD 0.24; 95% CI -0.05 to 0.53).<sup>103,104</sup> These results are consistent with those in the Kurtz 2008 systematic review described above, which also reported a positive effect of social skills training on psychosocial function (seven trials, N=371); effect size 0.52, 95% CI 0.31 to 0.73).<sup>293</sup> The evidence on improvements during treatment was low strength; evidence on maintenance of effect after discontinuing treatment was limited to one small study and is therefore insufficient to draw conclusions.

### Improvement in Core Illness Symptoms

#### Overall Symptoms

Significantly greater reduction in overall symptoms was found following completion of social skills training compared with usual care in the two trials (N=119 and 98) that exclusively enrolled patients with schizophrenia (Appendix Table E-18).<sup>97,105</sup> SMD in total PANSS scores was -1.50 (95% CI -1.92 to -1.09) and -0.81 (95% CI -1.22 to -0.40) after 6 months and 1 year, respectively. This evidence was low strength. In the third study, there was a small, nonsignificant effect in favor of social skills training based on BPRS score (N=183; SMD -0.04, 95% CI -0.33 to 0.25). This study enrolled a combination of patients with schizophrenia/schizoaffective disorder (56%), depression (24%), and bipolar disorder (20%), potentially limiting the effect on symptom scores.<sup>103,104</sup>

#### Negative Symptoms

Negative symptoms were consistently improved following 6 months (SMD -1.30, 95% CI -1.70 to -0.90),<sup>97</sup> 1 year (SMD -0.82; 95% CI -1.23 to -1.40),<sup>105</sup> and 2 years (SMD -0.45; 95% CI -0.74 to -0.15)<sup>104</sup> of social skills training based on the SANS (1 study) and PANSS (two trials) scores (low-strength evidence). Results from these trials are consistent with the findings in the Kurtz systematic review, which also found that social skills training significantly improved negative symptom scores (6 trials, N=363; effect size 0.40, 95% CI 0.19 to 0.61).<sup>293</sup> In the only study meeting inclusion criteria to follow patients after the cessation of treatment, negative symptom scores were still significantly better in social skills training patients 1 year after treatment had ended (SMD -0.45, 95% CI -0.74 to -0.15).<sup>103</sup> Evidence on maintenance of effect

after treatment discontinuation is insufficient due to study limitations, lack of confirmatory studies, and imprecision.

### **Treatment Discontinuation**

There was no difference in treatment discontinuation, based on two trials with 1- (88% [43/49] vs. 80% [39/49]; RR 1.10, 95% CI 0.92 to 1.31) and 2-year (82% [76/93] vs. 81% [73/90]; RR 1.01; 95% CI 0.88 to 1.16) followup (Appendix Table E-18).<sup>97,104</sup> This was low-strength evidence.

### **Relapse**

In one study with 1-year followup reporting undefined relapse, patients in the social skills training group were half as likely to relapse compared with those in the usual care group (5% vs. 10%), but absolute number of patients relapsing was small (5/49 vs. 10/49) and the risk estimate was not significant (RR 0.50; 95% CI 0.18 to 1.36).<sup>97</sup> Due to the lack of confirmatory studies in relevant populations, and small sample size, this evidence is insufficient. The 2008 Kurtz review reported a combined effect size for relapse and hospitalization, indicating a small (0.23) but significant finding (95% CI 0.04 to 0.41) in favor of social skills training based on nine trials (N=485).<sup>293</sup>

## **Supported Employment Versus Usual Care**

### **Key Points**

- Supported employment, using the individual placement and support (IPS) model, results in better employment outcomes than usual care with 2 years of followup. The evidence is based on one fair-quality trial (N=204), and is supported by evidence from a systematic review of 14 RCTs with vocational training comparisons, and a large RCT (N=1,273) with both usual care and vocational training comparisons.
- Patients receiving IPS were significantly more likely to obtain competitive work than those receiving usual care (75% vs. 27.5%, p=0.001). These findings are consistent with findings of a large trial of various supported employment interventions that included other comparison groups (SOE: moderate). The time to obtaining first competitive employment was 22 days shorter with IPS than with usual care (p<0.001, SOE: low).
- IPS resulted in more patients working more than 20 hours per week (13% vs. 34%; p=0.00), having more weeks of employment overall (24 more weeks competitive and 11 more weeks any employment; p< 0.001), and longer tenure per individual job (4 weeks; p= 0.048) than those in either usual care, other vocational interventions, or both. These findings are consistent with findings of a large trial and a systematic review of 14 trials that included other comparison groups (SOE: moderate).
- Patients receiving IPS earned more money than those in usual care (\$2,078/month vs \$617.59/month; p< 0.001). These findings are consistent with findings of a large trial of supported employment interventions that included other comparison groups, except that the overall earnings and the magnitude of difference between groups was smaller. (\$122/month vs \$99/month; p=0.04, SOE: moderate)

## Detailed Synthesis

### Description of Included Studies

In our review, we included studies that compared supported employment with usual care as direct evidence. We identified one fair-quality trial (N=204) that examined the effect of the IPS model of supported employment compared with standard services offered off-site from the mental health center (usual care) and a psychosocial rehabilitation intervention (Appendix Tables E-19 and F-4).<sup>109</sup> The target population included patients with severe mental illness receiving care at a state mental health department with an Axis I diagnosis and severe impairment in psychosocial functioning or self-care; lacking competitive employment; desire for competitive work; capable of providing informed consent. Comprehensive employment data were collected and interviews were conducted at baseline and every 6 months for the 2-year study duration. Fidelity to the IPS model was evaluated yearly, with the IPS group achieving high fidelity scores (using the IPS Fidelity Scale). Study participants received services at the lead community mental health center in Hartford, Connecticut. The study was conducted in a population that was mainly African American and Latino; the proportion of eligible patients enrolled was highest among Latinos (86%) and African Americans (81%) with a lower rate among white patients (66%). Participants in the study were mostly men in their 40s (mean age 41 years, 63% male).

A number of employment outcomes were collected, with the two main outcomes categorized as competitive work, “jobs paying competitive wages in integrated settings, contracted by clients, and not reserved for persons with disabilities,” and any paid work, which could include jobs set aside for persons with disabilities. Nonvocational outcomes were evaluated using standardized scales, but were reported as “trends” because of the large number of tests conducted. Although intention-to-treat analysis was undertaken, the impact of missing data was a concern, as less than 40 percent of patients assigned to usual care contributed data in the second year versus 90 percent for the IPS group.

Because there was only one eligible study comparing supported employment with usual care, we included evidence, comparing supported employment with other vocational interventions. This evidence included a good quality systematic review of 14 RCTs with other vocational training interventions as controls (N=2,265)<sup>106</sup> (Appendix Tables E-20 and F-3). The psychosocial rehabilitation intervention arm of the study described above was also included. Thirteen of the 14 included studies used IPS as the model for supported employment. Duration of followup was 12 to 24 months. We also included a large, United States-based, fair quality RCT of supported employment conducted in eight states (N=1,273) which made comparisons to usual care and active vocational interventions, depending on the study site<sup>108</sup> (Appendix Tables E-19 and F-4). Approximately half of the study sites used a usual care comparison group, and three of eight states explicitly used the IPS model. Duration of followup was two years. An analysis of results in patients with and without a schizophrenia diagnosis was also published.<sup>107</sup> The review and the trial reported similar outcome measures as the RCT described above.

## Findings

### Occupational Function

Based on intention-to-treat analysis, the trial of IPS versus usual care described above found that patients in the IPS group were significantly more likely to obtain competitive work (75% vs. 27.5%  $p<0.001$ ).<sup>109</sup> The other RCT, with both usual care and vocational intervention

comparators, also found that more patients obtained competitive employment while receiving supported employment interventions than other interventions, including usual care (55% vs 34%;  $p < 0.001$ ).<sup>108</sup> Subgroup analysis of only patients diagnosed with schizophrenia showed a similar pattern although the overall success in obtaining competitive employment was lower (22% vs. 12%;  $p < 0.001$  with mixed effects logistic regression).<sup>107</sup> Overall, this evidence was moderate strength. Based on the trial data comparing IPS to usual care, the mean time for patient to obtain their first competitive employment was 22 days ( $p < 0.001$ ) shorter with IPS than with usual care.<sup>109</sup> This was low-strength evidence.

Patients receiving IPS were also significantly more likely to obtain any work than those receiving usual care (75% vs. 53.6%,  $p = 0.001$ ).<sup>109</sup> This finding is supported by the systematic review findings, where the risk ratio, based on seven RCTs (N=951) for finding any employment was 2.62 (95% CI 2.18 to 3.16) with IPS over vocational training interventions.<sup>106</sup> Combined, this was moderate-strength evidence.

The measures of how much a patient worked, how consistently they were employed and for how long varied, but all showed that supported employment interventions were beneficial over either usual care or other vocational interventions. Compared with usual care, the RCT found that significantly more patients receiving IPS worked more than 20 hours per week (33.8% vs. 13%;  $p = 0.001$ ).<sup>109</sup> This evidence is consistent with evidence that finds that more patients receiving supported employment interventions work 40 or more hours per month than those receiving other vocational training or usual care (51% vs. 39%;  $p < 0.001$ ).<sup>107,108</sup> Patients receiving IPS worked more weeks in competitive employment than those in usual care (mean 29.72 vs 5.45 weeks;  $p < 0.001$ ).<sup>109</sup> The systematic review also found that IPS results in more days of competitive employment than other interventions (MD 70.63 days, 95% CI 43.22 to 98.04).<sup>106</sup> Similarly, evidence with both usual care and active controls find that patients receiving IPS have more time in any employment than those receiving usual care (30.18 weeks vs. 19.08 weeks;  $p < 0.001$  for IPS versus usual care,<sup>109</sup> and MD of 84.94 days more [95% CI 51.99 to 117.89] versus other vocational interventions). The tenure on any individual job was also longer with IPS. Compared with usual care, IPS resulted in a mean 19.75 weeks compared with 15.56 weeks per job with usual care ( $p < 0.001$ ).<sup>109</sup> Findings from the systematic review, based on two trials, were very similar with a MD of 3.86 weeks (95% CI -5.66 to 13.38).<sup>106</sup> These findings were moderate SOE.

Patients receiving supported employment interventions earned more money than those in usual care (\$2,078/month with IPS vs \$617.59/month with usual care;  $p < 0.001$ ).<sup>109</sup> Findings from a trial with both vocational training and usual care comparison groups supports this finding, although the amount earned per month and the relative difference was smaller (\$122/month vs \$99/month;  $p = 0.04$ ).<sup>107,108</sup> Combined, this evidence was moderate strength for the direction of effect. The variation in magnitude of effect was lower strength.

### **Improvement in Core Illness Symptoms**

Differences in nonvocational outcomes were reported as not being significant between IPS and usual care.<sup>109</sup> This outcome was either not significantly different or not reported in the other studies.

### **Treatment Discontinuation**

Treatment discontinuation (withdrawal from study) was much higher in the usual care group compared with the IPS group; rates of retention in the study were less than 40 percent for standard services in the second year versus 90 percent for IPS.<sup>109</sup>

# Supportive Therapy Versus Usual Care

## Key Points

- A good-quality systematic review evaluated five trials of supportive therapy versus usual care and found no differences in global functioning (SOE: low).

## Detailed Synthesis

### Description of Included Studies

We identified one good-quality systematic review comparing supportive therapy or supportive care that included 24 RCTs (total N=2126, range 12 to 315 per study) and 10 weeks to 3 years of followup (Appendix Tables E-21 and F-3).<sup>110</sup> Only five of the trials used a usual care control group (N=822). Three of these were conducted in the outpatient setting and two were conducted in the United States. Most of the patients in the trials had been diagnosed with schizophrenia and the ages ranged from 16 to 72. Four of the trials specified that the patients had to be suffering from on-going hallucinations and/or delusions. Four of the trials enrolled patients with long-standing disease, but one enrolled majority experiencing their first episode and included inpatients.<sup>284</sup> This study also had a lower median age (27 years) than the mean in other trials (36 to 47 years). All studies enrolled more men than women.

Definitions of the interventions were not consistent, but generally the study interventions were aimed at maintaining current functioning or to assist the patients with pre-existing coping abilities. Specific treatments received in the usual care group were not reported. The frequency and duration of treatments varied, ranging from twice a week for 3 months with monthly booster sessions for 4 months, to sessions every 2 weeks for a total of 10 sessions, with no booster sessions. Although this review was good quality, the trials themselves were mostly fair or even poor quality (only 1 of the 5 was good quality).

## Findings

### Function

The effect of supportive therapy on function was reported in two trials in the systematic review, but differences were not found at 9 months in either global or social functioning (Appendix Table E-21).<sup>110</sup> Although two trials used similar scales to measure global functioning, the results were not pooled GAF (modified version), N=29, MD 1.40, 95% CI -5.09 to 7.89; GAS, N=260, MD -2.66, 95% CI -6.20 to 0.88). Only one of these trials also measured social functioning (using the SFS), and found no difference between the groups. (N=260, MD-0.67, 95% CI -7.05 to 5.71). The trials were small, such that this evidence is imprecise. The evidence on global functioning was low strength, whereas the evidence on social functioning is insufficient.

### Health-Related Quality of Life

In the systematic review, a single study reported outcomes that were categorized as quality of life, although the three scales reported do not measure global health-related quality of life (Appendix Table E-21). The scales used were the Rosenberg Self-Esteem Scale (RSES) noted to measure positive aspects of psychological functioning, the Well-being Scale (WBS) Global

health questionnaire (GHQ) noted to measure nonpsychotic psychiatric symptoms. No differences were found on these measures and the evidence is insufficient.

## **Improvement in Core Illness Symptoms**

### **Overall Symptoms**

The systematic review identified one study reporting general symptomatology using the PANSS, one in the short term and one in the long term, with neither study finding significant differences between groups: short term (13 to 26 weeks; N=131, MD -4.42 (95% CI -10.13 to 1.29); long term (more than 26 weeks; N=36, MD 4.70 (95% CI -6.71 to 16.11; Appendix Table E-21). This evidence is insufficient.

### **Negative Symptoms**

The systematic review found only one study that reported negative symptoms, using the SANS, but determined that the data were skewed and did not analyze the significance of the findings. In the short term the endpoint scores were very similar (10.19 and 10.73 for treatment and control), although in the long term the scores were more different (9.90 and 11.46, respectively). The study was very small (N=47) so this evidence is insufficient.

### **Treatment Discontinuation**

Leaving the study early was reported in four RCTs (N=354) in the systematic review, resulting in a pooled estimate that indicated no significant difference between groups (RR 0.86, 95% CI 0.53 to 1.40). This was low-strength evidence.

### **Relapse**

Only one study reported on relapse, but defined it as readmission to hospital for clinical deterioration that lasted at least 5 days and resulted in functional impairment (Appendix Table E-21). The systematic review found no significant difference in relapse rates between supportive therapy and usual care at either medium-term followup (13 to 26 weeks, N=54, RR 0.12, 95% CI 0.01 to 2.11), or long-term followup (more than 26 weeks, N=54, RR 0.96, 95% CI 0.44 to 2.11). This evidence is insufficient.

## **Key Question 2b. Variation of Benefits and Harms of Psychosocial and Other Nonpharmacological Treatments Versus Usual Care for Adults With Schizophrenia by Patient Characteristics**

### **Key Points**

#### **Clinical Subgroups**

- Patients experiencing a first episode of psychosis: Pooled results found that the team-based multi-component interventions resulted in higher global functioning, based on GAF and GAS scores after up to 2 years of treatment (three RCTs; WMD: 3.88; 95% CI 0.91 to 6.85) (SOE: moderate).

- Team-based multi-component interventions resulted in significantly more people (22%) working or in school after up to 2 years of treatment (three RCTs; RR 1.22; 95% CI 1.01 to 1.47) (SOE: moderate).
- There were no significant differences between multi-component treatment programs and usual care on housing status for up to 2-year treatment duration based on two RCTs (SOE: low).
- Two RCTs found significant differences between multi-component programs and usual care on quality of life scores for up to 2-year treatment duration (effect size 0.84; 95% CI 0.14 to 1.55) (SOE: moderate).
- There was no difference in reduction in self-harm in two trials of multi-component programs versus usual care (SOE: low).
- There was no difference between multi-component programs and usual care in total PANSS scores based on three RCTs (WMD -2.53; 95% CI -5.45 to 0.39). (SOE: low). Removal of one study with between-group baseline differences resulted in a small but significant estimate (-1.40, 95% CI -2.25 to -0.55) (SOE: low).
- Team-based multi-component program participants were significantly less likely to relapse compared with those in usual care based on two RCTs (RR 0.64; 95% CI 0.52 to 0.79) (SOE: moderate).
- Comorbidities:
  - Substance use: One good-quality systematic review of 32 trials (N=3,165) of co-occurring SUD and schizophrenia found no differences between integrated assertive community treatment and usual care in function at 12 months and mortality, and substance use at 36 months in people with co-occurring SUD (SOE: low for all outcomes).

## Demographic Subgroups

- Evidence from systematic reviews and RCTs of CBT, cognitive remediation, and social skills training found no difference for any outcome when results were stratified according to patient age, or when comparing results from trials conducted in younger versus older adults.
  - A systematic review of CBT found no difference in negative symptom outcomes when results were stratified according to sex. Limited evidence from one RCT of a mixed population (about 50% diagnosed with schizophrenia or schizoaffective disorder) of social skills training suggested that the intervention may be more effective in men than women for function and symptoms.

## Detailed Synthesis

### Findings

#### Clinical Subgroups

##### Early Interventions for Patients With a First Episode of Psychosis Versus Usual Care

We identified one fair-quality systematic review comparing 12 early intervention programs for treating first-episode psychosis with usual care.<sup>296</sup> This review was subsequently excluded, as 11 of the included studies did not meet our inclusion criteria, either due to small sample size, enrollment of inpatients, lack of applicability to the United States population, and/or use of a one-off intervention. One trial (the Danish OPUS trial) of team-based multi-component treatment programs included in the systematic review met our inclusion criteria (Appendix Table E-22).<sup>111</sup>

Literature searches identified three additional RCTs (in seven publications) not included in the systematic review reporting on the effect of team-based multi-component treatment compared to usual care (Appendix Table E-22).<sup>112-117,119</sup> We identified one other study reporting 10-year outcomes from the OPUS trial.<sup>118</sup> The number of participants enrolled in these studies ranged from 99 to 1,268. Mean age ranged from 23 to 27 years, and 32 to 46 percent of participants were female. In two trials reporting race, Blacks comprised about 50 percent of the study population in both. Baseline psychotic symptom severity was similar in two studies (mean PANSS total score ranging from 67.4 to 77.5),<sup>113,116</sup> but was lower in a third study (mean total PANSS 44.6).<sup>115</sup> Mean duration of untreated psychosis, was 50 weeks<sup>118</sup> to over 3 years<sup>116</sup> in two trials. Duration of followup ranged from 1 to 10 years. Two trials were rated good quality,<sup>111,112</sup> one was rated fair quality,<sup>115</sup> and one was rated poor quality.<sup>116</sup> Methodological limitations in the fair- and poor-quality trials included unclear randomization method and high attrition rates (Appendix Table F-4).

#### Function

**Global.** The effect of team-based multi-component treatment programs on global function was reported in three RCTs.<sup>111,113,114</sup> Pooled results found that the multi-component programs resulted in higher functioning, based on GAF and GAS scores during up to 2 years of intervention (three RCTs; WMD 3.88, 95% CI 0.91 to 6.85,  $I^2=64%$ ). This evidence was moderate strength. Treatment effects were not sustained at 5<sup>111</sup> and 10 years<sup>118</sup> after treatment removal.

**Employment or school attendance.** The effect of multi-component programs versus usual care on participation in work and school was reported in three RCTs.<sup>111,113,114</sup> Pooled results found that multi-component programs resulted in significantly more people working or in school for the (up to) 2-year intervention period (three RCTs; pooled RR 1.22, 95% CI 1.01 to 1.47). This evidence was moderate strength. These effects were not sustained at 5<sup>111</sup> and 10 years<sup>118</sup> after treatment removal.

**Living situation.** Pooled results from two RCTs found no significant differences between the team-based multi-component interventions and usual care during the up to 2-year intervention period (two RCTs; pooled RR 1.06, 95% CI 0.86 to 1.30).<sup>111,113</sup> This SOE was low. Five-year

followup data suggest findings in favor of the team-based approach, with significantly more participants living in noninstitutional supported housing (N=547, RR 0.42 CI 0.21 to 0.83).<sup>111</sup> This result was not significant at 10-year followup.<sup>118</sup>

### **Health-Related Quality of Life**

Team-based multi-component programs resulted in greater quality of life ratings after 18 months to 2 years treatment, based on results from two trials (pooled effect size 0.84, 95% CI 0.14 to 1.55, p=0.02).<sup>113,116</sup> This evidence was moderate strength.

### **Reduction in Self-Harm**

One trial, included in the systematic review, reported suicide incidence, finding no difference in risk between multi-component treatment programs and usual care (N=506, RR, CI 0.93 0.06 to 14.81)<sup>111</sup> A second trial found that the proportion of participants who, at 10-year followup, had experienced thoughts of suicide within the preceding 2 years was similar within multi-component programs (39.4%) and in usual care (37.9%, p=0.77).<sup>118</sup> This was low SOE.

### **Improvement in Core Illness Symptoms**

The effect of team-based multi-component programs on psychotic symptoms, based on PANSS scores, was reported in three trials.<sup>113,114,116</sup> Pooled results found no difference between groups in scores (WMD -2.53; 95% CI -5.45 to 0.39;  $I^2=55\%$ ). Sensitivity analysis removing a study with a 5.9-point difference at baseline results in a very small but significant difference and no heterogeneity (WMD -1.40; 95% CI -2.25 to -0.55; Cochran Q for heterogeneity 0.0014, df=1).<sup>114,116</sup> This evidence was low strength. There was no effect on depressive symptoms, based on the Calgary Depression Scale (two RCTs; WMD -0.44; 95% CI -1.08 to 0.20). This was low strength evidence.

### **Treatment Discontinuation**

Results from two trials found participants in team-based multi-component treatment programs had a significantly greater rate of treatment retention compared with usual care after 12 to 18 months treatment (RR 1.27; 95% CI 1.16 to 1.38; Cochran Q=0.03, df=1).<sup>112,114</sup> This evidence was moderate strength. When rates were adjusted for baseline differences in sex, previous psychotic episode, and ethnicity, drop-out rates remained significant based on one trial (RR 0.28, CI 0.12 to 0.73).<sup>112</sup> While a third RCT<sup>116</sup> found significant differences in treatment retention, favoring team-based programs, this study had a 49 percent attrition rate, so those findings are not included here.

### **Relapse**

Pooled analysis from two trials found that participants in team-based multi-component treatment programs were significantly less likely to relapse (defined as worsening of psychotic symptoms and/or hospitalization) than those in usual care (RR 0.64; 95% CI 0.52 to 0.79; Cochran Q=0.024, df=1).<sup>112,114</sup> This evidence was moderate strength.

### **Harms**

One trial found no significant differences between team-based multi-component care and usual care in rates of accidental death (RR 0.31; 95% CI 0.01 to 7.59) or unexplained death (RR 0.31; 95% CI 0.01 to 7.56).<sup>111</sup> Ten-year followup from the same trial found no difference in between-group mortality (RR 0.92; 95% CI 0.45 to 1.88).<sup>118</sup>

## **Comorbidities: Substance Use Disorder and Schizophrenia**

One good-quality Cochrane systematic review included 32 randomized trials that enrolled a total of 3,165 patients (aged 18 years to 65 years) with severe mental illness and comorbid substance misuse (Appendix Table E-23).<sup>120</sup> Most trial participants were diagnosed with a schizophrenia spectrum disorder or psychosis with a concurrent diagnosis of substance misuse (e.g., cannabis, cocaine, opioids) and were diagnosed using American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria. Studies that enrolled only patients with major depressive disorder, bipolar disorder, or patients who only misused tobacco were excluded. Interventions were more intense (e.g., integrated models of care with assertive community treatment) or were stand-alone treatments (e.g., cognitive behavioral therapy, social skills training). Three trials were conducted solely in the hospital (10% of patients), 19 in community, and the remaining were a combination of settings. Function, mortality, relapse rates, and treatment maintenance (reported as loss to treatment) were among the reported outcomes. None of the included trials met all quality criteria. Three trials met most criteria, with the majority of trials reporting adequate randomization techniques. However, few trials reported appropriate allocation concealment or blinding of participants. Most SOE was rated as low strength or insufficient.

## **Long-Term Intervention: Integrated Models of Care Versus Usual Care**

Integrated models of care refer to the coordination of care at the provider (or team of providers) level for both the mental health and substance misuse diagnoses and the actual services provided vary according to the needs of the patient. Within the Cochrane review, four RCTs provided data for 735 participants.<sup>120</sup> SOE was low for all outcomes.

### **Function**

One trial (N=198) provided data on global functioning using the GAF and found low-strength evidence of no difference between assertive community treatment compared with usual care at 12 months (40.4 vs. 39.7, MD 0.70; 95% CI -2.07 to 3.47).<sup>120</sup> Findings were similar at multiple timepoints, beginning at 6 months through 36 months and continued to show no difference between treatments based on low-strength evidence (Appendix Table E-23).

### **Treatment Discontinuation**

Pooled analysis of three trials (N=603) indicated no difference in likelihood of being lost to treatment between integrated treatment and usual care at 36 months (24% vs. 21%, RR 1.09, 95% CI 0.82 to 1.45,  $I^2=0\%$ ) based on low-strength evidence.<sup>120</sup>

### **Substance Use**

One trial (N=143) found low-strength evidence of no difference between integrated assertive community treatment compared with standard case management at 36 months for not being in remission for alcohol use (57% vs. 50%, RR 1.15, 95% CI 0.84 to 1.56) and for drug use (58% vs. 65%, RR 0.89, 95% CI 0.63 to 1.25).<sup>120</sup>

### **Harms**

Two trials (N=421) reported all-cause mortality and found low strength evidence of no difference between assertive community treatment and usual care through 36 months (3% vs. 3%, RR 1.18, 95% CI 0.39 to 3.57,  $I^2=0\%$ ).<sup>120</sup>

### **Long-Term Intervention: Nonintegrated Models of Care Versus Usual Care**

Nonintegrated models of care describe interventions where care teams do not coordinate care. ICM with higher skilled case managers with smaller caseloads is included as a nonintegrated model. However, models still had to address the patient's substance misuse. Within the Cochrane review four trials (N=163) met criteria for nonintegrated models of care.<sup>120</sup> Included interventions were nonintegrated assertive community treatment (2 trials, N=84) and intense case management (two trials, N=79). Trials were small and of lower quality and provided insufficient strength evidence to compare patient function and loss to treatment between nonintegrated models of care and usual care.

### **Short-Term, Patient-Focused Interventions: Cognitive-Behavioral Therapy Versus Usual Care**

CBT was an included intervention to address substance misuse in patients with a dual diagnosis of schizophrenia and substance misuse disorder.<sup>120</sup>

**Treatment discontinuation.** Pooled analysis from two trials (N=152) found no difference between treatment with CBT and usual care at 3 months in risk of discontinuing treatment (12% vs. 10%, RR 1.12; 95% CI 0.44 to 2.86,  $I^2=0\%$ ) based on low-strength evidence.<sup>120</sup>

### **Short-Term, Patient-Focused Interventions: Social Skills Training Versus Usual Care**

Social skills training was included help patients improve interpersonal skills and relationships and manage conflict in social situations involving substance misuse.<sup>120</sup> Evidence for loss to treatment was considered insufficient to draw meaningful conclusions based on data from two trials (N=94).

## **Demographic Characteristics**

### **Age**

Evidence of the effect of nonpharmacological interventions on schizophrenia outcomes from subgroup analyses based on patient age, whereas very limited, suggests that age is not a moderating factor. Systematic reviews of CBT<sup>79</sup> and cognitive remediation<sup>84</sup> review found no difference between interventions and usual care when trials were stratified according to age. In individual trials of cognitive remediation<sup>89</sup> and social skills training<sup>103,104</sup> enrolling older adults (over age 50), there was also no difference in outcomes when compared with trials enrolling a younger population.<sup>86-88,90,97,105</sup> Age-based subgroup analyses were not reported for other nonpharmacological interventions.

### **Sex**

Evidence on differences in outcomes based on sex is extremely limited. One systematic review of 30 RCTs of CBT found no difference in negative symptom outcomes when results were stratified according to sex.<sup>79</sup>

One study of social skills training that exclusively enrolled older adults (mean age 60 years) had an effect size for men that was consistently better than that for women for outcomes related to function and symptoms, suggesting that social skills training was more effective in men compared with women.<sup>103,104</sup> Of note is the fact that only about half of participants in this study had a diagnosis of schizophrenia or schizoaffective disorder, whereas the remaining participants

had various mood disorders. This potentially limits the applicability of these findings, as additional subgroup analysis found consistently lower benefit of social skills training for all outcomes when compared with participants with mood disorders.

Other trials of nonpharmacological interventions did not report subgroup analyses according to sex.

# Discussion

## Key Findings and Strength of Evidence

This systematic review evaluated the evidence on treatments for schizophrenia, comparing drug treatments to each other and psychosocial and other nonpharmacological interventions to usual care. The purpose was to inform clinicians, patients and their families, and guideline authors with the ultimate goal of improving patient care. The key findings and strength of evidence (SOE) for these findings are summarized in the summary of evidence tables (Tables 10 and 11). The complete assessments of strength of the evidence, according to comparisons and outcomes, are in Appendix H. In this summary, we do not include findings where the evidence was insufficient to draw conclusions. Generally, these were situations where the evidence was limited to a single study, with inadequate sample size, and only fair quality. Unfortunately, even with the large volume of studies available, there were no instances of high-strength evidence. This was primarily due to specific intervention comparisons having only a few fair-quality trials with few studies contributing evidence for a particular outcome, resulting in moderate and low-strength evidence. The key findings are presented below by key question and prioritized outcomes. The findings are then discussed in relation to what is already known about these interventions, applicability of the findings, implications of the findings for policy and decisionmaking, limitations of the review and the evidence, and finally our research recommendations based on gaps in the evidence,

## Key Questions 1a and 1b: Comparative Evidence Regarding Antipsychotic Drugs

The findings on antipsychotic drugs come from two large systematic reviews<sup>27-29</sup> and a total of 28 additional, newer trials<sup>43-70</sup> (One trial is included in both the first-generation antipsychotic (FGA) versus second generation antipsychotic (SGA) and SGA versus SGA sections.<sup>57</sup>) The prioritized outcomes were function, quality of life, response and/or remission, mortality, self-harm, core illness symptoms, overall adverse events, and withdrawal from treatment due to adverse events. 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 Drugs: SGA Versus SGA

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 injectable (LAI) formulations of aripiprazole and paliperidone) is limited, with few studies, none finding a newer drug superior to an older SGA on any outcome. Similarly, quetiapine and ziprasidone were not found superior to another SGA on any outcome (Table 10). Tables showing the summary results for each drug, indicating magnitude, direction, and strength of evidence for an effect across all seven prioritized outcomes are included in Appendix I.

## 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 strength evidence from 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 functional outcomes. Findings on quality of life show that there was no difference between olanzapine and risperidone or ziprasidone (moderate-strength evidence); olanzapine or risperidone oral or LAI and quetiapine; oral aripiprazole and aripiprazole monthly LAI (low-strength evidence) in studies with up to 2 years of followup.

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 randomized controlled trials (RCTs), although the most common definition was 20 percent improvement on a core illness symptoms scale, such as the Positive and Negative Syndrome Scale (PANSS). Low-strength evidence from 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. Other comparisons and meta-regression examining the influence of study duration, dose-level, population (either treatment-resistant or first-episode status), and category of response definition did not result in any statistically significant differences between the SGAs (low-strength evidence). Remission was reported too infrequently to assess comparatively.

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

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 a United States Food and Drug Administration (FDA) Boxed Warning against their use in older patients with dementia due to increased risk of mortality. Low-strength evidence suggests that the mortality rate is low in SGA trials and cohort studies (0 to 1.17%), and that 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. Comparative evidence on the risk of cardiovascular or all-cause mortality was not available for the other SGA drugs. Self-harm, including suicide deaths, while infrequent 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, there is moderate strength evidence supporting 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 (vs. olanzapine) and in patients with unknown or mixed risk for these outcomes (vs. olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole).

## **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-strength evidence) or 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 strength evidence). 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. 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. Olanzapine had lower risk than five other SGAs: clozapine, lurasidone, quetiapine, risperidone, and ziprasidone. Aripiprazole had lower risk than clozapine and ziprasidone, and cariprazine and iloperidone had lower risk than clozapine. Comparative evidence on extrapyramidal symptoms (EPS), cardiovascular events, diabetes, weight gain, metabolic syndrome, and sexual function is summarized in the Drug Effectiveness Review Project report.<sup>29</sup> 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 EPS are more mixed.

## **Subgroups**

Evidence in subgroups was sparse and 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. Although core illness symptoms were more improved with paliperidone than ziprasidone or aripiprazole, 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. Findings on core illness symptoms or response 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, or amenorrhea). Aripiprazole had either lower rates of or longer time to discontinuation due to adverse events than ziprasidone or quetiapine.

In treatment-resistant patients, a network meta-analysis of 40 RCTs 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 patients 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 treatment discontinuations indicated no significant differences among the older SGAs. Clozapine had fewer discontinuations due to lack of efficacy than risperidone and quetiapine.

Across the 46 trials reporting response, the rates ranged from 20 to 80 percent across SGA trial arms. The variation appears to be associated with prior drug exposure of patients enrolled; patients resistant to previous treatment had lower rates of response and those with a first episode had greater rates.

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 Antipsychotic Versus Second-Generation Antipsychotic**

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 did not find perphenazine to be inferior 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, such that a thorough review of the comparative evidence is still necessary. 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 (two good quality, three fair 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 is largely about haloperidol, with 108 studies, and only 7 of perphenazine and 4 of fluphenazine. Olanzapine was the most commonly compared SGA.

## **Benefits Outcomes**

Quality of life, a highly prioritized outcome, was not different between the FGAs and SGAs, based on low (quetiapine and risperidone) to moderate (olanzapine) strength evidence. Only ziprasidone was found better than haloperidol with low strength evidence. Evidence on functional outcomes was insufficient to draw conclusions. Moderate strength evidence suggests that risperidone is not different from haloperidol in response rates. Low strength evidence finds that 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.

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

## **Harms Outcomes**

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

## **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 improvement in core illness symptoms was comparable for risperidone and haloperidol.

Evidence on pharmacological treatments is summarized in Table 10.

**Table 10. Summary of evidence for pharmacological treatments**

Comparison	Outcome	Strength of Evidence	Conclusions
SGA vs. SGA	Function	Low	<p>No difference in social functioning was found between paliperidone palmitate LAI (monthly) and risperidone LAI (every two weeks) (PSP scale mean change from baseline 16.8 and 18.6, respectively; LSM difference 0.5, 95% CI -2.14 to 3.12) based on one RCT (N=452).<sup>29</sup> A single study (N=666) found risperidone LAI to result in greater improvements in social function over 24 months compared with quetiapine (change at endpoint 6.6 vs. 1.1; p&lt;0.0001). (1 RCT; N=666).<sup>138</sup></p> <p>Although both groups improved significantly from baseline, risperidone LAI resulted in greater improvements in SOFAS at 6 months (6.1 vs. 2.7; p=0.02), 12 months (9.5 vs. 6.1; p=0.009).<sup>138</sup></p> <p>CATIE Phase 1 found no significant differences in rates of employment between risperidone, olanzapine, quetiapine, and ziprasidone at 18 months.<sup>29</sup></p> <p>Global functioning was not different (based on the GAF) between olanzapine and either risperidone (4 cohort studies; Pooled WMD 0.61, 95% CI -1.78 to 2.99; I<sup>2</sup>=43%) or quetiapine (2 RCTs; pooled WMD 1.14, 95% CI -4.75 to 7.02; Q=3.99, df=1; p=0.045).<sup>29</sup></p>
	Quality of life	Moderate	Olanzapine was not found significantly different than risperidone (2 RCTs) or ziprasidone (2 RCTs) at 12 months using the QLS scale (change in scores ranged from 0.19 to 0.26). <sup>29</sup>
	Quality of life	Low	<p>Olanzapine was not found significantly different than quetiapine (1 RCT) at 12 months using the QLS scale.<sup>29</sup></p> <p>Risperidone was not found significantly different from quetiapine or ziprasidone at 12 months using the QLS scale (1 RCT each; range of change in scores 0.19 to 0.26).<sup>29</sup></p> <p>Risperidone LAI was not found different from quetiapine on the SF-12 or SQLS-R4 at 24 months.<sup>138</sup></p>
	Response/remission	Low	<i>Response</i> was significantly more likely with olanzapine (OR 1.71, 95% CI 1.11 to 2.68) and risperidone (OR 1.41, 95% CI 1.01 to 2.00) than quetiapine, based on a network meta-analysis of 46 head-to-head RCTs.
	Mortality	Low	<p>With incidence rates of 0 to 1.17%, significant differences in mortality were not found in two RCTs each (4 to 24 months duration) of asenapine with olanzapine (RR 2.49, 95% CI 0.54 to 11.5),<sup>154,187</sup> quetiapine and risperidone (RR 3.24, 95% CI 0.72 to 14.6)<sup>184,186</sup> and paliperidone palmitate LAI (monthly) versus risperidone LAI (RR 1.26, 95% CI 0.21 to 7.49).<sup>136,188</sup></p> <p>Retrospective cohort studies found no significant difference in the risk of all-cause (1 study, N=48,595) or cardiovascular mortality (2 studies, N=55,582) between risperidone, olanzapine, and quetiapine.<sup>29</sup></p>
Reduction in self-harm	Low	Clozapine was found superior to olanzapine in preventing significant suicide attempts or hospitalization to prevent suicide (HR 0.76, 95% CI 0.58 to 0.97) and CGI-Suicide Severity (SS) ratings of "much worse" or "very much worse" (HR 0.78, 95% CI 0.61 to 0.99); NNT=12) among patients at high risk. Observational studies confirm these findings in broader populations. <sup>29</sup>	

Comparison	Outcome	Strength of Evidence	Conclusions
SGA vs. SGA	Core illness symptoms: Total symptoms	Low	<p>Clozapine was found to improve core illness symptoms significantly more than the other SGAs, except for olanzapine (network meta-analysis of 212 RCTs; SMDs on PANSS or BPRS -0.32 to -0.55).<sup>194</sup> All of the SGAs were superior to placebo (SMDs -0.33 to -0.88).</p> <p>Olanzapine and risperidone were found to improve symptoms more than the other SGAs, except for each other and paliperidone (SMDs -0.13 to -0.26).<sup>194</sup></p> <p>Paliperidone was found to improve symptoms more than lurasidone and iloperidone (SMDs=-0.17).<sup>194</sup></p> <p>In a separate network analysis of 40 RCTs of clozapine, risperidone, olanzapine, quetiapine, and ziprasidone in patients who were resistant to treatment, the only significant difference was that the mean change in the PANSS was greater with olanzapine than quetiapine (SMD -0.29, 95% CI -0.56 to -0.13).<sup>183</sup></p>
	Overall/any adverse events	Moderate	There was no significant difference in overall adverse event reporting between asenapine and olanzapine in five RCTs (in 4 publications). <sup>154,176,187,225</sup>
	Overall/any adverse events	Low	There was no difference between groups based on two to three trials each comparing: quetiapine 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. <sup>45-47,49-51,54-56,61,123,125,133,136,148,150,151,154,155,161,163,167,169,171,172,174-178,184,186-188,196-227</sup>
	Withdrawal due to adverse events	Low	<p>Risperidone LAI had significantly lower risk than clozapine (OR 0.27, 95% CI 0.10 to 0.71); lurasidone (OR 0.39, 95% CI 0.18 to 0.84); quetiapine ER (OR 0.43, 95% CI 0.22 to 0.81); risperidone (OR 0.50, 95% CI 0.25 to 0.99); and ziprasidone (OR 0.40, 95% CI 0.20 to 0.82) based on a network meta-analysis of 90 trials.</p> <p>Olanzapine had lower risk than clozapine (OR 0.39, 95% CI 0.19 to 0.79); lurasidone (OR 0.57, 95% CI 0.34 to 0.94); quetiapine (OR 0.62, 95% CI 0.44 to 0.87); risperidone (OR 0.72, 95% CI 0.55 to 0.96); and ziprasidone (OR 0.58, 95% CI 0.41 to 0.82) clozapine based on a network meta-analysis of 90 trials</p> <p>Aripiprazole had lower risk than clozapine (OR 0.43, 95% CI 0.21 to 0.88) and ziprasidone (OR 0.64, 95% CI 0.44 to 0.94). Cariprazine (OR 0.40, 95% CI 0.17 to 0.95) and iloperidone (OR 0.34, 95% CI 0.13 to 0.91) had lower risk than clozapine based on a network meta-analysis of 90 trials.</p> <p>Meta-regression examining the influence of study duration, dose-level, and either treatment-resistant or first-episode status did not result in any significant findings.</p>
FGA vs. SGA	Quality of life	Moderate	There were no differences between haloperidol and olanzapine in quality of life scores. (SOE: Moderate); or perphenazine and olanzapine, quetiapine, risperidone or ziprasidone. <sup>28</sup>
	Quality of life	Low	<p>One trial comparing haloperidol with ziprasidone found a positive effect favoring ziprasidone (effect estimate -12.12; 95% CI -22.06 to -2.17) with no difference between groups in another trial.<sup>28</sup></p> <p>There were no differences between haloperidol and olanzapine; or perphenazine and quetiapine, risperidone or ziprasidone.<sup>28</sup></p>
	Response/Remission	Moderate	There was no difference in response rates between haloperidol and risperidone (16 RCTs, N=3,452; RR 0.94; 95% CI 0.87 to 1.02). <sup>28</sup>

Comparison	Outcome	Strength of Evidence	Conclusions
FGA vs. SGA	Response/ Remission	Low	<p>Pooled results from 14 RCTs comparing haloperidol with olanzapine found a significant effect on response rate favoring olanzapine (N=4,099; RR 0.86; 95% CI 0.78 to 0.96).<sup>28</sup></p> <p>Three trials comparing haloperidol with olanzapine found a significant difference in remission rates favoring olanzapine (pooled RR 0.65; 95% CI 0.45 to 0.94; I<sup>2</sup>=54%).<sup>28</sup></p> <p>There was no difference in response rates between haloperidol and aripiprazole (5 RCTs, N=2,185; RR 1.01; 95% CI 0.76 to 1.34), quetiapine (6 RCTs, N=1,421; RR 0.99; 95% CI 0.76 to 1.30) and ziprasidone (6 RCTs, N=1,283; RR 0.98; 95% CI 0.74 to 1.30).<sup>28</sup></p> <p>There was no difference in remission rates between haloperidol and ziprasidone based on three trials (RR 0.89; 95% CI 0.71 to 1.12).<sup>28</sup></p>
	Core illness symptoms: Total symptom score	Moderate	There were significant difference in total PANSS between haloperidol and olanzapine (15 RCTs, N=4,209; mean difference 2.31; 95% CI 0.44 to 4.18) and risperidone (21 RCTs, N=4,020; mean difference 3.24; 95% CI 1.62 to 4.86), both favoring the SGA over haloperidol. <sup>28</sup>
	Core illness symptoms: Total symptom score	Low	There were no differences in total PANSS, BPRS, CGI-S and CGI-I scores for other FGA versus SGA comparisons. <sup>28</sup>
	Core illness symptoms: Negative symptom score	Moderate	Olanzapine was more effective than haloperidol at improving negative symptoms based on SANS scores (5 RCTs, N=535; mean difference 2.56; 95% CI 0.94 to 4.18). <sup>28</sup>
	Core illness symptoms: Negative symptom score	Low	Using the negative symptoms subscale of the PANSS scale, mean differences (although small) between haloperidol and aripiprazole (3 RCTs, N=1,701; 0.80; 95% CI 0.14 to 1.46), olanzapine (14 RCTs, N=3,742; 1.06; 95% CI 0.46 to 1.67), and risperidone (22 RCTs, N=4,142; 0.80; 95% CI 0.14 to 1.46) all favored the SGA. <sup>28</sup>
	Overall/any adverse events	Moderate	Overall adverse event rates favored SGAs when comparing haloperidol with aripiprazole (3 RCTs, N=1,713; RR 1.11; 95% CI 1.06 to 1.17; I <sup>2</sup> =0%), risperidone (8 RCTs, N=1313; RR 1.20; 95% CI 1.01 to 1.42; I <sup>2</sup> =84%), and ziprasidone (6 RCTs, N=1448; RR 1.13; 95% CI 1.03 to 1.23; I <sup>2</sup> =31%). <sup>28</sup>
	Withdrawal due to adverse events	Moderate	When comparing haloperidol with specific SGAs, withdrawals due to adverse events were significantly higher with haloperidol use compared with aripiprazole (8 RCTs, N=3,232; RR 1.25; 1.07 to 1.47; I <sup>2</sup> =0%), olanzapine (24 RCTs, N=5,708; RR 1.89; 95% CI 1.57 to 2.27; I <sup>2</sup> =0%), risperidone (25 RCTs, N=4,581; RR 1.32; 95% CI 1.09 to 1.60; I <sup>2</sup> =0%), and ziprasidone (7 RCTs, N=1,597; RR 1.68; 95% CI 1.26 to 2.23; I <sup>2</sup> =0%). <sup>28</sup>

BPRS = Brief Psychiatric Rating Scale; CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness; CGI = Clinical Global Impressions scale; CI = confidence interval; df = degrees of freedom; ER = extended release; FGA = first-generation antipsychotic; GAF = Global Assessment of Functioning; HR = hazard ratio; IR = immediate release; LAI = long-acting injectable; LSM = least squares mean; NNT = number needed to treat; OR = odds ratio; PANSS = Positive and Negative Syndrome Scale; PSP = Personal and Social Performance Scale; RCTs = randomized controlled trials; RR = risk ratio; SANS = Scale for the Assessment of Negative Symptoms; SF-12 = 12-item Short Form Health Survey; SGA = second-generation antipsychotic; SMD = standardized mean difference, SOE = strength of evidence; SOFAS = Social and Occupational Functioning Assessment Scale; SQLS-R4 = Schizophrenia Quality of Life Scale- Revision 4; WMD = weighted mean difference

## Key Questions 2a and 2b: Evidence on Psychosocial and Other Nonpharmacological Interventions Versus Usual Care

The studies included in our review evaluated 13 discrete psychosocial interventions in comparison with usual care. The purpose was not to evaluate head-to-head comparisons of active interventions to each other. The evidence base is comprised of 13 systematic reviews (11 good quality, 2 fair quality) that included 271 trials relevant to this report. In addition, we included 27 trials that were not included in these reviews. Of these new trials, four were good, 20 were fair, and three were poor quality. The strength of the body of evidence for each intervention-outcome pair was moderate and low strength overall (Table 11).

### Benefit Outcomes

Patients receiving **assertive community treatment** were more likely to be living independently and employed and were less likely to be homeless or to discontinue treatment compared with patients assigned to usual care (moderate SOE). There were no significant difference 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). Rehospitalization, the target of this intervention, was also significantly lower with assertive community treatment than usual care, as well as the duration of hospital stay.

**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 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.

**Family interventions** resulted in significantly lower relapse rates than usual care at up to 24 months treatment and at 5 years followup, although differences were not found from 25 to 36 months. Family interventions were also associated with improved core illness symptoms. Differences were not noted in social function, including employment and housing situation, reduction in self-harm (moderate SOE for reduced relapse from 7 to 12 months, low SOE for all others).

**Intensive case management (ICM)** was not found to improve global function, quality of life, or core illness symptoms more than usual care (low SOE).

**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). Greater 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 nine 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.

**Supported employment**, specifically the individual placement and support (IPS) 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 worked more

hours, were employed longer, and earned more money than those receiving usual care. Evidence with comparisons with other vocational training confirmed these findings (moderate SOE).

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

## Subgroups

### Demographic Subgroups

We found limited subgroup analyses across psychosocial interventions to identify potential patient characteristics that might predict outcomes. Limited evidence on **social skills training** from one RCT 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.

### Clinical Subgroups

**Early team-based multi-component treatment programs for first-episode psychosis** resulted in significant improvements in global function with up to 2 years of treatment compared with usual care; participants were more likely to be working or in school, 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 and schizophrenia**, long-term integrated models of care did not result in different improvements in function, mortality, or substance abuse than usual care.

### 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.

Evidence for Key Question 2 is summarized in Table 11.

**Table 11. Summary of evidence for psychosocial and nonpharmacological interventions**

Intervention vs. Usual Care	Outcome	Strength of Evidence	Conclusions
<i>Assertive community treatment (ACT)</i>	Social Function	Low	ACT did not improve improved social function more than usual care, based on pooled analysis of 3 studies (MD 0.03; 95% CI -0.28 to 0.34); an additional trial also found no difference. <sup>71,72</sup>  Compared with usual care, there were no significant differences in arrests (2 trials, total N=604; OR 1.17, 95% CI 0.60 to 2.29; I <sup>2</sup> =0%), imprisonment (4 trials, total N=471; OR 1.19, 95% CI 0.70 to 2.01; I <sup>2</sup> =27%), or police contacts (2 trials, total N=149; OR 0.76, 95% CI 0.32 to 1.79; I <sup>2</sup> =84%). <sup>71</sup>
<i>ACT</i>	Housing Function	Moderate	Patients receiving ACT had lower likelihood of not living independently (4 trials; OR 0.52, 95% CI 0.35 to 0.79), <sup>71</sup> or being homeless (4 trials, OR 0.24, 95% CI 0.12 to 0.48) compared with usual care. <sup>71,72</sup>

<b>Intervention vs. Usual Care</b>	<b>Outcome</b>	<b>Strength of Evidence</b>	<b>Conclusions</b>
	Employment	Moderate	Patients receiving ACT had lower likelihood of being unemployed than those receiving usual care (3 trials; OR 0.46, 95% CI 0.21 to 0.99). <sup>71</sup>
	Core illness symptoms: symptoms	Moderate	Core illness symptoms improved with both ACT and usual care, with no differences between groups (MD, -0.14; 95% CI -0.36 to 0.08); one additional trial also found no difference in symptom improvement. <sup>71,72</sup>
<i>Cognitive behavioral therapy (CBT)</i>	Global, Social and Occupational Function Short-term ( $\leq$ 6 months since initiation)	Moderate	CBT improved global function more than usual care in the short-term (GAF scale, 6 trials; MD 5.49; 95% CI 1.85 to 9.14). CBT improved social and occupational function more than usual care in the short-term (SOFAS scores, 2 trials; MD 9.11; 95% CI 6.31 to 11.91) <sup>78,83,95,274,278,279</sup>
	Global, Social and Occupational Function Long-term ( $>$ 1 year since initiation)	Low	Global and social/occupational function were not different to usual care in longer-term followup ( $>$ 1 year, GAF and SOFAS scores in one systematic review and three RCTs; one other RCT found a positive effect in favor of CBT). <sup>76,78,93,276,279</sup>
	Quality of life	Low	CBT improved quality of life more than usual care in the short term (12 to 24 weeks followup) based on two trials, <sup>80,83</sup> but this difference was not found in two trials with longer followup (18 to 24 months). <sup>93,279</sup>
	Core Illness symptoms	Moderate	CBT had a greater effect on core illness symptoms than usual care during treatment (8 weeks to 5 years) based on a good-quality systematic review of 34 studies (SMD -0.33, 95% CI -0.47 to -0.19). <sup>77</sup>
	Negative symptoms	Low	No meaningful difference between CBT and usual care in negative symptom improvement based on two systematic reviews. <sup>77,79</sup> The target of the CBT was varied in the studies included, with few targeting negative symptoms.
	<i>Cognitive Remediation</i>	Global, Social, Occupational Function	Low
Core Illness symptoms		Moderate	Cognitive remediation resulted in small improvements in core illness symptoms, based on 2 trials (SMD -0.62 (95% CI -1.01 to -0.24)). <sup>86,89</sup>
Negative symptoms		Moderate	Negative symptoms were significantly improved with cognitive remediation compared with usual care (1SR of 18 RCTs, effect size -0.36, 95% CI -0.52 to -0.20). <sup>85</sup>
<i>Early Interventions for First-Episode Psychosis</i>	Global Function	Moderate	Pooled results found that the early team-based multi-component treatment programs resulted in higher functioning, based on GAF and GAS scores after up to 2 years of treatment (3 RCTs; WMD: 3.88; 95% CI 0.91 to 6.85; $I^2=64\%$ ). <sup>111,113,114,296</sup>
	Social Function	Moderate	Early team-based multi-component treatment programs resulted in significantly more people (22%) working or in school after up to 2 years of treatment (3 RCTs; RR 1.22; 95% CI 1.01 to 1.47). <sup>111,113,114,296</sup>
<i>Early Interventions for First-Episode Psychosis</i>	Housing Function	Low	There was no significant differences between early team-based multi-component treatment programs and usual care on housing status for up to 2-year treatment duration based on two RCTs. <sup>111,113,296</sup>

<b>Intervention vs. Usual Care</b>	<b>Outcome</b>	<b>Strength of Evidence</b>	<b>Conclusions</b>
	Quality of life	Moderate	Two RCTs found significant differences between early team-based multi-component treatment programs and usual care on quality of life scores for up to 2-year treatment duration (pooled effect size 0.84; 95% CI 0.14 to 1.55). <sup>113,117</sup>
	Reduction in self-harm	Low	There was no difference in reduction in self-harm in two trials of early team-based multi-component treatment programs versus usual care.
	Core Illness symptoms	Low	There was no difference between early team-based multi-component treatment programs and usual care in core illness symptoms, based on three RCTs (WMD on PANSS - 2.53; 95% CI -5.45 to 0.39; I <sup>2</sup> =55%). <sup>113,114,117</sup>
	Relapse	Moderate	Early team-based multi-component treatment program participants were significantly less likely to relapse compared with those in usual care based on two RCTs (RR 0.64; 95% CI 0.52 to 0.79). <sup>112,114</sup>
<i>Supported Employment</i>	Occupational Function	Low	Supported employment, using the individual placement and support (IPS) model resulted in significantly better employment outcomes over 2 years compared with usual care (more patients were employed, competitive or any job, worked more hours, were employed longer, and earned more money). <sup>109</sup> Evidence with vocational training control groups supports these findings.
<i>Family Interventions</i>	Social Function	Low	There were no differences in social functioning scale scores or not being able to live independently between family intervention and usual care based on one RCT. <sup>95</sup>
	Occupational Function	Low	There were no differences in unemployment rates between participants in family interventions and usual care at 1 year based on one systematic review. <sup>91</sup>
	Reduction in self-harm	Low	Suicide rates were similar in family intervention participants and those who received usual care in one SR, but events were few. <sup>91</sup>
	Core Illness symptoms	Low	Family interventions reduced core illness symptoms based on 4 trials (SMD -0.46, 05% CI -0.73 to -0.20). <sup>91,93,96</sup> but there was no difference in core illness symptoms.
	Relapse	Moderate	Family interventions resulted in significantly lower relapse rates at 7 to 12 months based on one systematic review <sup>91</sup> and four additional studies <sup>93,96,97,290</sup> (31% vs. 45%, RR 0.67; 95% CI 0.54 to 0.83).
		Low	Family interventions resulted in lower relapse rates at 0 to 6 months compared with usual care based on one systematic review <sup>91</sup> plus one additional trial <sup>290</sup> (23% vs. 37%, RR 0.62; 95% CI 0.41 to 0.92), at 13-24 months based on a systematic review <sup>91</sup> (49% vs. 61%; RR 0.75, 95% CI 0.58 to 0.99) and at 5 years followup based on a systematic review <sup>91</sup> plus one additional trial <sup>289</sup> (78% vs. 94%, RR 0.82; 95% CI 0.72 to 0.94). The difference at 25 to 36 months was not significant. <sup>91</sup>
<i>Intensive Case Management (ICM)</i>	Global Function	Low	ICM did not differ significantly from usual care in change in global function, based on pooled analysis of 3 studies (MD 0.46; 95% CI -0.34 to 1.26). <sup>98,99</sup>  There was no difference in rates of imprisonment based on pooled analysis of 5 trials (OR 0.90, 95% CI 0.45 to 1.82). <sup>98</sup>
<i>ICM</i>	Core Illness symptoms	Low	ICM was not significantly different to usual care in improvement in core illness symptoms, based on pooled analysis of 2 studies (MD, 0.46; 95% CI -3.67 to 4.60). One subsequent trial also reported no difference in symptoms using a different scale. <sup>98,99</sup>

Intervention vs. Usual Care	Outcome	Strength of Evidence	Conclusions
<i>Illness self-management</i>	Core Illness symptoms	Moderate	Participants receiving a self-management education intervention were significantly more likely to demonstrate a reduction in severity of core illness symptoms based on the BPRS (5 RCTs; pooled WMD=-4.19, 95% CI -5.84 to -2.54). <sup>100</sup>
	Negative symptoms	Low	There was no change in negative symptoms based PANSS – negative subscale based on five RCTs. <sup>100</sup>
	Relapse	Low	Patients receiving more than 10 self-management intervention sessions had a greater reduction in the likelihood of experiencing relapse compared with usual care (OR 0.41; 95% CI 0.21-0.79), whereas those receiving 10 or fewer sessions had a smaller, nonsignificant, reduction in the risk of relapse (OR 0.67, 95% CI 0.39 to 1.15) based on one SR. <sup>100</sup>
<i>Psychoeducation</i>	Global Function	Low	Psychoeducation had a greater effect than usual care on global functional outcomes at 1 year of followup based on one good-quality systematic review of three studies (MD -5.23, 95% CI -8.76 to -1.71; I <sup>2</sup> =79%). <sup>102</sup>
	Relapse	Moderate	Psychoeducation had a greater effect than usual care on relapse rates (with or without readmission) at nine to 18 months of followup based on one good-quality systematic review of six studies (RR 0.80, 95% CI 0.70 to 0.92; I <sup>2</sup> =54%). <sup>102</sup>
	Harms	Low	There was no difference between psychoeducation and usual care in rate of harms based on 10 RCTs. <sup>102</sup>
<i>Social Skills Training</i>	Social Function	Low	Social Function was significantly better in patients receiving 6 months (SMD 1.60; 95% CI 1.19 to 2.02), 1 year (SMD 2.02; 95% CI 1.53 to 2.52) and 2 years (SMD 0.65; 95% CI 0.36 to 0.95) of social skills training in three studies (in four publications). <sup>97,103-105</sup>
	Core Illness symptoms	Low	Core illness symptoms improved more with social skills training vs. usual care at 6 months based on two RCTs (SMD on PANSS -1.50 (95% CI -1.92 to -1.09 and 2 years -0.81 (95% CI -1.22 to -0.40)). <sup>97,105</sup>
	Negative symptoms	Low	Negative symptoms were consistently and significantly improved with social skills training relative to usual care in three studies (SMD range -0.45 to -1.30; in four publications). <sup>97,103-105</sup>
<i>Supportive Therapy</i>	Global and Social Function	Low	There was no difference between supportive therapy and usual care for global or social function based on two studies in a systematic review. <sup>110</sup>

ACT = assertive community treatment; BPRS = Brief Psychiatric Rating Scale; CBT = cognitive behavioral therapy; CI = confidence interval; GAF = Global Assessment of Functioning; GAS = Global Assessment Scale; ICM = intensive case management; MD = mean difference; OR = odds ratio; PANSS = Positive and Negative Syndrome Scale; RCT = randomized controlled trial; RR = risk ratio; SMD = standardized mean difference; SOFAS = Social and Occupational Functioning Assessment Scale; SR = systematic review; WMD = weighted mean difference

## 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.<sup>183,194,263,264,297,298</sup> 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 by 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.<sup>183,194,297-301</sup> 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).<sup>263,300,302-304</sup> 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 several 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 report, with nine new trials included.<sup>27,28</sup> 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 only 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 (in this case, primarily studies conducted in China). 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 were not handled consistently across reviews. For example, 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 psychosocial interventions that made comparisons to usual care. The implications of this choice certainly have been contemplated in the literature before<sup>77,305-307</sup> with no clear conclusion, although some have found little difference in analyses limiting to usual care comparisons and those including other comparisons.<sup>77</sup> 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, 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 interventions. In this case, both a prior Cochrane review 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.<sup>308</sup> 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 healthcare 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, based on domains including study methodological limitations, directness and consistency of evidence, and precision of estimates of effect. Our finding that the SOE for psychosocial interventions was moderate and low is consistent with our findings for antipsychotic drugs, and with numerous reviews across other populations and interventions. This system 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, where there may be concern over how our and why findings differ. Because 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, we include their findings as well as individual reviews of these specific interventions.<sup>295</sup>

## **Cognitive Behavioral Therapy**

Overall, our findings are consistent with prior findings, except that we find additional outcomes where CBT showed benefit over usual care, and we did not find strong evidence regarding duration of effects. The use of CBT in schizophrenia has historically been focused on reducing positive symptoms.<sup>309,310</sup> 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, even when those outcomes were not the focus of the CBT.<sup>78,309</sup> Specifically, we found short-term measures of global, social and occupational function, quality of life and relapse requiring hospitalization to be significantly better with CBT based on low to moderate SOE. These findings build on the findings of prior reviews and the PORT publication, which noted that there was evidence that CBT improved symptoms (positive, negative, and overall) and social function - but that there were also studies that did not find these effects, and that there was no good evidence on relapse and suicidality.<sup>295</sup> With respect to the

durability of these effects after CBT ends, there is less clarity. A 2011 meta-analysis finds 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.<sup>311</sup> Results related to durability of treatment from individual trials with longer post-treatment followup have been mixed. One trial<sup>312</sup> of 9 months of CBT versus befriending found sustained benefit on overall and negative symptoms at 5-year followup with CBT, while a second trial<sup>313</sup> 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.

As with a previous meta-analysis,<sup>309</sup> the studies we included rarely targeted negative symptoms. Our findings regarding negative symptoms, based on two good-quality systematic reviews,<sup>77,79</sup> are somewhat in contrast with a 2008 review by Wykes et al. that found CBT resulted in significant improvements in negative symptoms.<sup>309</sup> The Velthorst 2015 review found study year to be correlated with effect size, in that studies published prior to 2003 reported larger and more positive effect sizes than studies published in 2004 and later. Although based on limited evidence, this may partially explain the disparity in negative symptom pooled effect sizes between the two more recent reviews and the older review. All three reviews found higher study quality to be associated with lower effect sizes, and when limited to high quality studies (based on established risk of bias measures), they were in accord in finding a nonsignificant effect on negative symptoms in favor of CBT.

Evidence assessing how individual versus group CBT effects outcomes was limited. One review<sup>79</sup> found individual CBT more effective than group CBT on negative symptom reduction, but Wykes<sup>309</sup> reported no difference in effectiveness between individual and group CBT directed at symptoms as the primary outcome. The reason for this disparity may be due to the focus of the CBT. The Velthorst review noted that of 30 included trials, only two had negative symptoms as the primary treatment target, whereas the Wykes review assessed the effect of individual and group CBT only on studies' primary treatment target.

## **Cognitive Remediation**

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,<sup>85</sup> and outcomes related to function and symptoms were commonly reported in trials of cognitive remediation. Our review found that cognitive remediation improved functional outcomes, overall symptoms and negative symptoms. Our findings on function and total symptoms are based on the 2011 Wykes review<sup>84</sup> that combined both passive and active control groups. This review was an update and expansion of an older review, which also found cognitive remediation had a positive effect on function and symptoms.<sup>314</sup> Our findings on negative symptoms are based on the Cella review<sup>85</sup> and limited to studies with a passive usual care control group. These 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 RCTs. Our findings are based on more than 39 trials included in two good-quality systematic reviews.<sup>295</sup>

## Family Interventions

Previous systematic reviews<sup>315</sup> and other reviews<sup>316</sup> and the 2009 PORT publication.<sup>295</sup> 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.<sup>315</sup> 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 psychoeducation<sup>316</sup> 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.<sup>317</sup> Similarly, we found the strongest evidence for interventions lasting seven to 12 months. In addition, we found that the number of sessions was more predictive of reduction in relapse than 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 others is that we excluded trials conducted in China as we are not confident that the findings from Chinese studies are applicable to a United States population. Two reviews have conducted sensitivity analyses removing Chinese studies and found pooled effect estimates were reduced when Chinese studies were excluded.<sup>91,318</sup>

## Social Skills Training

Our inclusion criteria were considerably stricter than those of other recent reviews<sup>293,294</sup> 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.<sup>293,294,319</sup> Our findings for relapse, another target of social skills training, were also consistent with other reviews<sup>293,319</sup> that found social skills training reduced relapse, although 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.<sup>293</sup> 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.<sup>295</sup> 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.<sup>295,320</sup> We found that supported employment, specifically the IPS 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 worked more hours, were employed longer, and earned more money than those receiving usual care. Because we found only one RCT that met our criteria for this review, we included other evidence; a review and a study that included other comparison

groups.<sup>106,108</sup> In using this evidence, our findings are similar to PORT and Marshall, with the exception that our SOE rating is moderate, while the Marshall rating is high. Our lower SOE 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 review<sup>106</sup> that we included in our evidence rated the evidence as very low quality (according to the Grading of Recommendations Assessment, Development and Evaluation [GRADE]<sup>321-327</sup> 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

### Key Question 1. Comparative Effectiveness of Pharmacological Treatments

The applicability of the evidence in this review is limited in part by the scope of the criteria we set (e.g., adults, outpatients, etc.), and the studies themselves. As a result the evidence in our report is applicable to the following:

- Populations: 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 newer drugs (those 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, with a wide range of dosing.
  - The evidence is less applicable to the newest SGAs (i.e., brexpiprazole, cariprazine, iloperidone, lurasidone, and the newest 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: The evidence is less applicable to long-term effectiveness 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, 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 3 years).
- Setting: For SGAs versus each other, the evidence only applies to outpatients, whereas in the systematic review we included on FGAs versus SGAs almost half of the studies were in inpatients.

## **Key Question 2. Psychosocial and Other Nonpharmacological Interventions Versus Usual Care**

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. We also applied sample size, duration, country, and comparison group (usual care) limits. As a result the evidence in our report is applicable to the following:

- Populations: Adults; age range 16 to 80 (teens to older adults), mostly with a diagnosis of schizophrenia or related disorder. The specific characteristics of patients varied somewhat by intervention category, for example:
  - Evidence on supportive therapy is most applicable to middle aged men with schizophrenia and related diseases, who were experiencing long-standing hallucinations and/or delusions.
  - Evidence on assertive community treatment is most applicable to patients with a history of severe mental illness and frequent hospitalizations over the past 2 to 5 years (e.g., 2 to 5 instances).
  - The evidence is not clearly applicable to patients with treatment resistance, or multiple comorbidities. Across the interventions, the severity of the disease of the patients included in the studies is unclear.
- Interventions/Comparisons: The evidence in this review, by prespecified design, applies to comparisons with usual care, and the 13 intervention categories identified here. The purpose was not to evaluate head-to-head comparisons of active interventions to each other.
  - Interventions were poorly defined or described for some intervention categories, such as family interventions and supportive therapy, seriously limiting the generalizability.
  - Similarly, what was considered usual care and what specific interventions or services patients received as part of usual care was infrequently described. As a result, the evidence is less applicable to variations in level or quality of these interventions, or emerging interventions.
  - The evidence is not applicable to comparative effectiveness questions and the review findings apply only to comparisons with usual care. The evidence may apply to other comparisons, as our analysis of evidence for supported employment indicated little difference in findings or conclusions between usual care and active control-group evidence.
- 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.
- Timing: Most of the interventions do not have evidence that is applicable to long-term followup (greater than 3 years).
- Setting: The settings were mostly applicable to the United States, as evidence clearly not applicable was excluded from our review.
- Although applicability is separate from the strength of the evidence, the overall SOE does impact why applicability of the included studies may be limited. Importantly, the

heterogeneity of interventions and treatment effects, including both clinical and methodological heterogeneity, detracts from the overall applicability of the findings.

## **Implications for Clinical and Policy Decisionmaking**

Our findings have implications for clinical and policy decisionmaking. The American Psychiatric Association's (APA's) most recent guideline for treating adults with schizophrenia was published in 2004,<sup>328</sup> with a focused update in 2009.<sup>329</sup> Also from 2009, are the Schizophrenia PORT recommendations for psychosocial treatments for individuals with schizophrenia.<sup>295</sup> Since these publications, important developments have occurred both in the pharmacological and nonpharmacological treatment interventions for schizophrenia. There are five new antipsychotics and five new LAI formulations approved in the United States since the 2009 APA guideline update. Similarly, many psychosocial and other nonpharmacological treatments have been developed, refined or expanded in recent years.<sup>295,329,330</sup> Given the ever-evolving nature of schizophrenia treatments and their potential for meaningful benefits and significant harms, this review will allow the APA to update their guideline, and for clinicians and patients to have a single source to access up-to-date evidence synthesis. Similarly, the review may allow policymakers to use the evidence in making decisions, depending on their priorities.

## **Limitations of the Systematic Review Process**

As with other types of research, the limitations of this systematic review are important to recognize. The generalizability of the results is limited by the scope of the review, based on the inclusion criteria, which determines the studies included and the specific methodology we applied to the review process. In terms of the review process, potential limitations are that we limited inclusion to studies with at least an abstract published in English (i.e., publications not available in an English form were not included) and had limitations on the number of databases we searched (Ovid MEDLINE<sup>®</sup>, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and PsycINFO<sup>®</sup>). As we were limiting the study characteristics to those relevant to a United States setting, and because we reviewed English-language abstracts of studies whose full publication was in another language, we feel that the risk of this limitation is low. We have found that searching these key databases has been adequate, and in this case we also have the advantage of using systematic reviews in our review that had access to other sources to search for literature, and also depend on the scientific information packet (SIP) process and involvement of our Technical Expert Panel (TEP) to help identify any missing literature.

With respect to the limitations of the scope identified a priori for this review, there are several potential limitations. For pharmacologic interventions, the scope of this review is on direct, head-to-head comparisons of the drugs and did not evaluate comparisons to placebo, no treatment or older antipsychotic drugs. This may have introduced some biases or gaps in the conclusions particularly for newer drugs that have minimal or no comparative evidence.

For psychosocial interventions, due to the large volume and heterogeneous nature of studies, we made inclusion decisions to narrow the scope to the most commonly used interventions and to the most common control (usual care). These scope restrictions were made based on the evidence available and consultation with experts and were intended to allow us to review the most pertinent evidence as in-depth as possible, within the given time frame and budget. Clearly they could have impacted some of the findings and conclusions. We excluded, for example, assisted outpatient treatment (also known as outpatient commitment therapy and compulsory

community treatment orders), because our clinical expert advisors felt these were mechanisms to get patients into treatment, rather than a treatment themselves. There is a review of these and other interventions aimed at reducing hospitalization in patients with serious mental illness.<sup>331</sup>

For both key questions, we limited our review to RCTs with a followup of at least 12 weeks, and for Key Question 2 we also required a patient population of at least 50 participants. For Key Question 2 on psychosocial interventions, these criteria resulted in excluding 35 trials (Figure 3). Limiting to usual care controls resulted in excluding 74 studies (compared with 271 studies included with usual care controls). These were primarily comparisons to other competing interventions (i.e. head to head comparisons) and comparisons of different intensities of the same intervention. In reviewing our findings in comparison with findings of reviews including active comparators, however, we did not find strong differences in direction or magnitude of effect. For example, our own findings on supported employment were consistent between usual care and the active comparator of pre-vocational training.

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, and as a result outcomes such as positive symptoms, rehospitalization and cognitive outcomes were generally not included in our review. For Key Question 2, we ultimately excluded 96 studies because no included outcome was reported. Rehospitalization was excluded because there is important variation in the indications for and length of psychiatric hospitalizations across time, in different localities, and with different financial contexts, and there is important variation across trials in how rehospitalization is measured/evaluated, which may confound study interpretation. However, it should be noted that other outcomes may also suffer from similar issues. For example, employment may be influenced by local economic conditions, and outcomes related to interactions with law enforcement can also vary over time and by location. Most of the psychosocial interventions have target patient-outcome pairs, for example family interventions were targeted at patients with a history of, or at high risk of, frequent relapses. These targeted outcomes were generally included in our list of included outcomes, but were not prioritized on an intervention-by-intervention basis. In the example of family interventions, the target outcome of relapse prevention is outcome number seven in priority order. Certainly some highly prioritized, and patient-important, outcomes such as function and quality of life (outcomes number one and two in priority order) were not the target of most interventions and may not be greatly improved by these interventions. However, across the interventions, it is important to consider the evidence for both of these highly prioritized outcomes, as well as the targeted outcomes.

A final potential limitation is that we considered any intervention for schizophrenia without explicit consideration of the patient characteristics that the intervention focuses on. Because several interventions have a specific population and outcome focus, this may have limited our ability to determine for whom each intervention is best.

## **Limitations of the Evidence Base**

For the pharmacological interventions, the limitations of the evidence base are fairly clear; there are few studies of the newer SGAs, few studies reporting the most important outcomes (i.e., function and quality of life), inadequate information on key subgroups such as older patients and those with multiple or serious comorbidities, and patients with severe illness, including treatment-resistance, clearly separated out. Study quality was not a key limitation, but

funding source may have been, given that over 80 percent of studies were funded by the manufacturer of one of the drugs in the trial.

Other issues making it more difficult to draw firm conclusions were the variability in which drugs compared across studies, outcomes reported and how they are measured, and of course, variability in patient characteristics, that are often poorly reported on. Consensus is needed regarding outcomes and measures used to assess outcomes; for example the primary outcome measure in the CATIE trials, which was well publicized as to how and why it was selected, was not given high priority by our TEP. Although many of the older studies suffered from problems with generalizability to the real-life practice setting because either they used doses that were higher or lower than those used in practice today or made unfair dose-comparisons (e.g., low dose of one drug versus high dose of a comparator drug); our analysis of these issues as part of our network analyses indicates that more recent studies have fewer issues with dosing. In the drug comparisons, an important limitation is the change in dosing over time, particularly with lower doses in more recent studies for several older drugs, and the prior treatment experience of patients enrolled (fewer patients with prior FGA exposure or resistance in more recent studies). The systematic review we included on this comparison attempted multiple sensitivity analyses to explore these issues, but no clear conclusions were drawn.

Although we excluded individual RCTs that enrolled inpatient populations, we included systematic reviews that included some studies conducted in inpatients. A few reviews conducted sensitivity analysis and found similar results regardless of setting.

Limitations for studies of psychosocial and nonpharmacological interventions included problems with reporting definitions of interventions and usual care groups, poor description of treatment versus followup periods, and variability in outcome reporting and methodological issues relating to small sample sizes, lack of power calculations, blinding of outcome assessors, post-treatment followup, and inadequate handling of missing data.

Many interventions were not clearly defined or described in the manuscripts and therefore difficult to categorize. In many studies the exact period of the intervention was unclear. Some reported a specific number of sessions but not the duration in weeks or months, while reporting outcomes at a specific time (e.g., 6 months). This was apparent in the CBT and family intervention studies, for example. There was also considerable variation in which how outcomes are reported, even when the same outcome measure was used. This was particularly true for symptom, functional and other outcomes measured using continuous scale scores. In many studies, there were small but significant improvements in scale scores with use of psychosocial interventions, but the clinical importance of these changes is largely unclear. This is an important limitation and is also related to the previous point about method of outcome reporting and to the small sample sizes in the majority of studies. For example, for those scales with known thresholds for clinical significance, we could not adequately assess if the threshold for clinical significance has been met if a study only reported effect size. For this review, the outcome of treatment discontinuation was included as a high priority outcome, but it was difficult to operationalize, and unclear what the meaning was for some interventions. In terms of study participant dropout, while only about a quarter of studies had rates higher than 30 percent, approximately 40 percent either did not conduct, or were unclear on conducting, an intention to treat analysis.

Few studies of psychosocial interventions reported on the effects of treatment after treatment cessation, while none of the included studies of antipsychotic drugs did so. For those studies that did report posttreatment followup, there tended to be a loss of effect after treatment withdrawal,

but this evidence is insufficient to draw conclusions. Evidence to inform the best duration or schedule of treatment is not available for either category of intervention. For many intervention–outcome pairs, evidence was too limited to draw conclusions about the effect of treatment, resulting in insufficient SOE (Appendix H). For both key questions, evidence on subgroups is limited by sample sizes and that most are post hoc subgroup analyses of trials rather than either preplanned analyses or trials designed to address these questions as the primary objective.

## Research Recommendations

Based on the gaps and limitations identified in this review, we recommend the following future research on comparative effectiveness of pharmacological interventions and general effectiveness of psychosocial and other nonpharmacological interventions. In general, these recommendations are for RCTs.

### Pharmacological Interventions Versus Each Other

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 direct, objective 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.
- Clearly inpatients need to be studied separately from outpatients, but future reviews should evaluate treatments for inpatients.

### Psychosocial and Other Nonpharmacological Interventions Versus Usual Care

Issues may vary by the specific intervention, but there are several key recommendations that are relevant to all of the interventions:

- 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<sup>332</sup>.
- 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 Criteria 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 the intensity and duration of the intervention required to achieve the best results.
- Additional, well-designed long-term studies are needed. The long-term benefits versus risks and costs of treatments remain unclear, in particular for individuals whose illness is resistant or only partially responsive to treatment.
- Future systematic review research should:
  - Include other nonpharmacological treatments, such as device-based somatic treatments (e.g., electroconvulsive therapy and transcranial magnetic stimulation).
  - Include an evaluation of comparative effectiveness of psychosocial interventions compared with each other.
  - Incorporate the concepts of complex interventions into the methods for reviewing the evidence for some of the psychosocial interventions.<sup>333,334</sup>
  - 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 SGA 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 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 first episode psychosis. Relapse was reduced with psychoeducation, illness self-management, family interventions, and early team-based multi-component treatment programs for first episode psychosis. Self harm, response and/or remission, and adverse events were rarely reported.

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# Abbreviations

<b>Abbreviation</b>	<b>Definition</b>
ACT	assertive community treatment
AHRQ	Agency for Healthcare Research & Quality
APA	American Psychiatric Association
BPRS	Brief Psychiatric Rating Scale
CAT	cognitive adaption training
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CBT	cognitive behavioral therapy
CGI	Clinical Global Impression Scale
CGI-I	Clinical Global Impression – Improvement scale
CGI-S	Clinical Global Impression – Severity scale
CGI-SS	Clinical Global Impression of severity –Suicidality Scale
CI	confidence interval
CPRS	Comprehensive Psychopathology Rating Scale
DACT	Dartmouth Assertive Community Treatment Scale
DERP	Drug Effectiveness Review Project
df	degrees of freedom
DSM	American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders
DSM-III	American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders, version 3
DSM-IV	American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders, version 4
DSM-5	American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders, version 5
EHC	Effective Health Care
EPC	Evidence-based Practice Center
EPS	extrapyramidal symptoms
EQ-5D	EuroQol five dimensions questionnaire
ER	extended release
FDA	U.S. Food and Drug Administration
FEP	first-episode psychosis
FGA	first-generation antipsychotic
GAF	Global Assessment of Functioning
GAF-M	Global Assessment of Functioning – Modified version
GAS	Global Assessment Scale
GHQ	Global Health Questionnaire
HAM-D	Hamilton Depression Scale
HDI	United Nations International Human Development Index
HR	hazard ratio
ICM	intensive case management
ILSS	Independent Living Skills Survey
IPS	individual placement and support
IR	immediate release
KQ	key question
LAI	long-acting injectable
LSM	least squares mean
MADRS	Montgomery-Asberg Depression Scale
MCAS	The Multnomah Community Ability Scale
MD	mean difference
N	Number
NNT	number needed to treat
ODT	oral dissolving tablet
OR	odds ratio
PACT	Program of Assertive Community Treatment
PANSS	Positive and Negative Syndrome Scale
PEAT	Penn Emotional Acuity Test
PICOT	population, intervention, comparison, outcomes, timing
PSP	Personal and Social Performance Scale
QLS	Heinrich Carpenter Quality of Life Scale
QOLI	Subjective Quaiity of Life

<b>Abbreviation</b>	<b>Definition</b>
RCT	randomized controlled trial
RFS	Role Functioning Scale
RR	relative risk
RSES	Rosenberg Self-Esteem Scale
SAS	Social Adjustment Scale – Severely Mentally Ill version
SADS-C +PD	Schedule for Affective Disorders and Schizophrenia – Change Version with psychosis and disorganization
SANS	Scale for Assessment of Negative Symptoms
SAPS	Scale for the Assessment of Positive Symptoms
SF-12	12-Item Short Form Health Survey
SFS	Social Function Scale
SGA	Second-generation antipsychotic
SIP	Scientific Information Packet
SMD	standardized mean difference
SOE	strength of evidence
SOFAS	Social and Occupational Functioning Assessment Scale
SOHO	Schizophrenia Outpatient Health Outcome
SQLS-R4	Schizophrenia Quality of Life Scale – Revision 4
SR	systematic review
SSPA	Social Skills Performance Assessment
SUD	substance use disorder
TEP	Technical Expert Panel
UPSA-B	San Diego Performance Based Skills Assessment - Brief
VPRS	Seven point verbal rating scale
vs.	Versus
WBI	Work Behavior Inventory
WBS	Well-being Scale
WMD	weighted mean difference

# Appendix A. Search Strategies

## Key Question 1

### FGA Versus SGA

#### Database: Ovid MEDLINE

- 1 exp Schizophrenia/dt [Drug Therapy]
- 2 (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Risperidone or Ziprasidone).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
- 3 (Fluphenazine or Haloperidol or Perphenazine).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
- 4 1 and 2 and 3
- 5 limit 4 to english language
- 6 limit 5 to (meta analysis or systematic reviews)
- 7 limit 5 to randomized controlled trial
- 8 limit 5 to controlled clinical trial
- 9 6 or 7 or 8
- 10 (201\* not 2010\*).ed,dp.
- 11 9 and 10

#### Database: EBM Reviews - Cochrane Database of Systematic Reviews

- 1 schizophren\*.mp. [mp=title, abstract, full text, keywords, caption text]
- 2 (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Risperidone or Ziprasidone).mp. [mp=title, abstract, full text, keywords, caption text]
- 3 (Fluphenazine or Haloperidol or Perphenazine).mp. [mp=title, abstract, full text, keywords, caption text]
- 4 1 and 2 and 3
- 5 limit 4 to yr="2011 -Current"

#### Database: EBM Reviews - Cochrane Central Register of Controlled Trials

- 1 schizophren\*.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
- 2 (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Risperidone or Ziprasidone).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
- 3 (Fluphenazine or Haloperidol or Perphenazine).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
- 4 1 and 2 and 3
- 5 limit 4 to yr="2011 -Current"

#### Database: PsycINFO

- 1 exp Schizophrenia/
- 2 (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Risperidone or Ziprasidone).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
- 3 (Fluphenazine or Haloperidol or Perphenazine).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
- 4 1 and 2 and 3
- 5 limit 4 to english language
- 6 limit 5 to systematic reviews
- 7 limit 5 to "2000 treatment outcome/clinical trial"
- 8 random\*.mp.

9 (clinical\* adj5 (trial\* or study or protocol\*)).mp.  
10 8 and 9  
11 ((random\* or control\*) adj5 (trial\* or study or protocol\*)).mp.  
12 5 and 10  
13 5 and 11  
14 6 or 7 or 12 or 13  
15 (201\* not 2010\*).dp,up.  
16 14 and 15

## SGA Versus SGA

### Database: Ovid MEDLINE

1 exp Schizophrenia/dt [Drug Therapy]

2 ((compar\* or contrast\* or evaluat\* or analy\* or measur\* or quanti\* or judg\*) adj7 (((second or 2nd) adj2 generation) or atypical\*) adj3 (antipsychotic\* or anti-psychotic\*)).mp.

3 (Aripiprazole and (Asenapine or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Risperidone or Ziprasidone)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

4 (Asenapine and (Aripiprazole or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Risperidone or Ziprasidone)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

5 (Brexpiprazole and (Aripiprazole or Asenapine or Cariprazine or Clozapine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Risperidone or Ziprasidone)).mp.

6 (Cariprazine and (Aripiprazole or Asenapine or Brexpiprazole or Clozapine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Risperidone or Ziprasidone)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

7 (Clozapine and (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Risperidone or Ziprasidone)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

8 (Iloperidone and (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Clozapine or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Risperidone or Ziprasidone)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

9 (Lurasidone and (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Olanzapine or Paliperidone or Quetiapine or Risperidone or Ziprasidone)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

10 (Olanzapine and (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Lurasidone or Paliperidone or Quetiapine or Risperidone or Ziprasidone)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

11 (Paliperidone and (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Lurasidone or Olanzapine or Quetiapine or Risperidone or Ziprasidone)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

12 (Quetiapine and (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Risperidone or Ziprasidone)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

13 (Risperidone and (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Ziprasidone)).mp. [mp=title, abstract, original title, name

of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]  
 14 (Ziprasidone and (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Risperidone)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]  
 15 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14  
 16 1 and 15  
 17 limit 16 to english language  
 18 limit 17 to systematic reviews  
 19 limit 17 to randomized controlled trial  
 20 limit 17 to controlled clinical trial  
 21 18 or 19 or 20  
 22 (2013\* or 2014\* or 2015\* or 2016\*).ed,dp.  
 23 21 and 22

**Database: EBM Reviews - Cochrane Database of Systematic Reviews**

1 Schizophren\*.mp. [mp=title, abstract, full text, keywords, caption text]  
 2 ((compar\* or contrast\* or evaluat\* or analy\* or measur\* or quanti\* or judg\*) adj7 (((second or 2nd) adj2 generation) or atypical\*) adj3 (antipsychotic\* or anti-psychotic\*)).mp.  
 3 (Aripiprazole and (Asenapine or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Risperidone or Ziprasidone)).mp. [mp=title, abstract, full text, keywords, caption text]  
 4 (Asenapine and (Aripiprazole or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Risperidone or Ziprasidone)).mp. [mp=title, abstract, full text, keywords, caption text]  
 5 (Brexpiprazole and (Aripiprazole or Asenapine or Cariprazine or Clozapine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Risperidone or Ziprasidone)).mp.  
 6 (Cariprazine and (Aripiprazole or Asenapine or Brexpiprazole or Clozapine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Risperidone or Ziprasidone)).mp. [mp=title, abstract, full text, keywords, caption text]  
 7 (Clozapine and (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Risperidone or Ziprasidone)).mp. [mp=title, abstract, full text, keywords, caption text]  
 8 (Iloperidone and (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Clozapine or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Risperidone or Ziprasidone)).mp. [mp=title, abstract, full text, keywords, caption text]  
 9 (Lurasidone and (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Olanzapine or Paliperidone or Quetiapine or Risperidone or Ziprasidone)).mp. [mp=title, abstract, full text, keywords, caption text]  
 10 (Olanzapine and (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Lurasidone or Paliperidone or Quetiapine or Risperidone or Ziprasidone)).mp. [mp=title, abstract, full text, keywords, caption text]  
 11 (Paliperidone and (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Lurasidone or Olanzapine or Quetiapine or Risperidone or Ziprasidone)).mp. [mp=title, abstract, full text, keywords, caption text]  
 12 (Quetiapine and (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Risperidone or Ziprasidone)).mp. [mp=title, abstract, full text, keywords, caption text]  
 13 (Risperidone and (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Ziprasidone)).mp. [mp=title, abstract, full text, keywords, caption text]  
 14 (Ziprasidone and (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Risperidone)).mp. [mp=title, abstract, full text, keywords, caption text]  
 15 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14

16 1 and 15  
17 limit 16 to english language [Limit not valid; records were retained]  
18 (2013\* or 2014\* or 2015\* or 2016\*).up.  
19 17 and 18

**Database: EBM Reviews - Cochrane Central Register of Controlled Trials**

1 Schizophren\*.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
2 ((compar\* or contrast\* or evaluat\* or analy\* or measur\* or quanti\* or judg\*) adj7 (((second or 2nd) adj2 generation) or atypical\*) adj3 (antipsychotic\* or anti-psychotic\*)).mp.  
3 (Aripiprazole and (Asenapine or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Risperidone or Ziprasidone)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
4 (Asenapine and (Aripiprazole or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Risperidone or Ziprasidone)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
5 (Brexpiprazole and (Aripiprazole or Asenapine or Cariprazine or Clozapine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Risperidone or Ziprasidone)).mp.  
6 (Cariprazine and (Aripiprazole or Asenapine or Brexpiprazole or Clozapine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Risperidone or Ziprasidone)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
7 (Clozapine and (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Risperidone or Ziprasidone)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
8 (Iloperidone and (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Clozapine or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Risperidone or Ziprasidone)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
9 (Lurasidone and (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Olanzapine or Paliperidone or Quetiapine or Risperidone or Ziprasidone)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
10 (Olanzapine and (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Lurasidone or Paliperidone or Quetiapine or Risperidone or Ziprasidone)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
11 (Paliperidone and (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Lurasidone or Olanzapine or Quetiapine or Risperidone or Ziprasidone)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
12 (Quetiapine and (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Risperidone or Ziprasidone)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
13 (Risperidone and (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Ziprasidone)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
14 (Ziprasidone and (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Risperidone)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
15 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14  
16 1 and 15  
17 limit 16 to english language  
18 (2013\* or 2014\* or 2015\* or 2016\*).up.  
19 17 and 18

**Database: PsycINFO**

1 exp Schizophrenia/  
2 ((compar\* or contrast\* or evaluat\* or analy\* or measur\* or quanti\* or judg\*) adj7 (((second or 2nd) adj2 generation) or atypical\*) adj3 (antipsychotic\* or anti-psychotic\*)).mp.

3 (Aripiprazole and (Asenapine or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Risperidone or Ziprasidone)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

4 (Asenapine and (Aripiprazole or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Risperidone or Ziprasidone)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

5 (Brexpiprazole and (Aripiprazole or Asenapine or Cariprazine or Clozapine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Risperidone or Ziprasidone)).mp.

6 (Cariprazine and (Aripiprazole or Asenapine or Brexpiprazole or Clozapine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Risperidone or Ziprasidone)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

7 (Clozapine and (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Risperidone or Ziprasidone)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

8 (Iloperidone and (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Clozapine or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Risperidone or Ziprasidone)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

9 (Lurasidone and (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Olanzapine or Paliperidone or Quetiapine or Risperidone or Ziprasidone)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

10 (Olanzapine and (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Lurasidone or Paliperidone or Quetiapine or Risperidone or Ziprasidone)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

11 (Paliperidone and (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Lurasidone or Olanzapine or Quetiapine or Risperidone or Ziprasidone)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

12 (Quetiapine and (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Risperidone or Ziprasidone)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

13 (Risperidone and (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Ziprasidone)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

14 (Ziprasidone and (Aripiprazole or Asenapine or Brexpiprazole or Cariprazine or Clozapine or Iloperidone or Lurasidone or Olanzapine or Paliperidone or Quetiapine or Risperidone)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

15 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14

16 1 and 15

17 limit 16 to english language

18 limit 17 to systematic reviews

19 limit 17 to "2000 treatment outcome/clinical trial"

20 random\*.mp.

21 17 and 20

22 ((random\* or control\*) adj5 (trial\* or study or protocol\*)).mp.

23 17 and 22

24 (clinical\* adj5 (trial\* or study or protocol\*)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

25 21 and 24

26 18 or 19 or 23 or 25

27 (2013\* or 2014\* or 2015\* or 2016\*).up,dp.

28 26 and 27

## Key Question 2

### Broad Search

**Database: Ovid MEDLINE(R)**

- 1 \*Schizophrenia/th [Therapy]
- 2 limit 1 to english language
- 3 limit 2 to (clinical trial or controlled clinical trial or randomized controlled trial)
- 4 limit 2 to (meta analysis or systematic reviews)
- 5 3 or 4

**Database: Ovid MEDLINE(R) without Revisions**

- 1 \*Schizophrenia/rh [Rehabilitation]
- 2 limit 1 to english language
- 3 limit 2 to (clinical trial or controlled clinical trial or randomized controlled trial)
- 4 limit 2 to (meta analysis or systematic reviews)
- 5 3 or 4

**Database: EBM Reviews - Cochrane Central Register of Controlled Trials**

- 1 \*Schizophrenia/th [Therapy]
- 2 Schizophrenia/
- 3 schizophrenia.ti,ab.
- 4 (non-pharmacolog\* or nonpharmacolog\* or psychosocial or psycho-social).mp.
- 5 (2 or 3) and 4
- 6 1 or 5
- 7 limit 6 to english language

**Database: PsycINFO**

- 1 Schizophrenia/
- 2 schizophrenia.ti,ab.
- 3 (non-pharmacolog\* or nonpharmacolog\* or psychosocial or psycho-social).mp.
- 4 (1 or 2) and 3
- 5 ((systematic\* adj3 (review\* or overview\*)) or (methodologic\* adj3 (review\* or overview\*))).ti,ab.
- 6 (meta-analy\* or metaanaly\* or systematic review\*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
- 7 4 and (5 or 6)

**Database: PsycINFO**

- 1 Schizophrenia/
- 2 schizophrenia.ti,ab.
- 3 (non-pharmacolog\* or nonpharmacolog\* or psychosocial or psycho-social).mp.
- 4 (1 or 2) and 3
- 5 ("randomi\*ed controlled trial" or "RCT").mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
- 6 ((random\* or control\*) adj5 (trial or study)).mp.
- 7 4 and (5 or 6)
- 8 limit 7 to english language

**Database: ClinicalTrials.gov**

NOT NOTEXT [FIRST-RECEIVED-RESULTS-DATE] AND EXACT "Interventional" [STUDY-TYPES] AND ( Schizophrenia OR Schizoaffective Disorder ) [DISEASE] AND Behavioral [TREATMENT] AND EXACT Adult [AGE-GROUP]

## Narrow Search

**Database: Ovid MEDLINE(R)**

- 1 exp schizophrenia/
- 2 exp Community Mental Health Services/
- 3 1 and 2

4 exp Cognitive Therapy/  
 5 1 and 4  
 6 (Cognit\* adj5 Remediat\*).mp.  
 7 1 and 6  
 8 exp Family Therapy/  
 9 (((family or families) adj5 psychoeducat\*) or ((family or families) adj3 (therap\* or counsel\*))).mp.  
 10 8 or 9  
 11 1 and 10  
 12 exp Peer Group/  
 13 1 and 12  
 14 (peer\* adj5 (support\* or group\*)).mp.  
 15 1 and 14  
 16 (Intensiv\* adj3 ((case or cases) adj3 manag\*)).mp.  
 17 1 and 16  
 18 exp Case Management/  
 19 1 and 18  
 20 Skills Training.mp.  
 21 ((skill\* or job or jobs or employment or vocation\*) adj5 train\*).mp.  
 22 1 and 21  
 23 exp Employment, Supported/  
 24 ((support\* or subsidiz\*) adj2 educat\*).mp.  
 25 exp Rehabilitation, Vocational/  
 26 exp Sheltered Workshops/  
 27 23 or 24 or 25 or 26  
 28 1 and 27  
 29 exp residential facilities/  
 30 ((support\* or subsidiz\*) adj2 hous\*).mp.  
 31 29 or 30  
 32 1 and 31  
 33 ("Illness Management and Recovery" or IMR) adj3 (toolkit\* or tool kit\*).mp.  
 34 1 and 33  
 35 3 or 5 or 7 or 11 or 13 or 15 or 17 or 19 or 22 or 28 or 32 or 34  
 36 limit 35 to english language  
 37 limit 36 to systematic reviews  
 38 limit 36 to randomized controlled trial  
 39 limit 36 to controlled clinical trial  
 40 37 or 38 or 39  
 41 limit 40 to yr="1902 - 1995"

**Database: Ovid MEDLINE(R) without Revisions**

1 exp schizophrenia/  
 2 exp Community Mental Health Services/  
 3 1 and 2  
 4 exp Cognitive Therapy/  
 5 1 and 4  
 6 (Cognit\* adj5 Remediat\*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]  
 7 1 and 6  
 8 exp Family Therapy/  
 9 (((family or families) adj5 psychoeducat\*) or ((family or families) adj3 (therap\* or counsel\*))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]  
 10 8 or 9  
 11 1 and 10  
 12 exp Peer Group/

13 1 and 12  
 14 (peer\* adj5 (support\* or group\*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]  
 15 1 and 14  
 16 (Intensiv\* adj3 ((case or cases) adj3 manag\*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]  
 17 1 and 16  
 18 exp Case Management/  
 19 1 and 18  
 20 Skills Training.mp.  
 21 ((skill\* or job or jobs or employment or vocation\*) adj5 train\*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]  
 22 1 and 21  
 23 exp Employment, Supported/  
 24 ((support\* or subsidiz\*) adj2 educat\*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]  
 25 exp Rehabilitation, Vocational/  
 26 exp Sheltered Workshops/  
 27 23 or 24 or 25 or 26  
 28 1 and 27  
 29 exp residential facilities/  
 30 ((support\* or subsidiz\*) adj2 hous\*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]  
 31 29 or 30  
 32 1 and 31  
 33 ("Illness Management and Recovery" or IMR) adj3 (toolkit\* or tool kit\*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]  
 34 1 and 33  
 35 3 or 5 or 7 or 11 or 13 or 15 or 17 or 19 or 22 or 28 or 32 or 34  
 36 limit 35 to english  
 37 limit 36 to systematic reviews  
 38 limit 36 to randomized controlled trial  
 39 limit 36 to controlled clinical trial  
 40 37 or 38 or 39

**Database: EBM Reviews - Cochrane Database of Systematic Reviews**

1 schizophren\*.mp. [mp=title, abstract, full text, keywords, caption text]  
 2 (Communit\* adj7 (mental\* or psych\*) adj5 (health\* or servic\* or clinic\*)).mp. [mp=title, abstract, full text, keywords, caption text]  
 3 1 and 2  
 4 (Cognit\* adj3 (therap\* or treat\*)).mp. [mp=title, abstract, full text, keywords, caption text]  
 5 1 and 4  
 6 (Cognit\* adj5 Remediat\*).mp. [mp=title, abstract, full text, keywords, caption text]  
 7 1 and 6  
 8 (((family or families) adj5 psychoeducat\*) or ((family or families) adj3 (therap\* or counsel\*))).mp. [mp=title, abstract, full text, keywords, caption text]  
 9 1 and 8  
 10 (peer\* adj5 (support\* or group\* or interact\* or relation\*)).mp. [mp=title, abstract, full text, keywords, caption text]  
 11 1 and 10

12 (Intensiv\* adj3 ((case or cases) adj3 manag\*)).mp. [mp=title, abstract, full text, keywords, caption text]  
13 1 and 12  
14 (case\* adj2 manag\*).mp. [mp=title, abstract, full text, keywords, caption text]  
15 1 and 14  
16 ((skill\* or job or jobs or employment or vocation\*) adj5 train\*).mp. [mp=title, abstract, full text, keywords, caption text]  
17 1 and 16  
18 (support\* adj3 (employ\* or job\* or occupation\* or workplac\* or vocation\*)).mp. [mp=title, abstract, full text, keywords, caption text]  
19 ((support\* or subsidiz\*) adj2 educat\*).mp. [mp=title, abstract, full text, keywords, caption text]  
20 (rehab\* adj3 (vocational\* or occupation\* or workplac\* or employment)).mp. [mp=title, abstract, full text, keywords, caption text]  
21 (shelter\* adj3 (Workshop\* or workplac\*)).mp. [mp=title, abstract, full text, keywords, caption text]  
22 18 or 19 or 20 or 21  
23 1 and 22  
24 ((support\* or subsidiz\*) adj2 hous\*).mp. [mp=title, abstract, full text, keywords, caption text]  
25 1 and 24  
26 ("Illness Management and Recovery" or IMR) adj3 (toolkit\* or tool kit\*).mp. [mp=title, abstract, full text, keywords, caption text]  
27 1 and 26  
28 3 or 5 or 7 or 9 or 11 or 13 or 15 or 17 or 23 or 25 or 27  
29 limit 28 to English

#### **Database: EBM Reviews - Cochrane Central Register of Controlled Trials**

1 schizophren\*.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
2 (Communit\* adj7 (mental\* or psych\*) adj5 (health\* or servic\* or clinic\*)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
3 1 and 2  
4 (Cognit\* adj3 (therap\* or treat\* or train\* or interven\*)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
5 1 and 4  
6 (Cognit\* adj5 Remediat\*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
7 1 and 6  
8 (((family or families) adj5 psychoeducat\*) or ((family or families) adj3 (therap\* or counsel\*))).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
9 1 and 8  
10 (peer\* adj5 (support\* or group\* or interact\* or relation\*)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
11 1 and 10  
12 (Intensiv\* adj3 ((case or cases) adj3 manag\*)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
13 1 and 12  
14 (case\* adj2 manag\*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
15 1 and 14  
16 ((skill\* or job or jobs or employment or vocation\*) adj5 train\*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
17 1 and 16  
18 (support\* adj3 (employ\* or job\* or occupation\* or workplac\* or vocation\*)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
19 ((support\* or subsidiz\*) adj2 educat\*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
20 (rehab\* adj3 (vocational\* or occupation\* or workplac\* or employment)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
21 (shelter\* adj3 (Workshop\* or workplac\*)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
22 18 or 19 or 20 or 21

23 1 and 22  
 24 ((support\* or subsidiz\*) adj2 hous\*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
 25 1 and 24  
 26 ("Illness Management and Recovery" or IMR) adj3 (toolkit\* or tool kit\*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
 27 1 and 26  
 28 3 or 5 or 7 or 9 or 11 or 13 or 15 or 17 or 23 or 25 or 27  
 29 limit 28 to english  
 30 limit 29 to yr="2011 -Current"  
 31 limit 29 to yr="1898 - 2010"

**Database: EBM Reviews - Cochrane Central Register of Controlled Trials**

1 schizophren\*.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
 2 (Communit\* adj7 (mental\* or psych\*) adj5 (health\* or servic\* or clinic\*)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
 3 1 and 2  
 4 (Cognit\* adj3 (therap\* or treat\* or train\* or interven\*)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
 5 1 and 4  
 6 (Cognit\* adj5 Remediat\*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
 7 1 and 6  
 8 (((family or families) adj5 psychoeducat\*) or ((family or families) adj3 (therap\* or counsel\*))).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
 9 1 and 8  
 10 (peer\* adj5 (support\* or group\* or interact\* or relation\*)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
 11 1 and 10  
 12 (Intensiv\* adj3 ((case or cases) adj3 manag\*)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
 13 1 and 12  
 14 (case\* adj2 manag\*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
 15 1 and 14  
 16 ((skill\* or job or jobs or employment or vocation\*) adj5 train\*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
 17 1 and 16  
 18 (support\* adj3 (employ\* or job\* or occupation\* or workplac\* or vocation\*)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
 19 ((support\* or subsidiz\*) adj2 educat\*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
 20 (rehab\* adj3 (vocational\* or occupation\* or workplac\* or employment)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
 21 (shelter\* adj3 (Workshop\* or workplac\*)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
 22 18 or 19 or 20 or 21  
 23 1 and 22  
 24 ((support\* or subsidiz\*) adj2 hous\*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
 25 1 and 24  
 26 ("Illness Management and Recovery" or IMR) adj3 (toolkit\* or tool kit\*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]  
 27 1 and 26  
 28 3 or 5 or 7 or 9 or 11 or 13 or 15 or 17 or 23 or 25 or 27  
 29 limit 28 to english  
 30 limit 29 to yr="2011 -Current"  
 31 limit 29 to yr="1898 - 2010"

**Database: PsycINFO**

1 exp schizophrenia/  
2 exp Community Mental Health Services/  
3 1 and 2  
4 exp Cognitive Therapy/  
5 1 and 4  
6 (Cognit\* adj5 Remediat\*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]  
7 1 and 6  
8 exp Family Therapy/  
9 (((family or families) adj5 psychoeducat\*) or ((family or families) adj3 (therap\* or counsel\*))).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]  
10 8 or 9  
11 1 and 10  
12 exp Peer Group/  
13 1 and 12  
14 (peer\* adj5 (support\* or group\*)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]  
15 1 and 14  
16 (Intensiv\* adj3 ((case or cases) adj3 manag\*)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]  
17 1 and 16  
18 exp Case Management/  
19 1 and 18  
20 Skills Training.mp.  
21 ((skill\* or job or jobs or employment or vocation\*) adj5 train\*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]  
22 1 and 21  
23 exp Employment, Supported/  
24 ((support\* or subsidiz\*) adj2 educat\*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]  
25 exp Rehabilitation, Vocational/  
26 exp Sheltered Workshops/  
27 23 or 24 or 25 or 26  
28 1 and 27  
29 exp residential facilities/  
30 ((support\* or subsidiz\*) adj2 hous\*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]  
31 29 or 30  
32 1 and 31  
33 ("Illness Management and Recovery" or IMR) adj3 (toolkit\* or tool kit\*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]  
34 1 and 33  
35 3 or 5 or 7 or 11 or 13 or 15 or 17 or 19 or 22 or 28 or 32 or 34  
36 limit 35 to english  
37 limit 36 to systematic reviews  
38 random\*.mp.  
39 (clinical\* adj5 (trial\* or study or protocol\*)).mp.  
40 38 and 39  
41 ((random\* or control\*) adj5 (trial\* or study or protocol\*)).mp.  
42 40 or 41  
43 36 and 42  
44 37 or 43  
45 limit 36 to "2000 treatment outcome/clinical trial"  
46 44 or 45

**Database: PsycINFO**

1 exp schizophrenia/  
2 exp Community Mental Health Services/  
3 1 and 2  
4 exp Cognitive Therapy/  
5 1 and 4  
6 (Cognit\* adj5 Remediat\*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]  
7 1 and 6  
8 exp Family Therapy/  
9 (((family or families) adj5 psychoeducat\*) or ((family or families) adj3 (therap\* or counsel\*))).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]  
10 8 or 9  
11 1 and 10  
12 exp Peers/ or exp peer relations/  
13 1 and 12  
14 (peer\* adj5 (support\* or group\*)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]  
15 1 and 14  
16 (Intensiv\* adj3 ((case or cases) adj3 manag\*)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]  
17 1 and 16  
18 exp Case Management/  
19 1 and 18  
20 Skills Training.mp.  
21 ((skill\* or job or jobs or employment or vocation\*) adj5 train\*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]  
22 1 and 21  
23 exp supported employment/  
24 ((support\* or subsidiz\*) adj2 educat\*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]  
25 exp Rehabilitation, Vocational/  
26 exp Sheltered Workshops/  
27 23 or 24 or 25 or 26  
28 1 and 27  
29 ((support\* or subsidiz\*) adj2 hous\*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]  
30 1 and 29  
31 (("Illness Management and Recovery" or IMR) adj3 (toolkit\* or tool kit\*)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]  
32 1 and 31  
33 3 or 5 or 7 or 11 or 13 or 15 or 17 or 19 or 22 or 28 or 30 or 32  
34 limit 33 to english  
35 limit 34 to systematic reviews  
36 random\*.mp.  
37 (clinical\* adj5 (trial\* or study or protocol\*)).mp.  
38 36 and 37  
39 ((random\* or control\*) adj5 (trial\* or study or protocol\*)).mp.  
40 38 or 39  
41 34 and 40  
42 35 or 41  
43 limit 34 to "2000 treatment outcome/clinical trial"  
44 42 or 43

## Appendix B. Included Studies

1. Abou-Setta AM, Mousavi SS, Spooner C, et al. First-generation versus second-generation antipsychotics in adults: comparative effectiveness. Comparative effectiveness review No. 63. (Prepared by the University of Alberta Evidence-based Practice Center under Contract No. 290-200-10021.) AHRQ Publication No. 12-EHC054-EF. Rockville, MD: Agency for Healthcare Research and Quality: 2012. [www.effectivehealthcare.ahrq.gov/reports/final.cfm](http://www.effectivehealthcare.ahrq.gov/reports/final.cfm) Accessed April 22, 2017. PMID: 23035275.
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## Appendix C. Excluded Studies With Reasons

- Aberg-Wistedt A, Cressell T, Lidberg Y, et al. Two-year outcome of team-based intensive case management for patients with schizophrenia. *Psychiatr Serv.* 1995 Dec;46(12):1263-6. PMID: 8590112. Study covered in a systematic review.
- Abraham KR, Kulhara P. The efficacy of electroconvulsive therapy in the treatment of schizophrenia. A comparative study. *Br J Psychiatry.* 1987 Aug;151:152-5. PMID: 3318990. Intervention not included in review.
- Addington DE, McKenzie E, Norman R, et al. Essential evidence-based components of first-episode psychosis services. *Psychiatr Serv.* 2013 May 1;64(5):452-7. doi: 10.1176/appi.ps.201200156. PMID: 23370444. Systematic review/meta-analysis used as a source document to identify individual studies.
- Addington DE, Mohamed S, Rosenheck RA, et al. Impact of second-generation antipsychotics and perphenazine on depressive symptoms in a randomized trial of treatment for chronic schizophrenia. *J Clin Psychiatry.* 2011 Jan;72(1):75-80. doi: 10.4088/JCP.09m05258gre. PMID: 20868641. Outcome not included in review.
- Addington J, McCleery A, Collins A, et al. Family work in early psychosis. *J Fam Psychother.* 2006;17(3-4):137-53. doi: 10.1300/J085v17n03\_09. Study design not included in review.
- Agid O, Schulze L, Arenovich T, et al. Antipsychotic response in first-episode schizophrenia: efficacy of high doses and switching. *Eur Neuropsychopharmacol.* 2013;23(9):1017-22. PMID: 23706529. Study design not included in review.
- Agius M, Shah S, Ramkisson R, et al. Three year outcomes of an early intervention for psychosis service as compared with treatment as usual for first psychotic episodes in a standard community mental health team. Preliminary results. *Psychiatr Danub.* 2007 Jun;19(1-2):10-9. PMID: 17603411. Study design not included in review.
- Aguglia E, Pascolo-Fabrizi E, Bertossi F, et al. Psychoeducational intervention and prevention of relapse among schizophrenic disorders in the Italian community psychiatric network. *Clin Pract Epidemiol Ment Health.* 2007;3:7. doi: 10.1186/1745-0179-3-7. PMID: 17593299. Not a study.
- Ahmed AO, Hunter KM, Goodrum NM, et al. A randomized study of cognitive remediation for forensic and mental health patients with schizophrenia. *J Psychiatr Res.* 2015 Sep;68:8-18. doi: 10.1016/j.jpsychires.2015.05.013. PMID: 26228394. Setting ineligible for review (i.e., inpatient only).
- Aho-Mustonen K, Tiihonen J, Repo-Tiihonen E, et al. Group psychoeducation for long-term offender patients with schizophrenia: an exploratory randomised controlled trial. *Crim Behav Ment Health.* 2011 Jul;21(3):163-76. doi: 10.1002/cbm.788. PMID: 20859932. Population ineligible for review.
- Almerie MQ, Okba Al Marhi M, Jawoosh M, et al. Social skills programmes for schizophrenia. *Cochrane Database Syst Rev.* 2015 Jun 09(6):Cd009006. doi: 10.1002/14651858.CD009006.pub2. PMID: 26059249. Excluded due to including a review that was more recent, more comprehensive, or had a more similar scope to this review scope.
- Alphs L, Benson C, Cheshire-Kinney K, et al. Real-world outcomes of paliperidone palmitate compared to daily oral antipsychotic therapy in schizophrenia: a randomized, open-label, review board-blinded 15-month study. *J Clin Psychiatry.* 2015 May;76(5):554-61. doi: 10.4088/JCP.14m09584. PMID: 25938474. Intervention not included in review.
- Alphs L, Bossie CA, Fu DJ, et al. Onset and persistence of efficacy by symptom domain with long-acting injectable paliperidone palmitate in patients with schizophrenia. *Expert Opin Pharmacother.* 2014 May;15(7):1029-42. doi: 10.1517/14656566.2014.909409. PMID: 24754314. Study design not included in review.
- Alphs L, Bossie CA, Sliwa JK, et al. Paliperidone palmitate and risperidone long-acting injectable in subjects with schizophrenia recently treated with oral risperidone or other oral antipsychotics. *Neuropsychiatr Dis Treat.* 2013 Mar;9:341 - 50. PMID: 23493643. Not a study.
- Alphs L, Mao L, Rodriguez SC, et al. Design and rationale of the Paliperidone Palmitate Research in Demonstrating Effectiveness (PRIDE) study: a novel comparative trial of once-monthly paliperidone palmitate versus daily oral antipsychotic treatment for delaying time to treatment failure in persons with schizophrenia. *J Clin Psychiatry.* 2014 Dec;75(12):1388-93. PMID: 25375367. Not a study.

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Beck K, McCutcheon R, Bloomfield MA, et al. The practical management of refractory schizophrenia--the Maudsley Treatment REview and Assessment Team service approach. *Acta Psychiatrica Scandinavica.* 2014 Dec;130(6):427-38. doi: 10.1111/acps.12327. PMID: 25201058. Study design not included in review.

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Beebe LH. Community nursing support for clients with schizophrenia. *Arch Psychiatr Nurs.* 2001 Oct;15(5):214-22. doi: 10.1053/apnu.2001.27018. PMID: 11584350. Outcome not included in review.

Behere RV, Arasappa R, Jagannathan A, et al. Effect of yoga therapy on facial emotion recognition deficits, symptoms and functioning in patients with schizophrenia. *Acta Psychiatr Scand.* 2011 Feb;123(2):147-53. doi: 10.1111/j.1600-0447.2010.01605.x. PMID: 20846271. Intervention not included in review.

Bell M, Bryson G, Greig T, et al. Neurocognitive enhancement therapy with work therapy: effects on neuropsychological test performance. *Arch Gen Psychiatry.* 2001 Aug;58(8):763-8. PMID: 11483142. Comparator not included in review.

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- Bell MD, Choi KH, Dyer C, et al. Benefits of cognitive remediation and supported employment for schizophrenia patients with poor community functioning. *Psychiatr Serv*. 2014 Apr 1;65(4):469-75. doi: 10.1176/appi.ps.201200505. PMID: 24382594. Study design not included in review.
- Bell MD, Lysaker PH. Clinical benefits of paid work activity in schizophrenia: 1-year followup. *Schizophr Bull*. 1997;23(2):317-28. PMID: 9165640. Intervention not included in review.
- Bell MD, Lysaker PH, Milstein RM. Clinical benefits of paid work activity in schizophrenia. *Schizophr Bull*. 1996;22(1):51-67. PMID: 8685664. Study covered in a systematic review.
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- Benton MK, Schroeder HE. Social skills training with schizophrenics: a meta-analytic evaluation. *J Consult Clin Psychol*. 1990 Dec;58(6):741-7. PMID: 2149858. Excluded due to including a review that was more recent, more comprehensive, or had a more similar scope to this review scope.
- Bhugra D, Ayonrinde O, Butler G, et al. A randomised controlled trial of assertive outreach vs. treatment as usual for black people with severe mental illness. *Epidemiol Psychiatr Sci*. 2011 Mar;20(1):83-9. PMID: 21657119. Country not eligible.
- Bio DS, Gattaz WF. Vocational rehabilitation improves cognition and negative symptoms in schizophrenia. *Schizophr Res*. 2011 Mar;126(1-3):265-9. doi: 10.1016/j.schres.2010.08.003. PMID: 20800453. Intervention not included in review.
- Birchwood M, Michail M, Meaden A, et al. The MRC command trial: results of a multi-centre, randomised controlled trial of cognitive therapy to prevent harmful compliance with command hallucinations. *Schizophr Res*. 2014;153(5)doi: 10.1016/S0920-9964(14)70239-7. Not a study.
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Boter H, Derks EM, Fleischhacker WW, et al. Generalizability of the results of efficacy trials in first-episode schizophrenia: comparisons between subgroups of participants of the European First Episode Schizophrenia Trial (EUFEST). *J Clin Psychiatry*. 2010 Jan;71(1):58-65. PMID: 19852905. Study design not included in review.

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## Appendix D. Scale Abbreviations and Scoring

Abbreviation	Measure	Scale	Direction
ABS	Agitated Behavior Scale	15 to 56	Higher score=more dangerous behavior
ACES	Agitation-Calmness Scale	1 to 9	Higher score=calmer
ADL	Activities of Daily Living	0 to 6	Higher score=greater independence in daily living
AIMS	Abnormal Involuntary Movement Scale	0 to 4	Higher score=greater severity of tardive dyskinesia
ASEX	Arizona Sexual Experiences Scale	5 to 30	Higher score=greater sexual dysfunction
BARS	Barnes Akathisia Rating Scale	0 to 9	Higher score=greater severity of akathisia
BPRS	Brief Psychiatric Rating Scale	16 to 112	Higher score=more severe symptoms
C-SSRS	Columbia Suicide Severity Rating Scale	2 to 25	Higher score=greater suicide ideation severity
CABS	Corrigan Agitated Behavior Scale	14 to 56	Higher score=more dangerous behavior
CDSS	Calgary Depression Rating Scale for Schizophrenia	0 to 27	Higher score=worse depression
CES	Coping Efficacy Scale	1 to 5	Higher score=more effective coping
CGI	Clinical Global Impression	1 to 7	Higher score=more severe illness
CGI-I	Clinical Global Impression – Improvement	1 to 7	Higher score=higher degree of mental illness relative to other patients with the same diagnosis
CGI-S	Clinical Global Impression-Severity	1 to 7	Higher score=higher degree of mental illness
CHOICE	CHoice of Outcome in Cbt for psychOsEs	0 to 210	Higher score=more satisfied and better
DIEPSS	Drug-Induced Extrapyrarnidal Symptoms Scale	0 to 36	Higher score=more severe symptoms
GAF	Global Assessment of Function	1 to 100	Higher score=better functioning
GAS	Goal Attainment Scaling	-2 to +2	Higher score=higher goal attainment
GPTS	Green Paranoid Thoughts Scale	32 to 160	Higher score=more paranoid thoughts
Heinrich's	Heinrichs-Carpenter Quality of Life Scale	0 to 126	Higher score=greater mental health
HoNDS	Health of the Nation Outcomes Scales	0 to 48	Higher score=more severe outcomes of mental illness
ILSS	Independent Living Skills Survey	0 to 70	Higher score=better functioning
ISSI	Interview Schedule for Social Interaction	0 to 30	Higher score=better social integration and attachment
ITAQ	Insight and Treatment Attitudes Questionnaire	0 to 22	Higher score=more complete insight
LOS	Strauss-Carpenter Level of Function Scale	0 to 36	Higher score=more functionality
LQLP or LQOLP	Lancashire Quality of Life Profile	105 to 735	Higher score=higher quality of life
LSP	Life Skills Profile	39 to 156	Higher score =higher levels of life skills
LUNSERS	Liverpool University Neuroleptic Side Effect Rating Scale	0 to 204	Higher score=worse neuroleptic side effects

<b>Abbreviation</b>	<b>Measure</b>	<b>Scale</b>	<b>Direction</b>
MANSA	Manchester Short Assessment of Quality of Life	16 to 112	Higher score=higher quality of life
MASC	Maryland Assessment of Social Competence	12 to 60	Higher score=better social skills
MCAS	Multnomah Community Ability Scale	17 to 85	Higher score=better functioning
MOAS	Modified Overt Aggression Scale	0 to 40	Higher score=higher frequency of aggressive behaviors
PANSS	Positive and Negative Syndromes Scale	30 to 210	Higher score=more severe symptoms
PSP	Personal and Social Performance Scale	0 to 100	Higher score=better personal and social functioning
PSR Toolkit	Psychosocial Rehabilitation Toolkit	0 to 5	Higher score=better functioning
PSWQ	Penn State Worry Questionnaire	16 to 18	Higher score=more worry
PSYRATS	The Psychotic Symptom Rating Scales	0 to 70	Higher score=more severe psychotic symptoms
PTQ	Perservative Thinking Questionnaire	0 to 60	Higher score=higher levels of repetitive thought
QLS	Quality of Life Scale	0 to 126	Higher score=better functioning
QOLI	Quality of Life Interview	143 to 1001	Higher score=better quality of life
R-SES	Revised Self-efficacy Scale	0 to 100	Higher score=higher self-efficacy
RFS	Role Functioning Scale	4 to 28	Higher score=more optimal functioning
SADS-C	Schedule for Affective Disorders and Schizophrenia - Change	75 to 406	Higher score=more severe symptoms
SAI	Scale for the Assessment of Insight Expanded	0 to 24	Higher score=better insight
SANS	Scale for Assessment of Negative Symptoms	0 to 130	Higher score=more severe negative symptoms
SAS or SAS-II	Social Adjustment Scale	0 to 125	Higher score=better functioning
SAPS	Scale for the Assessment of Positive Symptoms	0 to 175	Higher score=more severe positive symptoms
SBS	Social Behavior Survey	0 to 84	Higher score=worse social function
SCL or SCL-90-R	Symptom Checklist-90-Revised	30 to 80	Higher score=more symptom severity
SF-36	36-Item Short Form health Survey	0 to 100	Higher score=more favorable health state
SFS	Social Functioning Scale	40 to 160	Higher score=greater social function
SOFAS	Social and Occupational Functioning Assessment Scale	1 to 100	Higher score=more impairment
SWBUNS	Subjective Well-being Under Narcoleptics Scale	20 to 120	Higher score=higher wellbeing
UPSA	UCSD Performance-based Skills Assessment	0 to 100	Higher score=higher levels of functioning
WBI	Work Behavior Inventory	35 to 175	Higher score=better work behavior
WEMWEBS	Warwick-Edinburgh Mental Wellbeing Scale	14 to 70	Higher score=higher wellbeing
WHOQOL-BREF	World Health Organization Brief Quality of Life Assessment Instrument	32 to 160	Higher score=better quality of life
YMRS	Young Mania Rating Scale	0 to 60	Higher score=greater severity of manic symptoms

## Appendix E. Data Abstraction

**Appendix Table E-1. Data abstraction of systematic reviews of pharmacological interventions**

Author, Year	Aims	Databases and Timeperiod Covered	Number of Studies Number of Patients	Characteristics of Identified Articles: Study Designs	Characteristics of Identified Articles: Populations	Characteristics of Identified Articles: Interventions
<p><i>Alberta CER</i> Abou-Setta 2012</p>	<p>Compare FGAs with SGAs antipsychotics in patients with schizophrenia, schizophrenia-related psychosis or bipolar disorder, with a focus on core illness symptoms, functional outcomes, health care utilization and adverse events</p>	<p>MEDLINE, Embase, PsycINFO, International Pharmaceuticals Abstracts, CINAHL, ProQuest Dissertations and Theses Full-Text, Cochrane Central Register of Controlled Trials and Scopus (1950 to July 2011)</p> <p>For adverse events TOXLINE and MedEffect (1950-July 2011)</p> <p>Grey literature and hand searches</p>	<p>113 studies (in people with schizophrenia or related psychosis) N=118,503; range 10-95,632, median 86</p>	<p>109 RCTs; 2 nonrandomized trials; 2 cohort RCTs; followup &lt;1 day to 22 years, median 8 weeks All had unclear or high risk of bias</p>	<p>Mean age range 21-50 years, median 37 years 50% of RCTs conducted in inpatient populations</p>	<p>Fluphenazine vs: -olanzapine (2 RCTs) -quetiapine (1 RCT) -risperidone (1 RCT)</p> <p>Haloperidol vs: -aripiprazole (8 RCTs) -asenapine (1 RCT) -clozapine (10 RCTs, 1 cohort study) -olanzapine (34 RCTs, 1 cohort study) -quetiapine (10 RCTs, 1 cohort study) -risperidone (37 RCTs, 1 nonrandomized trial and 1 cohort study) -ziprasidone (8 RCTs, 1 nonrandomized trial)</p> <p>Perphenazine vs: -aripiprazole (1 RCT) -olanzapine (2 RCTs) -quetiapine (1 RCT) -risperidone (2 RCTs) -ziprasidone (1 RCT)</p> <p>No included RCTs for any FGA vs: -Brexipiprazole -Cariprazine -lloperidone -Lurasidone -Paliperidone</p>

Author, Year	Outcomes Reported	Effectiveness Outcomes
<p>Alberta CER Abou-Setta 2012</p>	<p>Mean between group difference for - Core illness symptoms: -negative symptoms -general psychopathology -global ratings and total scores Functional outcomes Other outcomes: -response rate -remission rate -adherence rate Health-related quality of life  Adverse events</p>	<p><b>Statistically significant comparisons and outcomes:</b> <u>Haloperidol vs. olanzapine</u> Negative symptoms: -SANS (5 RCTs): MD 1.79 (95% CI 1.57 to 2.02; favors olanzapine); I<sup>2</sup>=0%; SOE: moderate Global ratings and total scores: -CGI-S (7 RCTs): MD 0.20 (95% CI 0.07 to 0.32; favors olanzapine); I<sup>2</sup>=33%; SOE: moderate -PANSS, total (15 RCTs): MD 2.31 (95% CI 0.44 to 4.18; favors olanzapine); I<sup>2</sup>=37%; SOE: moderate Other outcomes: -Response rate (14 RCTs): RR 0.86 (95% CI 0.78 to 0.96; favors olanzapine); I<sup>2</sup>=55%; SOE: not assessed -Remission rate (3 RCTs): RR 0.65 (95% CI 0.45 to 0.94; favors olanzapine); I<sup>2</sup>=54%; SOE: not assessed  <u>Haloperidol vs. quetiapine</u> Global ratings and total scores: -CGI-S (4 RCTs): MD -0.23 (95% CI -0.42 to -0.04; favors haloperidol); I<sup>2</sup>=0%; SOE: moderate</p>

Author, Year	Harms Outcomes	Subgroups	Funding/ Comments	Quality Rating
<p>Alberta CER Abou-Setta 2012</p>	<p><b>Statistically significant comparisons and outcomes:</b>  <u>Haloperidol vs. aripiprazole</u>            Any adverse event (3 RCTs): RR 1.11 (95% CI 1.06 to 1.17); I<sup>2</sup>=0%; SOE not assessed            Withdrawals due to adverse events (7 RCTs): RR 1.25 (95% CI 1.06 to 1.47); I<sup>2</sup>=0%; SOE not assessed            EPS (6 RCTs): RR 2.22 (95% CI 1.37 to 3.59); I<sup>2</sup>=83%; SOE not assessed            Akathisia (7 RCTs): RR 2.04 (95% CI 1.70 to 2.44); I<sup>2</sup>=0%; SOE not assessed            Dystonia (1 RCT): RR 7.83 (95% CI 1.47 to 41.76); SOE not assessed            Rigidity (1 RCT): RR 8.10 (95% CI 1.89 to 34.66); SOE not assessed            Tremor (5 RCTs): RR 1.99 (95% CI 1.42 to 2.78); I<sup>2</sup>=4%; SOE not assessed</p> <p><u>Haloperidol vs. clozapine</u>            Mortality (1 cohort study): RR 1.98 (95% CI 1.30 to 3.00); SOE: not reported            Metabolic syndrome (1 RCT): RR 0.27 (95% CI 0.10 to 0.75); SOE: insufficient            Hyperkinesia (1 RCT): RR 2.01 (95% CI 1.13 to 3.56); SOE not assessed            Tardive dyskinesia (1 cohort study): RR 34.50 (95% CI 2.07 to 573.55); SOE: insufficient</p>	<p><b>Comparisons and outcomes for which there was a difference between subgroups:</b>  <u>Haloperidol vs. aripiprazole</u>            Response rate - First episode:            Mixed first and previous episode (4 studies) RR 1.06 (95% CI 0.72 to 1.57) vs. <b>Multiple episodes only (1 study): RR 0.85 (95% CI 0.75 to 0.96; favors aripiprazole)</b></p> <p><u>Haloperidol vs. olanzapine</u>            Positive symptoms (PANSS) - Comorbid drug/alcohol use:            Excluded (4 RCTs): MD -0.44 (95% CI -2.75 to 1.87) vs            Included only (1 RCT): MD -2.00 (95% CI -4.82 to 0.82) vs  <b>Mixed (9 RCTs): MD 0.70 (95% CI 0.15 to 1.26; favors olanzapine)</b>            Negative symptoms (PANSS) - Comorbid drug/alcohol use:            Excluded (4 RCTs): MD 0.88 (95% CI -0.63 to 2.39) vs.  <b>Included only (1 RCT): MD -3.20 (95% CI -6.03 to -0.37; favors haloperidol) vs Mixed (9 RCTs): MD 1.27 (95% CI 0.82 to 1.72; favors olanzapine)</b>            Negative symptoms (PANSS) - Treatment resistant:  <b>Treatment resistant (5 RCTs); MD 1.28 (95% CI 0.11 to 2.44; favors olanzapine)</b> vs No treatment resistance (1 RCT):            MD 1.02 (95% CI -2.39 to 4.43) vs Mixed population (8 RCTs):            MD 0.90 (95% CI -0.02 to 1.81)            Total symptom score (PANSS) - Comorbid drug/alcohol use:            Excluded (3 RCTs): MD -0.73 (95% CI -5.83 to 4.38) vs.  <b>Mixed (12 RCTs): MD 2.71 (95% CI 0.75 to 4.67; favors olanzapine)</b>            Total symptom score (BPRS) - Race:  <b>Asian (1 RCT): MD 4.40 (95% CI 0.33 to 8.47; favors olanzapine)</b> vs. Other race (12 RCTs): MD 0.28 (95% CI -1.48 to 2.04)</p>	<p>AHRQ</p>	<p>Good</p>

Author, Year	Outcomes Reported	Effectiveness Outcomes
<p>Alberta CER Abou-Setta 2012</p> <p>Cont.</p>	<p>see above</p>	<p><u>Haloperidol vs. risperidone</u> Negative symptoms: -SANS (4 RCTs): MD 0.58 ((5% CI 0.37 to 0.80; favors risperidone); I<sup>2</sup>=0%: SOE: moderate Global ratings and total scores: -SCL-90-R (1 RCT): MD 0.31 (95% CI 0.12 to 0.50; favors risperidone); SOE: insufficient Other outcomes: -Relapse (6 RCTs): RR 1.35 (95% CI 1.17 to 1.57; favors risperidone); I<sup>2</sup>=0%; SOE not assessed</p> <p><u>Haloperidol vs. ziprasidone</u> Health-related quality of life: -QLS (1 RCT): MD -12.12 (95% CI -22.06 to -2.17; favors ziprasidone); SOE not assessed</p> <p><u>Perphenazine vs. olanzapine</u> Global ratings and total scores: -CGI-S (1 RCT): MD 0.25 (95% CI 0.06 to 0.43; favors olanzapine); SOE: insufficient -PANSS, total (1 RCT): MD -4.59 (95% CI -7.42 to -1.77; favors perphenazine); SOE: insufficient Medication adherence: -Time to all-cause discontinuation (1 RCT): -78.70 days (95% CI -119.34 to -38.06; favors olanzapine); SOE not assessed</p>

Author, Year	Harms Outcomes	Subgroups	Funding/ Comments	Quality Rating
<p><i>Alberta CER</i> Abou-Setta 2012</p> <p>Cont.</p>	<p><u>Haloperidol vs. olanzapine</u> Withdrawals due to adverse events (21 RCTs): RR 1.87 (95% CI 1.55 to 2.27); I<sup>2</sup>=0%; SOE not assessed EPS (6 RCTs): RR 3.88 (95% CI 2.19 to 6.85); I<sup>2</sup>=69%; SOE not assessed Akathisia (14 RCTs): RR 3.11 (95% CI 2.43 to 3.98); I<sup>2</sup>=38%; SOE not assessed Ataxia (1 RCT): RR 1.84 (95% CI 1.01 to 3.35) SOE not assessed Bradykinesia (1 RCT): RR 8.36 (95% CI 1.98 to 35.32); SOE not assessed Dyskinesia (4 RCTs): RR 3.55 (95% CI 2.01 to 6.27); SOE not assessed Hypertonia (4 RCTs): RR 2.54 (95% CI 1.65 to 3.91); SOE not assessed Parkinsonism (8 RCTs): RR 4.28 (95% CI 2.49 to 7.35); I<sup>2</sup>=50%; SOE not assessed Rigidity (2 RCTs): RR 10.65 (95% CI 2.08 to 54.50) I<sup>2</sup>=0%; SOE not assessed Tremor (9 RCTs): RR 2.30 (95% CI 1.58 to 3.34); I<sup>2</sup>=58%; SOE not assessed Overweight/obesity (2 RCTs): RR 0.35 (95% CI 0.21 to 0.58); I<sup>2</sup>=46%; SOE not assessed Hypercholesterolemia (2 RCTs): RR 0.43 (95% CI 0.26 to 0.72); I<sup>2</sup>=0%; SOE not assessed</p> <p><u>Haloperidol vs. quetiapine</u> Akathisia (5 RCTs): RR 3.51 (95% CI 1.84 to 6.72); I<sup>2</sup>=38%; SOE not assessed Parkinsonism (2 RCTs): RR 4.04 (95% CI 1.97 to 8.26) I<sup>2</sup>=53%; SOE not assessed Orthostatic hypotension (3 RCTs): RR 0.49 (95% CI 0.25 to 0.95); I<sup>2</sup>=0%; SOE not assessed</p>	<p>Total symptom score (BPRS) - Comorbid drug/alcohol use: Excluded (6 RCTs): MD -2.37 (95% CI -6.19 to 1.44) vs. <b>Mixed (7 RCTs): MD 2.05 (95% CI 0.55 to 3.55; favors olanzapine)</b></p> <p>Total symptom score (BPRS) - Treatment resistance: Treatment resistant (4 RCTs); MD -5.50 (95% CI -14.1 to 3.07) vs. <b>Mixed population (9 RCTs): MD 1.10 (95% CI 0.62 to 1.58; favors olanzapine)</b></p> <p>Total symptom score (CGI-S) - Comorbid drug/alcohol use: Excluded (5 RCTs): MD 0.30 (95% CI -0.13 to 0.20) vs. <b>Mixed (3 RCTs): MD 0.28 (95% CI 0.19 to 0.38; favors olanzapine)</b></p> <p>Total symptom score (CGI-S) - Treatment resistance: <b>Treatment resistant (2 RCTs): MD 0.24 (95% CI 0.01 to 0.47; favors olanzapine)</b> vs. No treatment resistance (1 RCT): MD 0.60 (95% CI -0.23 to 1.43) vs. Mixed population (5 RCTs): MD 0.07 (95% CI -0.10 to 0.24)</p> <p>Response rate - Race: Asian (1 RCT): RR 0.87 (95% CI 0.76 to 1.00) vs. <b>Other race (13 RCTs): RR 0.86 (95% CI 0.76 to 0.97; favors olanzapine)</b></p> <p>Response rate - Comorbid drug/alcohol use: Only (1 RCT): RR 1.33 (95% CI 0.38 to 4.72) vs. Excluded (2 RCTs): RR 1.02 (95% CI 0.79 to 1.32) vs. <b>Mixed (11 RCTs): RR 0.84 (95% CI 0.75 to 0.94; favors olanzapine)</b></p> <p>Response rate - Treatment resistant: Treatment resistant (5 RCTs): RR 0.81 (95% CI -0.62 to 1.04) vs. No treatment resistance (1 RCT): RR 0.52 (95% CI 0.37 to 0.72; favors olanzapine) vs. <b>Mixed population (8 RCTs): RR 0.92 (95% CI 0.85 to 0.99; favors olanzapine)</b></p> <p><u>Haloperidol vs. quetiapine</u> Response rate - Comorbid drug/alcohol use: <b>Excluded (1 RCT): RR 1.62 (95% CI 1.24 to 2.11; favors haloperidol)</b> vs Mixed population (5 RCTs): RR 0.90 (95% CI 0.73 to 1.10)</p>	<p>see above</p>	<p>see above</p>

Author, Year	Harms Outcomes	Subgroups	Funding/ Comments	Quality Rating
<p><i>Alberta CER</i> Abou-Setta 2012  Cont.</p>	<p><u>Halopredone vs. risperidone</u> Any adverse event (8 RCTs): RR 1.20 (95% CI 1.01 to 1.42); I<sup>2</sup>=84%; SOE not assessed Withdrawals due to adverse events (23 RCTs): RR 1.27 (95% CI 1.04 to 1.55); I<sup>2</sup>=0%; SOE not assessed Mortality (1 cohort study): RR 1.70 (95% CI 1.13 to 2.20); SOE: insufficient EPS (5 RCTs): RR 1.86 (95% CI 1.46 to 2.36); I<sup>2</sup>=0%; SOE not assessed Akathisia (7 RCTs): RR 1.79 (95% CI 1.31 to 2.44); I<sup>2</sup>=0%; SOE not assessed Tremor (4 RCTs): RR 2.09 (95% CI 1.23 to 3.53); I<sup>2</sup>=0%; SOE not assessed Weight gain (1 RCT): RR 0.19 (95% CI 0.05 to 0.81): SOE not assessed</p>	<p><u>Haloperidol vs. risperidone</u> Positive symptoms (PANSS) - Treatment resistant: Treatment resistant (2 RCTs): MD -0.00 (95% CI -3.04 to 3.03) vs. <b>Mixed population (14 RCTs): 0.84 (95% CI 0.07 to 1.60; favors risperidone)</b> vs. No treatment resistant (4 RCTs): MD 0.32 (95% CI -1.44 to 2.08) Positive symptoms (PANSS) - First episode: First episode only (1 RCT): MD 0.10 (95% CI -1.98 to 2.18) vs. Multiple episodes only (7 RCTs): MD 0.10 (95% CI -1.17 to 1.36) vs. <b>Mixed first and multiple episodes (12 RCTs): MD 1.04 (95% CI 0.21 to 1.86; favors risperidone)</b> Negative symptoms (PANSS) - Treatment resistant: Treatment resistant (2 RCTs): MD 1.00 (95% CI -1.74 to 3.73) vs. <b>Mixed population (14 RCTs): 0.71 (95% CI 0.15 to 1.27; favors risperidone)</b> vs. No treatment resistant (4 RCTs): MD -0.04 (95% CI -1.78 to 1.70) Negative symptoms (PANSS) - First episode: Multiple episodes only (7 RCTs): MD 0.05 (95% CI -1.19 to 1.29) vs. <b>Mixed first and multiple episodes (13 RCTs): MD 0.88 (95% CI 0.30 to 1.47; favors risperidone)</b></p>	<p>see above</p>	<p>see above</p>

Author, Year	Harms Outcomes	Subgroups	Funding/ Comments	Quality Rating
<p>Alberta CER Abou-Setta 2012  Cont.</p>	<p><u>Haloperidol vs. ziprasidone</u> Any adverse event (6 RCTs): RR 1.13 (95% CI 1.03 to 1.23); I<sup>2</sup>=31%; SOE not assessed Withdrawals due to adverse events (6 RCTs): RR 1.73 (95% CI 1.30 to 2.32); I<sup>2</sup>=0%; SOE not assessed EPS (5 RCTs): RR 2.34 (95% CI 1.56 to 3.53); I<sup>2</sup>=63%; SOE not assessed Dystonia (3 RCTs): RR 2.19 (95% CI 1.34 to 3.60); I<sup>2</sup>=15%; SOE not assessed Hypertonia (3 RCTs): RR 2.45 (95% CI 1.52 to 3.94); I<sup>2</sup>=0%; SOE not assessed Movement disorder (1 RCT): RR 2.73 (95% CI 1.77 to 4.19); SOE not assessed Tremor (5 RCTs): RR 2.55 (95% CI 1.79 to 3.63); I<sup>2</sup>=4%; SOE not assessed</p> <p><u>Perphenazine vs. olanzapine</u> AIMS global severity score ≥2 (1 RCT): RR 1.65 (95% CI 1.07 to 2.54); SOE not assessed Weight gain (1 RCT): RR 0.41 (95% CI 0.28 to 0.60); SOE not assessed</p> <p><u>Perphenazine vs. quetiapine</u> AIMS global severity score ≥2 (1 RCT): RR 1.76 (95% CI 1.13 to 2.75); SOE not assessed</p>	<p>Total symptom score (PANSS) - Comorbid drug/alcohol use: <b>Excluded (14 RCTs): MD 2.56 (95% CI 0.65 to 4.47; favors risperidone)</b> vs Mixed population (6 RCTs): MD 1.95 (95% CI -3.14 to 7.04) Total symptom score (PANSS) - First episode: First episode only (1 RCT): MD 1.60 (95% CI -5.61 to 8.81) vs. Multiple episodes only (7 RCTs): MD -0.56 (95% CI -3.98 to 2.86) vs. <b>Mixed first and multiple episodes (12 RCTs): MD 3.78 (95% CI 1.37 to 6.18; favors risperidone)</b> Total symptom score (BPRS) - Comorbid drug/alcohol use: <b>Excluded (7 RCTs): MD 0.84 (95% CI 0.36 to 1.32; favors risperidone)</b> vs Mixed population (6 RCTs): MD 0.23 (95% CI -1.44 to 1.90)</p> <p><u>Haloperidol vs. ziprasidone</u> Response rate - Treatment resistance: <b>Treatment resistant (1 RCT): RR 1.54 (95% CI 1.19 to 2.00; favors ziprasidone)</b> vs. <b>Mixed population (3 RCTs): RR 1.46 (95% CI 1.16 to 1.84; favors ziprasidone)</b> vs. No treatment resistant (3 RCTs): RR 0.79 (95% CI 0.56 to 1.13)</p>	<p>see above</p>	<p>see above</p>

Author, Year	Aims	Databases and Timeperiod Covered	Number of Studies Number of Patients	Characteristics of Identified Articles: Study Designs	Characteristics of Identified Articles: Populations	Characteristics of Identified Articles: Interventions
McDonagh 2013 Drug Effectiveness Review Project Report	Comparative effectiveness of second-generation antipsychotics in multiple populations, including schizophrenia	Medline and Cochrane from inception to August 2013	138 RCTs (N=47,189) 31 observational studies (N=602, 547)	Head-to-head randomized controlled trials with at least 6 weeks duration	Patients with schizophrenia or schizoaffective or nonaffective functional psychosis	2 or more of 14 possible second generation antipsychotics available in the United States as of 2013

Author, Year	Outcomes Reported	Effectiveness Outcomes
McDonagh 2013 Drug Effectiveness Review Project Report	Quality of life, mortality, functional capacity, hospitalization, emergency department visits, medication persistence, symptom response, response rates, duration of response, remission, relapse, speed of response, time to discontinuation of medication, overall (total) adverse events, withdrawals due to adverse events, time to withdrawal due to adverse events, major adverse events, general adverse events.	<p><u>Functioning</u>: Olanzapine, risperidone, immediate-release quetiapine, or ziprasidone were not different on employment or general function outcomes. Social function was not different between paliperidone palmitate and long-acting risperidone injections. Global function was superior with olanzapine vs. ziprasidone in patients with depressive symptoms and with immediate-release quetiapine in patients with prominent negative symptoms, but similar between immediate-release quetiapine and risperidone in patients with a first-episode of schizophrenia.</p> <p><u>Quality of life</u>. Good-quality trial evidence did not differentiate asenapine, olanzapine, immediate-release quetiapine, risperidone, or ziprasidone.</p> <p><u>Suicide</u>. Clozapine was superior to olanzapine in preventing suicide or suicidality in patients at high risk of suicide (NNT=12) (InterSePT).</p> <p><u>Response</u>: Rates ranged from 45% to 80%, with variation in definition of response, patient populations and duration of treatment contributing to variability. Limited evidence did not identify statistically significant differences between risperidone long-acting injection and oral risperidone or olanzapine or olanzapine and extended-release paliperidone. Evidence was mixed for risperidone long-acting injection and paliperidone palmitate injection. Evidence was insufficient for iloperidone and lurasidone.</p> <p><u>Relapse</u>. Risk of relapse may be lower with olanzapine and risperidone than immediate-release quetiapine and with risperidone long-acting injection than oral risperidone (first-episode patients). Results were mixed with risperidone vs. olanzapine. No differences between risperidone long-acting injection and aripiprazole, lurasidone and oral risperidone or lurasidone and extended-release quetiapine</p> <p><u>Symptoms</u> Consistent differences in efficacy were not found between clozapine, olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole, or asenapine in shorter-term trials</p>

Author, Year	Harms Outcomes	Funding/ Comments	Quality Rating
McDonagh 2013 Drug Effectiveness Review Project Report	Discontinuation due to adverse events. Mixed-treatment comparisons analysis indicated clozapine resulted in statistically significantly higher rates than olanzapine, immediate-release quetiapine, or risperidone. Sensitivity analyses of studies of greater and less than 6 months found no statistically significant differences, although the point estimates were in the same direction as the overall analysis. Fewer data were available for the lurasidone, new formulations of olanzapine, asenapine, and paliperidone palmitate long-acting injection, and no data for iloperidone.	Drug Effectiveness Review Project (collaboration of 12 Medicaid agencies)	Good

**Please see Appendix B. Included Studies for full study references**

BPRS= Brief Psychiatric Rating Scale, CGI-S= Clinical Global Impressions-Severity scale, CI= confidence interval, EPS= extrapyramidal symptoms, ES= effect size, FGA= first-generation antipsychotic, MD= mean difference, NNT= number needed to treat, PANSS= positive and negative syndrome scale, QLS= Quality of Life Scale, RCT= randomized control trial, RR= relative risk, SANS= Scale for the Assessment of Negative Symptoms, SGA= second-generation antipsychotic, SOE= strength of evidence, US= United States

**Appendix Table E-2. Data abstraction of randomized controlled trials of pharmacological interventions**

Author, Year	Setting Country	Inclusion Criteria	Interventions and Ns per Group	Duration (intervention and longest followup)	Age Gender Race/Ethnicity
Amr, 2013	Amman, Jordan; 10/2009 to 9/2011	Age: 18-60; Met DSM diagnosis of schizophrenia; First episode of schizophrenia; Exclusion: current or past use of antipsychotics; concurrent DSM Axis 1 diagnosis; DSM-VI Axis II diagnosis of borderline personality disorder, antisocial personality, substance dependence or abuse, clinically significant or unstable medical illness.	Initial doses: haloperidol=5 mg/day quetiapine=200 mg/day; Co-admin of psychotropic medications not allowed, except lorazepam and zopiclone and biperiden.  Dose at 12 weeks: haloperidol=14.2 mg; quetiapine=705.8 mg	12 weeks	Age: haloperidol=30.7; quetiapine=31.3. Sex (M/F): H: 21/12; Q: 25/15; Duration of illness (mos; SD): haloperidol=4.8 (1.6); quetiapine=5.0 (2.1); Marital status (unmarried/married): haloperidol=19/14; quetiapine=23.17; Employment (unemployed/ employed): haloperidol= 22/11; quetiapine=28/12; Education (above/below secondary): haloperidol=23/10; quetiapine=31/9; Income (satisfactory/ unsatisfactory): haloperidol=7/26; quetiapine=8/32; Type of schizophrenia (paranoid/not paranoid): haloperidol=24/9; quetiapine=32/8.

Author, Year	Other Population Characteristics	Total N	Benefits Outcomes
Amr, 2013	NR	156	<p><b><u>PANSS Positive:</u></b>  haloperidol (n=33); quetiapine (n=40); t-test; p-value:  Baseline: haloperidol=23.8 (SD=5.12); quetiapine=26.0 (SD=4.41);  t=1.90; p=0.06  6 weeks: haloperidol=18.2 (5.90); quetiapine=21.3 (2.51); t=2.86;  p=0.006;  12 weeks: haloperidol=18.9 (7.84); quetiapine=15.3 (2.18); t=2.55;  p=0.013</p> <p><b><u>PANSS Negative:</u></b>  Baseline: haloperidol=22.2 (8.51); quetiapine 21.3 (6.38); t=0.48;  p=0.63  6 weeks: haloperidol=20.4 (8.28); quetiapine=18.9 (6.21); t=0.86;  p=0.39  12 weeks: haloperidol=15.5 (7.39); quetiapine=11.6 (4.76); t=2.58;  p=0.012</p> <p><b><u>PANSS General Psychopathology:</u></b>  Baseline: haloperidol=39.0 (11.01); quetiapine=43.4 (8.36); t=1.939;  p=0.056  6 weeks: haloperidol=35.1 (11.3); quetiapine=37.3 (11.01); t=0.79;  p=0.43  12 weeks: haloperidol=23.8 (6.24); quetiapine=27.7 (6.33); t=2.58;  p=0.012</p> <p><b><u>PANSS Depression/Anxiety:</u></b>  Baseline: haloperidol=10.18 (2.11); quetiapine=9.88 (1.92); t=0.6;  p=0.55  6 weeks: haloperidol=9.88 (1.95); quetiapine=9.29 (1.64); t=1.53;  p=0.183  12 weeks: haloperidol=9.56 (1.87); quetiapine=4.74 (1.50); t=11.92;  p&lt;0.0001</p> <p><b><u>PANSS Total:</u></b>  Baseline: haloperidol=82.3 (21.88); quetiapine=90.8 (11.32); t=1.939;  p=0.056  6 weeks: haloperidol=73.8 (19.50); quetiapine=77.6 (8.90); t=1.02;  p=0.31  12 weeks: haloperidol=58.3 (16.59); quetiapine=54.8</p>

Author, Year	Harms Outcomes	Funding	Quality Rating
Amr, 2013	<p>Haloperidol= out of 78; quetiapine= out of 78;            Akathisia: haloperidol=53/78 (78%); quetiapine=0; p&lt;.00001;            Cold: haloperidol=23 (29.5%); quetiapine=18 (23%); p=0.363            Headache: haloperidol=9 (11.5%); quetiapine=28 (35.9%); p&lt;0.0001;            Fatigue: haloperidol=66 (84.6%); quetiapine=52 (66.6%); p=0.009;            Parkinsonism: haloperidol=52 (66.6%); quetiapine=0; p&lt;0001;            Insomnia: haloperidol=37 (47.4%); quetiapine=41 (52.5%); p=0.521;            Dizziness: haloperidol=28 (35.9%); quetiapine=22.28.2%); p=0.303.</p> <p><b>SAS: H (n-33); Q (n-40); t-test; p-value</b>            6 weeks: haloperidol=5.94 (1.83); quetiapine=0.18 (0.38); t=18.020; p&lt;0.0001;            12 weeks haloperidol=8.62 (2.08); quetiapine=0.26 (0.45); t=22.949; p&lt;0.0001</p>	Not stated	Poor

Author, Year	Setting Country	Inclusion Criteria	Interventions and Ns per Group	Duration (intervention and longest followup)	Age Gender Race/Ethnicity
Citrome, 2016	US	Adult patients (18 to 65 years) with DSM-IV-TR diagnosis of schizophrenia confirmed by the MINI International Neuropsychiatric Interview.	Brexiprazole 3 mg/day (N=64) vs. Aripiprazole 15 mg/day (N=33)	6 weeks	Age, year: 42.2  Gender, % Female: 29.2%  Ethnicity, %: White: 23.1% African-American: 73.9% Asian: 0.8% Other: 2.3%

Author, Year	Other Population Characteristics	Total N	Benefits Outcomes
Citrome, 2016	PANSS total score baseline, mean: 93.7 Duration of current episode: 3.1 weeks	97	Brexiprazole vs. Aripiprazole  Change in baseline PANSS total score, LS mean at 6 w: -22.9; P<0.0001 vs. -19.4; P<0.0001 Response rate at 6 w, % (n/N)*: 60.9% (39/64), (95% CI 47.9 to 72.9) vs. 48.5% (16/33), (95% CI 30.8 to 66.5)

Author, Year	Harms Outcomes	Funding	Quality Rating
Citrome, 2016	<p>Brexpiprazole vs. Aripiprazole</p> <p>Overall AEs, % (n/N): 57.8% (37/64) vs. 63.6% (21/33)  Withdrawal due to AEs, % (n/N): 4.7% (3/64) vs. 3.0% (1/33)  All-cause mortality: 0 vs. 0  Clinically relevant weight gain (<math>\geq 7\%</math> increase from baseline) at 6 weeks, % (n/N): 35% (14/40) vs. 19% (4/21)  Extrapyramidal AEs, % (n/N): 14.1% (9/64) vs. 30.3% (10/33).  Simpson Angus, Abnormal Involuntary Movement, and BARS global clinical assessment scales used but no differences were found between them.</p>	<p>Funding: Otsuka Pharmaceutical Commercialization and Development Inc.; H. Lundbeck A/S</p> <p>*Reduction of 30% or more from baseline in PANSS total score, or CGI-I score of 1 or 2.</p>	Fair

Author, Year	Setting Country	Inclusion Criteria	Interventions and Ns per Group	Duration (intervention and longest followup)	Age Gender Race/Ethnicity
Crespo-Facorro, 2011 Crespo-Facorro, 2012 Spain	Spain	Age 15-60 years, experiencing first psychotic episode, <6 weeks lifetime antipsychotic treatment, meet DSM-IV criteria for brief psychotic disorder, schizophreniform disorder, schizophrenia, schizoaffective disorder. Excluded DSM-IV criteria for drug dependence or mental retardation, history of neurological disease or head injury.	Haloperidol: n, 56; mean dose, 2.9 (1.4) mg/day Olanzapine: n, 55; mean dose, 10.1 (3.9) mg/day Risperidone: n, 63; mean dose, 3.4 (1.8) mg/day	156 weeks	Age, mean: 27.4 Gender: 38% female Ethnicity: NR

Author, Year	Other Population Characteristics	Total N	Benefits Outcomes
Crespo-Facorro, 2011 Crespo-Facorro, 2012 Spain	Age, psychosis onset: 26 years Duration of illness: 25 months Duration of psychosis: 11 months Diagnosis: Schizophrenia, 60.8%; Schizophreniform, 24.1%; Schizoaffective, 2.4%, Brief psychotic disorder, 5.4%; Unspecified psychotic disorder, 7.2%	174	<p>Haloperidol vs. Olanzapine vs. Risperidone: Relapse Rate: 11.1% vs. 18.5% vs. 13.8%; p=0.541 Time to relapse, mean (95% CI): 10.9 (10.89-11.72) vs. 10.78 (9.99-11.56) vs. 10.98 (10.25-11.71); p=0.857 Relapse, adherent vs. nonadherent: 11.2% vs. 26.9%, p=0.040 Remission at 1 year: 25% vs. 32.7% vs. 34.9%; <math>\chi^2=1.471</math>, p=0.479 Remission at 1 year, patients continuing on drug: 25% vs. 43.2% vs. 41.5%, p=0.308 Remission, adherent vs. nonadherent: 36.9% vs. 27.6%, p=0.347 Treatment discontinuation at 1 year: (Haloperidol %, Olanzapine %, Risperidone %, p) Discontinuation for any cause: 57% (32/56) vs. 33% (18/55) vs. 35% (22/63) Discontinuation due to adverse events: 25% (14/56) vs. 6% (3/55) vs. 11% (7/63) Treatment discontinuation at 3 years: Discontinuation for any cause: 80% (45/56) vs. 51% (28/55) vs. 67% (42/63) Discontinuation for adverse events: 32% (18/56) vs. 13% (7/55) vs. 25% (16/63) Adherence and global functioning at 3 year followup: Adherence NSD between treatment (83.3% haloperidol, 68.2% olanzapine, 78.9% risperidone, p=0.605) Global functional outcome NSD between treatment (81.8% haloperidol-treated, 63% olanzapine-treated, 71.4% risperidone-treated with good functionality at 3 year followup, p=0.505) Clinical efficacy: No advantages to any of the 3 treatments in reduction of symptomology at 3 years Safety: NSD in increment of extrapyramidal signs @ 3 yrs between treatments (p=0.132) NSD in treatment-emergent parkinsonism between treatment arms (p=0.114) Greater increase in akathisia severity w/ haloperidol treatment @ 3 yr assessment (p=0.013) Sig. increase in akathisia severity in risperidone-treated patients compared to olanzapine-treated patients (p=0.042) Sig. higher number in haloperidol-treated group experienced treatment-emergent akathisia compared to risperidone-treated and olanzapine-treated patients (p=0.013)</p>

Author, Year	Harms Outcomes	Funding	Quality Rating
Crespo-Facorro, 2011 Crespo-Facorro, 2012 Spain	Haloperidol % vs. Olanzapine % vs. Risperidone %, P Concentration difficult: 9.1 vs. 7.7 vs. 0.0, 0.419 Asthenia: 9.1 vs. 23.1 vs. 0.0, 0.057 Daytime drowsiness: 0.0 vs. 34.6 vs. 10.0, 0.022 Increased sleep hours: 9.1 vs. 11.5 vs. 5.0, 0.739 Akathisia: 27.3 vs. 0.0 vs. 5.0, 0.011 Sialorrhea: 0.0 vs. 0.0 vs. 15.0, 0.053 Dry mouth: 0.0 vs. 7.7 vs. 10.0, 0.571 Weight gain: 9.1 vs. 26.9 s. 20.0, 0.473 Amenorrhea (only females, n=23): 0.0 vs. 0.0 vs. 40.0, 0.043 Sexual dysfunctions (only males, n=34): 14.3 vs. 5.9 vs. 40.0, 0.078	NR	Fair

<b>Author, Year</b>	<b>Setting Country</b>	<b>Inclusion Criteria</b>	<b>Interventions and Ns per Group</b>	<b>Duration (intervention and longest followup)</b>	<b>Age Gender Race/Ethnicity</b>
Detke, 2014	Multisite, USA and France	Outpatients (18 to 65 years) who met the criteria for schizophrenia based on DSM-IV or the DSM-IV Text Revision. Required to be "at risk for relapse" (at least 2 episodes of clinical worsening of schizophrenia symptoms in the previous 24 months)	Olanzapine long-acting injection 405 mg/4 weeks (n=264) vs. Oral olanzapine 10 mg/day (n=260)	2 years	Age, mean years: 40.9  Gender, % female: 32.8  Ethnicity, %: White: 62.0 African: 16.8 Hispanic: 8.0 East Asian: 8.8 West Asian: 3.6 Native American: 0.8
Di Fiorino 2014	Italy	Adults (aged 18 to 65 years) with a documented DSM-IV diagnosis of diagnosis of schizophrenia or schizoaffective disorder.	Quetiapine extended-release 400 to 800 mg/day (n=109) vs. Risperidone 4 to 6 mg/day (n=107)	12 weeks	Age, years: 42.3  Gender, % female: 43.3  Ethnicity, %: White: 100
Durgam, 2014	International	Adults ages 18 to 60 years with schizophrenia (first episode excluded).	Cariprazine 1.5 mg/day (n=145) vs. Cariprazine 3.0 mg/day (n=146) vs. Cariprazine 4.5 mg/day (n=147) vs. Risperidone 4.0 mg/day (n=140)  (Placebo arm also included.)	6 weeks	Age, mean years: 36.5  Gender, % female: 31.0  Ethnicity, %: White: 50.0 African American: 24.0% Asian: 25.0 Other: 0.7  (Placebo arm excluded.)

Author, Year	Other Population Characteristics	Total N	Benefits Outcomes
Detke, 2014	Age of onset of schizophrenia, mean y (SD): 26.2 (8.9) Previous episodes in last 24 months, mean (SD): 2.7 (1.6) Length of current episode, mean days (SD): 175.0 (148.0) Poor medication adherence, n (%): 24.0 (4.6)	524	Olanzapine long-acting injection vs. oral olanzapine  All-cause discontinuation rate, %: 53.8 vs. 51.2; p=0.600 Time to all-cause discontinuation, median days: 645 vs. 678; p=0.612 Rate of relapse, %: 20.1 vs. 18.5, p=0.659 Time to relapse/rescue, median days: 539 vs. 281; p<0.001 Baseline-to-endpoint least-squares mean change on PANSS total score, (SE): -0.82 (1.2) vs. -1.14 (1.2); p=0.834
Di Fiorino 2014	PANSS severity of illness score: 101.4 Schizoaffective, %: 47.7	216	Quetiapine extended-release 400 to 800 mg/day vs. risperidone 4 to 6 mg/day  PANSS total score, LSM (SD): -30.0 (22.9) vs. -21.1 (23.8) Treatment difference: -8.9, P=0.0002
Durgam, 2014	Duration of illness: 11.5 years Duration of current illness/psychosis: less than 2 weeks to be eligible Hospitalization data (current): NR Severity of illness: 97.3 (PANSS) Schizoaffective: 0% (excluded) Substance use: 0% (excluded) Antipsychotic drug naïve: first episode of psychosis excluded	578 (active treatment arms)	Cariprazine 1.5 mg/day vs. cariprazine 3.0 mg/day vs. cariprazine 4.5 mg/day vs. risperidone 4.0 mg/day  PANSS responders (≥30% improvement from baseline): % (n/N) 31.4 (44/140) vs. 35.7 (50/140) vs. 35.9 (52/145) vs. 43.5 (60/138) (No p-values comparing active treatments reported.)

Author, Year	Harms Outcomes	Funding	Quality Rating
Detke, 2014	<p>Olanzapine long-acting injection vs. Oral olanzapine</p> <p>Any adverse event, n/N (%): 182/264 (68.9) vs. 176/260 (67.7)  Discontinuations due to adverse events, n/N (%): 26/264 (9.8) vs. 25/260 (9.6)  Death, n/N (%): 0/264 vs. 2/260 (0.8)  Weight increased, n/N (%): 44/264 (16.7) vs. 43/260 (16.5)  Weight decreased, n/N (%): 15/264 (5.7) vs. 14/260 (5.4)  Extrapyramidal symptoms/akathisia, n/N (%): 7/264 (2.7) vs. 10/260 (3.8)</p>	Eli Lilly and Co.	Poor
Di Fiorino 2014	<p>Quetiapine extended-release 400 to 800 mg/day vs. risperidone 4 to 6 mg/day</p> <p>Overall AE, n/N (%): 40/107 (37.4) vs. 36/103 (35.0)  Withdrawals due to AE, n/N (%): 10/107 (9.4) vs. 7/103 (6.8)</p>	<p>AstraZeneca Italy</p> <p>*Included disorientation, psychotic disorder, delusion, and extrapyramidal syndrome vs. fainting, acute psychosis, acute respiratory failure, social stay hospitalization, and cardiocirculatory arrest</p>	Fair
Durgam, 2014	<p>Cariprazine 1.5 mg/day vs. cariprazine 3.0 mg/day vs. cariprazine 4.5 mg/day vs. risperidone 4.0 mg/day</p> <p>Treatment-emergent adverse events: % (n/N)  68.3 (99/145) vs. 71.2 (104/146) vs. 73.5 (108/147) vs. 67.9 (95/140)</p> <p>WAE: % (n/N)  9.7 (14/145) vs. 5.5 (8/146) vs. 8.2 (12/147) vs. 9.3 (13/140)</p> <p>Extrapyramidal disorder (treatment-emergent):  9.0 (13/145) vs. 8.9 (13/146) vs. 11.6 (17/142) vs. 12.9 (18/140)</p>	Forest Research Institute and Gedeon Richter Plc.	Fair

Author, Year	Setting Country	Inclusion Criteria	Interventions and Ns per Group	Duration (intervention and longest followup)	Age Gender Race/Ethnicity
Fleischhacker, 2014 ASPIRE EU, NCT00706654	International	Adults ages 18 to 60 years, DSM-IV-TR schizophrenia for ≥3 years and a history of symptom exacerbation when not receiving antipsychotic treatment.	Aripiprazole once-monthly 400 mg (n = 265) vs. Oral aripiprazole 10 to 30 mg/day (n = 266) vs. Aripiprazole once-monthly 50 mg (n = 131)	38 weeks	Age, mean years: 41.0  Gender, % female: 38.7  Ethnicity, %: White: 58.5 Black or African American: 23.1 Asian: 10.4 Other: 8.0

Author, Year	Other Population Characteristics	Total N	Benefits Outcomes
Fleischhacker, 2014 ASPIRE EU, NCT00706654	PANSS total score, mean: 56.9 CGI-Severity score, mean: 3.07 CGI-Improvement score, mean: 3.2	662	<p>Aripiprazole once-monthly 400 mg vs. oral aripiprazole (10 to 30 mg/day) vs. aripiprazole once-monthly 50 mg</p> <p>Estimated relapse rate, %: 7.12 vs. 7.76 vs. 21.80 Treatment difference: -0.6 (95% CI -5.26 to 3.99)</p> <p>Discontinued, n (%): 69 (26) vs. 83 (33.1) vs. 70 (53.4)</p> <p>Observed impending relapse (ITT sample): 22/265 (8.30) vs. 21/266 (7.89) vs. 29/131 (22.14); HR (vs. aripiprazole once-monthly 50 mg) 3.158 (95% CI 1.81 to 5.50) vs. 3.131 (95% CI 1.78 to 5.49)</p> <p>Responders (ITT sample), %: 237/264 (89.8) vs. 235/263 (89.4) vs. 97/129 (75.2)</p> <p>Remitters (ITT sample), %: 105/215 (48.8) vs. 107/201 (53.2) vs. 43/72 (59.7)</p> <p>PANSS Total Score (efficacy sample, LOCF): Change from baseline at w 38, least square mean (SE): -1.66 (0.72) vs. 0.58 (0.71) vs. 3.08 (1.01)</p> <p>CGI Severity (efficacy sample, LOCF): Change from baseline at w 38, least square mean (SE): -0.13 (0.05) vs. 0.05 (0.05) vs. 0.23 (0.07)</p> <p>CGI Improvement (efficacy sample, LOCF): At week 38, mean (SD): 3.27 (1.16) vs. 3.66 (1.16) vs. 4.02 (1.32)</p> <p>Safety sample, observed cases: SAS total score, change from baseline at week 38, LS mean (SE): -0.16 (0.09) vs. -0.22 (0.09) vs. -0.21 (0.16)</p> <p>AIMS movement rating score, change from baseline at week 38, LS mean (SE): -0.00 (0.07) vs. -0.11 (0.07) vs. -0.01 (0.12)</p> <p>BARS global score, change from baseline at week 38, LS mean (SE): 0.06 (0.03) vs. -0.05 (0.03) vs. -0.06 (0.06)</p>

Author, Year	Harms Outcomes	Funding	Quality Rating
<p>Fleischhacker, 2014 ASPIRE EU, NCT00706654</p>	<p>Aripiprazole once-monthly 400 mg vs. oral aripiprazole (10 to 30 mg/day) vs. aripiprazole once-monthly 50 mg</p> <p>Discontinued due to AE, n (%): 8 (3.0) vs. 7 (2.6) vs. 7 (5.3)  Weight increased, n (%): 24 (9.1) vs. 35 (13.2) vs. 7 (5.3)  Suicidality, safety sample, observed cases:  CGI-SS, change from baseline at week 38, LS mean (SE): -0.01 (0.10) vs. 0.00 (0.00) vs. -0.02 (0.13)  C-SSRS, change from baseline at week 38, LS mean (SE): -0.1 (1.0) vs. 0.1 (1.3) vs. 0.0 (0.0)</p>	<p>Otsuka Pharmaceutical Commercialization, Inc.</p>	<p>Fair</p>

<b>Author, Year</b>	<b>Setting Country</b>	<b>Inclusion Criteria</b>	<b>Interventions and Ns per Group</b>	<b>Duration (intervention and longest followup)</b>	<b>Age Gender Race/Ethnicity</b>
Green, 2015	CMHCs and VA clinics (four total)	Age 18-65, with EtOH Use Disorder plus schizophrenia (48.4%) or schizoaffective disorder	LAI risperidone 25-50 mg every 2 weeks (49) vs. oral risperidone (up to 6mg/day) (46)	6 months	Age, mean years: 41.7 Gender, % female: 23.2 Ethnicity, %: White: 51.6 Black: 44.2

Author, Year	Other Population Characteristics	Total N	Benefits Outcomes
Green, 2015	Education 11.0 years Ever employed 97% Single 51% Lifetime Hospitalizations 7.5 Cannabis use 1.1 days/week Other drugs 0.3 days/week	95	ITT analyses: no significant difference in drinking Explanatory analyses using weeks 5-23: Trend significance change in days heavy drinking (5 or more/day) oral (0.68 days/week) vs. LAI (-0.11 days/week) $t_{63.5} = -1.96$ , $p=0.054$  Good adherence (exposed to meds 75% of study days): oral 61% vs. LAI 88%, $\chi^2=9.08$ , $p=0.003$ (oral vs. LAI: 28/46 [61%] vs. 43/49 [88%], RR 3.20 [95% CI 1.39 to 7.34])  No between-group differences in total PANSS, GAF, or CGI

<b>Author, Year</b>	<b>Harms Outcomes</b>	<b>Funding</b>	<b>Quality Rating</b>
Green, 2015	No differences in side effects between oral and LAI	Janssen	Fair

Author, Year	Setting Country	Inclusion Criteria	Interventions and Ns per Group	Duration (intervention and longest followup)	Age Gender Race/Ethnicity
Ishigooka, 2015	Asia	Asian adults (18 years and older) diagnosed with schizophrenia according to DSM-IV-TR criteria.	Aripiprazole 300 to 400 mg once-monthly injection (n=228)* vs. Aripiprazole 6 to 24 mg/day orally (n=227)	52 weeks (double-blind phase)	Age, years: 39.2 Gender, % female: 39.2 Ethnicity, % Asian: 100

Author, Year	Other Population Characteristics	Total N	Benefits Outcomes
Ishigooka, 2015	Duration of illness (time since first episode), months (mean): 151.6 PANSS severity of illness: 53.9	455	<p>Aripiprazole 300 to 400 mg monthly vs. aripiprazole 6 to 24 mg/day</p> <p>Nonexacerbation of psychotic symptoms/nonrelapse rate at week 26 (Kaplan-Meier)**: 95.0 vs. 94.7 Difference 0.3 (95% CI -3.9 to 4.5)</p> <p>Time to exacerbation of psychotic symptoms/relapse (Kaplan-Meier): HR 0.94 (95% CI 0.46 to 1.92)</p> <p>Proportion of patients achieving remission** exacerbation of psychotic symptoms/relapse, % (n/N): 6.6% (15/228) vs. 6.6% (15/227) Stabilization of psychotic symptoms/relapse, % (n/N): 92.5% (211/228) vs. 92.5% (210/227) Remission, % (n/N): 69.4% (129/228) vs. 71.1% (123/227)</p> <p>Quality of life, mean change from baseline in MOS 36-item SF-36 at week 52 Mental component: 0.82 vs. 0.38 Difference 0.44 (95% CI -1.24 to 2.12) ANCOVA Physical component: 0.23 vs. -0.27 Difference 0.50 (95% CI -1.11 to 2.11) ANCOVA</p> <p>All-cause discontinuation: 25.9% vs. 33.5% Time to all-cause discontinuation: HR 0.74 (95% CI 0.52 to 1.03)</p>

Author, Year	Harms Outcomes	Funding	Quality Rating
Ishigooka, 2015	<p>Aripiprazole 300 to 400 mg monthly vs. aripiprazole 6 to 24 mg/day</p> <p>Overall AE: % (n/N): 77.2% (176/228) vs. 79.3% (180/227)  Withdrawal due to AE: % (n/N): 7.5% (17/228) vs. 11.5% (25/227)  Extrapyramidal AE: % (n/N): 16.2% (40/228) vs. 14.1% (32/227)  Tardive dyskinesia: % (n/N): 0 vs. 0.4% (1/227)  Akathisia: % (n/N): 6.6% (12/228) vs. 6.2% (14/227)</p>	<p>Otsuka Pharmaceutical Co., Ltd.</p> <p>*Injection arm patients received 6 or 12 mg/day of oral aripiprazole for 2 weeks after start of randomized period  **Exacerbation/relapse based on CCG-I and PANSS scores, hospitalization, violent behavior resulting in injury</p>	Fair

Author, Year	Setting Country	Inclusion Criteria	Interventions and Ns per Group	Duration (intervention and longest followup)	Age Gender Race/Ethnicity
Koshikawa, 2016  Companion: Takekita, 2016	Japan	≥20 years old, DSM-IV-TR diagnosis of schizophrenia or schizoaffective disorder (nonacute phase of the disease), PANSS total score ≤120, received risperidone long- acting for ≥2 months.	Risperidone long-acting injection, adjustable dose (upper limit of 50 mg) every 2 weeks (N=16) vs. Paliperidone palmitate adjustable dose (upper limit of 150 mg) every 4 weeks (N=14)	28 weeks	Age, year: 45.0  Gender, % female: 38.0  Ethnicity: Japanese (% NR)

Author, Year	Other Population Characteristics	Total N	Benefits Outcomes
Koshikawa, 2016  Companion: Takekita, 2016	Duration of illness, year*: 13.8  PANSS total score, mean: 80.6  Schizoaffective disorder, %: 5.0	30	Risperidone long-acting injection vs. paliperidone palmitate  Koshikawa, 2016: Social Functioning Scale total score, mean change from baseline (SD): -1.64 (17.56) vs. 14.60 (18.75), p=0.038  No difference in PANSS total score between treatment groups at 6 months  Takekita, 2016: PANSS total score, mean change from baseline to 6 months (SD): -5.09 (8.18) vs. -1.70 (5.08), p=0.349

Author, Year	Harms Outcomes	Funding	Quality Rating
Koshikawa, 2016  Companion: Takekita, 2016	Risperidone long-acting injection vs. paliperidone palmitate  Koshikawa, 2016: Overall AEs, n: 0 vs. 2  Takekita, 2016: DIEPSS** total score, mean change from baseline (SD): -0.09 (0.30) vs. 0.30 (1.06), p=0.220	Funding: NR  *Duration of illness calculated based on average age at onset and average age at study enrollment.  **Drug-induced extrapyramidal symptoms scale.	Fair

Author, Year	Setting Country	Inclusion Criteria	Interventions and Ns per Group	Duration (intervention and longest followup)	Age Gender Race/Ethnicity
Li, 2014	China	Adults (18 to 65 years) with a DSM-IV diagnosis of schizophrenia.	Aripiprazole 10 to 30 mg/day orally (n=139) vs. Risperidone 2 to 6 mg/day orally (n=140)	6 weeks	Age, year: 32.4  Gender, % female: 67.0  Ethnicity, %: Han Chinese 100
Lieberman, 2005 (CATIE Study) Rosenheck, 2014 Fervaha, 2014 Caroff, 2011 Arnold, 2013	57 sites United States	Patients age 18-65, DSM-IV criteria for schizophrenia, be appropriate candidates for oral therapy (patient's assessment in conjunction with clinician), have adequate decisional capacity to decide to participate.	Olanzapine 7.5 mg Quetiapine 200 mg Risperidone 1.5 mg Perphenazine 8 mg Ziprasidone 40 mg  The dose of medications was flexible, ranging from one to four capsules daily, and was based on the study doctor's judgment	78 weeks	Mean age: 40.6 years 26% female Ethnicity: white 60%; black 35%; Hispanic 12%; 5% other
Liu, 2014	China	Female patients (age 18 to 44 years) with first-episode schizophrenia diagnosis based on Chinese Classification of Mental Disorders-3rd edition.	Risperidone 3.4 mg/day (mean) orally (n=40) vs. Quetiapine 420 mg/day (mean) (n=40)	52 weeks	Age, years: 29.0  Gender, % Female: 100  Ethnicity, % Asian: 100 (Chinese)

Author, Year	Other Population Characteristics	Total N	Benefits Outcomes
Li, 2014	Duration of illness: 7.3 years PANSS severity of illness: 87.1 Schizoaffective, %: 0 Substance use, %: 0	279	Aripiprazole 10 to 30 mg/day vs. risperidone 2 to 6 mg/day  PANSS responders ( $\geq 30\%$ decrease in total score from baseline), n/N (%): 99/139 (71.0) vs. 107/140 (76.0); $p=0.323$
Lieberman, 2005 (CATIE Study) Rosenheck, 2014 Fervaha, 2014 Caroff, 2011 Arnold, 2013	Depression 28% Alcohol dependence or alcohol abuse 25% Drug dependence or drug abuse 29% Obsessive-compulsive disorder 5% Other anxiety disorder 14%	NR/NR/1493	<p><b>Rosenheck 2014</b> Olanzapine vs. quetiapine vs. risperidone PANSS, difference in total score from perphenazine at 18 months: 1.79 (95% CI -0.04 to 3.54) vs. -0.30 (95% CI -2.08 to 1.49) vs. -1.92 (95% CI -3.70 to -0.14)</p> <p><b>Fervaha 2014</b> Olanzapine vs. quetiapine vs. risperidone Life satisfaction score, difference in total score from perphenazine at 12 months: 0.15 (SD 1.62) vs. 0.26 (SD 1.30) vs. 0.32 (SD 1.55); <math>p=0.93</math></p> <p><b>Caroff 2011: Tardive dyskinesia vs. no tardive dyskinesia</b> No difference in time to discontinuation (<math>p=0.743</math>), rates of discontinuation (74% vs. 74%), or change in PANSS total score (<math>p=0.366</math>)</p> <p><b>Arnold 2013: Ethnicity subgroups</b> No differences between whites, blacks, and Hispanics in all-cause discontinuations, discontinuation due to adverse events, change in total PANSS scores, or quality of life.</p>
Liu, 2014	Duration of illness, mean months: 4.5 PANSS severity of illness: 80.4	80	Risperidone 3.4 mg/day vs. quetiapine 420 mg/day  PANSS total score, change at 12 weeks: -37.2 vs. -40.9

Author, Year	Harms Outcomes	Funding	Quality Rating
Li, 2014	<p>Aripiprazole 10 to 30 mg/day vs. risperidone 2 to 6 mg/day</p> <p>Overall AE, n/N (%): 105/139 (76.0) vs. 116/140 (83.0)  Withdrawal due to AE, n/N (%): 0 vs. 1/140 (&lt;1.0)  Clinically relevant weight increase (<math>\geq 7\%</math> in body weight), n/N (%): 4/139 (3.0) vs. 17/140 (12.0)  Extrapyramidal symptoms, n/N (%): 35/139 (25.0) vs. 34/140 (24.0)  Akathisia, n/N (%): 32/139 (23.0) vs. 31/140 (22.0)  Cardiovascular system, n/N (%): 11/139 (8.0) vs. 9/140 (6.0)</p>	<p>Jiangsu Nhwa Pharmaceutical Co., Ltd and the National Key Project (2012ZX09303-003), and the Shanghai municipal incubation grant for talented researcher of health care (XBR2011049)</p>	Fair
Lieberman, 2005 (CATIE Study) Rosenheck, 2014 Fervaha, 2014 Caroff, 2011 Arnold, 2013	NR	NR	Good
Liu, 2014	<p>Risperidone 3.4 mg/day vs. quetiapine 420 mg/day</p> <p>Dropout rate of 20% over 1-year treatment period.</p>	Huzhou Ministry of Technology	Fair

Author, Year	Setting Country	Inclusion Criteria	Interventions and Ns per Group	Duration (intervention and longest followup)	Age Gender Race/Ethnicity
Maat, 2014	The Netherlands	Patients ages 16 to 50 years with clinical diagnosis of schizophrenia (DSM- IV-TR criteria) and an adequate understanding of Dutch.	Aripiprazole 7.5 or 15 mg (n=20) vs. Risperidone 1 or 2 mg (n=28)  Dosage could be increased to maximum of 6 mg risperidone or 30 mg of aripiprazole.	8 weeks	Age, mean years: 26.2  Gender, % female: 20.4  Ethnicity, %: Caucasian: 66.2 Moroccan: 8.4 Surinamese: 8.3 Turkish: 6.2 Other: 10.9

Author, Year	Other Population Characteristics	Total N	Benefits Outcomes
Maat, 2014	Baseline drug abuse, %: Nicotine: 69.8 Alcohol: 64.1 Cannabis: 49.8 Cocaine: 9.2	80 randomized (48 completed study)	Aripiprazole vs. risperidone  Mean change in PANSS total score (SD): -17.24 (15.89) vs. -12.85 (17.58) Quality of life, mean (SD): 4.88 (9.41) vs. 6.47 (12.73); p=0.37 Mean change in SFS* (SD): 4.94 (17.55) vs. -3.25 (17.14); p=0.35

Author, Year	Harms Outcomes	Funding	Quality Rating
Maat, 2014	Aripiprazole vs. risperidone  Discontinuations due to lack of tolerability, n/N (%): 6/38 (15.8) vs. 6/42 (14.3)	Bristol-Myers Squibb	Poor

Author, Year	Setting Country	Inclusion Criteria	Interventions and Ns per Group	Duration (intervention and longest followup)	Age Gender Race/Ethnicity
McEvoy, 2014 (ACCLAIMS)	22 US clinical research sites: March 2011 to July 2013	Inclusion: Adults with schizophrenia or schizoaffective disorder who were clinically assessed to be at risk of relapse or likely to benefit from a long-acting injectable antipsychotic.	Haloperidol decanoate 25-200 mg (n-145); Paliperidone palmitate 39-234 mg (n-145);	Monthly for as long as 24 months	Paliperidone versus haloperidol: Age, mean (SD): 43 (12.6); 45 (12.3); % Men: 106 (73.1%); 110 (75.9); Race, White: 56 (38.6%); 54 (37.2%); Race, Black: 83 (57.2%); 83 (57.2%); Race, Other: 6 (4.1%); 8 (5.5%); Spanish, Hispanic, or Latino: 6 (4.1%); 8 (5.5%);

Author, Year	Other Population Characteristics	Total N	Benefits Outcomes
McEvoy, 2014 (ACCLAIMS)	Paliperidone versus haloperidol: Age at first treatment, mean (SD): 23 (9.3); 24 (10.9); Age at first antipsychotic med, mean (SD): 26 (9.0); 27 (10.1)	311	Adjusted HR for rate of efficacy failure: Paliperidone compared to haloperidol: HR=0.98 (95% CI: 0.64 to 1.47); Paliperidone: 49 (33.8%) experienced efficacy failure; Haloperidol: 47 (32.4%) experienced efficacy failure.

Author, Year	Harms Outcomes	Funding	Quality Rating
McEvoy, 2014 (ACCLAIMS)	<p>Weight change at 6 months, as least squares mean weight change:  Paliperidone: +2.17 kg (95% CI 1.25 to 3.09);  Haloperidol : -0.96 kg (95% CI -1.88 to -0.04).  Weight change at 24 months:  Paliperidone: 6.04 kg (95% CI 2.88 to 9.20); Haloperidol :  -3.88 (95% CI -7.92 to -0.73); p&lt;0.001; AIMS Global  Severity Score (incidence of AIMS &gt;2), n(%):  Paliperidone: 28 (21.4%); Haloperidol: 30 (23.85); p=0.57;  BAS Global Score (incidence of BAS ≥3), n (%);  Paliperidone: 4 (2.8%); Haloperidol: 15 (10.6%); p=0.006;  SAS Mean Score (Incidence of SAS ≥1), n (%);  Paliperidone: 109 (79%); Haloperidol: 101 (74.8%);  Maximum levels of serum prolactin (men):  Paliperidone: 34.56 mcg/L (95% CI 29.75 to 39.37);  Haloperidol : 15.41 mcg/L (95% CI 10.73 to 20.08); p&lt;0.001;  Maximum levels of serum prolactin (women):  Paliperidone: 75.19 (95% CI 63.03 to 87.36);  Haloperidol: 26.84 (95% CI 13.29 to 40.40); p&lt;0.001.  Global rating scale of akathisia  Paliperidone: 0.73 (95% CI 0.59 to 0.87);  Haloperidol: 0.45 (95% CI 0.31 to 0.59); p=0.006.</p> <p>No significant difference in mean change in glycated hemoglobin, glucose, total cholesterol, LDL, triglycerides or lowest recorded HDL.  No significant differences in mean change in AIMS global score or tardive dyskinesia.</p> <p>AEs (ITT, n=147 per arm);  Any serious AE: Paliperidone=53 (36.1%); Haloperidol=45 (30.6%);  Suicidal or homicidal ideation: Paliperidone=23 (15.6%); Haloperidol=21 (14.3%);  Any moderate or severe AE: Paliperidone=100 (68.0%); Haloperidol=88 (59.9%)</p>	NIMH	Good

Author, Year	Setting Country	Inclusion Criteria	Interventions and Ns per Group	Duration (intervention and longest followup)	Age Gender Race/Ethnicity
Naber, 2013 RECOVER NCT00600756	International	Adults 18 to 65 year, a DSM-IV-TR diagnosis of schizophrenia, schizoaffective disorder or schizophreniform disorder, and a certain level of reduced subjective well-being.	Quetiapine XR (400 to 800 mg) (n=395) vs. Risperidone (2 to 6 mg) (n=403) once daily	52 weeks	Age, mean year: 39.65  Gender, % female: 41.8  Ethnicity, %: NR
Naber, 2015 QUALIFY  Companion: Potkin, 2015	International	Adults (18 to 60 y) with DSM-IV-TR–defined schizophrenia.	Aripiprazole 300 to 400 mg monthly injection (n=148) vs. Paliperidone 50 to 150 mg (EU/Canada) or Paliperidone palmitate 78 to 234 mg (US) monthly injection (n=147)	28 weeks	Age, years: 41.9  Gender, % female: 40.2  Ethnicity, %: White: 69.7 Black/African American: 27.0 Asian: 1.5 Other: 1.1 Unknown: 0.7

Author, Year	Other Population Characteristics	Total N	Benefits Outcomes
Naber, 2013 RECOVER NCT00600756	Concurrent substance abuse: Alcohol use, %: 12.1 Cannabis use, %: 1.9 DSM-IV schizophrenia subtype diagnosis, %: Schizoaffective disorder of bipolar type: 8.3 Schizoaffective disorder of depressive type: 7.8 Median duration of present episode, m: 2.5 Mean years since first known schizophrenia diagnosis: 11.35 Hospitalizations due to schizophrenia in the previous 6 months, % patients: 16.1 SWN-K total score, mean: 64.35	798	Quetiapine XR (400 to 800 mg) vs. Risperidone (2 to 6 mg)  Discontinued at month 12, n (%): 183 (46.3) vs. 176 (43.7)  CGI-SCH overall severity: Month 12 mean, change from baseline to m 12, mean (SD): 2.3 vs. 2.5; -1.5 (1.07) vs. -1.3 (1.15) CGI change score improved n (%): 176/379 (83.4) vs. 178/392 (78.4) Treatment effect for improved: 1.46 (95% CI 0.87 to 2.43) CDSS Total score: Month 12 mean, change from baseline to m 12, mean (SD): 1.7 vs. 2.6; -5.3 (5.10) vs. -3.8 (4.6) Treatment difference: -1.0 (95% CI -1.6 to -0.4)
Naber, 2015 QUALIFY  Companion: Potkin, 2015	CGI-S severity of illness score: 4.0	295	Aripiprazole 300 to 400 mg monthly vs. paliperidone 50-150 mg/ paliperidone palmitate 78 to 234 mg monthly  Naber, 2015: Heinrichs-Carpenter QLS, LSM change from baseline at week 28: 7.47 (n=136) vs. 2.80 (n=132) LSM difference 4.67 (95% CI 0.32 to 9.02)  Potkin, 2015: QLS total score, difference in change from baseline to 28 weeks: 4.67 (95% CI 0.32 to 9.02) QLS total score, LS mean changes (SE): 7.47 (1.53) vs. 2.80 (1.62) CGI-S LS mean (SE) change from baseline to 28 weeks: -0.75 (0.07) vs. -0.46 (0.07) LS mean difference: -0.28 (95% CI -0.48 to -0.09) Patient-rated Tool scale, LSM treatment difference: -0.70 (95% CI: -1.51 to 0.12) Clinician-rated WoRQ total scores, LSM treatment difference: -1.16 (95% CI: -1.96 to -0.37) 'No' to 'Yes' in readiness to work at 28 weeks, %: 26.4 vs. 12.2

Author, Year	Harms Outcomes	Funding	Quality Rating
<p>Naber, 2013 RECOVER NCT00600756</p>	<p>Quetiapine XR (400 to 800 mg) vs. Risperidone (2 to 6 mg)</p> <p>Discontinued due to AE at month 12, n (%): 53 (13.4) vs. 44 (10.9)</p> <p>n/N (%); number of events TEAE: 238/391 (60.9); 791 vs. 258/402 (64.2); 834 TEAE leading to discontinuation: 57/391 (14.6); 72 vs. 48/402 (11.9); 80 Serious TEAE: 45/391 (11.5); 49 vs. 26/402 (6.5); 31 Serious TEAE leading to death: 0 (0) vs. 1/402 (0.2); 1 Weight increased: 18/391 (4.6); 18 vs. 25/402 (6.2); 25</p>	<p>AstraZeneca.</p>	<p>Fair</p>
<p>Naber, 2015 QUALIFY</p> <p>Companion: Potkin, 2015</p>	<p>Aripiprazole 300 to 400 mg monthly vs. paliperidone 50-150 mg/ paliperidone palmitate 78 to 234 mg monthly</p> <p>Naber, 2015: Overall AE: % (n/N): 62/119 (52.1%) vs. 72/109 (66.1%)* Overall withdrawal due to AE: % (n/N): 11.1% (16/148) vs. 19.7% (27/147) AE related extrapyramidal symptoms: % (n/N) Akathisia: 2.5% (2/119) vs. 1.8% (2/109)* Dystonia: 0.8% (1/119) vs. 0%* Extrapyramidal disorder: 0% vs. 0% * Muscle rigidity: 0.8% (1/119) vs. 0 Muscle spasms: 0 vs. 0.9% (1/109) Tremor: 1.7% (2/119) vs. 1.8% (2/109)</p> <p>Potkin, 2015: Discontinuation due to AE, n/N (%): 16/144 (11.1) vs. 27/137 (19.7) Weight increased, n/N (%): 0 (0.0) vs. 2/137 (1.5) ASEX total score mean (SD) change from baseline to 28 weeks: -1.9 (6.3) vs. -0.8 (6.1) Decrease in sexual dysfunction at 28 weeks, %: 30 vs. 4</p>	<p>H. Lundbeck A/S and Otsuka Pharmaceutical Development &amp; Commercialization, Inc</p> <p>*Treatment continuation period (main period of interest with respect to safety evaluation (n=119 vs. n=109)</p>	<p>Fair</p>

Author, Year	Setting Country	Inclusion Criteria	Interventions and Ns per Group	Duration (intervention and longest followup)	Age Gender Race/Ethnicity
Nemeth, 2017	66 study centers in 11 European countries (Bulgaria, Croatia, Czech Republic, France, Hungary, Poland, Romania, Serbia, Spain, Russia, and Ukraine)	Adults aged 18–65 years who had a diagnosis of schizophrenia (DSM-IV-TR) criteria, with onset occurring at least 2 years before screening. Patients had to be in a stable condition for at least 6 months before screening (i.e., no psychiatric hospital admissions, acute exacerbations, or imprisonments) and meet the following clinical criteria: predominant negative symptoms for at least 6 months (based on medical records/investigator judgment), Positive and Negative Syndrome Scale factor score for negative symptoms (PANSS-FSNS) of 24 or more, and score of 4 or more on at least two of three core negative PANSS items (blunted affect, passive or apathetic social withdrawal, lack of spontaneity, and flow of conversation) at screening and during a lead-in period. Additionally, patients were required to have a PANSS-FSNS score that diverged less than 25% from the screening score during a lead-in period.	Cariprazine 4.5 mg (target dose) daily (n=230) Risperidone 4 mg (target dose) daily (n=231)	26 weeks	Cariprazine vs. risperidone: Age, mean years: 40.2 vs. 40.7 Gender, % female: 46 vs. 39 Ethnicity, %: White: 96 vs. 94 (Ethnicity not recorded: 4 vs. 6)

Author, Year	Other Population Characteristics	Total N	Benefits Outcomes
Nemeth, 2017	Cariprazine vs. risperidone: Time from schizophrenia diagnosis to informed consent, years: 11.98 vs. 12.96 Number of acute exacerbations <5: 64% (148/230) vs. 55% (126/230) 5-10: 27% (61/230) vs. 34% (79/230) 11-15: 5% (11/230) vs. 9% (20/230) >15: 4% (10/230) vs. 2% (5/230)	461 randomized 460 included in safety population 456 in modified ITT	Cariprazine vs. risperidone: CGI-S score: -0.95 vs. -0.74, LSMD -0.21 (95% CI -0.36 to -0.06), p=0.0052 PANSS total score: -16.90 vs. -14.80, LSMD -2.10 (95% CI -4.34 to 0.13), p=0.065 PANSS negative subscale score: -8.63 vs. -7.16, LSMD -1.48 (95% CI -2.38 to -0.57), p=0.0015 CGI-I score: 2.53 vs. 2.89, LSMD -0.37 (95% CI -0.55 to -0.19), p<0.0001 SAS items 1-8: 0.01 vs. 0.05, LSMD 0.05 (95% CI -0.21 to 0.12), p=0.58 Achieved response to treatment (decrease $\geq$ 20% in PANSS-FSNS): 69% (157/227) vs. 58% (133/229), OR 2.08, p=0.0022, NNT 9

Author, Year	Harms Outcomes	Funding	Quality Rating
Nemeth, 2017	Cariprazine vs. risperidone: Discontinuations due to adverse events: 10% (22/230) vs. 11% (25/230) Any serious adverse events: 3% (7/230) vs. 3% (7/230) Any adverse events: 53% (123/230) vs. 57% (131/230)	Gedeon Richter Plc (Budapest, Hungary)	Good

<b>Author, Year</b>	<b>Setting Country</b>	<b>Inclusion Criteria</b>	<b>Interventions and Ns per Group</b>	<b>Duration (intervention and longest followup)</b>	<b>Age Gender Race/Ethnicity</b>
Parabiaghi, 2016  Companion to Parabiaghi, 2011	Italy	>18 years old, DSM-IV diagnosis of schizophrenia based on the Mini-International Neuropsychiatric Interview.	Aripiprazole 19.7 mg/day* (N=100) vs. Olanzapine 13.7 mg/day* (N=103) Haloperidol 4.0 mg/day (N=97)	52 weeks	Age, years: 42.7  Gender, % female: 42.0  Ethnicity: Italian (% NR)
Park, 2013	South Korea	Age 18-65 years; diagnosed by a psychiatrist with a brief psychotic disorder, schizophreniform disorder, schizophrenia, or schizoaffective disorder (DSM-IV criteria); no other active illness.	Ziprasidone 40 mg initial dose (range 20-160 mg; mean 109 mg) (n=10) vs. Olanzapine 10 mg initial dose (range 5-20 mg; mean 11.6 mg) (n=10)	12 weeks	Age, mean years: 33.0  Gender, % female: 50.0  Ethnicity: NR
Robinson, 2015  See also: Zhang, 2015	US and Canada	Adults and adolescent (15 to 40 years) with DSM-IV-defined diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder or psychotic disorder not otherwise specified.	Aripiprazole 5 to 30 mg/day orally (n=106) vs. Risperidone 1 to 6 mg/day orally (n=103)	12 weeks	Age, years: 22.1  Gender, % female: 29  Ethnicity, %: Caucasian: 24.0 African-American: 37.0 Hispanic: 10.0 Other/mixed: 9.0

Author, Year	Other Population Characteristics	Total N	Benefits Outcomes
Parabiaghi, 2016  Companion to Parabiaghi, 2011	Duration of illness, year from first psychiatric contact (%): 0-2 years: 12.0 3+ years: 72.0  Hospitalization, % in-patient: 20.0  Current substance abuse or dependence, %: 5.0  Antipsychotic drug-naïve, %: 6.0	300	NR
Park, 2013	PANSS total score at baseline: 74.8	20	NR
Robinson, 2015  See also: Zhang, 2015	Duration of current illness/psychosis, weeks: 125.5* BPRS-A severity of illness: 45.1 Schizoaffective, %: 3 Substance use, %: 0 Antipsychotic drug naïve: lifetime antipsychotic drug medication treatment 2 weeks or less	209	Aripiprazole 5-30 mg/day vs. risperidone 1-6 mg/day  Cumulative response rate at week 12**: 62.8% (95% CI 50.8 to 74.8) vs. 56.8% (95% CI 43.9 to 69.9) Mean time to response, w: 8.0 (95% CI 7.9 to 8.1) vs. 8.2 (95% CI 7.3 to 9.2) Discontinuation of controlled treatment before 12 weeks (n, due to safety concerns): 0 vs. 3 (1 metabolic syndrome, 1 tardive dyskinesia, 1 hematologic abnormalities )  <b>Zhang, 2015</b> C/C homozygotes vs. T carriers BPRS Positive Symptoms Scores at week 12 (Least Square Estimate, mean±SE, unadjusted; sample size): 6.51±0.52 38 vs. 7.64±0.57 33 p=0.143

Author, Year	Harms Outcomes	Funding	Quality Rating
Parabiaghi, 2016  Companion to Parabiaghi, 2011	Aripiprazole vs. olanzapine vs. haloperidol  Metabolic syndrome at 1 year in ITT population, n/N (%): 37/100 (37.0) vs. 48/103 (46.6) vs. 41/97 (42.3); aripiprazole vs. olanzapine: OR 1.50 (95% CI 0.8 to 2.6); aripiprazole vs. haloperidol: OR 0.88 (95% CI 0.62 to 1.24); olanzapine vs. haloperidol: OR 1.10 (95% CI 0.81 to 1.51)  Withdrawals due to AEs, n (%): 6 (12.6) vs. 6 (18.8) vs. 8 (22.2); aripiprazole vs. olanzapine: OR 0.98 (95% CI 0.3 to 3.19); aripiprazole vs. haloperidol: OR ); olanzapine vs. haloperidol: OR 1.10 (95% CI 0.81 to 1.51)	Funding: IRCCS-Istituto di Ricerche Farmacologiche 'Mario Negri' and Bristol-Myers Squibb  *Mean dose of treatment.	Fair
Park, 2013	Ziprasidone vs. olanzapine  Body weight, median change in kg (IQR): 3.43 (0.61, 9.20) vs. 10.35 (9.27, 14.65); p=0.016	Pfizer Pharmaceuticals Korea	Poor
Robinson, 2015  See also: Zhang, 2015	Aripiprazole 5-30 mg/day vs. risperidone 1-6 mg/day  Sexual dysfunction, % (n/N): 7.8% (8/102) vs. 12.5% (12/96)	National Institutes of Health and NARSAD Young Investigator Grant to J.A.G. from the Brain & Behavior Research Foundation  *Report states: "duration of psychotic symptoms before study week (weeks)"  **Response criteria based on BPRS-A and CGI scores	Fair

Author, Year	Setting Country	Inclusion Criteria	Interventions and Ns per Group	Duration (intervention and longest followup)	Age Gender Race/Ethnicity
San, 2012 RCT Spain	Spain	18 years old, presence of psychotic symptoms at admission (4 or more on PANSS items 1, 3, 5 or 6 and 3), naïve to psychotropic drugs. Excluded: presence of major medical or neurological disease or mental retardation, suspicion of substance use directly contributing to the symptoms	Haloperidol 1.5–8.5 olanzapine 7.5–40 risperidone 1.5–7.0 quetiapine 100–1500 and ziprasidone 40–240 mg/day	52 weeks	Mean age 25.6 74.6% male Ethnicity NR
Sanz-Fuentenebro, 2013	Spain	Diagnosis of schizophrenia or schizophreniform disorder (DSM-IV criteria); age <35 years in males and <40 years in females.	Clozapine 12.5-900 mg (n=15) vs. Risperidone 2-10 mg (n=15)	1 year	Age, mean years: 24.5  Gender, % female: 30.0  Ethnicity, %: Caucasian: 77.0

Author, Year	Other Population Characteristics	Total N	Benefits Outcomes
San, 2012 RCT Spain	BMI 22.7 82.5% single 46.5% elementary school education 44.7% diagnosed with schizophrenia Duration of untreated psychosis: 52.5 weeks baseline PANSS: 91.0	114	Proportion discontinuing treatment by 12 months: 85.7% (18/21) vs. 40% (10/25) vs. 56.5% (13/23) vs. 64% (16/20) vs. 80% (16/25) Mean time to all-cause discontinuation: haloperidol 125 days; olanzapine 260 days; quetiapine 187 days; risperidone 206 days; ziprasidone 142 days (p=0.005)
Sanz-Fuentenebro, 2013	Active substance abuse: Alcohol, %: 10 Cannabis, %: 3.3 Cocaine, %: 6.7 DUP*, months: 9.9	30	Clozapine vs. Risperidone  Total rate of protocol discontinuation was 53.3% Maintenance of initial treatment, weeks (SD): 41.1 (15.9) vs. 23.3 (20.1); p=0.015 LOCF** change from baseline in PANSS total score, mean (SD): -35.5 (26.6) vs. -17.1 (27.7) 12-month change from baseline in PANSS total score, mean (SD): - 48.0 (24.7) vs. NR

Author, Year	Harms Outcomes	Funding	Quality Rating
San, 2012 RCT Spain	Discontinuations due to adverse events: 11.1% haloperidol; 20% olanzapine, 7.7% quetiapine; 6.2% risperidone; 25% ziprasidone Time to discontinuation due to adverse events: NR UKU scores were higher in haloperidol group compared to second-generation drugs, and no differences were found between the other drugs. Weight gain ranged from 3 kg with ziprasidone to 9 kg with olanzapine but no statistically significant differences were found.	La Marato' TV3 Foundation and Eli Lilly	Good
Sanz-Fuentenebro, 2013	NR	Spanish Ministry of Health, Ayudas para el fomento de la traslación de la aplicación terapéutica de medicamentos huérfanos y terapias avanzadas (grant number: TRA-035); and the Instituto de Salud Carlos III (grant number: PI-060219).	Poor

Author, Year	Setting Country	Inclusion Criteria	Interventions and Ns per Group	Duration (intervention and longest followup)	Age Gender Race/Ethnicity
Savitz, 2016	International	Adult patients age 18 to 70 years with a DSM-IV diagnosis of schizophrenia.	Paliperidone palmitate 3-month injection (N=504) vs. Paliperidone palmitate 1-month injection (N=512)	48 weeks	Age, years: 38.7  Gender, % Female: 47%  Ethnicity, %: White: 58% African American: 6% American Indian: 35% Other: 1%
Shoja Shafti, 2015	Iran	Female inpatients diagnosed as having schizophrenia, according to the DSM-V.	Aripiprazole 5 to 25 mg/day orally (n=25) vs. Quetiapine 25 to 600 mg/day (n=25)	12 weeks	Age, years: 36.8  Gender, % female: 100  Ethnicity: NR

Author, Year	Other Population Characteristics	Total N	Benefits Outcomes
Savitz, 2016	Prior hospitalizations, %: None: 41.0 Once: 37.0 Twice: 16.0 Three times: 3.0 Four or more: 2.0 PANSS Total Score at baseline: 85.0 (ITT); 57.8 (double blind) Previous antipsychotic use, %: 76.0 (new-generation antipsychotics)	1,016	Paliperidone palmitate 3-month injection vs. paliperidone palmitate 1-month injection  Relapse-free patients, % (n/N)*: 8.0% (37/504) vs. 9.0% (45/512) Clinical response ( $\geq 20\%$ reduction in PANSS total score), % (n/N): 50.1% (241/481) vs. 47.3% (237/501) $\geq 30\%$ : 36.4% (175/481) vs. 36.1% (181/501) $\geq 40\%$ : 26.4% (127/481) vs. 27.1% (136/501) Symptomatic remission (meeting Andreasen remission criteria 6 months before end of study), %: 58.0% vs. 59.0% Psychiatric hospitalizations, % (n/N): 3.0% (16/504) vs. 4.0% (22/512)
Shoja Shafti, 2015	Duration of illness, y: 6.4 Hospitalization, %: 100 CGI-S severity of illness: 3.74 Schizoaffective, %: 0	50	NR

Author, Year	Harms Outcomes	Funding	Quality Rating
Savitz, 2016	<p>Paliperidone palmitate 3-month injection vs. paliperidone palmitate 1-month injection</p> <p>Overall AEs, % (n/N): 68.0% (342/504) vs. 66.0% (340/512)  Withdrawals due to AEs, % (n/N): 3.0% (15/504) vs. 3.0% (13/512)  All-cause mortality, n: 1 vs. 3  Diabetes mellitus/hyperglycemia, % (n/N): 2.6% (13/504) vs. 4.9% (25/512)  Extrapyramidal AEs, % (n/N): 8.0% (42/504) vs. 7.0% (38/512)  Weight change of ≥7%, % (n/N): 27.0% (136/504) vs. 30.0% (150/512)  Tardive dyskinesia, n: 1 vs. 1</p>	<p>Funding: Otsuka, Janssen, Cilag, and Lundbeck</p> <p>*Relapse as ≥1 of following:  1) hospitalization for schizophrenia symptoms; 2) 25% increase in PANSS total score for patients scoring &gt;40 or a 10-point increase for patients scoring ≤40; 3) increase PANSS items; 4) clinically significant self-injury or violent behavior resulting in suicide, injury, or damage; 5) suicidal/homicidal ideation</p>	Good
Shoja Shafti, 2015	<p>Aripiprazole 5 to 25 mg/day vs. quetiapine 25 to 600 mg</p> <p>Withdrawal due to AE, n/N (%): 0 vs. 0</p>	<p>Research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors</p>	Fair

<b>Author, Year</b>	<b>Setting Country</b>	<b>Inclusion Criteria</b>	<b>Interventions and Ns per Group</b>	<b>Duration (intervention and longest followup)</b>	<b>Age Gender Race/Ethnicity</b>
Subotnik, 2015	United States	Adults (18 to 45 years) with DSM-IV diagnosis of schizophrenia, schizoaffective disorder, mainly depressed type, or schizophreniform disorder, with an onset of psychosis within the last 2 years.	Risperidone modal dosage 25 mg biweekly (12.5 to 37.5 mg) long acting injectable (n=43) vs. Risperidone modal dosage 2 mg daily (1.0 to 7.5mg) oral (n=43)  Both arms subsequently randomized in cognitive remediation or healthy-behaviors training.	52 weeks	Age, years: 21.5  Gender, % female: 22.0  Ethnicity, %: White: 49.0 Asian: 11.0 Native American: 5.0 African American: 28.0 Pacific Islander: 1.0 Mixed: 6.0
Tybura, 2013	Poland	Caucasian patients of Polish descent with paranoid schizophrenia (confirmed with Polish CIDI* and ICD-10 criteria).	Olanzapine 10-20 mg (n=19) vs. Ziprasidone 120-160 mg (n=20) vs. Perazine 300-600 mg (n=19)	3 months	Age, mean years (SD): 36.2 (12.0)  Gender, % female: 51.7  Ethnicity, %: Caucasian: 100.0
Tybura, 2014	Poland	Caucasian patients of Polish descent suffering from paranoid schizophrenia. Diagnosis based on Polish version of the CIDI and the ICD-10 criteria.	Ziprasidone 120-160 mg/day orally (n=59) vs. Olanzapine 10-20 mg/day orally (n=72) vs. Perazine 300-600 mg/day orally (n=60)	12 weeks	Age, years: 35.8  Gender, % female: 55.1  Ethnicity, %: Caucasian: 100 (Polish descent)

Author, Year	Other Population Characteristics	Total N	Benefits Outcomes
Subotnik, 2015	Duration of illness, months: 7.4 (time since psychosis onset) Severity of illness (BPRS): Thought disturbance factor at randomization: 2.1 Withdrawal-retardation factor at randomization: 1.9 Schizophrenia, %: 55.0 Schizophreniform disorder, %: 33.0 Schizoaffective, %: 12.0 Substance use, %: 0	86	Risperidone 25 mg biweekly long acting vs. risperidone 2 mg daily  Psychotic exacerbation/relapse, n/N (%)*: 2/40 (5.0) vs. 14/43 (33.0); P<0.001 Hospitalizations due to mental illness, n/N (%): 2/40 (5.0) vs. 8/43 (18.6); P=0.05 Early discontinuation due to inadequate treatment response, n/N (%): 1/40 (2.5) vs. 7/42 (17.0), P=0.01 Risk of exacerbation and/or relapse over time was significantly lower for long-acting injectable risperidone than for oral risperidone: p<0.004 Mean time to relapse, days: 298.5 vs. 218.6 Medication adherence was better for long-acting risperidone vs. oral risperidone: p<0.001 Medication adherence was associated with prevention of exacerbation and/or relapse (p=0.003) and control of breakthrough psychotic symptoms (p=0.04).
Tybura, 2013	Mean age (SD) at first psychotic episode, years: 26.9 (6.9)	58	Olanzapine vs. ziprasidone vs. perazine  PANSS total score (SD) after 3 months: -64.8 (18.9) vs. -75.2 (27.1) vs. - 68.0 (28.3)
Tybura, 2014	Duration of illness: 9.9 years* PANSS severity of illness: 99.8 Schizoaffective, %: 0 Antipsychotic drug naïve, %: 0	191	Ziprasidone 120-160 mg/day vs. olanzapine 10-20 mg/day vs. perazine 300-600 mg/day  All-cause discontinuation at week 12, n/N (%)**: 41/60 (68.0) vs. 52/72 (76.0) vs. 40/59 (68.0)

Author, Year	Harms Outcomes	Funding	Quality Rating
Subotnik, 2015	<p>Risperidone 25 mg biweekly long acting vs. risperidone 2 mg daily</p> <p>WAE, n/N (%): 4/40 (10.0) vs. 9/43 (21.0)</p>	<p>NIH and Janssen Scientific Affairs, LLC</p> <p>*Based on BPRS scale</p>	Fair
Tybura, 2013	NR	<p>Grant of Ministry of Science and High Education (grant no. N N402 456738) and by a Pfizer Independent Research Grant (grant no. 2005-0039).</p>	Poor
Tybura, 2014	NR	<p>Pfizer Independent Research Grant</p> <p>*Based mean age upon entering trial and mean age of first psychotic episode</p> <p>**Based on retention rate</p>	Fair

Author, Year	Setting Country	Inclusion Criteria	Interventions and Ns per Group	Duration (intervention and longest followup)	Age Gender Race/Ethnicity
Wani, 2015	India	Adult patients with schizophrenia who had achieved clinical stability with olanzapine and who were assessed as having metabolic syndrome using modified NCEP ATP-III criteria. Schizophrenia diagnoses were made using the DSM IV.	Olanzapine 10-20 mg/day orally (n=31) vs. Aripiprazole 5-20 mg/day orally (n=31)*	24 weeks	Age (years): 29.8  Gender, % female: 37.1  Ethnicity: Asian (Indian)

Author, Year	Other Population Characteristics	Total N	Benefits Outcomes
Wani, 2015	Duration of illness: 4.75 years PANSS severity of illness: 68.9 Antipsychotic drug naïve, %: 0	62	Olanzapine 10-20 mg/day vs. aripiprazole 5 to 20mg/day  All-cause hospitalization, n/N %: 2/26 (7.7) vs. 2/21 (9.5)

Author, Year	Harms Outcomes	Funding	Quality Rating
Wani, 2015	<p>Olanzapine 10-20 mg/day vs. aripiprazole 5 to 20mg/day</p> <p>Patients meeting modified NCEP ATP-III criteria for the presence of metabolic syndrome, n/N (%)**: 26/26 (100) vs. 15/31 (42.8); P&lt;0.001</p>	<p>Funding NR</p> <p>*With accompanying reduction of continuing olanzapine (reduction from 25% to 100% after 3 weeks</p> <p>**Based on modified NCEP ATP-III criteria for the Asian population (waist circumference, triglycerides, HDL, Systolic BP, fasting glucose)</p>	Fair

**Please see Appendix B. Included Studies for full study references**

AE=adverse event, AIMS=Abnormal Involuntary Movement Scale, ANOVA=analysis of variance, AP=antipsychotic, BARS=Brief Adherence Rating Scale, BAS=behavioral activation system, BHL=behavioral health lab, BP=blood pressure, BPRS=Brief Psychiatric Rating Scale, BMI=body mass index, BMS=Bristol-Myers Squibb, CATIE=Clinical Antipsychotic Trials of Intervention Effectiveness, CCMD-3=3<sup>rd</sup> edition of the Chinese Classification of Mental Disorders, CDSS=Calgary Depression Scale for Schizophrenia, CGI-I=Clinical Global Impressions-Improvement scale, CGI-S=Clinical Global Impressions-Severity scale, CHAT=clozapine haloperidol aripiprazole trial, CI=confidence interval, CIDI=Composite International Diagnostic Interview, CMHCs=Certified Mental Health Clinics, C-SSRS=Columbia Suicide Severity Rating Scale, DC=discontinuation, DIEPSS=drug-induced extrapyramidal symptoms scale, d/o=diagnosis, DUP=duration of untreated psychosis, ECG=electrocardiogram, EPS=extrapyramidal symptoms, ETOH=alcohol/ethanol, EU=European Union, F=female, FGA=first-generation antipsychotic, GAF=global assessment functioning, HDL=high-density lipoprotein, HR=hazard ratio, ICD-10=10th revision of the International Statistical Classification of Diseases and Related Health Problems, IQR=interquartile range, ITT=intention-to-treat, J&J=Johnson and Johnson, kg=kilogram, LAI=long acting injectable, LDL=low-density lipoprotein, LOCF=last observation carried forward, LOS=living on site, LUNSERS=Liverpool University Neuroleptic Side Effect Rating Scale, LS=life skills, LSM=life skills mean, M=male, MINI=International Neuropsychiatric Interview, mos=months, NARSAD=National Association for Research on Schizophrenia and Depression, NCEP ATP-III=National Cholesterol Education Program Adult Treatment Panel III, NSD=no significant difference, PANSS=positive and negative syndrome scale, PSP=Personal and Social Performance scale, QLS=Quality of Life Scale, RCT=randomized controlled trial, RR=relative risk, SANS=scale for assessment of negative symptoms, SAPS=scale for the assessment of positive symptoms, SAS=social adjustment scale, SD=standard deviation, SDS=Sheehan Disability Scale, SE=side effects, SES=socioeconomic status, SFS=social functioning scale, SGA=second-generation antipsychotic, TD=tardive dyskinesia, TEAE=treatment emergent adverse event, UKU=UKU Side Effect Rating Scale, VA=Veteran's Affairs, WAE=withdrawals due to adverse events, w=weeks, WHO=World Health Organization, XR=extended release, y=years, YMRS=Young Mania Rating Scale

**Appendix Table E-3. Data abstraction of systematic reviews of assertive community treatment**

<b>Author, Year</b>	<b>Aims</b>	<b>Databases and Timeperiod Covered (actual dates)</b>	<b>Number of Studies Number of Patients</b>	<b>Characteristics of Identified Articles: Study Designs</b>	<b>Characteristics of Identified Articles: Populations</b>	<b>Characteristics of Identified Articles: Interventions</b>
Marshall 2000a (ACT)	Effect of ACT vs standard community care in people with severe mental disorders	MEDLINE (1966-1995); CINAHL (1982-1997); EMBASE (1980-1997); PsycLIT (1974-1997); SCISEARCH (1997); Cochrane Schizophrenia Group Register of Trials (1997)	14 studies (ACT vs. standard care) n=2,821	Randomized controlled trials of ACT vs. standard care	Age 18-65 years with schizophrenia or schizophrenia-like disorders; bipolar disorder; or depression with psychotic features. Proportion with schizophrenia: <50%: 3 studies; >50%: 8 studies; unknown: 3 studies	ACT: Any intervention described as Assertive Community Treatment, Assertive Case Management or PACT; or as being based on the Madison, Treatment in Community Living, Assertive Community Treatment or Stein and Test models.

Author, Year	Outcomes Reported	Effectiveness Outcomes	Harms Outcomes	Funding/ Comments	Quality rating
Marshall 2000a (ACT)	Symptoms: combined BPRS, Brief Symptom Inventory, Colorado Symptom Index Function: Contact with law enforcement Function: Not living independently Function: Unemployed Social function: combined Social Adjustment Scale, Personality and Social Network Adjustment Scale Mortality	<u>ACT vs. standard care</u> Symptoms (3 studies): SMD -0.14 (95% CI -0.36 to 0.08; I <sup>2</sup> =23%) Function, contact with law enforcement - -Arrested (2 studies): OR 1.17 (95% CI 0.60 to 2.29; I <sup>2</sup> =0%) -Imprisoned (4 studies): OR 1.19 (95% CI 0.70 to 2.01; I <sup>2</sup> =27%) -Police contact (2 studies): OR 0.76 (95% CI 0.32 to 1.79; I <sup>2</sup> =84%) Function, not living independently (3 studies): OR 0.46 (95% CI 0.29 to 0.74; I <sup>2</sup> =0%) Function, unemployed (2 studies): OR 0.31 (95% CI 0.19 to 0.50; I <sup>2</sup> =34%) Function, social function (3 studies): SMD 0.03 (95% CI -0.28 to 0.34; I <sup>2</sup> =7%)	<u>ACT vs. standard care</u> Mortality (5 studies): OR 1.13 (95% CI 0.35 to 3.68; I <sup>2</sup> =0%)	Manchester University Department of Psychiatry; Nuffield Trust	Good

**Please see Appendix B. Included Studies for full study references**

ACT=assertive community treatment, BPRS=Brief Psychiatric Rating Scale, CI=confidence interval, OR=odds ratio, PACT=Program of Assertive Community Treatment, SMD=standard mean difference

Appendix Table E-4. Data abstraction of randomized controlled trial of assertive community treatment

Author, Year	Setting Country	Inclusion Criteria	Interventions and Ns per Group	Description of Intervention	Description of Comparator	Duration (intervention and longest followup)	Age Gender Race/Ethnicity
Sytema 2007	Winchschoten, Netherlands; local mental health organization	Long-term severely mentally ill patients with Health of the Nation Outcomes Scales total score of $\geq 15$ .	Assertive community treatment (n=59) vs. standard community mental health care (n=59)	Assertive community treatment teams included the following characteristics: maximum FTE caseload of 10 patients; work style: shared caseload. All patients are discussed in weekly and daily team meetings Location: Always there where the patient is Engagement with client: Assertive; keep trying to make contact; no drop-out policy. Working hours: office hours 24-h arrangement: The 24-h service of the institute Skills: Multidisciplinary team; all skills are available for each client because all team members may have contact with each client Disciplines available: Psychiatrist, Psychologist Psychiatric Nurse, Social Worker, Client Worker Dependency Specialist	Community mental health teams included the following characteristics: maximum FTE caseload: 40 patients Work style: Individual caseloads Location: Mostly at the office, partly at home of the patient Engagement with client: Not assertive; the client should express a need for care; client will drop out of contact when contact is refused or when the client does not show up Working hours: Office hours 24-hour arrangement: The 24-hour service of the institute Skills: Client and practitioner are matched according to the needs of the patient and the skills of the practitioner Disciplines available: Psychiatrist, Psychologist, Psychiatric Nurse, Social Worker	April 2004-June 1, 2005 Followup until August 2006, maximum of 2 years of followup	Demographics (intervention, control) Age, mean years: 41.5, 37 Gender, % female: 56%, 63% Ethnicity, % NR

Author, Year	Other Population Characteristics	Total N	Benefits Outcomes	Harms Outcomes	Funding	Quality Rating
Sytema 2007	Years in treatment (intervention, control) 7.9, 8.6	118	<p>Patients out of contact with mental health services (last 12 months of observation): 0 vs.13; Peto OR 0.10 95% CI 0.03 to 0.33</p> <p>Homeless patients (end of observation): 1 vs. 5; Peto OR 0.24 95% CI 0.05 to 1.25</p> <p>BRPS (intervention, control) Baseline: 42, 45 After 12 months: 38, 42</p> <p>MANSA Baseline: 4.7, 4.5 After 12 months: 4.5, 4.3</p> <p>SFS Baseline: 102, 103 After 12 months: 102, 103</p>	NR	ZonMW, The Netherlands Organization for Health Research and Development	Fair

**Please see Appendix B. Included Studies for full study references**

BPRS=Brief Psychiatric Rating Scale, FTE=full time employment, GAF=global assessment functioning, MANSA=Manchester Short Assessment of Quality of Life, SFS=Social Functioning Scale

**Appendix Table E-5. Data abstraction of randomized controlled trials of cognitive adaptation training\***

Author, Year	Interventions (n) Duration	Population characteristics	Results	Quality Rating
Velligan 2008a and Velligan 2009	CAT (n=40) Usual care (n=40)  Duration of intervention and followup: 24 months	CAT vs. usual care: Mean age 41 vs. 40 years 50% vs. 51% female Race/ethnicity - 42% vs. 36% Hispanic 47% vs. 36% white Mean SOFAS 44.1 vs. 45.6	Function, based on SOFAS score, improved more with CAT vs. usual care (effect size 1.10)	Fair
Velligan 2008b	CAT (n=73) Usual care (n=32)  Duration of intervention: 9 months Duration of longest followup: 15 months	CAT vs. usual care: Mean age 38 vs. 39 years 45% vs. 38% female Race/ethnicity – 34% vs. 28% Hispanic 34% vs. 45% white Mean SOFAS 45.8 vs. 45.6	For function, based on SOFAS score, there was nonsignificant trend favoring CAT over usual care (p<0.07).  Significantly fewer patients in the CAT groups relapsed compared with usual care.	Fair
Velligan 2015b	CAT (n=68) Usual care (n=37)  Duration of intervention: 9 months Duration of longest followup: 15 months	CAT vs. usual care: Mean age 41 vs. 40 year 46% vs. 46% female Race/ethnicity – 40% Hispanic 31% white 25% Black Mean MCAS score 3.7 vs. 3.8	Function, based on MCAS score, improved more in CAT vs. non-CAT groups (effect size 0.4).	Fair

**Please see Appendix B. Included Studies for full study references**

CAT=cognitive adaption training, MCAS= Multnomah Community Ability Scale, SOFAS=Social and Occupational Assessment Scale

\*Overall evidence for this intervention was insufficient

**Appendix Table E-6 Data abstraction of systematic reviews of cognitive-behavioral therapy**

Author, Year	Aims	Databases and Timeperiod Covered	Number of Studies Number of Patients	Characteristics of Identified Articles: Study Designs	Characteristics of Identified Articles: Populations	Characteristics of Identified Articles: Interventions
Velthorst 2015	Effect of CBT on negative symptoms; assess which subgroups most likely to respond	Databases not reported (1993-July 2013)	30 studies n=2312	Randomized controlled trials of CBT targeted at psychotic symptoms, negative symptoms, social functioning, self esteem or cannabis use; duration of followup up to 12 months	Patients with resent onset (3 studies) and mixed chronic and resent onset (27 studies) schizophrenia; outpatients (18 studies), inpatient (4 studies), mixed inpatient and outpatient (7 studies) <i>*table only provides this information for 29 studies</i>	CBT vs. control (usual care, supportive care, befriending, waitlist, psychoeducation)
Jauhar 2014	Effect of CBT on schizophrenia symptoms	MEDLINE (1993-March 2013); PsycINFO (1993-March 2013); EMBASE (1993-March 2013); CCRCT (1993-March 2013)	50 studies n=3947	Randomized controlled trials of CBT reporting positive, negative and overall symptom outcomes	Patients with schizophrenia or schizoaffective or nonaffective functional psychosis; inpatient/outpatient not reported	CBT vs. control (waitlist, usual care, or intervention designed to control for nonspecific effects of psychotherapy)

Author, Year	Outcomes Reported	Effectiveness Outcomes	Harms Outcomes	Funding	Quality Rating
Velthorst 2015	Negative symptoms	<p><u>CBT vs. control, standardized mean difference</u></p> <p>Change in negative symptoms as a secondary outcome (28 trials): 0.093 (95% CI -0.028 to 0.214; <math>I^2=62\%</math>)</p> <p>Change in negative symptoms as a primary outcome (2 trials): 0.157 (95% CI -0.010 to 0.409; <math>I^2</math> not reported)</p> <p>Change in negative symptoms, 3-6 months (13 trials): 0.207 (95% CI -0.049 to 0.463; <math>I^2</math> not reported)</p> <p>Change in negative symptoms, 9-12 months (10 trials): 0.01 (95% CI -0.020 to 0.182; <math>I^2</math> not reported)</p> <p><u>Subgroup analyses - treatment strategies</u></p> <p>CBT focused on functioning (4 trials): 0.137 (95% CI -0.301 to 0.574)</p> <p>CBT focused on self esteem (1 trial): 1.76 (95% CI 0.823 to 2.70)</p> <p>CBT with many behavioral techniques (number of studies not reported): 0.253 (95% CI not reported; <math>p=0.04</math>)</p> <p>CBT with few behavioral techniques (number of studies not reported): 0.020 (95% CI not reported; <math>p=0.84</math>)</p> <p>Individual CBT (number of studies not reported): 0.210 (95% CI not reported; <math>p=0.011</math>)</p> <p>Group CBT (number of studies not reported): -0.174 (95% CI not reported; <math>p=0.20</math>)</p>	Not reported	None reported	Good
Jauhar 2014	Overall symptoms Positive symptoms Negative symptoms Hallucinations	<p><u>CBT vs. control, effect size</u> (<i>negative effect size favors CBT</i>)</p> <p>Overall symptoms (34 trials): -0.33 (95% CI -0.47 to -0.19; <math>I^2=68\%</math>)</p> <p>Positive symptoms (33 trials): -0.25 (95% CI -0.37 to -0.13; <math>I^2=49\%</math>)</p> <p>Negative symptoms (34 trials): -0.13 (95% CI -0.25 to -0.01; <math>I^2=48\%</math>)</p> <p>Hallucinations (15 trials): -0.34 (95% CI -0.61 to -0.06; <math>I^2=70\%</math>)</p>	Not reported	Centro de Investigacion Biomedica en Red de Salud Mental (CIBERSAM)	Good

<b>Author, Year</b>	<b>Aims</b>	<b>Databases and Timeperiod Covered</b>	<b>Number of Studies Number of Patients</b>	<b>Characteristics of Identified Articles: Study Designs</b>	<b>Characteristics of Identified Articles: Populations</b>	<b>Characteristics of Identified Articles: Interventions</b>
Jones 2010	Effect of CBT for people with schizophrenia	Cochrane Schizophrenia Group Trials Register (March 2010; comprises searches of CINAHL, EMBASE, MEDLINE PsycINFO)	9 comparing CBT with nonactive control (of 20 studies included in review) n=895	Randomized controlled trials of CBT; duration of followup 8 weeks to 5 years (mean 20 months)	Patients with current diagnosis of schizophrenia (at least 50% of study participants); inpatient/outpatient not reported	CBT vs. nonactive control (psychosocial interventions which act as a control for the nonspecific effects of therapy); active-control comparisons not abstracted as not akin to usual care

Author, Year	Outcomes Reported	Effectiveness Outcomes	Harms Outcomes	Funding	Quality Rating
Jones 2010	Mortality Global state Quality of life Engagement with services Adverse effects  (Symptoms addressed in more recent Jauhar 2014 review)	<u>CBT vs. nonactive control</u> Global state - relapse: • Long term (>1 year since onset; 3 trials): RR 1.06 (95% CI 0.87 to 1.28) Global state - general functioning score mean difference (higher score = better outcome): • Short term (<24 weeks since onset; 2 trials): 9.02 (95% CI 4.29 to 13.75) • Long term (3 trials): 4.20 (95% CI -0.63 to 9.03) Global state - Social and Occupational Functioning Assessment Scale score mean difference (higher score = better outcome) : • Short term (1 trial): 9.09 (95% CI 2.79 to 15.39) • Long term (1 trial): 1.30 (95% CI -6.26 to 8.86) Ability to maintain treatment (5 trials): RR 0.90 (95% CI 0.68 to 1.19; $I^2=0\%$ )	<u>CBT vs. nonactive control</u> Mortality (1 trial; reported as suicide): RR 0.68 (95% CI 0.12 to 3.93)	None	Good

**Please see Appendix B. Included Studies for full study references**

BPRS= Brief Psychiatric Rating Scale, CBT=cognitive-behavioral therapy, CI=confidence interval, RR=relative risk, SMD=standard mean difference

**Appendix Table E-7. Data abstraction of randomized controlled trials of cognitive-behavioral therapy**

Author, Year Trial Name	Setting Country	Inclusion Criteria	Interventions and Ns per Group	Description of Intervention	Description of Comparator	Duration (intervention and longest followup)
Freeman 2015	2 centers United Kingdom	Age 18-65 years with a current persecutory delusion as defined by Freeman and Garety; score at least 3 on the conviction scale of the PSYRATS; delusion had persisted for at least 3 months; a clinical diagnosis of schizophrenia, schizoaffective disorder, or delusional disorder; score of more than 44 on the PSWQ Exclude: Primary diagnosis of alcohol or substance dependency or personality disorder; organic syndrome or learning disability; adequate English language skills to engage in therapy; current CBT	CBT + standard care (n=73)  Standard care alone (n=77)	CBT to reduce worry: Psychoeducation about worry, identification and reviewing of positive and negative beliefs about worry, increasing awareness of the initiation of worry and individual triggers, use of worry periods, planning activity at times of worry (which could include relaxation), and learning to let go of worry. Practical application: the use of worry periods (confining worry to about a 20-min set period each day) and planning of activities at peak worry times.	Standard care: Delivered according to national and local service protocols and guidelines. Generally consists of prescription antipsychotic drugs, visits from a community mental health worker, and regular outpatient appointments with a psychiatrist.	Intervention: 8 weeks Followup: 24 weeks
Lysaker 2009	2 centers United States	Confirmed diagnosis of schizophrenia or schizoaffective disorder in post-acute phase of illness (no hospitalizations, changes in psychotropic medication or housing in the month before entering the study. Excluded: diagnosis of mental retardation or another neurological disorder	IVIP n=50  Social support n=50	IVIP: weekly group CBT centered on a rotating curriculum of four 2-week modules focusing on addressing dysfunctional beliefs about self and work experiences + individual sessions	Social support: usual VA work support including weekly hour group sessions offering support and discussion of work-related issues and concerns	26 weeks

Author, Year Trial Name	Age Gender Race/Ethnicity	Other Population Characteristics	Total N	Outcome Measures
Freeman 2015	<u>CBT vs. standard care</u> Mean age 41 vs. 42 years 42% vs. 43% female Race - 93% vs. 89% White 1% vs. 0% Black 0% vs. 3% Chinese 0% vs. 4% Indian 6% vs. 4% other	<u>CBT vs. standard care</u> Age at onset not reported Time since diagnosis (reported as time in contact with services) - <1 year: 8% vs. 9% 1-5 years: 16% vs. 22% 6-10 years: 22% vs. 16% 11-20 years: 25% vs. 34% >20 years: 29% vs. 19% Baseline symptom severity - PANSS mean score: 82.0 (SD 13.6) vs. 79.0 (SD 13.5) CHOICE mean score: 49.4 (SD 17.3) vs. 49.5 (SD 18.5) WEMWEBS mean score: 36.4 (SD 9.6) vs. 34.5 (SD 9.2) Comorbidity not reported Substance use not reported Treatment resistance not reported Socioeconomic status not reported Pregnancy status not reported	150	Symptoms - Delusions (PSYRATS - Delusion) Worry (PSWQ) Distress (PSYRATS - Distress) Overall symptoms (PANSS) Paranoia (GPTS) Rumination (PTQ)  Quality of Life - Self-confidence, coping skills, sense of being in control (CHOICE) Wellbeing (WEMWBS)  Mortality Suicide attempts Serious violent incidents
Lysaker 2009	<u>IVIP vs. support</u> Mean age 46 vs. 47 years 16% vs. 14% female Race not stratified by intervention group - 58% African-American 41% Caucasian 1% Latino	<u>IVIP vs. support</u> Age at first hospitalization: 28 vs. 27 years Baseline symptom severity - Total PANSS: 76.86 vs. 76.30 SF-36 physical health: 61.22 vs. 58.30 SF-36 mental health: 58.64 vs. 60.32 Comorbidities not reported Substance use not reported Treatment resistant not reported Socioeconomic status not reported Pregnancy status not reported	100	Function - Mean total hours worked Mean hours worked per week Mean number of weeks at least 1 hour worked Work Behavior Inventory (WBI; scale 35-175; higher score=better outcome)

Author, Year Trial Name	Benefits Outcomes	Harms Outcomes	Funding	Quality Rating
Freeman 2015	<u>CBT vs. standard care</u> Overall symptoms, mean PANSS: 71.5 (SD 15.4) vs. 76.3 (SD 16.7); treatment effect 6.16 (SE 1.69; p<0.001) Quality of life, CHOICE: 61.6 (SD 21.4) vs. 52.5 (SD 22.4); treatment effect 10.45 (SE 2.42; p<0.001) Quality of life, WEMWEBS: 40.2 (SD 10.8) vs. 36.6 (SD 10.5); treatment effect 10.45 (SE 2.42; p<0.001)	Mortality: 0/73 vs. 0/77 Suicide attempts: 2/73 vs. 4/77 Serious violent incidents: 2/73 vs. 1/77	UK Medical Research Council	Good
Lysaker 2009	<u>IVIP vs. support</u> Mean total hours worked: 360.86 (SD 246.58) vs. 228.82 (SD 193.36); p<0.01 Mean hours worked per week (data from figure): 11.5 vs. 6.5; p=NS (not reported) Mean number of weeks at least 1 hour worked: 18.64 (SD 9.12) vs. 14.46 (SD 10.40); p<0.05 Mean WBI: 113.34 (SD 13.05) vs. 105.43 (SD 15.76); p<0.05	Not reported	VA Rehabilitation Research and Development Service	Fair

Author, Year Trial Name	Setting Country	Inclusion Criteria	Interventions and Ns per Group	Description of Intervention	Description of Comparator	Duration (intervention and longest followup)
Malik 2009 and Turkington 2002	6 centers United Kingdom	ICD-10 diagnosis of schizophrenia with ongoing positive/negative symptoms or were at risk of relapse Excluded: active relapse, primary diagnosis of substance or alcohol dependence, organic brain disease, learning disability severe enough to interfere with rating.	CBT: n=257 (76% [205/257] included in 2-year followup results)  Usual care: n=165 ([125/165] included in 2-year followup results)	CBT: 6 CBT sessions with a mental health nurse over 2-3 months. With patient consent, main caregivers were offered 3 sessions of CBT	Usual care: Regular review by a psychiatrist, free antipsychotic medication including clozapine, access to day hospital, social support in the community	24 months
Velligan 2015b	Community mental health center United States	Age 18 to 60 years; diagnosis of schizophrenia or schizoaffective disorder; ongoing oral antipsychotic treatment; persistent positive symptoms (expanded BPRS score $\geq 4$ ); SOFAS $< 70$	CBT: n=43  Usual care: n=42 (also included CAT individual arm - see CAT section)	CBT: Weekly session focused on patient-identified problems, particularly those that interfered with daily functioning or were distressing, normalizing symptoms, and using CBT techniques to develop alternative explanatory models of events.	Usual care: Case management and medication followup appointments provided by the local community mental health center.	Intervention: 9 months Followup: 15 months
Zimmer 2007	Single center Brazil	18-65 years; ICD-10 diagnosis of schizophrenia or schizoaffective disorder; no organic brain disease; no history of drug use; not participating in a rehabilitation program; resident of Porta Alegre, Brazil; stable symptomatology; absence of acute symptoms for 6 months preceding study entry	IPT: n=23  Usual care: n=43	IPT: one 60-min session per week for a period of 3 months, incorporating five modules: Cognitive Differentiation; Social Perception; Verbal Communication; Social Skills Training; Interpersonal Problem-Solving.	Usual care: individual outpatient consultations, conducted once every two weeks with psychiatry residents, according to the usual standard of care.	12 weeks

Author, Year Trial Name	Age Gender Race/Ethnicity	Other Population Characteristics	Total N	Outcome Measures
Malik 2009 and Turkington 2002	Not stratified by intervention group Mean age 40 years 23% female Race – 89% white 8% Black 3% other	<u>CBT vs usual care</u> Comprehensive Psychopathological Rating Scale 23.27 vs. 24.30	422 (78% [330/422] included at final followup)	Relapse (need for hospitalization)  Function - Occupational recovery (return to paid or voluntary work or resumption of education or training)
Velligan 2015b	<u>CBT vs. usual care</u> Mean age 30 vs. 40 years 54% vs. 46% female Race - 54% vs. 49% Hispanic 24% vs. 24% Black 22% vs. 27% white	<u>CBT vs. usual care</u> Mean MCAS: 3.8 (SD 0.3) vs. 3.8 (SD 0.4)	85 (CBT vs. Usual care; 87% [74/85] included at final followup)	Function - Community function (MCAS)
Zimmer 2007	<u>IPT vs. usual care</u> Mean age 36 vs. 39 years 15% vs. 31% female Race not reported	<u>IPT vs. usual care</u> Age at onset: 21 vs. 22 years Mean illness duration: 15 vs. 17 years GAF mean score: 34.70 (SD 4.27) vs. 35.25 (SD 5.46) SOFAS mean score: 34.20 (SD 5.31) vs. 35.81 (SD 5.56) SAS mean score: 2.02 (SD 0.33) vs. 2.15 (SD 0.46) WHOQOL-BREF mean score: 71.82 (SD 18.09) vs. 61.81 (SD 21.33)	66 (85% [56/66] included at final followup)	Function - Overall function (GAF; SOFAS; SAS)  Quality of life (WHOQOL-BREF)

Author, Year Trial Name	Benefits Outcomes	Harms Outcomes	Funding	Quality Rating
Malik 2009 and Turkington 2002	<u>CBT vs. usual care</u> Proportion of patients with relapse: 25% (64/257) vs. 35% (57/165); RR 0.72 (95% CI 0.53 to 0.97) Mean time to relapse: 356.8 days (SD 241.9) vs. 296.1 days (SD 215.7); p=0.03 Proportion of patients with occupational recovery: 10% (21/205) vs. 14% (17/125); RR 0.75 (95% CI 0.41 to 1.37)	Not reported	Pfizer UK	Fair
Velligan 2015b	<u>CBT vs. usual care</u> Data not shown for CBT vs. usual care; narratively reported a nonsignificant treatment effect on function with CBT using a regression model that included time and treatment by time effects. No description of the effect of usual care was reported.	Not reported	NIMH	Fair
Zimmer 2007	<u>IPT vs. usual care</u> GAF mean score: 39.50 (SD 5.36) vs. 33.81 (SD 5.12); p=0.00 SOFAS mean score: 43.25 (SD 6.54) vs. 34.14 (SD 4.53); p=0.00 SAS mean score: 1.86 (SD 0.47) vs. 2.27 (SD 0.61); p=0.04 WHOQOL-BREF mean score: 39.15 (SD 27.82) vs. 35.63 (SD 24.89); p=0.03	Not reported	Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq); Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES); Instituto de Cooperação Científica e Tecnológica Internacional (ICCTI); Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS); Brazilian Ministry of Education.	Fair

**Please see Appendix B. Included Studies for full study references**

BPRS=Brief Psychiatric Rating Scale, CAT=cognitive adaptation therapy, CBT=cognitive-behavioral therapy, CHOICE=Choice of Outcome in Cbt for psychosEs, CI=confidence interval, GAF=global assessment functioning, GPTS=Green Paranoid Thoughts Scale, IPT=integrated psychological therapy, IVIP=Indianapolis Vocational Intervention Program, MCAS=Multnomah Community Ability Scale, NS=not significant, PANSS=positive and negative syndrome scale, PSWQ=Penn State Worry Questionnaire, PSYRATS=Psychotic Symptom Rating Scales, PTQ=Preservative Thinking Questionnaire, RR=relative risk, SAS=Social Adjustment Scale, SD=standard deviation, SE=side effects, SF-36=36 Item Short Form Health Survey, SOFAS=Social and Occupational Functioning Assessment Scale, UK=United Kingdom, VA=Veteran's Affairs, WBI=work behavior inventory, WEMWBS=Warwick-Edinburgh Mental Wellbeing Scale, WHOQOL=World Health Organization Quality of Life

**Appendix Table E-8. Data abstraction of systematic reviews of cognitive remediation therapy**

Author, Year	Aims	Databases and Timeperiod Covered	Number of Studies Number of Patients	Characteristics of Identified Articles: Study Designs	Characteristics of Identified Articles: Populations
Cella 2017	Effect of cognitive remediation on negative symptoms	EMBASE, MEDLINE, Web of Science, PsycINFO, CCRCT (dates not reported)	45 studies (18 versus usual care + active intervention 26 studies) n=781	Randomized controlled trials comparing cognitive remediation to usual care or an active treatment reporting negative symptoms measured using a validated tool	Adults ≥ 18 with diagnosis of schizophrenia or schizoaffective disorder (at least 75% of study population; mean age 35 years, 71% male)
Wykes 2011	Effect of cognitive remediation on schizophrenia symptoms and function	EMBASE, MEDLINE, Current Contents, Web of Science, PsycINFO, CCRCT (start date not reported-June 2009)	39 studies n=2,104	Randomized controlled trials comparing cognitive remediation to standard care reporting cognitive or functional outcomes	Patients with schizophrenia exclusively (22 studies), combined schizophrenia and schizoaffective disorder (13 studies) or condition not reported (4 studies); inpatients (19 studies), outpatients (18 studies), mixed inpatient and outpatient (2 studies); mean age range 18-48 years (38 studies; one study enrolled adolescents, mean age 15 years)

Author, Year	Characteristics of Identified Articles: Interventions	Outcomes Reported	Effectiveness Outcomes	Harms Outcomes	Funding	Quality Rating
Cella 2017	Cognitive remediation versus usual care (18 studies) or active treatment (26 studies)	Negative symptoms measured by PANSS (34 studies), BPRS (6 studies), SANS (5 studies)	<u>Cognitive remediation vs treatment as usual</u> Negative symptoms: Random effects - SMD -0.36 (95% CI -0.52 to -0.20); Fixed effects - SMD -0.36 (95% CI -0.52 to -0.20)	Not reported	None reported	Good
Wykes 2011	Individual (31 studies) or group (9 studies) cognitive remediation (Cognitive Remediation Experts Workshop definition) vs. standard care. Treatment strategy drill and practice (21 studies); drill + strategy (19 studies) Mean treatment time 32 hours (range 4 to 130 hours); mean treatment duration 17 weeks (range 2 to 104 weeks); mean sessions/week 2.2 (range 0.6 to 5)	Total symptoms (combined measure including Scale for the Assessment of Positive Symptoms; Scale for the Assessment of Negative Symptoms; Positive and Negative Syndrome Scale; Brief Psychiatric Rating Scale; Present State Exam; Paranoid Depression Scale; Thought, language, and communication; Holtzman Inkblot Test) Function (combined measure including Bay Area Functional Performance Evaluation; Percent "sick talk"/ incoherence during the interview; Life skills profile; Global Assessment Scale; Nurses' Observation Scale for Inpatient Evaluation; Disability Assessment Schedule; Employment; Social Behaviour Schedule; Micro-Module Learning Test; Assessment of Interpersonal Problem-Solving Skills; Social adjustment)	<u>Cognitive remediation vs. control, effect size (mean)</u> Total symptoms, posttreatment (20 studies): 0.177 (95% CI 0.034 to 0.321) Function, posttreatment (12 studies): 0.418 (95% CI 0.216 to 0.620) Symptoms, posttreatment followup (8 studies): 0.174 (95% CI -0.031 to 0.481) Function, posttreatment followup (12 studies): 0.372 (95% CI 0.110 to 0.635)	Not reported	National Institute for Health Research; Maudsley National Health Service Foundation; Institute of Psychiatry, King's College London	Good

Please see Appendix B. Included Studies for full study references

CI=confidence interval

**Appendix Table E-9. Data abstraction of randomized controlled trials of cognitive remediation therapy**

Author, Year Trial Name	Setting Country	Inclusion Criteria	Interventions and Ns per Group	Description of Intervention	Description of Comparator
Deste 2015 and Vita 2011	3 centers Italy	Age 18–50 years; DSM-IV-TR diagnostic criteria for schizophrenia; followed in the rehabilitative centers of the Departments of Mental Health of Brescia and Cremona Hospitals (Italy). Excluded: Concomitant diagnosis of mental retardation or of substance use disorder; severe positive symptoms or impulsive behavior requiring a higher security setting; significant changes in psychopathologic status (requiring hospitalization or major change in pharmacologic treatment) in the last 3 months.	CR: n=39  Usual care: n=17	CR: Twice weekly sessions for 6 months including one of two CR modalities: (1) computerized CR including different neurocognitive exercises that can be divided into domain-specific exercises, aimed at training specific cognitive areas among those known to be impaired in schizophrenia (verbal memory, verbal fluency, psychomotor speed and coordination, executive function, working memory, attention) and nondomain-specific exercises; or (2) neurocognitive and social cognitive remediation integrated with psychosocial rehabilitation, made up of five modules, applied in the following order: cognitive differentiation, social perception, verbal communication, social skills, and interpersonal problem solving	Usual care: Noncognitive oriented rehabilitation interventions, with the same intensity and duration of CR

Author, Year Trial Name	Duration (intervention and longest followup)	Age Gender Race/Ethnicity	Other Population Characteristics	Total N	Outcome Measures
Deste 2015 and Vita 2011	Intervention: 6 months Followup: 1 year	<i>Not stratified by intervention group</i> Mean age 40 years 37% female Race not reported	<u>CR vs. usual care</u> Mean age at onset of illness: 25 years Mean duration of illness: 16 years Total PANSS: 88.06 (SD 18.26) vs. 79.12 (SD 19.84) Negative PANSS: 24.03 (SD 8.55) vs. 20.35 (SD 7.88)	54 (included at final followup; original trial [published separately] included 86 patients)	Symptoms - Overall symptoms (PANSS) Negative symptoms (PANSS)

Author, Year Trial Name	Benefits Outcomes	Harms Outcomes	Funding	Quality Rating
Deste 2015 and Vita 2011	<p><u>CR vs. usual care</u></p> <p>Overall symptoms, total PANSS, 6 months: 65.03 (SD 13.89) vs.80.29 (SD 22.01); SMD -0.90 (95% CI -1.50 to -0.31) ANCOVA p&lt;0.001</p> <p>Overall symptoms, total PANSS, 1 year: 67.59 (SD 14.68) vs. 79.65 (SD 23.05); SMD -0.68 (95% CI -1.26 to -0.09) ANCOVA p=0.001</p> <p>Negative symptoms, PANSS, 6 months: 24.03 (SD 8.55) vs. 20.35 (SD 7.88); SMD 0.43 (95% CI -0.14 to 1.01); ANCOVA p&lt;0.001</p> <p>Negative symptoms, PANSS, 1 year: 19.44 (SD 5.87) vs. 21.29 (SD 6.19); SMD -0.31 (95% CI -0.88 to 0.27); ANCOVA p=0.02</p> <p>Treatment maintenance: Narrative report of no difference between groups in number of sessions attended; p=0.08 (data not shown)</p>	Not reported	Health Authority of the Lombardia Region	Fair

Author, Year Trial Name	Setting Country	Inclusion Criteria	Interventions and Ns per Group	Description of Intervention	Description of Comparator
Farreny 2012	Single center Spain	Diagnosis of schizophrenia or schizoaffective disorder and more than 2 years of illness duration; finished primary studies or they were able to successfully complete a reading comprehension task used for 13-year-old students; Mini Mental State Examination score of 24 or more and a Global Assessment of Functioning score between 40 and 70. Excluded: Acute illness exacerbation; intellectual disability or any neurological disorder; participating in social skills training, cognitive remediation, or any other psychological intervention differing from usual care; switch of antipsychotic drug the month before the trial or during the 40 week study period; and/or a diagnosis of alcohol or drug dependence within 6 months prior to inclusion.	CR: n=34  Leisure control n=28	CR: Group meetings (4–6 participants), over 4 months twice a week and consisting of 32 sessions lasting 1 hour each focusing on problem solving and cognitive flexibility	Control: participation in 32 stimulating and socializing activities (e.g., card games, board games, “coffee & talk”, etc.).
Mueller 2015	8 outpatient centers Switzerland, Germany, and Austria	Age 18-50 years; diagnosis of schizophrenia or schizoaffective disorder; current enrollment in outpatient treatment; duration of illness >2 years; IQ>80 Excluded: Neurological disorders, substance dependence and/or abuse according to DSM-IV-TR or ICD-10 within 6 months before baseline assessments; hospitalization or changes in medication doses within 2 months before baseline assessments.	CR: n=81  Usual care: n=75	CR: 30 manualized, biweekly, 90-minute group (6-8 patients) sessions administered by a therapist and a co-therapist of four therapy modules: (1) speed of processing and attention and emotion processing; (2) verbal and visual learning and memory, and social perception and theory of mind; (3) reasoning and problem solving, and social schema; and (4) working memory and social attributions and emotion regulation. Modules progressively increase in complexity and emotional strain.	Usual care: Standard care including a broad array of interventions used in clinical practice for schizophrenia patients (e.g., medication, individual therapy, case management).

Author, Year Trial Name	Duration (intervention and longest followup)	Age Gender Race/Ethnicity	Other Population Characteristics	Total N	Outcome Measures
Farreny 2012	Intervention: 4 months Followup: 10 months	<u>CR vs. control</u> Mean age 41 years (not reported by intervention group) 32% female Race not reported	<u>CR vs. control</u> Total PANSS: 65.6 (SD 9.4) vs. 64.2 (SD 13) Negative PANSS: 19.2 (SD 4.1) vs. 18.1 (SD 5.4) Total LSP: 126.7 (SD 15.5) vs. 135.7 (SD 7.7) Mean duration of illness (not reported by intervention group): 18 years	62 (76% [47/62] included at final followup)	Symptoms - Overall symptoms (PANSS) Negative symptoms (PANSS)  Function - Overall function (LSP)
Mueller 2015	Intervention: 15 weeks Followup: 9 months	<u>CR vs. usual care</u> Mean age 35 vs. 34 years 36% vs. 25% female Race not reported	<u>CR vs. usual care</u> Mean duration of illness: 10 vs. 10 years Function (GAF): 49.12 (SD 8.12) vs. 48.40 (SD 8.9)	156 (78% [121/156] included at final followup)	Function - Overall function (GAF)

Author, Year Trial Name	Benefits Outcomes	Harms Outcomes	Funding	Quality Rating
Farreny 2012	<p><u>CR vs. control</u></p> <p>Overall symptoms, total PANSS, 16 weeks: 55.6 (SD 10.6) vs. 60.4 (SD 12.3); SMD -0.42 (95% CI -0.92 to 0.09); standardized effect size, based on longitudinal modeling: NS</p> <p>Overall symptoms, total PANSS, 40 weeks: 61.4 (SD 9.5) vs. 61.8 (SD 10.5); SMD -0.04 (95% CI -0.54 to 0.46); standardized effect size, based on longitudinal modeling: NS</p> <p>Negative symptoms, PANSS, 16 weeks: 16.6 (SD 4.1) vs. 17.5 (SD 5.2); SMD -0.19 (95% CI -0.69 to 0.31); standardized effect size, based on longitudinal modeling: 0.36 (95% CI 0.01 to 0.7)</p> <p>Negative symptoms, PANSS, 40 weeks: 17.6 (SD 3.7) vs. 16.9 (SD 3.8); SMD -0.18 (95% CI -0.32 to 0.69); standardized effect size, based on longitudinal modeling: NS</p> <p>Function, total LSP, 16 weeks: 137.4 (SD 6.9) vs. 133.6 (SD 11.4); SMD 0.41 (95% CI -0.10 to 0.91); standardized effect size, based on longitudinal modeling: 0.33 (95% CI 0.006 to 0.6)</p> <p>Function, total LSP, 40 weeks: 135.7 (SD 7.7) vs. 132.9 (SD 12); SMD 0.41 (95% CI -0.10 to 0.91); standardized effect size, based on longitudinal modeling: 0.43 (95% CI 0.07 to 0.78)</p> <p>Treatment maintenance: 85% (29/34) vs. 86% (24/28); RR 1.0 (95% CI 0.81 to 1.22)</p>	Not reported	Fundació La Caixa and Instituto de Salud Carlos III	Fair
Mueller 2015	<p><u>CR vs. usual care</u></p> <p>Function, GAF: 55.4 (SD 7.3) vs. 50.7 (SD 9.4); P&lt;0.01; SMD 0.56 (95% CI 0.34 to 0.88)</p> <p>Treatment maintenance: 90% (73/81) vs. 89% (67/75); RR 1.01 (95% CI 0.91 to 1.12)</p>	Not reported	Swiss National Science Foundation	Fair

Author, Year Trial Name	Setting Country	Inclusion Criteria	Interventions and Ns per Group	Description of Intervention	Description of Comparator
Twamley 2012	Two centers United States	Age ≥18 years with primary psychotic disorder (including schizophrenia, schizoaffective disorder, psychotic mood disorder, or psychosis NOS; 97% enrolled population diagnosed with schizophrenia or schizoaffective disorder) and fluency in English. Excluded: Dementia, neurological conditions affecting cognition, mental retardation, substance use disorder within the past month, and participation in other intervention trials.	CT: n=38  Usual care: n=31	CT: 12 weekly 2-hour sessions in groups of 5 patients and 2 therapists that included a review of homework, troubleshooting of strategy use, psychoeducation, and rationale for the targeted domains (1) prospective memory; (2) attention and vigilance; (3) learning and memory; and (4) executive functioning, demonstration and practice of each strategy, feedback on strategy use, and individualized discussion regarding implementation of the strategies in daily life.	Usual care: Standard pharmacotherapy

Author, Year Trial Name	Duration (intervention and longest followup)	Age Gender Race/Ethnicity	Other Population Characteristics	Total N	Outcome Measures
Twamley 2012	Intervention: 12 weeks Followup: 6 months	<u>CT vs. usual care</u> Mean age 38 vs. 31 years 36% vs. 33% female Race - 63% vs. 55% white; other races not reported	<u>CT vs. usual care</u> Negative symptoms, PANSS: 15.66 (SD 6.24) vs. 14.23 (SD 4.90) Function, UPSA score: 82.44 (SD 9.90) vs. 85.47 (SD 8.42) Quality of life, QOLI: 4.16 (SD 1.59) vs. 4.43 (SD 1.38)	69 (74% [51/69] included at final followup)	Symptoms - Negative symptoms (PANSS)  Function - Functional capacity (UPSA)  Quality of life - Self assessed quality of life (QOLI)

Author, Year Trial Name	Benefits Outcomes	Harms Outcomes	Funding	Quality Rating
Twamley 2012	<u>CT vs. usual care</u> Negative symptoms, PANSS, conclusion of treatment: adjusted effect estimate (for group and time) -4.57 (SE 1.44); p=0.002 Negative symptoms, PANSS, post-treatment followup: adjusted effect estimate (for group and time) -3.23 (SE 1.42); p=0.03 Function, UPSA, conclusion of treatment: adjusted effect estimate (for group and time) 3.12 (SE 2.31); p=0.181 Function, UPSA, post-treatment followup: adjusted effect estimate (for group and time) 6.57 (SE 2.21); p=0.004 Quality of life, QOLI, conclusion of treatment: adjusted effect estimate (for group and time) 0.52 (SE 0.38); p=0.17 Quality of life, QOLI, post-treatment followup: adjusted effect estimate (for group and time) 1.15 (SE 0.36); p=0.002 Treatment maintenance: 61% (23/38) vs. 90% (28/31); RR 0.67 (95% CI 0.51 to 0.89)	Not reported	National Alliance for Research on Schizophrenia and Depression; NIMH	Fair

**Please see Appendix B. Included Studies for full study references**

ANCOVA=analysis of covariance, CI=confidence interval, CR=cognitive remediation, CT=cognitive training, GAF=global assessment functioning, LSP=life skills profile, NIMH=National Institute of Mental Health, PANSS=positive and negative syndrome scale, UPSA=UCSD Performance-based Skills Assessment, QOLI=quality of life interview, RR=relative risk, SD=standard deviation, SE=side effects, SMD=standard mean difference

**Appendix Table E-10. Data abstraction of systematic reviews of family interventions**

Author, Year	Aims	Databases and Timeperiod Covered	Number of Studies Number of Patients	Characteristics of Identified Articles: Study Designs	Characteristics of Identified Articles: Populations	Characteristics of Identified Articles: Interventions	Outcomes Reported
Pharoah 2010	Effect of family psychosocial interventions in community settings for people with schizophrenia or schizophrenia - like conditions compared with standard care on schizophrenia outcomes	Cochrane Schizophrenia Group Trials Register (through 2008)	53 trials n=5767	Trials	Families of patients with schizophrenia or schizoaffective disorder  25/53 trials conducted in China	Any family-based psychosocial intervention for schizophrenia with >5 sessions (varied from 6 weeks to 3 years)	<p>Primary outcomes: Suicide and all sources of mortality Clinical global response Relapse</p> <p>Secondary outcomes: Global state Leaving the study early Mental state and behavior (positive and negative symptoms) Social functioning Employment status Work related activities Independent living Imprisonment Family outcomes QOL</p>

Author, Year	Effectiveness Outcomes
Pharoah 2010	<p>Any family-based psychosocial intervention for schizophrenia (&gt;5 sessions) vs. standard care  <i>Selected outcomes reported below (excludes studies with N&lt;50, skewed data, and most Chinese studies)</i></p> <p>Global state (relapse) at 0-6 months (3 trials, n=213): RR 0.71 (95% CI 0.46 to 1.09)</p> <p>Global state (relapse) at 13 to 18 months (3 trials, n=181): <b>RR 0.64 (95% CI 0.47 to 0.88)</b></p> <p>Global state (relapse) at 5 years (1 trial, n=63): RR 0.88 (95% CI 0.70 to 1.11)</p> <p>Global state (relapse) at 8 years (1 trial, n=62): RR 0.86 (95% CI 0.71 to 1.05)</p> <p>Mental state (average endpoint score, BPRS, high score=poor) at 6 months (1 trial, n=62): MD -0.30 (95% CI -0.90 to 0.30)</p> <p>Mental state (average change score, BPRS total, high score=poor) (3 trials, n=156): MD -0.30 (95% CI -0.76 to 0.17)</p> <p>Compliance (leaving the study early) at 3 to 6 months (7 trials; n=552): RR 0.92 (95% CI 0.59 to 1.42)</p> <p>Compliance (leaving the study early) at 7 to 12 months (10 trials; n=733): RR 0.74 (95% CI 0.53 to 1.03)</p> <p>Compliance (leaving the study early) at 25 to 36 months (3 trials; n=290): <b>RR 0.42 (95% CI 0.26 to 0.67)</b></p> <p>Compliance (leaving the study early) at 36 months (1 trial; n=63): RR 1.72 (95% CI 0.71 to 4.16)</p> <p>Compliance (poor compliance with standard community care) at 1 year (1 trial; n=51): RR 0.68 (95% CI 0.41 to 1.11)</p> <p>Compliance (poor compliance with standard community care) at 2 years (1 trial; n=51): RR 0.85 (95% CI 0.55 to 1.30)</p> <p>Social functioning (unemployed) at 6 to 12 months (5 trials; n=285): RR 1.06 (95% CI 0.89 to 1.25)</p> <p>Social functioning (unemployed) at 2 years (1 trial; n=52): RR 1.33 (95% CI 0.84 to 2.10)</p> <p>Social functioning (unemployed) at 3 years (1 trial; n=99): RR 1.19 (95% CI 0.92 to 1.55)</p> <p>Social functioning (unable to live independently) at 1 year (3 trials, n=164): RR 0.83 (95% CI 0.66 to 1.03)</p> <p>Social functioning (unable to live independently) at 3 years (1 trial, n=99): RR 0.82 (95% CI 0.59 to 1.14)</p> <p>QOL (average endpoint change; high score=good) at 1 year (1 trial; n=50): MD -5.05 (95% CI -15.44 to 5.34)</p>

Author, Year	Harms Outcomes	Funding/ Comments	Quality Rating
Pharoah 2010	<p>Any family-based psychosocial intervention for schizophrenia (&gt;5 sessions) vs. standard care  <i>Selected outcomes reported below (excludes studies with N&lt;50, skewed data, and most Chinese studies)</i></p> <p>Death (suicide) (7 trials; n=377): RR 0.79 (95% CI 0.35 to 1.78)            Death (other cause) (4 trials; n=176): RR 0.78 (95% CI 0.19 to 3.11)            Family outcome (burden, not improved/worse; objective burden related to self-sufficiency) at 1 year (1 trial, n=51): RR 0.53 (95% CI 0.21 to 1.37)            Family outcome (burden, not improved/worse; objective burden related to self-sufficiency) at 2 years (1 trial, n=51): RR 1.92 (95% CI 0.19 to 19.90)            Family outcome (burden, not improved/worse; objective burden related to social functioning) at 1 year (1 trial, n=51): RR 2.40 (95% CI 0.51 to 11.27)            Family outcome (burden, not improved/worse; objective burden related to social functioning) at 2 years (1 trial, n=51): RR 2.88 (95% CI 0.64 to 12.97)            Family outcome (burden, not improved/worse; subjective burden) at 1 year (1 trial, n=51): RR 1.44 (95% CI 0.60 to 3.46)            Family outcome (burden, not improved/worse; subjective burden) at 2 years (1 trial, n=51): RR 0.58 (95% CI 0.15 to 2.16)</p>	<p>McMaster University, Ontario Canada            Universidade Federal de Sao Paulo, Brazil            Hinchingsbrook Health Care,            Cambridgeshire, UK            International Clinical Epidemiology Network (INCLIN), USA</p>	Good

**Please see Appendix B. Included Studies for full study references**

CI=confidence interval, MD=mean difference, QOL=quality of life, RR=relative risk, UK=United Kingdom, US=United States of America

**Appendix Table E-11. Data abstraction of randomized controlled trials of family interventions**

Author, Year	Setting Country	Inclusion Criteria	Interventions and Ns per Group	Description of Intervention	Description of Comparator
Dyck, 2000	Large community health center in Spokane, Washington	Diagnosis of schizophrenia or schizoaffective disorder, 18-45 years of age, enrollment in a community outpatient facility in Spokane, residence with family of origin or regular contact with family, patients with either a history of substance abuse or current substance abuse were not excluded	Multifamily group: n=64 Standard care: n=31	Patients assigned to multiple-family group treatment received standard care plus the group treatment. Multiple-family group treatment was intended to improve illness management, social support, and coping skills for the patient and family members. The approach was based on the previous research reported by McFarlane and colleagues. Treatment interventions were designed to educate the family and patients about the biological underpinnings of schizophrenia and engage them in the treatment process by using a standardized protocol of videotapes, lecture, and written guidelines. Treatment components including ongoing support, formal clinical problem solving, and expansion of social support networks.	Patients assigned to standard care received usual services, including medication management, case management, and, for some patients, therapeutic and rehabilitation services. A treatment team consisting of a case manager, a nurse, a psychiatrist, and a social worker delivered the mental health services. The team provided clinical case management services and out-of-facility services as needed.
Garety 2008	Multicenter trial in UK	Diagnosis of non-affective psychosis, age 18-65, psychotic episode starting not more than 3 months before entering trial, rate of at least 4 on PANSS	Family intervention: n=28 Usual care: 27	Family intervention emphasized improving communication, offering discussion of up-to-date information about psychosis, problem-solving, reducing criticism and conflict, improving activity, and the emotional processing of grief, loss and anger. There was a particular focus on relapse prevention, including how family members might understand warning signs and agree on appropriated intervention, including medication	Usual care

Author, Year	Duration	Age Gender Race/Ethnicity	Other Population Characteristics	Total N	Benefits Outcomes	Harms Outcomes	Funding	Quality Rating
Dyck, 2000	2 years	MFG vs. Usual Care Age, mean years: 33, 30 % male: 72, 74 White, %: 94, 97	MFG vs. Usual care previous Lifetime hospitalizations, mean: 5, 5 Comorbid SUD %: 45, 50	63	MFG vs. Usual care: MSANS baseline 7.9, 8.7 Months 1-3: 7.4, 9.1 Months 4-6: 7.2, 8.9 Months 7-9: 7.2, 8.9 Months 10-12: 7.2, 8.4	Not reported	Grand NIMH	Poor
Garety 2008	9 months	FI vs. usual care: Age, mean, years: 35, 38.6 % Male: 71, 68 % White: 86, 82	FAI vs. usual care: % Employed: 11, 14 % Unemployed: 71, 71	56 + 27 in CBT group which is not included	FI vs. usual care: Mean difference in change scores: Total PANSS at 12 months: -6.44 (-14.12 to 1.24) Total PANSS at 24 months: -6.25 (-14.77 to 2.28) Negative PANSS at 12 months: -2.42 (-5.18 to 0.35) Negative PANSS at 24 months: -1.32 (-4.42 to 1.78) BAI at 12 months: -0.42 (-6.97 to 6.13) BAI at 24 months: -2.36 (-9.13 to 4.40) BDI at 12 months: 3.35 (-2.46 to 9.34) BDI at 24 months: -0.11 (-6.91 to 6.68) EuroQol at 24 months: -7.38 (-22.07 to 7.31)	Not reported	Welcome Trust Programme Grant	Good

Author, Year	Setting Country	Inclusion Criteria	Interventions and Ns per Group	Description of Intervention	Description of Comparator
Kopeolwicz 2012	Two community mental health centers in Los Angeles, California	Diagnosis of schizophrenia or schizoaffective disorder, 18-50 years of age, of Mexican origin and spoke Spanish fluently, history of nonadherence (had been without antipsychotic medication without medical authorization for 1 continuous week in the month prior to study enrollment), lived with their family of origin, had at least 1 family member willing to participate in the family treatment	MFG-A, n=64 MFG-S, n=54 Usual care, n=60	Culturally adapted, multifamily group therapy based on McFarlane's model that combines psychoeducation and skills training. MFG-S consisted of 3 initial "joining sessions" conducted separately with each family, a 6 hour "survival skills" educational workshop, and multifamily group sessions. Modified therapy in the MFG-A arm was to target improved adherence using principles of the Theory of Planned Behavior. MFG arms convened twice monthly in 90 minute sessions.	All study participants received treatment as usual. Rigid medication protocols were not used. Patients received all services as needed from the Mental Health Department of Los Angeles County. After inpatient discharge, patients received a psychiatric evaluation and medication, and if clinically stable, received monthly 20-minute sessions. If patients needed additional services or rehospitalization, that was accommodated.
Mayoral, 2015	Four mental health centers Spain	Age >18 years of age; confirmed diagnosis of schizophrenia according to the DSM-IV criteria; live with, at least, one relative; understand and speak Spanish; no admission within the 6 months prior to the beginning of the study; treatment with antipsychotic drugs; and capacity to sign an informed consent	Family group therapy (n=44) Treatment as usual (n=44)	24 weekly 60-minute sessions (in home or at a health center) of practical and role- playing exercises, with modules on disease and treatment, assessment of needs and family relations, communication skills training, and problem facing and solving	Usual care in specialized mental health centers

Author, Year	Duration	Age Gender Race/Ethnicity	Other Population Characteristics	Total N	Benefits Outcomes	Harms Outcomes	Funding	Quality Rating
Kopeolwicz 2012	Intervention and followup: 1 year	MFG-A vs. MFG-S vs. usual care Age, mean years: 33, 30, 33 % male: 67, 68, 61 Ethnicity Mexican American, %: 100, 100, 100	MFG-A vs. MFG-S vs. usual care % inpatient at entry: 88, 83, 84 Age at onset, years: 25, 23, 23 Lifetime hospitalizations, mean: 5.5, 5.6, 7.1 BPRS total score, mean: 87.5, 85.8, 81.1	178	BPRS: No differences at baseline among 3 groups, p=0.18 No differences at 12 month followup among 3 groups, p=0.32 All groups improved significantly at 12 month followup compared to baseline, p<0.001	Dropped out of treatment immediately after undergoing baseline assessments and before engaging in outpatient care: 26% (45/174) overall  Attrition (leaving treatment before a 12-month assessment could be made): MFG-A 27% vs. usual care 51%, p=0.007 MFG-S 37% vs. usual care 51%, p=0.11	National Institute of Mental Health	Poor
Mayoral, 2015	Intervention: 12 months Followup: 18 months	Family therapy vs. treatment as usual Age, mean years: 30 vs. 30 years % male: 85% vs. 78% Ethnicity: NR	Family therapy vs. usual care Previous admissions, mean: 2.83 vs. 2.17 Suicide attempts, mean: 1.3 vs. 3.0 BPRS total score, mean: 2.07 vs. 2.13	88	Family therapy vs. usual care End of treatment (12 months) BPRS total, mean: 1.66 vs. 2.14 (p=0.0046) Hospitalization: 0% vs. 21% (8/38); RR 0.06 (95% CI 0.004 to 1.04)  Post-intervention followup (18 months) BPRS total, mean: 1.70 vs. 2.05 (p=0.44)	NR	Spain's Ministry of Health	Fair

Author, Year	Setting Country	Inclusion Criteria	Interventions and Ns per Group	Description of Intervention	Description of Comparator
Sellwood 2001 Sellwood 2007 Barrowclough 1999	2 centers United Kingdom	ICD-10 diagnosis of schizophrenia, schizoaffective disorder or delusional disorder of at least 2 years' duration; at least one relapse of psychotic symptoms leading to in patient admission in the 2 years preceding study entry and a minimum duration of illness of 2 years; aged between 18 and 65 years; at least 10 hours of face-to-face contact with a carer for each week over the previous month.	Family CBT: n=39 Standard care: n=38	Family CBT: 10 to 20 sessions over 24 weeks aimed at delivering problem-solving techniques, cognitive-behavioral intervention for families, and cognitive-behavioral interventions with patients to reduce psychotic symptoms	Standard care: Standard psychiatric management by the clinical team, maintenance neuroleptic medication, monitoring through out-patient and community followup and the care programmed approach to case management.

Author, Year	Duration	Age Gender Race/Ethnicity	Other Population Characteristics	Total N	Benefits Outcomes	Harms Outcomes	Funding	Quality Rating
Sellwood 2001 Sellwood 2007 Barrowlough 1999	12 months	<i>Data not stratified by intervention group</i> Mean age 36 (SD 10) years 35% female Race- 85% White 9% Black 6% Southeast Asian	Family CBT vs. standard care Mean PANSS: 59.10 vs. 53.89 Mean score, Social Functioning scale: 99.61 vs. 101.12 Mean score, Global Assessment of Function: 43.00 vs. 45.79	79 (80% [63/79] included at final followup)	Family CBT vs. standard care Overall symptoms, PANSS, total score: 62.40 (95% CI 57.10 to 67.70) vs. 52.32 (47.92 to 56.72); p=0.005; mean change from baseline 1.08 (0.99 to 1.17) vs. 0.98 (0.89 to 1.06); p=0.09 Relapse: 16% (6/38) vs. 49% (19/39) Overall function, Social Functioning scale: 102.93 (SD 10.69) vs. 101.03 (SD 11.04); p=NS; mean change from baseline 1.29 vs. 2.42; p=NS Overall function, GAF: 42.67 (SD 10.88) vs. 48.50 (SD 8.81); p=0.02; mean change from baseline 1.50 vs. 1.50; p=NS	Not reported	National Health Service Tameside and Glossop Community Priority Care trust	Fair

Author, Year	Setting Country	Inclusion Criteria	Interventions and Ns per Group	Description of Intervention	Description of Comparator
Valencia, 2007	Single center Mexico	Outpatients age 16 to 50 with DSM-IV schizophrenia; taking antipsychotic medication; clinically stable in terms of psychotic symptoms (PANSS score <60); completed at least 6 years of elementary education; lived with their families and resided in Mexico City or the metropolitan area	SST: n=49  Usual care: n=49	SST: 48 weekly group sessions (75 mins/session) composed of seven sequential treatment areas (each area includes a specific set of skills) as follows: (1) symptom management; (2) medication management; (3) social relations; (4) occupational; (5) money management; (6) couple relations; and (7) family relations  Additional component of 8 group and 4 individual family therapy sessions for relatives	Usual care: Monthly appointments (20 mins/session) with clinical psychiatrist who controlled the prescription of their AP medication based upon the assessment of their psychotic symptoms, checked their medication compliance, recorded their consultation attendance.

Author, Year	Duration	Age Gender Race/Ethnicity	Other Population Characteristics	Total N	Benefits Outcomes	Harms Outcomes	Funding	Quality Rating
Valencia, 2007	1 year	SST vs usual care Mean age 30 vs. 30 years 30% vs. 15% female Race not reported	SST vs. usual care Mean age at onset of illness 21 vs. 21 years Mean duration of illness: 9 vs 9 years Total PANSS: 115.2 (SD 30.5) vs. 107.9 (SD 22.6) Negative PANSS: 29.7 (SD 8.5) vs. 28.7 (SD 6.3)	98	SST vs. usual care Overall symptoms, total PANSS: 46.9 (SD 14.6) vs. 60.4 (SD 18.2); SMD -0.65 (95% CI -1.06 to -0.24) Negative symptoms, PANSS: 13.0 (SD 5.7) vs. 17.9 (SD 6.2); SMD -0.82 (95% CI -1.23 to -0.40) Function, GAF: 66.0 (SD 8.9) vs. 44.9 (SD 11.6); p<0.001; SMD 2.02 (95% CI 1.53 to 2.52) Relapse 5/49 vs.10/49; RR 0.50 (95% CI 0.18 to 1.36) Treatment maintenance: 88% (43/49) vs. 80% (39/49); RR 1.10 (95% CI 0.92 to 1.31)	Not reported	National Institute of Psychiatry Ramón de la Fuente; National Council on Science and Technology	Fair

**Please see Appendix B. Included Studies for full study references**

CI=confidence interval, MD=mean difference, MFG-A=multifamily group therapy-adherence, MFG-S=multifamily group therapy-standard, SD=standard deviation

**Appendix Table E-12. Descriptions of family interventions in randomized controlled trials with relapse as an outcome**

Study, Year	N Intervention N Control	Description of Intervention
Barrowclough, 1999, Sellwood 2001, 2007	38 39	The planned intervention period was 24 weeks; sessions took place in the caregiver's homes. All patients in the study were allocated a family support worker from the volunteer organization Making Space. The services of this support worker included providing information, giving advice on benefits, advocacy, emotional support, and practical help. The frequency and nature of contact with the support worker was decided by mutual agreement between caregiver and support worker. The integrated treatment program attempted to combine three treatment approaches: motivational interviewing, individual cognitive behavior therapy, and family or caregiver intervention. Patients and carers in the treatment group were offered specific psychosocial interventions. The focus, content and quantity of the interventions were determined by a systematic assessment of caregiver needs for psychosocial interventions, measured using the relatives' version of the Cardinal Needs Schedule. Three broad types of interventions are differentiated: problem-solving techniques; cognitive-behavioral interventions; and individual cognitive behavioral interventions with patients with psychosis.
Barrowclough, 2001	18 18	The planned intervention period was 9 months; sessions took place in the caregivers' and patients' homes, except when patients or caregivers expressed a preference for a clinic-based appointment (one individual in the integrated care group expressed this preference). All patients in the study were allocated a family support worker from the volunteer organization Making Space. The services of this support worker included providing information, giving advice on benefits, advocacy, emotional support, and practical help. The frequency and nature of contact with the support worker was decided by mutual agreement between caregiver and support worker. The integrated treatment program attempted to combine three treatment approaches: motivational interviewing, individual cognitive behavior therapy, and family or caregiver intervention.
Bradley, 2006	25 25	The multiple-family-group procedure was followed with minimal variation. Consumers and caregivers were provided up to three single-family joining sessions (described below) and then invited to attend two half-day multiple-family psychoeducation sessions. The family psychoeducation sessions provided information about schizophrenia using the approach described by Anderson and colleagues. The sessions gave family members the opportunity for informal social networking. Topics included the nature of the illness, treatment approaches (medication and psychosocial), consumer and family needs, common family reactions to illness, common problems that consumers and families face, and guidelines about what the family can do to help. The education was provided to the families by psychiatrists, psychologists, social workers, and occupational therapists. Each group of six or seven consumer-caregiver pairs was then invited to participate in a multiple-family group with two trained group leaders; groups met every other week for 12 months.

Study, Year	Description of Control	Treatment Duration and Number of Sessions	Target or Primary Outcome
Barrowclough, 1999, Sellwood 2001, 2007	Family support worker	10-20 sessions over 24 weeks	Relapse
Barrowclough, 2001	Routine care in the context of the National Health Service of Great Britain consists of psychiatric management by the clinical team, coordinated through case management and including maintenance neuroleptic medication, monitoring through outpatient and community follow-up, and access to community based rehabilitative activities, such as day centers and drop-in clinics. All of the patients in the integrated treatment program also received routine care.	29 sessions over 9 months	Global function
Bradley, 2006	The case management intervention that was provided to all participants and that constituted the control condition consisted of regular appointments with a case manager and doctor to assess mental health and to provide medication and individual psychosocial rehabilitation on the basis of consumers' needs. Appointment frequency was every 2 to 3 weeks on average, and the sessions lasted from 30 minutes to 1 hour. Family contact was provided on an individual basis as required for all participants in the control and treatment groups. Family contact consisted of phone or direct contact and focused on providing psychoeducation, monitoring the consumer's mental state, and giving general support. Case management for Vietnamese participants in the control group was provided by a Vietnamese bilingual case manager when possible or with the use of Vietnamese interpreters.	26 sessions over 12 months	Relapse, clinical and social function

Study, Year	N Intervention N Control	Description of Intervention
Buchkremer, 1995	67 32	The relatives' groups met every 2 weeks and were guided by an experienced psychiatrist/psychologist. They started with a contact phase (one meeting), followed by psychoeducational training which covered the provision of information on the illness and treatment plus training in symptom assessment. It comprised two phases: an information phase (two to three meetings) and a problem-solving phase (about seven meetings). The problem-solving skills were aimed at imparting general competence in problem solving to make it possible to develop strategies for coping with difficult situations, irrespective of any current problem. In the last phase (after 10 meetings), topic-centered personal therapy of the relative was emphasized, but psychoeducation was continued if requested by the relatives.
Carra, 2007	26 25	Weekly meetings with an information group composed of 16-18 relatives for 24 sessions (1.75 hours per session) using an informative approach. Contents and goals are mainly derived from the model of the relatives group (Leff, 1989) but the preliminary in-home individual family sessions. Curricula include: etiology, positive symptoms, negative symptoms, mood disorders, problem behaviors, medical and psychiatric treatment, denial and non-compliance, interpersonal and social issues, relationship with family, education, independence and dependence, resources and benefits. Educational tools include lectures, videos and leaflets. The second element comprises weekly meetings for 48 sessions (1.5 hours per session) over 2 years with a support group made up of 8-9 relatives who have previously attend the information group. The first phase involves training on communication and coping skills, stress identification and management, and multiple family group-based problem solving, basically derived from the second stage of the psychoeducational multiple family group approach. This usually occurs during the first year. The second phase emphasized mutual support and consists of deliberate efforts to mould the group into a social network than can persist for an extended period and satisfy family needs for social contact, support, and ongoing monitoring. Expansion of the families' social networks occurs through problem solving, direct emotional support, and out-of-group socializing, all involving members of different families in the group
Dyck, 2002	55 51	Patients assigned to multiple-family group treatment received standard care plus the group treatment. Because the clinicians who provided the group treatment typically were not the case managers for the patients in the group, it was necessary to ensure that they communicated regularly with the case managers about changes in patients' functional status, medication problems, or service needs. Multiple-family group treatment was intended to improve illness management, social support, and coping skills for the patient and family members. The approach was based on the previous research reported by McFarlane and colleagues. Treatment interventions were designed to educate the family and patients about the biological underpinnings of schizophrenia and engage them in the treatment process by using a standardized protocol of videotapes, lecture, and written guidelines. Treatment components including ongoing support, formal clinical problem solving, and expansion of social support networks.

Study, Year	Description of Control	Treatment Duration and Number of Sessions	Target or Primary Outcome
Buchkremer, 1995	2-year group pending therapy. Relatives' groups were then implemented (although for only 8 sessions).	26 biweekly meetings over 1 year with an additional 2 year followup	Hospitalization
Carra, 2007	Usual care	72 weekly sessions over > 2 years	Hospitalization, relapse, compliance with community mental health care, employment
Dyck, 2002	Patients assigned to standard care received usual services, including medication management, case management, and, for some patients, therapeutic and rehabilitation services. A treatment team consisting of a case manager, a nurse, a psychiatrist, and a social worker delivered the mental health services. The team provided clinical case management services and out-of-facility services as needed.	Weekly sessions over 2 years	Hospitalization

Study, Year	N Intervention N Control	Description of Intervention
Falloon, 1981 (1982)	20 19	The family-management approach recognizes that effective community after-care of schizophrenia requires both optimal drug therapy and a supportive milieu. The family-treatment approach was designed to train patients and their parents to reduce environmental stress effectively. All family-therapy sessions were conducted in the home. This served to enhance generalization of learning to family life and to minimize failure to keep appointments. The first two sessions were devoted to educating the patient and family about the nature, course, and treatment of schizophrenia. Schizophrenia was presented as a major mental illness with both biologic and psychosocial components. The notion that families somehow "cause" schizophrenia was refuted, but it was pointed out that families can play an important part in improving the course of the illness. Considerable attention was given to discussing the rationale for maintenance of neuroleptic medication. Subsequent family sessions were devoted to reducing existing family tensions and improving the problem solving skills of the family in coping with the causes of stress. The strength and weakness of the family group were pinpointed, and major deficits became the focus of subsequent sessions. Specifically, behavioral reversal, modeling, feedback, and social reinforcement were used to enhance skills in the expression of positive and negative feelings, reflective listening, requests for behavioral change, and reciprocity of conversation. Each family was taught a structured problem-solving method in which it was encouraged to convene a family meeting whenever an issue arose, in order to discuss and specify the exact nature of the problem, list and consider alternative solutions, and select and implement the consensual "best" solution. In most families the therapist merely assisted the family in its structured problem-solving efforts, but if patients had persisting symptoms of schizophrenia or major discord was observed, additional specific strategies were employed. These included methods to improve marital relationships, to deal with unacceptable behavior, and to expand the social contacts of any family member.
Garety, 2008	28 28	Family intervention emphasized improving communication, offering discussion of up-to-date information about psychosis, problem-solving, reducing criticism and conflict, improving activity, and the emotional processing of grief, loss and anger. There was a particular focus on relapse prevention, including how family member might understand warning signs and agree on appropriated intervention, including medication
Glynn, 1992	21 20	Behavioral family therapy provided patients and their families with education about schizophrenia, communication skills, and problem-solving training to improve the family's ability to cope with stress. These three components were provided sequentially. Behavioral family therapy techniques include instruction, role reversal, modeling, social reinforcement, and homework tasks. The study protocol called for 25 behavioral family therapy sessions to be held with families over a 12-month period on a declining contact basis. Overall, a mean of 21 behavioral family therapy sessions were actually held.
Goldstein, 1978	52 52	A crisis-oriented six-session family therapy was devised, directed at the following sequence of objectives: (1) the patient and his family are able to accept the fact that he has had a psychosis; (2) they are willing to identify some of the probable precipitating stresses in his life at the time the psychosis occurred; (3) they attempt to generalize from that to identification of future stresses to which the patient and his family are likely to be vulnerable; and (4) they attempt to do some planning on how to minimize or avoid these future stresses.

Study, Year	Description of Control	Treatment Duration and Number of Sessions	Target or Primary Outcome
Falloon, 1981 (1982)	The comparison treatment was clinic-base, individual supportive psychotherapy. It was our intention to provide individual treatment comparable to the best available at well-staffed community after-care clinics. In addition to receiving maintenance pharmacotherapy and rehabilitation counseling, individually treated patients were educated about the nature, course, and treatment of schizophrenia and assisted in their efforts to cope with problems of everyday living. Although the issues addressed in treatment were similar to those that arose in the family treated group, the problems were death with primarily from the patient's perspective.	Weekly visits for 3 months the biweekly visits for 6 months then monthly visits thereafter evaluated at 9 months	Stress management
Garety, 2008	Usual care	20 sessions over 9 months	Relapse, remission
Glynn, 1992	Customary care services to all subjects were provided by a special Veteran's Health Administration outpatient clinic treatment team consisting of 4 psychiatrists, 2 social workers and 1 clinical nurse specialist. All members of the team were blind to treatment assignment. This team provided monthly clinical evaluation and medication management, vocational and rehabilitation referrals, and crisis intervention services. Outpatient services available included training in social and independent living skills, and a variety of recreational and occupational therapy groups and vocation rehabilitation services.	25 sessions over 12 months	Relapse, work adjustment
Goldstein, 1978	No therapy	6 weeks	Relapse

Study, Year	N Intervention N Control	Description of Intervention
Herz, 2000	41 41	Program for relapse prevention: (1) education for patients and family members about the process of relapse in schizophrenia and how to recognize prodromal symptoms and behaviors; (2) active monitoring for prodromal symptoms by treatment team members, patients, family members and others in frequent contact with patient; (3) clinical intervention within 24-48 hours of prodromal episode (4) 1-hour weekly supportive group therapy emphasizing improving coping skills or individual supportive therapy sessions if patients refused group treatment and (5) 90-minute multifamily psychoeducation groups that family members were encouraged to attend biweekly for 6 months and monthly thereafter.
Hogarty, 1986	30 45	Our family approach was designed as an education and management strategy intended to lower the emotional climate of the home while maintaining reasonable expectations for patient performance. As frequently indicated to us by many relatives, this strategy should not be formally designated as "family therapy." Rather, through the provision of formal education about the disorder and strategies for managing more effectively, family members become allies in the treatment process as their anxiety and distress are decreased. More traditional attempts to promote disclosure, "insight," or direct modification of family systems, including the resolution of intergenerational and marital issues, were, for the most part, avoided. For ease of communication, we refer to the process as family treatment. The goal was to reduce both the positive and negative symptoms of schizophrenia that might be associated with the extremes of stimulation contained in either the therapeutic process or family life. Treatment sought to increase the stability and predictability of family life by decreasing the family's guilt and anxiety, increasing their self-confidence, and providing a sense of cognitive mastery through the provision of information concerning the nature and course of schizophrenia as well as specific management strategies thought to be helpful in coping with schizophrenic symptoms on a day-to-day basis.
Hogarty, 1997	24 24	Family psychoeducation/management. Family therapy was provided by the other two full-time master's-level psychiatric nurse clinical specialists and by one part-time master's-level psychologist. These included the three broad phases of joining, survival skills training and reintegration within the home, and reintegration into the community. The principal modification to the family therapy approach was a change in didactic content that reflected issues of importance to the families of first-episode patients, such as diagnostic uncertainty and variable prognosis. (27% [Number=26] of patients who lived with family in trial 1 were first-episode patients.)

Study, Year	Description of Control	Treatment Duration and Number of Sessions	Target or Primary Outcome
Herz, 2000	Individual supportive therapy and medication management	6 months biweekly psychoeducation and monthly thereafter, weekly group therapy evaluated at 18 months	Relapse
Hogarty, 1986	Drug-maintained control group	Biweekly then monthly for 2 years	Relapse
Hogarty, 1997	Supportive therapy	1-2 visits per month for 3 years	Patient adjustment

Study, Year	N Intervention N Control	Description of Intervention
Kopelowicz, 2012	64 54 60	The multifamily group-standard consisted of 3 components: (1) three initial "joining" sessions conducted separately with each family, (2) a 1-day (6- hour) multifamily "Survival Skills" educational workshop, and (3) multifamily group sessions. The joining sessions were offered to each family (without the patient) to introduce the family to the therapist of the multifamily group sessions and to educate them about the need for ongoing treatment. The sessions also helped the family identify and overcome the obstacles to pursuing outpatient treatment. The Survival Skills Workshop provided verbal and videotape information about the etiology, biology, genetics, symptoms, and treatment of schizophrenia. It was conducted in elementary school-level Spanish by 2 clinicians and one study author. Following the workshop, each cohort began their multifamily group sessions twice monthly for 12 months (24 sessions total). The first 3 sessions consisted of (1) introducing the participants to one another without a formal discussion of the illness, (2) discussing how schizophrenia had affected each of their lives, and (3) teaching problem-solving skills. Participants learned a 6- step problem-solving process: define the problem, generate possible solutions, evaluate each, select one, implement it, and evaluate its outcomes. The subsequent 21 group sessions started with a brief "caring and sharing period" followed by group discussion. In multifamily group-adherence, the joining sessions, the Survival Skills workshop, and the first 3 sessions were performed in the same manner as the multifamily group-standard approach. After the session on problem-solving skills, the remaining 21 bimonthly multifamily group-adherence sessions differed from the multifamily group-standard by focusing on specific obstacles to maintaining medication adherence guided by the Theory of Planned Behavior constructs. These obstacles were identified through individualized interviews with patients using the Theory for Planned Behavior Inventory (see Kopelowicz et al. for a complete description). Finally, the problem-solving activity in the multifamily group-adherence was particularly relevant in addressing perceived behavioral control because the Mexican American patients' relatives typically control resources, such as time and money needed to implement a solution. Other families within the multifamily group often generated a wide range of solutions by recounting their successful and unsuccessful attempts to solve the same or similar problems.
Leff, 1982	12 12	The package of social interventions. The education program: This consisted of four lectures on the etiology, symptoms, course and treatment and management of schizophrenia. Initially four visits were made, one for each topic, but after a few relatives had been instructed in this way we decided it would be preferable to give two lectures at a time. Following each lecture, we allowed unlimited time for the relative to ask questions. The relatives' group: the group was deliberately set up so that the therapists acted as facilitators. Both high expressed emotion and low expressed emotion relatives were encouraged to bring their problems and their solutions to the meeting and share them with others in a similar position. The purpose of this was to enable them to learn about coping strategies of which they were unaware, and finally to help them try a different approach at home. The focus of the group was thus on potential or actual difficulties that relatives experienced, and not primarily on interpretations of the relatives' own behavior. This latter was more useful in discussions between the professionals about the group process that occurred after each group meeting. Family sessions: Because the relatives' group was not appropriate for dealing with the whole range of problems or for dynamic work, and because patients were excluded from it, we felt that it needed to be complemented by sessions with the whole family.
Leff, 2001	16 14	Two sessions of education about schizophrenia plus techniques for improving communication within the family, reducing relatives' criticism and over-involvement, lowering contact between patient and high expressed emotion relatives, increasing the social networks of family members and setting realistic objectives. The approach includes cognitive and behavioral elements as well as techniques from strategic and systemic family therapy
Linszen, 1996	37 39	Behavioral family intervention including psychoeducation, communication training and the development of problem solving skills were the main components

Study, Year	Description of Control	Treatment Duration and Number of Sessions	Target or Primary Outcome
Kopelowicz, 2012	Usual care	24 sessions over 12 months	Medication adherence, hospitalization
Leff, 1982	Routine outpatient care	4 sessions education + biweekly relatives group for 9 months + 1 to 25 family sessions	Relapse
Leff, 2001	2 education sessions	Bi weekly then monthly sessions over one year	Relapse
Linszen, 1996	Psychosocial intervention	18 sessions over 12 months	Relapse

Study, Year	N Intervention N Control	Description of Intervention
Mayoral, 2015	44 44	The family psychoeducation intervention carried out for the group subject to treatment consisted of 24 sessions, which involved, at least, the patient and a key relative, apart from other direct relatives who wanted to participate in the sessions. Sessions lasted approximately 60 minutes and were distributed into weekly sessions during the first quarter, fortnightly sessions during the 3 subsequent months and monthly sessions during the remaining 6 months. The total intervention period lasted 12 months. The content of the treatment programme included 4 modules whose objectives were the following: basic information about the disease and its treatment; assessment of needs and family relations; training on communication skills; and problem facing and solving
Merinder, 1991	23 23	An 8-session intervention using a mainly didactic interactive method and focusing on the following headings: 1. Introduction 2. What is schizophrenia? Diagnosis, prognosis, symptoms 3. What causes schizophrenia? 4. Medication: effect and side effects 5. Psychosocial treatment 6. Stress and early signs of relapse, emergency plan 7. What can you and your family do about it? 8. Laws and regulations The programme was standardized with a manual for group leaders, overhead presentations and a booklet for participants, to increase comparability of the intervention between centers. Further, teachers had regular meetings with the aim of increasing the commitment to the intervention protocol. Patient and relative interventions were conducted separately, with group sizes in both patient and relative groups of five to eight participants. The programme was the same for both patients and relatives. Sessions were weekly.
TARRIER, 1988	31 32	Education program (2 sessions), stress management (3 sessions), goal setting (8 sessions)
Valencia, 2007	43 39	Psychosocial skills training focusing on (1) symptom management, (2) medication management, (3) social relations, (4) occupational management, (5) money management, (6) couple relations, (7) family relations (48 sessions); family therapy consisted of psychoeducation (8 sessions) and problem solving (4 sessions)
Vaughan, 1992	18 18	Relatives' counseling. Therapists attempted to (1) form an alliance with relatives (2) increase stability and predictability of family life by decreasing family guilt and anxiety, increasing self-confidence and providing a sense of mastery through providing information about schizophrenia. In addition, an attempt was made to improve the relatives' problem solving and communication skills.

<b>Study, Year</b>	<b>Description of Control</b>	<b>Treatment Duration and Number of Sessions</b>	<b>Target or Primary Outcome</b>
Mayoral, 2015	Normal standard treatment	24 sessions over 12 months	Hospitalization
Merinder, 1991	The usual treatment provided in community psychiatry, i.e., psychopharmacological treatment, psychosocial rehabilitation efforts and to some extent supportive psychotherapy	8-sessions	Relapse, compliance, knowledge of schizophrenia, satisfaction with services
Tarrier, 1988	Routine care without specialist intervention	13 sessions over 9 months	Relapse
Valencia, 2007	Usual care	48 weekly sessions for psychosocial skills training and 12 sessions for family therapy	Relapse, hospitalization, positive and negative symptom, psychosocial and global functioning, treatment adherence
Vaughan, 1992	Standard after-care which consisted of outpatient appointments every 2 to 4 weeks for medication and support	10 weekly sessions	Relapse

Please see Appendix B. Included Studies for full study references

**Appendix Table E-13. Data abstraction of systematic reviews of intensive case management**

<b>Author, Year</b>	<b>Aims</b>	<b>Databases and Timeperiod Covered</b>	<b>Number of Studies Number of Patients</b>	<b>Characteristics of Identified Articles: Study Designs</b>	<b>Characteristics of Identified Articles: Populations</b>	<b>Characteristics of Identified Articles: Interventions</b>
Marshall 2000b (ICM)	Effect of ICM for people with severe mental disorders	MEDLINE (1966-1995); CINAHL (1997); EMBASE (1980-1995); PsycLIT (1974-1995); SCISEARCH (1997); Cochrane Schizophrenia Group Register of Trials (1997)	10 studies n=1652	Randomized controlled trials of ICM vs. control	Age 18-65 years with schizophrenia or schizophrenia-like disorders; bipolar disorder; or depression with psychotic features. Proportion with schizophrenia: <50%: 2 studies; >50%: 5 studies; unknown: 2 studies	ICM: Any intervention described as case management within a study; excluded: Assertive Community Treatment and Home-based Care

Author, Year	Outcomes Reported	Effectiveness Outcomes	Harms Outcomes	Funding/ Comments	Quality Rating
Marshall 2000b (ICM)	Symptoms: BPRS Function: scales not reported Quality of life: Quality of Life interview Mortality	<u>ICM vs. control</u> Symptoms, BPRS (2 studies): WMD 0.46 (95% CI -3.67 to 4.60) Social function, scales used not reported (3 studies): SMD 0.46 (95% CI -0.34 to 1.26) Quality of life, Quality of Life Interview (2 studies): SMD 0.09 (95% CI -0.23 to 0.42)	<u>ICM vs. control</u> Mortality (6 studies): OR 1.29 (95% CI 0.68 to 2.45; I <sup>2</sup> =59%)	Manchester University Department of Psychiatry; Oxford University Department of Socio-Legal Studies	Good

**Please see Appendix B. Included Studies for full study references**

BPRS=Brief Psychiatric Rating Scale, CI=confidence interval, ICM=Intensive Case Management, SMD=standard mean difference, WMD=weighted mean difference

**Appendix Table E-14. Data abstraction of randomized controlled trials of intensive case management**

Author, Year	Setting Country	Inclusion Criteria	Interventions and Ns per Group	Description of Intervention	Description of Comparator	Duration
Bjorkman 2002	One case management service in Sweden	Ages 18-55, a diagnosed mental illness and impairment due to the illness with serious and continuous difficulties in functioning in social relationships, housing or work situation for more than 2 years.	Case management service (n=33) vs. standard care (n=44)	The case management service included two RNs and two social workers. All members in the team worked full-time and all had experience of working in social services, psychiatric services or vocational rehabilitation. The caseload was on average nine clients considering that four clients not included in the study were later admitted to the service. Clients could get in contact with a case manager after working hours by telephone. A psychiatrist and psychologist were available for supervision. The characteristics of the case management service were a moderate emphasis on skills training, low emphasis on integration of services and a high level of consumer input, where the client had the major input, deciding on the planning and the content of the case management relationship. The clients in the case management services had access to all services in the standard care services.	The psychiatric services were comprehensive with a joint management for outpatient, inpatient and day-care facilities, as well as a couple of small therapeutic communities (with a total number of beds of around 30). One ward was aimed for patients with dual diagnosis (12 beds), another ward for psychiatric patients (not dementia cases) aged 65 years or over (15 beds), and a third ward for general psychiatric cases (19 beds). The outpatient care was organized in two general psychiatric teams and one team for long-term mentally ill patients. The total number of staff mainly working with outpatients was around 65. The local social service offered sheltered accommodation for around 70 people with long-term mental illness.	18- and 36-month followup with last followup at 36 months

Author, Year	Age Gender Race/Ethnicity	Other Population Characteristics	Total N	Benefits Outcomes	Harms Outcomes	Funding	Quality Rating
Bjorkman 2002	Demographics (intervention, control) Age, mean years: 40, 35 Gender, % female: 51%, 54% Ethnicity, % NR	NR	77	SCL symptoms, mean (SD) (intervention, control) Baseline: 124.8-128.0 (70.8-71.5), 101.4-102.0 (53.2-55.0) 18 months: 114.9 (66.8), 93.7 (57.0) 36 months: 102.0 (68.5), 81.4 (55.1)  ISSI social network Baseline: 11.1-11.2 (6.1-6.3), 15.1-15.2 (6.2-6.3) 18 months: 16.7 (6.3), 18.1 (6.4) 36 months: 14.3 (6.4), 17.5 (5.9)  Strauss Carpenter social functioning Baseline: 10.6 (2.4), 10.5-10.6 (2.7-2.8) 18 months: 11.5 (2.9), 10.9 (2.9) 36 months: 11.4 (2.5), 11.5 (2.5)  GAF Functioning Baseline: 55.7-56.3 (11.6-12.3), 46.5-50.2 (14.6-15.4) 18 months: 57.0 (13.0), 60.3 (13.3) 36 months: 52.3 (14.6), 55.3 (17.0)  LQOLP Overall quality of life Baseline: 4.3 (0.7), 4.5 (0.6) 18 months: 4.6 (0.7), 40.9 (0.7) 36 months: 4.6 (0.7), 40.9 (0.7)	NR	NR	Fair

**Please see Appendix B. Included Studies for full study references**

GAF=global assessment of functioning, ISSI=Interview Schedule for Social Interaction, LQOLP=Lancashire Quality of Life Profile, RN=registered nurse, SCL=Symptom Checklist, SD=standard deviation

**Appendix Table E-15. Data abstraction of systematic reviews of illness self-management and recovery**

Author, Year	Aims	Databases and Timeperiod Covered	Number of Studies Number of Patients	Characteristics of Identified Articles: Study Designs	Description of Intervention	Characteristics of Identified Articles: Populations	Characteristics of Identified Articles: Interventions
Zou, 2012	Examine self-management education interventions in patients with schizophrenia.	CCRCT; PubMed MEDLINE; CINAHL; EMBASE; PsycINFO; Web of Science (all databases 1996-2010)	13 RCTs N = 1404  China (n=4) USA (n=3) France (N=1) Germany (n=2), Denmark (n=1), Mexico (n=1); inpatient (n=3), outpatient (n=7), community health centers (n=3)	Randomized controlled trial of self management education interventions in persons with schizophrenia; Duration of followup: immediate to 24 months post intervention	Self-management education teaches problem solving skills to allow patients to take appropriate actions to improve their health by providing both education and practical self management skills to promote active illness management	Adults >18, ICD-10 diagnosis of schizophrenia; control group receiving standard care or on wait list	Self management education: n=726  Standard care: n=678 (standard care)

Author, Year	Outcomes Reported	Effectiveness Outcomes	Harms	Funding	Quality
Zou, 2012	Relapse Rehospitalization, Adherence to medication regimen Psychiatric symptoms Psychosocial functioning Symptom scales: PANSS, BPRS	<u>Self management education vs. standard care</u> Relapse: OR 0.54 (0.36-0.83) Rehospitalization: OR 0.55 (0.39-0.77) Negative PANSS : WMD -4.01 (-5.23 to -2.79) Total PANSS: WMD-3.39 (-4.5 to -2.29) BPRS: WMD: -4.19 (-5.84 to -2.54) Relapse, >10 intervention sessions: OR 0.41 (0.21-0.79) Relapse, <10 intervention sessions: OR 0.67 (0.39-1.15)	NR	China Medical Board Grant	Fair

**Please see Appendix B. Included Studies for full study references**

BPRS=brief psychiatric rating scale, RCT=randomized control trial, OR=odds ratio, PANSS=positive and negative syndrome scale, SC=standard care, SME=self management education, WMD=weighted means difference, USA=United States of America

**Appendix Table E-16. Data abstraction of randomized controlled trials of illness self-management and recovery**

Author, Year	Setting Country	Inclusion Criteria	Interventions and Ns per Group	Description of Intervention	Description of Comparator	Duration (intervention and longest followup)
Hasson-Ohayon, 2007	13 community rehabilitation centers Israel	Severe mental illness; receiving treatment and rehabilitation services at one of the 13 centers; fluency in Hebrew; sufficient competence to provide informed consent	IMR: n=119  Usual care: n=91	IMR: 1-hour, weekly intervention sessions led by two clinicians, for 8 months using educational handouts covered sequentially in the same order at all 13 sites	Usual care: Individual supportive therapy and medication management biweekly for 15-30 minutes	8-11 months

Author, Year	Age Gender Race/Ethnicity	Other Population Characteristics	Total N	Outcomes Measures	Benefits Outcomes	Harms Outcomes	Funding	Quality Rating
Hasson-Ohayon, 2007	IMR vs. usual care Mean age 34 vs. 35 years 32% vs. 38% female Race not reported	IMR vs. usual care Schizophrenia: 80% vs. 89% Other mental illness: 20% vs. 11% Coping Efficacy Scale 2.85 (SD 0.95) vs. 3.09 (SD 0.98)	210	Symptoms - CES	Scores on scale before and after the IMR group intervention CES, mean score: 3.25 (SD 0.95) vs. 3.09 (SD 0.87); p=NS	NR	Israel's ministry of health, national council for the rehabilitation of persons with a psychiatric disability	Fair

**Please see Appendix B. Included Studies for full study references**

CES=Coping Efficacy Scale, CMHC=community mental health center, IMR=Illness management recovery, NS=not significant, PANSS Positive and Negative Syndrome Scale, PRP=program for relapse, QLS=quality of life scale, VA=veteran's affairs

**Appendix Table E-17. Data abstraction of systematic reviews of psychoeducation**

Author, Year	Aims	Databases and Timeperiod Covered	Number of Studies Number of Patients	Characteristics of Identified Articles: Study Designs	Characteristics of Identified Articles: Populations	Characteristics of Identified Articles: Interventions	Outcomes Reported
Pekkala 2009	Assess the effects of psychoeducational interventions compared to the standard levels of knowledge provision in schizophrenia patients	CINAHL (1982 to 1999) Cochrane Library CENTRAL (Issue 1, 1999) Cochrane Schizophrenia Group Register (January and May 2001) EMBASE (1980 to June 1999) MEDLINE (January 1966 to January 1999) PsycLIT (January 1974 to January 1999) SOCIOFILE (January 1974 to January 1999)	10 studies n=1125	Randomized clinical trials of psychoeducation for schizophrenia and/or related serious mental illnesses involving individuals or groups	People suffering from schizophrenia, schizoaffective disorder, schizophreniform disorder, or schizotypal personality disorder.	Group and individual psychoeducation interventions compared to usual care (e.g., psychosocial rehabilitation or supportive psychotherapy) or waiting list comparison groups	Adherence Knowledge Symptoms Function

Author, Year	Effectiveness Outcomes
Pekkala 2009	<p data-bbox="306 269 806 293"><u>Any form of psychoeducation vs. standard care</u></p> <p data-bbox="306 326 1304 383">Global functioning (no clinically significant improvement) at discharge (1 study, 92 participants) Risk ratio 0.52, 95% CI 0.24 to 1.10</p> <p data-bbox="306 415 1272 472">Global functioning (no clinically significant improvement) 6 months (1 study, 92 participants) Risk ratio 0.83, 95% CI 0.50 to 1.38</p> <p data-bbox="306 505 1287 561">Global functioning (no clinically significant improvement) 18 months (1 study, 92 participants) Risk ratio 0.90, 95% CI 0.58 to 1.39</p> <p data-bbox="306 594 1346 651">Global functioning (average scale score GAF/GAS) at end of intervention (1 study, 41 participants) Mean difference -2.64, 95% CI -12.74 to 7.46</p> <p data-bbox="306 683 1247 740">Global functioning (average scale score GAF/GAS) at 1 year (3 studies, 260 participants) Mean difference -5.23, 95% CI -8.76 to -1.71, <math>I^2=79%</math></p> <p data-bbox="306 773 1226 829">Global functioning (average scale score GAF/GAS) at 2 years (1 study, 59 participants) Mean difference -6.70, 95% CI -13.38 to -0.02</p> <p data-bbox="306 862 1226 919">Global functioning (average scale score GAF/GAS) at 5 years (1 study, 60 participants) Mean difference -3.80, 95% CI -8.04 to 0.44, <math>I^2=0.0%</math></p> <p data-bbox="306 951 768 1008">BPRS at 1 year (1 study, 159 participants) Mean difference -6.0, 95% CI -9.15 to -2.85</p> <p data-bbox="306 1040 858 1097">BPRS post treatment (1 study, 19 participants) Mean difference -0.06 95% CI -0.53 to 0.41, <math>I^2=93%</math></p> <p data-bbox="306 1130 1083 1187">Social functioning (SAS-II) at end of intervention (1 study, 19 participants) Mean difference -0.10, 95% CI -0.37 to 0.17</p> <p data-bbox="306 1219 1150 1276">Quality of life (Heinrich's Scale) at end of intervention (1 study, 114 participants) Mean difference -8.20, 95% CI -14.78 to -1.62</p>

Author, Year	Effectiveness Outcomes
Pekkala 2009	<p>Quality of life (Heinrich's Scale) at 3 months (1 study, 108 participants)  Mean difference -9.70 95% CI -17.22 to -2.18, I<sup>2</sup>=0.0%</p> <p><u>Standard length group psychoeducation vs. standard care</u></p> <p>BPRS Post treatment (1 study, 19 participants)  Mean difference -0.06 95% CI -0.53 to 0.41  Social functioning (SAS-II) at end of intervention (1 study, 19 participants)  Mean difference -0.10 95% CI -0.37 to 0.17</p> <p>Quality of life (Heinrich's Scale) at end of intervention (1 study, 114 participants)  Mean difference -8.20 95% CI -14.78 to -1.62</p> <p>Quality of life (Heinrich's Scale) at 3 months (1 study, 108 participants)  Mean difference -9.70 95% CI -17.22 to -2.18, I<sup>2</sup>= 0.0%</p> <p><u>Brief group psychoeducation vs. standard care</u></p> <p>Global functioning (no clinically significant improvement) at discharge (1 study, 92 participants)  Risk ratio 0.52 95% CI 0.24 to 1.10</p> <p>Global functioning (no clinically significant improvement) 6 months (1 study, 92 participants)  Risk ratio 0.83 95% CI 0.50 to 1.38</p> <p>Global functioning (no clinically significant improvement) 18 Months (1 study, 92 participants)  Risk ratio 0.90 95% CI 0.58 to 1.39</p> <p>BPRS at 1 year (1 study, 159 participants)  Mean difference -6.0 95% CI -9.15 to -2.85</p>

Author, Year	Harms Outcomes	Funding/ Comments	Quality Rating
Pekkala 2009	<p><u>Any form of psychoeducation vs. standard care</u></p> <p>Death (2 studies, 170 participants) Risk ratio 0.53, 95% CI 0.07 to 3.95, I<sup>2</sup>=0.0%</p> <p>Leaving study any reason (8 studies, 788 participants) Risk ratio 1.13, 95% CI 0.89 to 1.44, I<sup>2</sup>=15%</p> <p><u>Standard length group psychoeducation vs. standard care</u></p> <p>Leaving study any reason (4 studies, 280 participants) Risk ratio 1.39, 95% CI 0.89 to 2.18, I<sup>2</sup>=0.0%</p> <p><u>Brief individual psychoeducation vs. standard care</u></p> <p>Leaving study/lost (1 study, 67 participants) Risk ratio 3.06, 95% CI 0.17 to 56.70, I<sup>2</sup>=0.0%</p> <p><u>Brief group psychoeducation vs. standard care</u></p> <p>Death (2 studies, 170 participants) Risk ratio 0.53, 95% CI 0.07 to 3.95, I<sup>2</sup>=0.0%</p> <p>Leaving study any reason (4 studies, 457 participants) Risk ratio 0.97, 95% CI 0.73 to 1.30, I<sup>2</sup>=59%</p>	<p>Dept of Psychiatry, Porvoo Hospital, Finland Dept of Psychiatric Demography, Institute of Basic Psychiatric Research, University Hospital of Aarhus, Denmark Finnish Office for Health Technology Assessment, Finland</p>	Good

**Please see Appendix B. Included Studies for full study references**

BPRS=Brief Psychiatric Rating Scale, CI=controlled interval, GAS=Global Assessment Scale, GAF=Global Assessment of Functioning, MD=mean difference RR=risk ratio, SAS-II=social adjustment scale II

**Appendix Table E-18. Data abstraction of randomized controlled trials of social skills training**

Author, Year Trial Name	Setting Country	Inclusion Criteria	Intervention s and Ns per Group	Description of Intervention	Description of Comparator	Duration (interventio n and longest followup)
Bartels 2014 and Mueser 2010	2 community mental health centers United States	Age ≥50 years able to provide informed consent; DSM-IV Axis I disorder diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder, or major depression based on the Structured Clinical Interview for DSM- IV in conjunction with documented persistent impairment in multiple areas of functioning. Excluded: Residence in a nursing home or other institutional setting; primary diagnosis of dementia or significant cognitive impairment as indicated by a Mini Mental Status Exam score<20; physical illness expected to cause death within 1 year, or current substance dependence.	Psychosocial skills training (HOPES): n=90  Usual care: n=93	HOPES: SST: Weekly sessions for 1 year followed by one year monthly sessions of social rehabilitation curriculum, based on social skills training is manualized and organized into seven modules: Communicating Effectively, Making and Keeping Friends, Making the Most of Leisure Time, Healthy Living, Using Medications Effectively, and Making the Most of a Health Care Visit.	Usual care: Routine mental health services including pharmacotherapy, case management or outreach by non-nurse clinicians, individual therapy, and access to rehabilitation services, such as groups and psychoeducation.	Intervention: 2 years Followup: 3 years
Valencia 2007	Single center Mexico	Outpatients age 16 to 50 with DSM-IV schizophrenia; taking antipsychotic medication; clinically stable in terms of psychotic symptoms (PANSS score <60); completed at least 6 years of elementary education; lived with their families and resided in Mexico City or the metropolitan area	SST: n=49  Usual care: n=49	SST: 48 weekly group sessions (75 mins/session) composed of seven sequential treatment areas (each area includes a specific set of skills) as follows: (1) symptom management; (2) medication management; (3) social relations; (4) occupational; (5) money management; (6) couple relations; and (7) family relations Additional component of 8 group and 4 individual family therapy sessions for relatives	Usual care: Monthly appointments (20 mins/session) with clinical psychiatrist who controlled the prescription of their AP medication based upon the assessment of their psychotic symptoms, checked their medication compliance, recorded their consultation	1 year

<b>Author, Year Trial Name</b>	<b>Age Gender Race/Ethnicit v</b>	<b>Other Population Characteristics</b>	<b>Total N</b>	<b>Outcome Measures</b>
Bartels 2014 and Mueser 2010	<u>SST vs. usual care</u> Mean age 60 vs. 60 years 59% vs. 57% female Race and ethnicity - 88% vs. 84% white 12% vs. 16% non-white 8% vs. 5% Latino 92% vs. 95% non-Latino	<u>SST vs. usual care</u> 55% vs. 54% schizophrenia or schizoaffective disorder BPRS: 55.54 (SD 13.86) vs. 54.23 (SD 12.75) SANS: 2.42 (SD 0.54) vs. 2.50 (SD 0.54) ILSS score: 0.66 (SD 0.10) vs. 0.65 (SD 0.11) MCAS score: 3.69 (SD 0.51) vs. 3.66 (SD 0.51) UPSA score: 72.85 (SD 15.93) vs. 68.54 (SD 19.04) SBS score: 51.42 (SD 8.94) vs. 51.17 (SD 7.97) R-SES score: 66.24 (SD 19.16) vs. 68.99 (SD 18.61)	183	Symptoms - Overall symptoms (BPRS) Negative symptoms (SANS)  Function - Community function (ILSS; MCAS) Social skills (SBS) Self-efficacy (R-SES)  Treatment  maintenance
Valencia 2007	<u>SST vs. usual care</u> Mean age 30 vs. 30 years 30% vs. 15% female Race not reported	<u>SST vs. usual care</u> Mean age at onset of illness 21 vs. 21 years Mean duration of illness: 9 vs 9 years Total PANSS: 115.2 (SD 30.5) vs. 107.9 (SD 22.6) Negative PANSS: 29.7 (SD 8.5) vs. 28.7 (SD 6.3)	98	Symptoms - Overall symptoms (PANSS) Negative symptoms (PANSS)  Function - Overall function (GAF) Proportion with functional improvement (defined as GAF >61 points) Treatment

Author, Year Trial Name	Benefits Outcomes	Harms Outcomes	Funding	Quality Rating	Comments
Bartels 2014 and Mueser 2010	<p><u>SST vs. usual care</u></p> <p>Overall symptoms, BPRS score: 49.92 (SD 13.75) vs. 50.53 (SD 14.98); SMD -0.04 (95% CI -0.33 to 0.25)</p> <p>Negative symptoms, SANS score, 2-year followup: 2.26 (SD 0.55) vs. 2.52 (SD 0.65); SMD -0.43 (95% CI -0.72 to -0.14)</p> <p>Negative symptoms, SANS score, 3-year followup: 2.21 (SD 0.64) vs. 2.50 (SD 0.65); SMD -0.45 (95% CI -0.74 to -0.15)</p> <p>Function, MCAS score, 2-year follow-up: 3.83 (SD 0.42) vs. 3.50 (SD 0.57); SMD 0.65 (95% CI 0.36 to 0.95)</p> <p>Function, MCAS score, 3-year follow-up: 3.83 (SD 0.44) vs. 3.72 (SD 0.48); SMD 0.24 (95% CI -0.05 to 0.53)</p> <p>Social skills, SBS score, 2-year followup: 46.74 (SD 8.41) vs. 49.14 (SD 9.58); SMD -0.26 (95% CI -0.56 to 0.03)</p> <p>-Men only: 46.90 (SD 8.10) vs. 52.62 (SD 9.74); SMD -0.63 (95% CI -1.09 to -0.17)</p> <p>Social skills, SBS score, 3-year followup: 48.56 (SD 10.06) vs. 50.29 (SD 10.39); SMD -0.17 (95% CI -0.46 to 0.12)</p> <p>Treatment maintenance, 2 years: 82% (76/93) vs. 81% (73/90); RR 1.01 (95% CI 0.88 to 1.16)</p>	Not reported	NIMH	Fair	Subgroups: Subgroup analysis for 2-year outcomes (reported in Mueser) found no difference in effect based on age. Effect sizes for all outcomes were consistently higher in men vs. women.
Valencia 2007	<p><u>SST vs. usual care</u></p> <p>Overall symptoms, total PANSS: 46.9 (SD 14.6) vs. 60.4 (SD 18.2); SMD -0.65 (95% CI -1.06 to -0.24)</p> <p>Negative symptoms, PANSS: 13.0 (SD 5.7) vs. 17.9 (SD 6.2); SMD -0.82 (95% CI -1.23 to -0.40)</p> <p>Function, GAF: 66.0 (SD 8.9) vs. 44.9 (SD 11.6); p&lt;0.001; SMD 2.02 (95% CI 1.53 to 2.52)</p> <p>Relapse 5/49 vs. 10/49; RR 0.50 (95% CI 0.18 to 1.36)</p> <p>Treatment maintenance: 88% (43/49) vs. 80% (39/49); RR 1.10 (95% CI 0.92 to 1.31)</p>	Not reported	National Institute of Psychiatry Ramón de la Fuente; National Council on Science and Technology	Fair	

Author, Year Trial Name	Setting Country	Inclusion Criteria	Intervention s and Ns per Group	Description of Intervention	Description of Comparator	Duration (intervention and longest followup)
Valencia 2013	Single center Mexico	Age 18-60 years; DSM-IV criteria for schizophrenia; completed at least 6 years of elementary education; currently living with relatives in Mexico City or it's metropolitan area; stable under antipsychotic medication and on an ambulatory basis for at least six months prior to their inclusion in the study. Excluded: history of major medical illness; alcohol or drug dependency; mental retardation or severe cognitive impairment as confirmed by the corresponding clinical chart.	SST: n=68  Usual care: n=51	SST: 24 (weekly) group 60-minute sessions consisting of four modules of 1) medication management, 2) symptom management, 3) social relations, and 4) family relations plus "Learning activities" training sessions that included: introduction of the skills that would be taught, skills demonstration by the trainers, role playing in sessions, and corrective feedback	Usual care: Regular pharmacologic treatment	6 months

<b>Author, Year Trial Name</b>	<b>Age Gender Race/Ethnicity</b>	<b>Other Population Characteristics</b>	<b>Total N</b>	<b>Outcome Measures</b>
Valencia 2013	<u>SST vs. usual care</u> Mean age 30 vs. 26 years 27% vs. 24% female Race not reported	<u>SST vs. usual care</u> Mean age at onset of illness 22 vs. 21 years Mean duration of illness: 8 vs. 8 years Total PANSS: 92.6 (SD 41.5) vs. 83.5 (33.9) Negative PANSS: 24.2 (SD 10.4) vs. 22.0 (SD 8.2) GAF: 43.1 (SD 6.3) vs. 42.9 (SD 6.3)	152	Symptoms - Overall symptoms (PANSS) Negative symptoms (PANSS)  Function - Overall function (GAF) Proportion with functional improvement (defined as GAF >61 points) Relapse  Treatment maintenance

Author, Year Trial Name	Benefits Outcomes	Harms Outcomes	Funding	Quality Rating
Valencia 2013	<u>SST vs. usual care</u> Overall symptoms, total PANSS: 43.4 (SD 8.0) vs. 55.7 (SD 8.3); SMD -0.63 (95% CI -1.04 to -0.23) Negative symptoms, PANSS: 11.2 (SD 2.6) vs. 14.9 (SD 3.1); SMD -1.30 (95% CI -1.70 to -0.90) Function, GAF: 67.0 (SD 14.9) vs. 43.7 (SD 13.9); SMD 1.60 (95% CI 1.19 to 2.02) Proportion with functional improvement: 59% (40/68) vs. 2% (1/51); RR 30 (95% CI 4.26 to 211)	Not reported	National Institute of Psychiatry Ramón de la Fuente	Fair

**Please see Appendix B. Included Studies for full study references**

BPRS= Brief Psychiatric Rating Scale, GAF= Global Assessment of Functioning, HOPES= Helping Older People Experience Success, ILSS= Independent Living Skills Survey, MCAS= Multnomah Community Ability Scale, PANSS= Positive and Negative Syndrome Scale, RES= Revised Self-Efficacy Scale, SBS= Social Behavior Survey, SD= standard deviation, SMD= standard mean difference, SST= social skills training

**Appendix Table E-19. Data abstraction of randomized controlled trials of supported employment**

Author, Year	Setting Country	Inclusion Criteria	Interventions and Ns per Group	Description of Intervention
Cook, 2008, 2005	7 sites US	Diagnosis, duration, and disability requirements for severe and persistent mental illness as defined by the US Government Center for Mental Health Services, age 18 years or older, willingness to work, and written informed consent	Different models of supported employment program: 333 Alternative vocational program or usual care: 315	Implementation effectiveness trial in which sites test different “experimental” models of supported employment. The experimental condition was always a form of enhanced best-practice supported employment. The Maryland, Connecticut, and South Carolina sites used Individual Placement and Support, the Massachusetts site used the Assertive Community Treatment vocational model, and the Texas, Maine, and Arizona sites used experimental models developed especially for this study. Specifically, Texas included supported employment services with social network enhancements, Maine used family-aided Assertive Community Treatment teams working with an employer consortium, and Arizona’s integrated treatment team included psychiatrists, case managers, rehabilitation counselors, employment specialists, job developers, and benefits specialists emphasizing rapid job placement and ongoing support.
Mueser, 2004	1 site US	Clients with severe mental illness receiving services at the lead community mental health center in Hartford, CT with severe mental illness, as defined by the DSM-IV; lack of competitive employment; desire for competitive work; attendance at two research introduction meetings; willingness and capability of giving informed consent	Individual placement and support : 68 Standard services: 69	The individual placement and support model employment specialists serve on treatment teams, including case managers and psychiatrists, in order to integrate vocational services with psychiatric treatment. Clients receive a full range of vocational services including engagement in services, identifying job interests and vocational assessment, job finding, and job support. Individual placement and support uses assertive outreach to deliver services in clients' natural settings in the community rather than at mental health agencies.

Author, Year	Description of Comparator	Duration (intervention and longest followup)	Age Gender Race/Ethnicity	Other Population Characteristics	Total N
Cook, 2008, 2005	Either services as usual (4 sites), an “unenanced” version of the experimental model (2 sites), or the Clubhouse model (1 site)	Intervention: Average of 74 hours of vocational services and 125 hours of clinical services per person Followup: 2 years	Age, mean years: 38 Gender, % female: 36 White race, %: 41	Age at first hospitalization, mean years: 24 Lifetime hospitalized, mean months: 19 PANSS Cognitive, mean score: 16 PANSS Negative, mean score: 13 PANSS Depressive, mean score: 15 PANSS Positive, means score: 11 PANSS Excitement, mean score: 11	648 with schizophrenia (of a larger sample of 1,273 that included those with other disorders)
Mueser, 2004	Access to all other vocational services in Hartford for clients with severe mental illness: a supported employment program located off-site from the mental health center (standard-supported), and a vocational program in which clients worked in jobs paying subminimum wage or competitive wages in supervised janitorial enclaves in the community, fulfilling contracts obtained by that program (standard-enclave).	24 months (includes time from enrollment through the 2-year collection of employment data with interviews conducted at baseline and every 6 months for 2 years)	Age, mean years: 41.7 vs. 40.9 Gender, % female: 38.2 vs. 36.2	Primary diagnosis, schizophrenia: 57% vs. 54% Primary diagnosis, schizoaffective: 19% vs. 22% Primary diagnosis, bipolar: 3% vs. 2% Primary diagnosis, major depression: 16% vs. 21% Lifetime hospitalization, mean: 15.3 vs. 18.8 months	204

Author, Year	Benefits Outcomes	Harms Outcomes	Funding	Quality Rating
Cook, 2008, 2005	<p><i>24 month results</i> Intervention vs. unenhanced/services as usual</p> <p><i>Schizophrenia only:</i> Competitively employed (defined as pays minimum wage or higher, is located in a mainstream, socially integrated setting, is not set aside for persons with disabilities, and is held independently/not agency owned), mean proportion estimated from figure: 22% vs. 12% (statistics not reported)</p> <p><i>All populations (50-50% schizophrenia spectrum disorders):</i> Employed 40 hours or more per month, mean proportion: 51% (330/648) vs. 39% (245/625), p&lt;0.001 Mean number of dollars earned per month: \$122/month vs. \$99/month, p=0.04 Attrition, %: 21 vs. 24</p>	Not reported	Center for Mental Health Services/ Substance Abuse and Mental Health Services Administration	Fair
Mueser, 2004	In competitive work: 75% (51/68) vs. 27.5% (19/69); RR 2.72 (95% CI 1.81 to 4.09) In any employment: vs. 75% (51/68) 53.6% (37/69); RR 1.40 (95% CI 1.08 to 1.82)	Treatment discontinuation at 2 years: 9% (6/68) vs. 83% (57/69); RR 0.11 (95% CI 0.05 to 0.23)	USDHHS, SAMHSA, NIMH	Fair

**Please see Appendix B. Included Studies for full study references**

PANSS=positive and negative syndrome scale, QLS=quality of life scale, QOL=quality of life, VA=veteran's affairs, WBI=Work Behavior Inventory

**Appendix Table E-20. Data abstraction of systematic reviews of supported employment**

Author, Year	Aims	Databases and Timeperiod Covered	Number of Studies Number of Patients	Characteristics of Identified Articles: Study Designs	Description of Intervention	Characteristics of Identified Articles: Populations	Characteristics of Identified Articles: Interventions
Kinoshita, 2013	To review the effectiveness of supported employment compared with other approaches to vocational rehabilitation or treatment as usual.	Cochrane Schizophrenia Group Trials Register (February 2010).	14 RCTs N = 2265	Randomized controlled trial of supported employment in primarily persons with schizophrenia; 13 of 14 trials used the Individual Placement and Support model (IPS). Duration of followup: mean of 18 months	Key principles of Individual Placement and Support (IPS): "(a) the goal is competitive employment in work settings integrated into a community's economy; (b) services are based on clients' choices; (c) clients are expected to obtain jobs directly, rather than following lengthy pre-employment training (rapid job search); (d) attention to patient preference in the job search; (e) integration between employment services and mental health treatment teams; (f) ongoing individual support; and (g) systematic benefits counseling"	Adults, most using DSM criteria for severe mental illnesses. Comparison groups all received some form of vocational training, with one also comparing to usual care.	Mean sample size per arm = 70

Author, Year	Outcomes Reported	Effectiveness Outcomes	Harms	Funding	Quality
Kinoshita, 2013	Primary: Employment: days in competitive employment (long term) Secondary: Other employment outcomes Education Leaving study early Glpba; state Mental state Service use Quality of life Social/general functioning Adverse effects Economic costs	Supported Employment vs. standard vocational training Days in competitive employment (primary outcome) - long term Mean Difference (95% CI) 70.63 [43.22, 98.04] Days in any form of paid employment - long term Mean Difference (95% CI) 84.94 [51.99, 117.89] Job tenure for competitive employment (weeks) - long term Mean Difference (95% CI) 9.86 [5.36, 14.36] Job tenure for any paid employment (weeks) - long term Mean Difference (95% CI) 3.86 [-5.66, 13.38] Obtained any job during the study (high=better) Risk Ratio (95% CI) 3.24 [2.17, 4.82] Days to first competitive employment (long-term) Mean Difference (95% CI) -161.60 [-225.73, -97.47] Leaving the study early for any reason Risk Ratio (95% CI) 0.76 [0.57, 1.01] PANSS negative symptoms Mean Difference (95% CI) -2.12 [-3.20, -1.05] Quality of Life: (high = better) Mean Difference (95% CI) 0.04 [-0.10, 0.18]	Death - natural and suicide long term Risk Ratio (95% CI) 1.5 [0.25, 8.85]	University	Good

**Please see Appendix B. Included Studies for full study references**

BPRS=brief psychiatric rating scale, RCT=randomized control trial, OR=odds ratio, PANSS=positive and negative syndrome scale, SC=standard care, SME=self management education, WMD=weighted means difference, USA=United States of America

**Appendix Table E-21. Data abstraction of systematic reviews in trials of supportive therapy**

<b>Author, Year</b>	<b>Aims</b>	<b>Databases and Timeperiod Covered</b>	<b>Number of Studies Number of Patients</b>	<b>Characteristics of Identified Articles: Study Designs</b>	<b>Characteristics of Identified Articles: Populations</b>	<b>Characteristics of Identified Articles: Interventions</b>
Buckley 2015	To review the effects of supportive therapy compared with usual care in patients with schizophrenia	Cochrane Schizophrenia Group Trials Register (28 November 2012)	5 studies vs. standard care (N=822)	Randomized controlled trials of supportive therapy compared with usual care reporting relapse, hospitalization, or general functioning as primary outcomes with multiple secondary outcomes	Schizophrenia or schizophrenia-like illnesses using any criteria including trials where it was implied that the majority of participants had a severe mental illness that was likely to be schizophrenia.	Supportive therapy and supportive care (provided by a single person with the main purpose of maintaining current functioning or assisting pre-existing coping abilities in people who have a diagnosis of schizophrenia or schizophrenia-like illness. The therapies can be aimed at individuals or groups of people) vs. standard care (health care a person would normally receive had they not been included in the research trial, including interventions such as medication, hospitalization, community psychiatric nursing input and/or day hospital).

Author, Year	Outcomes Reported	Effectiveness Outcomes	Harms Outcomes	Funding/ Comments	Quality Rating
Buckley 2015	Change in general functioning quality of life Overall symptoms Discontinuation of treatment Relapse	Supportive therapy or care vs. standard care Change in general functioning (GAS): Mean general functioning in the intervention groups was 1.4 higher (95% CI 5.09 lower to 7.89 higher) Quality of life: Mean quality of life in the intervention groups was 2.73 lower (95% CI 6.04 lower to 0.58 higher) Overall symptoms: Mental state: No clinically important improvement (followup 1 to 2 years) (RR 0.95, 95% CI 0.82 to 1.11) Discontinuation of treatment: (RR 0.86, 95% CI 0.53 to 1.4) Relapse: RR 0.96, 95% CI 0.44 to 2.11	Not reported	Affinity Healthcare, Cheadle Royal Hospital, UK. Leeds Community and Mental Health Services, NHS Teaching Trust, UK. Northumberland Tyne and Wear NHS Trust, UK.	Good

**Please see Appendix B. Included Studies for full study references**

CI=confidence interval, GAS=Global Assessment Scale, NHS=National Health Service, RR=relative risk, UK=United Kingdom

**Appendix Table E-22. Data abstraction of randomized controlled trials of early interventions for patients with first-episode psychosis**

Author, Year	Setting Country	Inclusion Criteria	Interventions and Ns per Group	Description of Intervention
<p>Early Treatment Program (ETP)-RAISE</p> <p>Kane 2015, 2016</p>	<p>U.S.</p>	<p>1) Ages 15-40</p> <p>2) ability to participate in research assessments in English</p> <p>3) ability to full consent (or assent if under 18)</p> <p>4) presence of definite psychotic symptoms and evidence of one of following diagnoses: schizophrenia, schizoaffective disorder, schizophreniform, psychotic disorder NOS, or brief psychotic disorder (DSM-IV)</p> <p>5) up to 6 months of cumulative exposure to antipsychotic medications.</p> <p>First-episode schizophrenia spectrum (89% for NAVIGATE, 90% for standard care)</p> <p>Schizophrenia-only: NAVIGATE (51%), standard care (56%)</p>	<p>By participant:</p> <p>NAVIGATE (n=223), Community Care (n=181)</p> <p>Cluster randomization by site:</p> <p>NAVIGATE (n=17), Community Care (n=17)</p>	<p>NAVIGATE model includes four core interventions delivered by a multidisciplinary team: personalized medication management via a secure web-based decision support system, family psychoeducation, individual resiliency therapy, and supported employment and education.</p>

Author, Year	Description of Comparator	Duration	Age Gender Race/Ethnicity	Other Population Characteristics	Total N
<p>Early Treatment Program (ETP)-RAISE</p> <p>Kane 2015, 2016</p>	<p>Called "Community Care;" Standard care for psychosis treatment</p>	<p>2 years</p>	<p>Demographics (intervention, control)</p> <p>Mean age: 23.18, 23.08</p> <p>Gender/males: 78%, 66% (significantly more males in NAVIGATE)</p> <p>Race/ethnicity:</p> <p>White=62%, 44%</p> <p>African American=28%, 49%</p> <p>Other=10%, 7%</p> <p>Hispanic=25%, 10%</p>	<p>(intervention, control)</p> <p>Weeks of duration of untreated psychosis: 178.91, 211.43</p> <p>Heinrich-Carpenter QLS total: 18.44, 18.99</p> <p>PANSS total: 14.95, 14.87 (significantly worse for NAVIGATE)</p> <p>Calgary Depression Scale: 4.27, 4.30</p> <p>CGI: 0.80, 0.83</p> <p>Duration of time on antipsychotics (days): 42.88, 48.98</p> <p>Patient's education:</p> <p>College or higher: 32%, 30%</p> <p>Completed high school: 34%, 32%</p> <p>Some high school: 30%, 32%</p> <p>Lifetime alcohol use (did not meet criteria): 60%, 68%</p> <p>Lifetime cannabis use (did not meet criteria): 61%, 68%</p>	<p>404</p>

Author, Year	Benefits Outcomes	Harms Outcomes	Funding	Quality Rating
<p>Early Treatment Program (ETP)-RAISE</p> <p>Kane 2015, 2016</p>	<p><b>Treatment retention:</b> NAVIGATE participants remained in treatment significantly longer (median=23 months) than community care participants (median=17 months) (p&lt;0.004).</p> <p><b>Quality of life (Heinrich's QLS):</b> NAVIGATE participants experienced significantly greater improvement in quality of life (change score=15.793) than those in community care (change score=9.891) during the 2-year assessment period (p=0.0145).</p> <p><b>Employment/education:</b> A higher proportion of NAVIGATE participants were either working or going to school at any time during each month over the 2-year period compared to community care participants (group by time interaction, p=0.044). These data do not reflect change over time within participant, only the end point each month.</p> <p><b>Psychotic symptoms (PANSS):</b> NAVIGATE participants experienced greater improvement on PANSS total scores (change score=-14.313) compared to standard care (change score=-9.989) at 2 years (p=0.0161).</p> <p><b>Depressive symptoms (Calgary Depression Scale for Schizophrenia):</b> NAVIGATE participants experienced significantly greater improvement in depressive symptoms (change score=-1.981) compared to standard care (change score=-1.196) (p=0.0318).</p>	<p>None reported.</p>	<p>NIMH</p>	<p>Poor</p>

Author, Year	Setting Country	Inclusion Criteria	Interventions and Ns per Group	Description of Intervention
Guo 2007, 2010	10 clinical sites in China	1) Ages 16-50 2) DSM-IV criteria for schizophrenia, or schizophreniform disorder for not more than 5 years 3) being confirmed to be clinically stable by the investigator (the total score $\leq 60$ on the PANSS or a decrease of 50% from acute period in the total score on PANSS) 4) taking maintenance therapy with any one of the following seven oral antipsychotics: chlorpromazine, sulpiride, clozapine, risperidone, olanzapine, quetiapine, and aripiprazole. First episode schizophrenia 84.6%, schizophreniform 15.4%	Combined Treatment (n=604), Medication Treatment (n=635)	Antipsychotic medication plus group psychoeducation, family intervention, skills training, and CBT (Once a month x 12 months, 48 sessions total).

Author, Year	Description of Comparator	Duration	Age Gender Race/Ethnicity	Other Population Characteristics	Total N
Guo 2007, 2010	Antipsychotic medication only	12 month intervention only	Demographics (intervention, control) Age, mean years: 26.1, 26.4 Gender, % Male: 54.3%, 55.7% Race/ethnicity: NR	(Intervention, control) Age at onset: 23.8, 24.2 Duration of schizophrenia: 24.6 months, 23.3 months PANSS total score: 44.7, 45.6 CGI severity score: 2.5, 2.6	1268

Author, Year	Benefits Outcomes	Harms Outcomes	Funding	Quality Rating
Guo 2007, 2010	<p><b>Discontinued treatment:</b> Rates of treatment discontinuation or change due to any cause were 32.8% (198) for combined treatment group vs. 46.8% (297) for medication treatment (HR 0.62; 95% CI 0.52-0.74; p&lt;0.001)</p> <p><b>Relapse:</b> Risk of relapse was lower among participants assigned to combined treatment (14.6%; 88) vs. medication treatment (22.5%; 143) (HR 0.57; 95% CI 0.44-0.74; p&lt;0.001)</p> <p><b>Psychotic symptoms (PANSS):</b> No significant difference over time between combined treatment (34.7) and medication treatment (36.4; F=0.41, p=0.81)</p> <p><b>Insight (Insight and Treatment Attitudes Questionnaire [ITAQ]):</b> Change in total ITAQ (poor insight) scores was significantly greater over time for combined treatment group (19.5) than in medication treatment (15.9; F=25.94; p&lt;0.001).</p> <p><b>Social functioning (Global Assessment Scale):</b> Combined treatment (82.9) showed significant improvement over time vs. medication treatment (80.8; F=4.33; p=0.002)</p> <p><b>Activities of Daily Living (ADL scale) scores:</b> Combined treatment (15.4) showed significant improvement over time vs. medication treatment (16.4; F=12.70; p&lt;0.001)</p> <p><b>Employment and education:</b> A significantly higher proportion of patients receiving combined treatment obtained employment or accessed education (30.1%) compared to those receiving medication treatment (22.2%; X<sup>2</sup>=10.09; p=0.001).</p>	<p>Extrapyramidal symptoms: No significant differences between combined treatment (135) and medication treatment (142; X<sup>2</sup>=0.20, p=0.66).</p> <p>Weight gain &gt;7% from baseline to last observation: No significant differences between combined treatment (149) and medication treatment (132; X<sup>2</sup>=1.39, p=0.24).</p>	Grants from National Key Technologies R&D Program, National Natural Science Foundation of China, and the National Basic Research Program of China	Fair

<b>Author, Year</b>	<b>Setting Country</b>	<b>Inclusion Criteria</b>	<b>Interventions and Ns per Group</b>	<b>Description of Intervention</b>
Lambeth Early Onset (LEO) trial  Craig 2004	England	<p>16-40 years living in the London borough of Lambeth and presenting to mental health services for the first time with nonaffective psychosis (schizophrenia, schizotypal, and delusional disorders). Also considered people who had presented once but had subsequently disengaged without treatment from routine community services.</p> <p>Schizophrenia: Specialized care = 51 (72%) Standard care = 49 (67%)</p>	Early intervention specialized care (n=71); Standard care (n=73)	Community team of 10 staff (team leader, 0.5 consultant psychiatrist, trainee psychiatrist, 0.5 clinical psychologist, OT, four psychiatric nurses, two healthcare assistants). Established on the principles of assertive outreach, providing an extended hours service by including weekends and public holidays. Evidence-based interventions adapted to the needs of people with early psychosis included low-dose atypical antipsychotic regimens, CBT based on manualized protocols, and family counseling and vocational strategies based on established protocols.

Author, Year	Description of Comparator	Duration	Age Gender Race/Ethnicity	Other Population Characteristics	Total N
Lambeth Early Onset (LEO) trial  Craig 2004	Standard care delivered by the community mental health teams. Teams received no additional training in the management of early psychosis, although they were encouraged to follow available guidelines	18 months	(intervention, control)  Mean age: 26 (6.0), 26.6 (6.4) Gender: Male, 39 (55%), 54 (74%) Race/ethnicity: White 27 (38%) 18 (25%) Black British 10 (14%) 6 (8%) Black Caribbean 9 (13%) 13 (18%) Black African 16 (23%) 25 (34%) Mixed 6 (8%) 6 (8%) Other 3 (4%) 5 (6%)	(intervention, control)  First episode: 61 (86%) 52 (71%)	144

Author, Year	Benefits Outcomes	Harms Outcomes	Funding	Quality Rating
Lambeth Early Onset (LEO) trial  Craig 2004	<p><b>Relapse:</b> Participants in the specialized care group were less likely to relapse (30%, 18 out of 61) than those in standard care (48%, 29 out of 61) (odds ratio 0.46, 95% CI 0.22 to 0.97; p=0.042). When rates were adjusted for baseline differences in sex, previous psychotic episode, and ethnicity, the difference in relapse was no longer significant (odds ratio 0.55, 95% CI 0.24 to 1.26, p=0.157).</p> <p><b>Retention in treatment/dropout:</b> At 18 months, 53 (86%) patients in the specialized group and 44 (68%) in standard care were in regular contact with the clinical team (lost to care: odds ratio 0.35, 95% CI 0.15 to 0.81). When rates were adjusted for baseline differences in sex, previous psychotic episode, and ethnicity, drop-out rates remained significant (0.28, 95% CI 0.12 to 0.73).</p>	None reported.	Directorate of Health and Social Care for London R&D Organisation and Management Programme	Good

<b>Author, Year</b>	<b>Setting Country</b>	<b>Inclusion Criteria</b>	<b>Interventions and Ns per Group</b>	<b>Description of Intervention</b>
Lambeth Early Onset (LEO) Trial  Garety 2006	England	16–40 years with an address in Lambeth for the first time with a nonaffective psychosis. Patients who met these demographic and diagnostic criteria who had presented once previously but had immediately disengaged and were not known to any of the existing mental health services were also deemed eligible. Majority met ICD–10 diagnostic criteria for schizophrenia (69%)	LEO/specialized care (n=55), standard care group (n=44)	A multidisciplinary team providing assertive outreach, a single point of access, and extended service hours. The interventions provided were specially adapted for a group with early psychosis and followed protocols and manuals from the Early Psychosis Prevention and Intervention Centre and, for CBT, pilot work conducted locally. A mix of medication management, CBT, vocational input and family interventions was provided according to individual need.

<b>Author, Year</b>	<b>Description of Comparator</b>	<b>Duration</b>	<b>Age Gender Race/Ethnicity</b>	<b>Other Population Characteristics</b>	<b>Total N</b>
Lambeth Early Onset (LEO) Trial  Garety 2006	Standard care by community mental health teams.	18 months	Average age: 26 years Gender: Male (65%) More than 50% were from a minority ethnic, predominantly of African or Caribbean parentage.	(intervention, control)  First episode: 61 (86%) 52 (71%) PANSS Total: 67.4, 73.3 GAF: 46.5, 42.2 Calgary Depression Scale: 4.1, 3.3	99

Author, Year	Benefits Outcomes	Harms Outcomes	Funding	Quality Rating
Lambeth Early Onset (LEO) Trial  Garety 2006	<p><b>Psychotic symptoms (PANSS scores):</b> No significant differences between specialized care (51.2) and standard care (58.9) at 18 months (F=5.74, 95% CI -0.30 to 11.79, p=0.06). This result attenuates when adjusting for baseline differences in ethnicity, gender, and episode (F=5.26, 95% CI 71.14 to 11.65; p=0.11).</p> <p><b>Social functioning (GAF scores):</b> Significantly improved for specialized care (64.1) vs. standard care (55.3) at 18 months (F=-8.72, 95% CI 15.46 to -1.98; p=0.01), even when adjusting for baseline differences (F=-8.77, 95% CI -15.89 to -1.65; p=0.02).</p> <p><b>Calgary Depression Scale scores:</b> No significant differences between specialized care (2.7) and standard care (2.7) at 18 months (F=0.93, 95% CI -0.47 to 2.33, p=0.19), a trend that continued when adjusting for baseline differences (F=0.98, 95% CI -0.51 to 2.47, p=0.19).</p>	Reported on deaths, prison, self-harm, violence to others and homelessness, but no statistical tests conducted.	Directorate of Health and Social Care for London R&D Organisation and Management Programme	Good

Author, Year	Benefits Outcomes	Harms Outcomes	Funding	Quality Rating
Lambeth Early Onset (LEO) Trial	<b>Insight (Scale for the Assessment of Insight scores):</b> No significant differences between specialized care (16.6) and standard care (12.7) at 18 months (F=-2.94, 95% CI 76.20 to 0.31; p=0.076), including when adjusting for baseline differences (F=-2.45, 95% CI -5.94 to 1.05; p=0.167).	see above	see above	see above
Garety 2006				
Continued	<p><b>Quality of life (Manchester Short Assessment of Quality of Life [MANSA] scores):</b> Significantly improved for specialized care (59.2) vs. standard care (53.3) at 18 months (F=-5.96, 95% CI 11.19 to -0.74), p=0.026, even when adjusting for baseline differences (F=-7.08, 95% CI -12.47 to -1.69, p=0.011).</p> <p><b>Vocational/educational outcomes:</b> No significant differences between specialized care (33%; 21 out of 64) and standard care (21%; 13 out of 61) on vocational/educational outcomes at 18 months (<math>\chi^2=2.086</math> [df=1], p=0.170); however, specialized care spent significantly more time in vocational and educational activity (6.9 months, SD=6.6; n=67) than standard care (4.2 months, SD=5.3; n=65); t=2.689, p=0.008 at 18 months.</p> <p><b>Housing outcomes:</b> No significant differences between specialized care (70%; 46 out of 66) and standard care (58%; 36 out of 62) on housing outcomes at 18 months (<math>\chi^2=1.879</math> [df=1], p=0.170) at 18 months.</p> <p><b>Relationships outcomes:</b> 55% (34 out of 62) of participants in specialized care engaged in social relationships vs. 25% (14 out of 57) at 18 months (<math>\chi^2=11.31</math>, [df=1], p&lt;0.001).</p>			

<b>Author, Year</b>	<b>Setting Country</b>	<b>Inclusion Criteria</b>	<b>Interventions and Ns per Group</b>	<b>Description of Intervention</b>
Secondary analysis of subset of participants from the Lambeth Early Onset (LEO) Trial  Tempier 2012	England	Residents of the London borough of Lambeth, ages 16-40, presented to mental health services with a first episode of nonaffective psychosis between January 2000 and October 2001.	Specialized care (n=57), standard care (n=50)	Specialized early intervention following the ACT model, including an interdisciplinary team, low patient-to-staff ratios and high availability of individualized care. Team adhered to Maudsley Prescribing Guidelines, and had access to good practice guidelines for the wider psychosocial management of first-episode psychosis, psychological advice, and CBT.
OPUS  Bertelsen, 2009	Multicenter Denmark	Age 18-45 years, first use of mental health services, diagnosis within the schizophrenia spectrum, and no prior use of antipsychotics for more than 12 weeks	Intensive early intervention program (n=275) Standard care (n=272)	Intensive intervention, including assertive community treatment, family treatment, social skills training, and antipsychotics

<b>Author, Year</b>	<b>Description of Comparator</b>	<b>Duration</b>	<b>Age Gender Race/Ethnicity</b>	<b>Other Population Characteristics</b>	<b>Total N</b>
<p>Secondary analysis of subset of participants from the Lambeth Early Onset (LEO) Trial</p> <p>Tempier 2012</p>	<p>Standard care provided by a generic community mental health team. Team adhered to Maudsley Prescribing Guidelines, and had access to good practice guidelines for the wider psychosocial management of first-episode psychosis, psychological advice, and CBT.</p>	<p>6- and 18-month followup</p>	<p>Demographics (intervention, control)</p> <p>Mean age: 25.7, 26.0</p> <p>Gender/males: 53%, 78% (significantly more males in standard care)</p> <p>Race/ethnicity: White=42%, 24% (difference not statistically significant) Black=42%, 58% Other=16%, 18%</p>	<p>None reported.</p>	<p>107</p>
<p>OPUS</p> <p>Bertelsen, 2009</p>	<p>Standard treatment at a community mental health center, including antipsychotics</p>	<p>Intervention: 2 years Follow-up: 5 years</p>	<p>Demographics (intervention, control)</p> <p>Mean age: 26.6 years, 26.6 years</p> <p>Female sex: 42%, 40%</p> <p>Race/ethnicity: NR</p>	<p>(Intervention, control)</p> <p>Inpatient at randomization: 43%, 47%</p> <p>Median duration of untreated psychosis: 46 weeks, 53 weeks</p> <p>Schizophrenia diagnosis: 67%, 65%</p> <p>Substance abuse: 27%, 27%</p>	<p>547</p>

Author, Year	Benefits Outcomes	Harms Outcomes	Funding	Quality Rating
<p>Secondary analysis of subset of participants from the Lambeth Early Onset (LEO) Trial</p> <p>Tempier 2012</p>	<p><b>Psychotic symptoms (PANSS Total score):</b> Participants in specialized care experienced significant improvement in symptoms (51.60±15.41) compared to those in standard care (59.70±14.12), t=2.51, df=85, p=0.01) at 18 months.</p> <p><b>Functioning (GAF):</b> Participants in specialized care experienced significant improvement in functioning (64.20±15.23) compared to those in standard care (55.89±14.04), t=2.59, df=85, p=0.01) at 18 months.</p> <p><b>Social networks:</b> Significantly larger social networks for those in specialized care (2.40+1.2) vs. standard care (1.71+1.06) t=2.77, df=84, p=0.01) at 18 months.</p>	<p>None reported.</p>	<p>Directorate of Health and Social Care for London R&amp;D Organisation and Management Programme</p>	<p>Fair</p>
<p>OPUS</p> <p>Bertelsen, 2009</p>	<p><b>End of intervention (2 years)</b>  GAF, symptoms: 51.2 vs. 48.7; mean difference 2.45 (95% CI -0.32 to 5.22)  GAF, function: 55.2 vs. 51.1; mean difference 3.12 (95% CI 0.37 to 5.88)</p> <p><b>End of follow-up (5 years)</b>  GAF, symptoms: 53.5 vs. 53.8; mean difference -0.16 (95% CI -3.97 to 3.37)  GAF, function: 55.4 vs. 54.2; mean difference 1.34 (95% CI -2.65 to 5.34)  Not living independently: 4% vs. 10%; OR 2.3 (95% CI 1.1 to 4.8) p=0.02  Unemployed: 57% vs. 54%; OR 1.1 (95% CI 0.8 to 1.6) p=0.57  Suicide attempts: 9% vs. 9%; OR 0.9 (95% CI 0.4 to 2.1) p=0.86</p>	<p>NR</p>	<p>Danish Ministry of Health; Danish Ministry of Social Affairs; University of Copenhagen; Copenhagen Hospital Cooperation; Danish Medical Research Council; Slagtermester Worners Foundation; and the Stanley Wada Research Foundation</p>	<p>Good</p>

Author, Year	Setting Country	Inclusion Criteria	Interventions and Ns per Group	Description of Intervention
<p>OPUS</p> <p>Secher 2015</p> <p>(Note: Referred to description of OPUS trial in Peterson, 2005; did not include Peterson due to its inclusion in SR)</p>	Denmark	<p>18–45 years of age, recent first diagnosis within the schizophrenic spectrum (F2X.X in ICD-10), and at most 12 consecutive weeks of antipsychotic medication. In the 10-year followup study reported here, interviewed 68% of the participants who were alive and lived in Denmark.</p> <p>First episode psychosis, including:          Schizophrenia (67% OPUS, 65% usual care),          Schizotypal (15% OPUS, 14% usual care),          Brief Psychosis (7% OPUS, 10% usual care)</p>	<p>OPUS (n=181), usual care (n=166) Included in ITT: OPUS (n=275), usual care (n=272)</p>	<p>Enhanced ACT, multi-family group psychoeducation, and social skills training. Also offered CBT and supportive therapy if needed. Staff-to-client ratio = 1:10. Antipsychotic medication based on same principles for both groups.</p>

Author, Year	Description of Comparator	Duration	Age Gender Race/Ethnicity	Other Population Characteristics	Total N
OPUS Secher 2015  (Note: Referred to description of OPUS trial in Peterson, 2005; did not include Peterson due to its inclusion in SR)	Usual care in community mental health, staff-to-client ratio = 1:30. Antipsychotic medication based on same principles for both groups.	Intervention length: 2 years Followup at 10 years	Demographics: (intervention, control) Mean age: 26.6 for both conditions Males: 58% for OPUS, 60% for usual care Race/ethnicity: Not reported	(intervention, control)  Median duration of untreated psychosis (duration of untreated psychosis; weeks): 46, 53  Psychopathology scores (SAPS/SANS) summarized into three dimensions: Psychotic dimension: 2.8, 2.6 Negative dimension: 2.2 for both Disorganized dimension: 1.0 for both  Substance Abuse Diagnosis: 27% for both  Education: None: 60%, 59% Currently being educated: 14%, 12% Short education/skilled: 20%, 20% Longer education: 6%, 9%	347

Author, Year	Benefits Outcomes	Harms Outcomes	Funding	Quality Rating
<p>OPUS Secher 2015</p> <p>(Note: Referred to description of OPUS trial in Peterson, 2005; did not include Peterson due to its inclusion in SR)</p>	<p>Functioning (GAF): At 10-year followup there were no significant differences in GAF functioning scores between OPUS (54.33) and usual care participants (54.65), (estimated mean difference=-0.76, 95% CI -4.01 to 2.49, p=0.65).</p> <p>Supported Housing: At 10-year followup, mean number of days in supported housing was not significantly different for OPUS (14.1) vs. usual care (20.8) (B=-6.63, 95% CI -19.86 to 6.61, p=0.30). The mean number of days in supported (vs. institutional) housing from year 1 to year 10 was statistically significant in favor of OPUS (p&lt;0.01); however, the difference at years 4 and 5 account for much of this finding.</p> <p>Employment/Education: At 10-year followup, there were no significant differences between OPUS (35.3%; 90) and usual care (35.8%; 87) participants regarding proportion working or studying (OR 0.99, 95% CI 0.67 to 1.45, p=0.97).</p>	<p>Deaths: After 10 years, 14 OPUS participants (5.1%) were deceased vs. 15 usual care participants (5.5%), p=0.83.</p> <p>Suicidal ideation: The proportion of participants who, at 10-year followup, had experienced suicidal ideation within the preceding two years was similar to OPUS (39.4%) and in usual care (37.9%), p=0.77.</p>	<p>Danish Council for Independent Research; Trygfonden; The Mental Health Services of the Capital Region of Denmark; the Danish Ministry of Health; the Danish Ministry of Social Affairs; the Psychiatry and Social Service Dept in Central Denmark Region</p>	<p>Good</p>

**Please see Appendix B. Included Studies for full study references**

ACT=assertive community treatment, CBT=cognitive behavioral therapy, CGI=clinical global impression, CI=confidence interval, df=degrees of freedom, ETP=early treatment program, F=fixation index, GAF=global assessment of functioning, HR=hazard ratio, ITT=intention to treat, LEO=Lambeth Early Onset, NIMH=National Institute of Mental Health, NOS=not otherwise specified, OPUS=Specialized Early Intervention Trail, OR=odds ratio, OT=occupational therapy, PANSS=positive and negative syndrome scale, QLS=quality of life scale, R&D=research and development, SAPS=Scale for the Assessment of Positive Symptoms, SANS=Scale for Assessment of Negative Symptoms, SD=standard deviation, SR=systematic review, U.S.=United States

**Appendix Table E-23. Data abstraction of systematic reviews of co-occurring substance use and schizophrenia**

Author, Year	Aims	Databases and Timeperiod Covered	Number of Studies Number of Patients	Characteristics of Identified Articles: Study Designs	Characteristics of Identified Articles: Populations	Characteristics of Identified Articles: Interventions	Outcomes Reported
Hunt, 2013	Effect of various psychosocial interventions compared with standard care for people with both severe mental illness and substance misuse on substance use and schizophrenia outcomes	Cochrane Schizophrenia Group Trials Register (2008-July 2012) CDSR, MEDLINE, PsycINFO (2008-January 2013) Web of Science, Scopus (2008-February 2013)	32 trials n=3,165	RCTs	Patients with both severe mental illness (majority schizophrenia, schizoaffective disorder, or psychosis) and substance misuse disorder Settings: 3 hospital-based studies, 19 community-based studies, 10 mixed setting studies including 2 with jail populations Countries: 19 US, 6 Australia, 3 UK, 1 each from Denmark, Germany, Ireland, and Switzerland	Various psychosocial interventions (Assertive Community Treatment, Intensive Case Management, Cognitive Behavioral Therapy, Motivational Interviewing, Contingency Management, Social Skills Training) compared with usual care	Primary outcomes: Loss to treatment Change in substance use Symptoms  Secondary outcomes: Death Substance use Mental state Global function Social function QOL Homelessness

Author, Year	Effectiveness Outcomes
Hunt, 2013	<p><i>Selected outcomes reported (excludes excluded interventions, skewed data, and studies with N&lt;50)</i></p> <p><u>Integrated/assertive community treatment vs. usual care</u>  Loss to treatment at 36 months (3 trials, n=603): RR 1.09 (95% CI 0.82 to 1.45), 231 per 1000 vs. 212 per 1000  Alcohol use (not in remission) at 36 months (1 trial, n=143): RR 1.15 (95% CI 0.84 to 1.56), 575 per 1000 vs. 500 per 1000  Drug use (not in remission) at 36 months (1 trial, n=85): RR 0.89 (95% CI 0.63 to 1.25), 578 per 1000 vs. 650 per 1000  Function (GAF Scale of 1 to 100) at 6 months (1 trial; n=162): MD 1.10 (95% CI -1.58 to 3.78)  Function (GAF Scale of 1 to 100) at 12 months (1 trial, n=171): MD of 0.70 (95% CI -2.07 to 3.47)  Function (GAF Scale of 1 to 100) at 18 months (1 trial, n=176): MD of 1.00 (95% CI -1.58 to 3.58)  Function (GAF Scale of 1 to 100) at 24 months (1 trial, n=166): MD of 1.70 (95% CI -1.18 to 4.58)  Function (GAF Scale of 1 to 100) at 30 months (1 trial, n=164): MD of -0.60 (95% CI -3.56 to 2.36)  Function (GAF Scale of 1 to 100) at 36 months (1 trial, n=170): MD of 0.40 (95% CI -2.47 to 3.27)</p> <p><u>Nonintegrated/intensive case management vs. usual care</u>  Lost to treatment (3 trials, n=134) at 6 months: RR 1.23 (95% CI 0.73 to 2.06)  Lost to treatment (3 trials, n=134) at 12 months: RR 1.21 (95% CI 0.73 to 1.99), 289 per 1000 vs. 239 per 1000,  Lost to treatment (3 trials, n=134) at 18 months: RR 1.35 (95% CI 0.83 to 2.19)  Function (Average Role Functioning Scale, RFS, score, high=better) at 6 months (1 trial; n=50): MD -0.78 (5% CI -2.91 to 1.35)  Function (Average Role Functioning Scale, RFS Scale, score, high=better) at 12 months (1 trial; n=50): MD 0.70 (5% CI -1.56 to 2.96)  Function (Average Social Adjustment Score, SAS, high=better) at 6 months (1 trial; n=50): MD -0.93 (95% CI -6.34 to 4.48)  Function (Average Social Adjustment Score, SAS, high=better) at 12 months (1 trial; n=50): MD 3.09 (95% CI -2.71 to 8.89)</p> <p><u>Cognitive behavioral therapy vs. usual care</u>  Lost to treatment at 3 months (2 trials, n=152): 108 per 1000 vs. 97 per 1000, RR 1.12 (95% CI 0.44 to 2.86)  Mental state (Average Insight Scale Score, low=poor) at 3 months (1 trial, n=105): MD 0.52 (95% CI -0.78 to 1.82)</p> <p><u>Skills training vs. usual care</u>  Lost to treatment at 6 months (2 trials, n=94): RR 0.49 (95% CI 0.24 to 0.97)  Lost to treatment at 12 months (2 trials, n=94): RR 0.70 (95% CI 0.44 to 1.10), 257 per 1000 vs. 367 per 1000</p>

Author, Year	Harms Outcomes	Funding	Quality Rating
Hunt, 2013	<i>Selected outcomes reported (excludes excluded interventions, skewed data, and studies with N&lt;50)</i> Integrated/assertive community treatment vs. usual care Death at 36 months (2 trials, n=421): RR 1.18 (95% CI 0.39 to 3.57) 33 per 1000 vs. 28 per 1000	Not reported	Good

**Please see Appendix B. Included Studies for full study references**

CI=confidence interval, GAF=Global Assessment of Functioning, MD=mean difference, QOL=quality of life, RCT=randomized controlled trial, RR=risk ratio, SAS=social adjustment scale, UK=United Kingdom, US=United States

## Appendix F. Quality Assessment

**Appendix Table F-1. Quality assessment of systematic reviews of pharmacological treatments**

Author, Year	1. Was an "a priori" design provided?	2. Was there duplicate study selection and data extraction?	3. Was a comprehensive literature search performed?	4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	5. Was a list of studies (included and excluded) provided?	6. Were the characteristics of the included studies provided?
Abou-Setta 2012	Yes	Yes	Yes	Yes	Yes	Yes
DERP SGA systematic review, 2013 (Update 4)	Yes	Yes Yes	Yes	Yes	Yes	Yes

Author, Year	7. Was the scientific quality of the included studies assessed and documented?	8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	9. Were the methods used to combine the findings of studies appropriate?	10. Was the likelihood of publication bias assessed?	11. Was the conflict of interest included?	Quality Rating
Abou-Setta 2012	Yes	Yes	Yes	Yes	Yes	Good
DERP SGA systematic review, 2013 (Update 4)	Yes	Yes	Yes	Not applicable due to number of poolable studies	Yes for report authors No for individual studies in this update, but they are likely mostly industry funded	Good

Please see Appendix B. Included Studies for full study references

**Appendix Table F-2. Quality assessment of randomized controlled trials of pharmacological treatments**

Author, Year Study Name	Random- ization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors blinded?	Clinician blinded?	Patient blinded?	Intention to treat?	Acceptable level of overall attrition (≤30%)?	Acceptable level of differential attrition (<10%)?	Overall Quality
Amr, 2013	Yes	Yes	Yes	No (clinicians were one of the raters)	No	Yes	No	No 73/156 = 47%	No 55% quetiapine, 39% haloperidol	Poor
Citrome, 2016	Unclear	Yes Interactive response system	Yes, though comorbidity NR	No (raters aware)	No (open-label)	No	Yes (none excluded)	No 37%	Yes (38% vs. 36%)	Fair
Crespo-Faccoro 2011	Yes	Unclear	No Not schizophrenia diagnosis	No	No	No	Yes	Yes	Yes	Fair
Detke, 2014	Unclear	Unclear	Yes Age, sex, age at onset, length of current episode, and baseline severity all similar	Unclear	No (open-label)	No	Yes	No 52.5%	Yes	Poor
Di Fiorino, 2014	Yes	Yes	Unclear	No	No	No	Yes	Yes (25%)	Yes 17% vs. 25%	Fair

Author, Year Study Name	Random- ization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors blinded?	Clinician blinded?	Patient blinded?	Intention to treat?	Acceptable level of overall attrition (≤30%)?	Acceptable level of differential attrition (<10%)?	Overall Quality
Durgam, 2014	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Yes	No Excluding placebo arm, 193/578 = 33% discontinued	Yes Excluding placebo, range 27.9 to 37.9%	Fair
Fleischhacker, 2014 ASPIRE EU	Unclear	Unclear	Yes	Unclear Dosing adjustments allowed - no explanation given for how conducted to maintain blinding	Unclear Dosing adjustments allowed - no explanation given for how conducted to maintain blinding	Yes	Yes	No 157/531 = 30%	Yes 26% vs. 33%	Fair
Green, 2015	Yes	Unclear	Yes	Yes	Yes	No	Yes	Yes	Yes	Fair
Ishigooka, 2015 ALPHA	Yes	Yes	Unclear Gender, age, baseline severity similar, but duration of illness 163 vs. 140 months	Unclear Dosing adjustments allowed - no explanation given for how conducted to maintain blinding	Unclear Dosing adjustments allowed - no explanation given for how conducted to maintain blinding	Yes	Yes	No 135/455 = 30%	Yes 26% to 33%	Fair

Author, Year Study Name	Random- ization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors blinded?	Clinician blinded?	Patient blinded?	Intention to treat?	Acceptable level of overall attrition (≤30%)?	Acceptable level of differential attrition (<10%)?	Overall Quality
Koshikawa, 2016	Yes Computer- generated	Unclear	Unclear Reported only for the 70% of participants completing the study	No Open-label	No Open-label	No Open-label	No 9/30 (30%) excluded	Yes 30%	Yes 29% vs. 31%	Fair
Li, 2014	Unclear Only described as randomized	Unclear "Assigned sequentially in ascending order"	Yes	Yes Double- dummy	Yes Double- dummy	Yes Double- dummy	Yes None excluded	Yes 41/279 = 15%	Yes 17% vs. 12%	Fair
Lieberman 2005 (CATIE Study)	Yes	Yes "Done under DB conditions"	Few minor differences	Yes	Yes	Yes	Yes	No	No	Good
Liu, 2014	Yes	Unclear	Unclear Age and baseline PANSS similar but duration of illness 4.5 vs. 5.5 months	No	No	No	Yes	Yes	Yes	Fair
Maat, 2014	Unclear Only described as randomized	Unclear	Yes	No Open-label	No Open-label	No Open-label	No 36/80 = 45% excluded	No 40% discontinued	No 47.4% vs. 33.3%	Poor
McEvoy, 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No 130/311 = 42%	Yes	Good
Naber, 2013 RECOVER	Unclear	Yes IVRS	Mostly yes	No	No	No	Yes With LOCF	No 45%	Yes	Fair

Author, Year Study Name	Random- ization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors blinded?	Clinician blinded?	Patient blinded?	Intention to treat?	Acceptable level of overall attrition (≤30%)?	Acceptable level of differential attrition (<10%)?	Overall Quality
Naber, 2015 QUALIFY	Yes Stratified random- ization	Unclear	Unclear Age, age at onset, and gender similar, but baseline severity not reported for all patients randomized (9% excluded)	Yes for QLS and IAQ but not for other assessments	No	No	No	No 112/295 = 38%	No 32% vs. 44%	Fair
Nemeth, 2017	Yes	Yes	Yes	Yes	Unclear	Yes	Yes (99% in each group)	Yes (23% in each group)	Yes	Good
Parabiaghi, 2016 GiSAS	Yes Computer- generated, stratified, block	Yes Central with IVRS	Yes Mostly similar though some baseline data incomplete	Yes Outcome assessment and data analysis blinded	No Open-label	No Open-label	Yes None excluded, both LOCF and multiple imputation used	No 86/200 = 43%	No 53% vs. 33%	Fair
Park, 2013	Yes Stratified random- ization	Unclear	Unclear PANSS 67.5 vs. 82.0 (small sample, N=20)	No Open-label	No Open-label	No Open-label	Unclear Followup and N's analyzed NR	Unclear Followup NR	Unclear	Poor
Robinson, 2015	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes Mixed models	No 93/209 = 44%	Yes	Fair
San, 2012	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Good
Sanz-Fuentenebro, 2013	No (alternating assignment)	No	Some differences: 60% vs. 80% male and duration of active psychosis 7.5 months vs. 12.3 months	Unclear	No	No	Yes with LOCF	No (53.3%)	No (20% vs. 47%)	Poor

Author, Year Study Name	Random- ization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors blinded?	Clinician blinded?	Patient blinded?	Intention to treat?	Acceptable level of overall attrition (≤30%)?	Acceptable level of differential attrition (<10%)?	Overall Quality
Savitz, 2016	Yes (computer- generated)	Yes (IWRS)	Yes, though comorbidity NR	Unclear	Yes (double dummy)	Yes (double dummy)	Yes (2.1% excluded from MITT set in double-blind phase)	Yes (17%)	Yes (16% vs. 18%)	Good
Shoja Shafti, 2015	Unclear Only described as randomized	Unclear	Yes	Yes	Yes	Yes	Unclear Followup and N's analyzed NR	Unclear Overall withdrawals NR	Unclear	Fair
Subotnik, 2015	Unclear	Unclear	Unclear Age, sex, % schizoaffective and baseline symptoms similar but time since onset 7.9 vs. 6.9 months	No	No	No	Yes	31%	No 25% vs 37%	Fair
Tybura, 2013	Unclear	Unclear	Unclear Age and baseline PANSS similar, but no other baseline characteristics reported	No Open-label	No Open-label	No Open-label	Yes Tables show N's at baseline and 3 months as the same	Yes Tables show N's at baseline and 3 months as the same	Yes Tables show N's at baseline and 3 months as the same	Poor
Tybura, 2014	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes 36/131 = 27% discontinued (SGAs only)	Yes 32% vs. 24%	Fair

Author, Year Study Name	Random- ization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors blinded?	Clinician blinded?	Patient blinded?	Intention to treat?	Acceptable level of overall attrition (≤30%)?	Acceptable level of differential attrition (<10%)?	Overall Quality
Wani, 2015	Unclear Only described as randomized	Unclear	Yes	No Open-label	No Open-label	No Open-label	Unclear States that LOCF but gives N's analyzed at 24 weeks as those continuing treatment (Fig 1; excludes 24%)	Yes 15/62 = 24%	No 16% vs. 32%	Fair

**Please see Appendix B. Included Studies for full study references**

CATIE=clinical Antipsychotic Trials of Intervention Effectiveness, DB=data base, EU=European Union, EUFEST=The European First Episode Schizophrenia Trial, IAQ=interviewer-administered questionnaires, IVRS=inverted repeats, IWRS=interactive web response system, LOCF=last observation carried forward, mITT=modified intention to treat, PANSS=Positive and Negative Syndrome Scale, QLS=quality of life scale, SGA=second-generation antipsychotics

**Appendix Table F-3. Quality assessment of systematic reviews of psychosocial and nonpharmacological treatments**

<b>Author, Year</b>	<b>1. Was an "a priori" design provided?</b>	<b>2. Was there duplicate study selection and data extraction?</b>	<b>3. Was a comprehensive literature search performed?</b>	<b>4. Was the status of publication used as an inclusion criterion (i.e. was grey literature included)?</b>	<b>5. Was a list of studies (included and excluded) provided?</b>	<b>6. Were the characteristics of the included studies provided?</b>
<b><i>Assertive community treatment</i></b>						
Marshall 2000a	Yes	Yes	Yes	Unclear	Yes	Yes
<b><i>Cognitive-behavioral therapy</i></b>						
Jauhar 2014	Yes	Yes	Yes	Yes	Yes	Yes
Jones 2010	Yes	Yes	Yes	Yes	Yes	Yes
Velthorst 2015	Yes	Unclear	Yes	No	No	Yes
<b><i>Cognitive remediation</i></b>						
Cella 2017	Yes	Yes	Yes	No	No	No
Wykes 2011	Yes	Yes	Yes	No	No	Yes
<b><i>Family interventions</i></b>						
Pharoah 2010	Yes	Yes Yes	Yes	Yes	Yes	Yes
<b><i>Intensive case management</i></b>						
Marshall 2000b	Yes	Yes	Yes	Unclear	Yes	Yes
<b><i>Illness self-management</i></b>						
Zou, 2012	Yes	Yes	Yes	Unclear	No	Yes
<b><i>Psychoeducation</i></b>						
Pekkala 2009	Yes	Yes	Yes	No	Yes	Yes

<b>Author, Year</b>	<b>7. Was the scientific quality of the included studies assessed and documented?</b>	<b>8. Was the scientific quality of the included studies used appropriately in formulating conclusions?</b>	<b>9. Were the methods used to combine the findings of studies appropriate?</b>	<b>10. Was the likelihood of publication bias assessed?</b>	<b>11. Was the conflict of interest included?</b>	<b>Quality Rating</b>
<b><i>Assertive community treatment</i></b>						
Marshall 2000a	Yes	Yes	Yes	No	Yes	Good
<b><i>Cognitive-behavioral therapy</i></b>						
Jauhar 2014	Yes	Yes	Yes	Yes	Yes	Good
Jones 2010	Yes	Yes	Yes	Yes	Yes	Good
Velthorst 2015	Yes	Yes	Yes	Yes	Yes	Good
<b><i>Cognitive remediation</i></b>						
Cella 2017	Yes	Yes	Yes	Yes	Yes	Good
Wykes 2011	Yes	Yes	Yes	Yes	Yes	Good
<b><i>Family interventions</i></b>						
Pharoah 2010	Yes	Yes	Yes	Yes	Yes	Good
<b><i>Intensive case management</i></b>						
Marshall 2000b	Yes	Yes	Yes	No	Yes	Good
<b><i>Illness self-management</i></b>						
Zou, 2012	Yes	Yes	Yes	Yes	Yes	Fair
<b><i>Psychoeducation</i></b>						
Pekkala 2009	Yes	Yes	Yes	Yes	No	Good

<b>Author, Year</b>	<b>1. Was an "a priori" design provided?</b>	<b>2. Was there duplicate study selection and data extraction?</b>	<b>3. Was a comprehensive literature search performed?</b>	<b>4. Was the status of publication used as an inclusion criterion (i.e. was grey literature included)?</b>	<b>5. Was a list of studies (included and excluded) provided?</b>	<b>6. Were the characteristics of the included studies provided?</b>
<b><i>Substance use and schizophrenia</i></b>						
Hunt, 2013	Yes	Yes Yes	Yes	Yes	Yes	Yes
<b><i>Supported employment</i></b>						
Kinoshita, 2013	Yes	Yes	Yes	Yes	Yes	Yes
<b><i>Supportive therapy</i></b>						
Buckley, 2015	Yes	Yes Yes	Yes	No	Yes	Yes

<b>Author, Year</b>	<b>7. Was the scientific quality of the included studies assessed and documented?</b>	<b>8. Was the scientific quality of the included studies used appropriately in formulating conclusions?</b>	<b>9. Were the methods used to combine the findings of studies appropriate?</b>	<b>10. Was the likelihood of publication bias assessed?</b>	<b>11. Was the conflict of interest included?</b>	<b>Quality Rating</b>
<i>Substance use and schizophrenia</i>						
Hunt, 2013	Yes	Yes	Yes	No	No	Good
<i>Supported employment</i>						
Kinoshita, 2013	Yes	Yes	Yes	Yes	Yes	Good
<i>Supportive therapy</i>						
Buckley, 2015	Yes	Unclear	Yes	No	Yes	Good

**Please see Appendix B. Included Studies for full study references**

ACT=assertive community treatment, ICM=intensive case management

Appendix Table F-4. Quality assessment of randomized controlled trials of psychosocial and nonpharmacological treatments

Author, Year Study name	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors blinded?	Intention to treat?	Acceptable level of overall attrition ( $\leq 30\%$ )?	Acceptable level of differential attrition (<10%)?	Overall Quality
<b><i>Assertive community Treatment</i></b>								
Sytema, 2007	Yes	Unclear	Yes	Unclear	Yes	No	No	Fair
<b><i>Cognitive-behavioral Therapy</i></b>								
Freeman 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Lysaker 2009	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Fair
Malik 2009	Yes	Unclear	Unclear	Yes	No	Yes	Yes	Fair
Velligan 2015b	Yes	Unclear	Yes	Yes	Unclear	Yes	Unclear	Fair
Zimmer 2007	Yes	Unclear	Yes	Yes	No	Yes	Yes	Fair
<b><i>Cognitive remediation</i></b>								
Farreny 2012	Yes	Unclear	Yes	Unclear	No	Yes	Yes	Fair
Mueller 2015	Yes	Unclear	Yes	Yes	No	Yes	Yes	Fair
Twamley 2012	Unclear	Unclear	No	Yes	Yes	Yes	Yes	Fair
Vita 2011 and Deste 2015	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Good

Author, Year Study name	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors blinded?	Intention to treat?	Acceptable level of overall attrition ( $\leq 30\%$ )?	Acceptable level of differential attrition ( $< 10\%$ )?	Overall Quality
<b>Early intervention for patients with first-episode psychosis</b>								
ETP-RAISE trial Kane 2015 and Kane 2016	Unclear	Unclear	No	Yes	Unclear	Unclear	Unclear	Poor
Guo 2007 and Guo 2010	Unclear	Unclear	Yes	Yes	Yes	No	No	Fair
LEO trial Craig 2004, Garety 2006	Yes	Yes	No	Yes	Yes	Yes	Yes	Good
LEO trial Tempier, 2012	Yes	Yes	No	Yes	Yes	No	No	Fair
OPUS trial Secher 2015, Bertelsen 2009	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
<b>Family interventions</b>								
Dyck 2000	Unclear	Unclear	Yes	Unclear	No	No	Yes	Poor
Garety 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Kopelowicz 2012	Yes	Unclear	Yes	Unclear	Yes	No	No, 27%, 37%, and 51%	Poor
Mayoral, 2015	Unclear	Unclear	Yes	Yes	Unclear; likely no	Yes	Yes	Fair
Sellwood 2001	Yes	Unclear	Unclear	Yes	Unclear	Yes	Yes	Fair
Valencia 2007	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Fair
<b>Intensive case Management</b>								
Bjorkman, 2002	Yes	Unclear	No	Unclear	Yes	Yes	No	Fair

Author, Year Study name	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors blinded?	Intention to treat?	Acceptable level of overall attrition (≤30%)?	Acceptable level of differential attrition (<10%)?	Overall Quality
<b><i>Illness self-management and recovery</i></b>								
Hasson-Ohayon, 2007	Yes	Unclear	Yes	Unclear	Unclear	Yes	Unclear	Fair
<b><i>Social skills training</i></b>								
Mueser 2010 and Bartels 2014	Yes	Unclear	No	Yes	No	Yes	Yes	Fair
Valencia 2007	Unclear	Unclear	Yes	Yes	No	Yes	Yes	Fair
Valencia 2013	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Fair
<b><i>Supported employment</i></b>								
Cook, 2008, 2005	Yes, for entire study population; data not reported for schizophrenia subgroup	Unclear	Yes, for entire study population; data not reported for schizophrenia subgroup (Numerous baseline differences were found between those with schizophrenia and those with other diagnoses)	Unclear	Unclear	Yes, for entire study population; data not reported for schizophrenia subgroup	Yes, for entire study population; data not reported for schizophrenia subgroup	Fair
Mueser, 2004	Unclear	Unclear	Yes	No	Yes	Yes	Yes	Fair

Please see Appendix B. Included Studies for full study references

# Appendix G. Forest Plots for Pooled Analyses and Matrixes of Results for Network Meta-Analyses

**Appendix Table G-1a. SGA versus SGA network analysis of response (odds ratio, 95% confidence interval)**

<b>ARI</b>	1.05 (0.35-3.02)	0.97 (0.57-1.68)	0.57 (0.20-1.63)	1.16 (0.56-2.58)	0.70 (0.35-1.45)	0.67 (0.45-1.02)	1.11 (0.65-2.00)	1.15 (0.77-1.78)	0.81 (0.58-1.16)	0.98 (0.59-1.58)
0.96 (0.33-2.86)	<b>ARI LAI-1</b>	0.93 (0.28-3.13)	0.55 (0.13-2.44)	1.12 (0.30-4.26)	0.67 (0.25-1.89)	0.65 (0.18-2.26)	1.06 (0.32-3.78)	1.08 (0.35-3.57)	0.78 (0.25-2.52)	0.93 (0.28-3.16)
1.03 (0.59-1.76)	1.08 (0.32-3.53)	<b>ASE</b>	0.59 (0.18-1.81)	1.20 (0.54-2.82)	0.72 (0.33-1.64)	0.69 (0.41-1.20)	1.15 (0.57-2.32)	1.18 (0.69-2.09)	0.83 (0.49-1.43)	1.01 (0.54-1.86)
1.75 (0.61-5.05)	1.83 (0.41-7.68)	1.69 (0.55-5.44)	<b>BRE</b>	2.03 (0.62-7.08)	1.23 (0.33-4.52)	1.18 (0.36-3.90)	1.94 (0.58-6.64)	1.99 (0.67-6.25)	1.43 (0.46-4.46)	1.70 (0.53-5.51)
0.86 (0.39-1.79)	0.90 (0.24-3.31)	0.83 (0.36-1.87)	0.49 (0.14-1.63)	<b>CAR</b>	0.59 (0.23-1.56)	0.58 (0.25-1.26)	0.95 (0.39-2.36)	0.98 (0.48-2.04)	0.70 (0.33-1.44)	0.84 (0.36-1.87)
1.43 (0.69-2.88)	1.50 (0.53-4.06)	1.38 (0.61-3.05)	0.82 (0.22-3.00)	1.69 (0.65-4.38)	<b>CLO</b>	0.96 (0.46-1.96)	1.58 (0.69-3.71)	1.63 (0.84-3.36)	1.16 (0.61-2.24)	1.39 (0.63-2.94)
1.49 (0.98-2.22)	1.54 (0.45-5.48)	1.44 (0.83-2.47)	0.85 (0.26-2.79)	1.74 (0.79-3.94)	1.04 (0.51-2.19)	<b>OLA</b>	1.65 (0.95-2.95)	<b>1.71</b> (1.11-2.68)	1.21 (0.94-1.59)	1.45 (0.94-2.25)
0.90 (0.50-1.54)	0.94 (0.26-3.12)	0.87 (0.43-1.75)	0.52 (0.15-1.74)	1.05 (0.42-2.56)	0.63 (0.27-1.45)	0.61 (0.34-1.05)	<b>PAL</b>	1.03 (0.55-1.94)	0.73 (0.42-1.27)	0.88 (0.44-1.71)
0.87 (0.56-1.29)	0.92 (0.28-2.85)	0.85 (0.48-1.46)	0.50 (0.16-1.49)	1.02 (0.49-2.09)	0.61 (0.30-1.19)	<b>0.59</b> (0.37-0.90)	0.97 (0.52-1.81)	<b>QUE</b>	<b>0.71</b> (0.50-0.99)	0.85 (0.50-1.39)
1.23 (0.86-1.71)	1.29 (0.40-4.08)	1.20 (0.70-2.02)	0.70 (0.22-2.16)	1.43 (0.69-3.00)	0.86 (0.45-1.65)	0.83 (0.63-1.07)	1.36 (0.79-2.40)	<b>1.41</b> (1.01-2.00)	<b>RIS</b>	1.20 (0.78-1.82)
1.03 (0.63-1.70)	1.08 (0.32-3.59)	0.99 (0.54-1.85)	0.59 (0.18-1.90)	1.19 (0.53-2.81)	0.72 (0.34-1.58)	0.69 (0.44-1.07)	1.14 (0.59-2.27)	1.18 (0.72-2.01)	0.84 (0.55-1.28)	<b>ZIP</b>

Drugs are reported in alphabetical order. Comparisons between treatments should be read from left to right and the estimate in each cell represents comparison between the row-defining treatment and the column-defining treatment. Odds ratios (ORs) higher than 1 favor the column-defining treatment, meaning less withdrawal in the column-defining treatment; and ORs less than 1 favor the row-defining treatment, meaning less withdrawal in the row-defining treatment. For example, the OR for comparing QUE (row-defining treatment) vs. RIS (column-defining treatment) is 0.71 (95% CrI 0.50 to 0.99), which means that QUE has lower odds of response and the comparison favors RIS, which has greater response. Each comparison is represented twice in the table, for example, for two treatments A and B, once with A versus B and once with B versus A (i.e. the reciprocal OR). For the example above, the OR for comparing RIS (now the row-defining treatment) vs. QUE (now the column-defining treatment) is 0.141 (95% CrI 1.01 to 2.00), which means that RIS has a higher odds of response and again, it means that the comparison favors RIS, which has greater response. Significant results are in bold.

ARI = aripiprazole- ASE = asenapine- BRE = brepripazole- CAR = cariprazine- CLO=clozapine- ILO = iloperidone- LUR = lurasidone- OLA = olanzapine. PAL=paliperidone, QUE=quetiapine, RIS=risperidone- ZIP=ziprasidone. LAI = long-acting injection; 1 = once monthly- 3 – every 3 months.

**Appendix Table G1b. Numbers of studies per comparison contributing to network meta-analysis of response for SGAs versus SGAs**

<b>Comparison</b>	<b>No. Studies</b>
Aripiprazole : Brexipiprazole	1
Aripiprazole : Olanzapine	3
Aripiprazole : Quetiapine IR	1
Aripiprazole : Risperidone	3
Aripiprazole Monthly LAI : Aripiprazole	1
Asenapine : Olanzapine	3
Cariprazine : Risperidone	1
Clozapine : Olanzapine	3
Clozapine : Risperidone	4
Paliperidone : Aripiprazole	1
Paliperidone : Olanzapine	1
Paliperidone Monthly LAI : Paliperidone 3-month LAI	1
Paliperidone Monthly LAI : Risperidone LAI	3
Quetiapine IR : Olanzapine	5
Quetiapine IR : Risperidone	9
Risperidone : Olanzapine	16
Ziprasidone : Aripiprazole	1
Ziprasidone : Olanzapine	3
Ziprasidone : Quetiapine IR	1
Ziprasidone : Risperidone	1

**Appendix Table G-1c. SGAs versus SGAs meta-regression results for response**

<b>Meta-regression variables</b>	<b>OR (95% CI)</b>
OR for duration	1.15 (0.57 to 2.07)
Drug dose: Low versus Medium	1.00 (0.53 to 1.78)
Drug dose: High versus Medium	1.02 (0.99 to 1.04)
Response definition category B, as compared to category A	0.94 (0.67 to 1.27)
Response definition category C, as compared to category A	0.94 (0.63 to 1.34)
Treatment Resistant	0.84 (0.44 to 1.49)
First Episode	1.29 (0.82 to 2.0)

**Appendix Table G-2a. SGA versus SGA network meta-analysis of withdrawals from study due to adverse events (odds ratio, 95% confidence interval)**

<b>ARI</b>	0.90 (0.31-2.69)	0.83 (0.54-1.25)	0.48 (0.02-5.34)	1.08 (0.56-2.12)	<b>0.43</b> <b>(0.21-0.88)</b>	1.25 (0.58-2.76)	0.62 (0.37-1.08)	1.11 (0.82-1.48)	0.69 (0.21-2.40)	0.72 (0.38-1.30)	0.80 (0.35-1.99)	0.73 (0.21-2.78)	0.32 (0.04-1.75)	0.68 (0.48-1.01)	0.80 (0.57-1.13)	1.60 (0.85-3.05)	<b>0.64</b> <b>(0.44-0.94)</b>
1.12 (0.37-3.19)	<b>ARI LAI-1</b>	0.92 (0.28-2.80)	0.52 (0.02-7.79)	1.21 (0.34-3.98)	0.49 (0.19-1.16)	1.43 (0.38-5.04)	0.71 (0.21-2.19)	1.24 (0.37-3.76)	0.78 (0.15-3.92)	0.81 (0.21-2.94)	0.89 (0.42-1.94)	0.82 (0.23-2.86)	0.36 (0.03-2.76)	0.77 (0.25-2.28)	0.89 (0.57-2.59)	1.77 (0.57-5.56)	0.72 (0.23-2.16)
1.21 (0.80-1.85)	1.09 (0.36-3.59)	<b>ASE</b>	0.58 (0.02-6.68)	1.32 (0.65-2.62)	0.52 (0.25-1.10)	1.51 (0.67-3.49)	0.75 (0.43-1.36)	1.34 (0.87-1.87)	0.85 (0.25-2.88)	0.88 (0.44-1.63)	0.96 (0.40-2.54)	0.90 (0.24-3.64)	0.39 (0.04-2.22)	0.83 (0.54-1.28)	0.97 (0.65-1.47)	1.93 (0.96-4.08)	0.78 (0.51-1.24)
2.08 (0.19-57.77)	1.92 (0.13-62.00)	1.72 (0.15-48.12)	<b>BRE</b>	2.34 (0.19-62.11)	0.89 (0.07-26.93)	2.57 (0.21-78.40)	1.27 (0.11-36.14)	2.29 (0.20-66.19)	1.50 (0.09-51.64)	1.52 (0.13-44.95)	1.71 (0.13-53.38)	1.60 (0.10-58.93)	0.68 (0.03-30.54)	1.42 (0.12-39.94)	1.65 (0.15-46.54)	3.32 (0.28-100.40)	1.33 (0.12-37.67)
0.92 (0.47-1.79)	0.83 (0.25-2.96)	0.76 (0.38-1.54)	0.43 (0.02-5.42)	<b>CAR</b>	<b>0.40</b> <b>(0.17-0.95)</b>	1.15 (0.46-2.88)	0.58 (0.28-1.18)	1.02 (0.51-1.99)	0.65 (0.18-2.32)	0.66 (0.28-1.50)	0.73 (0.29-2.06)	0.67 (0.18-2.75)	0.30 (0.03-1.73)	0.63 (0.35-1.15)	0.74 (0.41-1.33)	1.47 (0.66-3.32)	0.60 (0.31-1.16)
<b>2.32</b> <b>(1.13-4.71)</b>	2.05 (0.87-5.26)	1.91 (0.91-3.96)	1.12 (0.04-13.61)	<b>2.52</b> <b>(1.06-5.90)</b>	<b>CLO</b>	1.46 (0.67-3.18)	1.46 (0.41-5.21)	<b>2.54</b> <b>(1.10-6.67)</b>	1.60 (0.64-4.20)	1.66 (0.80-4.37)	1.85 (0.80-6.38)	1.71 (0.46-6.38)	0.75 (0.07-4.66)	1.58 (0.81-3.08)	1.84 (0.96-3.58)	<b>3.66</b> <b>(1.42-10.05)</b>	1.50 (0.76-2.91)
0.80 (0.36-1.73)	0.70 (0.20-2.65)	0.66 (0.29-1.49)	0.39 (0.01-4.68)	0.87 (0.35-2.17)	<b>0.34</b> <b>(0.13-0.91)</b>	0.50 (0.22-1.16)	0.89 (0.41-1.88)	0.55 (0.22-1.22)	0.57 (0.14-2.24)	0.57 (0.22-1.43)	0.63 (0.21-2.06)	0.58 (0.13-2.85)	0.25 (0.02-1.60)	0.54 (0.26-1.16)	0.64 (0.31-1.27)	1.27 (0.47-3.40)	0.51 (0.24-1.13)
1.61 (0.93-2.69)	1.42 (0.46-4.87)	1.33 (0.74-2.34)	0.78 (0.03-8.97)	1.73 (0.85-3.54)	0.68 (0.31-1.50)	2.01 (0.86-4.57)	<b>LUR</b>	1.77 (1.06-2.90)	1.11 (0.32-3.93)	1.15 (0.51-2.39)	1.27 (0.51-3.50)	1.17 (0.30-4.71)	0.52 (0.06-3.02)	1.09 (0.67-1.79)	1.28 (0.79-2.03)	2.55 (1.19-5.62)	1.03 (0.63-1.68)
0.90 (0.68-1.23)	0.81 (0.27-2.71)	0.75 (0.54-1.05)	0.44 (0.02-4.92)	0.98 (0.50-1.95)	<b>0.39</b> <b>(0.19-0.79)</b>	1.13 (0.53-2.48)	<b>0.57</b> <b>(0.34-0.94)</b>	0.63 (0.19-2.18)	0.65 (0.29-1.44)	0.72 (0.29-1.95)	0.76 (0.27-2.74)	0.66 (0.18-2.74)	0.29 (0.03-1.61)	<b>0.62</b> <b>(0.44-0.87)</b>	<b>0.72</b> <b>(0.55-0.96)</b>	1.44 (0.72-2.98)	<b>0.58</b> <b>(0.41-0.82)</b>
1.44 (0.42-4.92)	1.28 (0.26-6.56)	1.19 (0.35-4.04)	0.67 (0.02-10.97)	1.54 (0.43-5.67)	0.63 (0.16-2.43)	1.81 (0.45-7.35)	0.90 (0.26-3.15)	1.59 (0.46-5.34)	<b>OLA LAI</b>	1.03 (0.16-3.81)	1.14 (0.28-4.90)	1.04 (0.20-6.14)	0.46 (0.04-3.89)	0.98 (0.29-3.38)	1.15 (0.33-4.00)	2.28 (0.66-8.33)	0.93 (0.27-3.15)
1.38 (0.77-2.65)	1.24 (0.34-4.78)	1.14 (0.62-2.26)	0.66 (0.02-8.01)	1.51 (0.67-3.62)	0.60 (0.24-1.57)	1.74 (0.70-4.56)	0.87 (0.42-1.88)	0.97 (0.27-3.65)	<b>PAL</b>	0.97 (0.26-3.40)	1.11 (0.24-4.60)	1.01 (0.24-4.60)	0.46 (0.05-2.79)	0.95 (0.51-1.82)	1.11 (0.60-2.09)	2.20 (0.96-5.38)	0.89 (0.48-1.73)
1.25 (0.50-2.90)	1.13 (0.52-2.41)	1.04 (0.40-2.50)	0.59 (0.02-7.96)	1.37 (0.49-3.41)	0.54 (0.23-1.25)	1.59 (0.49-4.76)	0.79 (0.29-1.99)	0.88 (0.21-3.43)	0.91 (0.30-3.54)	<b>PAL LAI</b>	1.09 (0.36-2.62)	0.92 (0.36-2.28)	0.41 (0.04-2.57)	0.86 (0.36-1.95)	1.01 (0.40-2.32)	1.99 (0.89-3.89)	0.81 (0.32-1.92)
1.37 (0.36-4.80)	1.22 (0.35-4.31)	1.12 (0.28-4.19)	0.63 (0.02-10.31)	1.50 (0.36-5.65)	0.59 (0.16-2.16)	1.73 (0.35-7.58)	0.85 (0.21-3.32)	0.96 (0.37-5.71)	0.99 (0.16-4.26)	1.09 (0.44-2.77)	<b>PAL LAI-3</b>	0.43 (0.03-3.66)	0.93 (0.25-3.35)	1.09 (0.25-4.05)	2.18 (0.69-6.83)	0.88 (0.23-3.20)	
3.13 (0.57-28.00)	2.80 (0.36-34.90)	2.56 (0.45-23.78)	1.48 (0.03-36.92)	3.32 (0.58-32.31)	1.34 (0.22-13.96)	3.93 (0.63-41.77)	1.94 (0.33-18.04)	<b>3.40</b> <b>(0.62-32.84)</b>	2.17 (0.26-24.49)	2.19 (0.36-22.09)	2.46 (0.39-28.03)	2.30 (0.27-31.13)	<b>QUE ER</b>	2.10 (0.39-20.33)	2.43 (0.47-23.59)	4.83 (0.82-47.58)	1.97 (0.36-18.35)
1.47 (0.99-2.10)	1.30 (0.44-4.04)	1.21 (0.78-1.85)	0.70 (0.03-8.16)	1.59 (0.87-2.89)	0.63 (0.33-1.23)	1.84 (0.87-3.82)	0.92 (0.56-1.50)	<b>1.62</b> <b>(1.15-2.26)</b>	1.05 (0.30-3.44)	1.05 (0.55-1.97)	1.17 (0.51-2.81)	1.07 (0.30-4.06)	0.48 (0.05-2.61)	<b>QUE</b>	1.17 (0.89-1.49)	<b>2.33</b> <b>(1.24-4.46)</b>	0.94 (0.66-1.33)
1.26 (0.89-1.77)	1.12 (0.39-3.53)	1.04 (0.68-1.54)	0.61 (0.02-6.63)	0.54 (0.28-2.45)	0.54 (0.14-2.04)	1.57 (0.79-3.24)	0.78 (0.49-1.26)	<b>1.39</b> <b>(1.04-1.81)</b>	0.91 (0.44-3.08)	0.91 (0.68-1.68)	0.99 (0.43-2.52)	0.92 (0.25-3.67)	0.41 (0.04-2.16)	0.85 (0.67-1.13)	<b>RIS</b>	<b>1.99</b> <b>(1.01-4.07)</b>	0.81 (0.58-1.11)
0.63 (0.33-1.17)	0.57 (0.18-1.74)	0.52 (0.25-1.04)	0.30 (0.01-3.54)	0.68 (0.30-1.52)	<b>0.27</b> <b>(0.10-0.71)</b>	0.79 (0.29-2.12)	<b>0.39</b> <b>(0.18-0.84)</b>	0.70 (0.34-1.40)	0.44 (0.12-1.53)	0.45 (0.19-1.04)	<b>0.50</b> <b>(0.26-1.00)</b>	0.46 (0.15-1.45)	0.21 (0.02-1.22)	<b>0.43</b> <b>(0.25-0.81)</b>	<b>0.50</b> <b>(0.25-0.99)</b>	<b>RIS LAI</b>	<b>0.40</b> <b>(0.20-0.82)</b>
1.55 (1.06-2.26)	1.39 (0.46-4.44)	1.28 (0.81-1.98)	0.75 (0.03-8.36)	1.68 (0.86-3.19)	0.67 (0.34-1.31)	1.95 (0.89-4.18)	0.97 (0.59-1.59)	<b>1.72</b> <b>(1.22-2.42)</b>	1.08 (0.32-3.77)	1.12 (0.58-2.09)	1.24 (0.52-3.10)	1.14 (0.31-4.44)	0.51 (0.05-2.80)	1.06 (0.75-1.52)	1.24 (0.90-1.73)	<b>2.47</b> <b>(1.23-5.08)</b>	<b>ZIP</b>

Drugs are reported in alphabetical order. Comparisons between treatments should be read from left to right and the estimate in each cell represents comparison between the row-defining treatment and the column-defining treatment. Odds ratios (ORs) higher than 1 favor the column-defining treatment, meaning less withdrawal in the column-defining treatment; and ORs less than 1 favor the row-defining treatment, meaning less withdrawal in the row-defining treatment. For example, the OR for comparing LUR (row-defining treatment) vs. OLA (column-defining treatment) is 1.77 (95% CrI 1.06 to 2.90), which means that LUR has higher odds of withdrawal and the comparison favors OLA, which has less withdrawal. Each comparison is represented twice in the table, for example, for two treatments A and B, once with A versus B and once with B versus A (i.e. the reciprocal OR). For the example above, the OR for comparing OLA (now the row-defining treatment) vs. LUR (now the column-defining treatment) is 0.57 (95% CrI 0.34 to 0.94), which means that OLA has a lower odds of withdrawal and again, it means that the comparison favors OLA, which has less withdrawal. Significant results are in bold.

ARI = aripiprazole- ASE = asenapine- BRE = brepiprazole- CAR = cariprazine- CLO=clozapine- ILO = iloperidone- LUR = lurasidone- OLA = olanzapine. PAL=paliperidone, QUE=quetiapine, RIS=risperidone- ZIP=ziprasidone. LAI = long-acting injection; 1 = once monthly- 3 – every 3 months.

**Appendix Table G-2b. SGA versus SGA: numbers of studies per comparison contributing to network meta-analysis of withdrawals due to adverse events**

Comparison	No. of studies
Aripiprazole : Brexpiprazole	1
Aripiprazole : Olanzapine	9
Aripiprazole : Quetiapine IR	3
Aripiprazole : Risperidone	6
Aripiprazole : Risperidone LAI	1
Aripiprazole : Ziprasidone	3
Aripiprazole Monthly LAI : Aripiprazole	2
Asenapine : Olanzapine	6
Asenapine : Risperidone	1
Cariprazine : Risperidone	2
Clozapine : Olanzapine	9
Clozapine : Risperidone	9
Iloperidone : Risperidone	2
Lurasidone : Olanzapine	1
Lurasidone : Risperidone	1
Lurasidone : Ziprasidone	1
Olanzapine LAI : Olanzapine	1
Paliperidone : Aripiprazole	2
Paliperidone : Olanzapine	3
Paliperidone : Risperidone	1
Paliperidone : Ziprasidone	1
Paliperidone Monthly LAI : Aripiprazole	1
Paliperidone Monthly LAI : Paliperidone 3-month LAI	1
Paliperidone Monthly LAI : Risperidone LAI	4
Quetiapine ER : Risperidone	1
Quetiapine IR : Clozapine	2
Quetiapine IR : Olanzapine	9
Quetiapine IR : Risperidone	14
Quetiapine IR : Risperidone LAI	1
Risperidone : Olanzapine	16
Risperidone LAI : Risperidone	1
Ziprasidone : Clozapine	1

Comparison	No. of studies
Ziprasidone : Olanzapine	9
Ziprasidone : Quetiapine IR	5
Ziprasidone : Risperidone	5

**Appendix Table G-2c. Meta-regression results for withdrawals due to adverse events**

Meta-regression variables	OR (95% CI)
Duration	0.69 (0.36 to 1.19)
Drug dose: Low versus Medium	1.67 (0.96 to 2.60)
Drug dose: High versus Medium	1.01 (0.99 to 1.03)
Treatment Resistant	1.63 (0.72 to 3.26)
First Episode	0.54 (0.25 to 1.03)

**Appendix Table G-3a. SGA versus SGA network meta-analysis of discontinuation from study for any cause (odds ratio, 95% confidence interval)**

ARI	1.18 (0.73-1.95)	0.84 (0.64-1.09)	0.94 (0.37-2.38)	0.84 (0.55-1.29)	1.45 (0.97-2.19)	<b>0.61</b> ( <b>0.40-0.94</b> )	0.76 (0.54-1.10)	<b>1.45</b> ( <b>1.20-1.76</b> )	0.66 (0.37-1.20)	0.97 (0.71-1.32)	0.81 (0.51-1.34)	0.88 (0.45-1.82)	2.16 (0.77-6.15)	<b>0.76</b> ( <b>0.61-0.95</b> )	0.99 (0.82-1.20)	1.02 (0.70-1.50)	0.84 (0.67-1.07)
0.85 (0.51-1.37)	ARI LAI-1	0.71 (0.41-1.23)	0.80 (0.27-2.25)	0.71 (0.38-1.31)	1.23 (0.79-1.93)	<b>0.52</b> ( <b>0.98</b> )	0.65 (0.36-1.17)	1.23 (2.10)	0.56 (0.27-1.17)	0.82 (0.45-1.47)	0.69 (0.37-1.09)	0.75 (0.37-1.44)	1.83 (5.84)	0.65 (1.08)	0.84 (1.39)	0.87 (1.55)	0.72 (1.21)
1.19 (0.92-1.57)	1.41 (0.81-2.44)	ASE	1.12 (0.42-2.94)	1.00 (0.64-1.56)	<b>1.73</b> ( <b>1.15-2.63</b> )	0.73 (0.46-1.14)	0.91 (0.62-1.32)	<b>1.73</b> ( <b>2.19</b> )	0.79 (0.43-1.43)	1.15 (0.81-1.64)	0.97 (0.57-1.63)	1.06 (0.51-2.17)	2.56 (7.47)	0.91 (1.19)	1.18 (1.51)	1.23 (1.85)	1.00 (0.78-1.33)
1.06 (0.42-2.74)	1.25 (0.44-3.77)	0.89 (0.34-2.41)	BRE	0.90 (0.32-2.57)	1.55 (0.57-4.38)	0.65 (0.23-1.80)	0.81 (0.30-2.27)	1.54 (0.60-4.02)	0.71 (0.23-2.14)	1.03 (0.40-2.75)	0.86 (0.31-2.52)	0.94 (0.31-3.10)	2.29 (9.56)	0.81 (0.31-2.11)	1.05 (0.41-2.73)	1.08 (0.40-3.03)	0.89 (2.37)
1.19 (0.77-1.83)	1.42 (0.76-2.63)	1.00 (0.64-1.57)	1.12 (0.39-3.12)	CAR	<b>1.72</b> ( <b>2.93</b> )	0.73 (0.42-1.25)	0.91 (0.56-1.48)	<b>1.73</b> ( <b>2.69</b> )	0.79 (0.40-1.53)	1.15 (0.71-1.90)	0.97 (0.57-1.71)	1.06 (0.50-2.24)	2.56 (7.72)	0.91 (1.37)	1.18 (1.75)	1.22 (2.01)	1.00 (1.58)
0.69 (0.46-1.03)	0.82 (0.52-1.26)	<b>0.58</b> ( <b>0.38-0.87</b> )	0.65 (0.23-1.76)	<b>0.58</b> ( <b>0.34-0.99</b> )	<b>0.42</b> ( <b>0.70</b> )	<b>0.53</b> ( <b>0.32-0.84</b> )	1.00 (0.68-1.45)	<b>0.46</b> ( <b>0.23-0.90</b> )	0.67 (0.41-1.07)	0.56 (0.33-0.92)	0.61 (0.29-1.24)	1.49 (4.52)	<b>0.53</b> ( <b>0.35-0.78</b> )	<b>0.69</b> ( <b>0.47-0.98</b> )	0.71 (1.24)	0.58 (0.84)	
1.65 (1.06-2.48)	<b>1.93</b> ( <b>1.02-3.62</b> )	1.37 (0.87-2.19)	1.53 (0.56-4.28)	1.38 (0.80-2.36)	<b>2.37</b> ( <b>4.42-4.03</b> )	1.25 (0.76-2.04)	1.09 (0.60-2.04)	<b>2.38</b> ( <b>3.60</b> )	1.34 (0.73-2.20)	1.44 (0.64-3.25)	1.44 (0.73-2.46)	<b>3.53</b> ( <b>10.58</b> )	1.25 (1.88)	<b>1.63</b> ( <b>1.11-2.34</b> )	1.68 (2.90)	1.38 (2.13)	
1.32 (0.91-1.87)	1.55 (0.86-2.82)	1.10 (0.76-1.60)	1.23 (0.44-3.37)	1.10 (0.68-1.78)	<b>1.89</b> ( <b>3.19-3.10</b> )	0.80 (0.49-1.31)	0.86 (0.52-1.41)	<b>1.91</b> ( <b>3.35-2.67</b> )	1.27 (0.62-2.17)	1.06 (0.83-1.94)	1.16 (0.62-2.53)	1.34 (8.57)	1.44 (2.53)	<b>1.19</b> ( <b>1.00-1.40</b> )	1.30 (1.79)	1.10 (2.15)	1.10 (1.54)
<b>0.69</b> ( <b>0.57-0.84</b> )	0.81 (0.48-1.40)	<b>0.58</b> ( <b>0.46-0.73</b> )	0.65 (0.25-1.68)	<b>0.58</b> ( <b>0.37-0.89</b> )	1.00 (0.69-1.48)	<b>0.42</b> ( <b>0.28-0.64</b> )	<b>0.52</b> ( <b>0.37-0.74</b> )	<b>0.46</b> ( <b>0.25-0.84</b> )	<b>0.67</b> ( <b>0.50-0.89</b> )	<b>0.56</b> ( <b>0.33-0.96</b> )	0.60 (0.29-1.31)	1.49 (4.29)	0.53 (0.65)	<b>0.68</b> ( <b>0.59-0.79</b> )	0.71 (1.09)	0.58 (0.71)	
1.52 (0.84-2.73)	1.78 (0.85-3.81)	1.27 (0.70-2.32)	1.41 (0.47-4.28)	1.27 (0.65-2.52)	<b>2.18</b> ( <b>4.32</b> )	0.92 (0.46-1.89)	1.16 (0.60-2.20)	<b>2.19</b> ( <b>3.99</b> )	1.47 (0.77-2.75)	1.23 (0.62-2.47)	1.34 (0.58-3.11)	<b>3.28</b> ( <b>10.80</b> )	1.16 (2.04)	1.50 (2.66)	1.55 (2.91)	1.27 (2.31)	
1.03 (0.76-1.41)	1.22 (0.68-2.20)	0.87 (0.61-1.24)	0.97 (0.37-2.52)	0.87 (0.53-1.40)	1.50 (0.93-2.43)	0.63 (0.38-1.03)	0.79 (0.52-1.21)	<b>1.50</b> ( <b>2.00</b> )	0.68 (0.36-1.30)	0.84 (0.48-1.48)	0.91 (0.43-1.99)	2.24 (6.63)	0.79 (1.08)	1.02 (1.39)	1.06 (1.75)	0.87 (1.67)	
1.23 (0.75-1.97)	1.44 (0.92-2.31)	1.03 (0.62-1.76)	1.16 (0.40-3.27)	1.03 (0.58-1.77)	<b>1.77</b> ( <b>3.01</b> )	0.75 (0.41-1.36)	0.94 (0.53-1.62)	<b>1.78</b> ( <b>3.03</b> )	1.19 (0.68-2.10)	1.19 (0.72-2.10)	PAL LAI-1	1.09 (0.68-1.72)	2.66 (8.31)	0.94 (1.50)	1.22 (1.99)	1.04 (1.80)	
1.14 (0.55-2.25)	1.33 (0.70-2.71)	0.95 (0.46-1.99)	1.06 (0.32-3.27)	0.94 (0.45-2.02)	1.63 (0.81-3.43)	0.70 (0.31-1.56)	0.86 (0.40-1.84)	1.65 (0.77-3.42)	0.75 (0.32-1.72)	1.10 (0.50-2.35)	0.92 (0.58-1.48)	PAL LAI-3	2.45 (8.27)	0.87 (1.72)	1.13 (2.27)	1.16 (2.06)	
0.46 (0.16-1.30)	0.55 (0.17-1.65)	0.39 (0.13-1.12)	0.44 (0.11-1.76)	0.39 (0.13-1.09)	0.67 (0.22-1.87)	<b>0.28</b> ( <b>0.09-0.84</b> )	0.36 (0.12-1.00)	0.67 (1.86)	<b>0.31</b> ( <b>0.09-0.99</b> )	0.45 (0.15-1.30)	0.38 (0.12-1.11)	0.41 (1.39)	QUE ER	<b>0.35</b> ( <b>0.12-0.98</b> )	0.46 (1.26)	0.47 (1.38)	
<b>1.31</b> ( <b>1.05-1.64</b> )	1.55 (0.93-2.63)	1.09 (0.84-1.45)	1.23 (0.48-3.20)	1.10 (0.73-1.66)	<b>1.90</b> ( <b>3.28</b> )	0.80 (0.53-1.20)	0.99 (0.71-1.41)	<b>1.90</b> ( <b>3.54</b> )	1.27 (0.49-1.76)	1.06 (0.92-1.70)	1.06 (0.67-1.70)	1.15 (2.35)	<b>2.82</b> ( <b>8.21</b> )	<b>1.30</b> ( <b>1.02-1.52</b> )	1.34 (1.91)	1.10 (1.40)	
1.01 (0.83-1.22)	1.19 (0.72-2.01)	0.85 (0.66-1.09)	0.95 (0.37-2.43)	0.85 (0.57-1.25)	<b>1.45</b> ( <b>2.12</b> )	<b>0.62</b> ( <b>0.43-0.90</b> )	0.77 (0.56-1.08)	<b>1.47</b> ( <b>1.70</b> )	0.98 (0.38-1.23)	0.98 (0.72-1.33)	0.82 (0.50-1.35)	0.89 (1.86)	<b>0.77</b> ( <b>0.66-0.91</b> )	<b>0.35</b> ( <b>0.21-0.54</b> )	0.46 (1.54)	0.39 (1.05)	
0.98 (0.67-1.43)	1.15 (0.65-2.14)	0.82 (0.54-1.28)	0.93 (0.33-2.50)	0.82 (0.50-1.34)	1.42 (2.49)	0.60 (0.34-1.03)	0.74 (0.47-1.19)	1.42 (2.21)	0.65 (0.34-1.21)	0.95 (0.60-1.51)	0.80 (0.56-1.17)	0.87 (1.54)	2.12 (6.34)	0.75 (1.08)	0.97 (1.45)	0.82 (1.22)	
1.19 (0.94-1.50)	1.40 (0.83-2.38)	1.00 (0.76-1.32)	1.12 (0.42-2.92)	1.00 (0.64-1.53)	<b>1.72</b> ( <b>2.56</b> )	0.72 (0.47-1.12)	0.91 (0.65-1.28)	<b>1.72</b> ( <b>2.10</b> )	0.79 (0.43-1.46)	1.16 (0.83-1.58)	0.96 (0.58-1.63)	1.05 (2.20)	2.55 (7.38)	0.91 (1.14)	1.18 (1.43)	1.22 (1.87)	ZIP

Drugs are reported in alphabetical order. Comparisons between treatments should be read from left to right and the estimate in each cell represents comparison between the row-defining treatment and the column-defining treatment. Odds ratios (ORs) higher than 1 favor the column-defining treatment, meaning less withdrawal in the column-defining treatment; and ORs less than 1 favor the row-defining treatment, meaning less withdrawal in the row-defining treatment. For example, the OR for comparing LUR (row-defining treatment) vs. OLA (column-defining treatment) is 1.91 (95% CrI 1.35 to 2.67), which means that LUR has higher odds of withdrawal and the comparison favors OLA, which has less withdrawal. Each comparison is represented twice in the table, for example, for two treatments A and B, once with A versus B and once with B versus A (i.e. the reciprocal OR). For the example above, the OR for comparing OLA (now the row-defining treatment) vs. LUR (now the column-defining treatment) is 0.52 (95% CrI 0.37 to 0.74), which means that OLA has a lower odds of withdrawal and again, it means that the comparison favors OLA, which has less withdrawal.

Significant results are in bold. ARI = aripiprazole- ASE = asenapine- BRE = brepiprazole- CAR = cariprazine- CLO=clozapine- ILO = iloperidone- LUR = lurasidone- OLA = olanzapine. PAL=paliperidone, QUE=quetiapine, RIS=risperidone- ZIP=ziprasidone. LAI = long-acting injection; 1 = once monthly- 3 – every 3 months.

**Appendix Table G-3b. SGA versus SGA: numbers of studies per comparison contributing to network meta-analysis of discontinuation for any cause**

<b>Comparison</b>	<b>No. of studies</b>
Aripiprazole : Brexpiprazole	1
Aripiprazole : Olanzapine	9
Aripiprazole : Quetiapine IR	3
Aripiprazole : Risperidone	6
Aripiprazole : Risperidone LAI	1
Aripiprazole : Ziprasidone	3
Aripiprazole Monthly LAI : Aripiprazole	2
A--senapine : Olanzapine	6
Asenapine : Risperidone	1
Cariprazine : Risperidone	1
Clozapine : Olanzapine	10
Clozapine : Risperidone	9
Iloperidone : Risperidone	2
Lurasidone : Olanzapine	1
Lurasidone : Risperidone	1
Lurasidone : Ziprasidone	1
Olanzapine LAI : Olanzapine	1
Paliperidone : Aripiprazole	2
Paliperidone : Olanzapine	3
Paliperidone : Risperidone	1
Paliperidone : Ziprasidone	1
Paliperidone Monthly LAI : Aripiprazole	1
Paliperidone Monthly LAI : Paliperidone	1
Paliperidone Monthly LAI : Risperidone	4
Quetiapine ER : Risperidone	1
Quetiapine IR : Clozapine	2
Quetiapine IR : Olanzapine	17
Quetiapine IR : Risperidone	19
Quetiapine IR : Risperidone LAI	1
Risperidone : Olanzapine	31
Risperidone LAI : Risperidone	1
Ziprasidone : Clozapine	1
--Ziprasidone : Olanzapine	10
Ziprasidone : Quetiapine IR	5
Ziprasidone : Risperidone	5

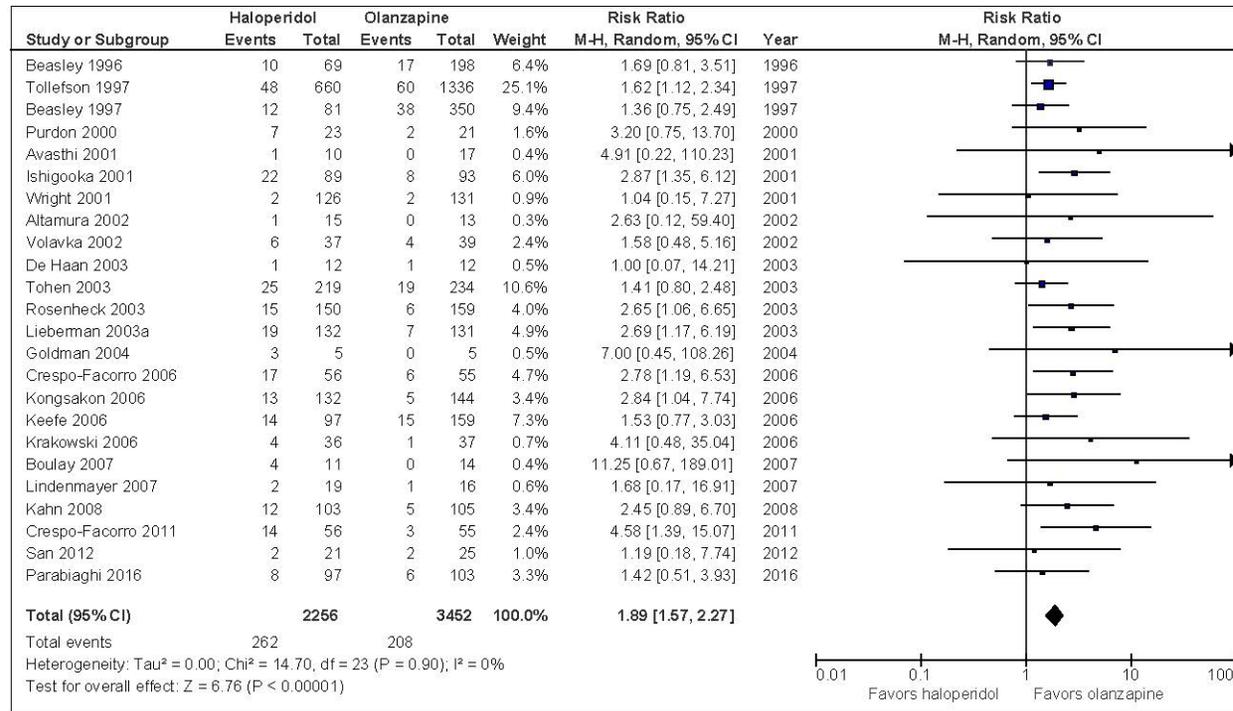
**Appendix Table G-3c. SGA versus SGA: meta-regression results for discontinuations for any cause**

<b>Meta-regression variables</b>	<b>OR (95% CI)</b>
Duration	1.14 (0.82 to 1.55)
Drug dose: Low versus Medium	1.13 (0.84 to 1.48)
Drug dose: High versus Medium	1.00 (0.99 to 1.01)
Treatment Resistant	1.47 (0.93 to 2.25)
First Episode	0.78 (0.58 to 1.02)

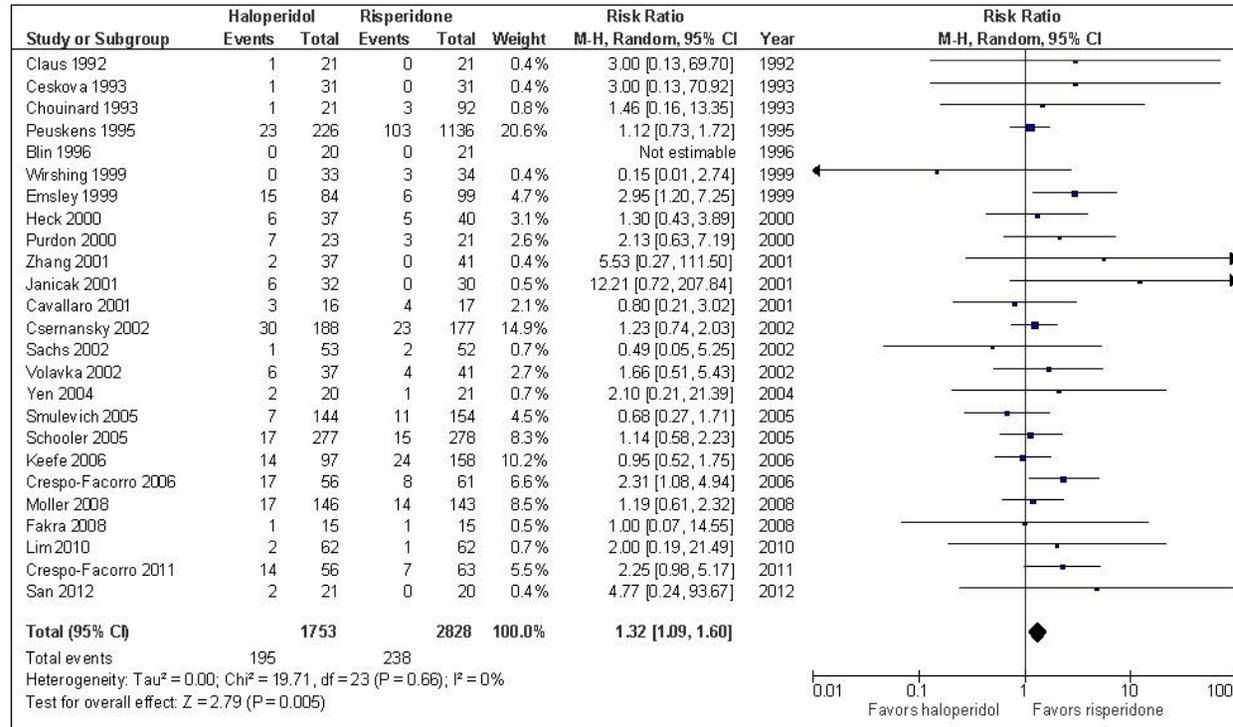
**Appendix Figure G-4. Haloperidol versus aripiprazole withdrawals due to adverse events**



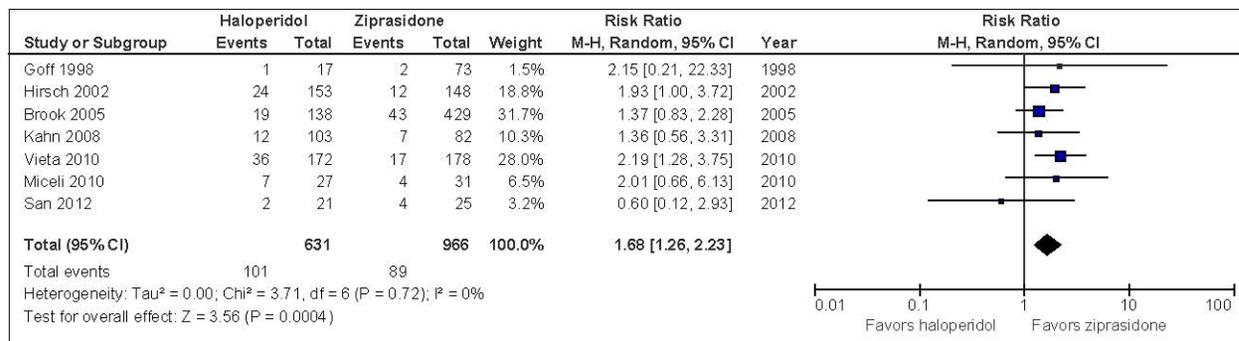
**Appendix Figure G-5. Haloperidol versus olanzapine withdrawals due to adverse events**



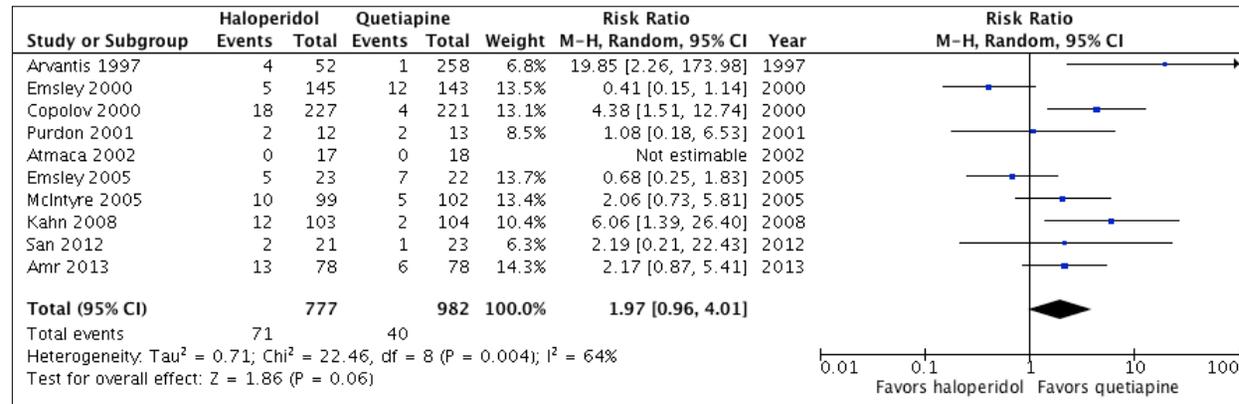
**Appendix Figure G-6. Haloperidol versus risperidone withdrawals due to adverse events**



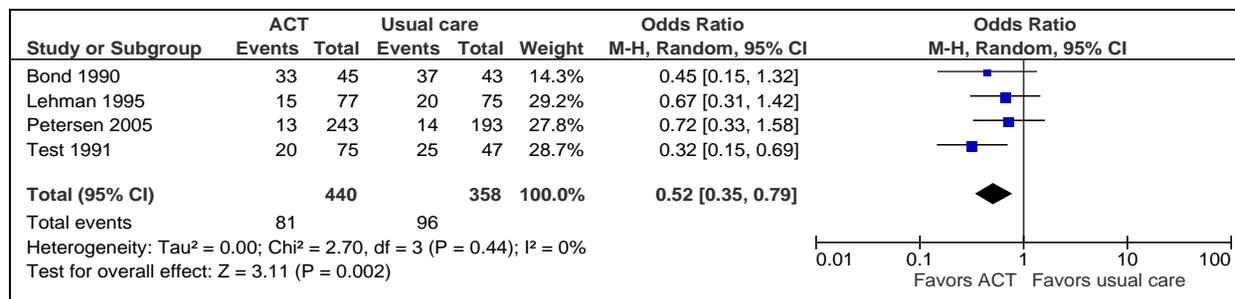
**Appendix Figure G-7. Haloperidol versus ziprasidone withdrawals due to adverse events**



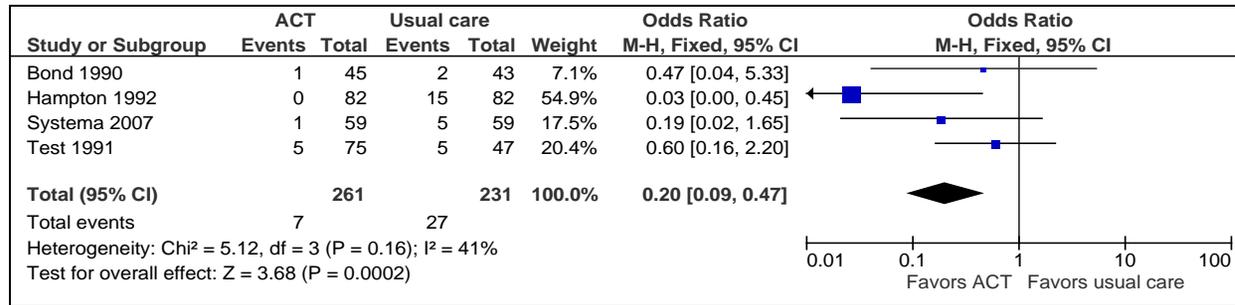
**Appendix Figure G-8. Haloperidol versus quetiapine withdrawals due to adverse events**



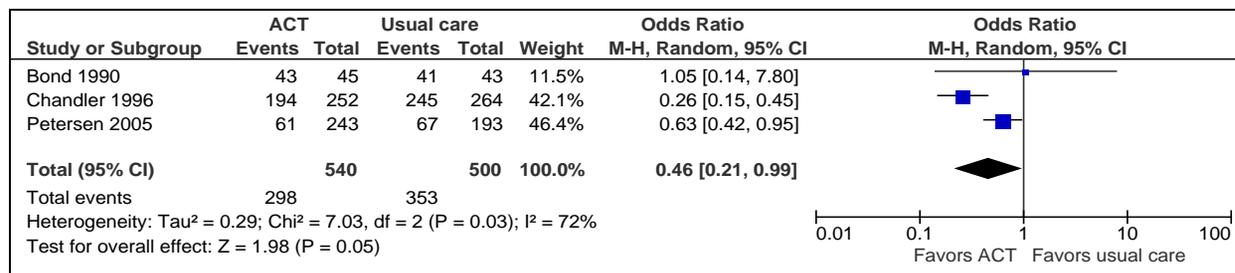
**Appendix Figure G-9. Assertive community treatment: unable to live independently**



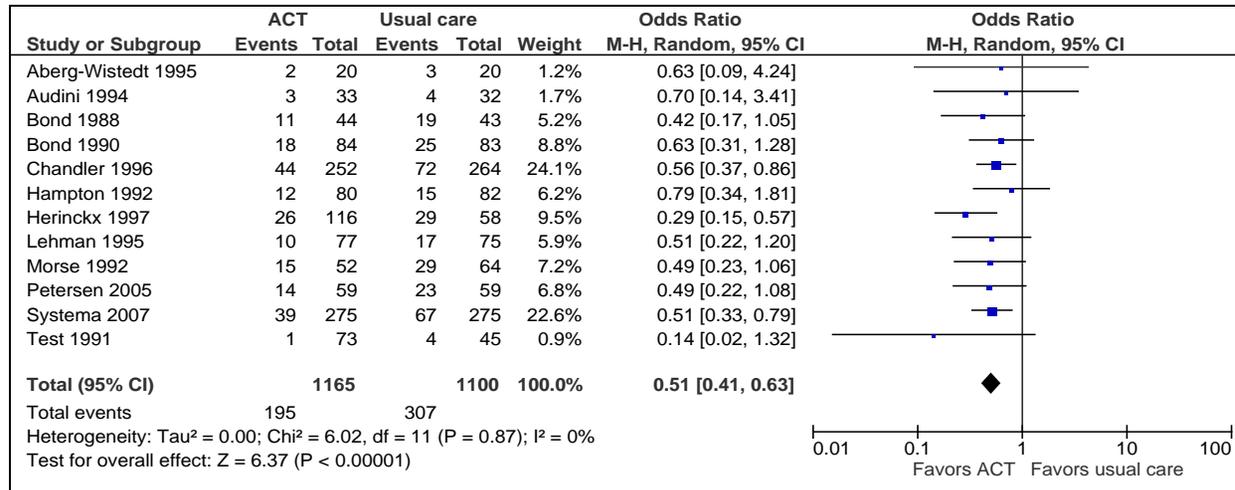
**Appendix Figure G-10. Assertive community treatment versus usual care: homelessness**



**Appendix Figure G-11. Assertive community treatment: unemployment**

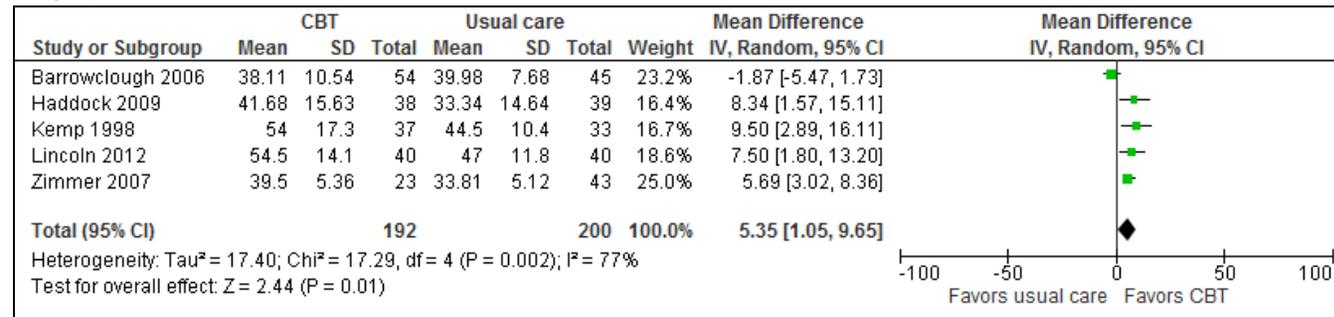


**Appendix Figure G-12. Assertive community treatment: loss to followup**

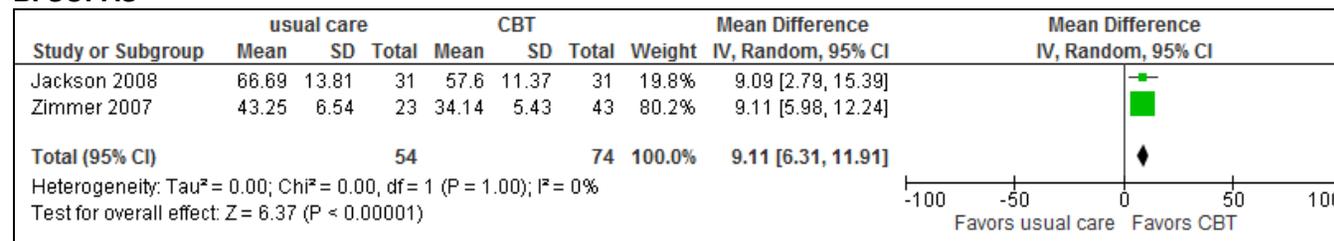


**Appendix Figure G-13. Cognitive behavioral therapy: short-term function**

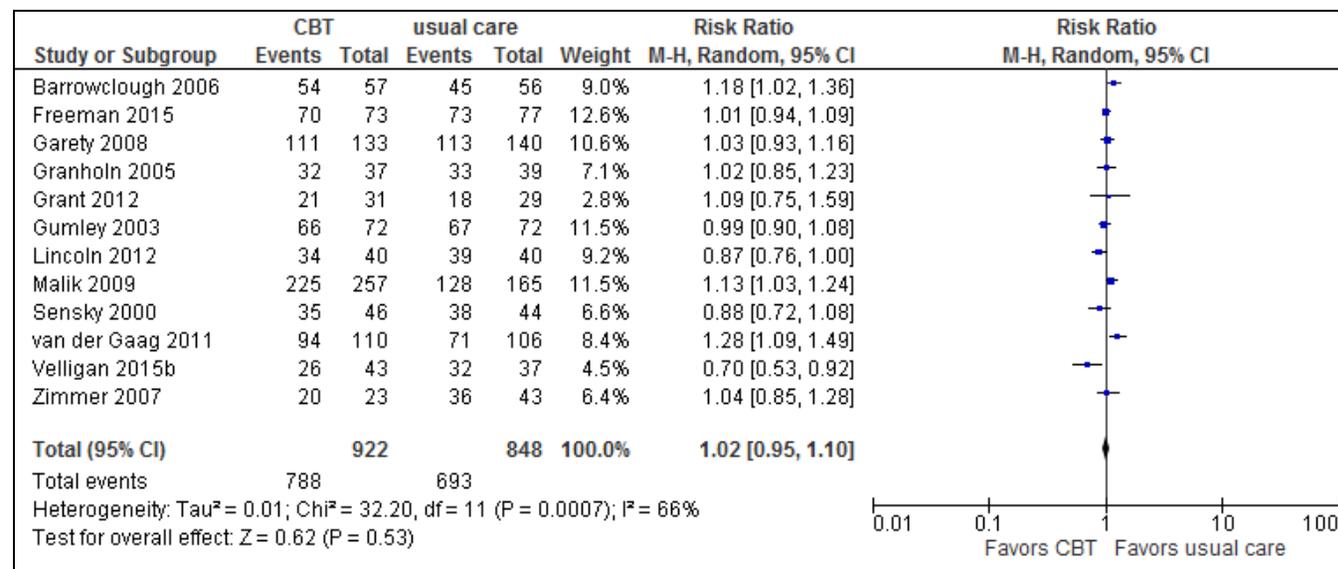
**A. GAF**



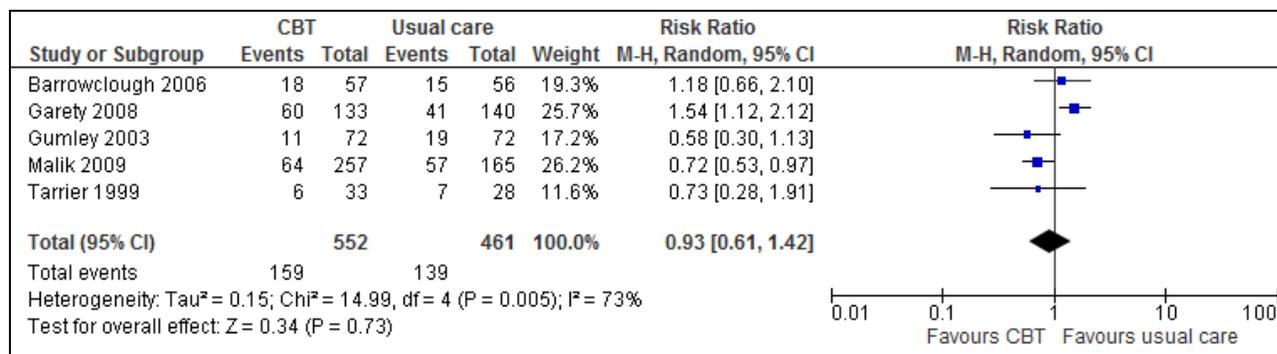
**B. SOFAS**



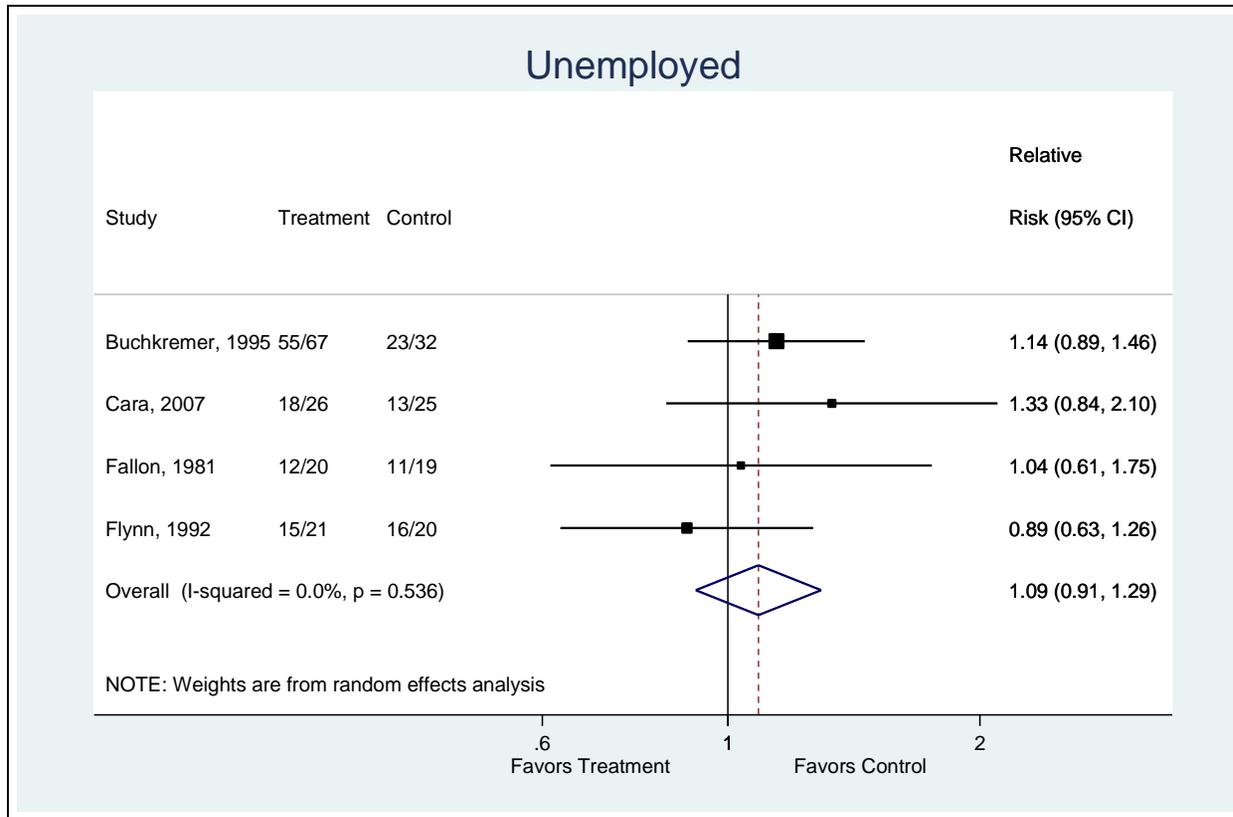
**Appendix Figure G-14. Cognitive behavioral therapy: treatment maintenance**



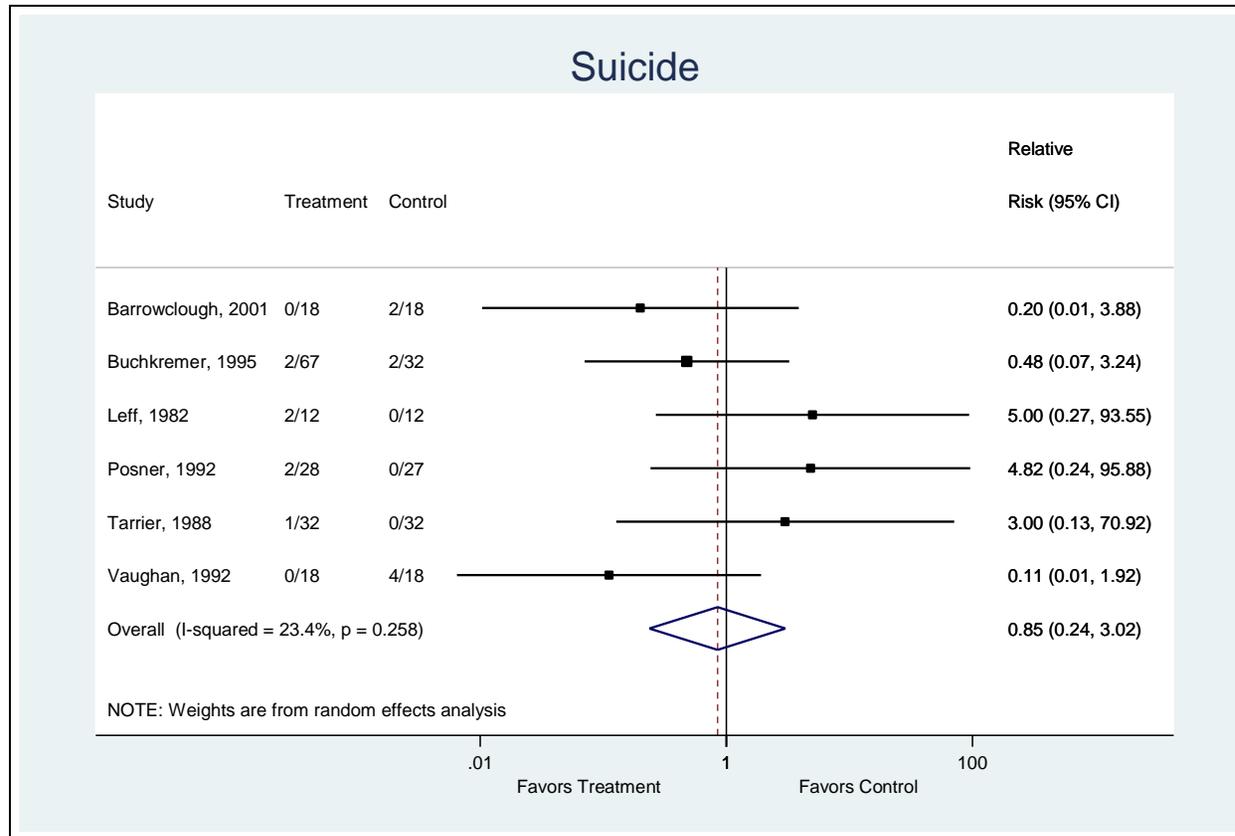
**Appendix Figure G-15. Cognitive behavioral therapy: relapse**



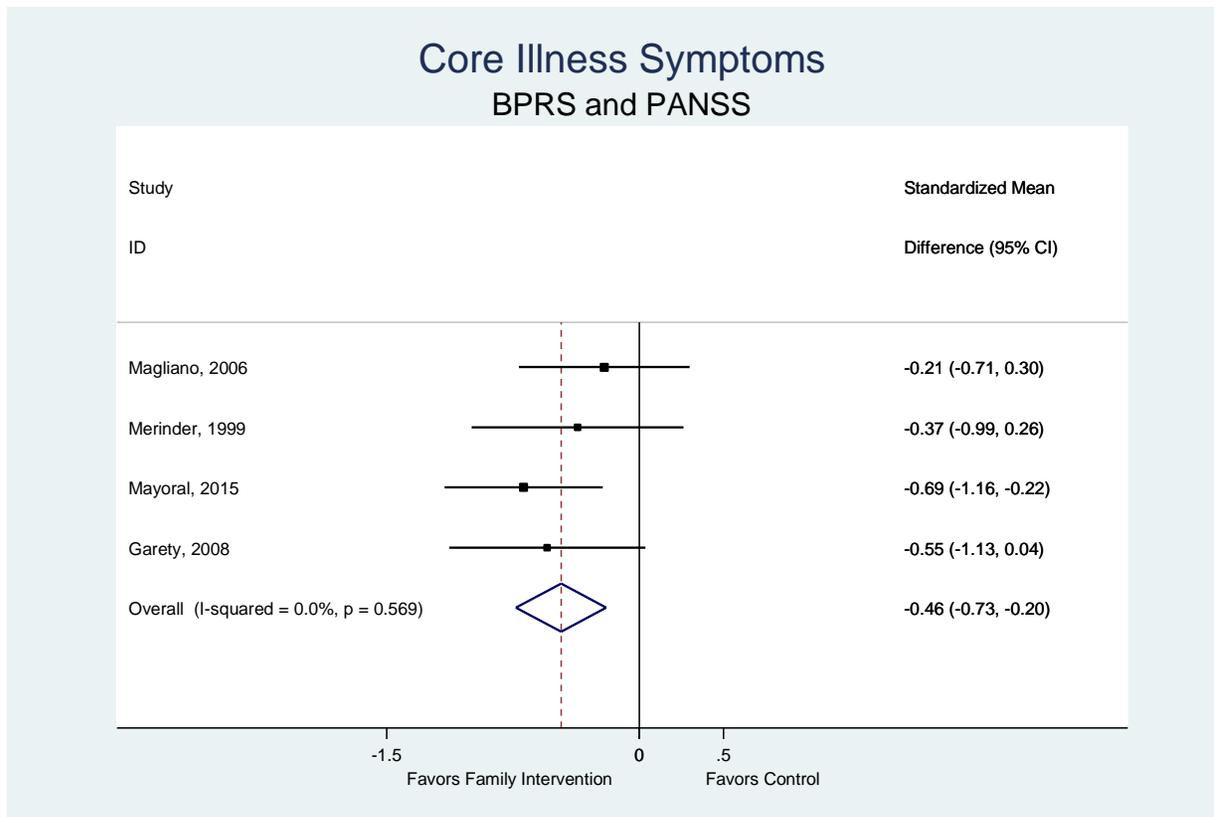
**Appendix Figure G-16. Family interventions: unemployment**



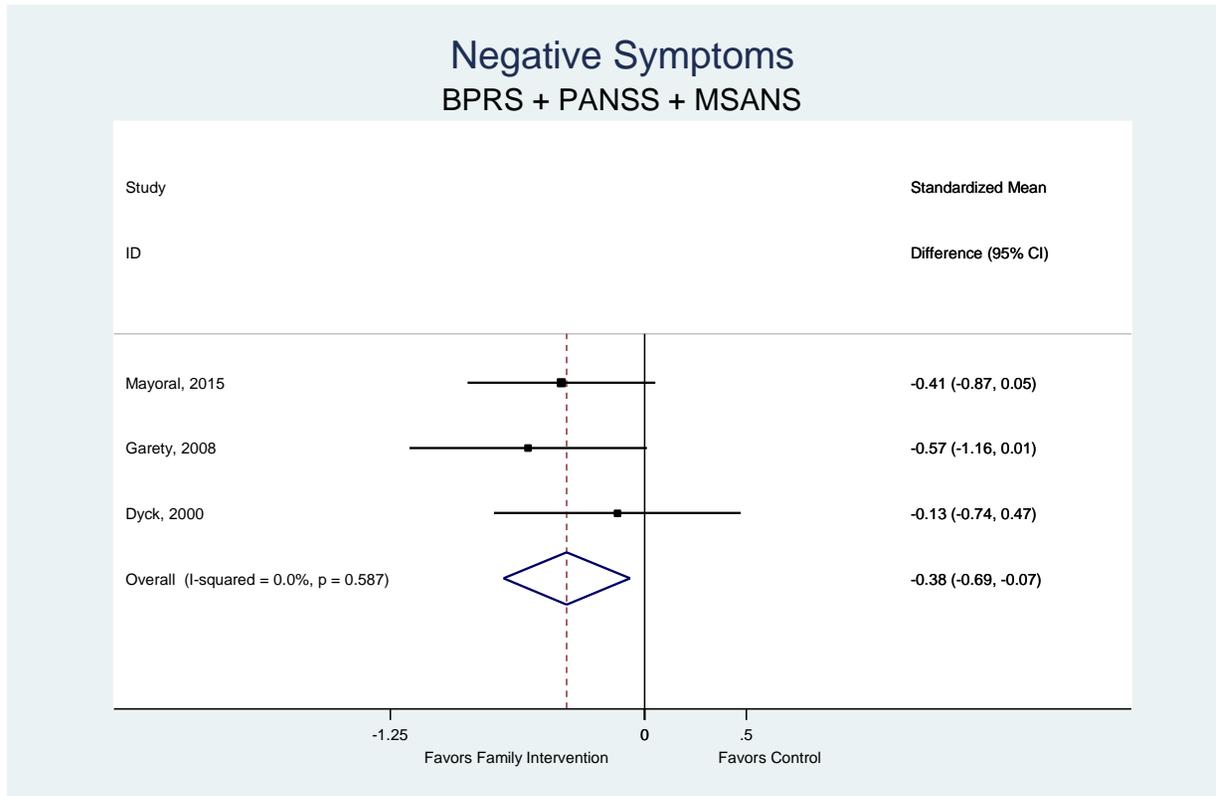
**Appendix Figure G-17. Family interventions: suicide**



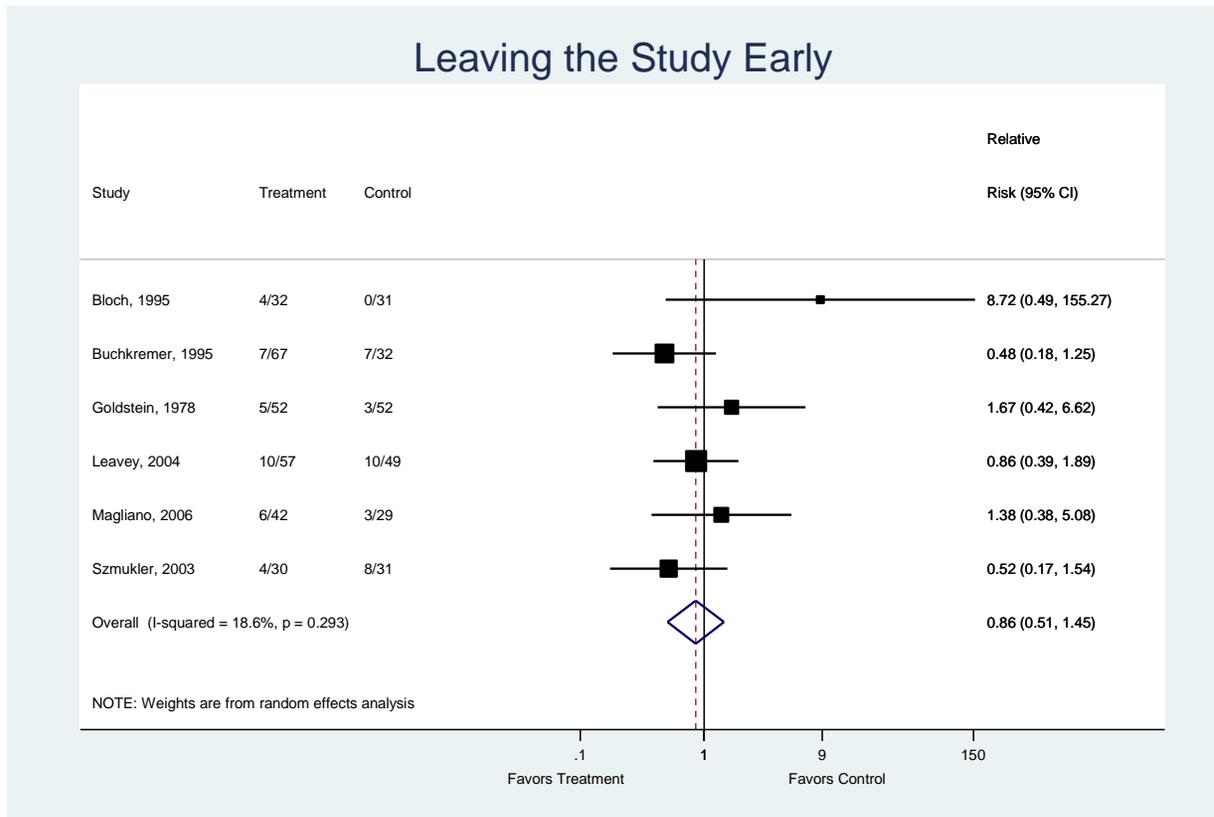
**Appendix Figure G-18. Family interventions: core illness symptoms**



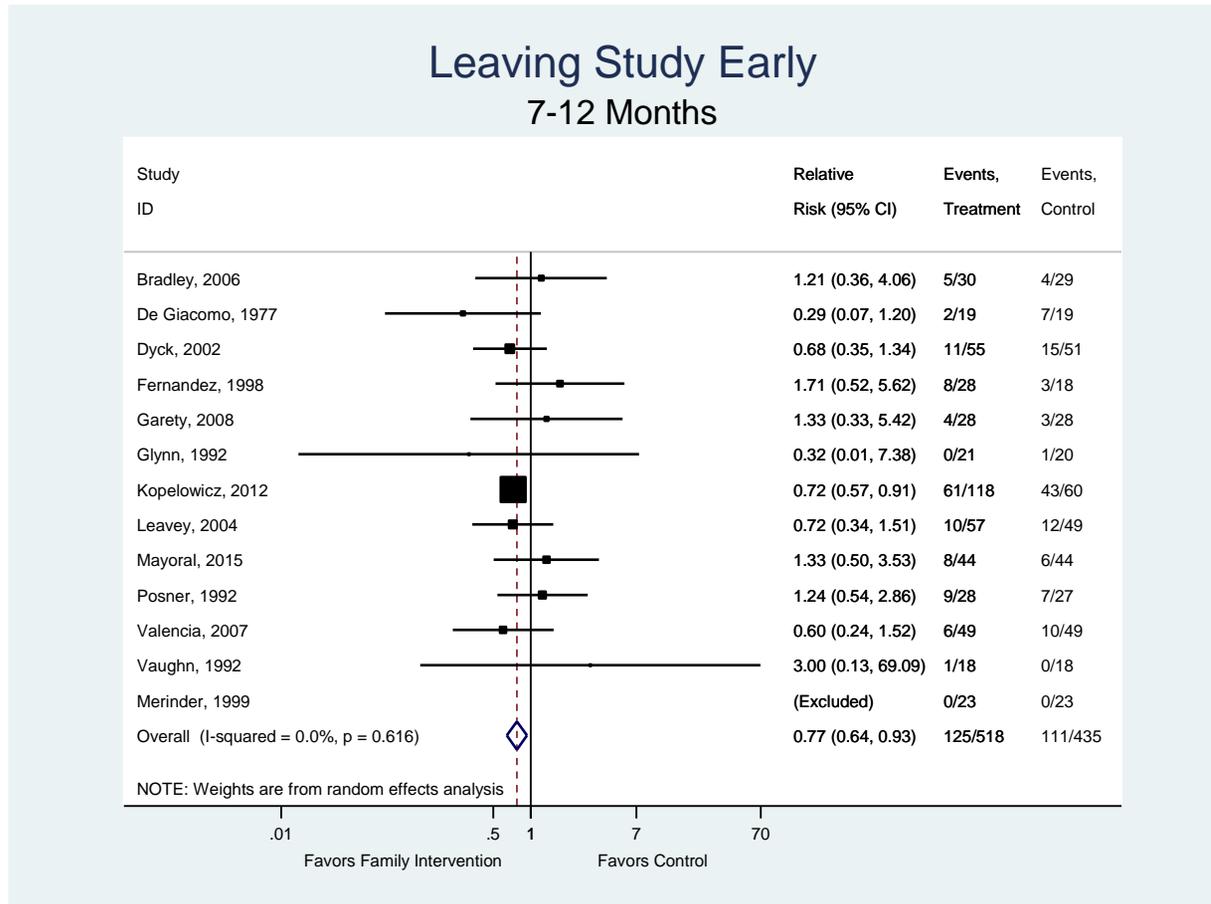
**Appendix Figure G-19. Family interventions: negative symptoms**



**Appendix Figure G-20. Family interventions: treatment maintenance at 3-6 months**



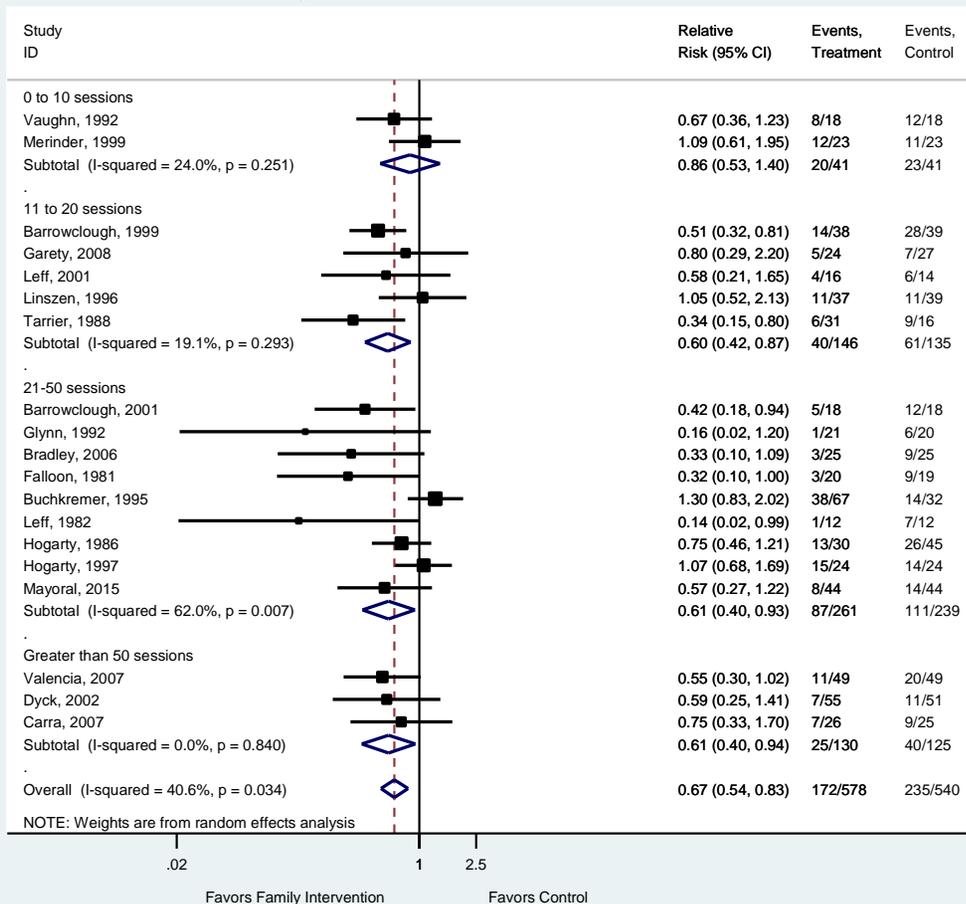
**Appendix Figure G-21. Family interventions: treatment maintenance at 7-12 months**





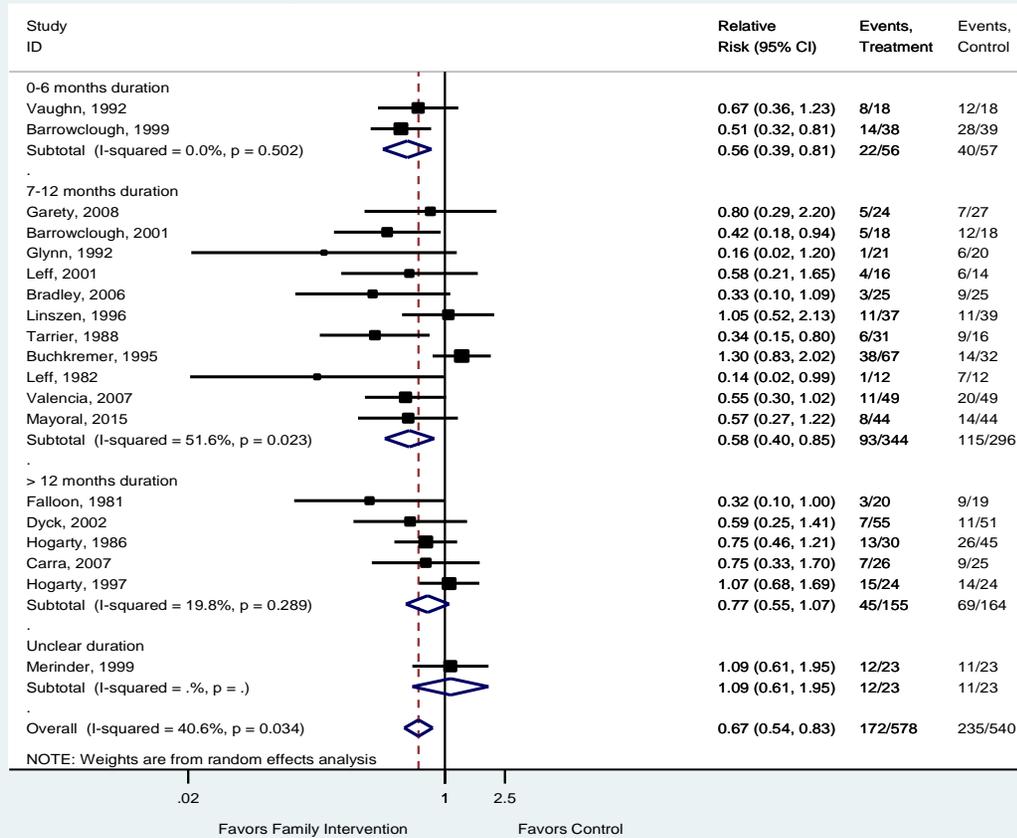
Appendix Figure G-23. Family interventions: relapse at 7-12 months by number of sessions

## Relapse 7-12 Months by Number of Sessions



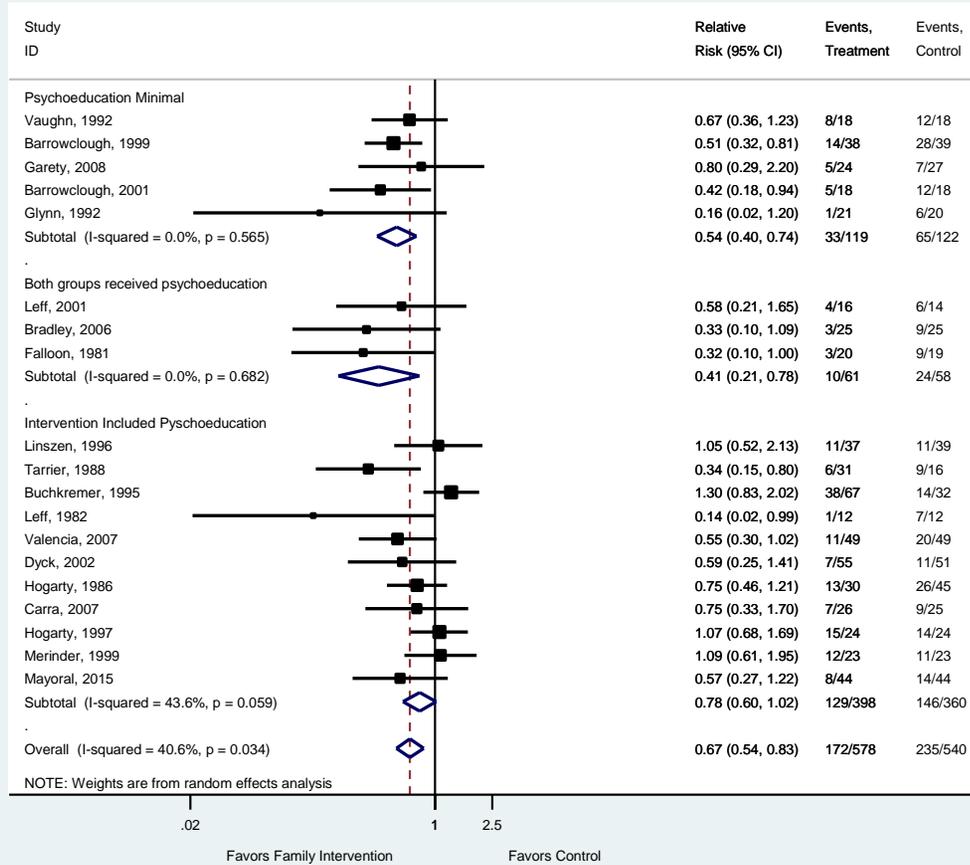
Appendix Figure G-24. Family interventions: relapse at 7-12 months by duration of intervention

## Relapse 7-12 Months by Duration of Intervention

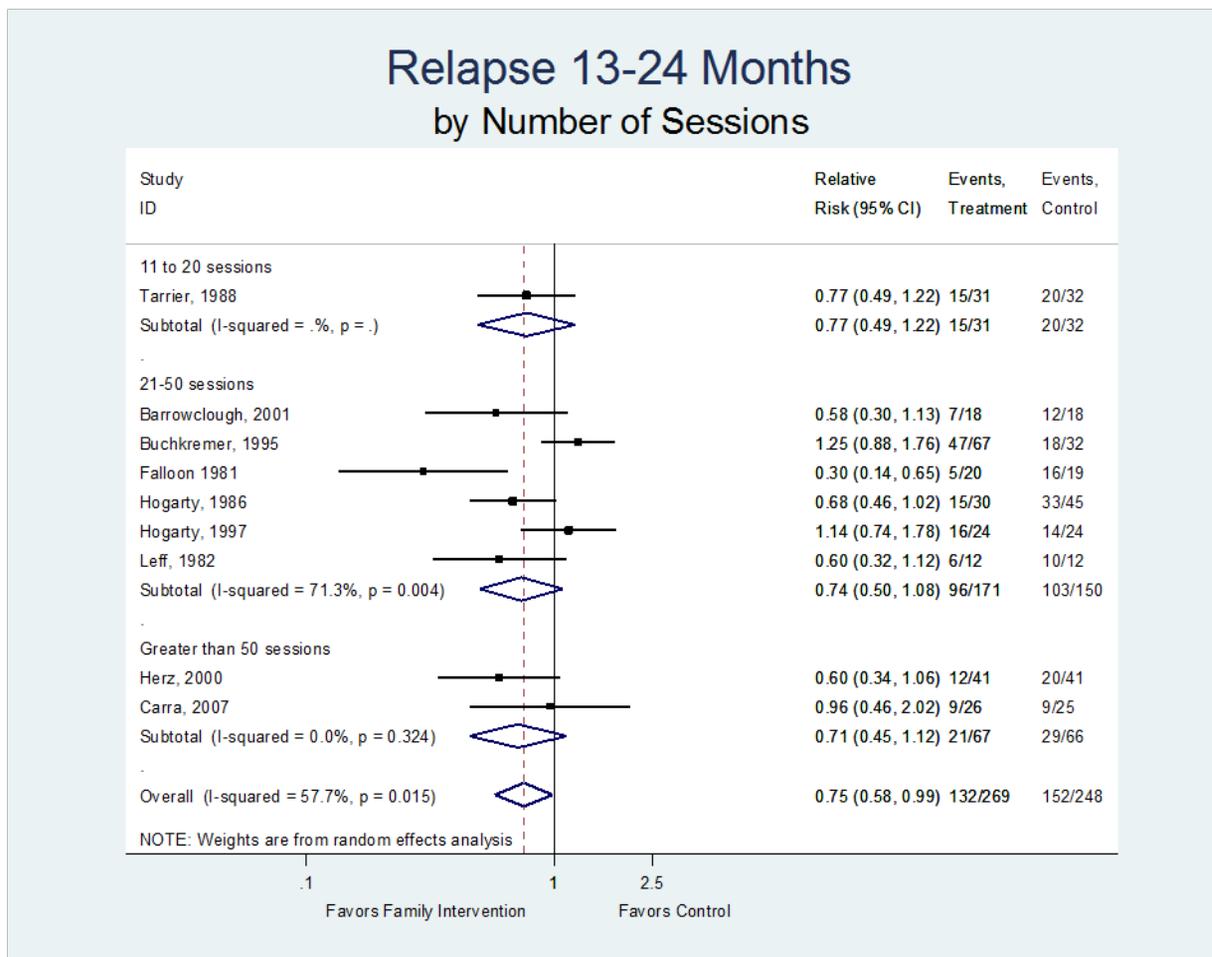


**Appendix Figure G-25. Family interventions: relapse at 7-12 months by psychoeducation**

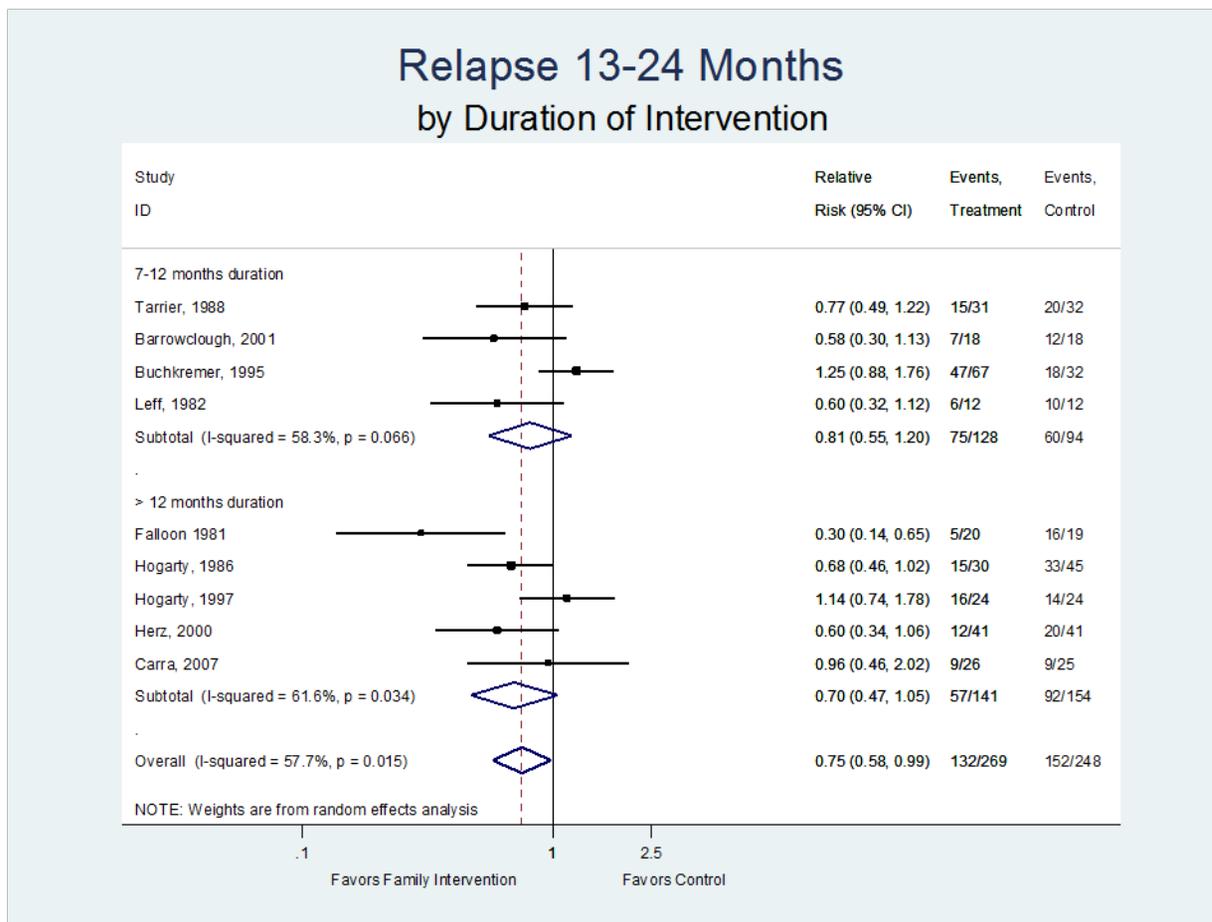
## Relapse 7-12 Months by Psychoeducation



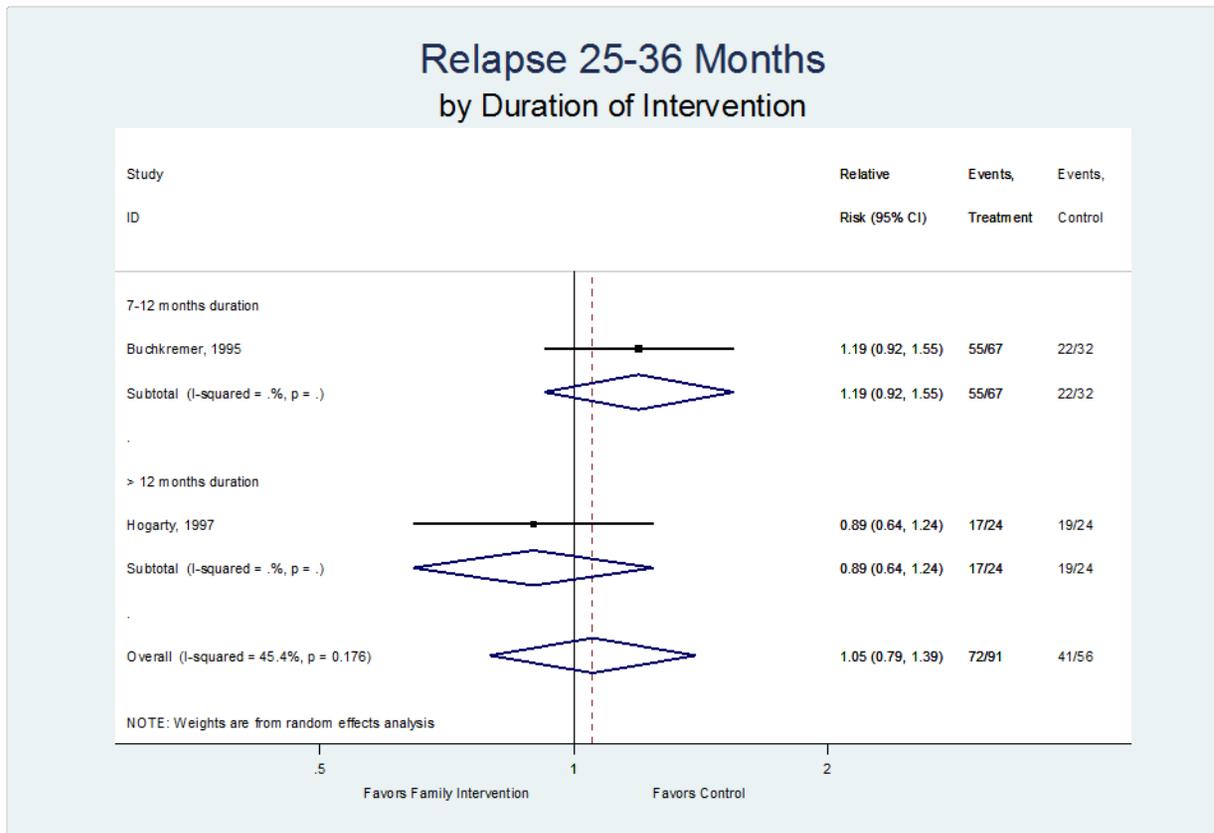
Appendix Figure G-26. Family interventions: relapse at 13-18 months by number of sessions



**Appendix Figure G-27. Family interventions; relapse at 13-24 months by duration of intervention**

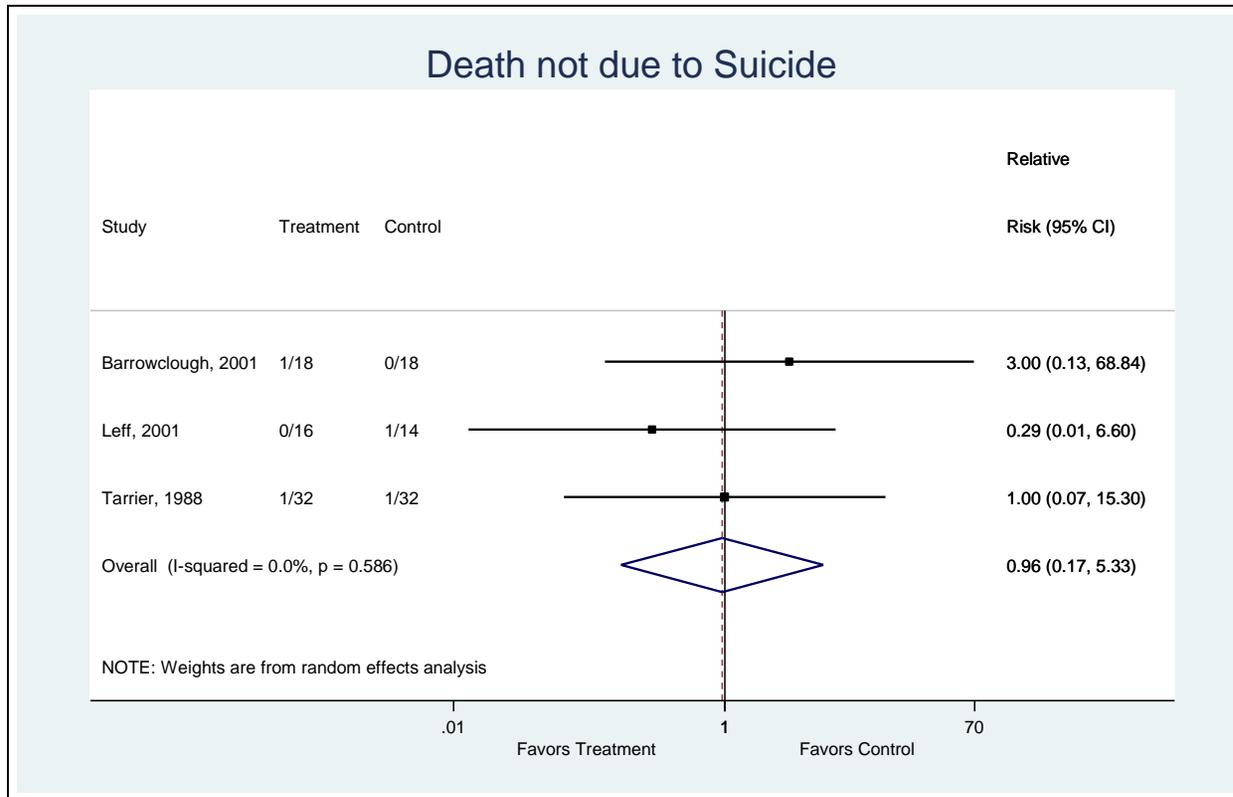


**Appendix Figure G-28. Family interventions: relapse at 25-36 months by duration of intervention**

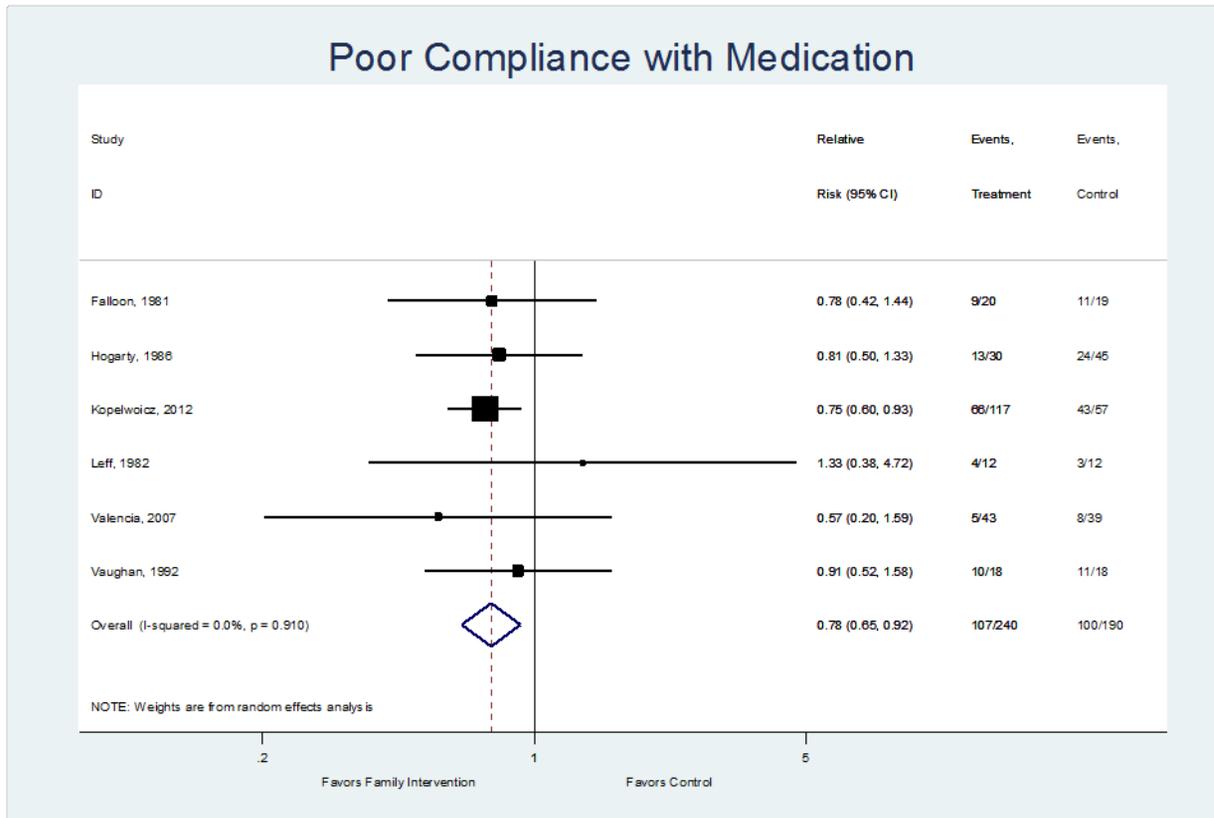




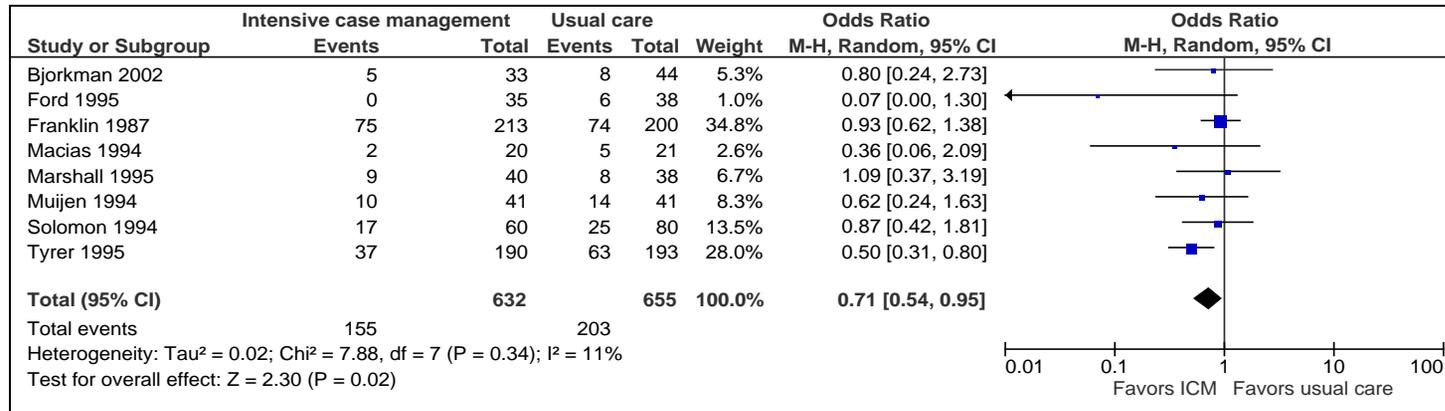
**Appendix Figure G-30. Family interventions: nonsuicide mortality**



**Appendix Figure G-31. Family interventions: poor compliance with medication**



**Appendix Figure G-32. Intensive case management: loss to followup**



# Appendix H. Strength of Evidence

**Appendix Table H-1. Strength of evidence: second-generation antipsychotic versus second-generation antipsychotic**

Outcome	Comparators	Number of Studies Number of Subjects	Study Limitations	Consistency	Directness	Precision	Magnitude of Effect: Summary Effect Size (95% CI)	Strength of Evidence (High, Moderate, Low, Insufficient)
<b>Social Functioning</b>	Olanzapine, risperidone, quetiapine immediate-release	1 SR <sup>1</sup> (2 RCTs; N =358;) (1 observational study; N = 9028)	Moderate  Observational evidence: Moderate	Inconsistent  Observational evidence: Unknown	Direct  Observational evidence: Direct	Imprecise  Observational evidence: Precise	Inconclusive: RCT 1: no significant differences on RFS or the SAS-SMI RCT 2: Change on SFS greater with App H olanzapine (+7.75) than risperidone (-0.92; P=0.0028) (Socially active: OR 1.27, 95% CI 1.05 to 1.54 olanzapine 84.6% vs. risperidone 82.4%).	Insufficient
Social Functioning	Paliperidone monthly LAI vs. risperidone q 2 wks LAI	1 SR <sup>1</sup> (2 RCTs; N = 452)	Moderate	Inconsistent	Direct	Precise	No statistically significant differences in PSP scale: mean change from baseline 16.8 paliperidone and 18.6 risperidone; (LSM difference 0.5, 95% CI -2.14 to 3.12)	Low
Social Functioning	Paliperidone extended release vs. olanzapine	1 Meta-analysis of selected studies <sup>2</sup>	High	Unknown	Direct	Precise	No significant difference in PSP scale (change 7.8 to 12.2 in paliperidone dose u vs. 8.7 in olanzapine group).	Insufficient
Social Functioning	Risperidone LAI vs. Quetiapine immediate release	1 RCT <sup>3</sup> (N = 666)	Moderate	Unknown	Direct	Precise	Risperidone LAI resulted in greater improvements in SOFA at 6 months (6.1 vs. 2.7; P = 0.02), 12 months (9.5 vs. 6.1; P = 0.009), and endpoint (6.6 vs. 1.1; P < 0.0001).	Low
<b>Employment Outcomes</b>	Older SGAs (olanzapine, risperidone, quetiapine, ziprasidone)	1 SR <sup>1</sup> (2 RCTs, 3 observational N = 1,379)	Low  Observational evidence: Moderate	Inconsistent  Observational evidence: Consistent	Direct  Observational evidence: Direct	Imprecise  Observational evidence: Imprecise	No significant differences in rates of employment (mean 18% in CATIE Phase I)	Low

Outcome	Comparators	Number of Studies Number of Subjects	Study Limitations	Consistency	: Directness	Precision	Magnitude of Effect: Summary Effect Size (95% CI)	Strength of Evidence (High, Moderate, Low, Insufficient)
Occupation and Residential Status	Older SGAs (olanzapine, risperidone, quetiapine, ziprasidone)	1 SR <sup>1</sup> (21 RCT, N = 771)	Moderate	Unknown	Direct	Imprecise	Inconclusive: 75.5% and 75.3% had stable status, 3.8% and 3.1% improved status (NS)	Insufficient
Global Functioning (GAF)	Olanzapine vs. Risperidone	1 SR <sup>1</sup> (4 cohort studies; N = 3211)	High	Inconsistent	Direct	Precise	No difference: Pooled WMD 0.61, 95% CI, -1.78 – 2.99; I <sup>2</sup> = 43%	Low
Global Functioning (GAF)	Olanzapine vs. Quetiapine	1 SR <sup>1</sup> (2 RCTs; N = 363)	Moderate	Consistent	Direct	Imprecise	Pooled WMD 1.14, 95% CI -4.75 to 7.02; Q = 3.99, df = 1; P = 0.045	Low
Quality of Life	Olanzapine vs. risperidone	1 SR <sup>1</sup> (2 RCTs; N = 492)	Moderate	Consistent	Direct	Precise	QLS Change = 12 months 0.19 v 0.26 (P = 0.53); 7 months 13.4 vs. 8.8 (P >0.074)	Moderate
Quality of Life	Olanzapine vs. ziprasidone	1 SR <sup>1</sup> (2 RCTs; N = 740)	Moderate	Consistent	Direct	Precise	QLS Change = 12 months 0.19 v 0.26 (P NR); 6-7 months Endpoint 61.3 vs. 58.9 (P = 0.36 using mixed-effect modeling)	Moderate
Quality of Life	Olanzapine vs. quetiapine immediate release	1 SR <sup>1</sup> (1 RCT; N = 227)	Low	Unknown	Direct	Imprecise	QLS Change = 12 months 0.19 v 0.09 (P >0.05)	Low
Quality of Life	Olanzapine vs. asenapine	1 SR <sup>1</sup> (1 RCT; N = 464)	Moderate	Unknown	Direct	Imprecise	QLS Change = 12 months 11.7 vs. 11.8 and 11.1 vs. 7.1 (multi-country study reported by hemisphere) P = NS	Insufficient
Quality of Life	Olanzapine vs. clozapine	1 SR <sup>1</sup> (1 RCT; N = 114)	Moderate	Unknown	Direct	Imprecise	SWN: 26 weeks O found non-inferior to C (difference 3.2, 95% CI: 4.2 to 10.5)	Insufficient
Quality of Life	Risperidone vs. ziprasidone	1 SR <sup>1</sup> (N = 154)	Low	Unknown	Direct	Imprecise	QLS Change = 12 months 0.19 v 0.26 (P >0.05)	Low
Quality of Life	Risperidone vs. Quetiapine	1 SR <sup>1</sup> (1 RCT; N = 189)	Low	Unknown	Direct	Imprecise	QLS Change = 12 months 0.26 v 0.26 (P >0.05);	Low
Quality of Life	Quetiapine-ER vs. Risperidone	1 RCT; N = 798 <sup>4</sup>	Moderate	Unknown	Direct	Imprecise	SWN 20% Response 12 months: 65% vs. 68%, adjusted difference (-5.7, 95% CI -15.1 to 3.7) but not meet non-inferiority criteria	Insufficient

Outcome	Comparators	Number of Studies Number of Subjects	Study Limitations	Consistency	: Directness	Precision	Magnitude of Effect: Summary Effect Size (95% CI)	Strength of Evidence (High, Moderate, Low, Insufficient)
Quality of Life	Aripiprazole oral vs. aripiprazole LAI (monthly)	1 RCT; N = 724 <sup>5</sup>	Moderate	Unknown	Direct	Precise	SF-36 12 months: mental component scores (0.82 vs. 0.38; difference 0.44, 95% CI -1.24 to 2.12) and physical component scores (0.23 vs. -0.27; difference 0.50, 95% CI -1.11 to 2.11)	Low
Quality of Life	Aripiprazole LAI vs. paliperidone palmitate LAI (monthly)	1 RCT; N = 295 <sup>6</sup>	Moderate	Unknown	Direct	Imprecise	QLS: 28 weeks change = 7.47 vs. 2.80 (least squares mean difference 4.67, 95% CI 0.32 to 9.02). Meets non-inferiority criteria; not meet MCID	Insufficient
Quality of Life	Risperidone LAI vs. quetiapine	1 RCT; N = 666 <sup>3</sup>	Moderate	Unknown	Direct	Precise	SF-12 physical and mental component scores and SQLS-R4 scores improved from baseline in both groups but were not significantly different at endpoint (24 months; SF-12 physical P= 0.09; SF-12 mental and SQLS-R4 P = NR).	Low
<b>Response</b>		Network meta-analysis of olanzapine, risperidone, quetiapine IR, aripiprazole, clozapine, ziprasidone> asenapine, paliperidone, aripiprazole LAI monthly, caripramine, brexpiprazole, lurasidone 46 RCTs (N = 12,536)	Moderate	Consistent	Indirect	Precise	There were 2 statistically significant differences between the drugs; both olanzapine (OR 1.71, 95% CI 1.11,2.68) and risperidone (OR 1.41, 95% CI 1.01,2.00) were significantly more likely to result in response than quetiapine IR.	Low
<b>Mortality (All-Cause)</b>	Olanzapine vs. risperidone vs. quetiapine	1 SR <sup>1</sup> (1 retrospective cohort study; N = 48, 595)	Low	Unknown	Direct	Precise	No difference in all-cause mortality between risperidone and olanzapine (HR 1.09, 95% CI 0.79 to 1.49) or quetiapine (HR 0.75, 95% CI 0.53 to 1.07).	Low

Outcome	Comparators	Number of Studies Number of Subjects	Study Limitations	Consistency	: Directness	Precision	Magnitude of Effect: Summary Effect Size (95% CI)	Strength of Evidence (High, Moderate, Low, Insufficient)
Mortality (All-Cause)	Clozapine, risperidone, olanzapine and quetiapine vs. no treatment	1 SR <sup>1</sup> (1 retrospective cohort study; N = 6, 987)	Low	Unknown	Direct	Imprecise	Clozapine and quetiapine had significantly lower risk of all-cause mortality (adjusted ORs 0.35, 95% CI 0.21 to 0.58 and 0.46, 95% CI 0.30 to 0.72), risperidone and olanzapine not statistically significantly different from control	Insufficient
Mortality (All-Cause)	Asenapine vs. Olanzapine	2 RCTs <sup>7,8</sup>	Moderate	Consistent	Direct	Imprecise	Inconclusive: 0.41% vs. 0.42%, 0% vs. 0%, 0.77% vs. 0.32%; RR 2.49 (95% CI 0.54 to 11.5)	Low
Mortality (All-Cause)	Paliperidone palmitate LAI (monthly) vs. Risperidone LAI	2 RCTs <sup>9,10</sup>	Moderate	Consistent	Direct	Imprecise	Inconclusive: 0.79% vs. 0.27%, 0% vs. 0.45%; RR 1.26 (95% CI 0.21 to 7.49)	Low
Mortality (All-Cause)	Quetiapine vs. Risperidone	2 RCTs <sup>11,12</sup>	Moderate	Consistent	Direct	Imprecise	Inconclusive: 1.17% vs. 0.40% and 0.72% vs. 0%; RR 3.24 (95% CI 0.72 to 14.6)	Low
<b>Cardio-vascular Mortality</b>	Olanzapine vs. risperidone vs. quetiapine	1 SR <sup>1</sup> (2 retrospective cohort study; N = 55,582)	Low	Consistent	Direct	Precise	No significant differences between the drugs (HRs 0.99, 95% CI 0.37 to 2.67 and 0.76, 95% CI 0.25 to 2.28, respectively).	Low
Cardio-vascular Mortality	Clozapine vs. risperidone	1 SR <sup>1</sup> (2 retrospective cohort studies; N =1,686)	Moderate	Unknown	Direct	Imprecise	Inconclusive: No significant differences between drugs 4.8% and 2.5%; RR 1.39, 95% CI 0.61 to 2.53	Insufficient
<b>Self-Harm: Suicidal Behavior, Suicide</b>	Clozapine versus olanzapine in high-risk patients	1 SR <sup>1</sup> (1 RCT; N = 980)	Low	Unknown	Direct	Imprecise	Suicidal behavior: HR 0.76, 95% CI 0.58 to 0.97;	Low
Self-Harm: Suicidal Behavior, Suicide	Clozapine vs. olanzapine in high-risk patients	1 SR <sup>1</sup> (1 RCT; N = 980)	Low	Unknown	Direct	Precise	Worsening on CGI-Suicide Severity: HR 0.78, 95% CI 0.61 to 0.99	Moderate
Self-Harm: Suicidal Behavior, Suicide	Clozapine vs. olanzapine in high-risk patients	1 SR <sup>1</sup> (1 RCT; N = 980)	Low	Unknown	Direct	Imprecise	Suicide deaths: No significant differences ( 5 clozapine, 3 olanzapine)	Low

<b>Outcome</b>	<b>Comparators</b>	<b>Number of Studies Number of Subjects</b>	<b>Study Limitations</b>	<b>Consistency</b>	<b>: Directness</b>	<b>Precision</b>	<b>Magnitude of Effect: Summary Effect Size (95% CI)</b>	<b>Strength of Evidence (High, Moderate, Low, Insufficient)</b>
Self-Harm: Suicidal Behavior, Suicide	Clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole	1 SR <sup>1</sup> (2 retrospective cohorts; N = 16,584)	Moderate	Consistent	Direct	Precise	Death by suicide lower with clozapine: OR 0.29 (0.14 to 0.63) compared with no treatment at 6 months and clozapine (1.1%) lower than baseline (2.2%) or other drugs (range 2.1% to 3.7%) at 1 year.	Low
Self-Harm: Suicidal Behavior, Suicide	Clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole	1 SR <sup>1</sup> (1 prospective cohort; N = 10,204)	High	Unknown	Direct	Precise	Suicide attempts (6 months): No statistically significant difference between drugs	Insufficient
Self-Harm: Suicidal Behavior, Suicide	Clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole	1 SR <sup>1</sup> (1 prospective cohort; N = 20,489)	High	Unknown	Direct	Precise	Inconclusive: Suicide attempts or death by suicide: aripiprazole vs. others combined HR 0.69, 95% CI 0.42 to 1.14	Insufficient
<b>Core Illness Symptoms</b>	Oral SGAs (except caripramine)	(212 RCTs) <sup>13</sup>	Moderate	Consistent	Indirect	Precise	Clozapine had significantly better improvement than the other drugs except olanzapine (SMDs on PANSS or BPRS -0.32 to - 0.55. Olanzapine and risperidone superior to the other drugs, except for each other and paliperidone (SMDs -0.13 to -0.26). Paliperidone superior to lurasidone and iloperidone (SMD -0.17). All drugs superior to placebo (SMDs – 0.33 to –0.88).	Low
Core Illness Symptoms	Treatment resistant patients: clozapine, risperidone, olanzapine, quetiapine, and ziprasidone	(40 RCTs) <sup>14</sup>	Moderate	Consistent	Indirect	Precise	The only significant difference was that the mean change in the PANSS greater with olanzapine than quetiapine (SMD -0.29, 95% CI -0.56 to -0.13).	Low

<b>Outcome</b>	<b>Comparators</b>	<b>Number of Studies Number of Subjects</b>	<b>Study Limitations</b>	<b>Consistency</b>	<b>: Directness</b>	<b>Precision</b>	<b>Magnitude of Effect: Summary Effect Size (95% CI)</b>	<b>Strength of Evidence (High, Moderate, Low, Insufficient)</b>
Core Illness Symptoms	Brexiprazole vs. aripiprazole	(N=97) <sup>15</sup>	Moderate	Unknown	Indirect	Imprecise	Inconclusive: PANSS scale -22.9 vs. -19.4 from baseline; direct comparison not reported.	Insufficient
<b>Overall/Any Adverse Events</b>								
Overall/Any Adverse Events	Asenapine vs. olanzapine	5 RCTs (4 publications); N = 2189) <sup>7,8,16,17</sup>	Moderate	Consistent	Direct	Precise	Pooled RR 1.00 (95% CI 0.96 – 1.05); I <sup>2</sup> 9%	Moderate
Overall/Any Adverse Events	Quetiapine vs. risperidone	7 RCTs (N = 3254) <sup>11,12,18-22</sup>	Moderate	Consistent	Direct	Precise	Pooled 1.04 (95% CI 0.97 to 1.12); I <sup>2</sup> 56%	Moderate
Overall/Any Adverse Events	Clozapine vs. olanzapine	2 RCTs (N = 182) <sup>6,20</sup>	Moderate	Consistent	Direct	Imprecise	Pooled RR 1.15 (95% CI = 1.00 to 1.33); I <sup>2</sup> 0%	Low
Overall/Any Adverse Events	Risperidone vs. olanzapine	5 RCTs (N = 873) <sup>20-24</sup>	Moderate	Inconsistent	Direct	Precise	Pooled = RR 1.02 (95% CI = 0.81 to 1.29); I <sup>2</sup> = 77%	Low
Overall/Any Adverse Events	Olanzapine vs. ziprasidone	5 RCTs (N = 1097; 6 weeks to 6 months durations) <sup>25-29</sup>	Moderate	Inconsistent	Direct	Precise	Pooled RR 1.00 (95% CI = 0.86 to 1.16); I <sup>2</sup> = 80%	Low
Overall/Any Adverse Events	Olanzapine vs. quetiapine	3 RCTs (N = 448) <sup>20-22</sup>	Moderate	Consistent	Direct	Imprecise	Pooled RR 0.90 (95% CI 0.74 to 1.11); I <sup>2</sup> = 30%	Low

Outcome	Comparators	Number of Studies Number of Subjects	Study Limitations	Consistency	: Directness	Precision	Magnitude of Effect: Summary Effect Size (95% CI)	Strength of Evidence (High, Moderate, Low, Insufficient)
Overall/Any Adverse Events	Quetiapine ER versus quetiapine IR 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. Additionally there were six trials comparing asenapine and olanzapine	1 SR (28 RCTs; N = 7810)	Moderate	Consistent	Direct	Imprecise	No statistically significant differences were found in each comparison.	Low

Outcome	Comparators	Number of Studies Number of Subjects	Study Limitations	Consistency	: Directness	Precision	Magnitude of Effect: Summary Effect Size (95% CI)	Strength of Evidence (High, Moderate, Low, Insufficient)
Overall/Any Adverse Events	Oral aripiprazole versus brexpiprazole, olanzapine, paliperidone, and risperidone LAI; ziprasidone versus clozapine, risperidone, iloperidone and lurasidone; risperidone versus asenapine, caripramine and risperidone LAI; clozapine versus quetiapine, quetiapine versus risperidone LAI; olanzapine versus olanzapine LAI and lurasidone; aripiprazole monthly LAI versus paliperidone; and paliperidone palmitate monthly LAI versus 3-monthly LAI.	1 SR (31 RCTs; N = 6700)	Moderate	Unknown	Direct	Imprecise	No statistically significant differences were found in single studies of each comparison.	Insufficient

Outcome	Comparators	Number of Studies Number of Subjects	Study Limitations	Consistency	: Directness	Precision	Magnitude of Effect: Summary Effect Size (95% CI)	Strength of Evidence (High, Moderate, Low, Insufficient)
<b>Discontinuation Due to Adverse Events</b>	Network meta-analysis of aripiprazole, aripiprazole monthly LAI, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone10, olanzapine, olanzapine LAI, paliperidone 3-month LAI, paliperidone, paliperidone Monthly LAI, quetiapine ER, quetiapine IR, risperidone, risperidone LAI, ziprasidone	89 RCTs (N = 29,678)	Moderate	Consistent	Indirect	Precise	LAI risperidone had statistically significantly lower risk of withdrawals due to adverse events than asenapine (OR 0.50, 95% CI 0.23,0.97); clozapine (OR 0.26, 95% CI 0.10,0.67); lurasidone (OR 0.38, 95% CI 0.17,0.79); paliperidone (OR 0.43, 95% CI 0.17,0.98); paliperidone LAI monthly (OR 0.51, 95% CI 0.26,0.98); quetiapine ER (OR 0.42, 95% CI 0.21,0.78); risperidone (OR 0.48, 95% CI 0.23,0.92); and ziprasidone (OR 0.39, 95% CI 0.18,0.76). Olanzapine had lower risk than clozapine (OR 0.40, 95% CI 0.21,0.79); lurasidone (OR 0.58, 95% CI 0.36,0.98); quetiapine IR (OR 0.64, 95% CI 0.45,0.93); risperidone (OR 0.74, 95% CI 0.55,0.98); and ziprasidone (OR 0.59, 95% CI 0.43,0.84). Aripiprazole had lower risk than ziprasidone (OR 0.65, 95% CI 0.44,0.95) and iloperidone had lower risk than clozapine (OR 0.35, 95% CI 0.13,0.91).	Low

BPRS= Brief Psychiatric Rating Scale, CATIE=clinical Antipsychotic Trials of Intervention Effectiveness, CGI-S=Clinical Global Impression - Severity, CI=confidence interval, ER=efficacy ratio, GAF=global assessment of functioning, HR=hazard ratio, LAI=long acting injectable, NR=normal range, NS=not significant, NSD=no significant difference, OR=odds ratio, PSP=, Q=Cochran's Q test, QLS=quality of life scale, RCT=randomized controlled trial, RR=relative risk, SF=short form, SFS=Social Functioning Scale, SGA=second-generation antipsychotic, SMD=standard mean difference, SOFA=Social and Occupational Functioning Assessment, SQLS=Schizophrenia Quality of Life Scale, SR=systematic review, WMD=weighted mean difference

**Appendix Table H-2. Strength of evidence: first-generation antipsychotic versus second-generation antipsychotic**

<b>Outcome</b>	<b>Comparators</b>	<b>Number of Studies Number of Subjects</b>	<b>Study Limitations</b>	<b>Consistency</b>	<b>Directness</b>	<b>Precision</b>	<b>Magnitude of Effect: Summary Effect Size (95% CI)</b>	<b>Strength of Evidence (High, Moderate, Low, Insufficient)</b>
<b>Function: General</b>	Haloperidol vs. olanzapine	1 SR (1 RCT) <sup>30</sup> N=208	Moderate	Unknown	Direct	Imprecise	Inconclusive: GAF effect estimate: -4.00; 95% CI -13.70 to 5.70	Insufficient
<b>Function: Encounters with Legal System</b>	Haloperidol vs. olanzapine	1 SR (1 RCT) <sup>30</sup> N=31	Moderate	Unknown	Direct	Imprecise	Inconclusive: Encounters with legal system: RR 3.20, 95% CI 0.76 to 13.46	Insufficient
<b>Function: Employment</b>	Haloperidol vs. risperidone	1 SR <sup>30</sup> (1 RCT) N=100	Moderate	Unknown	Direct	Imprecise	Inconclusive: Proportion of patients with economic independence: RR 0.94; 95% CI 0.68 to 1.29	Insufficient
Function: Employment	Perphenazine vs. olanzapine	1 SR <sup>30</sup> (1 RCT) N=597	Moderate	Unknown	Direct	Imprecise	Inconclusive: Proportion with paid employment: RR 1.29; 95% CI 0.70 to 2.38	Insufficient
Function: Employment	Perphenazine vs. quetiapine	1 SR <sup>30</sup> (1 RCT) N=598	Moderate	Unknown	Direct	Imprecise	Inconclusive: Proportion with paid employment: RR 1.75; 95% CI 0.90 to 3.43	Insufficient
Function: Employment	Perphenazine vs. risperidone	1 SR <sup>30</sup> (1 RCT) N=602	Moderate	Unknown	Direct	Imprecise	Inconclusive: Proportion with paid employment: RR 1.38; 95% CI 0.74 to 2.57	Insufficient
Function: Employment	Perphenazine vs. ziprasidone	1 SR <sup>30</sup> (1 RCT) N=446	Moderate	Unknown	Direct	Imprecise	Inconclusive: Proportion with paid employment: RR 1.22; 95% CI 0.60 to 2.51	Insufficient
<b>Quality of Life</b>	Haloperidol vs. olanzapine	1 SR <sup>30</sup> (5 RCTs) N=816	Moderate	Consistent	Direct	Precise	Inconclusive: Effect sizes ranged from - 3.62 to 0 using different measures; CIs were not significant	Moderate
Quality of Life	Haloperidol vs. quetiapine	1 SR <sup>30</sup> (1 RCT) N=207	Moderate	Unknown	Direct	Imprecise	Inconclusive: Effect estimate 0.00; 95% CI -1.38 to 1.38	Insufficient
Quality of Life	Haloperidol vs. risperidone	1 SR <sup>30</sup> (2 RCTs) N=352	Moderate	Inconsistent	Direct	Imprecise	Inconclusive: Effect estimates ranged from -0.10 to 0.10; CIs were not significant	Insufficient

Outcome	Comparators	Number of Studies Number of Subjects	Study Limitations	Consistency	Directness	Precision	Magnitude of Effect: Summary Effect Size (95% CI)	Strength of Evidence (High, Moderate, Low, Insufficient)
Quality of Life	Haloperidol vs. ziprasidone	1 SR <sup>30</sup> (2 RCTs) N=784	High	Inconsistent	Direct	Imprecise	Studies favored ziprasidone in quality of life measures. One trial found effect favoring ziprasidone based on QLS (effect estimate 12.12; 95% CI -22.06 to -2.17); there was no difference in another trial in MANSA (effect estimate -0.10; 95% CI -1.48 to 1.28)	Low
Quality of Life	Perphenazine vs. aripiprazole	1 SR <sup>30</sup> (1 RCT) N=300	Moderate	Unknown	Direct	Imprecise	Inconclusive: Proportion with 20% improvement: RR 4.74; 95% CI 2.58 to 8.69	Insufficient
Quality of Life	Perphenazine vs. olanzapine	1 SR <sup>30</sup> (1 RCT) N=597	Moderate	Unknown	Direct	Precise	No difference: Effect estimate 0.00; 95% CI -0.16 to 0.16	Low
Quality of Life	Perphenazine vs. quetiapine	1 SR <sup>30</sup> (1 RCT) N=598	Moderate	Unknown	Direct	Precise	No difference: Effect estimate 0.10; 95% CI -0.07 to 0.27	Low
Quality of Life	Perphenazine vs. risperidone	1 SR <sup>30</sup> (1 RCT) N=602	Moderate	Unknown	Direct	Precise	No difference: Effect estimate -0.07; 95% CI -0.24 to 0.10	Low
Quality of Life	Perphenazine vs. ziprasidone	1 SR <sup>30</sup> (1 RCT) N=446	Moderate	Unknown	Direct	Precise	No difference: Effect estimate -0.07; 95% CI -0.27 to 0.13	Low
Response	Fluphenazine vs. olanzapine	1 SR <sup>30</sup> (1 RCT) N=60	Moderate	Unknown	Direct	Imprecise	Inconclusive: RR 0.74 (95% CI 0.51 to 1.07)	Insufficient
Response	Fluphenazine vs. quetiapine	1 SR <sup>30</sup> (1 RCT) N=25	Moderate	Unknown	Direct	Imprecise	Inconclusive: RR 0.62 (95% CI 0.12 to 3.07)	Insufficient
Response	Fluphenazine vs. risperidone	1 SR <sup>30</sup> (1 RCT) N=26	Moderate	Unknown	Direct	Imprecise	Inconclusive: RR 0.67 (95% CI 0.13 to 3.35)	Insufficient
Response	Haloperidol vs. aripiprazole	1 SR <sup>30</sup> (5 RCTs) N=2,185	Moderate	Inconsistent	Direct	Precise	No difference: RR 1.01 (95% CI 0.76 to 1.34; I <sup>2</sup> =83%)	Low
Response	Haloperidol vs. asenapine	1 SR <sup>30</sup> (1 RCT) N=335	Moderate	Unknown	Direct	Imprecise	Inconclusive: RR 0.82 (95% CI 0.64 to 1.04)	Insufficient

Outcome	Comparators	Number of Studies Number of Subjects	Study Limitations	Consistency	Directness	Precision	Magnitude of Effect: Summary Effect Size (95% CI)	Strength of Evidence (High, Moderate, Low, Insufficient)
Response	Haloperidol vs. clozapine	1 SR <sup>30</sup> (2 RCTs) N=144	Moderate	Inconsistent	Direct	Imprecise	Inconclusive: RR 0.64 (95% CI 0.28 to 1.47; I <sup>2</sup> = 72%)	Insufficient
Response	Haloperidol vs. olanzapine	1 SR <sup>30</sup> (14 RCTs) N=4,099	Moderate	Inconsistent	Direct	Precise	RR 0.86 (95% CI 0.78 to 0.96; I <sup>2</sup> =55%); favors olanzapine	Low
Response	Haloperidol vs. quetiapine	1 SR <sup>30</sup> (6 RCTs) N=1,421	Moderate	Inconsistent	Direct	Precise	No difference: RR 0.99 (95% CI 0.76 to 1.30; I <sup>2</sup> =77%)	Low
Response	Haloperidol vs. risperidone	1 SR <sup>30</sup> (16 RCTs) N=3,452)	Moderate	Consistent	Direct	Precise	No difference: RR 0.94 (95% CI 0.87 to 1.02; I <sup>2</sup> =29%)	Moderate
Response	Haloperidol vs. ziprasidone	1 SR <sup>30</sup> (6 RCTs) N=1,283	Moderate	Inconsistent	Direct	Imprecise	Inconclusive: RR 0.98 (95% CI 0.74 to 1.30; I <sup>2</sup> =80%)	Low
Response	Perphenazine vs. aripiprazole	1 SR <sup>30</sup> (1 RCT) N=300	Moderate	Unknown	Direct	Imprecise	Inconclusive: RR 0.95 (95% CI 0.64 to 1.40)	Insufficient
Remission	Haloperidol vs. clozapine	1 SR <sup>30</sup> (1 RCT) N=71	Moderate	Unknown	Direct	Imprecise	Inconclusive: RR 0.16 (95% CI 0.02 to 1.20)	Insufficient
Remission	Haloperidol vs. olanzapine	1 SR <sup>30</sup> (3 RCTs) N=582	Moderate	Consistent	Direct	Imprecise	RR 0.65 (95% CI 0.45 to 0.94; I <sup>2</sup> =54%); favors olanzapine	Low
Remission	Haloperidol vs. quetiapine	1 SR <sup>30</sup> (1 RCT) N=207	High	Unknown	Direct	Imprecise	Inconclusive: RR 0.72 (95% CI 0.41 to 1.25)	Insufficient
Remission	Haloperidol vs. risperidone	1 SR <sup>30</sup> (2 RCTs) N=179	Moderate	Consistent	Direct	Imprecise	Inconclusive: RR 0.84 (95% CI 0.56 to 1.24; I <sup>2</sup> =0%)	Low
Remission	Haloperidol vs. ziprasidone	1 SR <sup>30</sup> (3 RCTs) N=1,085	High	Consistent	Direct	Precise	No difference: RR 0.89 (95% CI 0.71 to 1.12; I <sup>2</sup> = 12%)	Low
Reduction in Self Harm	Haloperidol vs. olanzapine	1 SR <sup>30</sup> (1 RCT) N=182	Moderate	Unknown	Indirect	Imprecise	Inconclusive: Attempted suicide: RR 3.13; 95% CI 0.13 to 76 and 0.64 Completed suicide: RR 3.13; 95% CI 0.13 to 76 and 3.86	Insufficient

Outcome	Comparators	Number of Studies Number of Subjects	Study Limitations	Consistency	Directness	Precision	Magnitude of Effect: Summary Effect Size (95% CI)	Strength of Evidence (High, Moderate, Low, Insufficient)
Reduction in Self Harm	Perphenazine and olanzapine	1 SR <sup>30</sup> (1 RCT) N=597	Moderate	Unknown	Indirect	Imprecise	Inconclusive: Attempted suicide: RR 0.64; 95% CI 0.06 to 7.06 Completed suicide: RR 3.86; 95% CI 0.40 to 37	Insufficient
<b>Overall Adverse Events</b>	Haloperidol vs. aripiprazole	1 SR <sup>30</sup> (3 RCTS) N=1,713	Moderate	Consistent	Direct	Precise	RR 1.11; 95% CI 1.06 to 1.17; I <sup>2</sup> =0%; less with aripiprazole	Moderate
Overall Adverse Events	Haloperidol vs. risperidone	1 SR <sup>30</sup> (8 RCTS) N=1,313	Moderate	Consistent	Direct	Precise	RR 1.20; 95% CI 1.01 to 1.42; I <sup>2</sup> = 84%; less with risperidone	Moderate
Overall Adverse Events	Haloperidol vs. ziprasidone	1 SR <sup>30</sup> (6 RCTS) N=1,448	Moderate	Consistent	Direct	Precise	RR 1.13; 95% CI 1.03 to 1.23; I <sup>2</sup> =31%; less with ziprasidone	Moderate
<b>Withdrawal Due to Adverse Events</b>	Fluphenazine vs. olanzapine	1 SR <sup>30</sup> (1 RCT) N=60	Moderate	Unknown	Indirect	Imprecise	Inconclusive: RR 0.74; 95% CI 0.51 to 1.07	Insufficient
	Fluphenazine vs. quetiapine	1 SR <sup>30</sup> (1 RCT) N=25	Moderate	Unknown	Indirect	Imprecise	Inconclusive: RR 0.19; 95% CI 0.01 to 3.52	Insufficient
Withdrawal Due to Adverse Events	Haloperidol vs. asenapine	1 SR <sup>30</sup> (1 RCT) N=335	Moderate	Unknown	Indirect	Imprecise	Inconclusive: RR 1.53; 95% 0.74 to 3.16	Insufficient
Withdrawal Due to Adverse Events	Haloperidol vs. aripiprazole	1 SR <sup>30</sup> (7 RCTS) + 1 additional RCT N= 3,232	Moderate	Consistent	Direct	Precise	RR 1.25; 1.07 to 1.47; I <sup>2</sup> =0%	Moderate
Withdrawal Due to Adverse Events	Haloperidol vs. clozapine	1 SR <sup>30</sup> (5 RCTS) N=719	Moderate	Consistent	Direct	Imprecise	Inconclusive: RR 1.00; 95% CI 0.66 to 1.50; I <sup>2</sup> =0%	Low
Withdrawal Due to Adverse Events	Haloperidol vs. olanzapine	1 SR <sup>30</sup> (21 RCTS) + 3 RCTS N= 5,708	Moderate	Consistent	Direct	Precise	RR 1.89; 95% CI 1.57 to 2.27; I <sup>2</sup> =0%	Moderate
Withdrawal Due to Adverse Events	Haloperidol vs. quetiapine	1 SR <sup>30</sup> (8 RCTS) + 2 RCTS N=1,759	Moderate	Consistent	Direct	Imprecise	Inconclusive: RR 1.97; 95% CI 0.96 to 4.01; I <sup>2</sup> =62%	Low

Outcome	Comparators	Number of Studies Number of Subjects	Study Limitations	Consistency	Directness	Precision	Magnitude of Effect: Summary Effect Size (95% CI)	Strength of Evidence (High, Moderate, Low, Insufficient)
Withdrawal Due to Adverse Events	Haloperidol vs. risperidone	1 SR <sup>30</sup> (23 RCTs) + 2 RCTs N=4,581	Moderate	Consistent	Direct	Precise	RR 1.32; 95% CI 1.09 to 1.60; I <sup>2</sup> =0%	Moderate
Withdrawal Due to Adverse Events	Haloperidol vs. ziprasidone	1 SR <sup>30</sup> (6 RCTs) + 1 RCT N=1597	Moderate	Consistent	Direct	Precise	RR 1.68; 95% CI 1.26 to 2.23; I <sup>2</sup> =0%	Moderate
Withdrawal Due to Adverse Events	Perphenazine vs. aripiprazole	1 SR <sup>30</sup> (1 RCT) N=300	Moderate	Unknown	Direct	Imprecise	Inconclusive: RR 0.53; 95% CI 0.27 to 1.05	Insufficient
Withdrawal Due to Adverse Events	Perphenazine vs. olanzapine	1 SR <sup>30</sup> (1 RCT) N=597	Moderate	Unknown	Direct	Imprecise	Inconclusive: RR 0.83; 95% CI 0.58 to 1.19	Insufficient
Withdrawal Due to Adverse Events	Perphenazine vs. quetiapine	1 SR <sup>30</sup> (1 RCT) N=598	Moderate	Unknown	Direct	Imprecise	Inconclusive: RR 1.05; 95% CI 0.72 to 1.55	Insufficient
Withdrawal Due to Adverse Events	Perphenazine vs. risperidone	1 SR <sup>30</sup> (1 RCT) N=602	Moderate	Unknown	Direct	Imprecise	Inconclusive: RR 1.54; 95% CI 1.00 to 2.36	Insufficient
Withdrawal Due to Adverse Events	Perphenazine vs. ziprasidone	1 SR <sup>30</sup> (1 RCT) N=446	Moderate	Unknown	Direct	Imprecise	Inconclusive: RR 1.01; 95% CI 0.65 to 1.58	Insufficient

CI=confidence interval, OR=odds ratio, RCT=randomized controlled trial, SR=systematic review

**Appendix Table H-3. Strength of evidence: assertive community treatment**

<b>Outcome</b>	<b>Comparators</b>	<b>Number of Studies Number of Subjects</b>	<b>Strength of Evidence Domain: Study Limitations</b>	<b>Strength of Evidence Domain: Consistency</b>	<b>Strength of Evidence Domain: Directness</b>	<b>Strength of Evidence Domain: Precision</b>	<b>Magnitude of Effect: Summary Effect Size (95% CI)</b>	<b>Strength of Evidence (High, Moderate, Low, Insufficient)</b>
<b>Function</b>	Assertive community treatment vs. usual care	1 SR <sup>31</sup> (3 RCTs) 1 RCT <sup>32</sup> N=118	Moderate	Consistent	Direct	Imprecise	No difference in social function compared with usual care. Social function, mean difference 0.03 (95% CI - 0.28 to 0.34)	Low
<b>Trouble With Police</b>	Assertive community treatment vs. usual care	1 SR <sup>31</sup> (4 RCTs)	Moderate	Consistent	Direct	Imprecise	No differences in arrests (2 trials; OR 1.17, 95% CI 0.60 to 2.29), imprisonment (4 trials; OR 1.19, 95% CI 0.70 to 2.01), or police contacts (2 trials; OR 0.76, 95% CI 0.32 to 1.79)	Low
<b>Housing and Independent Living</b>	Assertive community treatment vs. usual care	1 SR <sup>31</sup> (3 RCTs) 1 RCT <sup>32</sup> N=118	Moderate	Consistent	Direct	Precise	Less likely to be not living independently (4 trials; OR 0.52, 95% CI 0.35 to 0.79), to be homeless (4 trials; OR 0.20, 95% CI 0.09 to 0.47). Less likely to be homeless (4 trials, OR 0.24, 95% CI 0.12 to 0.48).	Moderate
<b>Employment</b>	Assertive community treatment vs. usual care	1 SR <sup>31</sup> (3 RCTs)	Moderate	Consistent	Direct	Precise	Less likely to be unemployed (3 trials; OR 0.46, 95% CI 0.21 to 0.99)	Moderate
<b>Quality of Life</b>	Assertive community treatment vs. usual care	1 SR <sup>31</sup> (1 RCT) N=125 1 RCT <sup>32</sup> N=118	Moderate	Inconsistent	Direct	Imprecise	Quality of life was slightly better with assertive community treatment (mean difference, -0.52, 95% CI -0.99 to -0.05) in one trial, but no differences found in the other trial.	Insufficient

Outcome	Comparators	Number of Studies Number of Subjects	Strength of Evidence Domain: Study Limitations	Strength of Evidence Domain: Consistency	Strength of Evidence Domain: Directness	Strength of Evidence Domain: Precision	Magnitude of Effect: Summary Effect Size (95% CI)	Strength of Evidence (High, Moderate, Low, Insufficient)
<b>Overall Symptoms</b>	Assertive community treatment vs. usual care	1 SR <sup>31</sup> (3 RCTs) 1 RCT <sup>32</sup> N=118	Moderate	Consistent	Direct	Precise	No differences were found in 4 trials. Mean difference, -0.14 (95% CI -0.36 to 0.08).	Moderate
<b>Treatment Maintenance (Loss to Followup)</b>	Assertive community treatment vs. usual care	1 SR <sup>31</sup> (10 RCTs) 1 RCT <sup>32</sup> N=118	Moderate	Consistent	Direct	Precise	Significantly less loss to followup with assertive community treatment (OR 0.51, 95% CI 0.40 to 0.65) based on 10 trials in SR; and significantly fewer patients "out-of-care" in the other trial (OR 0.10, 95% CI 0.03 – 0.33)	Moderate

CI=confidence interval, N=number, OR=odds ratio, RCT=randomized controlled trial, SR=systematic review

**Appendix Table H-4. Strength of evidence: cognitive behavioral therapy**

<b>Outcome</b>	<b>Comparators</b>	<b>Number of Studies Number of Subjects</b>	<b>Strength of Evidence Domain: Study Limitations</b>	<b>Strength of Evidence Domain: Consistency</b>	<b>Strength of Evidence Domain: Directness</b>	<b>Strength of Evidence Domain: Precision</b>	<b>Magnitude of Effect: Summary Effect Size (95% CI)</b>	<b>Strength of Evidence (High, Moderate, Low, Insufficient)</b>
<b>Function: Global Function – Short term (≤6 months since CBT initiation)</b>	CBT vs. usual care	1 SR <sup>33</sup> (3 RCTs) 5 RCTs <sup>34-38</sup> N=701	Moderate	Consistent	Direct	Precise	GAF (6 RCTs): mean difference 5.49 (95% CI 1.85 to 9.14; I <sup>2</sup> =75%); excluding one outlier: 6.62 (95% CI 4.68 to 8.56; I <sup>2</sup> =0%) SOFAS (2 RCTs): mean difference 9.11 (95% CI 6.31 to 11.91) Proportion with normal function (1 RCT): RR 2.21 (95% CI 1.25 to 3.93)	Moderate
<b>Function: Global Function – Medium term (&gt;6 months to 1 year since CBT initiation)</b>	CBT vs. usual care	3 RCTs <sup>34,36,39</sup> N=465	Moderate	Inconsistent	Direct	Imprecise	Inconclusive: GAF: One trial found with 6 months posttreatment followup found no difference; another trial found effect favoring CBT SOFAS, SFS: No difference between groups	Insufficient
<b>Function: Global Function – Long term (&gt;1 year since CBT initiation)</b>	CBT vs. usual care	1 SR <sup>33</sup> (4 RCTs) 4 RCTs <sup>37,39-41</sup> n=851	Moderate	Consistent	Direct	Imprecise	Inconclusive: GAF: 1 SR found mean difference 4.20 (95% CI -0.63 to 9.03). One other RCT found positive effect of CBT. 3 RCTs found no difference in SOFAS, global function (scale not reported) and proportion of patients with normal function.	Low
<b>Function: Basic Living Skills</b>	CBT vs. usual care	1 RCT <sup>42</sup> N=76	Moderate	Unknown	Direct	Imprecise	No difference between groups.	Insufficient

Outcome	Comparators	Number of Studies Number of Subjects	Strength of Evidence Domain: Study Limitations	Strength of Evidence Domain: Consistency	Strength of Evidence Domain: Directness	Strength of Evidence Domain: Precision	Magnitude of Effect: Summary Effect Size (95% CI)	Strength of Evidence (High, Moderate, Low, Insufficient)
<b>Function: Employment Outcomes</b>	CBT vs. usual care	2 RCTs <sup>43,44</sup> N=522	Moderate	Inconsistent	Direct	Imprecise	Inconclusive: One RCT of vocational- focused CBT favored CBT for hours worked and WBI score; another trial found no difference in proportion of patients with occupational recovery	Insufficient
<b>Quality of Life</b>	CBT vs. usual care	12-24 weeks followup; 2 RCTs <sup>38,45</sup> N = 216	Moderate	Consistent	Direct	Imprecise	CBT led to improved quality of life 0 and 16 weeks after cessation of treatment based on CHOICE, WEMWEBS and WHOQoL-BREF scales.	Low
Quality of Life	CBT vs. usual care	18 to 24 months followup; 2 RCTs <sup>37,39</sup> N=489	Moderate	Consistent	Direct	Imprecise	CBT not different from usual care based on WHOQoL and EROQOL scales	Low
<b>Suicide and Suicidality</b>	CBT vs. usual care	2 RCTs <sup>45,46</sup> N=307	Moderate	Consistent	Direct	Imprecise	Inconclusive: RR 0.68 (95% CI 0.12 to 3.93) and RR 0.53 (95% CI 0.12 to 2.79)	Insufficient
<b>Core Illness Symptoms</b>	CBT vs. usual care	1 SR (34 RCTs) <sup>47</sup> N=2,989	Moderate	Consistent	Direct	Precise	SMD -0.33, 95% CI -0.47 to - 0.19); subgroup with outcome assessment blinding SMD - 0.15, 95% CI -0.27 to -0.03),	Moderate
<b>Negative Symptoms</b>	CBT vs. usual care	2 SRs (34 RCTs) <sup>47,48</sup> N=3,393	Moderate	Inconsistent	Direct	Precise	Standardized mean difference -0.13, 95% CI -0.25 to -0.01; $I^2=48%$ [in this review a negative estimate favors CBT]; and SMD 0.09, 95% CI -0.03 to 0.21; $I^2=63%$ [in this review, a positive estimate favors CBT])	Low
<b>Ability to Maintain Treatment</b>	CBT vs. usual care	13 RCTs <sup>34-42,44,45,49,50</sup> N=1,847	Moderate	Inconsistent	Direct	Precise	No difference: Relative risk 1.03, 95% CI 0.96 to 1.10; $I^2=64%$ .	Low
<b>Relapse</b>	CBT vs. usual care	6 RCTs <sup>34,36,39,44,49,51</sup> N=1,090	Moderate	Inconsistent	Direct	Imprecise	Inconclusive: Relative Risk: 0.80, 95% CI 0.51 to 1.25; $I^2=77%$ ) Subanalysis limited to relapse defined as "hospitalization" (3 RCTs): 0.70, 95% CI 0.54 to 0.91; $I^2=0%$	Insufficient
<b>Harms</b>	CBT vs. usual care	1 RCT <sup>45</sup>						Insufficient

CBT=cognitive behavioral therapy, CI=confidence interval, EROQOL= European Quality of Life scale, GAF=global assessment of functioning, OR=odds ratio, RCT=randomized controlled trial, RR=relative risk, SMD=standard mean difference, SOFAS=Social and Occupational Functioning Assessment Scale, SR=systematic review, WHOQOL= World Health Organization Quality of Life

**Appendix Table H-5. Strength of evidence: cognitive remediation**

Outcome	Comparators	Number of Studies Number of Subjects	Strength of Evidence Domain: Study Limitations	Strength of Evidence Domain: Consistency	Strength of Evidence Domain: Directness	Strength of Evidence Domain: Precision	Magnitude of Effect: Summary Effect Size (95% CI)	Strength of Evidence (High, Moderate, Low, Insufficient)
Function	Cognitive remediation vs. usual care	1 SR <sup>52</sup> (19 RCTs) 3 RCTs <sup>53-55</sup> N=1,323	Moderate	Consistent	Direct	Imprecise	In studies comparing with usual care, cognitive remediation resulted in a small positive effect on function that was not consistently statistically significant. (effect size 0.16, 95% CI -0.16 to 0.49; SMD 0.56, 95% CI 0.34 to 0.88, and SMD 0.41, 95% CI -.10 to 0.91).	Low
Quality of life	Cognitive remediation vs. usual care	1 RCT <sup>55</sup> N=69	Moderate	Unknown	Direct	Imprecise	Quality of life was only reported in one trial, with no difference between cognitive remediation and usual care.	Insufficient
Overall symptoms	Cognitive remediation vs. usual care	2 RCTs <sup>55,56</sup> N=153	Moderate	Consistent	Direct	Imprecise	Cognitive remediation improved total symptoms, based on 2 trials (N=153, SMD -0.62 (95% CI -1.01 to -0.24). Four trials included in the Wykes review reported effect sizes ranging from 0.05 to 0.45 (95% CIs were not reported).	Moderate
Negative symptoms	Cognitive remediation vs. usual care	1 SR <sup>57</sup> (18 RCTs; N=781)	Moderate	Consistent	Direct	Precise	Negative symptoms improved more in CR groups (effect size <b>-0.36 (95% CI -0.52 to -0.20; a negative effect size favors cognitive remediation)</b> ).	Moderate
Ability to maintain treatment	Cognitive remediation vs. usual care	3 RCTs <sup>53,54,56,58</sup> N=302	Moderate	Consistent	Direct	Imprecise	There was no difference in ability to maintain treatment in three RCTs of cognitive remediation	Low

CI=confidence interval, CR=cognitive remediation, RCT=randomized controlled trial, QLS= quality of life survey, QOL=quality of life, SR=systematic review, WBI=Work Behavior Inventory

**Appendix Table H-6. Strength of evidence: family interventions**

<b>Outcome</b>	<b>Comparators</b>	<b>Number of Studies Number of Subjects</b>	<b>Strength of Evidence Domain: Study Limitations</b>	<b>Strength of Evidence Domain: Consistency</b>	<b>Strength of Evidence Domain: Directness</b>	<b>Strength of Evidence Domain: Precision</b>	<b>Magnitude of Effect: Summary Effect Size (95% CI)</b>	<b>Strength of Evidence (High, Moderate, Low, Insufficient)</b>
<b>Function: Occupational (Unemployed) - 1 year</b>	Family intervention vs. usual care	1 SR <sup>59</sup> (4 RCTs; N=230)	Moderate	Consistent	Direct	Imprecise	RR 1.09 (0.92 to 1.29)	Low
<b>Function: Occupational (Unemployed) - 2 years</b>	Family intervention vs. usual care	1 SR <sup>59</sup> (1 RCT; N=51)	Moderate	Unknown	Direct	Imprecise	RR 1.33 (0.84 to 2.10)	Insufficient
<b>Function: Occupational (Unemployed) - 3 years</b>	Family intervention vs. usual care	1 SR <sup>59</sup> (1 RCT; N=99)	Moderate	Unknown	Direct	Imprecise	RR 1.19 (0.92 to 1.55)	Insufficient
<b>Function: Living situation (cannot live independently) - 1 year</b>	Family intervention vs. usual care	1 SR <sup>59</sup> (3 RCTs; N=164)	Moderate	Consistent	Direct	Imprecise	RR 0.83 (0.66 to 1.03)	Low
<b>Function: Living situation (cannot live independently) - 3 years</b>	Family intervention vs. usual care	1 SR <sup>59</sup> (1 RCT; N=99)	Moderate	Unknown	Direct	Imprecise	RR 0.82 (0.59 to 1.14)	Insufficient
<b>Function: Living situation (cannot live independently, months in psychiatric facility) - 5 years</b>	Family intervention vs. usual care	1 RCT <sup>60</sup> ; N=63)	Moderate	Unknown	Direct	Imprecise	10.87 vs. 21.18 months, p=0.04)	Insufficient
<b>Social Functioning</b>	Family intervention vs. usual care	1 RCT <sup>36</sup> N=69	Moderate	Unknown	Direct	Imprecise		Insufficient
<b>Quality of Life</b>	Family intervention vs. usual care	1 SR <sup>59</sup> (1 RCT; N=50) plus one RCT not in SR; <sup>39</sup> N=55	Moderate	Unknown	Direct	Imprecise	Heinrichs scale: MD -5.05 (-15.44 to 5.34) EuroQoL: MD -7.38 (-22.07 to 7.31)	Insufficient

Outcome	Comparators	Number of Studies Number of Subjects	Strength of Evidence Domain: Study Limitations	Strength of Evidence Domain: Consistency	Strength of Evidence Domain: Directness	Strength of Evidence Domain: Precision	Magnitude of Effect: Summary Effect Size (95% CI)	Strength of Evidence (High, Moderate, Low, Insufficient)
<b>Depression</b>	Family intervention vs. usual care	2 RCTs; <sup>36,39</sup> N=124	Moderate	Consistent	Direct	Imprecise	1 RCT, 6 months: -1.0 (-12, 22) vs. 0 (-15, 17) 1 RCTs 12 months: 3.0 (-15, 17) vs. 0 (-14 to 17) 1 RCT 12 months; 3.35 (-2.64 to 9.34) 1 RCT 24 months: -0.11 (-6.91 to 6.68)	Low
<b>Anxiety</b>	Family intervention vs. usual care	1 RCT; <sup>39</sup> N=55	Low	Unknown	Direct	Imprecise	12 months: -0.42 (-6.97 to 6.13) 24 months: -2.36 (-9.13 to 4.40)	Insufficient
<b>Suicide</b>	Family intervention vs. usual care	1 SR <sup>59</sup> (6 RCTs; N=314)	Moderate	Consistent	Direct	Imprecise	RR 0.85 (0.24 to 3.02)	Low
<b>Core Illness Symptoms:</b>	Family intervention vs. usual care	1 SR <sup>59</sup> (2 RCTs; <sup>39,61</sup> N=223)	Moderate	Consistent	Direct	Imprecise	SMD -0.46 (-0.73 to -0.20)	Low
<b>Negative Symptoms</b>	Family intervention vs. usual care	3 RCTs; <sup>36,39,61</sup> N=163	Moderate	Consistent	Direct	Imprecise	SMD -0.38, 95% CI -0.69 to -0.07	Low
<b>Leaving the study early (3-6 months)</b>	Family intervention vs. usual care	1 SR <sup>59</sup> (6 RCTs; N=504)	Moderate	Consistent	Indirect	Imprecise	RR 0.86 (0.50 to 1.47)	Low
<b>Leaving the study early (7-12 months)</b>	Family intervention vs. usual care	1 SR <sup>59</sup> (9 RCTs; N=487) plus 4 RCTs; <sup>39,61-63</sup> N=466	Moderate	Consistent	Indirect	Imprecise	RR 0.77 (0.64 to 0.93)	Low
<b>Leaving the study early (13-24 months)</b>	Family intervention vs. usual care	1 SR <sup>59</sup> (6 RCTs; N=362)	Moderate	Consistent	Indirect	Imprecise	RR 0.82 (0.57 to 1.16)	Low
<b>Leaving the study early (25-36 months)</b>	Family intervention vs. usual care	1 SR <sup>59</sup> (2 RCTs; N=90)	High	Consistent	Indirect	Imprecise	RR 0.59 (0.24 to 1.49)	Insufficient
<b>Leaving the study early after 3 years</b>	Family intervention vs. usual care	1 SR <sup>59</sup> (1 RCT; N=63)	Moderate	Unknown	Indirect	Imprecise	RR 1.72 (0.71 to 4.16)	Insufficient
<b>Poor compliance with medication</b>	Family intervention vs. usual care	1 SR <sup>59</sup> (4 RCTs; N=174) plus 2 RCTs <sup>62,63</sup> N=256	Moderate	Consistent	Indirect	Imprecise	RR 0.78 (0.65 to 0.92)	Low
<b>Relapse 0-6 months</b>	Family intervention vs. usual care	1 SR <sup>59</sup> (2 RCTs; N=167)	Moderate	Consistent	Direct	Imprecise	RR 0.62 (0.41 to 0.92)	Low
<b>Relapse (7-12 months)</b>	Family intervention vs. usual care	1 SR <sup>59</sup> (16 RCTs; N=861) plus 4 RCTs; <sup>39,61,63,64</sup> N=314	Moderate	Consistent	Direct	Imprecise	RR 0.67 (0.54 to 0.83)	Moderate

<b>Outcome</b>	<b>Comparators</b>	<b>Number of Studies Number of Subjects</b>	<b>Strength of Evidence Domain: Study Limitations</b>	<b>Strength of Evidence Domain: Consistency</b>	<b>Strength of Evidence Domain: Directness</b>	<b>Strength of Evidence Domain: Precision</b>	<b>Magnitude of Effect: Summary Effect Size (95% CI)</b>	<b>Strength of Evidence (High, Moderate, Low, Insufficient)</b>
<b>Relapse (13-24 months)</b>	Family intervention vs. usual care	1 SR <sup>59</sup> (9 RCTs; N=517)	Moderate	Consistent	Direct	Imprecise	RR 0.75 (0.58 to 0.99)	Low
<b>Relapse (25-36 months)</b>	Family intervention vs. usual care	1 SR <sup>59</sup> (2 RCTs; N=147)	Moderate	Inconsistent	Direct	Imprecise	RR 1.05 (0.80 to 1.39)	Low
<b>Relapse (5 years)</b>	Family intervention vs. usual care	1 SR <sup>59</sup> (1 RCT; N=63) plus 1 RCT; <sup>64</sup> N=77	Moderate	Consistent	Direct	Imprecise	RR 0.82 (0.72 to 0.94)	Low
<b>Relapse (8 years)</b>	Family intervention vs. usual care	1 SR <sup>59</sup> (1 RCT; N=62)	Moderate	Unknown	Direct	Imprecise	RR 0.86 (0.71 to 1.05)	Insufficient
<b>Family Burden Not Improved or Worse</b>	Family intervention vs. usual care	1 SR <sup>59</sup> (1 RCT; N=51)	Moderate	Unknown	Direct	Imprecise	Social functioning: RR 2.40 (0.51 to 11.27) at 1 year RR 2.88 (0.64 to 12.97) at 2 years Subjective burden: RR 1.44 (0.60 to 3.46) at 1 year RR 0.58 (0.15 to 2.16) at 2 years	Insufficient
<b>Nonsuicide mortality</b>	Family intervention vs. usual care	1 SR <sup>59</sup> (3 RCTs; N=113)	Moderate	Consistent	Direct	Imprecise	RR 0.96 (0.17 to 5.33)	Insufficient

BPRS=Brief Psychiatric Rating Scale, MD=mean difference, RR=relative risk, RCT=randomized controlled trial, SR=systematic review

**Appendix Table H-7. Strength of evidence: intensive case management**

<b>Outcome</b>	<b>Comparators</b>	<b>Number of Studies Number of Subjects</b>	<b>Strength of Evidence Domain: Study Limitations</b>	<b>Strength of Evidence Domain: Consistency</b>	<b>Strength of Evidence Domain: Directness</b>	<b>Strength of Evidence Domain: Precision</b>	<b>Magnitude of Effect: Summary Effect Size (95% CI)</b>	<b>Strength of Evidence (High, Moderate, Low, Insufficient)</b>
<b>Function</b>	Intensive case management vs. usual care	1 SR <sup>65</sup> (3 RCTs) 1 RCT <sup>66</sup> (n=77)	Moderate	Consistent	Direct	Imprecise	Inconclusive: Pooled mean difference, 0.46 (95% CI -0.34 to 0.1.26); one subsequent trial also found no difference using a different scale	Low
<b>Quality of Life</b>	Intensive case management vs. usual care	1 SR <sup>65</sup> (2 RCTs) 1 RCT <sup>66</sup> (n=77)	Moderate	Consistent	Direct	Imprecise	Inconclusive: Pooled mean difference, 0.09 (95% CI -0.23 to 0.42); One subsequent trial also found no difference between groups in quality of life using a different scale.	Insufficient
<b>Overall Symptoms</b>	Intensive case management vs. usual care	1 SR <sup>65</sup> (2 RCTs) 1 RCT <sup>66</sup> (n=77)	Moderate	Consistent	Direct	Imprecise	Inconclusive: Pooled mean difference, 0.46 (95% CI -3.67 to 4.60); one subsequent trial also reported no difference.	Low
<b>Loss to Followup</b>	Intensive case management vs. usual care	1 SR <sup>65</sup> (7 RCTs) 1 RCT <sup>66</sup> (n=77)	Moderate	Consistent	Direct	Precise	Less loss to followup with intensive case management compared to usual care (OR 0.70, 95% CI 0.54 to 0.90)	Moderate
<b>Imprisonment</b>	Intensive case management vs. usual care	1 SR <sup>65</sup> (5 RCTs)	Moderate	Consistent	Direct	Imprecise	No significant differences in imprisonment (OR 0.90, 95% CI 0.45 to 1.82)	Low

CI=confidence interval, RCT=randomized controlled trial, OR=odds ratio, SR=systematic review

**Appendix Table H-8. Strength of evidence: illness management and recovery**

Outcome	Comparators	Number of Studies Number of Subjects	Strength of Evidence Domain: Study Limitations	Strength of Evidence Domain: Consistency	Strength of Evidence Domain: Directness	Strength of Evidence Domain: Precision	Magnitude of Effect: Summary Effect Size (95% CI)	Strength of Evidence (High, Moderate, Low, Insufficient)
<b>Functioning</b>	Illness self-management/ self-management education intervention vs. usual care	1 SR of 10 RCTs (N = 409) <sup>67</sup> + 1 RCT; N = 210	Moderate	Inconsistent	Direct	Imprecise	Inconclusive: Heterogeneous methods for measuring various types of functioning were used, with 5 finding benefit ad 6 not.	Insufficient
<b>Symptoms</b>	Illness self-management/ self-management education intervention vs. usual care	1 SR <sup>67</sup> 5 RCTs n=409	Moderate	Consistent	Direct	Precise	BPRS (n=409), WMD: -4.19 (-5.84 to -2.54)	Moderate
<b>Negative Symptoms</b>	Illness self-management/ self-management education intervention vs. usual care	1 SR, <sup>67</sup> 3 RCTs; N = 257	Moderate	Consistent	Direct	Imprecise	PANSS negative -4.01 (-5.23 to -2.79)	Low
<b>Relapse</b>	Illness self-management/ self-management education intervention vs. usual care	1 SR, <sup>67</sup> 3 RCTs; N=534	Moderate	Consistent	Direct	Imprecise	Relapse (>10 interventions), n=233 OR= 0.41 (0.21-0.79), p=0.008 Relapse (<10 interventions), n=269 OR= 0.67 (0.39-1.15), p=0.014	Low

BPRS=Brief Psychiatric Rating Scale, CI=confidence interval, IMR=illness management and recovery, RCT=randomized controlled trial, SR=systematic review, WMD=weighted mean difference

**Appendix Table H-9. Strength of evidence: psychoeducation**

<b>Outcome</b>	<b>Comparators</b>	<b>Number of Studies Number of Subjects</b>	<b>Strength of Evidence Domain: Study Limitations</b>	<b>Strength of Evidence Domain: Consistency</b>	<b>Strength of Evidence Domain: Directness</b>	<b>Strength of Evidence Domain: Precision</b>	<b>Magnitude of Effect: Summary Effect Size (95% CI)</b>	<b>Strength of Evidence (High, Moderate, Low, Insufficient)</b>
<b>Global Functioning (GAF/GAS) at end of intervention</b>	Psychoeducation vs. standard care	1 SR <sup>68</sup> (1 RCT; N = 41)	Medium	Unknown	Direct	Imprecise	Inconclusive: Mean Difference - 2.64 CI - 12.74 to 7.46	Insufficient
<b>Global Functioning (GAS) at 6 Months</b>	Psychoeducation vs. standard care	1 SR <sup>68</sup> (1 RCT; N = 92)	Medium	Unknown	Direct	Imprecise	Inconclusive: Risk Ratio 0.83 CI 0.50 to 1.38	Insufficient
<b>Global Functioning (GAF/GAS) at 1 Year</b>	Psychoeducation vs. standard care	1 SR <sup>68</sup> (3 RCTs; N = 260)	Medium	Consistent	Direct	Imprecise	Mean Difference - 5.23 CI -8.76 to -1.71 I <sup>2</sup> 79%	Low
<b>Global Functioning (GAS) at 18 Months</b>	Psychoeducation vs. standard care	1 SR <sup>68</sup> (1 RCT; N = 92)	Medium	Unknown	Direct	Imprecise	Inconclusive: Risk Ratio 0.90 CI 0.58 to 1.39	Insufficient
<b>Global Functioning (GAF/GAS) at 2 Years</b>	Psychoeducation vs. standard care	1 SR <sup>68</sup> (1 RCT; N = 59)	Medium	Unknown	Direct	Imprecise	Mean Difference - 6.70 CI - 13.38 to - 0.02	Insufficient
<b>Global Functioning (GAF/GAS) at 5 Years</b>	Psychoeducation vs. standard care	1 SR <sup>68</sup> (1 RCT; N = 60)	Medium	Unknown	Direct	Imprecise	Inconclusive: Mean Difference - 3.80 CI -8.04 to 0.44	Insufficient
<b>Social Functioning (SAS-II) at End of Intervention</b>	Psychoeducation vs. standard care	1 SR <sup>68</sup> (1 RCT; N = 19)	Medium	Unknown	Direct	Imprecise	Inconclusive: Mean Difference - 0.10 CI -0.37 to 0.17	Insufficient

<b>Outcome</b>	<b>Comparators</b>	<b>Number of Studies Number of Subjects</b>	<b>Strength of Evidence Domain: Study Limitations</b>	<b>Strength of Evidence Domain: Consistency</b>	<b>Strength of Evidence Domain: Directness</b>	<b>Strength of Evidence Domain: Precision</b>	<b>Magnitude of Effect: Summary Effect Size (95% CI)</b>	<b>Strength of Evidence (High, Moderate, Low, Insufficient)</b>
Quality of Life (Heinrich's Scale) at End of Intervention	Psychoeducation vs. standard care	1 SR <sup>68</sup> (1 RCT; N = 114)	Medium	Unknown	Direct	Imprecise	Mean Difference - 8.20 CI - 14.78 to - 1.62	Insufficient
<b>Quality of Life (Heinrich's Scale) at 3 Months</b>	Psychoeducation vs. standard care	1 SR <sup>68</sup> (1 RCT; N = 108)	Medium	Unknown	Direct	Imprecise	Mean Difference - 9.70 CI - 17.22 to - 2.18	Insufficient
<b>BPRS at 3 Months</b>	Psychoeducation vs. standard care	1 SR <sup>68</sup> (1 RCT; N = 19)	Medium	Unknown	Direct	Imprecise	Inconclusive: Mean Difference - 0.06 CI -0.53 to 0.41	Insufficient
<b>BPRS at 1 Year</b>	Psychoeducation vs. standard care	1 SR <sup>68</sup> (1 RCT; N = 159)	Medium	Unknown	Direct	Imprecise	Mean Difference - 6.0 CI -9.15 to -2.85	Insufficient
<b>Relapse With or Without Readmission: 9 to 18 Months</b>		1 SR <sup>68</sup> (6 RCTs; N = 720)	Medium	Consistent	Direct	Precise	Risk Ratio 0.80 CI 0.70 to 0.92 I <sup>2</sup> 54%	Moderate
<b>Relapse Without Readmission: Total</b>	Psychoeducation vs. standard care	1 SR <sup>68</sup> (3 RCTs; N = 385)	Medium	Consistent	Direct	Imprecise	Inconclusive: Risk Ratio 1.05 CI 0.84 to 1.31 I <sup>2</sup> 60%	Low
<b>Relapse Without Readmission: 1 Year</b>	Psychoeducation vs. standard care	1 SR <sup>68</sup> (2 RCTs; N = 303)	Medium	Consistent	Direct	Imprecise	Inconclusive: Risk Ratio 1.16 CI 0.92 to 1.46 I <sup>2</sup> 0.0%	Low

<b>Outcome</b>	<b>Comparators</b>	<b>Number of Studies Number of Subjects</b>	<b>Strength of Evidence Domain: Study Limitations</b>	<b>Strength of Evidence Domain: Consistency</b>	<b>Strength of Evidence Domain: Directness</b>	<b>Strength of Evidence Domain: Precision</b>	<b>Magnitude of Effect: Summary Effect Size (95% CI)</b>	<b>Strength of Evidence (High, Moderate, Low, Insufficient)</b>
<b>Relapse Without Readmission: 18 Months</b>	Psychoeducation vs. standard care	1 SR <sup>68</sup> (1 RCT; N = 382)	Medium	Unknown	Direct	Imprecise	Inconclusive: Risk Ratio 0.5 CI 0.23 to 1.11	Insufficient
<b>Harms: Mortality</b>	Psychoeducation vs. standard care	1 SR <sup>68</sup> (2 RCTs; N = 170)	Medium	Consistent	Direct	Imprecise	Inconclusive: Risk Ratio 0.53 CI 0.07 to 3.95 I <sup>2</sup> 0.0%	Low

BPRS=Brief Psychiatric Rating Scale, CI=confidence interval, GAF =global assessment functioning, GAS=global assessment scale, RCT=randomized controlled trial, SAS=social adjustment score, SR=systematic review

**Appendix Table H-10. Strength of evidence: social skills training**

<b>Outcome</b>	<b>Comparators</b>	<b>Number of Studies Number of Subjects</b>	<b>Strength of Evidence Domain: Study Limitations</b>	<b>Strength of Evidence Domain: Consistency</b>	<b>Strength of Evidence Domain: Directness</b>	<b>Strength of Evidence Domain: Precision</b>	<b>Magnitude of Effect: Summary Effect Size (95% CI)</b>	<b>Strength of Evidence (High, Moderate, Low, Insufficient)</b>
<b>Function</b>	Social skills training vs. usual care	3 RCTs (4 publications) <sup>63,69-71</sup> N = 384	Moderate	Consistent	Direct	Imprecise	Significant improvement in scale scores during treatment for 6 months to 2 years (SMD 0.65 to 1.60)	Low
Function	Social skills training vs. usual care	1 RCT <sup>69,70</sup> N = 183	Moderate	Unknown	Direct	Imprecise	Social function not different from control after treatment cessation (1 study; SMD 0.24; 95% CI -0.05 to 0.53)	Insufficient
<b>Overall Symptoms</b>	Social skills training vs. usual care	2 RCTs <sup>63,71</sup> N = 201	Moderate	Consistent	Direct	Imprecise	Inconclusive: PANSS: SMD -1.50 (95% CI -1.92 to -1.09 and -0.81 (95% CI -1.22 to -0.40) BPRS (mixed population): SMD -0.04 (95% CI -0.33 to 0.25)	Low
Overall Symptoms	Social skills training vs. usual care	1 RCT <sup>69,70</sup> N = 183	Moderate	Unknown	Direct	Imprecise	Inconclusive: Mixed population (55% schizophrenia): no significant effect on symptoms (BPRS) SMD -0.04; 95% CI -0.33 to 0.25.	Insufficient
<b>Negative Symptoms</b>	Social skills training vs. usual care	3 RCTs (4 publications) <sup>63,69-71</sup> N = 384	Moderate	Consistent	Direct	Imprecise	Negative symptoms improved with SST versus usual care based on PANSS-negative and SANS SMD range -0.45 to -1.30) at 6 months to 2 years	Low
Negative Symptoms	Social skills training vs. usual care	1 RCT <sup>69,70</sup> N = 183	Moderate	Unknown	Direct	Imprecise	Negative symptoms were better with SST than usual care 1 year after treatment discontinuation (SMD -0.45; 95% CI -0.74 to -0.15)	Insufficient
<b>Ability to Maintain Treatment</b>	Social skills training vs. usual care	2 RCTs <sup>63,70</sup> N = 384	Moderate	Consistent	Direct	Imprecise	No difference: One year: RR 1.10 (95% CI 0.92 to 1.31) Two-year: RR 1.01; 95% CI 0.88 to 1.16	Low

<b>Outcome</b>	<b>Comparators</b>	<b>Number of Studies Number of Subjects</b>	<b>Strength of Evidence Domain: Study Limitations</b>	<b>Strength of Evidence Domain: Consistency</b>	<b>Strength of Evidence Domain: Directness</b>	<b>Strength of Evidence Domain: Precision</b>	<b>Magnitude of Effect: Summary Effect Size (95% CI)</b>	<b>Strength of Evidence (High, Moderate, Low, Insufficient)</b>
<b>Relapse</b>	Social skills training vs. usual care	1 RCT <sup>63</sup> N = 82	Moderate	Unknown	Direct	Imprecise	Inconclusive: RR 0.50; 95% CI 0.18 to 1.36	Insufficient

BPRS= Brief Psychiatric Rating Scale, CI=confidence interval, RCT=randomized controlled trial, RR=relative risk, SANS=scale for assessment of negative symptoms, SMD=standard mean difference, SST=social skills training

**Appendix Table H-11. Strength of evidence: supported employment**

<b>Outcome</b>	<b>Comparators</b>	<b>Number of Studies Number of Subjects</b>	<b>Strength of Evidence Domain: Study Limitations</b>	<b>Strength of Evidence Domain: Consistency</b>	<b>Strength of Evidence Domain: Directness</b>	<b>Strength of Evidence Domain: Precision</b>	<b>Magnitude of Effect: Summary Effect Size (95% CI)</b>	<b>Strength of Evidence (High, Moderate, Low, Insufficient)</b>
<b>Functional (occupational) - # in competitive employment</b>	Individual placement and support (IPS) vs. standard services	1 trial <sup>72</sup> N=204	Moderate	Unknown	Direct	Imprecise	IPS vs. standard services: 75% vs 27.5% (p<0.001)	Low
	Supported Employment (primarily IPS) vs. vocational training or usual care	1 RCT <sup>73,74</sup> (N = 1,273)	Moderate	Consistent	Indirect for this review question	Precise	IPS vs. vocational training or usual care 55% vs 34% (P<0.001) Subgroup analysis of only patients with schizophrenia: 22% vs. 12% (from figure) P< 0.001 with mixed effects logistic regression	Moderate
<b>Combined SOE</b>								Moderate
<b>Functional (occupational) - Days to first competitive employment</b>	Individual placement and support (IPS) vs. standard services	1 trial <sup>72</sup> N=204	Moderate	Unknown	Direct	Imprecise	IPS vs. standard services: Days to first job, 196.63 vs. 218.84; P = 0.019	Low
<b>Functional (occupational) – Worked more than 20 hours per week</b>	Individual placement and support (IPS) vs. standard services	1 trial <sup>72</sup> N=204	Moderate	Unknown	Direct	Imprecise	IPS vs. standard services: Worked > 20 hrs per week 33.8% vs 13%; P=0.001	Low
	Supported Employment (primarily IPS) vs. vocational training or usual care	1 RCT <sup>73,74</sup> (N = 1,273)	Moderate	Consistent	Indirect for this review question	Precise	IPS vs. vocational training or usual care # working $\geq$ 40 hours per month 51% vs 39%; P <0.001	Moderate
<b>Combined SOE</b>								Moderate
<b>Functional (occupational) – Wages earned</b>	Individual placement and support (IPS) vs. standard services	1 trial <sup>72</sup> N=204	Moderate	Unknown	Direct	Imprecise	IPS vs. standard services: \$2,078/mo vs \$617.59/mo; P< 0.001	Low
	Supported Employment (primarily IPS) vs. vocational training or usual care	1 RCT <sup>73,74</sup> (N = 1,273)	Moderate	Consistent	Indirect for this review question	Precise	IPS vs. vocational training or usual care \$122/mo vs \$99/mo; P=.04	Moderate
<b>Combined SOE</b>								Moderate

Outcome	Comparators	Number of Studies Number of Subjects	Strength of Evidence Domain: Study Limitations	Strength of Evidence Domain: Consistency	Strength of Evidence Domain: Directness	Strength of Evidence Domain: Precision	Magnitude of Effect: Summary Effect Size (95% CI)	Strength of Evidence (High, Moderate, Low, Insufficient)
<b>Functional (occupational) – Weeks worked (mean)</b>	Individual placement and support (IPS) vs. standard services	1 trial <sup>72</sup> N=204	Moderate	Unknown	Direct	Imprecise	IPS vs. standard services: Total weeks worked 29.72 vs 5.45; P<0.001	Low
	Supported Employment (primarily IPS) vs. vocational training	1 SR <sup>75</sup> (N = 2,265)	Moderate	Consistent	Indirect for this review question	Precise	Supported Employment vs. vocational training Days employed Mean Difference 70.63 (95% CI 43.22, 98.04)	Moderate
<b>Combined SOE</b>								Moderate

BPRS=Brief Psychiatric Rating Scale, CI=confidence interval, NNT=number needed to treat, OR=odds ratio, PANSS=positive and negative syndrome scale, QOL=quality of life, RCT=randomized controlled trial, RR=relative risk, SR=systematic review, WBI=Work Behavior Inventory

**Appendix Table H-12. Strength of evidence: supportive therapy**

<b>Outcome</b>	<b>Comparators</b>	<b>Number of Studies Number of Subjects</b>	<b>Strength of Evidence Domain: Study Limitations</b>	<b>Strength of Evidence Domain: Consistency</b>	<b>Strength of Evidence Domain: Directness</b>	<b>Strength of Evidence Domain: Precision</b>	<b>Magnitude of Effect: Summary Effect Size (95% CI)</b>	<b>Strength of Evidence (High, Moderate, Low, Insufficient)</b>
<b>Global Functioning</b>	Supportive therapy vs. standard care	1 SR <sup>76</sup> (2 RCTs; N =289)	Moderate	Consistent	Direct	Imprecise	Inconclusive: GAF-M, n = 29, mean difference 1.40 CI -5.09 to 7.89; GAS, n = 260, mean difference -2.66 CI -6.20 to 0.88.	Low
<b>Social Functioning</b>	Supportive therapy vs. standard care	1 SR <sup>76</sup> (1 RCT; N = 260)	Moderate	Unknown	Direct	Imprecise	Inconclusive: SFS: n = 260, mean difference -0.67 CI -7.05 to 5.71.	Insufficient
<b>Quality of Life</b>	Supportive therapy vs. standard care	1 SR <sup>76</sup> (1 RCT; N = 260)	Moderate	Unknown	Direct	Imprecise	Inconclusive: Rosenberg Self-Esteem Scale (RSES) n = 260, MD -1.21 CI -2.85 to 0.43. Well-being scale (WBS) score = 260,MD-2.73 CI -6.04 to 0.58. Global health quotient (GHQ) n = 260, MD -2.45 CI -2.41 to 7.31.	Insufficient
<b>Relapse</b>	Supportive therapy vs. standard care	1 SR <sup>76</sup> (1 RCT, N = 54)	Moderate	Unknown	Direct	Imprecise	Inconclusive: Medium term followup (13 to 26 weeks, N= 54, RR 0.12 CI 0.01 to 2.11s), or long term followup (more than 26 weeks, n = 54, RR 0.96 CI 0.44 to 2.11)	Insufficient
<b>Core Symptoms</b>	Supportive therapy vs. standard care	1 SR <sup>76</sup> (2 RCTs, N = 167)	Moderate	Unknown	Direct	Imprecise	Inconclusive: PANSS: Short term (13 to 26 weeks; N = 131 Mean Difference -4.42 (95% CI -10.13, 1.29). Long term (more than 26 weeks, n = 36, Mean Difference 4.70 (95% CI -6.71, 16.11).	Insufficient

<b>Outcome</b>	<b>Comparators</b>	<b>Number of Studies Number of Subjects</b>	<b>Strength of Evidence Domain: Study Limitations</b>	<b>Strength of Evidence Domain: Consistency</b>	<b>Strength of Evidence Domain: Directness</b>	<b>Strength of Evidence Domain: Precision</b>	<b>Magnitude of Effect: Summary Effect Size (95% CI)</b>	<b>Strength of Evidence (High, Moderate, Low, Insufficient)</b>
<b>Negative Symptoms</b>	Supportive therapy vs. standard care	1 SR <sup>76</sup> (1 RCT, N = 47)	Moderate	Unknown	Direct	Imprecise	Inconclusive: Short term: 10.19 and 10.73; long-term: 9.90 and 11.46 (no statistical analysis because of skewed data).	Insufficient
<b>Discontinuing Treatment</b>	Supportive therapy vs. standard care	1 SR <sup>76</sup> (4 RCTs, N = 354)	Moderate	Consistent	Direct	Imprecise	Inconclusive: Relative Risk 0.86 (95% CI 0.53, 1.40)	Low

CI=confidence interval, GAF=global assessment functioning, GAS=global assessment scale, GHQ=global health quotient, MD=mean difference, PANSS=positive and negative syndrome scale, RCT=randomized controlled trial, RR=relative risk, RSES=Rosenberg Self-Esteem Scale, SR=systematic review

**Appendix Table H-13. Strength of evidence: early interventions for patients with first-episode psychosis**

<b>Outcome</b>	<b>Number of Studies Number of Subjects</b>	<b>Strength of Evidence Domain: Study Limitations</b>	<b>Strength of Evidence Domain: Consistency</b>	<b>Strength of Evidence Domain: Directness</b>	<b>Strength of Evidence Domain: Precision</b>	<b>Magnitude of Effect: Summary Effect Size (95% CI)</b>	<b>Strength of Evidence (High, Moderate, Low, Insufficient)</b>
<b>Functional: Global (GAS, GAF)</b>	1 SR <sup>77</sup> , 1 RCT <sup>78</sup> N=369 (two-year data only) 2 RCTs N=744 <sup>79</sup> N=98 <sup>80</sup>	Moderate	Consistent	Direct	Precise	GAS and GAF results only Team-based CSC result in higher functioning scores. Pooled WMD: 3.88 (95% CI = 0.91 to 6.85) I <sup>2</sup> = 64%	Moderate
<b>Functional: Working or School</b>	1 SR <sup>77</sup> , 1 RCT <sup>78</sup> (OPUS- Scandinavia) N=547)  2 RCTs N=125 <sup>80</sup> N=744 <sup>79</sup>	Moderate	Consistent	Direct	Precise	Significantly more people (22%) are working or in school with team- based CSC Pooled RR 1.22 (95% CI = 1.01 to 1.47)	Moderate
<b>Functional: Housing Status</b>	1 SR <sup>77</sup> 1 RCT N=547 <sup>78</sup> )  1 RCT N=128 <sup>80</sup>	Moderate	Consistent	Direct	Imprecise	No significant difference between groups Pooled RR 1.06 (95% CI = 0.86 to 1.30)	Low
<b>Health-Related Quality of Life</b>	2 RCTs N=92 <sup>80</sup> N=403 <sup>81</sup>	Moderate	Consistent	Direct	Precise	Team-based CSC results in greater quality of life ratings as endpoint. Pooled effect size 0.84 (95% CI = 0.14 to 1.55); P = 0.02. Cochrane Q for heterogeneity = 7.43, p = 0.0064 (significant heterogeneity)	Moderate

Outcome	Number of Studies Number of Subjects	Strength of Evidence Domain: Study Limitations	Strength of Evidence Domain: Consistency	Strength of Evidence Domain: Directness	Strength of Evidence Domain: Precision	Magnitude of Effect: Summary Effect Size (95% CI)	Strength of Evidence (High, Moderate, Low, Insufficient)
<b>Core Illness Symptoms (PANSS)</b>	3 RCTs N=99 <sup>80</sup> N=403 <sup>81</sup> N=1,184 <sup>79</sup>	Moderate	Inconsistent	Direct	Precise	No clinically important difference between groups in endpoint scores. Pooled WMD of all 3 RCTs = -2.53 (95% CI -5.45 to 0.39; I <sup>2</sup> = 55%). Sensitivity analysis removing a study with a 5.9-point difference at baseline results in a very small but statistically significant difference and no heterogeneity. Pooled WMD of 2 RCTs = -1.40 (95% CI -2.25 to -0.55; Cochran Q for heterogeneity = 0.0014 (df = 1) P = 0.97)	Low
<b>Core Illness Symptoms (Calgary Depression Scale)</b>	2 RCTs N=99 <sup>80</sup> N=205 <sup>82</sup>	Moderate	Consistent	Direct	Precise	No significant difference between groups in endpoint scores. Pooled WMD -0.44 (95% CI -1.08 to 0.20). Heterogeneity: Cochran Q = 0.528157 (df = 1) P = 0.4674	Moderate
<b>Discontinuation of Treatment</b>	2 RCTs N=1239 <sup>79</sup> N=136 <sup>83</sup>	Moderate	Consistent	Direct	Precise	Team-based CSC had a significantly greater rate of treatment retention compared to standard care Pooled relative risk = 1.27 (95% CI 1.16 to 1.38); Cochran Q = 0.03 (df = 1) P = 0.86	High
<b>Rates of Relapse</b>	2 RCTs N=1239 <sup>79</sup> N=122 <sup>83</sup>	Moderate	Consistent	Direct	Imprecise	Participants in team-based CSC were significantly less likely to relapse than those in standard care. Pooled relative risk = 0.64 (95% CI 0.52 to 0.79) Cochran Q = 0.024 (df = 1) P = 0.88	Moderate

CI=confidence interval, FEP=first episode psychosis, GAF=global assessment functioning, GAS=global assessment scale, GAF=Global Assessment of Functioning, GAS=Global Assessment Scale, PANSS=Positive and Negative Syndrome Scale, RCT=randomized controlled trial, RR=relative risk, SR=systematic review, WMD=weighted mean difference

**Appendix Table H-14. Strength of evidence: co-occurring substance use and schizophrenia**

<b>Outcome</b>	<b>Number of Studies Number of Subjects</b>	<b>Strength of Evidence Domain: Study Limitations</b>	<b>Strength of Evidence Domain: Consistency</b>	<b>Strength of Evidence Domain: Directness</b>	<b>Strength of Evidence Domain: Precision</b>	<b>Magnitude of Effect: Summary Effect Size (95% CI)</b>	<b>Strength of Evidence (High, Moderate, Low, Insufficient)</b>
<b>Function: Global Function (Integrated: GAF; 6 months)</b>	1 SR <sup>84</sup> (1 RCT; N=162)	Moderate	Unknown	Direct	Imprecise	Inconclusive: MD 1.10 (-1.58 to 3.78)	Low
<b>Function: Global Function (Integrated: GAF; 18 months)</b>	1 SR <sup>84</sup> (1 RCT; N=176)	Moderate	Unknown	Direct	Imprecise	Inconclusive: MD 1.00 (-1.58 to 3.58)	Low
<b>Function: Global Function (Integrated: GAF; 24 months)</b>	1 SR <sup>84</sup> (1 RCT; N=166)	Moderate	Unknown	Direct	Imprecise	Inconclusive: MD 1.70 (-1.18 to 4.58)	Low
<b>Function: Global Function (Integrated: GAF; 30 months)</b>	1 SR <sup>84</sup> (1 RCT; N=164)	Moderate	Unknown	Direct	Imprecise	Inconclusive: MD -0.60 (-3.56 to 2.36)	Low
<b>Function: Global Function (Integrated: GAF; 36 months)</b>	1 SR <sup>84</sup> (1 RCT; N=170)	Moderate	Unknown	Direct	Imprecise	Inconclusive: MD 0.40 (-2.47 to 3.27)	Low
<b>Function: Global Function (Non-Integrated: mean RFS score; 6 months)</b>	1 SR <sup>84</sup> (1 RCT; N=50)	Moderate	Unknown	Direct	Imprecise	Inconclusive: MD -0.78 (-2.91 to 1.35)	Insufficient
<b>Function: Global Function (Non-Integrated: mean RFS score; 6 months)</b>	1 SR <sup>84</sup> (1 RCT; N=29)	Moderate	Unknown	Direct	Imprecise	MD -2.67 (-5.28 to -0.06)	Insufficient
<b>Ability to maintain treatment (6 months)</b>	1 SR <sup>84</sup> (3 RCTs; N=134)	Moderate	Consistent	Direct	Imprecise	Inconclusive: RR 1.23 (0.73 to 2.06)	Insufficient

<b>Outcome</b>	<b>Number of Studies Number of Subjects</b>	<b>Strength of Evidence Domain: Study Limitations</b>	<b>Strength of Evidence Domain: Consistency</b>	<b>Strength of Evidence Domain: Directness</b>	<b>Strength of Evidence Domain: Precision</b>	<b>Magnitude of Effect: Summary Effect Size (95% CI)</b>	<b>Strength of Evidence (High, Moderate, Low, Insufficient)</b>
<b>Ability to maintain treatment (18 months)</b>	1 SR <sup>84</sup> (3 RCTs; N=134)	Moderate	Consistent	Direct	Imprecise	Inconclusive: RR 1.35 (0.83 to 2.19)	Insufficient

GAF=global assessment functioning, MD=mean difference, RCT=randomized controlled trial, RFS=role functioning score, SR=systematic review

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# Appendix I. Strength of Evidence—Drug Comparisons

Appendix Table I-1. Summary of findings for aripiprazole LAI-1 versus other SGAs

Drug	Comparator	Function	QOL	Response	Mortality	Self-harm	Symptoms	Any AE	W/D AEs
Aripiprazole LAI-1	Aripiprazole	–	No difference*	No difference*	–	–	–	No difference*	No difference*
Aripiprazole LAI-1	Aripiprazole LAI-6w	–	–	–	–	–	–	–	–
Aripiprazole LAI-1	Asenapine	–	–	No difference*	–	–	–	–	No difference*
Aripiprazole LAI-1	Brexpiprazole	–	–	No difference*	–	–	–	–	No difference*
Aripiprazole LAI-1	Cariprazine	–	–	No difference*	–	–	–	–	No difference*
Aripiprazole LAI-1	Clozapine	–	–	No difference*	–	–	–	–	No difference*
Aripiprazole LAI-1	Iloperidone	–	–	–	–	–	–	–	Moderate (2)*
Aripiprazole LAI-1	Lurasidone	–	–	–	–	–	–	–	No difference*
Aripiprazole LAI-1	Olanzapine	–	–	No difference*	–	–	–	–	No difference*
Aripiprazole LAI-1	Olanzapine LAI	–	–	–	–	–	–	–	No difference*
Aripiprazole LAI-1	Paliperidone	–	–	No difference*	–	–	–	Insufficient	No difference*
Aripiprazole LAI-1	Paliperidone LAI-1	–	Insufficient	–	–	–	–	–	No difference*
Aripiprazole LAI-1	Paliperidone LAI-3	–	–	–	–	–	–	–	No difference*
Aripiprazole LAI-1	Quetiapine	–	–	No difference*	–	–	–	–	No difference*
Aripiprazole LAI-1	Quetiapine ER	–	–	–	–	–	–	–	No difference*
Aripiprazole LAI-1	Risperidone	–	–	No difference*	–	–	–	–	No difference*
Aripiprazole LAI-1	Risperidone LAI	–	–	–	–	–	–	–	No difference*
Aripiprazole LAI-1	Ziprasidone	–	–	No difference*	–	–	–	–	No difference*

\* = Low SOE, \*\* = Moderate SOE, \*\*\* = High SOE, – = No data, (1) = Estimate favors Drug 1, (2) = Estimate favors Drug 2

Appendix Table I-2. Summary of findings for aripiprazole LAI 4-6w versus other SGAs

Drug	Comparator	Function	QOL	Response	Mortality	Self-harm	Symptoms	Any AE	W/D AEs
Aripiprazole LAI-6w	Aripiprazole	-	-	-	-	-	-	-	-
Aripiprazole LAI-6w	Aripiprazole LAI-1	-	-	-	-	-	-	-	-
Aripiprazole LAI-6w	Asenapine	-	-	-	-	-	-	-	-
Aripiprazole LAI-6w	Brexpiprazole	-	-	-	-	-	-	-	-
Aripiprazole LAI-6w	Cariprazine	-	-	-	-	-	-	-	-
Aripiprazole LAI-6w	Clozapine	-	-	-	-	-	-	-	-
Aripiprazole LAI-6w	Iloperidone	-	-	-	-	-	-	-	-
Aripiprazole LAI-6w	Lurasidone	-	-	-	-	-	-	-	-
Aripiprazole LAI-6w	Olanzapine	-	-	-	-	-	-	-	-
Aripiprazole LAI-6w	Olanzapine LAI	-	-	-	-	-	-	-	-
Aripiprazole LAI-6w	Paliperidone	-	-	-	-	-	-	-	-
Aripiprazole LAI-6w	Paliperidone LAI-1	-	-	-	-	-	-	-	-
Aripiprazole LAI-6w	Paliperidone LAI-3	-	-	-	-	-	-	-	-
Aripiprazole LAI-6w	Quetiapine	-	-	-	-	-	-	-	-
Aripiprazole LAI-6w	Quetiapine ER	-	-	-	-	-	-	-	-
Aripiprazole LAI-6w	Risperidone	-	-	-	-	-	-	-	-
Aripiprazole LAI-6w	Risperidone LAI	-	-	-	-	-	-	-	-
Aripiprazole LAI-6w	Ziprasidone	-	-	-	-	-	-	-	-

\* = Low SOE, \*\* = Moderate SOE, \*\*\* = High SOE, - = No data, (1) = Estimate favors Drug 1, (2) = Estimate favors Drug 2

**Appendix Table I-3. Summary of findings for aripiprazole versus other SGAs**

Drug	Comparator	Function	QOL	Response	Mortality	Self-harm	Symptoms	Any AE	W/D AEs
Aripiprazole	Aripiprazole LAI-1	–	No difference*	No difference*	–	–	–	No difference*	No difference*
Aripiprazole	Aripiprazole LAI-6w	–	–	–	–	–	–	–	–
Aripiprazole	Asenapine	–	–	No difference*	–	–	–	–	No difference*
Aripiprazole	Brexiprazole	–	–	No difference*	Insufficient	–	Insufficient	Insufficient	No difference*
Aripiprazole	Cariprazine	–	–	No difference*	–	–	–	–	No difference*
Aripiprazole	Clozapine	–	–	No difference*	–	Insufficient	–	–	No difference*
Aripiprazole	lloperidone	–	–	–	–	–	–	–	No difference*
Aripiprazole	Lurasidone	–	–	–	–	–	–	–	No difference*
Aripiprazole	Olanzapine	–	–	No difference*	–	Insufficient	–	–	No difference*
Aripiprazole	Olanzapine LAI	–	–	No difference*	–	–	–	–	No difference*
Aripiprazole	Paliperidone	–	–	No difference*	–	–	–	–	No difference*
Aripiprazole	Paliperidone LAI-1	–	Insufficient	–	–	–	–	–	No difference*
Aripiprazole	Paliperidone LAI-3	–	–	–	–	–	–	–	No difference*
Aripiprazole	Quetiapine	–	–	No difference*	–	Insufficient	–	–	No difference*
Aripiprazole	Quetiapine ER	–	–	No difference*	–	–	–	–	No difference*
Aripiprazole	Risperidone	–	–	No difference*	–	Insufficient	–	No difference*	No difference*
Aripiprazole	Risperidone LAI	–	–	–	–	Insufficient	–	–	No difference*
Aripiprazole	Ziprasidone	–	–	No difference*	–	Insufficient	–	–	Medium* (1)
							Possibly data out there		

\* = Low SOE, \*\* = Moderate SOE, \*\*\* = High SOE, – = No data, (1) = Estimate favors Drug 1, (2) = Estimate favors Drug 2

**Appendix Table I-4. Summary of findings for asenapine versus other SGAs**

Drug	Comparator	Function	QOL	Response	Mortality	Self-harm	Symptoms	Any AE	W/D AEs
Asenapine	Aripiprazole	–	–	No difference*	–	–	–	–	No difference*
Asenapine	Aripiprazole LAI-1	–	–	No difference*	–	–	–	–	No difference*
Asenapine	Aripiprazole LAI-6w	–	–	–	–	–	–	–	–
Asenapine	Brexpiprazole	–	–	No difference*	–	–	–	–	No difference*
Asenapine	Cariprazine	–	–	No difference*	–	–	–	–	No difference*
Asenapine	Clozapine	–	–	No difference*	–	–	–	–	No difference*
Asenapine	lloperidone	–	–	–	–	–	–	–	No difference*
Asenapine	Lurasidone	–	–	–	–	–	–	–	No difference*
Asenapine	Olanzapine	–	–	No difference*	No difference*	Insufficient	–	No difference**	No difference*
Asenapine	Olanzapine LAI	–	–	–	–	–	–	–	–
Asenapine	Paliperidone	–	–	No difference*	–	–	–	–	No difference*
Asenapine	Paliperidone LAI-1	–	–	–	–	–	–	–	No difference*
Asenapine	Paliperidone LAI-3	–	–	–	–	–	–	–	No difference*
Asenapine	Quetiapine	–	–	No difference*	–	–	–	–	No difference*
Asenapine	Quetiapine ER	–	–	–	–	–	–	–	No difference*
Asenapine	Risperidone	–	–	No difference*	–	–	–	Insufficient	No difference*
Asenapine	Risperidone LAI	–	–	–	–	–	–	–	No difference*
Asenapine	Ziprasidone	–	–	No difference*	–	–	–	–	No difference*

\* = Low SOE, \*\* = Moderate SOE, \*\*\* = High SOE, – = No data, (1) = Estimate favors Drug 1, (2) = Estimate favors Drug 2

**Appendix Table I-5. Summary of findings for brexpiprazole versus other SGAs**

Drug	Comparator	Function	QOL	Response	Mortality	Self-harm	Symptoms	Any AE	W/D AEs
Brexpiprazole	Aripiprazole	–	–	No difference*	Insufficient	–	Insufficient	Insufficient	No difference*
Brexpiprazole	Aripiprazole LAI-1	–	–	No difference*	–	–	–	–	No difference*
Brexpiprazole	Aripiprazole LAI-6w	–	–	–	–	–	–	–	–
Brexpiprazole	Asenapine	–	–	No difference*	–	–	–	–	No difference*
Brexpiprazole	Cariprazine	–	–	No difference*	–	–	–	–	No difference*
Brexpiprazole	Clozapine	–	–	No difference*	–	–	–	–	No difference*
Brexpiprazole	lloperidone	–	–	–	–	–	–	–	No difference*
Brexpiprazole	Lurasidone	–	–	–	–	–	–	–	No difference*
Brexpiprazole	Olanzapine	–	–	No difference*	–	–	–	–	No difference*
Brexpiprazole	Olanzapine LAI	–	–	–	–	–	–	–	No difference*
Brexpiprazole	Paliperidone	–	–	No difference*	–	–	–	–	No difference*
Brexpiprazole	Paliperidone LAI-1	–	–	–	–	–	–	–	No difference*
Brexpiprazole	Paliperidone LAI-3	–	–	–	–	–	–	–	No difference*
Brexpiprazole	Quetiapine	–	–	No difference*	–	–	–	–	No difference*
Brexpiprazole	Quetiapine ER	–	–	–	–	–	–	–	No difference*
Brexpiprazole	Risperidone	–	–	No difference*	–	–	–	–	No difference*
Brexpiprazole	Risperidone LAI	–	–	–	–	–	–	–	No difference*
Brexpiprazole	Ziprasidone	–	–	No difference*	–	–	–	–	No difference*

\* = Low SOE, \*\* = Moderate SOE, \*\*\* = High SOE, – = No data, (1) = Estimate favors Drug 1, (2) = Estimate favors Drug 2

**Appendix Table I-6. Summary of findings for cariprazine versus other SGAs**

Drug	Comparator	Function	QOL	Response	Mortality	Self-harm	Symptoms	Any AE	W/D AEs
Cariprazine	Aripiprazole	–	–	No difference*	–	–	–	–	No difference*
Cariprazine	Aripiprazole LAI-1	–	–	No difference*	–	–	–	–	No difference*
Cariprazine	Aripiprazole LAI-6w	–	–	–	–	–	–	–	–
Cariprazine	Asenapine	–	–	No difference*	–	–	–	–	No difference*
Cariprazine	Brexpiprazole	–	–	No difference*	–	–	–	–	No difference*
Cariprazine	Clozapine	–	–	No difference*	–	–	–	–	Moderate (2)*
Cariprazine	lloperidone	–	–	–	–	–	–	–	No difference*
Cariprazine	Lurasidone	–	–	–	–	–	–	–	No difference*
Cariprazine	Olanzapine	–	–	No difference*	–	–	–	–	No difference*
Cariprazine	Olanzapine LAI	–	–	–	–	–	–	–	No difference*
Cariprazine	Paliperidone	–	–	No difference*	–	–	–	–	No difference*
Cariprazine	Paliperidone LAI-1	–	–	–	–	–	–	–	No difference*
Cariprazine	Paliperidone LAI-3	–	–	–	–	–	–	–	No difference*
Cariprazine	Quetiapine	–	–	No difference*	–	–	–	–	No difference*
Cariprazine	Quetiapine ER	–	–	–	–	–	–	–	No difference*
Cariprazine	Risperidone	–	–	No difference*	–	–	–	–	No difference*
Cariprazine	Risperidone LAI	–	–	–	–	–	–	Insufficient	No difference*
Cariprazine	Ziprasidone	–	–	No difference*	–	–	–	–	No difference*

\* = Low SOE, \*\* = Moderate SOE, \*\*\* = High SOE, – = No data, (1) = Estimate favors Drug 1, (2) = Estimate favors Drug 2

**Appendix Table I-7. Summary of findings for clozapine versus other SGAs**

Drug	Comparator	Function	QOL	Response	Mortality	Self-harm	Symptoms	Any AE	W/D AEs
Clozapine	Aripiprazole	–	–	No difference*	–	–	Small (1)*	No difference*	Moderate (2)*
Clozapine	Aripiprazole LAI-1	–	–	No difference*	–	–	Small (1)*	–	No difference*
Clozapine	Aripiprazole LAI-6w	–	–	–	–	–	Small (1)*	–	–
Clozapine	Asenapine	–	–	No difference*	–	–	Small (1)*	–	No difference*
Clozapine	Brexipiprazole	–	–	No difference*	–	–	Small (1)*	–	No difference*
Clozapine	Cariprazine	–	–	No difference*	–	–	Small (1)*	–	Moderate (2)*
Clozapine	Iloperidone	–	–	–	–	–	Small (1)*	Insufficient	Large (2)*
Clozapine	Lurasidone	–	–	–	–	–	Small (1)*	Insufficient	No difference*
Clozapine	Olanzapine	Insufficient	–	No difference*	Insufficient	Small (1)*	No difference*	–	Moderate (2)*
Clozapine	Olanzapine LAI	–	–	–	–	–	Small (1)*	–	No difference*
Clozapine	Paliperidone	–	–	No difference*	–	–	Small (1)*	–	No difference*
Clozapine	Paliperidone LAI-1	–	–	–	–	–	Small (1)*	–	No difference*
Clozapine	Paliperidone LAI-3	–	–	–	–	–	Small (1)*	–	No difference*
Clozapine	Quetiapine	–	–	No difference*	Insufficient	Insufficient	Small (1)*	Insufficient	No difference*
Clozapine	Quetiapine ER	–	–	–	–	–	Small (1)*	–	No difference*
Clozapine	Risperidone	No difference*	–	No difference*	Insufficient	Insufficient	Small (1)*	No difference*	No difference*
Clozapine	Risperidone LAI	–	–	–	–	–	Small (1)*	–	Large (2)*
Clozapine	Ziprasidone	–	–	No difference*	–	–	Small (1)*	Insufficient	No difference*

\* = Low SOE, \*\* = Moderate SOE, \*\*\* = High SOE, – = No data, (1) = Estimate favors Drug 1, (2) = Estimate favors Drug 2

**Appendix Table I-8. Summary of findings for iloperidone versus other SGAs**

Drug	Comparator	Function	QOL	Response	Mortality	Self-harm	Symptoms	Any AE	W/D AEs
Iloperidone	Aripiprazole	-	-	-	-	-	-	-	No difference*
Iloperidone	Aripiprazole LAI-1	-	-	-	-	-	-	-	No difference*
Iloperidone	Aripiprazole LAI-6w	-	-	-	-	-	-	-	-
Iloperidone	Asenapine	-	-	-	-	-	-	-	No difference*
Iloperidone	Brexpiprazole	-	-	-	-	-	-	-	No difference*
Iloperidone	Cariprazine	-	-	-	-	-	-	-	No difference*
Iloperidone	Clozapine	-	-	-	-	-	-	Insufficient	Moderate (1)*
Iloperidone	Lurasidone	-	-	-	-	-	-	Insufficient	No difference*
Iloperidone	Olanzapine	-	-	-	-	-	-	-	No difference*
Iloperidone	Olanzapine LAI	-	-	-	-	-	-	-	No difference*
Iloperidone	Paliperidone	-	-	-	-	-	Small (2)*	-	No difference*
Iloperidone	Paliperidone LAI-1	-	-	-	-	-	-	-	No difference*
Iloperidone	Paliperidone LAI-3	-	-	-	-	-	-	-	No difference*
Iloperidone	Quetiapine	-	-	-	-	-	-	-	No difference*
Iloperidone	Quetiapine ER	-	-	-	-	-	-	-	No difference*
Iloperidone	Risperidone	-	-	-	-	-	-	Insufficient	No difference*
Iloperidone	Risperidone LAI	-	-	-	-	-	-	-	No difference*
Iloperidone	Ziprasidone	-	-	-	-	-	-	Insufficient	No difference*

\* = Low SOE, \*\* = Moderate SOE, \*\*\* = High SOE, - = No data, (1) = Estimate favors Drug 1, (2) = Estimate favors Drug 2

**Appendix Table I-9. Summary of findings for lurasidone versus other SGAs**

Drug	Comparator	Function	QOL	Response	Mortality	Self-harm	Symptoms	Any AE	W/D AEs
Lurasidone	Aripiprazole	-	-	-	-	-	-	-	No difference*
Lurasidone	Aripiprazole LAI-1	-	-	-	-	-	-	-	No difference*
Lurasidone	Aripiprazole LAI-6w	-	-	-	-	-	-	-	-
Lurasidone	Asenapine	-	-	-	-	-	-	-	No difference*
Lurasidone	Brexpiprazole	-	-	-	-	-	-	-	No difference*
Lurasidone	Cariprazine	-	-	-	-	-	-	-	No difference*
Lurasidone	Clozapine	-	-	-	-	-	-	Insufficient	No difference*
Lurasidone	Iloperidone	-	-	-	-	-	-	Insufficient	No difference*
Lurasidone	Olanzapine	-	-	-	-	-	-	Insufficient	Moderate (2)*
Lurasidone	Olanzapine LAI	-	-	-	-	-	-	Insufficient	No difference*
Lurasidone	Paliperidone	-	-	-	-	-	-	-	Small (2)*
Lurasidone	Paliperidone LAI-1	-	-	-	-	-	-	-	No difference*
Lurasidone	Paliperidone LAI-3	-	-	-	-	-	Moderate (2)*	-	No difference*
Lurasidone	Quetiapine	-	-	-	-	-	-	-	No difference*
Lurasidone	Quetiapine ER	-	-	-	-	-	-	-	No difference*
Lurasidone	Risperidone	-	-	-	-	-	-	Insufficient	No difference*
Lurasidone	Risperidone LAI	-	-	-	-	-	-	-	Moderate (2)*
Lurasidone	Ziprasidone	-	-	-	-	-	-	Insufficient	No difference*

\* = Low SOE, \*\* = Moderate SOE, \*\*\* = High SOE, - = No data, (1) = Estimate favors Drug 1, (2) = Estimate favors Drug 2

Appendix Table I-10. Summary of findings for olanzapine LAI versus other SGAs

Drug	Comparator	Function	QOL	Response	Mortality	Self-harm	Symptoms	Any AE	W/D AEs
Olanzapine LAI	Aripiprazole	-	-	-	-	-	-	-	No difference*
Olanzapine LAI	Aripiprazole LAI-1	-	-	-	-	-	-	-	No difference*
Olanzapine LAI	Aripiprazole LAI-6w	-	-	-	-	-	-	-	-
Olanzapine LAI	Asenapine	-	-	-	-	-	-	-	No difference*
Olanzapine LAI	Brexpiprazole	-	-	-	-	-	-	-	No difference*
Olanzapine LAI	Cariprazine	-	-	-	-	-	-	-	No difference*
Olanzapine LAI	Clozapine	-	-	-	-	-	-	-	No difference*
Olanzapine LAI	Iloperidone	-	-	-	-	-	-	-	No difference*
Olanzapine LAI	Lurasidone	-	-	-	-	-	-	Insufficient	No difference*
Olanzapine LAI	Olanzapine	-	-	-	-	-	-	Insufficient	No difference*
Olanzapine LAI	Paliperidone	-	-	-	-	-	-	-	No difference*
Olanzapine LAI	Paliperidone LAI-1	-	-	-	-	-	-	-	No difference*
Olanzapine LAI	Paliperidone LAI-3	-	-	-	-	-	-	-	No difference*
Olanzapine LAI	Quetiapine	-	-	-	-	-	-	-	No difference*
Olanzapine LAI	Quetiapine ER	-	-	-	-	-	-	-	No difference*
Olanzapine LAI	Risperidone	-	-	-	-	-	-	-	No difference*
Olanzapine LAI	Risperidone LAI	-	-	-	-	-	-	-	No difference*
Olanzapine LAI	Ziprasidone	-	-	-	-	-	-	-	No difference*

\* = Low SOE, \*\* = Moderate SOE, \*\*\* = High SOE, - = No data, (1) = Estimate favors Drug 1, (2) = Estimate favors Drug 2

**Appendix Table I-11. Summary of findings for olanzapine versus other SGAs**

Drug	Comparator	Function	QOL	Response	Mortality	Self-harm	Symptoms	Any AE	W/D AEs
Olanzapine	Aripiprazole	–	–	No difference*	–	–	Small (1)*	–	No difference*
Olanzapine	Aripiprazole LAI-1	–	–	No difference*	–	–	–	–	No difference*
Olanzapine	Aripiprazole LAI-6w	–	–	–	–	–	–	–	–
Olanzapine	Asenapine	–	–	No difference*	No difference*	Insufficient	Small (1)*	No difference**	No difference*
Olanzapine	Brexpiprazole	–	–	No difference*	–	–	Small (1)*	–	No difference*
Olanzapine	Cariprazine	–	–	No difference*	–	–	Small (1)*	–	No difference*
Olanzapine	Clozapine	No difference*	No difference*	No difference*	–	Small (2)*	No difference*	–	Moderate (1)*
Olanzapine	Iloperidone	–	–	–	–	–	Small (1)*	–	No difference*
Olanzapine	Lurasidone	–	–	–	–	–	Small (1)*	Insufficient	Moderate (1)*
Olanzapine	Olanzapine LAI	–	–	–	–	–	–	Insufficient	No difference*
Olanzapine	Paliperidone	Insufficient	–	No difference*	–	–	No difference*	No difference*	No difference*
Olanzapine	Paliperidone LAI-1	–	–	–	–	–	–	–	No difference*
Olanzapine	Paliperidone LAI-3	–	–	–	–	–	–	–	No difference*
Olanzapine	Quetiapine	No difference*	No difference**	Moderate (1)*	No difference*	–	Small (1)*	–	Moderate (1)*
Olanzapine	Quetiapine ER	–	–	–	–	–	–	–	No difference*
Olanzapine	Risperidone	No difference*	No difference**	No difference*	No difference*	–	No difference*	–	Moderate (1)*
Olanzapine	Risperidone LAI	–	No difference*	–	–	–	–	–	No difference*
Olanzapine	Ziprasidone	–	No difference**	No difference*	–	–	Small (1)*	–	Moderate (1)*

\* = Low SOE, \*\* = Moderate SOE, \*\*\* = High SOE, – = No data, (1) = Estimate favors Drug 1, (2) = Estimate favors Drug 2

Appendix Table I-12. Summary of findings for paliperidone LAI-1 versus other SGAs

Drug	Comparator	Function	QOL	Response	Mortality	Self-harm	Symptoms	Any AE	W/D AEs
Paliperidone LAI-1	Aripiprazole	–	–	–	–	–	–	–	No difference*
Paliperidone LAI-1	Aripiprazole LAI-1	–	Insufficient	–	–	–	–	–	No difference*
Paliperidone LAI-1	Aripiprazole LAI-6w	–	–	–	–	–	–	–	–
Paliperidone LAI-1	Asenapine	–	–	–	–	–	–	–	No difference*
Paliperidone LAI-1	Brexpiprazole	–	–	–	–	–	–	–	No difference*
Paliperidone LAI-1	Cariprazine	–	–	–	–	–	–	–	No difference*
Paliperidone LAI-1	Clozapine	–	–	–	–	–	–	–	No difference*
Paliperidone LAI-1	Iloperidone	–	–	–	–	–	–	–	No difference*
Paliperidone LAI-1	Lurasidone	–	–	–	–	–	–	–	No difference*
Paliperidone LAI-1	Olanzapine	–	–	–	–	–	–	–	No difference*
Paliperidone LAI-1	Olanzapine LAI	–	–	–	–	–	–	–	No difference*
Paliperidone LAI-1	Paliperidone	–	–	–	Insufficient	–	–	–	No difference*
Paliperidone LAI-1	Paliperidone LAI-3	–	–	–	Insufficient	–	–	Insufficient	No difference*
Paliperidone LAI-1	Quetiapine	–	–	–	–	–	–	–	No difference*
Paliperidone LAI-1	Quetiapine ER	–	–	–	–	–	–	–	No difference*
Paliperidone LAI-1	Risperidone	–	–	–	–	–	–	–	No difference*
Paliperidone LAI-1	Risperidone LAI	No difference*	–	–	No difference*	Insufficient	–	No difference*	Moderate (2)*
Paliperidone LAI-1	Ziprasidone	–	–	–	–	–	–	–	No difference*

\* = Low SOE, \*\* = Moderate SOE, \*\*\* = High SOE, – = No data, (1) = Estimate favors Drug 1, (2) = Estimate favors Drug 2

Appendix Table I-13. Summary of findings for paliperidone LAI-3 versus other SGAs

Drug	Comparator	Function	QOL	Response	Mortality	Self-harm	Symptoms	Any AE	W/D AEs
Paliperidone LAI-3	Aripiprazole	-	-	-	-	-	-	-	No difference*
Paliperidone LAI-3	Aripiprazole LAI-1	-	-	-	-	-	-	-	No difference*
Paliperidone LAI-3	Aripiprazole LAI-6w	-	-	-	-	-	-	-	-
Paliperidone LAI-3	Asenapine	-	-	-	-	-	-	-	No difference*
Paliperidone LAI-3	Brexpiprazole	-	-	-	-	-	-	-	No difference*
Paliperidone LAI-3	Cariprazine	-	-	-	-	-	-	-	No difference*
Paliperidone LAI-3	Clozapine	-	-	-	-	-	-	-	No difference*
Paliperidone LAI-3	Iloperidone	-	-	-	-	-	-	-	No difference*
Paliperidone LAI-3	Lurasidone	-	-	-	-	-	-	-	No difference*
Paliperidone LAI-3	Olanzapine	-	-	-	-	-	-	-	No difference*
Paliperidone LAI-3	Olanzapine LAI	-	-	-	-	-	-	-	No difference*
Paliperidone LAI-3	Paliperidone	-	-	-	-	-	-	-	No difference*
Paliperidone LAI-3	Paliperidone LAI-1	-	-	-	Insufficient	-	-	Insufficient	No difference*
Paliperidone LAI-3	Quetiapine	-	-	-	-	-	-	-	No difference*
Paliperidone LAI-3	Quetiapine ER	-	-	-	-	-	-	-	No difference*
Paliperidone LAI-3	Risperidone	-	-	-	-	-	-	-	No difference*
Paliperidone LAI-3	Risperidone LAI	-	-	-	-	-	-	-	No difference*
Paliperidone LAI-3	Ziprasidone	-	-	-	-	-	-	-	No difference*

\* = Low SOE, \*\* = Moderate SOE, \*\*\* = High SOE, - = No data, (1) = Estimate favors Drug 1, (2) = Estimate favors Drug 2

**Appendix Table I-14. Summary of findings for paliperidone versus other SGAs**

Drug	Comparator	Function	QOL	Response	Mortality	Self-harm	Symptoms	Any AE	W/D AEs
Paliperidone	Aripiprazole	–	–	No difference*	–	–	–	Insufficient	No difference*
Paliperidone	Aripiprazole LAI-1	–	–	No difference*	–	–	–	Insufficient	No difference*
Paliperidone	Aripiprazole LAI-6w	–	–	–	–	–	–	–	–
Paliperidone	Asenapine	–	–	No difference*	–	–	–	–	No difference*
Paliperidone	Brexpiprazole	–	–	No difference*	–	–	–	Insufficient	No difference*
Paliperidone	Cariprazine	–	–	No difference*	–	–	–	–	No difference*
Paliperidone	Clozapine	–	–	No difference*	–	–	–	–	No difference*
Paliperidone	Iloperidone	–	–	–	–	–	Small (1)*	–	No difference*
Paliperidone	Lurasidone	–	–	–	–	–	Small (1)*	–	No difference*
Paliperidone	Olanzapine	Insufficient	–	No difference*	–	–	No difference*	No difference*	No difference*
Paliperidone	Olanzapine LAI	–	–	–	–	–	–	–	No difference*
Paliperidone	Paliperidone LAI-1	–	–	–	Insufficient	–	–	–	No difference*
Paliperidone	Paliperidone LAI-3	–	–	–	–	–	–	–	No difference*
Paliperidone	Quetiapine	–	–	No difference*	–	–	–	–	No difference*
Paliperidone	Quetiapine ER	–	–	–	–	–	–	–	No difference*
Paliperidone	Risperidone	–	–	No difference*	–	–	–	–	No difference*
Paliperidone	Risperidone LAI	–	–	–	–	–	–	Insufficient	No difference*
Paliperidone	Ziprasidone	–	–	No difference*	–	–	–	–	No difference*

\* = Low SOE, \*\* = Moderate SOE, \*\*\* = High SOE, – = No data, (1) = Estimate favors Drug 1, (2) = Estimate favors Drug 2

Appendix Table I-15. Summary of findings for quetiapine ER versus other SGAs

Drug	Comparator	Function	QOL	Response	Mortality	Self-harm	Symptoms	Any AE	W/D AEs
Quetiapine ER	Aripiprazole	-	-	-	-	-	-	-	No difference*
Quetiapine ER	Aripiprazole LAI-1	-	-	-	-	-	-	-	No difference*
Quetiapine ER	Aripiprazole LAI-6w	-	-	-	-	-	-	-	
Quetiapine ER	Asenapine	-	-	-	-	-	-	-	No difference*
Quetiapine ER	Brexpiprazole	-	-	-	-	-	-	-	No difference*
Quetiapine ER	Cariprazine	-	-	-	-	-	-	-	No difference*
Quetiapine ER	Clozapine	-	-	-	-	-	-	-	No difference*
Quetiapine ER	Iloperidone	-	-	-	-	-	-	-	No difference*
Quetiapine ER	Lurasidone	-	-	-	-	-	-	-	No difference*
Quetiapine ER	Olanzapine	-	-	-	-	-	-	-	No difference*
Quetiapine ER	Olanzapine LAI	-	-	-	-	-	-	-	No difference*
Quetiapine ER	Paliperidone	-	-	-	-	-	-	-	No difference*
Quetiapine ER	Paliperidone LAI-1	-	-	-	-	-	-	-	No difference*
Quetiapine ER	Paliperidone LAI-3	-	-	-	-	-	-	-	No difference*
Quetiapine ER	Quetiapine	-	-	-	Insufficient	-	-	No difference*	No difference*
Quetiapine ER	Risperidone	-	Insufficient	-	-	-	-	No difference*	No difference*
Quetiapine ER	Risperidone LAI	-	-	-	-	-	-	-	No difference*
Quetiapine ER	Ziprasidone	-	-	-	-	-	-	-	No difference*

\* = Low SOE, \*\* = Moderate SOE, \*\*\* = High SOE, - = No data, (1) = Estimate favors Drug 1, (2) = Estimate favors Drug 2

**Appendix Table I-16. Summary of findings for quetiapine versus other SGAs**

Drug	Comparator	Function	QOL	Response	Mortality	Self-harm	Symptoms	Any AE	W/D AEs
Quetiapine	Aripiprazole	–	–	No difference*	–	–	–	–	No difference*
Quetiapine	Aripiprazole LAI-1	–	–	No difference*	–	–	–	–	No difference*
Quetiapine	Aripiprazole LAI-6w	–	–	–	–	–	–	–	–
Quetiapine	Asenapine	–	–	No difference*	–	–	–	–	No difference*
Quetiapine	Brexpiprazole	–	–	No difference*	–	–	–	–	No difference*
Quetiapine	Cariprazine	–	–	No difference*	–	–	–	–	No difference*
Quetiapine	Clozapine	–	No difference*	No difference*	–	–	–	Insufficient	No difference*
Quetiapine	lloperidone	–	–	–	–	–	–	–	No difference*
Quetiapine	Lurasidone	–	–	–	–	–	–	–	No difference*
Quetiapine	Olanzapine	No difference*	No difference*	Moderate (2)*	–	–	–	–	Moderate (1)*
Quetiapine	Olanzapine LAI	–	–	–	–	–	–	–	No difference*
Quetiapine	Paliperidone	–	–	No difference*	–	–	–	–	No difference*
Quetiapine	Paliperidone LAI-1	–	–	–	–	–	–	–	No difference*
Quetiapine	Paliperidone LAI-3	–	–	–	–	–	–	–	No difference*
Quetiapine	Quetiapine ER	–	–	–	Insufficient	–	–	No difference*	No difference*
Quetiapine	Risperidone	Insufficient	No difference*	Moderate (2)*	No difference*	Insufficient	–	No difference**	No difference*
Quetiapine	Risperidone LAI	Small (2)*	No difference*	–	–	–	–	Insufficient	Moderate (2)*
Quetiapine	Ziprasidone	–	No difference*	No difference*	–	–	–	–	No difference*

\* = Low SOE, \*\* = Moderate SOE, \*\*\* = High SOE, – = No data, (1) = Estimate favors Drug 1, (2) = Estimate favors Drug 2

**Appendix Table I-17. Summary of findings for risperidone LAI versus other SGAs**

Drug	Comparator	Function	QOL	Response	Mortality	Self-harm	Symptoms	Any AE	W/D AEs
Risperidone LAI	Aripiprazole	-	-	-	-	-	-	Insufficient	No difference*
Risperidone LAI	Aripiprazole LAI-1	-	-	-	-	-	-	-	No difference*
Risperidone LAI	Aripiprazole LAI-6w	-	-	-	-	-	-	-	-
Risperidone LAI	Asenapine	-	-	-	-	-	-	-	Moderate (1)*
Risperidone LAI	Brexpiprazole	-	-	-	-	-	-	-	No difference*
Risperidone LAI	Cariprazine	-	-	-	-	-	-	-	No difference*
Risperidone LAI	Clozapine	-	-	-	-	-	-	Insufficient	Large (1)*
Risperidone LAI	Iloperidone	-	-	-	-	-	-	-	No difference*
Risperidone LAI	Lurasidone	-	-	-	-	-	-	-	Moderate (1)*
Risperidone LAI	Olanzapine	-	-	-	-	-	-	-	No difference*
Risperidone LAI	Olanzapine LAI	-	-	-	-	-	-	-	No difference*
Risperidone LAI	Paliperidone	No difference*	-	-	-	-	-	No difference*	Moderate (1)*
Risperidone LAI	Paliperidone LAI-1	No difference*	-	-	No difference*	-	-	No difference*	Moderate (1)*
Risperidone LAI	Paliperidone LAI-3	-	-	-	-	-	-	-	No difference*
Risperidone LAI	Quetiapine	Small (1)*	No difference*	-	-	-	-	-	No difference*
Risperidone LAI	Quetiapine ER	-	-	-	-	-	-	-	Moderate (1)*
Risperidone LAI	Risperidone	-	-	-	-	-	-	Insufficient	Moderate (1)*
Risperidone LAI	Ziprasidone	-	-	-	-	-	-	-	Moderate (1)*

\* = Low SOE, \*\* = Moderate SOE, \*\*\* = High SOE, - = No data, (1) = Estimate favors Drug 1, (2) = Estimate favors Drug 2

**Appendix Table I-18. Summary of findings for risperidone versus other SGAs**

Drug	Comparator	Function	QOL	Response	Mortality	Self-harm	Symptoms	Any AE	W/D AEs
Risperidone	Aripiprazole	–	–	No difference*	–	–	Small (1)*	No difference*	No difference*
Risperidone	Aripiprazole LAI-1	–	–	No difference*	–	–	–	–	No difference*
Risperidone	Aripiprazole LAI-6w	–	–	–	–	–	–	–	–
Risperidone	Asenapine	–	–	No difference*	No difference*	–	Small (1)*	Insufficient	No difference*
Risperidone	Brexpiprazole	–	–	No difference*	–	–	Small (1)*	–	No difference*
Risperidone	Cariprazine	–	–	No difference*	–	–	–	Insufficient	No difference*
Risperidone	Clozapine	–	–	No difference*	–	–	–	No difference*	No difference*
Risperidone	lloperidone	–	–	–	–	–	Small (1)*	–	No difference*
Risperidone	Lurasidone	–	–	–	–	–	Small (1)*	–	No difference*
Risperidone	Olanzapine	No difference**	No difference**	No difference*	–	–	No difference*	–	Small (2)*
Risperidone	Olanzapine LAI	–	–	–	–	–	–	–	No difference*
Risperidone	Paliperidone	–	–	No difference*	–	–	–	–	No difference*
Risperidone	Paliperidone LAI-1	–	–	–	–	–	–	–	No difference*
Risperidone	Paliperidone LAI-3	–	–	–	–	–	–	–	No difference*
Risperidone	Quetiapine	Insufficient	No difference*	Moderate (1)*	No difference*	–	–	No difference**	No difference*
Risperidone	Quetiapine ER	–	–	–	Insufficient	–	–	No difference*	No difference*
Risperidone	Risperidone LAI	–	–	–	–	–	–	Insufficient	Moderate (2)*
Risperidone	Ziprasidone	–	No difference*	No difference*	–	–	–	Insufficient	No difference*

\* = Low SOE, \*\* = Moderate SOE, \*\*\* = High SOE, – = No data, (1) = Estimate favors Drug 1, (2) = Estimate favors Drug 2

**Appendix Table I-19. Summary of findings for ziprasidone versus other SGAs**

Drug	Comparator	Function	QOL	Response	Mortality	Self-harm	Symptoms	Any AE	W/D AEs
Ziprasidone	Aripiprazole	–	–	No difference*	–	–	–	–	Moderate (2)*
Ziprasidone	Aripiprazole LAI-1	–	–	No difference*	–	–	–	–	No difference*
Ziprasidone	Aripiprazole LAI-6w	–	–	–	–	–	–	–	–
Ziprasidone	Asenapine	–	–	No difference*	–	–	–	–	No difference*
Ziprasidone	Brexpiprazole	–	–	No difference*	–	–	–	–	No difference*
Ziprasidone	Cariprazine	–	–	No difference*	–	–	–	–	No difference*
Ziprasidone	Clozapine	–	No difference*	No difference*	–	–	–	Insufficient	No difference*
Ziprasidone	lloperidone	–	–	–	–	–	–	Insufficient	No difference*
Ziprasidone	Lurasidone	–	–	–	–	–	–	Insufficient	No difference*
Ziprasidone	Olanzapine	Insufficient	No difference**	No difference*	–	–	–	–	Moderate (2)*
Ziprasidone	Olanzapine LAI	–	–	–	–	–	–	–	No difference*
Ziprasidone	Paliperidone	–	–	No difference*	–	–	–	–	No difference*
Ziprasidone	Paliperidone LAI-1	–	–	–	–	–	–	–	No difference*
Ziprasidone	Paliperidone LAI-3	–	–	–	–	–	–	–	No difference*
Ziprasidone	Quetiapine	–	No difference*	No difference*	–	–	–	–	No difference*
Ziprasidone	Quetiapine ER	–	–	–	–	–	–	–	No difference*
Ziprasidone	Risperidone	–	No difference*	No difference*	–	–	–	Insufficient	No difference*
Ziprasidone	Risperidone LAI	–	–	–	–	–	–	–	Moderate (2)*

\* = Low SOE, \*\* = Moderate SOE, \*\*\* = High SOE, – = No data, (1) = Estimate favors Drug 1, (2) = Estimate favors Drug 2