

Draft Comparative Effectiveness Review

Number XX

**Strategies To Improve Cardiovascular Risk Factors in
People With Serious Mental Illness**

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Preface

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Strategies To Improve Cardiovascular Risk Factors in People With Serious Mental Illness

Structured Abstract

Objectives: Individuals with serious mental illness (SMI) have excess mortality from cardiovascular disease (CVD) and high rates of CVD risk factors such as diabetes, obesity, and hyperlipidemia. We conducted a systematic review to evaluate strategies to improve cardiovascular risk factors in adults with SMI.

Data Sources: We searched PubMed[®], Embase[®], PsycINFO[®], and the Cochrane Database of Systematic Reviews for English-language trials published since 1980 that evaluated patient-focused behavioral interventions, peer or family support interventions, pharmacological treatments, and multicondition lifestyle interventions, or their combination, that targeted weight control, glucose levels, lipid levels, or cardiovascular risk profile among adults with SMI at elevated risk of CVD.

Review Methods: Two investigators screened each abstract and full-text article for inclusion, abstracted data, and performed quality ratings, efficacy-effectiveness ratings, and evidence grading. Qualitative and quantitative methods, using random-effects models, were used to summarize results.

Results: Of 33 eligible studies, most enrolled patients with schizophrenia who were prescribed antipsychotics. Most studies were designed to control weight (n=26); 1 study specifically addressed diabetes management, none targeted hyperlipidemia, and 3 were multicondition interventions. Most studies were efficacy trials comparing behavioral interventions with control; none evaluated peer and family support. There were few direct comparisons of active interventions; effects on overall CVD risk, physical functioning, or CVD events were reported rarely.

Compared with controls, behavioral interventions (mean difference [MD] -3.13 kg; 95% CI, -4.21 to -2.05), antiseizure medications (MD -5.11kg; 95% CI, -9.48 to -0.74), adjunctive or antipsychotic switching to aripiprazole, and metformin improved weight control. However, aripiprazole-switching may be associated with higher rates of treatment failure. Nizatidine did not improve any outcome. The evidence was insufficient for all other interventions and effects on glucose and lipid control.

Conclusions: Few studies have evaluated interventions to address one or more CVD risk factors in patients with SMI. Comparative effectiveness studies are needed to test multimodal strategies, agents known to be effective in non-SMI populations, and antipsychotic-management strategies.

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Effective Health Care

Strategies To Improve Cardiovascular Risk Factors in People With Serious Mental Illness

Executive Summary

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders including consumers.

The full report and this summary are available at www.effectivehealthcare.ahrq.gov/reports/final.cfm

Background

Serious Mental Illness and Cardiovascular Health

Serious mental illness (SMI) is defined generally as a major mental or behavioral disorder, causing substantial impairment in multiple areas of daily functioning. It includes disorders such as schizophrenia and bipolar disorder, but not substance abuse or developmental disorders, and affects about 4 to 8 percent of adults.¹⁻³ Individuals with SMI have shortened life expectancies relative to the general population to an extent that is not explained by suicide and accidents alone.^{4,5} This population experiences higher rates of morbidity from multiple general medical conditions, including diabetes⁶⁻⁸ and cardiovascular disease (CVD).^{9,10} Excess CVD-related mortality among individuals with SMI may be due to a number of factors. Mental illness may be an independent risk factor that acts both directly through physiological effects such as underlying genetic vulnerabilities, or indirectly through effects on an individual's access to or interaction with the health care system.¹¹⁻¹³ Also, modifiable cardiovascular risk factors, such as smoking,¹⁴ obesity,^{15,16} and physical inactivity¹⁷ are highly prevalent among individuals with SMI. Adverse effects of psychotropic drugs (notably second-generation antipsychotics) also may contribute to the development of CVD by increasing the risk of conditions such as hyperglycemia, hyperlipidemia, and obesity.¹⁸ Moreover, numerous studies have demonstrated disparities in the quality of general medical care provided to individuals with SMI.¹⁹⁻²³ In contrast to individuals with less severe mental disorders, who largely receive mental health treatment in primary care settings, most individuals with SMI receive mental health treatment in specialized mental health settings. Consequently, people with SMI receive fewer preventive medical services^{19,20} and less frequent guideline-concordant treatment to manage chronic physical illnesses such as diabetes^{21,22} and CVD.²³ Given these issues, identifying intervention strategies that address

cardiovascular risk in individuals with SMI is a pressing priority to avoid early morbidity and mortality.

Scope and Key Questions

This comparative effectiveness review was funded by the Agency for Healthcare Research and Quality (AHRQ). The review was designed to evaluate strategies to improve cardiovascular risk factors in adults with SMI. SMI has been defined variously by different groups over time.²⁴ For the purposes of this evidence review, people with SMI are defined as individuals who have: (1) schizophrenia or schizoaffective disorder (or other related primary psychotic disorder), (2) bipolar disorder, or (3) current major depression with psychotic features. We also included studies that enrolled adults with SMI or severe and persistent mental illness but did not specify diagnoses. Individuals with a primary diagnosis of substance abuse, dementia, personality disorder, or mental retardation are excluded from this definition.

To prioritize interventions for review, we examined published systematic reviews of strategies to improve cardiovascular risk factors in individuals with SMI and consulted with our stakeholder panel. Based on this assessment, we included randomized controlled trials (RCTs) of the pharmacological and patient-focused behavioral strategies, along with peer and family support interventions. We included both active and control comparators. For patient-level intervention strategies, RCTs yield the highest quality evidence. We excluded from our review general health advice, interventions for smoking cessation only, and models to provide integrated mental health-general medical care, because these topics had been the subject of recent high-quality reviews.²⁵⁻²⁹ Major outcomes of interest for this report are the primary cardiovascular risk factor of interest, physical functioning or health-related quality of life, adverse effects, and all-cause mortality.

Key Questions

With input from our Technical Expert Panel, we constructed Key Questions (KQs) using the general approach of specifying the population of interest, interventions, comparators, outcomes, timing of outcomes, and settings (PICOTS). The KQs considered in this comparative effectiveness review were:

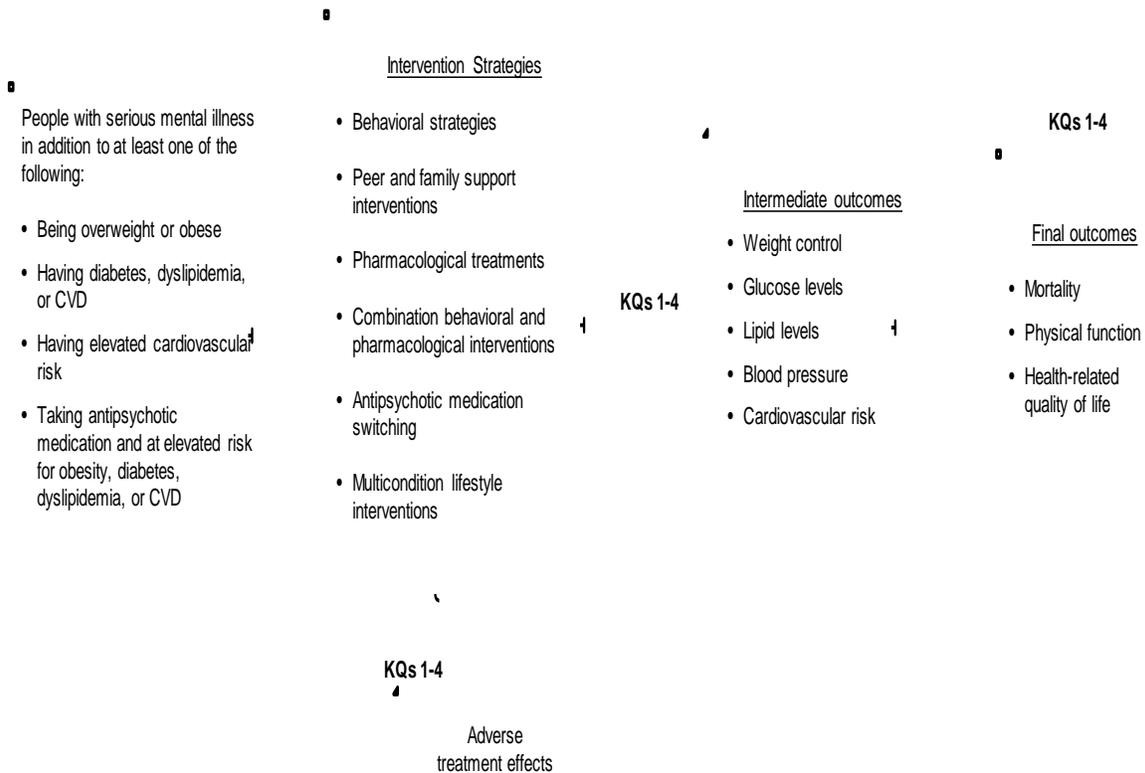
- **KQ 1:** What is the effectiveness of weight-management behavioral interventions (e.g., behavioral counseling, health education), peer or family support interventions, pharmacological treatments (e.g., orlistat, topiramate), antipsychotic medication-switching to an antipsychotic with a low or neutral impact on weight, or their combination on weight control and related physical health outcomes (e.g., health-related quality of life, mortality) compared with each other or with usual care (or other control) among adults with serious mental illness (SMI) who are overweight, obese, or taking antipsychotics?
- **KQ 2:** What is the effectiveness of diabetes-management behavioral interventions (e.g., behavioral counseling, health education), peer or family support interventions, pharmacological treatments (e.g., rosiglitazone, metformin), antipsychotic medication-switching to an antipsychotic with a low or neutral impact on glucose level, or their combination on glucose-level control and related physical health outcomes (e.g., health-

related quality of life, mortality) compared with each other or with usual care (or other control) among adults with SMI who have diabetes or are taking antipsychotics?

- **KQ 3:** What is the effectiveness of dyslipidemia-management behavioral interventions (e.g., behavioral counseling, health education), peer or family support interventions, pharmacological treatments (e.g., statins), antipsychotic medication-switching to an antipsychotic with a low or neutral impact on lipid levels, or their combination on lipid-level control and related physical health outcomes (e.g., health-related quality of life, mortality) compared with each other or with usual care (or other control) among adults with SMI who have dyslipidemia or are taking antipsychotics?
- **KQ 4:** What is the effectiveness of multicondition lifestyle interventions (e.g., combinations of smoking cessation, physical activity, and nutrition counseling with or without medication management) on cardiovascular risk factors and related physical health outcomes (e.g., health-related quality of life, mortality) among adults with SMI who have cardiovascular disease, elevated cardiovascular risk (e.g., hypertension), or are taking antipsychotics?

Figure A depicts the KQs in the context of the PICOTS.

Figure A. Analytic framework



Methods

The methods for this comparative effectiveness review follow those suggested in the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (available at <http://www.effectivehealthcare.ahrq.gov/methodsguide.cfm>; hereafter referred to as the *Methods Guide*).³⁰

During the topic refinement stage, we solicited input from Key Informants representing clinicians, patient advocates, scientific experts, and payers to help define Key Questions (KQs). The KQs were posted for a 4-week public comment period, and comments received were considered in the development of the research protocol. We next convened a Technical Expert Panel (TEP) comprising clinical, content, and methodological experts to provide input in defining populations, interventions, comparisons, and outcomes, as well as identifying particular studies or databases to search. TEP members were invited to provide feedback on an initial draft of the review protocol which was then refined based on their input, reviewed by AHRQ, and posted for public access at the AHRQ Effective Health Care Website.³¹

Literature Search Strategy

To identify the relevant published literature, we searched MEDLINE[®], Embase[®], PsycINFO[®], and the Cochrane Database of Systematic Reviews. Where possible, we used existing validated search filters (such as the Clinical Queries Filters in PubMed[®]). An experienced search librarian guided all searches that included terms for the SMI disorders, cardiovascular risk factors, interventions, and RCTs. Exact search strings are included in the main report Appendix. We supplemented the electronic searches with a manual search of citations from a set of key primary and review articles. The reference lists for these articles were manually searched and cross-referenced against our library of search results, and additional manuscripts were retrieved. All citations were imported into an electronic database (EndNote[®] X4; Thomson Reuters, Philadelphia, PA).

We used two approaches to identify relevant grey literature: (1) a request for scientific information packets submitted to drug manufacturers and (2) a search of trial records listed in ClinicalTrials.gov. The search of ClinicalTrials.gov was also used as a mechanism to ascertain publication bias by identifying completed but unpublished studies. We also explored the possibility of publication bias specifically in our quantitative synthesis of the included literature using meta-analysis techniques.

Inclusion and Exclusion Criteria

Criteria used to screen articles for inclusion/exclusion at both the title-and-abstract and full-text screening stages are detailed in the main report. In brief, eligibility criteria were English-language RCTs that assess patient-focused behavioral interventions, peer or family support interventions, pharmacological treatments (including antipsychotic switching), multicondition lifestyle interventions or their combination targeting weight control, glucose levels, lipid levels, or cardiovascular risk profile among adults with SMI at elevated risk of CVD. We excluded articles describing studies that (a) had as their primary goal improving psychiatric outcomes, (b) assessed only mass media strategies, (c) evaluated pharmacological agents not currently available on the U.S. market, or (d) took place in hospital or inpatient settings. Outcomes of interest were weight control (KQ 1); glucose level (i.e., hemoglobin A1c) (KQ 2); lipid level (i.e., change in low-density lipoprotein [LDL]) (KQ 3); cardiovascular risk profile (e.g.,

Framingham CVD scores) or multiple individual components of modifiable cardiovascular risk (e.g., lipid values, blood pressure, smoking status) (KQ 4); and health-related quality of life, all-cause mortality, physical function, serious adverse effects, and adverse effects (KQs 1–4).

Study Selection

Using the prespecified inclusion and exclusion criteria, titles and abstracts were reviewed independently by two investigators for potential relevance to the KQs. Articles included by either reviewer underwent full-text screening. At the full-text review stage, paired researchers independently reviewed the articles and indicated a decision to “include” or “exclude” the article for data abstraction. When the two reviewers arrived at different decisions about whether to include or exclude an article, they reconciled the difference through review and discussion, or through a third-party arbitrator if needed. Full-text articles meeting our eligibility criteria were included for data abstraction. Relevant review articles, meta-analyses, and methods articles were flagged for manual searching of references and cross-referencing against the library of citations identified through electronic database searching. For citations retrieved by searching the grey literature, the above-described procedures were modified such that a single screener initially reviewed all search results; final eligibility of citations for data abstraction was determined by duplicate screening review. All screening decisions were made and tracked in a DistillerSR database (Evidence Partners Inc, Manotick, ON, Canada).

Data Extraction

The investigative team created data abstraction forms and evidence table templates for abstracting data for KQs. Based on clinical and methodological expertise, a pair of investigators was assigned to abstract data from each eligible article. One investigator abstracted data, and the second reviewed the article and accompanying completed abstraction form to check for accuracy and completeness. Quality ratings and efficacy–effectiveness ratings (see below) were completed independently by two investigators. Disagreements were resolved by consensus, or by obtaining a third reviewer’s opinion if consensus could not be reached. To aid in both reproducibility and standardization of data collection, researchers received data abstraction instructions directly on each form created specifically for this project within the DistillerSR database.

We designed data abstraction forms for this project to collect data required to evaluate specified eligibility criteria for inclusion in this review, as well as demographic and other data needed for determining outcomes. We gave particular attention to describing details of the interventions (e.g., pharmacotherapy used, intensity of behavioral interventions), patient characteristics (e.g., SMI diagnosis), and comparators that may be related to outcomes. When critical data were missing, we contacted study authors. Of the seven authors contacted, five replied with the requested information.

Quality Assessment of Individual Studies

We evaluated the quality of individual studies using the key criteria for RCTs described in the *Methods Guide*.³⁰ Criteria of interest included similarity of groups at baseline, extent to which outcomes were described, blinding of subjects and providers, blinded assessment of the outcome(s), intention-to-treat analysis, differential loss to followup between the compared groups or overall high loss to followup, conflicts of interest, methods of randomization, and allocation concealment.

To indicate the summary judgment of the quality of the individual studies, we used the summary ratings of good, fair, or poor based on their adherence to well-accepted standard methodologies and adequate reporting. For each study, two investigators independently assigned a summary quality rating; disagreements were resolved by consensus or by discussion with a third investigator if agreement could not be reached. Quality ratings were assigned separately for “hard” outcomes (e.g., mortality, laboratory measurements) and all other outcomes (e.g., health-related quality of life); thus, a given study may have been categorized differently for two individual outcomes reported within that study.

Data Synthesis

We began by summarizing key features of the included studies for each KQ. To the degree that data were available, we summarized information on study design; patient characteristics; clinical settings; interventions; and intermediate, final, and adverse effects outcomes. We then determined the feasibility of completing a quantitative synthesis (i.e., meta-analysis). Feasibility depended on the volume of relevant literature (≥ 3 studies), conceptual homogeneity of the studies, and completeness of the reporting of results. When a meta-analysis was appropriate, we used random-effects models to quantitatively synthesize the available evidence. For other outcomes we analyzed the results qualitatively. The outcomes amenable to meta-analysis were continuous; we therefore summarized these outcomes by a weighted difference of the means when the same scale (e.g., weight) was used and a standardized mean difference when the scales (e.g., health-related quality of life) differed across studies. We standardized results presentation such that a negative value indicates a greater intervention effect. When needed, we converted reported outcomes to a common unit (e.g., cholesterol from mmol/L to mg/dl). We present summary estimates, standard errors, and confidence intervals in our data synthesis.

We organized our analyses by KQ. When a single study reported outcomes relevant to multiple key questions, it was included in the analyses for each question. For example, a study evaluating a weight-loss intervention that specified weight as the primary outcome—but which also reported effects on glucose and lipid parameters—was described in each relevant KQ. We specified, a priori, weight control as measured by change in kilograms (or pounds), hemoglobin A1c (HbA1c) as the preferred measure of glucose control since it reflects average glucose values over a 3-month interval, and total and LDL cholesterol as measures of lipid control. For adverse effects, we report significant worsening of psychiatric status and discontinuations due to adverse effects. Interventions were categorized as: behavioral, pharmacological, peer or family support, or multicondition (e.g., specifically targeting more than one condition such as smoking cessation and weight loss). Drug classes were psychotropics, neurologics, metformin, antihistamines, nutritional (i.e., carnitine), and switching between antipsychotic medications.

We tested for heterogeneity using graphical displays and test statistics (Q statistic), while recognizing that the ability of statistical methods to detect heterogeneity may be limited.³² The I^2 describes the percentage of total variation across studies due to heterogeneity rather than to chance. Heterogeneity was categorized as low, moderate, or high based on I^2 values of 25 percent, 50 percent, and 75 percent respectively.³² When there were sufficient studies, we explored heterogeneity in study effects by using subgroup analyses. When there were sufficient studies ($n \geq 10$), we assessed for publication bias using funnel plots and test statistics.³³ All analyses were conducted using Comprehensive Meta-Analysis software (Version 2; Biostat, Englewood, NJ).

Strength of the Body of Evidence

The strength of evidence for each KQ and outcome was assessed using the approach described in the *Methods Guide*.^{30,34} In brief, the approach requires assessment of four domains: risk of bias, consistency, directness, and precision. Additional domains were used when appropriate: coherence, and publication bias. These domains were considered qualitatively, and a summary rating of high, moderate, or low strength of evidence was assigned after discussion by two reviewers. In some cases, high, moderate, or low ratings were impossible or imprudent to make; for example, when no evidence was available or when evidence on the outcome was too weak, sparse, or inconsistent to permit any conclusion to be drawn. In these situations, a grade of insufficient was assigned.

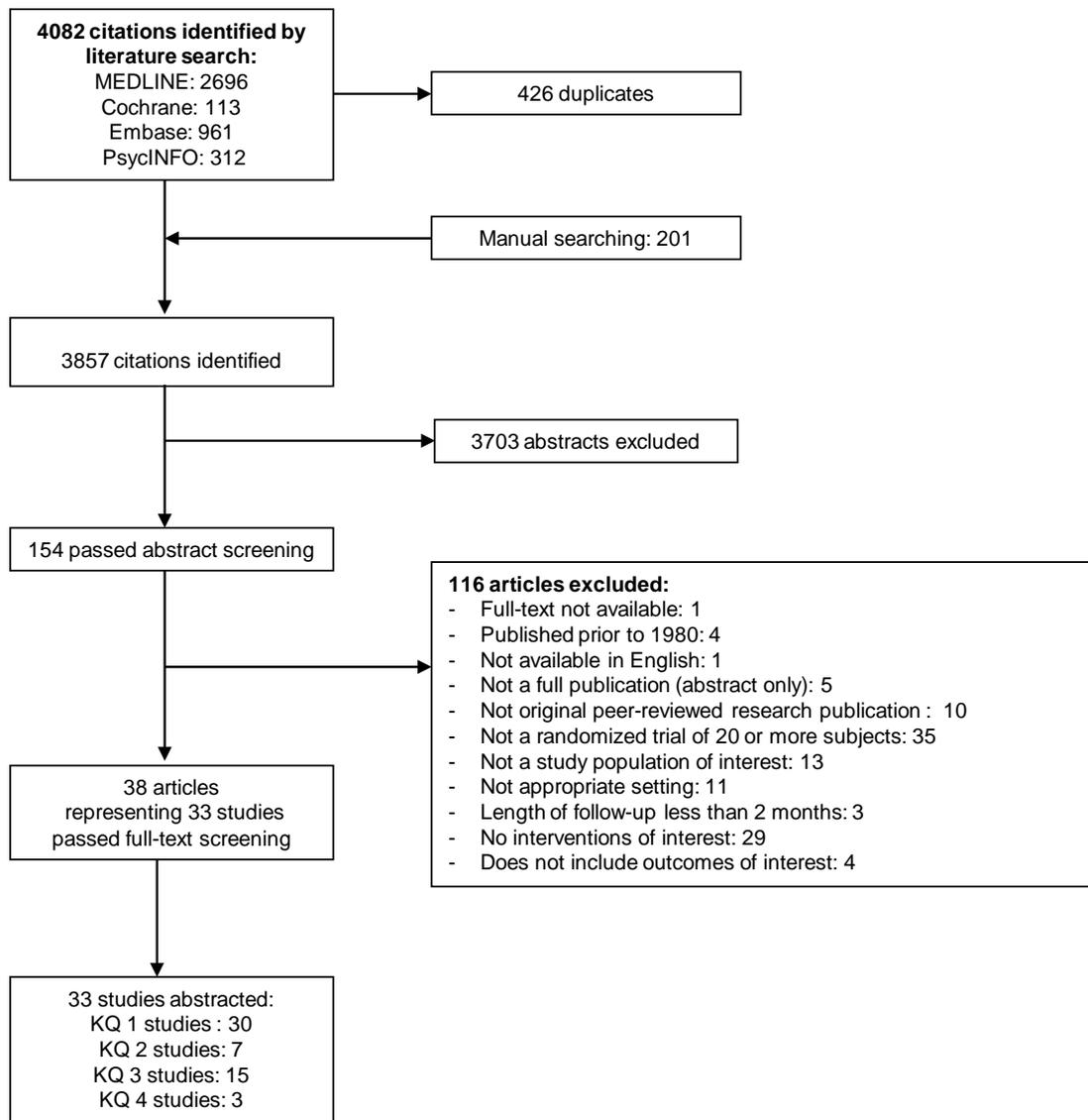
Applicability

We assessed applicability across our KQs using the method described in the *Methods Guide*.^{30,35} In brief, this method uses the PICOTS format as a way to organize information relevant to applicability. The most important issue with respect to applicability is whether the outcomes are different across studies that recruit different populations (e.g., age groups, exclusions for comorbidities) or use different methods to implement the interventions of interest; that is, important characteristics are those that affect baseline (control-group) rates of events, intervention-group rates of events, or both. We used a checklist to guide the assessment of applicability. We used these data to evaluate the applicability to clinical practice, paying special attention to study eligibility criteria, demographic features of the enrolled population in comparison to the target population, characteristics of the intervention used in comparison with care models currently in use, and clinical relevance and timing of the outcome measures. We summarized issues of applicability qualitatively.

Results

Figure B depicts the flow of articles through the literature search and screening process. Searches of PubMed[®], Embase[®], and the Cochrane Database of Systematic Reviews yielded 4082 citations, 426 of which were duplicate citations. Manual searching identified 201 additional citations, for a total of 3857 citations. After applying inclusion/exclusion criteria at the title-and-abstract level, 154 full-text articles were retrieved and screened. Of these, 116 were excluded at the full-text screening stage, leaving 38 articles (representing 33 unique studies) for data abstraction. No additional information was found through our grey literature search. Many articles/studies were relevant to more than one KQ: 30 studies were relevant to KQ 1, 7 to KQ 2, 15 to KQ 3, and 3 to KQ 4. Studies were conducted in Europe (24%); Asia (9%); the United States (39%); and South America (6%); or multiple continents (21%). Sixty-one percent of included studies enrolled individuals with schizophrenia or schizoaffective disorder, 12 percent recruited individuals with schizophrenia, schizoaffective disorder, or bipolar disorder, 21 percent recruited patients either taking antipsychotics or with a unspecified SMI diagnosis, and only 6 percent recruited individuals with bipolar disorder. The vast majority of studies were specifically designed to control weight (79%); only one study was designed to target diabetes management, and no studies were designed to target dyslipidemia.

Figure B. Literature flow diagram



Abbreviations: KQ=Key Question

Key Question 1. Effectiveness of Weight-Management Interventions

Key points from the Results chapter are:

- Of the 30 studies identified, most were specifically designed to control weight gain for persons with SMI. Other studies targeted diabetes management or antipsychotic metabolic effects but also addressed weight management.
- No studies evaluated the weight loss medication orlistat in this population.
- The antiseizure agents topiramate and zonisamide and behavioral interventions were associated with greater weight loss than controls. However, there were few studies of antiseizure agents with small samples sizes. The magnitude of effect was small for both intervention strategies.
- For psychotropic agents and nizatidine, there was no advantage in favor of intervention compared with control for the management of weight gain among patients with SMI. However, few trials evaluated these medication interventions.
- In three relatively short-term trials, participants randomized to treatments containing metformin lost more weight than control conditions. The magnitude of effect was small.
- Switching from standard oral olanzapine to a different antipsychotic medication yielded mixed results across a variety of switching strategies.
- Few studies reported effects on physical functioning or health-related quality of life, and no studies reported all-cause mortality.

We identified 30 RCTs that assessed the effects of behavioral and pharmacological strategies on weight control among adults with SMI. Most studies (n=18) were rated fair quality, with 8 studies rated good quality and 4 poor quality. In total, 21 studies targeted weight control, 5 obesity prevention, 3 antipsychotic metabolic effects, and 1 diabetes management. Of the 3333 participants across the 30 included studies, most were male and white.

We had sufficient studies to perform three meta-analyses: behavioral interventions, the antiseizure medications topiramate and zonisamide, and the antihistamine nizatidine compared with controls. Other comparisons were synthesized qualitatively. We found moderate SOE that behavioral interventions are associated with small decreases in weight compared with controls (mean difference -3.13 kg; 95% CI, -4.21 to -2.05). We found low SOE that switching to or adding adjunctive aripiprazole, adding the antiseizure medications topiramate and zonisamide (mean difference -5.11 kg; 95% CI, -9.484 to -0.735), or adding metformin yield small to moderate weight loss. Nizatidine, an antihistamine, did not show any consistent effect on weight (mean difference -0.496 kg; 95% CI, -1.256 to 0.266) with a low SOE. The SOE was insufficient for all other interventions. No studies evaluated orlistat, an FDA-approved medication for the treatment of obesity that is also available without prescription at a lower dose.

Key Question 2. Effectiveness of Diabetes-Management Interventions

Key points from the Results chapter are:

- Only one study evaluated an intervention specifically designed to target glucose control in individuals with SMI who have diabetes. Two studies evaluated interventions targeting nondiabetic individuals who had or were at risk for poor glycemic control. Four studies evaluated interventions targeting weight, with glycemic control as a secondary outcome.
- The intervention types represented in the seven studies reporting HbA1c outcomes were psychotropic medication ramelteon, antipsychotic switching, metformin, neurologic agent amantadine, and behavioral interventions.
- Small improvements in HbA1c were seen in one study of metformin compared to placebo control and one study that used a sequenced medication algorithm of amantadine, metformin and zonisamide plus olanzapine compared to olanzapine alone.
- Only one study reported on the effects on physical functioning or health related quality of life and no studies report cardiovascular mortality.

We identified only seven trials that assessed the impact of behavioral and pharmacological interventions to address glucose control as measured by HbA1c in patients with SMI and elevated risk for CVD. Of these, one study was rated good quality, five fair, and one poor. Only one study enrolled patients with diabetes and addressed glucose control directly; the other six studies assessed HbA1c as a secondary outcome. Of the 681 participants, most were male, white and middle-aged.

There was an insufficient number of studies to conduct meta-analyses on the effects of any of the intervention classes by HbA1c. Just two of the trials found significant advantages for the intervention in controlling HbA1c, with both of these studies involving the use of metformin, an FDA-approved drug for the treatment of type 2 diabetes. However, we found insufficient evidence for all interventions.

Key Question 3. Effectiveness of Dyslipidemia-Management Interventions

Key points from the Results chapter are:

- No studies evaluated an intervention specifically designed to target lipid levels in individuals with SMI who have or are at risk for dyslipidemia. However, 15 RCTs reported lipid levels as a secondary outcome.
- No studies examined a drug (e.g., HMG-CoA reductase inhibitors) or dietary intervention known to be effective for managing dyslipidemia in non-SMI populations.
- The one meta-analysis that was justified examined three small, 3- to 12-month behavioral interventions for weight control and found no advantage in favor of behavioral interventions compared with control for LDL levels.

- Compared with control interventions, small improvements in lipids were seen in one study of ramelteon, one study of topiramate, and one study that used a sequenced medication algorithm of amantadine, metformin, and zonisamide.
- Two studies of aripiprazole—one that added aripiprazole to chronic clozapine and one that switched patients from olanzapine to aripiprazole—improved lipids modestly. Switching from oral to injectable olanzapine increased LDL cholesterol.

We identified no articles reporting on trials in which the intervention was designed to target lipid levels. Specifically, no study evaluated HMG-CoA reductase inhibitors (statins), niacin, fibrates, or low-fat diets. However, 15 of the eligible studies, involving 2322 patients, reported on total cholesterol (n=12) or LDL cholesterol (n=14) as a secondary outcome. Most studies (n=8) were rated fair quality, with 4 studies rated good quality and 3 poor quality. The experimental intervention was psychotropic medication in three trials, antipsychotic switching in four trials, behavioral interventions in three trials, neurological agents in three trials, an antihistamine in one trial, and a neurological agent or a biguanide in one trial (this trial was the only one with three arms instead of two). The majority of patients were male, white, and middle-aged.

We had sufficient studies with cohesive intervention strategies to conduct a meta-analysis only for the effect of behavioral interventions on lipid levels. Results for the other effects are summarized qualitatively. We found low SOE that behavioral interventions focusing on weight loss or diabetes management have no substantial effects on lipids (LDL levels mean difference=1.91 mg/dl; 95% CI, -6.06 to 9.88). The SOE was insufficient for all other interventions. However, small benefits were seen when aripiprazole was used as an adjunct or as an antipsychotic switch strategy and single studies suggested possible benefit with ramelteon or topiramate.

Key Question 4. Effectiveness of Multicondition Lifestyle Interventions

Key points from the Results chapter are:

- Only three studies evaluated lifestyle interventions.
- One study reported significant effects on body mass index (BMI), weight, and cholesterol:
 - This good-quality study showed benefit in switching from olanzapine, quetiapine, or risperidone to aripiprazole in the context of a manualized, behaviorally oriented diet and exercise program.
 - The effects of the behavioral component of the lifestyle intervention in this study are unknown, since both the intervention and comparison arm received the behavioral component.
- Two studies reported significant effects of multicondition lifestyle interventions for self-reported health-related quality of life.

We identified 1 good and 2 fair quality studies involving 286 patients that assessed the effects of lifestyle interventions on cardiovascular risk factors and related physical health outcomes among adults with SMI. Most participants were male and white. There was an insufficient number of studies with cohesive intervention strategies to conduct a meta-analysis;

results are summarized qualitatively. Two studies evaluated multicomponent lifestyle interventions alone, and one evaluated switching from one of three second-generation antipsychotic medications to aripiprazole in combination with a structured diet and exercise program. None of these studies evaluated lifestyle interventions in combination with medications that directly address weight (e.g., orlistat), glucose (e.g., metformin), or lipids (e.g., statins). Studies reported each outcome separately; only one reported an overall CVD risk score which was unaffected by the intervention. As described above, when adding or switching to aripiprazole, there is low SOE for a small benefit on weight but the evidence is insufficient for overall CVD risk. The two multicomponent behavioral interventions did not have a positive effect on the individual CVD risk factors, although one of the two studies showed a large positive effect on health-related QOL.

Discussion

Key Findings and Strength of Evidence

We identified 33 trials that tested a wide array of behavioral and pharmacological interventions to address one or more cardiovascular risk factors in patients with SMI and elevated risk for CVD. Given that CVD is the most prevalent cause of death in this population, it is a surprisingly small number of studies. Further, we identified no peer and family support interventions to address elevated CVD risk, nor did we find any interventions designed specifically to address lipids. No interventions targeted individuals with psychotic depression specifically. Outcomes reported were primarily metabolic outcomes such as glucose control or weight; effects on physical function and overall CVD risk (e.g., Framingham index) were reported infrequently, and all-cause mortality was not reported.

Table A presents a brief overview of key findings by intervention as well as the strength of evidence (SOE) by key question for major outcomes. Our drug classes sometimes include drugs with diverse mechanisms of action. When results varied by drug, we assigned separate SOE. Publication bias was difficult to assess because only one comparison had sufficient studies for statistical analysis. For adverse effects, we considered discontinuation due to adverse effects and worsening of psychiatric status as the key outcomes when rating SOE. When the majority of studies reported only one of these outcomes, we considered the evidence for adverse effects incomplete and rated the limited evidence as indirect. In brief, evidence was insufficient for most intervention strategies, and there were too few studies to conduct quantitative synthesis for all outcomes of interest, except for weight.

Table A. Overview of treatment effects and strength of evidence by intervention and key outcomes

Intervention	(KQ 1) Weight	(KQ 2) Diabetes (HbA1c)	(KQ 3) Lipids^a	Overall CVD risk and Other Outcomes
Behavioral	Small benefit (-3.1 kg) Moderate SOE	Insufficient SOE	No important effect from weight control interventions Low SOE	1 study assessed health-related quality of life and found no differences Only 2 studies reported discontinuation due to adverse effects Insufficient SOE
Peer or family support	No studies Insufficient SOE	No studies Insufficient SOE	No studies Insufficient SOE	No studies Insufficient SOE
Metformin	Small benefit (-2 to -4.7 kg) Low SOE	Insufficient SOE	No studies Insufficient SOE	Insufficient SOE for CVD risk
Antiseizure medication	Small to moderate benefit (-5.1 kg) Low SOE	Insufficient SOE	Possible benefit with topiramate Insufficient SOE	Insufficient SOE for CVD risk
Antihistamine	No benefit Low SOE	Insufficient SOE	Single study did not suggest benefit Insufficient SOE	Insufficient SOE for CVD risk
Other medications	Insufficient SOE	Insufficient SOE	No study suggested possible benefit Insufficient SOE	Insufficient SOE for CVD risk
Antipsychotic switching	Small benefit (-2 to -3 kg) with aripiprazole Moderate SOE	Insufficient SOE	Possible benefit with aripiprazole Insufficient SOE	Insufficient SOE for CVD risk Possible higher rate of mental health worsening; low SOE
Multicomponent lifestyle	Insufficient SOE	Insufficient SOE	Insufficient SOE	Two studies suggested benefit for health-related QOL 1 study reported no benefit on CVD risk score Insufficient SOE

^aNo studies of lipid-focused interventions.

Our results complement prior reports by examining a broad array of interventions for patients at increased risk for worsening health outcomes due to cardiovascular risk factors such as obesity, hyperlipidemia, diabetes mellitus, or chronic administration of antipsychotic medication that negatively impact metabolic parameters. Earlier narrative and systematic reviews have focused primarily on behavioral interventions for weight control in patients with schizophrenia

or who were on antipsychotic medications.³⁶⁻³⁸ The conclusions of these reviews were largely consistent with our findings in that behavioral interventions were associated with small improvements in weight. Our review builds on these findings by identifying clear omissions in treatments known to be effective in non-SMI populations, including guideline-concordant care, and promising treatments strategies such as aripiprazole, metformin, and topiramate, which deserve further investigation.

Applicability

In our review, only 15 of 33 trials were conducted in the United States, and most studies (n=20) were classified as efficacy studies and were relatively short in duration. Studies typically enrolled midlife adults; none specifically enrolled older adults. Women, as well as racial minorities, were well represented. Most were conducted in mental health outpatient settings, typical of the principal locus of medical care for patients with SMI; none were conducted in patient-centered medical homes or in settings that integrated mental health and general medical services. None were classified as effectiveness studies, but for many interventions, initial studies are justifiably designed to answer the question, Can it work under ideal conditions?—before moving to a test of effectiveness. Probably the most important constraint on applicability is the inconsistent reporting of the CVD-related outcomes of interest and the nearly total lack of reporting (only reported in one study) for overall CVD risk indices (e.g., Framingham Risk Score).

Implications for Clinical and Policy Decisionmaking

The U.S. Preventive Services Task Force makes recommendations for CVD screening in adults, including blood pressure³⁹ and tobacco use,⁴⁰ screening for diabetes in patients with elevated blood pressure,⁴¹ and lipid screening in midlife adults or young adults at increased risk for CVD.⁴² Increasing guideline-concordant care for individuals with SMI—given the current lack of evidence for SMI-specific interventions—could be considered a starting point for minimizing CVD risk in patients with SMI. These guidelines for the general population should then be modified to consider the special risks for patients with SMI

Our review, together with other reviews on interventions to decrease CVD risk in patients with or without SMI, suggests a few actionable strategies and others requiring further study. For weight control, moderate evidence supports behavioral interventions and more limited evidence supports metformin, topiramate, or aripiprazole as an adjunctive or antipsychotic-switching strategy. All of these interventions yield small to moderate effects, and the benefits must be weighed against the potential harms, including the small risk of lactic acidosis and need for monitoring renal function with metformin. Data are much more limited for effects on average glucose control or lipid levels in patients at increased risk. The antihistamine nizatidine was not effective for any CVD risk factor and is unlikely to be a useful treatment. Other reviews identify bupropion as the best supported treatment for smoking cessation;^{25,26} nicotine replacement therapy is effective in non-SMI populations but has not been adequately studied in patients with schizophrenia, bipolar disorder or psychotic depression. Other reviews identified tailored mood management in patients with depressive symptoms^{43,44} and behavioral support interventions in individuals with mental illness as potentially effective.⁴⁵ Although the evidence is limited, the meta-finding is that, of the interventions tested in SMI populations to date, effects on intermediate outcomes (e.g., weight) are similar to the effects found in the general population.

Studies of guideline adherence show significant gaps between current practice and recommendations for cardiovascular risk screening and followup.⁴⁶ Studies show screening rates ranging from about 10 to 26 percent for lipids and 22 to 52 percent for glucose.⁴⁷⁻⁵⁰ Data on monitoring of these risk factors in patients treated with second-generation antipsychotics are more limited but also show gaps between guidelines and practice. Assessment and monitoring is only a first step. When abnormalities are detected, they must be addressed, either by the mental health professional or by a general medicine clinician. Integrated mental health–general medical care has shown promise as the optimal way to deliver this care, and the current move to medical homes has the potential to make this type of care more readily available. Unfortunately, few medical home models to date have explicitly included mental healthcare.⁵¹ Until integrated care is better established and more readily available, there are a number of implementation strategies to consider when a change to a metabolically more neutral antipsychotic is not sufficient to address elevated CVD risk factors. When patients have access to both mental health specialty care and general medical care, it is important that these clinicians coordinate care across issues that may impact both physical and mental health. Coordinating care with the mental health professional about roles and specific strategies for addressing cardiovascular risk factors has the potential to improve care and clinical outcomes. When general medical care is unavailable, one pragmatic strategy to consider is an expanded role for psychiatrists that may include weight and blood pressure screening and monitoring, and medication treatments for CVD risk factors when safe, effective treatments are available that require little monitoring.

Research Gaps

We used the framework recommended by Robinson et al.⁵² to identify gaps in evidence and classify why these gaps exist. This approach considers PICOTS to identify gaps and classifies gaps as due to (a) insufficient or imprecise information, (b) biased information; (c) inconsistency or unknown consistency, and (d) not the right information. In addition, we considered studies in progress identified from ClinicalTrials.gov when making recommendations for future research. Gaps and recommendations are presented in Table B. Although we recommend multicenter RCTs to address some evidence gaps, we are aware that there are particular challenges to conducting RCTs in this population. Recruitment and retention is an important issue for all trials and may be particularly challenging in patients with SMI. Symptoms of mental illness and effects on cognition along with substantial rates may make it difficult for patients with SMI to fully participate in planned interventions. Some important outcomes, such as cardiovascular events, may take large sample sizes and long followup periods to evaluate.

Table B. Evidence gaps and future research

Evidence Gap	Reason	Type of Studies to Consider
Patients		
Limited data for patients with conditions other than schizophrenia	Insufficient information	Single and multisite RCTs
No data in older adults who have more comorbid medical illness	Insufficient information	Single and multisite RCTs
Few studies of ethnic and racial minorities	Insufficient information	Single and multisite RCTs
Interventions		
No interventions evaluating peer and family support interventions	Insufficient information	Single and multisite RCTs

Evidence Gap	Reason	Type of Studies to Consider
No studies on the effects of the most recently approved second-generation antipsychotics such as paliperidone, iloperidone, asenapine and lurasidone	Insufficient information	Single and multisite RCTs
Limited evidence about the benefits and harms of switching from one antipsychotic to another on metabolic parameters	Insufficient information	Secondary analyses of existing studies such as the CATIE trial or large observational datasets
No studies comparing optimized antipsychotic management (e.g., start with or switch to drugs with more favorable metabolic profiles) vs. continuing current antipsychotics in responders and treating adverse metabolic effects directly using treatments (e.g., statins) with known efficacy	Insufficient information	Single and multisite RCTs
Few multimodal interventions	Insufficient information	Single and multisite RCTs
Uncertainty about the details of the intervention	Not the right information	Provide manuals to promote replication/implementation of successful interventions
Interventions to improve guideline concordant care	Insufficient information	Single and multisite RCTs
Comparators		
Few studies comparing two active interventions	Insufficient information	Single and multisite RCTs comparing effective treatments
Outcomes		
Uncertain effects on overall cardiovascular risk or cardiovascular events	Insufficient information	Use risk indices (e.g., Framingham) and/or cardiovascular events as outcome measures
Intervention adherence	Insufficient information	Improve study reporting
Uncertainty about adverse effects on mental health status	Insufficient information	Define and report proportion of patients who mental health status worsens
Timing		
Few studies with outcomes measured beyond 6 months	Insufficient information	RCTs with longer term followup and/or quasi experimental or observational studies
Setting		
Lack of studies designed to evaluate “real world” effects of the intervention (effectiveness studies)	Insufficient information	RCTs or quasi experimental studies with broad inclusion criteria, conducted in community practices, with long term follow up and that include clinically important outcomes such as physical functioning, cardiovascular events and adverse events. Improve reporting of efficacy–effectiveness characteristics

Abbreviations: CATIE=Clinical Antipsychotic Trials in Intervention Effectiveness; RCT=randomized controlled trial

Conclusions

In summary, patients with SMI are at risk for increased CVD—in part due to health behaviors (tobacco use, physical inactivity), possibly due to direct effects of the illness (e.g., changes in the neuroendocrine system that are associated with atherosclerosis), and due to adverse effects from some treatments (e.g., increased metabolic syndrome from antipsychotics). Surprisingly few studies addressed one or more cardiovascular risk factors in patients with SMI and most studies were skewed towards efficacy trials. Behavioral interventions, switching to or adding adjunctive aripiprazole, adding antiseizure medications topiramate and zonisamide, or adding metformin yield small to moderate weight loss compared to controls. We found

insufficient evidence to support any strategy to control glucose. We found limited support of behavioral interventions focusing on weight loss or diabetes management on lipid control; SOE was insufficient for all other interventions. We found no studies testing a number of important interventions (e.g., orlistat, statins) known to be effective in non-SMI populations. Comparative effectiveness trials are needed that test multimodal strategies, known effective agents in non-SMI population (e.g., statins), and antipsychotic management strategies. However, in the absence of evidence for SMI-specific interventions, guideline-concordant care for individuals with SMI may help mitigate the unequal burden of CVD that SMI populations sustain.

Glossary

AHRQ	Agency for Healthcare Research and Quality
CI	confidence interval
CVD	cardiovascular disease
df	degrees of freedom
HR	hazard ratio
HRQOL	health-related quality of life
kg	kilogram
KQ	Key Question
MI	myocardial infarction
NA	not available
NR	not reported
OR	odds ratio
PICOTS	population, intervention, comparator, outcomes, timing, setting
QOL	quality of life
RCT	randomized controlled trial
ROB	risk of bias
RR	risk ratio
SMI	serious mental illness
SOE	strength of evidence
TEP	Technical Expert Panel

References

1. Epstein J., Barker P, Vorburger M, et al. Serious mental illness and its co-occurrence with substance use disorders, 2002 (DHHS Publication No. SMA 04-3905, Analytic Series A-24). Rockville, MD: Substance Abuse and Mental Health Services Administration, Office of Applied Studies. Available at: <http://www.samhsa.gov/data/CoD/CoD.pdf>. Accessed June 22, 2012. 2004.
2. National Institute of Mental Health. Statistics. Schizophrenias. Available at: <http://www.nimh.nih.gov/statistics/1SCHIZ.shtml>. Accessed June 22, 2012.
3. National Institute of Mental Health. Statistics. Available at: <http://www.nimh.nih.gov/statistics/index.shtml>. Accessed June 22, 2012.
4. Chang C-K, Hayes R, Broadbent M, et al. All-cause mortality among people with serious mental illness (SMI), substance use disorders, and depressive disorders in southeast London: a cohort study. *BMC Psychiatry*. 2010;10(1):77. PMID: 20920287.
5. Brown AS, Birthwhistle J. Excess mortality of mental illness. *Br J Psychiatry*. 1996;169(3):383-4. PMID: 8879735.
6. Hsu JH, Chien IC, Lin CH, et al. Incidence of diabetes in patients with schizophrenia: a population-based study. *Can J Psychiatry*. 2011;56(1):19-26. PMID: 21324239.
7. Dixon L, Weiden P, Delahanty J, et al. Prevalence and correlates of diabetes in national schizophrenia samples. *Schizophr Bull*. 2000;26(4):903-12. PMID: 11087022.
8. van Winkel R, De Hert M, Van Eyck D, et al. Prevalence of diabetes and the metabolic syndrome in a sample of patients with bipolar disorder. *Bipolar Disord*. 2008;10(2):342-8. PMID: 18271914.
9. Bresee LC, Majumdar SR, Patten SB, et al. Prevalence of cardiovascular risk factors and disease in people with schizophrenia: a population-based study. *Schizophr Res*. 2010;117(1):75-82. PMID: 20080392.
10. Weiner M, Warren L, Fiedorowicz JG. Cardiovascular morbidity and mortality in bipolar disorder. *Ann Clin Psychiatry*. 2011;23(1):40-7. PMID: 21318195.
11. Fagiolini A, Goracci A. The effects of undertreated chronic medical illnesses in patients with severe mental disorders. *J Clin Psychiatry*. 2009;70 Suppl 3:22-9. PMID: 19570498.
12. Ryan MC, Collins P, Thakore JH. Impaired fasting glucose tolerance in first-episode, drug-naive patients with schizophrenia. *Am J Psychiatry*. 2003;160(2):284-9. PMID: 12562574.
13. Kupfer DJ. The increasing medical burden in bipolar disorder. *JAMA*. 2005;293(20):2528-30. PMID: 15914754.
14. McCreadie RG. Diet, smoking and cardiovascular risk in people with schizophrenia: descriptive study. *Br J Psychiatry*. 2003;183:534-9. PMID: 14645025.
15. McElroy SL. Obesity in patients with severe mental illness: overview and management. *J Clin Psychiatry*. 2009;70 Suppl 3:12-21. PMID: 19570497.
16. Fountoulakis KN, Siamouli M, Panagiotidis P, et al. Obesity and smoking in patients with schizophrenia and normal controls: a case-control study. *Psychiatry Res*. 2010;176(1):13-6. PMID: 20079934.
17. Brown S, Birtwistle J, Roe L, et al. The unhealthy lifestyle of people with schizophrenia. *Psychol Med*. 1999;29(3):697-701. PMID: 10405091.
18. Newcomer JW. Metabolic considerations in the use of antipsychotic medications: a review of recent evidence. *J Clin Psychiatry*. 2007;68 Suppl 1:20-7. PMID: 17286524.
19. Desai MM, Rosenheck RA, Druss BG, et al. Receipt of nutrition and exercise counseling among medical outpatients with psychiatric and substance use disorders. *J Gen Intern Med*. 2002;17(7):556-60. PMID: 12133146.
20. Druss BG, Rosenheck RA, Desai MM, et al. Quality of preventive medical care for patients

- with mental disorders. *Med Care*. 2002;40(2):129-36. PMID: 11802085.
21. Green JL, Gazmararian JA, Rask KJ, et al. Quality of diabetes care for underserved patients with and without mental illness: site of care matters. *Psychiatr Serv*. 2010;61(12):1204-10. PMID: 21123404.
 22. Frayne SM, Halanych JH, Miller DR, et al. Disparities in diabetes care: impact of mental illness. *Arch Intern Med*. 2005;165(22):2631-8. PMID: 16344421.
 23. Mitchell AJ, Lord O. Do deficits in cardiac care influence high mortality rates in schizophrenia? A systematic review and pooled analysis. *J Psychopharmacol*. 2010;24(4 Suppl):69-80. PMID: 20923922.
 24. Peck MC, Scheffler RM. An analysis of the definitions of mental illness used in state parity laws. *Psychiatr Serv*. 2002;53(9):1089-95. PMID: 12221306.
 25. Tsoi DT, Porwal M, Webster AC. Interventions for smoking cessation and reduction in individuals with schizophrenia. *Cochrane Database Syst Rev*. 2010(6):CD007253. PMID: 20556777.
 26. Tsoi DT, Porwal M, Webster AC. Efficacy and safety of bupropion for smoking cessation and reduction in schizophrenia: systematic review and meta-analysis. *Br J Psychiatry*. 2010;196(5):346-53. PMID: 20435957.
 27. Tosh G, Clifton A, Bachner M. General physical health advice for people with serious mental illness. *Cochrane Database Syst Rev*. 2011;2:CD008567. PMID: 21328308.
 28. Tosh G, Clifton A, Mala S, et al. Physical health care monitoring for people with serious mental illness. *Cochrane Database Syst Rev*. 2010(3):CD008298. PMID: 20238365.
 29. Bradford DW, Slubicki MN, McDuffie JR, et al. Effects of care models to improve general medical outcomes for individuals with serious mental illness. VA-ESP Project #09-010; [In press.].
 30. Agency for Healthcare Research and Quality. *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. Rockville, MD: Agency for Healthcare Research and Quality. Available at: <http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=318>. Accessed June 12, 2012.
 31. Anonymous. Evidence-based Practice Center Systematic Review Protocol. Project Title: Strategies To Improve Cardiovascular Risk Factors in People With Serious Mental Illness: A Comparative Effectiveness Review. Available at: <http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=933&pageaction=displayproduct>. Accessed June 22, 2012.
 32. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine*. 2002;21(11):1539-58. PMID: 12111919.
 33. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50(4):1088-101. PMID: 7786990.
 34. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: Grading the strength of a body of evidence when comparing medical interventions--Agency for Healthcare Research and Quality and the Effective Health-Care Program. *J Clin Epidemiol*. 2010;63(5):513-23. PMID: 19595577.
 35. Atkins D, Chang SM, Gartlehner G, et al. Assessing applicability when comparing medical interventions: AHRQ and the Effective Health Care Program. *J Clin Epidemiol*. 2011;64(11):1198-207. PMID: 21463926.
 36. Wildes JE, Marcus MD, Fagiolini A. Obesity in patients with bipolar disorder: a biopsychosocial-behavioral model. *J Clin Psychiatry*. 2006;67(6):904-15. PMID: 16848650.
 37. Loh C, Meyer JM, Leckband SG. A comprehensive review of behavioral interventions for weight management in schizophrenia. *Ann Clin Psychiatry*. 2006;18(1):23-31. PMID: 16517450.
 38. Gabriele JM, Dubbert PM, Reeves RR. Efficacy of behavioural interventions in managing atypical antipsychotic weight gain. *Obes Rev*. 2009;10(4):442-55. PMID: 19389059.
 39. U.S. Preventive Services Task Force. Screening for High Blood Pressure: U.S. Preventive Services Task Force Reaffirmation

- Recommendation Statement. AHRQ Publication No. 08-05105-EF-2, December 2007. First published in *Ann Intern Med* 2007;147-783-786. Available at: <http://www.uspreventiveservicestaskforce.org/uspstf07/hbp/hbprs.htm>. Accessed June 15, 2012.
40. U.S. Preventive Services Task Force. Counseling to Prevent Tobacco Use and Tobacco-Caused Disease Recommendation Statement. Available at: <http://www.uspreventiveservicestaskforce.org/3rduspstf/tobaccoun/tobcounrs.htm>. Accessed June 15, 2012. 2003.
 41. Norris SL, Kansagara D, Bougatsos C, et al. Screening for Type 2 Diabetes: Update of 2003 Systematic Evidence Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 61. AHRQ Publication No. 08-05116-EF-1. Rockville, Maryland: Agency for Healthcare Research and Quality. June 2008. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK33981/>. Accessed June 15, 2012.
 42. Helfand M, Carson S. Screening for Lipid Disorders in Adults: Selective Update of 2001 U.S. Preventive Services Task Force Review. Evidence Synthesis No. 49. Rockville, MD: Agency for Healthcare Research and Quality, April 2008. AHRQ Publication no. 08-05114-EF-1. Available at <http://www.ncbi.nlm.nih.gov/books/NBK33494/>. Accessed June 15, 2012.
 43. Gierisch JM, Bastian LA, Calhoun PS, et al. Smoking cessation interventions for patients with depression: a systematic review and meta-analysis. *J Gen Intern Med*. 2012;27(3):351-60. PMID: 22038468.
 44. Gierisch JM, Bastian LA, Calhoun PS, et al. Comparative Effectiveness of Smoking Cessation Treatments for Patients With Depression: A Systematic Review and Meta-analysis of the Evidence. VA-ESP Project #09-010; 2010.
 45. Bryant J, Bonevski B, Paul C, et al. A systematic review and meta-analysis of the effectiveness of behavioural smoking cessation interventions in selected disadvantaged groups. *Addiction*. 2011;106(9):1568-85. PMID: 21489007.
 46. Mitchell AJ, Delaffon V, Vancampfort D, et al. Guideline concordant monitoring of metabolic risk in people treated with antipsychotic medication: systematic review and meta-analysis of screening practices. *Psychol Med*. 2012;42(1):125-47. PMID: 21846426.
 47. Haupt DW, Rosenblatt LC, Kim E, et al. Prevalence and predictors of lipid and glucose monitoring in commercially insured patients treated with second-generation antipsychotic agents. *Am J Psychiatry*. 2009;166(3):345-53. PMID: 19147694.
 48. Morrato EH, Newcomer JW, Kamat S, et al. Metabolic screening after the American Diabetes Association's consensus statement on antipsychotic drugs and diabetes. *Diabetes Care*. 2009;32(6):1037-42. PMID: 19244091.
 49. Morrato EH, Druss B, Hartung DM, et al. Metabolic testing rates in 3 state Medicaid programs after FDA warnings and ADA/APA recommendations for second-generation antipsychotic drugs. *Arch Gen Psychiatry*. 2010;67(1):17-24. PMID: 20048219.
 50. Morrato EH, Druss BG, Hartung DM, et al. Small area variation and geographic and patient-specific determinants of metabolic testing in antipsychotic users. *Pharmacoepidemiol Drug Saf*. 2011;20(1):66-75. PMID: 21182154.
 51. Williams JW, Jackson GL, Powers BJ, et al. Closing the Quality Gap Series: Revisiting the State of the Science. The Patient-Centered Medical Home. (Prepared by the Duke Evidence-based Practice Center under Contract No. 290-2007-10066-I.) Rockville, MD. Agency for Healthcare Research and Quality. [in press].
 52. Robinson KA, Saldanha IJ, Mckoy NA. Frameworks for Determining Research Gaps During Systematic Reviews. Methods Future Research Needs Report No. 2. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. HHS A 290-2007-10061-I.) AHRQ Publication No. 11-EHC043-EF. Rockville, MD: Agency for Healthcare Research and Quality. June 2011. Available at: www.effectivehealthcare.ahrq.gov/reports/financialcfm. Accessed May 22, 2012.

Introduction

Background

Serious Mental Illness and Cardiovascular Health

Serious mental illness (SMI) is defined generally as a major mental or behavioral disorder, causing substantial impairment in multiple areas of daily functioning. It includes disorders such as schizophrenia and bipolar disorder, but not substance abuse or developmental disorders, and affects about 4 to 8 percent of adults.¹⁻³ Individuals with SMI have shortened life expectancies relative to the general population to an extent that is not explained by suicide and accidents alone.^{4,5} This population experiences higher rates of morbidity from multiple general medical conditions, including diabetes⁶⁻⁸ and cardiovascular disease (CVD).^{9,10} Among patients using the public mental health system, heart disease was the leading cause of death.¹¹ This excess CVD-related mortality may be due to a number of factors including direct effects of the illness, medications used to treat SMI, modifiable behavioral risk factors, and disparities in access and quality of health care.

For CVD, mental illness may be an independent risk factor that acts both directly through physiological effects such as underlying genetic vulnerabilities, or indirectly through effects on an individual's access to or interaction with the health care system.¹²⁻¹⁴ Modifiable cardiovascular risk factors, such as smoking,¹⁵ obesity,^{16,17} and physical inactivity¹⁸ are highly prevalent among individuals with SMI. Adverse effects of psychotropic drugs (notably second-generation antipsychotics) also may contribute to the development of CVD by increasing the risk of conditions such as hyperglycemia, hyperlipidemia, and obesity.¹⁹ Moreover, numerous studies have demonstrated disparities in the quality of general medical care provided to individuals with SMI.²⁰⁻²⁴ Given these issues, identifying intervention strategies that address cardiovascular risk in individuals with SMI is a pressing priority to avoid early morbidity and mortality.

Context of Care for Individuals With SMI

In contrast to individuals with less severe mental disorders, who largely receive mental health treatment in primary care settings, most individuals with SMI receive mental health treatment in specialized mental health settings. The normative treatment setting for individuals with SMI is outpatient treatment, with acute inpatient treatment for severe exacerbations. A minority of individuals with severe and treatment-resistant symptoms receive long-term inpatient treatment. Furthermore, general medical services have less commonly been offered in sites colocated in mental health settings^{25,26} or by those who are dually trained in both a mental health and a general medical discipline.²⁷ Consequently, people with SMI receive fewer preventive medical services^{20,21} and less frequent guideline-concordant treatment to manage chronic physical illnesses such as diabetes^{22,23} and CVD.²⁴ In addition to reduced quality of care for general medical services, multiple studies have demonstrated reduced access to outpatient general medical care among individuals with SMI. The results of an analysis of a nationally representative survey²⁸ showed that individuals with psychotic disorders and bipolar disorder, but not major depression, were less likely than the general population to have a primary care provider even after controlling for demographics, income, and insurance status.

Current Treatment Approaches

Managing CVD risk in individuals with SMI includes standard pharmacological and behavioral interventions used in the general population (Table 1) as well as treatments specific to this population (e.g., antipsychotic medication-switching to manage adverse effects). Multicondition lifestyle interventions such as combinations of smoking cessation, physical activity promotion, and nutrition counseling with or without medical management may be used to manage cardiovascular risk factors in individuals with SMI. In addition, peer support interventions have been used to improve mental health outcomes and show promise in improving general medical outcomes;²⁹ family interventions may have this potential as well. However, interventions and treatments used to improve cardiovascular risk may vary importantly in efficacy, adverse effects, complexity of regimen, need for monitoring, costs, and potential for drug-drug and drug-disease interactions.

The *efficacy* of most pharmacological agents used to reduce CVD risk is expected to be similar in patients with SMI when compared to general populations, but the potential for more severe or higher frequency adverse effects may be greater in individuals with SMI than in general populations due to drug-drug interactions (e.g., thiazides and lithium) or drug-disease interactions (e.g., varenicline and mood disorders). For behavioral interventions, direct effects of SMI and the limited social and economic support systems often available to these individuals may decrease *effectiveness*. To be optimally effective, health behavior interventions used in the general population to manage CVD risk may benefit from customization to the context and needs of individuals with SMI. Given the broad range of potential interventions and uncertainty about the effectiveness of competing strategies, an evidence synthesis was requested to inform guidelines and policy decisions.

Table 1. Selected pharmacological treatments and other behavioral strategies to manage cardiovascular risk factors

Comorbid Risk Factors in People With SMI	Pharmacological Treatments	Behavioral Strategies
Obesity	Orlistat Metformin Amantadine Topiramate Diethylpropion Phentermine Antipsychotic medication-switching	Patient education Behavioral counseling Exercise interventions Nutrition interventions Weight loss program Patient-focused strategies to optimize adherence Peer and family support interventions
Hyperglycemia/diabetes mellitus	Standard pharmacological treatment (multiple agents) Antipsychotic medication-switching	Patient education Patient-focused strategies to optimize adherence Behavioral counseling Exercise interventions Nutrition interventions Weight loss program Peer and family support interventions

Comorbid Risk Factors in People With SMI	Pharmacological Treatments	Behavioral Strategies
Hyperlipidemia	Statins, fibrates, niacin, etc. (standard treatment) Antipsychotic medication-switching	Patient education Exercise program Nutrition counseling Patient-focused strategies to optimize adherence Peer and family support interventions
Hypertension	Standard pharmacologic treatment (multiple agents) Antipsychotic medication-switching	Patient education Patient-focused strategies to optimize adherence Behavioral counseling Relaxation training Exercise interventions Nutrition interventions Weight loss program Peer and family support interventions
Smoking	Bupropion Nicotine replacement therapy Varenicline	Patient education Behavioral counseling Peer and family support interventions

Scope and Key Questions

Scope of the Review

This comparative effectiveness review was funded by the Agency for Healthcare Research and Quality (AHRQ). The review was designed to evaluate strategies to improve cardiovascular risk factors in adults with SMI. SMI has been defined variously by different groups over time.³⁰ For the purposes of this evidence review, people with SMI are defined as individuals who have: (1) schizophrenia or schizoaffective disorder (or other related primary psychotic disorder), (2) bipolar disorder, or (3) current major depression with psychotic features. We also included studies that enrolled adults with SMI or severe and persistent mental illness (SPMI) but did not specify diagnoses. Individuals with a primary diagnosis of substance abuse, dementia, personality disorder, or mental retardation are excluded from this definition.

To prioritize interventions for review, we examined published systematic reviews of strategies to improve cardiovascular risk factors in individuals with SMI and consulted with our stakeholder panel. Based on this assessment, we included randomized controlled trials (RCTs) of the pharmacological and patient-focused behavioral strategies listed in Table 1, along with peer and family support interventions. For patient-level intervention strategies, RCTs yield the highest quality evidence. We included both active and control comparators. We excluded from our review general health advice, interventions for smoking cessation only, and models to provide integrated mental health-general medical care, because these topics had been the subject of recent high-quality reviews.³¹⁻³⁵ Major outcomes of interest for this report are the primary cardiovascular risk factor of interest, physical functioning or health-related quality of life, adverse effects, and all-cause mortality.

Key Questions

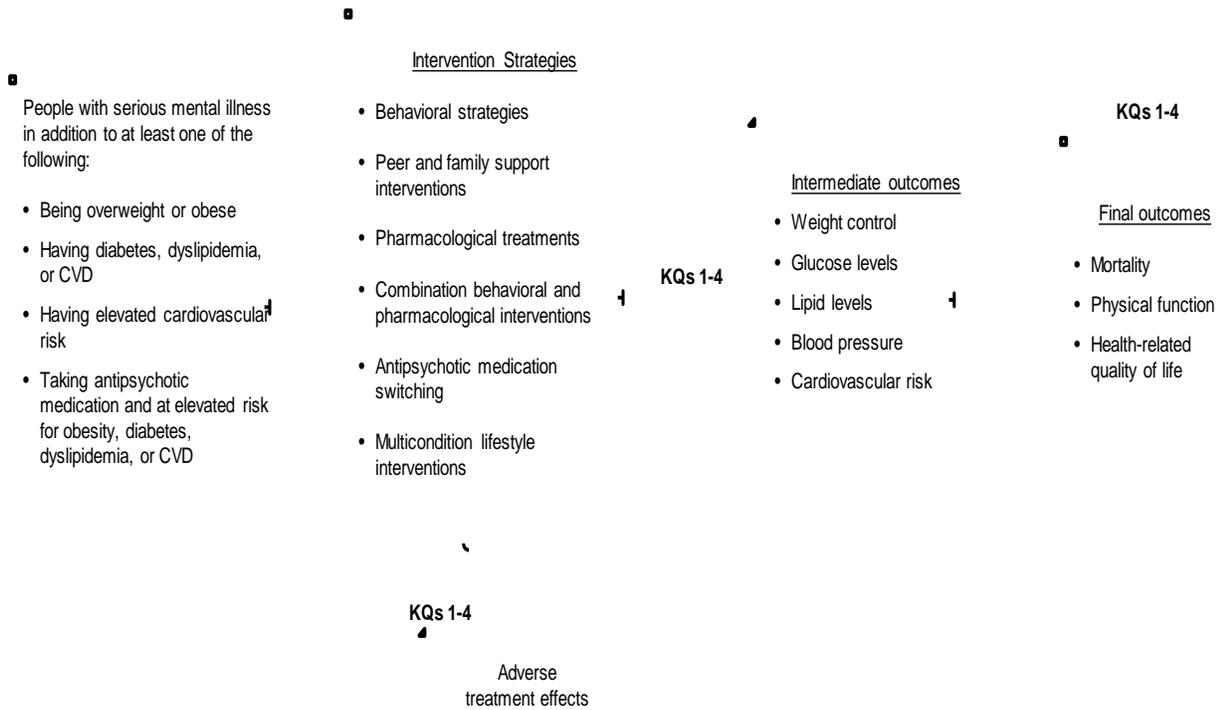
With input from our Technical Expert Panel, we constructed Key Questions (KQs) using the general approach of specifying the population of interest, interventions, comparators, outcomes, timing of outcomes, and settings (PICOTS; see the section on “Inclusion and Exclusion Criteria” in the Methods chapter for details). The draft KQs developed during this process were available for public comment from 28 October 2011 to 28 November 2011. Comments received led to revisions including the addition of a separate KQ for dyslipidemia and the inclusion of peer and family support interventions in the strategies examined for each KQ. The final KQs considered in this comparative effectiveness review were:

- **KQ 1:** What is the effectiveness of weight-management behavioral interventions (e.g., behavioral counseling, health education), peer or family support interventions, pharmacological treatments (e.g., orlistat, topiramate), antipsychotic medication-switching to an antipsychotic with a low or neutral impact on weight, or their combination on weight control and related physical health outcomes (e.g., health-related quality of life, mortality) compared with each other or with usual care (or other control) among adults with serious mental illness (SMI) who are overweight, obese, or taking antipsychotics?
- **KQ 2:** What is the effectiveness of diabetes-management behavioral interventions (e.g., behavioral counseling, health education), peer or family support interventions, pharmacological treatments (e.g., rosiglitazone, metformin), antipsychotic medication-switching to an antipsychotic with a low or neutral impact on glucose level, or their combination on glucose-level control and related physical health outcomes (e.g., health-related quality of life, mortality) compared with each other or with usual care (or other control) among adults with SMI who have diabetes or are taking antipsychotics?
- **KQ 3:** What is the effectiveness of dyslipidemia-management behavioral interventions (e.g., behavioral counseling, health education), peer or family support interventions, pharmacological treatments (e.g., statins), antipsychotic medication-switching to an antipsychotic with a low or neutral impact on lipid levels, or their combination on lipid-level control and related physical health outcomes (e.g., health-related quality of life, mortality) compared with each other or with usual care (or other control) among adults with SMI who have dyslipidemia or are taking antipsychotics?
- **KQ 4:** What is the effectiveness of multicondition lifestyle interventions (e.g., combinations of smoking cessation, physical activity, and nutrition counseling with or without medication management) on cardiovascular risk factors and related physical health outcomes (e.g., health-related quality of life, mortality) among adults with SMI who have cardiovascular disease, elevated cardiovascular risk (e.g., hypertension), or are taking antipsychotics?

Analytic Framework

Figure 1 shows the analytic framework for this systematic review.

Figure 1. Analytic framework



Abbreviations: CVD = cardiovascular disease; KQ = key question

The population evaluated in this comparative effectiveness review will be adults with SMI who also have at least one of the following conditions: are overweight or obese; have diabetes, dyslipidemia, or cardiovascular disease (CVD); are at elevated CVD risk, or are taking antipsychotic medication and so are at elevated risk for obesity, diabetes, dyslipidemia, or CVD. Intervention strategies considered by the four KQs are (1) behavioral strategies, (2) peer and family support interventions, (3) pharmacological treatments, (4) combinations of behavioral and pharmacological interventions, (5) antipsychotic medication switching, and (6) multicondition lifestyle interventions. The intermediate outcomes considered will be weight control, glucose levels, lipid levels, blood pressure, and cardiovascular risk. The final outcomes considered will be mortality, physical function, and health-related quality of life. All four KQs will consider the adverse effects of treatment interventions.

Organization of This Report

The remainder of this report is organized to describe detailed methods, overview of included studies, and results by KQ. Each Results section describes primary outcomes relevant to the KQ and cross-references other sections for related outcomes. For example, studies evaluating weight loss interventions are summarized in KQ 1 (weight-management behavioral interventions), but secondary outcomes such as effects on glucose and lipid parameters are cross-referenced to the specific KQ that evaluated those interventions. In the Discussion chapter, we present a table summarizing the strength of evidence across outcomes for each type of intervention.

Methods

The methods for this comparative effectiveness review follow those suggested in the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (available at <http://www.effectivehealthcare.ahrq.gov/methodsguide.cfm>; hereafter referred to as the *Methods Guide*).³⁶ The main sections in this chapter reflect the elements of the protocol established for the systematic review; certain methods map to the PRISMA checklist.³⁷

Topic Refinement and Review Protocol

During the topic refinement stage, we solicited input from Key Informants representing clinicians (psychiatry, psychology, mental health education and treatment), patient advocates, scientific experts, and payers to help define the Key Questions (KQs). The KQs were then posted for a 4-week public comment period, and the comments received were considered in the development of the research protocol. We next convened a Technical Expert Panel (TEP) comprising clinical, content, and methodological experts to provide input in defining populations, interventions, comparisons, and outcomes, as well as identifying particular studies or databases to search. The Key Informants and members of the TEP were required to disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Any potential conflicts of interest were balanced or mitigated. Key Informants and members of the TEP did not perform analysis of any kind or contribute to the writing of the report. Members of the TEP were invited to provide feedback on an initial draft of the review protocol which was then refined based on their input, reviewed by AHRQ, and posted for public access at the AHRQ Effective Health Care Web site.³⁸

Literature Search Strategy

Sources Searched

To identify the relevant published literature, we searched MEDLINE[®], Embase[®], PsycINFO[®], and the Cochrane Database of Systematic Reviews. Where possible, we used existing validated search filters (such as the Clinical Queries Filters in PubMed[®]). An experienced search librarian guided all searches. Exact search strings are included in Appendix A. We supplemented the electronic searches with a manual search of citations from a set of key primary and review articles.³⁹⁻⁷⁸ The reference lists for these articles were manually searched and cross-referenced against our library of search results, and additional manuscripts were retrieved. All citations were imported into an electronic database (EndNote[®] X4; Thomson Reuters, Philadelphia, PA).

We used two approaches to identify relevant grey literature: (1) a request for scientific information packets submitted to drug manufacturers and (2) a search of trial records listed in ClinicalTrials.gov (see Appendix A for search date and exact search terms). The search of ClinicalTrials.gov was also used as a mechanism to ascertain publication bias by identifying completed but unpublished studies. We also explored the possibility of publication bias specifically in our quantitative synthesis of the included literature using meta-analysis techniques. While the draft report is under peer review, we will update the search and include

any eligible studies identified either during that search or through peer or public reviews in the final report.

Inclusion and Exclusion Criteria

The PICOTS criteria used to screen articles for inclusion/exclusion at both the title-and-abstract and full-text screening stages are detailed in Table 2.

Table 2. Inclusion and exclusion criteria

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Population	<p>KQs 1–4: According to standardized diagnostic criteria (e.g., <i>DSM-IV</i>, ICD), people ≥ 18 years of age who currently have (or at any time during the past year had) one of the following:</p> <ul style="list-style-type: none"> • Schizophrenia or schizoaffective disorder (or other related primary psychotic disorder) • Bipolar disorder • Psychotic depression • No specified diagnosis but are classified as having SMI or severe and persistent mental illness (refer to definition in Introduction of this report). If the sample includes a mixed population of people with SMI, 70% of the sample must comprise the first two conditions above, or the outcomes must be reported separately for this subgroup. 	<p>KQs 1–4:</p> <ul style="list-style-type: none"> • People <18 years of age • People with a primary diagnosis of substance abuse, dementia, personality disorder, or mental retardation. (Studies of individuals with dual diagnoses [e.g., bipolar disorder and substance abuse] will be eligible.) • People with a primary diagnosis of other mood disorders

Study Characteristic	Inclusion Criteria	Exclusion Criteria
	<p><i>In addition to these population criteria:</i></p> <p>KQ 1:</p> <ul style="list-style-type: none"> • Individuals who are overweight or obese <i>or</i> • Individuals who are taking antipsychotics and consequently at increased risk for obesity <p>KQ 2:</p> <ul style="list-style-type: none"> • Individuals who have diabetes <i>or</i> • Individuals who are taking antipsychotics and consequently at risk for elevated glucose levels <p>KQ 3:</p> <ul style="list-style-type: none"> • Individuals who have dyslipidemia <i>or</i> • Individuals who are taking antipsychotics and consequently at risk for elevated lipid levels <p>KQ 4:</p> <ul style="list-style-type: none"> • Individuals who have cardiovascular disease (CVD) or elevated cardiovascular risk (e.g., hyperlipidemia, hypertension, metabolic syndrome) <i>or</i> • Individuals who are taking antipsychotics and consequently at increased risk for CVD 	
Interventions ^a	<p>KQs 1–4:</p> <ul style="list-style-type: none"> • Patient-focused behavioral interventions (e.g., behavioral counseling, patient education, adherence-enhancing interventions), peer or family support interventions, pharmacological treatments, or their combination targeting weight control, glucose levels, or cardiovascular risk profile • Changing from one antipsychotic to another (antipsychotic switching) to manage weight issues <i>or</i> elevated glucose levels <i>or</i> cardiovascular risk <p>KQ 4: Multicondition lifestyle interventions (e.g., combinations of smoking cessation, physical activity, nutrition counseling with or without medication management) for elevated cardiovascular risk</p>	<p>KQs 1–4:</p> <ul style="list-style-type: none"> • Studies with the primary goal of improving psychiatric outcomes • Mass media strategies • Studies of pharmacological agents that are not currently on the US market

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Comparators	<p>KQs 1–4: (control conditions)</p> <ul style="list-style-type: none"> • Usual care • Placebo • Other control (e.g., attention control; waitlist) <p>KQs 1–4: (active comparators)</p> <ul style="list-style-type: none"> • Patient-focused behavioral interventions, pharmacological treatments, or their combination targeting weight control, glucose levels, or cardiovascular risk profile • Changing from one antipsychotic to another (antipsychotic switching) to manage weight issues, or elevated glucose levels or cardiovascular risk <p>KQ 4: (active comparator) Other multicondition lifestyle interventions</p>	None
Outcomes	<p>KQ 1: Weight control (i.e., weight loss or maintenance of current weight)</p> <p>KQ 2: Glucose level (e.g., hemoglobin A_{1c})</p> <p>KQ 3: Lipid level (e.g., change in low-density lipoprotein)</p> <p>KQ 4: Cardiovascular risk profile (i.e., Framingham CVD scores) or multiple individual components of modifiable cardiovascular risk (e.g., lipid values, blood pressure, smoking status, glucose level)</p> <p>KQs 1–4:</p> <ul style="list-style-type: none"> • Health-related quality of life • All-cause mortality • Physical function • Serious adverse effects • Adverse effects (i.e., significant worsening of psychiatric status, discontinuations due to serious or nonserious adverse effects) 	Article reports only physical function/health-related quality of life outcomes and does not also include a primary cardiovascular risk measure of interest (e.g., weight, glucose level)
Timing	≥2 months	<2 months
Setting	<ul style="list-style-type: none"> • Outpatient mental health and outpatient general medical settings • Community settings 	Intervention delivered primarily in hospital inpatient setting
Study design	RCTs	<ul style="list-style-type: none"> • Not a clinical study (e.g., editorial, nonsystematic review, letter to the editor, case series) • Prospective and retrospective observational studies • N ≤20

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Publications	<ul style="list-style-type: none"> • English-language only • Peer-reviewed articles • Relevant systematic review, meta-analysis, or methods article (used for background only) • 1980 forward^b 	Non-English-language articles ^c

^aStudies were classified by primary study goal (i.e., weight management, diabetes management, CVD management). To meet criteria for inclusion in KQ 4, a study must recruit participants with multiple elevated CVD risk factors and state a goal to improve more than one condition related to cardiovascular risk.

^b1980 was selected as a date restriction since this was the year the *DSM-III* was introduced.

^cGiven the high volume of English-language publications (including the majority of known important studies), and concerns about the applicability of non-English publication studies to settings in the United States, non-English-language articles were excluded.

Abbreviations: CVD = cardiovascular disease; KQ = Key Question; RCTs = randomized controlled trials; SMI=serious mental illness

Study Selection

Using the prespecified inclusion and exclusion criteria described in Table 2, two investigators independently reviewed titles and abstracts for potential relevance to the KQs. Articles included by either reviewer underwent full-text screening. At the full-text screening stage, two investigators independently reviewed each article to determine if it met eligibility criteria, and indicated a decision to “include” or “exclude” the article for data abstraction. When the paired reviewers arrived at different decisions about whether to include or exclude an article, or about the reason for exclusion, they reconciled the difference through review and discussion, or through a third-party arbitrator if needed. Articles meeting our eligibility criteria were included for data abstraction. Relevant review articles and meta-analyses were flagged for manual searching of references and cross-referencing against the library of citations identified through electronic database searching.

For citations retrieved by searching the grey literature, the above-described procedures were modified such that a single screener initially reviewed all search results; final eligibility of citations for data abstraction was determined by duplicate screening review. All screening decisions were made and tracked in a DistillerSR database (Evidence Partners Inc, Manotick, ON, Canada).

Data Extraction

The investigative team created data abstraction forms and evidence table templates for abstracting data for the KQs. Based on clinical and methodological expertise, a pair of investigators was assigned to abstract data from each eligible article. One investigator abstracted the data, and the second reviewed the article and the accompanying completed abstraction form to check for accuracy and completeness. Quality ratings and efficacy–effectiveness ratings (see below) were completed independently by two investigators. Disagreements were resolved by consensus, or by obtaining a third reviewer’s opinion if consensus could not be reached. To aid in both reproducibility and standardization of data collection, researchers received data abstraction instructions directly on each form created specifically for this project within the DistillerSR database.

We designed the data abstraction forms for this project to collect the data required to evaluate the specified eligibility criteria for inclusion in this review, as well as demographic and other data needed for determining outcomes. We gave particular attention to describing the details of the interventions (e.g., pharmacotherapy used, intensity of behavioral interventions), patient characteristics (e.g., SMI diagnosis), and comparators that may be related to outcomes. Data necessary for assessing quality and applicability, as described in the *Methods Guide*,³⁶ were also abstracted. When critical data were missing, we contacted study authors. Of the seven authors contacted, five replied with the requested information.

We adapted a previously published efficacy–effectiveness instrument (Appendix B) to assess eight domains:⁷⁹ (1) setting/practitioner expertise, (2) restrictiveness of eligibility criteria, (3) health outcomes, (4) flexibility of the intervention and study duration, (5) assessment of adverse effects, (6) adequate sample size for important health outcomes, (7) intention-to-treat approach to analyses, and (8) identity of the comparison intervention. We developed definitions for each domain that were specific to the literature reviewed. We rated each of the eight domains as effectiveness (score=1) or efficacy (score=0); scores on each of the domains were summed and could range from 0–8. Studies were categorized as efficacy (0–2), mixed efficacy–effectiveness (3–5) or effectiveness (6–8) based on summed scores. Simple agreement between investigator pairs was 78 percent and unweighted kappa 0.57, indicating moderate agreement beyond chance for efficacy–effectiveness categories.

Before they were used, abstraction form templates were pilot-tested with a sample of included articles to ensure that all relevant data elements were captured and that there was consistency/reproducibility between abstractors. Forms were revised as necessary before full abstraction of all included articles. Some outcomes were reported only in figures. In these instances, we used the web-based software, EnGauge Digitizer (<http://digitizer.sourceforge.net/>) to convert graphical displays to numerical data. Appendix C lists the elements included in the data abstraction forms.

Quality Assessment of Individual Studies

We evaluated the quality of individual studies using the key criteria for RCTs described in the *Methods Guide*.³⁶ Criteria of interest included similarity of groups at baseline, extent to which outcomes were described, blinding of subjects and providers, blinded assessment of the outcome(s), intention-to-treat analysis, differential loss to followup between the compared groups or overall high loss to followup, conflicts of interest, methods of randomization, and allocation concealment.

To indicate the summary judgment of the quality of the individual studies, we used the summary ratings of good, fair, or poor based on their adherence to well-accepted standard methodologies and adequate reporting (Table 3). For each study, two investigators independently assigned a summary quality rating; disagreements were resolved by consensus or by discussion with a third investigator if agreement could not be reached. Quality ratings were assigned separately for “hard” outcomes (e.g., mortality, laboratory measurements) and all other outcomes (e.g., health-related quality of life); thus, a given study may have been categorized differently for two individual outcomes reported within that study.

Table 3. Definitions of overall quality ratings

Quality Rating	Description
Good	A study with the least bias; results are considered valid. A good study has a clear description of the population, setting, interventions, and comparison groups; uses a valid approach to allocate patients to alternative treatments; has a low dropout rate; and uses appropriate means to prevent bias, measure outcomes, and analyze and report results.
Fair	A study that is susceptible to some bias but probably not enough to invalidate the results. The study may be missing information, making it difficult to assess limitations and potential problems. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are possibly not valid, while others are probably valid.
Poor	A study with significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information; or have discrepancies in reporting. The results of a poor-quality study are at least as likely to reflect flaws in the study design as to indicate true differences between the compared interventions.

Data Synthesis

We began by summarizing key features of the included studies for each Key Question. To the degree that data were available, we abstracted information on study design; patient characteristics; clinical settings; interventions; and intermediate, final, and adverse effects outcomes. We then determined the feasibility of completing a quantitative synthesis (i.e., meta-analysis). Feasibility depended on the volume of relevant literature (≥ 3 studies), conceptual homogeneity of the studies, and completeness of the reporting of results. When a meta-analysis was appropriate, we used random-effects models to quantitatively synthesize the available evidence. For other outcomes we analyzed the results qualitatively. The outcomes amenable to meta-analysis were continuous; we therefore summarized these outcomes by a weighted difference of the means when the same scale (e.g., weight) was used and a standardized mean difference when the scales (e.g., health-related quality of life) differed across studies. We standardized results presentation such that a negative value indicates a greater intervention effect. When needed, we converted reported outcomes to a common unit (e.g., cholesterol from mmol/L to mg/dl). We present summary estimates, standard errors, and confidence intervals in our data synthesis.

We organized our analyses by KQ. When a single study reported outcomes relevant to multiple Key Questions, it was included in the analyses for each question. For example, a study evaluating a weight-loss intervention that specified weight as the primary outcome—but which also reported effects on glucose and lipid parameters—was described in each relevant KQ. We specified, a priori, weight control as measured by change in kilograms (or pounds), hemoglobin A1c (HbA1c) as the preferred measure of glucose control since it reflects average glucose values over a 3-month interval, and total and LDL cholesterol as measures of lipid control. For adverse effects, we report significant worsening of psychiatric status and discontinuations due to adverse effects. Interventions were categorized as: behavioral, pharmacological, peer or family support, or multicondition (e.g., specifically targeting more than one condition such as smoking cessation and weight loss). Drug classes were psychotropics, neurologics, metformin, antihistamines, nutritionals (i.e., carnitine), and switching between antipsychotic medications.

We tested for heterogeneity using graphical displays and test statistics (Q statistic), while recognizing that the ability of statistical methods to detect heterogeneity may be limited.⁸⁰ The I^2 describes the percentage of total variation across studies due to heterogeneity rather than to chance. Heterogeneity was categorized as low, moderate, or high based on I^2 values of 25

percent, 50 percent, and 75 percent respectively.⁸⁰ When there were sufficient studies, we explored heterogeneity in study effects by using subgroup analyses. When there were sufficient studies ($n \geq 10$), we assessed for publication bias using funnel plots and test statistics.⁸¹ All analyses were conducted using Comprehensive Meta-Analysis software (Version 2; Biostat, Englewood, NJ).

Strength of the Body of Evidence

The strength of evidence for each KQ and outcome was assessed using the approach described in the *Methods Guide*.^{36,82} In brief, the approach requires assessment of four domains: risk of bias, consistency, directness, and precision (Table 4).

Table 4. Strength of evidence required domains

Domain	Rating	How Assessed
Quality (risk of bias)	Good Fair Poor	Assessed primarily through study design (RCT versus observational study) and aggregate study quality
Consistency	Consistent Inconsistent Unknown/not applicable	Assessed primarily through whether effect sizes are generally on the same side of “no effect,” the overall range of effect sizes, and statistical measures of heterogeneity
Directness	Direct Indirect	Assessed by whether the evidence involves direct comparisons or indirect comparisons through use of surrogate outcomes or use of separate bodies of evidence
Precision	Precise Imprecise	Based primarily on the size of the confidence intervals of effect estimates, the optimal information size and considerations of whether the confidence interval crossed the clinical decision threshold for using a therapy

Additional domains were used when appropriate: coherence, and publication bias. These domains were considered qualitatively, and a summary rating of high, moderate, or low strength of evidence was assigned after discussion by two reviewers. In some cases, high, moderate, or low ratings were impossible or imprudent to make; for example, when no evidence was available or when evidence on the outcome was too weak, sparse, or inconsistent to permit any conclusion to be drawn. In these situations, a grade of insufficient was assigned. This four-level rating scale consists of the following definitions:

- High—High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate—Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- Low—Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
- Insufficient—Evidence either is unavailable or does not permit estimation of an effect.

Applicability

We assessed applicability across our KQs using the method described in the *Methods Guide*.^{36,83} In brief, this method uses the PICOTS format as a way to organize information relevant to applicability. The most important issue with respect to applicability is whether the outcomes are different across studies that recruit different populations (e.g., age groups, exclusions for comorbidities) or use different methods to implement the interventions of interest; that is, important characteristics are those that affect baseline (control-group) rates of events, intervention-group rates of events, or both. We used a checklist to guide the assessment of applicability (Appendix C). We used these data to evaluate the applicability to clinical practice, paying special attention to study eligibility criteria, demographic features of the enrolled population in comparison to the target population, characteristics of the intervention used in comparison with care models currently in use, and clinical relevance and timing of the outcome measures. We summarized issues of applicability qualitatively.

Peer Review and Public Commentary

The peer review process is our principal external quality-monitoring device. Nominations for peer reviewers were solicited from several sources, including the TEP and interested Federal agencies. Experts in psychiatry, mental illness, chronic medical conditions, systematic review methodology, pharmacoepidemiology of SMI, public health, and integration of mental health and primary care, along with individuals representing stakeholder and user communities, have been invited to provide external peer review of this draft report; AHRQ and an associate editor will also provide comments. The draft report will be posted on the AHRQ Web site for 4 weeks to elicit public comment. We will address all reviewer comments, revising the text as appropriate, and will document everything in a disposition of comments report that will be made available 3 months after the Agency posts the final report on the AHRQ Web site. We will include a list of peer reviewers submitting comments on this draft in the final report.

Results

Introduction

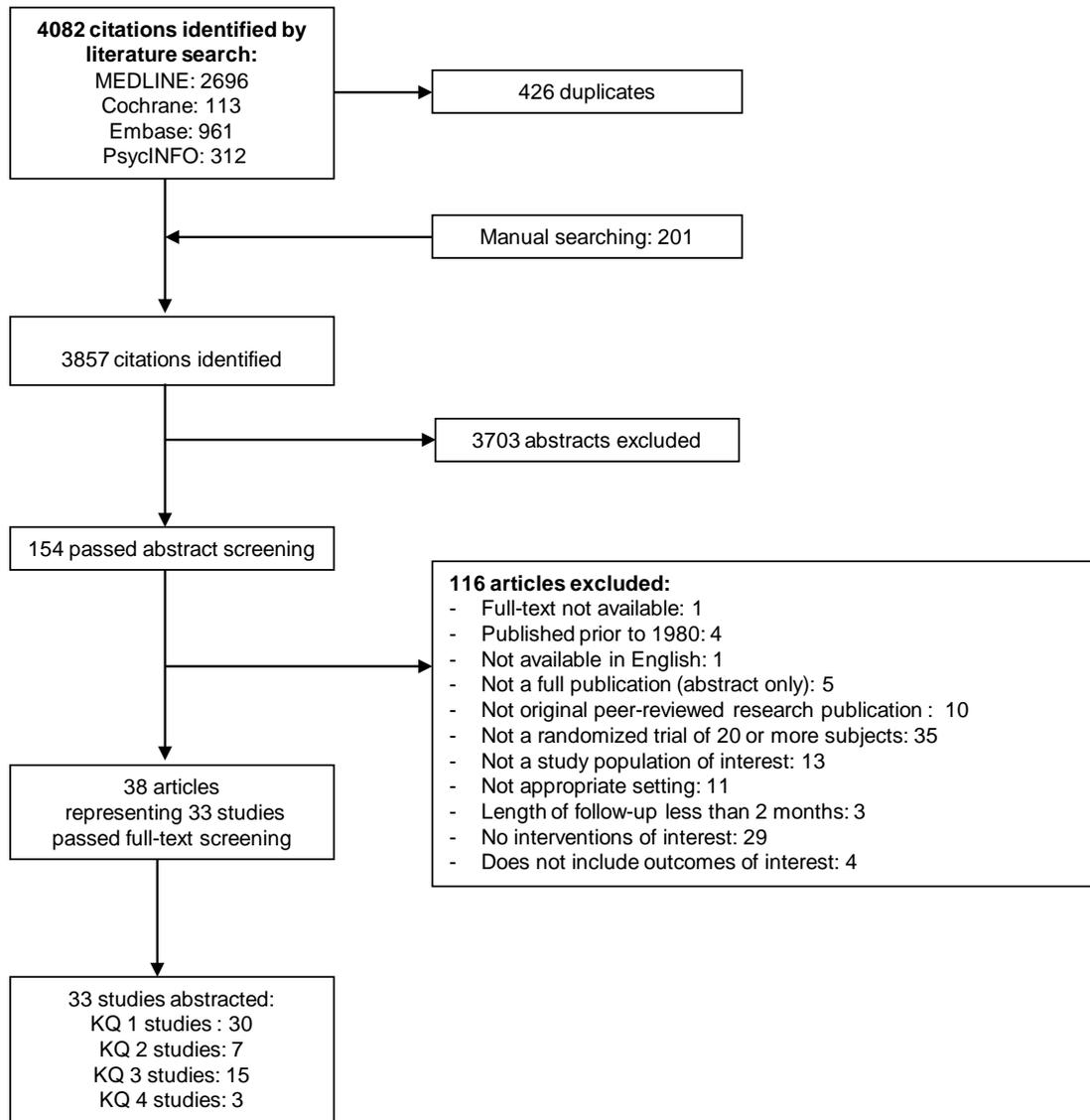
In what follows, we begin by presenting the results of our literature searches. We then provide a brief description of the included studies. The remainder of the chapter is organized by Key Question (KQ). Under each KQ, we begin by listing the key points of the findings, followed by a brief description of included studies, followed by a more detailed synthesis of the evidence. The detailed syntheses are organized by intervention and primary outcomes: cardiovascular risk factor, functional status or health-related quality of life, adverse effects and cardiovascular mortality. We conducted quantitative analyses (i.e., meta-analyses) where possible, as described in the Methods chapter. Results of these analyses are presented graphically in the form of forest plots. A list of abbreviations and acronyms used in this chapter is provided at the end of the report.

Results of Literature Searches

Figure 2 depicts the flow of articles through the literature search and screening process. Searches of PubMed[®], Embase[®], and the Cochrane Database of Systematic Reviews yielded 4082 citations, 426 of which were duplicate citations. Manual searching identified 201 additional citations, for a total of 3857 citations. After applying inclusion/exclusion criteria at the title-and-abstract level, 154 full-text articles were retrieved and screened. Of these, 116 were excluded at the full-text screening stage, leaving 38 articles (representing 33 unique studies) for data abstraction. As indicated in Figure 2, many articles/studies were relevant to more than one KQ. The information request strategy described in the Methods chapter (contacts to pharmaceutical manufacturers) did not result in any additional data for consideration.

Appendix D provides a detailed listing of included articles. Appendix E provides a complete list of articles excluded at the full-text screening stage, with reasons for exclusion.

Figure 2. Literature flow diagram



Abbreviation: KQ=Key Question

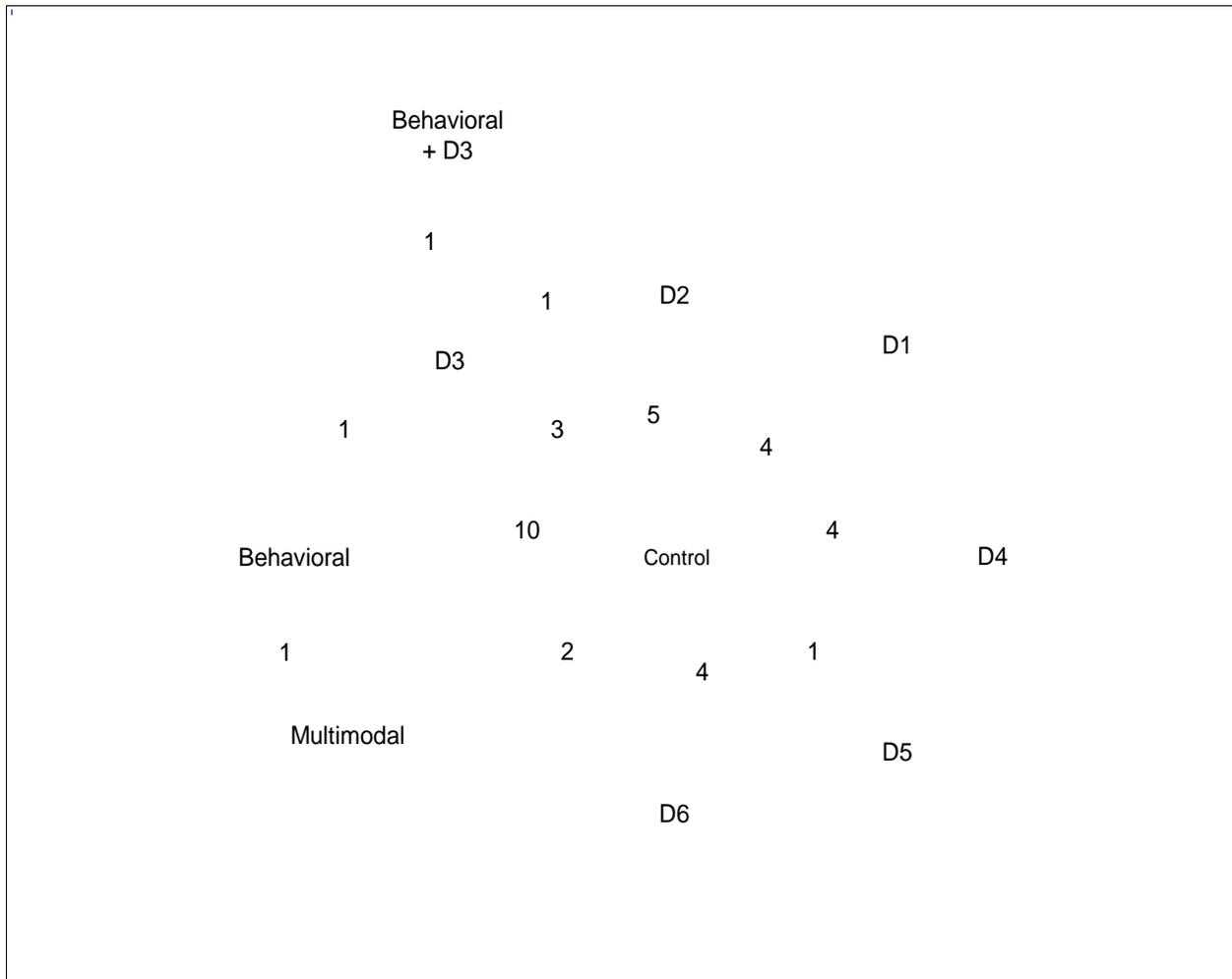
Description of Included Studies

Overall, we included 33 studies, some of which were relevant to more than one KQ: 30 studies were relevant to KQ 1, 7 to KQ 2, 15 to KQ 3, and 3 to KQ 4. Studies were conducted in Europe (24%); Asia (9%); the United States (39%); and South America (6%); or multiple continents (21%). Sixty-one percent of included studies enrolled individuals with schizophrenia or schizoaffective disorder, 12 percent recruited individuals with schizophrenia, schizoaffective disorder, or bipolar disorder, 21 percent recruited patients either taking antipsychotics or with an unspecified SMI diagnosis, and only 6 percent recruited individuals with bipolar disorder. The vast majority of studies were specifically designed to control weight (79%); only one study was designed to target diabetes management, and no studies were designed to target dyslipidemia. Table F-1 in Appendix F details the study characteristics for the 33 included studies.

Treatment Network Map

Figure 3 maps the direct comparisons between treatments evaluated in this report. The drugs, treatment indications, and major mechanisms of action are summarized in Table 5. The most common comparisons were between behavioral interventions and control (27% of comparisons), followed by neurologics (14%) and psychotropics or antihistamines compared with control (11%). Relatively few studies compared two active interventions. No studies evaluated standard medications for hyperlipidemia (e.g., HMG-CoA reductase inhibitors) or orlistat (a Food and Drug Administration [FDA]-approved medication for weight control), and only a few studies evaluated hypoglycemic medication.

Figure 3. Treatment network describing the number of comparisons for each intervention (n=33 trials)^a



^aBecause some trials had more than two arms, there are more comparisons than trials.

D1=Psychotropics (aripiprazole, atomoxetine, fluoxetine, ramelteon)

D2=Neurologics (amantadine, topiramate, zonisamide)

D3=Metformin

D4=Antihistamines (nizatidine)

D5=Nutritionals (carnitine)

D6=Antipsychotic switching (from oral olanzapine to aripiprazole, olanzapine long-acting injection, olanzapine oral disintegrating)

Drugs Evaluated

Table 5 lists the drugs evaluated in the included studies and their FDA indications and mechanism of action.

Table 5. Drugs evaluated

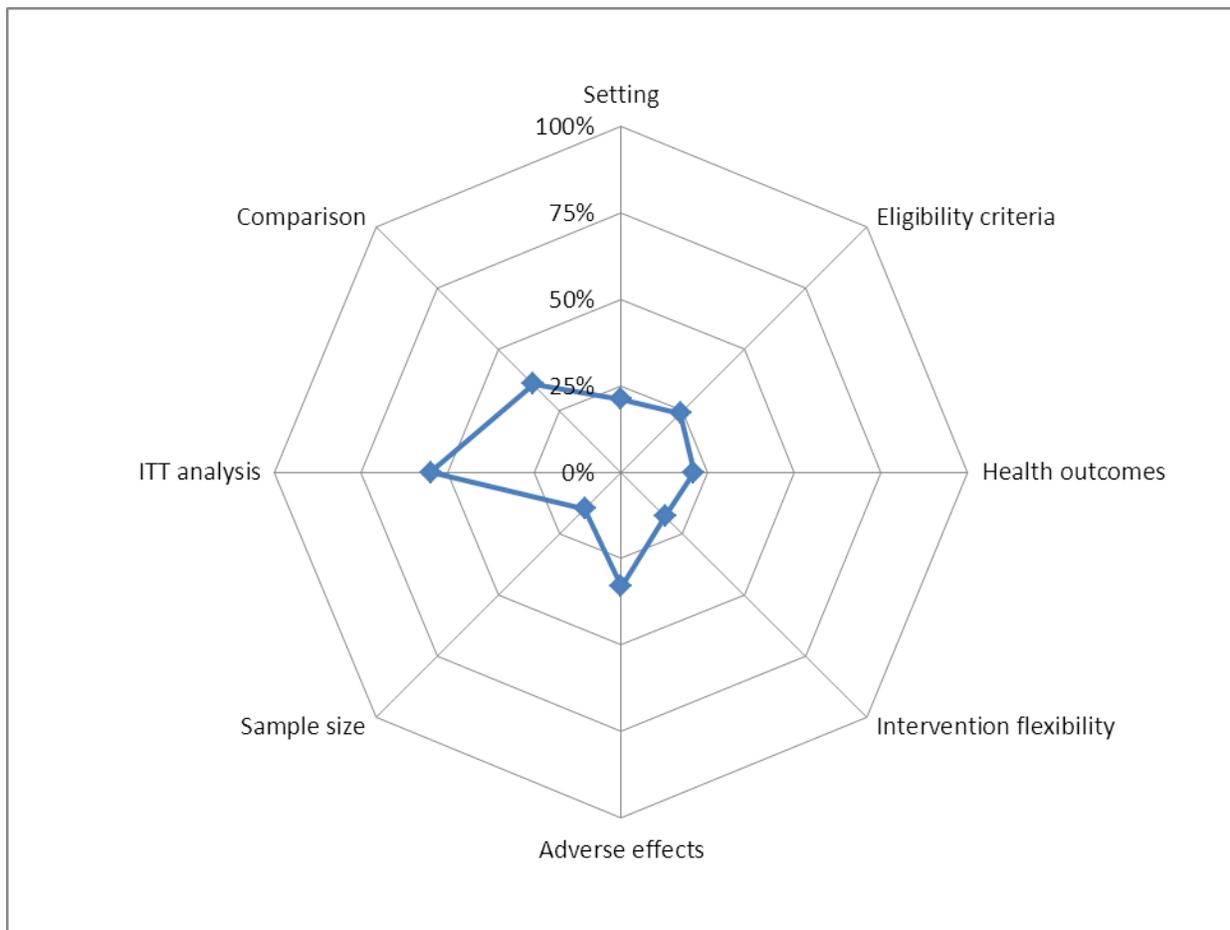
Drug	FDA Indications	Major Mechanism of Action
<i>Psychotropics</i>		
Atomoxetine	Attention deficit hyperactivity disorder	Selectively inhibits norepinephrine reuptake
Fluoxetine	Major depressive disorder Bipolar disorder Obsessive compulsive disorder Panic disorder Bulimia nervosa	Selectively inhibits serotonin reuptake
Aripiprazole	Schizophrenia Bipolar disorder-manic/mixed Major depressive disorder (adjunctive treatment)	Partially agonizes dopamine D2 and serotonin 5-HT1A receptors; antagonizes serotonin at 5-HT2A receptors
Olanzapine	Schizophrenia Bipolar disorder-depressive Bipolar disorder-manic/mixed Major depressive disorder-treatment resistant	Antagonizes dopamine, serotonin 5-HT2, and other receptors
Quetiapine	Schizophrenia Bipolar disorder-depressive Bipolar disorder-manic Major depressive disorder (adjunctive treatment)	Antagonizes dopamine, serotonin 5-HT2, and other receptors
Ramelteon	Insomnia	Melatonin receptor agonist
<i>Neurologics</i>		
Amantadine	Influenza Extrapyramidal disorders Parkinsonism	Potentiate CNS dopaminergic response; inhibits viral replication
Topiramate	Seizure disorders Migraine prophylaxis	Exact mechanism unknown; blocks sodium channels, increases GABA, antagonizes kainite
Zonisamide	Partial seizures	Exact mechanism unknown; blocks sodium channels and T-type calcium channels, mild carbonic anhydrase inhibiting effects; some augmentation of dopaminergic and serotonergic transmission
<i>Other drugs</i>		
Metformin	Diabetes mellitus Polycystic ovary syndrome	Decreases hepatic glucose production and intestinal glucose absorption; increases insulin sensitivity
Nizatidine	Duodenal or gastric ulcer treatment Gastroesophageal reflux	Selectively antagonizes histamine H2 receptors
Carnitine	Nutritional (no FDA indication)	Lipid metabolism, lots of studies for many other disease

Of the 33 studies, 9 (27%) were judged to be of good quality, 20 (61%) of fair quality, and 4 (12%) of poor quality. Considering individual components of study design and conduct, the strengths were comparable groups at baseline and valid outcome measures. However, 73 percent of studies had inadequate or unclear specification of allocation sequence and concealment, 67 percent had inadequate or unclear specification of protocols for blinding, and 39 percent had high rates of differential attrition. Nearly 70 percent of studies were supported at least in part by industry.

Efficacy–Effectiveness Scale

We also categorized studies using an efficacy–effectiveness scale (Appendix B). Studies that have more effectiveness characteristics may be more likely to yield intervention effects that more closely mirror outcomes seen in usual practice. No study was categorized as an effectiveness study. Of the 33 studies, 20 were categorized as efficacy and 13 as mixed efficacy–effectiveness. As shown in Figure 4, the minority of studies were categorized as effectiveness on each of the eight domains examined.

Figure 4. Proportion of studies rated effectiveness on each efficacy–effectiveness domain



Further details are provided in the relevant KQ Results sections that follow and in Appendix F, which reports details of the characteristics of each included study, including geographical location, clinical setting, study population, intervention(s), comparator(s), and quality rating.

As described in the Methods chapter, we searched ClinicalTrials.gov to identify completed but unpublished studies as a mechanism for ascertaining publication bias. Our search yielded 1349 citations. A single reviewer identified 70 of these as potentially relevant; 42 of these had been completed at least 1 year prior to our search of the published literature. Of these 42, 18 were published and 4 are among our included studies; 24 had no identified published literature. A total of 28 studies were not completed at least 1 year prior to our search of the published literature. Twenty-seven of these are ongoing (12 applicable to KQ 1; 2 applicable to KQ 2; 2 applicable to KQ 3; 3 applicable to KQ 4; 8 applicable to multiple KQs) and 1 was terminated. In summary, our search of ClinicalTrials.gov found evidence for completed but unpublished studies relevant to our KQs.

Key Question 1. Effectiveness of Weight-Management Interventions

KQ 1: What is the effectiveness of weight-management behavioral interventions (e.g., behavioral counseling, health education), peer or family support interventions, pharmacological treatments (e.g., orlistat, topiramate), antipsychotic medication-switching to an antipsychotic with a low or neutral impact on weight, or their combination on weight control and related physical health outcomes (e.g., health-related quality of life, mortality) when compared with each other or with usual care (or other control) among adults with serious mental illness (SMI) who are overweight, obese, or taking antipsychotics?

Key Points

- Of the 30 studies identified, most were specifically designed to control weight gain for persons with SMI. Other studies targeted diabetes management or antipsychotic metabolic effects but also addressed weight management.
- No studies evaluated the weight loss medication orlistat in this population.
- The antiseizure agents topiramate and zonisamide and behavioral interventions were associated with greater weight loss than controls. However, there were few studies of antiseizure agents with small samples sizes. The magnitude of effect was small for both intervention strategies.
- For psychotropic agents and nizatidine, there was no advantage in favor of intervention compared with control for the management of weight gain among patients with SMI. However, few trials evaluated these medication interventions.
- In three relatively short-term trials, participants randomized to treatments containing metformin lost more weight than control conditions. The magnitude of effect was small.
- Switching from standard oral olanzapine to a different antipsychotic medication yielded mixed results across a variety of switching strategies.
- Few studies reported effects on physical functioning or health-related quality of life, and no studies reported all-cause mortality.

Detailed Synthesis

We identified 30 RCTs encompassing 3333 patients that assessed the effects of weight management strategies among adults with SMI.⁸⁴⁻¹¹² In total, 21 studies targeted weight control,^{85-87,89-96,98-100,102,103,105,106,108-110,113} 5 obesity prevention,^{84,97,107,111,113} 3 antipsychotic metabolic effects,^{88,104,112} and 1 diabetes management.¹⁰¹ All identified studies were published from 2003 forward, reflecting the recent clinical interest in weight control among individuals with SMI. Ten trials assessed behavioral intervention strategies compared with control,^{84,89,90,93,95,99-101,109,110} 14 assessed pharmacological strategies compared with placebo,^{85-88,92,94,96,105-108,111-113} 4 assessed antipsychotic-switching strategies,^{91,98,102,104} and 1 four-arm trial assessed metformin alone, lifestyle intervention alone, metformin plus lifestyle intervention, or placebo.¹⁰³ Of the 30 trials that reported on weight control, 7 are included in Key Question 2 (diabetes control), 14 are included in Key Question 3 (dyslipidemia control), and none is included in Key Question 4 (multicondition interventions).

Study Characteristics

Table 6 summarizes the study characteristics of the 30 included studies. Most studies (n=18) were rated fair quality, with 8 studies rated good quality and 4 poor quality. Common reasons for reduced study quality were inadequate or unclear specification of the following: allocation sequence and concealment, protocols for blinding of assessments, reported conflicts of interest. We identified no studies rated as effectiveness trials, 19 as efficacy trials, and 11 as mixed efficacy–effectiveness trials. The most common reasons studies were coded as efficacy trials were because they were conducted in a highly specialized setting, had short-term followup only (<6 months), had inadequate or unspecified sample sizes, or focused on intermediate health outcomes rather than clinically important outcomes. Twelve studies were conducted exclusively with U.S.-based populations. Most studies (n=20) were conducted in outpatient mental health settings. Twenty-one studies received at least partial funding support from industry sponsors.

Of the 3333 participants across the 30 included studies, most were male and white. Of note, 14 studies did not report race/ethnicity data and 3 studies did not provide information on sex of the randomized samples. Nineteen studies recruited patients with schizophrenia/schizoaffective disorder, three recruited patients with schizophrenia/schizoaffective disorder or bipolar disorder, two recruited participants with bipolar disorder only, and six did not specify psychiatric illness but defined the sample as having SMI or taking antipsychotics. Only 10 studies stated that they recruited participants who were classified as obese or overweight at baseline.

Table 6. Study characteristics for KQ 1: Weight-management interventions

Characteristic	Details
Studies: N (patients) ^a	30 studies (3333 patients)
Mean age of sample: Median (range)	38.9 (26.3 – 54.0)
Sex: N patients (%)	
Female	1237 (37.1%)
Male	1730 (57.3%)
NR	363 (10.9%)
Race: N patients (%)	
White	1568 (47.0%)
Nonwhite	776 (23.3%)
NR	989 (29.7%)

Characteristic	Details
Setting: N studies (%)	
Mental health	23 (77%)
General medical	1 (3%)
Community	2 (7%)
Integrated mental health-medical	0 (0%)
Not reported	4 (13%)
Study quality: N studies (%)	
Good	8 studies (27%)
Fair	18 studies (60%)
Poor	4 studies (13%)
Efficacy–effectiveness rating: N studies (%)	
Efficacy (0–2)	19 studies (63%)
Mixed (3–5)	11 studies (37%)
Effectiveness (6–7)	0 studies (0%)
Comparisons: N studies (patients randomized)	
Drug vs. placebo/control	14 (897)
Antipsychotic vs. antipsychotic switching	4 (1520)
Behavioral vs. placebo/control	10 (662)
Drug vs. Behavioral vs. both vs. placebo/control	1 (128)
Drug vs. Drug vs. placebo/control	1 (199)

^aThe number of patients with demographic data reported is fewer than the number randomized.

^bQuality ratings in the table are reported on the basis of how studies were conducted in relation to laboratory-based physical health outcomes. Ratings were also applied on the basis of patient-reported outcomes. Only one quality rating differed on the basis of physical versus patient-reported outcomes⁹⁹ and was rated as fair on laboratory-based physical health outcomes and poor on patient-reported outcomes.

Meta-analysis and Qualitative Review

We classified studies and organized findings by the following intervention categories: (1) behavioral interventions, (2) peer or family support interventions, (3) pharmacological treatments (psychotropic agents [e.g., atomoxetine, aripiprazole, fluoxetine], neurologic agents [e.g., topiramate, amantadine, zonisamide], metformin, nizatidine, and carnitine), and (4) antipsychotic-switching interventions.

We had sufficient studies to perform three meta-analyses. The other comparisons were synthesized qualitatively. Below, we focus on the weight control outcomes and, when reported, adverse effects (i.e., discontinuation due to adverse effects, significant worsening of psychiatric symptoms), and health-related quality of life. While mortality was an outcome of interest, no study reported on this outcome. Details for HbA1c are in the Results section of KQ 2, and details for lipids are in KQ 3.

Effect of Behavioral Interventions on Weight Control

Eleven studies (3 good quality, 6 fair, 2 poor) measured the impact of behavioral interventions on weight control among individuals with SMI.^{84,89,90,93,95,99-101,103,109,110} As expected, most patients also were on antipsychotics or mood stabilizers at baseline and continued these medications throughout the intervention. The number of treatment sessions ranged from 4 to 24 and the treatment duration ranged from 8 weeks to 6 months. Six of these studies were classified as more intensive behavioral strategies, operationalized as at least six contacts over 12 weeks, a written manual of counseling protocol, and skills-based versus education-based intervention content. Selected details of each intervention are detailed in Table 7.

Table 7. Details of behavioral interventions

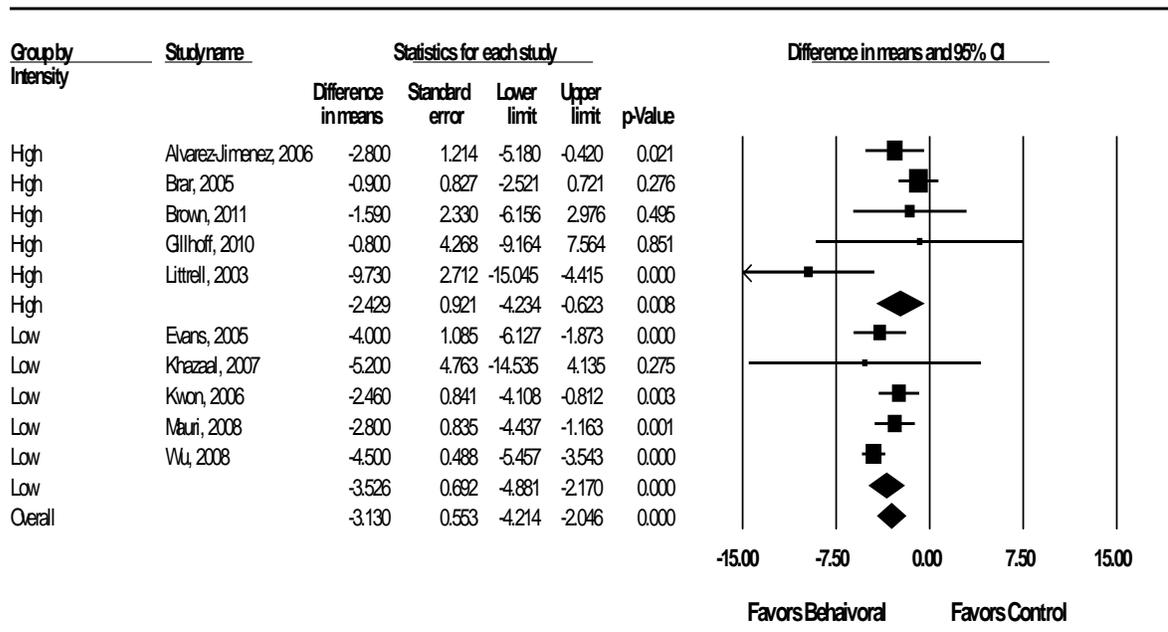
Citation	Planned Contacts	Written Manual?	Strategies Used
Alvarez-Jimenez, 2006 ⁸⁴	10 to 14 weekly or twice-weekly individual therapy sessions over 3 months	Yes	Education about diet and physical activity Problem solving Goal setting Motivational techniques Self-monitoring Activity scheduling Personalized or tailored written communications
Brar, 2005 ⁸⁹	20 behavioral therapy sessions, twice weekly for 6 weeks followed by weekly for 8 weeks	Yes	Education about diet and physical activity Self-monitoring Cognitive and behavioral approaches to reduce overeating
Brown, 2011 ⁹⁰	12 weekly individual visits followed by monthly individual visits and weekly phone calls for the following 3 months	Yes	Education about diet and physical activity Problem solving Goal setting Activity scheduling Strategies to enhance social support Meal replacements
Evans, 2005 ⁹³	6 individual nutrition education sessions over 3 months	No	Education about diet and physical activity Goal-setting
Gillhoff, 2010 ⁹⁵	Weekly fitness training, 7 psychotherapeutic/educational sessions, and 4 cooking and nutrition classes over the course of 5 months.	No	Patient psychoeducation about bipolar disorders Education about diet and physical activity Goal setting Motivational techniques Activity scheduling Stress management techniques
Khazaal, 2007 ¹⁰⁹	12 weekly CBT-based group sessions over 6 months	Yes	Education about diet and physical activity Psychoeducation about links between weight gain and antipsychotic drugs Self-monitoring Meal tastings
Kwon, 2006 ⁹⁹	8 individual sessions of CBT weight management counseling over 3 months	No	Education about diet and physical activity Problem-solving skills Goal setting Self-monitoring Activity scheduling
Littrell, 2003 ¹⁰⁰	16 weekly 1-hour classes over 4 months	Yes	Education about diet and physical activity Goal setting Self-monitoring Activity scheduling Strategies to enhance social support
Mauri, 2008 ¹¹⁰	5 to 7 psychoeducational groups over 4 months	No	Education about diet and physical activity Goal setting Self-monitoring Personalized or tailored written communications Education on controlling stimuli to overeat
McKibbin, 2006 ¹⁰¹	24 weekly 90-minute group classes over 6 months	Yes	Education about diet and physical activity Diabetes education Self-monitoring Reinforcements (i.e., raffle tickets for small health-related prizes) Behavioral modeling Skills practice

Citation	Planned Contacts	Written Manual?	Strategies Used
Wu, 2008 ¹⁰³	4 psychoeducational session and 7 sessions with an exercise physiologist (during the first week only) and consultation with a dietitian (frequency not stated) over 3 months	No	Education about diet and physical activity Education about monitoring adherence with family member/caregiver Goal setting Self-monitoring Activity scheduling Personalized or tailored written communications Homework assignments

Of the 11 studies, one assessed weight control only as change in BMI and could not be combined with the other studies that assessed weight control as change in kilograms or pounds;¹⁰¹ this study is discussed in detail in KQ 2. In brief, the study found that participants in the behavioral intervention group experienced greater improvements in BMI from baseline to 12-month followup compared with usual care (approximately -1 versus +0.05 BMI points, $p < 0.01$).

Figure 5 shows the forest plot of the meta-analysis examining the effect of behavioral interventions compared with control on weight gain, which included the remaining 10 studies (n=735 participants).^{84,89,90,93,95,99,100,103,109,110} In these studies, the combined estimate for behavioral intervention was a weight loss of -3.13 kg (95% CI, -4.21 to -2.05), an effect of small magnitude (approximately 4% reduction in body weight over baseline). In an exploratory subgroup analysis by intervention intensity, high-intensity behavioral intervention resulted in -2.43 kg weight loss compared with placebo (CI, -4.23 to -0.62). There was some evidence of moderate heterogeneity (Q-value=10.428, df=4, $p=0.034$; $I^2=61.643$.) Low-intensity behavioral intervention resulted in -3.53 kg weight loss compared with placebo (CI, -4.88 to -2.17). There was some evidence of low heterogeneity as assessed by the I^2 value of 34.925 but no evidence of heterogeneity as assessed by the Q-value of 6.147 for 4 degrees of freedom, $p = 0.188$. There was no significant difference between low- and high-intensity behavioral interventions (chi-square=0.91, df=1, $p=0.34$.)

Figure 5. Forest plot of meta-analysis of effect of behavioral interventions on weight gain



For the studies that reported adverse effects, none reported significant differences between conditions in serious adverse effects as defined by the study protocol and only two studies^{89,103} reported discontinuations due to serious or nonserious adverse effects and found no difference between groups. One study reported health-related quality of life,⁹⁹ assessing physical health status with the World Health Organization-Quality of Life Brief Version instrument, and found no significant differences between behavioral weight management and control. Funnel plots for publication bias did not demonstrate evidence of publication bias.

Effect of Peer or Family Support Interventions on Weight Control

We identified no eligible studies for this category of intervention for KQ 1.

Effect of Pharmacological Treatments on Weight Control

Psychotropic Agents

Four studies (1 good quality, 3 fair) assessed the impact of psychotropic agents atomoxetine,⁸⁷ fluoxetine,¹⁰⁵ aripiprazole,⁹⁴ and ramelteon⁸⁸ on weight control among second-generation antipsychotic-treated individuals with schizophrenia. Although each medication is classified as psychotropic, the mechanisms of action vary. Thus, we did not perform a meta-analysis; instead, key findings are synthesized qualitatively.

Across included studies, participants treated with psychotropic agents experienced variable levels of weight control on the four medications. For participants who lost weight, effects were modest (range: -0.15 to -2.53 kg), which translates into a less than 3 percent change in body weight from baseline. Only one study demonstrated significant weight loss; this study was also

the only one that reported discontinuation due to side effects and health-related quality of life outcomes.⁹⁴

A study of good quality⁹⁴ assessed weight gain in clozapine-treated outpatients with schizophrenia (n=207). First, patients on a fixed dose of clozapine (200 to 900 mg/day) were randomized to an adjunctive flexible dose of aripiprazole (5 to 15 mg/day) or clozapine plus placebo. After 16 weeks, patients who completed the 16-week double blind phase could enter a 12-week open-label extension phase. All patients received 5 to 15 mg/day of aripiprazole and flexible dosing of clozapine. At 16 weeks, adjunctive aripiprazole significantly decreased weight compared with placebo control (-2.53 versus -0.38 kg, $p<0.001$). A total of 180 participants entered the 12-week open-label phase in which everyone received adjunctive aripiprazole. Participants originally randomized to adjunctive aripiprazole continued to lose weight and, at the end, experienced a mean change in weight of -3.26 kg from baseline weight. Those who had originally received placebo had a -1.88kg mean weight loss over the 12-week open-label phase. Treatment with adjunctive aripiprazole did not differentially impact health-related quality of life compared with placebo control as measured by the Subjective Well Being Under Neuroleptics scale ($p=0.20$). Only one participant in the placebo arm and five in the aripiprazole arm discontinued the trial due to adverse effects. However, 0 out of 99 patients in the placebo group and 10 out of 108 patients in the aripiprazole group experienced a serious adverse effect.

In another study rated fair quality,⁸⁷ 37 olanzapine- or clozapine-treated individuals with schizophrenia were randomized to 24 weeks of either atomoxetine or placebo. Atomoxetine was titrated from 40 mg/day to 120 mg/day, which is above the normal recommended dosage. All participants also received a diet and exercise program that consisted of 10 weeks of a Weight Watchers program and exercise sessions three times a week. Participants could receive tokens for compliance with exercise and diet programs; tokens could be used to acquire prizes at the end of the study. Both atomoxetine and placebo groups lost weight; however, results were modest and not significant (-1.7 versus -2.1 kg, $p=0.82$). Adherence to the exercise and diet program was low; only nine participants who completed the study also adhered to the program. However these nine participants lost more weight (range: -15.9 to -4.5 kg).

In a fair-quality study of olanzapine-treated schizophrenic patients,¹⁰⁵ patients who had gained at least 3 percent over baseline weight (5 to 20 mg/day) were randomized to a double-blind 4-month treatment of placebo or fluoxetine (20 to 60 mg/day). During the olanzapine-only phase, two patients were hospitalized for worsening of psychiatric symptoms, and one died for causes deemed unrelated to the study. Fifty-one patients started on olanzapine and 31 met weight-gain criteria for randomization to fluoxetine or placebo with continued treatment on olanzapine. Both groups gained weight. The fluoxetine-treated patients did not gain less weight than the placebo controls ($p=0.3$).

In a small, double-blind, 8-week trial rated fair quality,⁸⁸ 20 participants with schizophrenia were randomized to adjunctive ramelteon (8 mg/day) or placebo. All patients entered the study on second-generation antipsychotics and were maintained on these during the trial. Patients on ramelteon did not experience significant weight loss compared with placebo control (-0.84 versus -0.15, $p=0.28$).

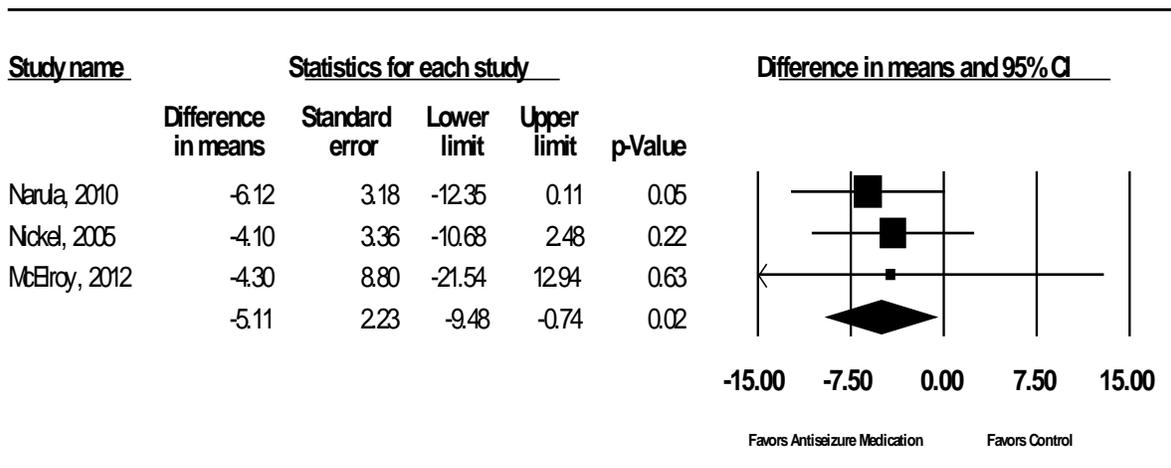
Neurologic Agents

Four studies (1 good quality, 2 fair, 1 poor) assessed the effects of neurologic agents topiramate, amantadine, or zonisamide on weight control among individuals with SMI treated with olanzapine.^{91,98,102,104} One of these studies was conducted with women only.¹⁰⁸ Two were

conducted with participants with schizophrenia,^{96,113} one with an SMI population on olanzapine,¹⁰⁸ and one with a mixed population of people with psychotic or bipolar disorder.¹¹¹ Three studies assessed antiseizure medications topiramate^{108,113} and zonisamide¹¹¹ versus placebo control on the effects of olanzapine-induced weight gain; these studies were able to be combined in a meta-analysis. Results for the amantadine placebo-controlled trial are summarized qualitatively.

Figure 6 shows the forest plot of the meta-analysis examining the effect of antiseizure medications compared with placebo control on olanzapine-induced weight gain, which included 3 studies (n=158 participants). The analysis demonstrated statistically significant difference in efficacy between neurologic agents topiramate and zonisamide versus placebo control on weight gain of -5.11 kg (95% CI, -9.484 to -0.735), a clinically significant weight loss of a small effect (percentage of body weight lost from baseline range: 4% to 11%). There was no evidence of heterogeneity (Q-value=0.332, df =2, p=0.733; $I^2=0.000$).

Figure 6. Forest plot of meta-analysis of effect of antiseizure medications on weight gain



Results of the one amantadine study mirror these findings. A 12-week study of amantadine versus placebo among 21 SMI patients who had gained at least 5 pounds on olanzapine also found significant but small improvements with adjunctive amantadine (-0.7 vs +1.24 kg).⁹⁶

One study reported on health-related quality of life; participants taking olanzapine and randomized to adjunctive topiramate had significant improvements on seven of eight scales of SF-36 compared with adjunctive placebo control. Two of these studies reported on discontinuation from the studies for adverse effects. One patient randomized to amantadine withdrew from the study due to significant worsening of psychosis.⁹⁶ Ten participants in the placebo-controlled study of zonisamide withdrew from the study for adverse effects (five in placebo group and five in zonisamide group).

Metformin

Three studies (1 good quality, 1 fair, 1 poor) assessed the effects of metformin on weight control for individuals with SMI.^{97,103,112} Comparators were too heterogeneous to conduct a meta-analysis. In all three studies, participants who were randomized to treatments containing metformin lost more weight than comparators; however, the magnitude of the effects were small (-2 to -4.7 kg). Also, because formal statistical techniques for publication bias are not effective with small numbers of studies, we did not conduct analyses for publication bias. Thus, we summarize the weight control finding of each of these studies below.

In a good-quality study, Wu et al.¹⁰³ randomly assigned 128 nondiabetic adults with first-episode schizophrenia who had gained 10 percent of their predrug body weight within 1 year of treatment on clozapine, olanzapine, risperidone, or sulpiride to one of four conditions: 12 weeks of placebo; 750 mg a day of metformin; 750 mg of metformin plus lifestyle intervention; or lifestyle intervention alone. Participants continued on their current antipsychotic medications as well. All groups experienced statistically significant weight loss compared with placebo at the 12-week assessment, with the greatest weight loss in the metformin plus lifestyle group (-4.7 kg, which translates to approximately 7 percent reduction in body weight.) Moreover, the metformin plus lifestyle group experienced significantly more weight loss when compared with the metformin-only group ($p=0.02$) and the lifestyle-only group ($p=0.01$). Across all groups, there were five serious adverse effects of exacerbations of psychosis that resulted in hospital admissions.

In a fair-quality study, Carrizo et al.¹¹² assessed the impact of adding 500 to 1000 mg a day of metformin compared with placebo control for 61 patients under prolonged clozapine treatment over 14 weeks. Of the participants who completed the study, most had schizophrenia (two had bipolar disorder). No participant had symptoms of type 2 diabetes, but those with abnormal fasting glucose levels were monitored carefully. For the 54 patients who completed the study, metformin outperformed placebo (-1.87 kg versus 0.2 kg; p -value=0.01). No participant discontinued the study due to adverse effects.

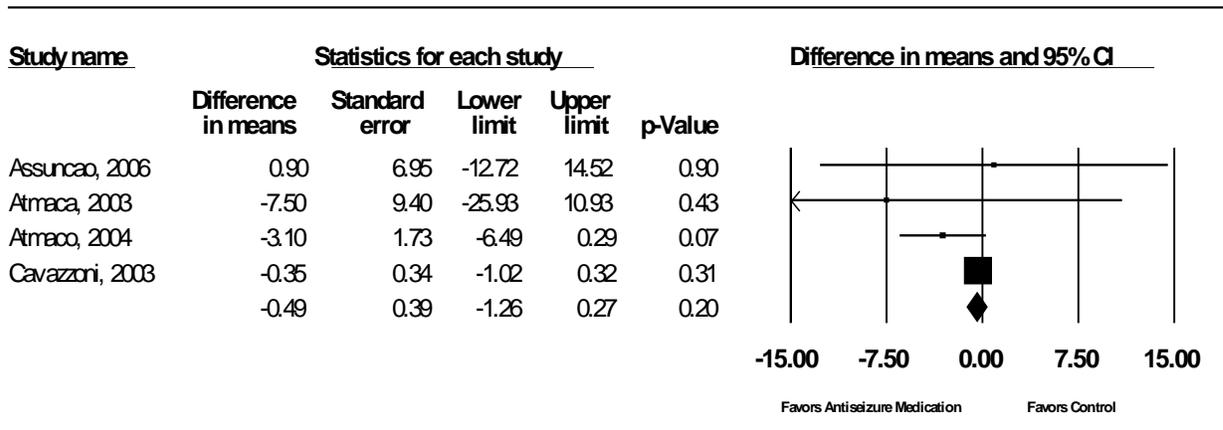
In a poor-quality study, Hoffmann et al.⁹⁷ randomly assigned 199 nondiabetic outpatients with schizophrenia or schizoaffective disorder to 1 of 3 conditions for 22 weeks: (1) olanzapine only, (2) olanzapine plus 200 mg/day amantadine with possible switches to 1000 to 1500 mg/day metformin and then switches to 100 to 400 mg/day zonisamide (treatment algorithm A), or (3) olanzapine plus 1000 to 1500 mg/day metformin with possible switches to 200 mg/day amantadine and then switches to 100 to 400 mg/day zonisamide (treatment algorithm B). Forty-two percent of participants of algorithm A and 35 percent of algorithm B switched to second treatment. The estimated time to switching to second treatment for 25 percent of the sample was 42 days for algorithm A and 66 days for algorithm B. A combined treatment group of both algorithm A and algorithm B did not differ significantly from the olanzapine-only group at 22-week followup (results not reported, $p=0.065$). However, patients treated with algorithm B compared with olanzapine-only resulted in significantly less weight gain (0.65 versus 2.76 kg $p=0.04$), though the magnitude of the effect was small. In total, 11 participants discontinued the study due to adverse effects (8 in algorithm A group, 4 in algorithm B group, and 2 in olanzapine only group); only three of these, all in the algorithm A group, were considered serious adverse effects. Ten subjects continued the study despite serious adverse effects (1 in algorithm A group, 4 in algorithm B group, and 5 in olanzapine only group).

Nizatidine

Four studies (1 good quality, 2 fair, 1 poor) assessed the effects of nizatidine, a histamine₂ (H₂)-receptor antagonist, on antipsychotic induced weight gain among people with schizophrenia.^{85,86,106,107} One study assessed weight gain among quetiapine-treated patients⁸⁶ while the remaining studies focused on weight gain among olanzapine-treated patients.^{85,106,107} Three studies tested nizatidine at recommended therapeutic doses of 300 mg/day;^{86,106,107} one study assessed nizatidine at twice the recommended daily dose.⁸⁵ Below, we focus on the weight and adverse effects outcomes of these studies.

Figure 7 shows the forest plot of the meta-analysis examining the effect of nizatidine compared with placebo control on antipsychotic-induced weight gain, which included 4 studies (n=286 participants). The estimated effect shows that nizatidine resulted in a -0.496 kg weight gain compared with placebo that was not statically significant (95% CI, -1.256 to 0.266). There was no evidence of heterogeneity (Q-value =3.030, df=3, p=0.387). However, the I^2 value displayed high heterogeneity (I^2 =0.98). Only one study reported discontinuation due to adverse events; Assuncao et al.⁸⁵ reported three patients discontinued the study due to adverse effects (two in the nizatidine treated group). No studies reported on health-related quality of life outcomes. Because formal statistical techniques for publication bias are not effective with small numbers of studies, we did not conduct analyses for publication bias.

Figure 7. Forest plot of meta-analysis of effect of nizatidine on weight gain



Carnitine

One good-quality study⁹² assessed the effects of 15 mg/kg daily carnitine, a nutritional supplement, compared with placebo among 60 bipolar patients taking sodium valproate for 26 weeks. All study participants also were on energy-restricted, low-fat diets (-500 kcal/day from usual consumption). There is no recommended dose of carnitine; dosages vary and several doses have been studied in scientific research (50 to 100 mg/kg/day, 2 to 6 grams daily, 990 mg two to three times per day). Carnitine had no significant effect on mean weight loss in the study compared with placebo (-1.9kg versus -0.9 kg, p=0.38). No other outcomes of interest were reported.

Effect of Antipsychotic-Switching Interventions on Weight Control

Four studies (1 good quality, 3 fair) assessed the effects of antipsychotic-switching strategies on weight control.^{91,98,102,104} Patients in all studies began on olanzapine, with the control group maintained on olanzapine. The intervention in two studies involved switching to a different form of olanzapine (an orally disintegrating tablet⁹⁸ or a long-acting injection¹⁰⁴) and in the other two studies, switching to a different antipsychotic medication, quetiapine⁹¹ or aripiprazole.¹⁰² Meta-analysis was not completed on these four studies due to the heterogeneity of switching strategies. Only one study reported on health-related quality of life outcomes. Results are summarized qualitatively.

Neither study that examined switching to a different form of olanzapine^{98,104} showed significant effects on weight control. In a good-quality study of a 16-week trial with SMI patients (n=149) that involved switching from 5 to 20 mg of standard olanzapine tablets (SOT) to 5 to 20 mg orally disintegrating olanzapine (ODO) tablets,⁹⁸ there was no difference between SOT or ODO groups for mean weight gain (+2.08 versus +1.42, p=0.39). Results for health-related quality of life as measured by the Subjective Well-being Under Neuroleptics Scale showed no significant change from baseline to followup between groups (p=0.16). Two patients in each group discontinued treatment due to adverse effects. Two patients in the ODO group experienced a serious adverse effect.

Another fair-quality study assessed switching from 10 to 20 mg of oral olanzapine to a long-acting intramuscular injection of olanzapine (150 mg/2 weeks, 405 mg/4 weeks or 300 mg/2 weeks) in a 24-week trial of 921 patients with schizophrenia.¹⁰⁴ Patients taking both formulations of olanzapine experienced statistically significant increases in weight compared with baseline (+1.3 [injection] versus +1.3 [oral]). However, there were no between-group differences (p=0.34). A total of 57 patients discontinued use due to adverse effects, but there were no differences between groups (p-value NR).

The studies that examined switching from olanzapine to a different antipsychotic medication^{91,102} had mixed results. In a fair-quality study, 133 overweight patients with schizophrenia were either switched to 300 to 800 mg/day of quetiapine or continued on 7.5 to 20 mg/day olanzapine.⁹¹ Treatment continued for 24 weeks. Mean weight change between olanzapine and quetiapine were not significant (+0.99 versus -0.82, p=0.089). Significantly more subjects in the olanzapine group completed 24 weeks of treatment than the quetiapine group (70.3% versus 43.1%, p=0.002). Discontinuation due to psychiatric adverse effects was higher in the quetiapine-treated group (p=0.003). However, no significant differences were observed for nonpsychiatric discontinuations (p-value NR). There were no significant differences in hospitalization rates (7.69% in the quetiapine group vs. 1.47% in the olanzapine group, p-value not reported). No other serious adverse events were reported.

In a fair-quality study, 173 patients with schizophrenia either stayed on 10 to 20 mg of olanzapine or switched to 10 to 30mg of aripiprazole in a 16-week trial.¹⁰² Patients who switched to aripiprazole experienced significantly more weight loss than those remaining on olanzapine (-1.84 versus +1.31 kg, p=0.001), a difference of small magnitude between groups. A total of 15 participants discontinued treatment due to adverse effects (7 aripiprazole-treated, 8 olanzapine-treated). Six participants treated with aripiprazole experienced a serious adverse effect compared with nine in the olanzapine-treated group (p-value NR). Another study, described in KQ 4, evaluated switching to aripiprazole as part of a multicomponent intervention.¹¹⁴ This study found that patients who switched to aripiprazole lost more weight than those who stayed on their current antipsychotic medication. (See KQ 4 Results for more details.)

Summary of Key Question 1

Overall, only 8 of the 30 trials identified as relevant for KQ 1 were of good quality. Thus, the majority of studies had important design or reporting deficits. Most trials were specifically designed to control weight gain for individuals with SMI. Other studies targeted diabetes management or antipsychotic metabolic effects but also addressed weight management. The 30 trials assessed the impact of a wide variety of pharmacological and behavioral strategies on weight among individuals with SMI. However, most of the pharmacological strategies assessed in the included interventions were used in treatment of individuals with mental illnesses; no studies evaluated the weight loss medication orlistat in this population. The antiseizure agents topiramate and zonisamide and behavioral interventions were associated with greater weight loss than controls, but the effects were modest. Metformin and switching to aripiprazole also showed promise. Again, the magnitude of effects was small. Discontinuation due to adverse effects and worsening of psychiatric symptoms were not consistently reported. Few studies reported effects on physical functioning or health-related quality of life, and no studies reported cardiovascular mortality.

Key Question 2. Effectiveness of Diabetes-Management Interventions

KQ 2: What is the effectiveness of diabetes-management behavioral interventions (e.g., behavioral counseling, health education), peer or family support interventions, pharmacological treatments (e.g., rosiglitazone, metformin), antipsychotic medication-switching to an antipsychotic with a low or neutral impact on glucose level, or their combination on glucose-level control and related physical health outcomes (e.g., health-related quality of life, mortality) when compared with each other or with usual care (or other control) among adults with SMI who have diabetes or are taking antipsychotics?

Key Points

- Only one study evaluated an intervention specifically designed to target glucose control in individuals with SMI who have diabetes. Two studies evaluated interventions targeting nondiabetic individuals who had or were at risk for poor glycemic control. Four studies evaluated interventions targeting weight, with glycemic control as a secondary outcome.
- The intervention types represented in the seven studies reporting HbA1c outcomes were psychotropic medication ramelteon, antipsychotic switching, metformin, neurologic agent amantadine, and behavioral interventions.
- Small improvements in HbA1c were seen in one study of metformin compared to placebo control and one study that used a sequenced medication algorithm of metformin, amantadine, metformin and zonisamide plus olanzapine compared to olanzapine alone.

- Only one study reported on the effects on physical functioning or health related quality of life and no studies report cardiovascular mortality.

Detailed Synthesis

Of the seven studies identified as relevant to KQ2 (n=681 participants),^{88,91,95,97,98,101,112} only one study¹⁰¹ tested an intervention intended specifically for individuals with diabetes mellitus. Two studies^{88,112} targeted antipsychotic-induced metabolic risks, including glycemic control as measured by HbA1c, and four studies^{91,95,97,98} targeted weight, with HbA1c as a secondary outcome. Of the seven trials that reported on HbA1c, all were included in Key Question 1 (weight control), 6 were included in Key Question 3 (lipid control), and none were included in Key Question 4 (multicondition interventions). All identified studies were published from 2006 forward, reflecting the recent clinical interest in glycemic control among persons with SMI.

Study Characteristics

Table 8 summarizes the study characteristics of the seven included studies. Of these, one study was rated good quality,⁹⁸ five fair,^{88,91,95,101,112} and one poor.⁹⁷ Common reasons for reduced study quality were inadequate reporting of randomization and concealment and recruiting procedures, lack of clarity about blinding of outcome assessors, and some difficulties implementing the study protocols as intended.

We identified no effectiveness studies, four efficacy studies,^{88,95,101,112} and three mixed efficacy–effectiveness studies.^{91,97,98} Three studies were conducted exclusively with U.S.-based populations, one was conducted in Europe, and three were conducted in multiple countries. Indicative of care patterns for this population, most studies were conducted in outpatient mental health settings. Trials were funded by private industries (n=4), government (n=1), or a combination of industry and government sources (n=2).

The intervention strategy assessed in these seven studies were psychotropic medication (one study⁸⁸), antipsychotic switching (two studies^{91,98}), metformin (two studies^{97,112}), and behavioral interventions (two studies^{95,101}). All five studies that primarily employed medications as the intervention strategy^{88,91,97,98,112} required participants to be on antipsychotic medications at baseline. Of the two behavioral interventions, one required use of a defined group of mood stabilizers (including some antipsychotic medications, some anticonvulsant mood stabilizers, and lithium)⁹⁵ and one had no requirement for entry based on medication use.¹⁰¹

A total of 681 participants were randomized in the seven studies, ranging from 20 to 199 participants. Most patients were middle-aged and White. Two studies representing 29.0 percent of the overall subjects for KQ 2^{91,112} did not report sex. In the five studies that reported sex, males outnumbered females 59 to 41 percent. Five studies recruited individuals with schizophrenia or schizoaffective disorder,^{88,91,97,101,112} one included individuals with bipolar disorder,⁹⁵[868], and one included individuals with any of these three diagnoses or another related psychotic disorder.⁹⁸ Only one study recruited patients with a diagnosis of diabetes.¹⁰¹ In this study, the mean A1c was 7.0 at baseline, indicating fair glycemic control. Average baseline HbA1c in the other studies ranged from 5.4 to 5.9 (median=5.6).

Table 8. Study characteristics for KQ 2: Diabetes-management interventions

Characteristic	Details
Studies: N (patients) ^a	7 studies (681 patients)
Mean age of sample: Median (range)	44.0 (38.5 to 54.0)
Sex: N patients (%)	
Female	197 patients (29.5%)
Male	278 patients (41.6%)
NR	194 patients (29.00%)
Race: N patients (%) ^b	
White	222 patients (34.8 %)
Black/African-American	31 patients (4.9%)
Hispanic	154 patients (24.1%)
Asian	46 patients (7.21%)
Other	2 patients (0.3%)
NR	183 patients (28.7%)
Setting: N studies (%)	
Mental health	4 studies (57%)
General medical	0 study (0%)
Community	2 studies (29%)
Integrated mental health-medical	0 (studies 0%)
Not reported	1 studies (14%)
Study quality: N studies (%) ^c	
Good	1 study (14%)
Fair	5 studies (71%)
Poor	1 studies (14%)
Efficacy–effectiveness rating: N studies (%)	
Efficacy (0–2)	4 studies (57%)
Mixed (3–5)	3 studies (43%)
Effectiveness (6–7)	0 studies (0%)
Comparisons: N studies (patients randomized)	
Drug vs. placebo/control	2 studies (81)
Antipsychotic switching vs. antipsychotic stay	2 studies (282)
Behavioral vs. placebo/control	2 studies (114)
Drug vs. drug vs. placebo/control	1 studies (199)

^aThe number of patients with demographic data reported is fewer than the number randomized.

^bAs some studies only reported White and non-White, the Other category is likely inclusive of some of the non-White race categories listed in the table.

^cQuality ratings in the table are reported on the basis of how studies were conducted in relation to laboratory-based physical health outcomes. Ratings were also applied on the basis of patient-reported outcomes. Raters were the same as for laboratory-based outcomes except that two studies (258, 868) did not report patient-reported outcomes.

Qualitative Review

HbA1c is the most consistently reported measure of glycemic control in these studies and is a widely accepted and reliable measure; therefore, we used it as the outcome measure for glycemic control for this evidence synthesis. There was an insufficient number of studies to conduct meta-analyses on the effects of any of the intervention classes by HbA1c. Results are summarized qualitatively. We focus on the HbA1c outcomes and, when reported, adverse effects (i.e. discontinuation due to adverse events, significant worsening of psychiatric symptoms). While health-related quality of life and mortality were outcomes of interest, only one study reported on health-related quality of life, and no studies reported on mortality. Details for weight and lipids can be found in KQ 1 and KQ 3, respectively. Also, because formal statistical techniques for publication bias are not effective with small numbers of studies, we did not conduct analyses for publication bias.

Effect of Behavioral Interventions on Diabetes Control

Two included studies evaluated behavioral interventions, one specifically designed to target diabetes,¹⁰¹ and one with the primary target of weight with glycemic control measured as a secondary outcome.⁹⁵ Intervention components are summarized in KQ 1.

McKibbin et al.¹⁰¹ conducted a fair-quality randomized 6-month trial of a lifestyle intervention in older individuals (mean age=54.0) with schizophrenia and diabetes mellitus compared with modestly enhanced usual care (provision of three American Diabetes Association brochures and treatment by a primary care provider alone) (n=64). Consistent with diabetes, mean HbA1c levels were elevated at baseline (HbA1c= 7.4 in the intervention group, 6.7 in the usual care group). Though a completers analysis showed that mean HbA1c decreased in the intervention group to 6.9 and increased in the usual care group to 6.8, between-group differences were not significant (p=0.44). There were no differences in overall rates of study discontinuation. Specific reasons for discontinuation were reported for 7 of the 64 participants who did not complete the study. Of these, three would be considered serious adverse effects (inpatient hospitalization, n=2; death prior to study commencement, n=1; psychiatric decompensation, n=1). Based on mean PANSS scores, there was no significant worsening of psychiatric symptoms among the study groups.

Gilhoff et al.⁹⁵ conducted a fair-quality randomized 5-month trial of a multicondition lifestyle intervention in individuals with bipolar disorder compared with a waiting control group (n=50). Mean HbA1c changed minimally (0.1 or less) in the two groups at study completion and at 6-month follow up, with a nonsignificant time by intervention term in a multivariate analysis (p-value not reported). Discontinuation due to adverse events and serious adverse events were not reported. Measures of psychiatric symptoms worsening were not reported.

Effect of Peer or Family Support Interventions on Diabetes Control

We identified no eligible studies for this category of intervention for KQ 2.

Effect of Pharmacological Treatments on Diabetes Control

Psychotropic Agents

Only one study assessed the effects of a psychotropic agent on HbA1c.⁸⁸ In this fair-quality study, individuals with schizophrenia (n=20) were randomized to an 8-week trial of the MT1 and MT2 melatonin-selective antagonist ramelteon compared with placebo control. Mean HbA1c changed negligibly at 8 weeks, with no significant between-group difference in mean change at study end between ramelteon and placebo (5.74 to 5.82 versus 5.45 to 5.45, baseline to followup, p=0.61). Five subjects (two in the ramelteon group and two in the placebo group) out of the 25 initially randomized withdrew consent before the Week 4 assessment. Reasons for discontinuation were not reported. No serious adverse effects were reported.

Metformin

Two studies evaluated interventions utilizing metformin, one with the primary target of metabolic control¹¹² including glycemic control, and one with the primary target of obesity prevention⁹⁷ with glycemic control measured as a secondary outcome.

Carrizo et al.¹¹² conducted a fair-quality 14-week trial (n=61) of extended release metformin in nondiabetic individuals receiving clozapine (94% with a diagnosis of schizophrenia) compared with placebo alone. Mean HbA1c was increased modestly in both groups (+0.13 for

metformin, +0.23 for placebo), though significantly less so in the metformin group ($p=0.04$). All 30 participants in the placebo group completed the study. No participant discontinued the study due to adverse effects, and no serious adverse effects were reported.

Hoffman et al.⁹⁷ conducted a poor-quality 22-week trial of two treatment algorithms that included both metformin and amantadine added to olanzapine compared with olanzapine alone in nondiabetic individuals with schizophrenia or schizoaffective disorder for prevention of weight gain ($n=199$). Treatment algorithm A consisted of 200 mg amantadine with possible switches to 1000 to 1500 mg metformin and then switches to 100 to 400 mg zonisamide. Treatment algorithm B was 1000 to 1500 mg metformin, with possible switches to 200 mg amantadine and then switches to 100 to 400 mg zonisamide. A combined-treatment group of both algorithm A and algorithm B did not differ significantly from the olanzapine only group at 22-week followup for HbA1c (results not reported, $p=0.0278$). Mean change in HbA1c for the algorithm A arm was negligibly higher (+0.01) at followup than in the olanzapine only group ($p=0.976$). However, patients treated with algorithm B (beginning with metformin, with possible switches to amantadine, and then to zonisamide) demonstrated a statistically significant (-0.03 vs. $+0.09$, $p=0.049$) improvement in mean changes compared with the olanzapine-only group in HbA1c values at followup, though the magnitude of the effect was small. In total, 11 participants discontinued the study due to adverse effects (8 in algorithm A group, 4 in algorithm B group, and 2 in olanzapine only group); only three of these, all in algorithm A groups, were considered serious adverse effects. Ten participants continued the study despite serious adverse effects (1 in algorithm A group, 4 in algorithm B group, and 5 in olanzapine only group). There was no significant worsening of psychiatric symptoms among the study groups for Brief Psychiatric Rating Scale (BPRS) and CGI-S scores.

Effect of Antipsychotic-Switching Interventions on Diabetes Control

Two studies evaluated antipsychotic-switching strategies.^{91,98} The primary outcome for these studies was weight management, with glycemic control measured as a secondary outcome. Patients in both studies began on olanzapine, and the control condition consisted of staying on olanzapine. The intervention involved switching to either quetiapine⁹¹ or orally disintegrating olanzapine.⁹⁸ Neither study reported significant changes in HbA1c. Details are reported below. A third study, described in KQ4, evaluated switching to aripiprazole as part of a multicomponent intervention. This study found no effect on HbA1c.

Deberdt et al.⁹¹ conducted a fair-quality 24-week trial of switching from olanzapine (baseline dose of 7.5 to 20 mg/day) to quetiapine (300 to 800mg/day) in overweight or obese individuals with schizophrenia or schizoaffective disorder compared with remaining on olanzapine ($n=133$). Final mean modal daily doses for patients switching to quetiapine ($n=68$) and staying on olanzapine ($n=65$) were 16.9 mg and 439.7 mg, respectively. Patients who switched to quetiapine did not have significantly different changes in their HbA1c levels than those who remained on olanzapine ($+0.07$ and -0.03 , $p=0.318$) in the last-outcome-carried-forward analysis. Significantly more patients in the olanzapine group completed 24 weeks of treatment than in the quetiapine group (70.3% vs. 43.1%, $p=0.002$).

Adverse effects leading to study discontinuation were classified as psychiatric adverse events and nonpsychiatric adverse events. Discontinuations due to psychiatric adverse events were more frequent in the quetiapine group than the olanzapine group ($p=0.031$). No significant differences were demonstrated for discontinuations due to nonpsychiatric adverse events or due to lack of efficacy, though a significant difference favoring olanzapine was demonstrated for the

combination of discontinuations due to psychiatric adverse events or lack of efficacy. There were no significant differences in hospitalization rates (7.69% in the quetiapine group vs. 1.47% in the olanzapine group, p-value not reported). No other serious adverse events were reported. Based on mean Positive and Negative Syndrome Scale (PANSS) scores, neither study arm demonstrated worsening of psychiatric symptoms.

Karagianis et al.⁹⁸ conducted a good-quality 16-week trial of switching from standard olanzapine tablets to orally disintegrating olanzapine in individuals with schizophrenia, schizoaffective disorder, bipolar disorder, or another related psychotic disorder who had gained significant weight (defined as 5 kg or more or an increase of 1 kg/m² in BMI) while on standard olanzapine tablets for 4 to 52 weeks compared with remaining on standard olanzapine tablets (n=149). Final mean daily doses of in the standard olanzapine tablets group (n=65) and orally disintegrating olanzapine (n=84) were 14.90 mg and 14.33 mg, respectively. Patients who switched to orally disintegrating olanzapine did not have significantly different changes in their HbA1c levels from those who remained on olanzapine (+0.0 and +0.0, p=0.83). Results for health-related quality of life as measured by the Subjective Well-being Under Neuroleptics Scale showed no significant change from baseline to followup between groups (p=0.16). Two patients in each group discontinued treatment due to adverse effects. Two patients in the orally disintegrating olanzapine group experienced serious adverse effects, with one being hospitalized for dizziness and one attempting suicide. There was no significant worsening of psychiatric symptoms between groups as measured by the Clinical Global Impressions-Severity of Illness Scale (CGI).

Summary of Key Question 2

Only one of the seven studies relevant to KQ 2 tested an intervention specifically intended to improve glucose control in individuals with diabetes and SMI.¹⁰¹ Of the other six studies, two had HbA1c as among the primary outcomes,^{88,112} and four focused more specifically on weight, with HbA1c measured as a secondary outcome.^{91,95,97,98} Overall, just two of the trials found significant advantages for the intervention in controlling HbA1c, with both of these studies involving the use of metformin. Carrizo et al.¹¹² demonstrated that metformin in nondiabetic individuals receiving clozapine led to significantly less increase in HbA1c during the 14-week study. Hoffman et al.⁹⁷ showed that a treatment algorithm, beginning with metformin and possible switches to amantadine and then to zonisamide, demonstrated a statistically significant improvement in mean changes in HbA1c when added to olanzapine treatment in nondiabetic individuals compared with those receiving only olanzapine over 22 weeks. In both of these instances, mean advantages for the interventions were modest (-0.10 to -0.12). Behavioral interventions,^{95,101} antipsychotic switching,^{91,98} and the psychotropic drug ramelteon⁸⁸ resulted in no significant differences in HbA1c control in individuals with SMI. Outcomes regarding weight and lipids are summarized in KQ 1 and KQ 3, respectively. In brief, health-related quality of life and serious adverse events were inconsistently reported in the seven trials. Health-related quality of life was reported in only one of the trials with no significant effect demonstrated. No trials reported on mortality.

Key Question 3. Effectiveness of Dyslipidemia-Management Interventions

KQ 3: What is the effectiveness of dyslipidemia-management behavioral interventions (e.g., behavioral counseling, health education), peer or family support interventions, pharmacological treatments (e.g., statins), antipsychotic medication-switching to an antipsychotic with a low or neutral impact on lipid levels, or their combination on lipid-level control and related physical health outcomes (e.g., health-related quality of life, mortality) when compared with each other or with usual care (or other control) among adults with SMI who have dyslipidemia or are taking antipsychotics?

Key Points

- No studies evaluated an intervention specifically designed to target lipid levels in individuals with SMI who have or are at risk for dyslipidemia. However, 15 RCTs reported lipid levels as a secondary outcome.
- No studies examined a drug (e.g., HMG-CoA reductase inhibitors) or dietary intervention known to be effective for managing dyslipidemia in non-SMI populations.
- The one meta-analysis that was justified examined three small, 3- to 12-month behavioral interventions and found no advantage in favor of behavioral interventions compared with control for managing low-density lipoprotein (LDL) levels.
- Compared with control interventions, small improvements in lipids were seen in one study of ramelteon, one study of topiramate, and one study that used a sequenced medication algorithm of amantadine, metformin, and zonisamide.
- Two studies of aripiprazole—one that added aripiprazole to chronic clozapine and one that switched patients from olanzapine to aripiprazole—improved lipids modestly. Switching from oral to injectable olanzapine increased LDL cholesterol.

Detailed Synthesis

We identified no articles reporting on trials in which the intervention was designed to target lipid levels. Specifically, no study evaluated HMG-CoA reductase inhibitors (statins), niacin, fibrates, or low-fat diets. However, 15 of the eligible studies, involving 2322 patients, reported on total cholesterol (n=12) or low density lipoprotein (LDL) cholesterol (n=14) as a secondary outcome.^{85,87,88,91,94-98,101,102,104,110,111,113} All of these trials were published from 2005 forward, with reported recruitment dates spanning from 2001 to 2010. The primary outcomes of interest were weight (n=12), glucose control (n=1), and all-purpose metabolic effects (n=2). Of the 15 trials that reported on lipid levels, all 15 were included in Key Question 1 (weight), 7 were included in Key Question 2 (glucose control), and none were included in Key Question 4 (multicondition interventions). Detailed analyses of the outcomes for weight control (KQ 1) and glucose control (KQ 2) are presented in other sections of the Results chapter. The experimental intervention was psychotropic medication in three trials, antipsychotic switching in four trials,

behavioral interventions in three trials, neurological agents in three trials, an antihistamine in one trial, and a neurological agent or a biguanide in one trial (this trial was the only one with three arms instead of two).

Common inclusion criteria were a diagnosis of schizophrenia (n=12), taking an antipsychotic medication (n=10), and being overweight or obese (n=7). Common exclusion criteria were active substance abuse (n=7), being pregnant or breastfeeding (n=8), being on non-study approved medication (n=8), and having a chronic medical condition (n=12). The number of participants randomized ranged from 21 to 1065, and the number of participants who completed studies ranged from 18 to 677.

Trials received funding from private industries (n=13) and government (n=4). Five of the 15 studies were conducted in multiple countries, with patients coming from the United States in 8 studies, Europe in 5 studies, Asia in 2 studies, South America in 1 study, and Africa in 1 study. Six studies were conducted at a single study site, and four studies contained 19 or more study sites. One study contained 112 study centers across 26 countries.¹⁰⁴ This study contained 44 percent of the overall number of patients across the 15 studies, with samples from the 6 largest studies^{91,94,97,98,102,104} accounting for 81 percent of the total sample size for KQ 3.

Study Characteristics

Table 9 shows the study characteristics for KQ 3. The majority of patients were male, white, and middle-aged. The vast majority were classified as having schizophrenia or schizoaffective disorder (92%), with 6 percent having bipolar disorder and less than 2 percent classified as having serious mental illness not further specified. None of the studies reported on whether patients were diagnosed with hyperlipidemia. Average baseline total cholesterol levels ranged in the studies from 133 mg/dl to 212 mg/dl (median=198 mg/dl), and average LDL levels ranged from 72 mg/dl to 138 mg/dl (median=120 mg/dl). Patients in the large majority of studies were reported as taking a second-generation antipsychotic medication. Studies were conducted primarily in outpatient mental health settings and most commonly examined medication compared with placebo. Nine studies lasted 2 to 4 months, four studies lasted 5 to 6 months, and two studies lasted 11 to 12 months. Most studies were rated fair quality, with common reasons for reducing study quality being insufficient details provided about the study, inadequate blinding, and conducting analyses only on treatment completers. There was a relatively even split between trials that were characterized as efficacy studies and trials that were characterized as a mix of efficacy and effectiveness.

Table 9. Study characteristics for KQ 3: Dyslipidemia-management interventions

Characteristic	Details
Studies: N (patients) ^a	15 studies (2322 patients)
Mean age of study samples: Median (range)	39.0 (31.1 to 54.0)
Sex: N patients (%)	
Female	810 patients (35%)
Male	1379 patients (59%)
NR	133 patients/1 study (6%)

Characteristic	Details
Race: N patients (%) White Black/African American Hispanic Asian Other ^b NR	1408 patients (61%) 132 patients (6%) 280 patients (12%) 128 patients (6%) 63 patients (3%) 299 patients/4 studies (13%)
Setting: N studies (%) Mental health outpatient Outpatient setting not otherwise specified Community NR	9 studies (60%) 2 studies (13%) 1 studies (7%) 3 studies (20%)
Study quality: N studies (%) ^c Good Fair Poor	4 studies (27%) 8 studies (53%) 3 studies (20%)
Efficacy–effectiveness rating: N studies (%) Efficacy (0–2) Mixed (3–5) Effectiveness (6–7)	8 studies (53%) 7 studies (47%) 0 studies (0%)
Comparisons: N studies (patients) Drug vs. placebo/control Behavioral vs. control Antipsychotic switching vs. antipsychotic stay Drug vs. drug vs. placebo control	7 studies (447 patients) 3 studies (156 patients) 4 studies (1,520 patients) 1 study (199 patients)

^aThe number of patients with demographic data reported is fewer than the number randomized.

^bAs some studies only reported White and non-White, the Other category is likely inclusive of some of the non-White race categories listed in the table.

^cQuality ratings in the table are reported on the basis of how studies were conducted in relation to physical health outcomes. Ratings were also applied on the basis of psychiatric outcomes. Quality ratings did not differ for any studies on the basis of physical versus psychiatric outcomes.

Abbreviations: NR=not reported

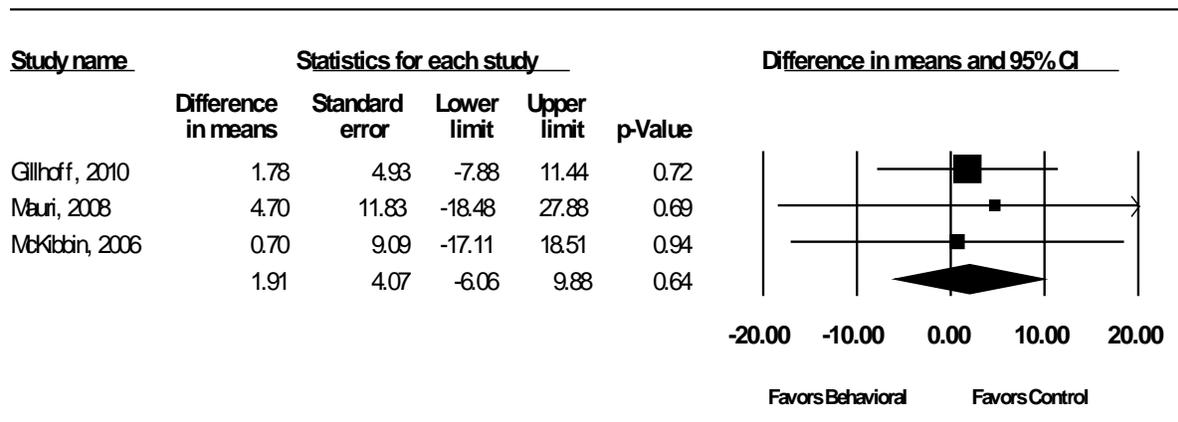
Meta-analysis and Qualitative Review

There was a sufficient number of studies with cohesive intervention strategies to conduct a meta-analysis only for the effect of behavioral interventions on lipid levels. Results for the other effects are summarized qualitatively.

Effect of Behavioral Interventions on Lipid Control

Figure 8 shows the forest plot of the meta-analysis examining the effect of behavioral interventions on LDL, which included three studies (n=156 patients).^{95,101,110} Two of the behavioral interventions focused on weight management, and one focused on diabetes management. All interventions included components that focused on physical activity and exercise as well as on diet and nutrition. The number of planned contacts ranged from 7 to 24 sessions, and duration of followup ranged from 3 to 12 months. Control conditions consisted of waitlist, no intervention, and usual care plus information (see Table 7 in KQ 1 results).

Figure 8. Forest plot of meta-analysis of effect of behavioral interventions on LDL



The analysis revealed no statistically significant difference in efficacy between behavioral interventions and control for managing LDL levels (mean difference=1.91 mg/dl; 95% CI, -6.06 to 9.88), with no evidence of heterogeneity (Cochran $Q=0.07$, $df=2$, $p=0.96$; $I^2=0\%$). Again, because formal statistical techniques for publication bias are not effective with small numbers of studies, we did not conduct analyses for publication bias. Only one of the three studies on behavioral interventions reported on adverse effects as defined in our study protocol,¹¹⁰ which reported that no drug-related severe adverse effects were observed. None of the studies reported on health-related quality of life.

Only two of the behavioral intervention studies reported on total cholesterol. In a 5-month multimodal lifestyle intervention that consisted of 11 group sessions and weekly fitness training for bipolar disorder patients ($n=50$), no significant differences were found between those in the lifestyle intervention group and those in a waiting control group.⁹⁵ In a 3-month psychoeducational program for weight control in patients who experienced weight gain on olanzapine ($n=33$), there were no significant differences in total cholesterol between those in the psychoeducational program and those receiving no intervention.¹¹⁰

Effect of Peer or Family Support Interventions on Lipid Control

We identified no eligible studies for this category of intervention for KQ 3.

Effect of Pharmacological Treatments on Lipid Control

Psychotropic Agents

A total of three studies examined the effect of psychotropic medications on lipids ($n=321$ patients);^{87,88,94} two of these studies recorded data on total cholesterol and all three on LDL. Study medications were ramelteon, aripiprazole, and atomoxetine, and the comparator in each study was placebo. The study durations ranged from 2 to 6 months.

Although ramelteon, aripiprazole, and atomoxetine all can be classified as psychotropic medications, we did not conduct a meta-analysis on the studies using these medications because their mechanisms of action vary substantially. Indeed, when examined qualitatively, results were mixed. The 24-week study of overweight schizophrenia patients ($n=37$) taking olanzapine or clozapine who were randomized to atomoxetine or placebo did not measure total cholesterol

levels and found no difference between groups on change in LDL levels.⁸⁷ However, two of the studies did find significant change between groups. The small 8-week pilot trial on ramelteon (n=25) found that stable outpatients with schizophrenia were significantly more likely to experience a decrease in total cholesterol (-9.79 mg/dl loss versus 3.84 mg/dl gain, $p=.03$) when taking ramelteon than placebo.⁸⁸ Change on LDL levels displayed the same pattern, but group differences were not significant in this small study. In a 16-week trial of aripiprazole versus placebo among 207 schizophrenia patients who had experienced weight gain while taking clozapine,⁹⁴ those in the aripiprazole group had greater percentage reductions in their total cholesterol levels (-6.9% versus -1.2%, $p=.002$) and LDL levels (-10.3% versus 0.0%, $p=.003$).

Of the three studies examining the effect of adding medication on lipid levels, only one reported on health-related quality of life or on serious adverse effects as defined by the study protocol.⁹⁴ This study found no significant differences between patients taking aripiprazole as an adjunctive medication to clozapine and patients taking placebo and clozapine on a measure of subjective well-being, but the study did find 0 out of 99 patients in the placebo group and 10 out of 108 patients in the aripiprazole group to experience a serious adverse effect.

Neurological Agents

There were a total of three two-arm studies (n=135 patients)^{96,111,113} and one three-arm study (n=199 patients)⁹⁷ that examined the effect of neurological agents on lipids. In all two-arm studies, the control condition was placebo. Study medications were amantadine, topiramate, and zonisamide (the three-arm study also involved metformin), and study durations ranged from 3 to 5 months. We were unable to complete meta-analysis on these studies due to heterogeneous study designs and unreported lipid outcome data (one study⁹⁶ stated only that results for lipids were not significant).

Results were mixed in the three two-arm studies that examined neurological agents compared to placebo. A 12-week study of amantadine versus placebo among 21 patients who had gained at least 5 pounds on olanzapine found no differences between groups on total cholesterol or LDL levels.⁹⁶ In a 12-week study of 72 first-episode schizophrenia patients randomized to either olanzapine plus topiramate or olanzapine plus placebo,¹¹³ patients taking topiramate were significantly less likely than those in the placebo group to experience a rise in LDL levels (0.34 mg% rise versus 10.53 mg% rise, $p=.009$). Finally, a 16-week study of zonisamide versus placebo in 42 patients beginning olanzapine for bipolar disorder or schizophrenia found no significant differences between groups on total cholesterol or LDL levels.¹¹¹ None of these three studies reported on health-related quality of life or serious adverse effects.

The three-arm, 22-week study⁹⁷ examined two different medication treatment-switching algorithms for prevention of weight gain compared with no medication in 199 patients with schizophrenia or schizoaffective disorder who were all taking olanzapine. The algorithms using amantadine, metformin, and zonisamide were significantly more effective at preventing increases in total cholesterol than olanzapine treatment alone (0.18 mg/dl gain and -1.44 mg/dl loss on algorithms versus 6.49 mg/dl gain on olanzapine alone). The algorithms had a less pronounced and nonsignificant effect for LDL. Health-related quality of life was not measured. Thirteen patients experienced a serious adverse effect, and a total of 14 patients discontinued the study due to a serious or nonserious adverse effect (group differences not tested).

Nizatidine

A 12-week study that examined the efficacy of nizatidine versus placebo for weight management in 54 patients with schizophrenia taking olanzapine found no statistically significant differences between groups with respect to the intervention's effect on lipid levels.⁸⁵ The study did not measure health-related quality of life. There was no significant difference between groups with respect to adverse effects, with one patient in the nizatidine group and two patients in the placebo group discontinuing due to an adverse effect.

Effect of Antipsychotic-Switching Interventions on Lipid Control

There were a total of four studies (n=1376 patients) that examined the effect of switching antipsychotic medications on lipids.^{91,98,102,104} Patients in all studies began on olanzapine, and in all studies the control condition consisted of staying on olanzapine. The intervention in two studies involved switching to a different form of olanzapine (an orally disintegrating tablet or a long-acting injection) and in the other two studies involved switching to a different antipsychotic medication (quetiapine or aripiprazole). Study durations ranged from 4 to 6 months. Meta-analysis was not completed on these four studies due to the heterogeneity of switching strategies.

There were mixed results in the two studies that examined switching to a different form of olanzapine.^{98,104} In the 16-week trial of 149 patients with SMI that involved switching from standard olanzapine tablets to orally disintegrating olanzapine tablets,⁹⁸ there was no difference between groups with respect to lipid levels. This study found no difference between groups on a measure of subjective well-being. Serious adverse effects were experienced by two patients in the orally disintegrating olanzapine group and none in the standard olanzapine tablet group.

In the 24-week trial of 921 patients with schizophrenia that involved switching from oral olanzapine to a long-acting injection of olanzapine,¹⁰⁴ patients continuing oral olanzapine experienced a significantly greater decrease in LDL levels than did patients in the long-acting injection group (-6.4 mg/dl loss versus -1.5 mg/dl loss, $p=.039$). The groups did not differ on total cholesterol. This study did not measure health-related quality of life. Serious adverse effects were reported in 42 patients, and 57 patients discontinued due to adverse effects, but the authors report that there was no statistically significant difference between groups for adverse effects.

The studies that examined switching from olanzapine to a different antipsychotic medication^{91,102} also had mixed results. In the 24-week study of 133 overweight patients with schizophrenia that examined switching from olanzapine to quetiapine,⁹¹ those who switched to quetiapine did not have significantly different changes in their total cholesterol or LDL levels than those who remained on olanzapine. This study did not report on health-related quality of life or serious adverse effects as defined by study protocol. In the 16-week trial of 173 patients with schizophrenia who either stayed on olanzapine or switched to aripiprazole,¹⁰² those who switched to aripiprazole had a significantly greater percentage decrease in total cholesterol (-9.5% versus -3.3%, $p=.005$) and a nonsignificantly greater percentage decrease in LDL (-11.2% versus -4.7%, $p=.072$). This study did not report on health-related quality of life but did find that six aripiprazole-treated subjects experienced a serious adverse effect and seven discontinued, compared with nine olanzapine-treated subjects who experienced a serious adverse effect and eight who discontinued.

Summary of Key Question 3

None of the 15 studies in KQ 3 contained an intervention specifically intended to target lipid levels. Instead, the primary outcomes of interest were weight in 12 of the studies, glucose control in 1 study, and all-purpose metabolic effects in 2 studies. Total cholesterol was measured in 12 studies and LDL in 14 studies. Overall, 6 of the 15 trials found significant changes between study groups on lipid levels. The interventions in these studies included ramelteon,⁸⁸ topiramate,¹¹³ medication treatment algorithms,⁹⁷ and aripiprazole.^{94,102} In all instances, intervention effects resulted in a 5 percent or less difference in lipid values compared with control. Also, one study testing a long-acting injection of olanzapine found that subjects receiving the injection were less likely than those remaining on oral olanzapine to experience a decrease in LDL.¹⁰⁴ Since all studies were evaluating lipids as a secondary outcome and are summarized in KQ 1, the details regarding other health outcomes are summarized in that section. In brief, health-related quality of life and serious adverse effects were infrequently reported in the 15 trials. Health-related quality of life was reported in only 2 of the 15 trials. Serious adverse effects were reported in four studies, and adverse effects leading to treatment discontinuation were reported in six studies.

Key Question 4. Effectiveness of Multicondition Lifestyle Interventions

KQ 4: What is the effectiveness of multicondition lifestyle interventions (e.g., combinations of smoking cessation, physical activity, and nutrition counseling with or without medication management) on cardiovascular risk factors and related physical health outcomes (e.g., health-related quality of life, mortality) among adults with SMI who have cardiovascular disease, elevated cardiovascular risk (e.g., hypertension), or are taking antipsychotics?

Key Points

- Only three studies evaluated lifestyle interventions.
- One study reported significant effects on BMI, weight, and cholesterol:
 - This good-quality study showed benefit in switching from olanzapine, quetiapine, or risperidone to aripiprazole in the context of a manualized, behaviorally oriented diet and exercise program.
 - The effects of the behavioral component of the lifestyle intervention in this study are unknown, since both the intervention and comparison arm received the behavioral component.
- Two studies reported significant effects of multicondition lifestyle interventions for self-reported health-related quality of life.

Detailed Synthesis

We identified three studies involving 286 patients that assessed the effects of lifestyle interventions on cardiovascular risk factors and related physical health outcomes among adults with SMI.¹¹⁴⁻¹¹⁶

Study Characteristics

Table 10 shows the study characteristics for KQ 4. The diagnostic samples identified by these studies included schizophrenia only¹¹⁴ and SMI (i.e., psychotic and mood disorders).^{115,116} Two studies were conducted in the United States^{114,116} and one in Europe.¹¹⁵ One study¹¹⁴ was conducted in several clinical research centers, while one¹¹⁵ was conducted in supported housing facilities. The third study¹¹⁶ reported that recruitment was conducted at a large mental health facility's inpatient and outpatient programs and surrounding community treatment centers, but the location of intervention delivery was unclear. The study by Stroup et al.¹¹⁴ was rated as a mixed efficacy–effectiveness study of good quality, Forsberg et al.¹¹⁵ as a mixed efficacy–effectiveness study of fair quality, and Skrinar et al.¹¹⁶ as an efficacy study of fair quality.

Table 10. Study characteristics for KQ 4: Multicondition lifestyle interventions

Characteristic	Details
Studies: N (patients) ^a	3 studies (286 patients)
Mean age of sample: Median (range)	41.0 (41.0 to 37.8)
Sex: N patients (%)	
Female	114 patients (39.86%)
Male	172 patients (60.14%)
NR	0 patients (0%)
Race: N patients (%)	
White	123 patients (43.00%)
Nonwhite	90 patients (31.47%)
NR	73 patients (25.52%)
Setting: N studies (%) ^d	
Mental health	2 studies (66.67%)
General medical	0 studies (0%)
Community	2 studies (66.67%)
Integrated mental health-medical	0 studies (0%)
Study quality: N studies (%)	
Good	1 study (33.33%)
Fair	2 studies (66.67%)
Poor	0 studies (0%)
Efficacy–effectiveness rating: N studies (%)	
Efficacy (0–2)	1 study (33.33%)
Mixed (3–5)	2 studies (66.67%)
Effectiveness (6–7)	0 studies (%)
Comparisons: N studies (patients)	
Drug + behavioral vs. drug	1 study (215 patients)
Lifestyle Intervention vs. placebo	2 studies (71 patients)

^aThe number of patients with demographic data reported is fewer than the number randomized.

^bStroup et al.¹¹⁴ selected participants from both mental health and community settings.

Qualitative Review

The three studies included in KQ 4 are described below qualitatively due to the variability in interventions and outcomes.

Effect of Multicondition Lifestyle Interventions on Cardiovascular Risk Factors

In a fair-quality mixed efficacy–effectiveness study by Forsberg et al.,¹¹⁵ 46 participants were randomized to receive either a health intervention program or a non–health-related control program for 12 months. Demographic and outcome data were reported for the 41 participants who completed the study. The health intervention program provided group dietary education and physical activity sessions. Group sessions were 2 hours in duration and were held twice weekly for the entire 12-month study. The control group attended art classes held once weekly for 2 hours.

No significant differences between the active and control groups were reported for BMI, weight in kilograms, HbA1c percentage, systolic blood pressure, diastolic blood pressure, smoking cessation, or a composite cardiovascular risk score at 13.5 months. There was a significant decrease in the number of individuals diagnosed with metabolic syndrome in the intervention group (from 13 to 10), while there was a nonsignificant increase in the number of individuals diagnosed with metabolic syndrome in the control group (from 4 to 6); however, these changes did not differ significantly between the intervention and control groups. A performance-based measure of physical functioning, the incremental shuttle walk test, was not affected by the intervention. Adverse effects were not reported. Quality issues included the low attendance at group sessions, the inability of the researchers to control whether participants in the comparison condition engaged in exercise or dieting while enrolled, no intent-to-treat analysis, and the absence of description of antipsychotic medication status of study participants.

In a fair-quality efficacy study by Skrinar et al.,¹¹⁶ 30 individuals with SMI were randomized to a healthy lifestyle group or to a waitlist control group for 12 weeks; outcome data were reported for the 20 participants who completed the study. The healthy lifestyle group consisted of four exercise sessions each week and one weekly health seminar covering a broad range of topics (e.g., healthy eating, weight management, stress relief).

There were no significant differences between groups at 12 weeks for BMI, weight, total cholesterol, glucose, or psychiatric symptom severity (as measured by SCL-90 score). Participants in the intervention group showed significantly greater increases in their subjective rating of general health as measured by the General Health factor of the SF-36 (intervention group mean difference=13.64 vs. control group mean difference = - 4.09, $p=.01$); self-reported physical health and role limitations due to physical health also improved more in the intervention group, but the differences were not statistically significant. Adverse effects were not reported. Quality issues included the low adherence rate (63%), small sample size, and lack of an intent-to-treat analysis. Study authors noted specific barriers to participation in the intervention (e.g., transportation, financial issues), which contributed to the low adherence rate—highlighting a common challenge of exercise interventions in the SMI population. They emphasized the positive impact of the intervention on perceived health-related well-being despite the lack of significant behavioral or metabolic changes.

In contrast to the other two studies, the third study by Stroup et al.¹¹⁴ was a large (N=215), good-quality, mixed efficacy–effectiveness trial (Comparison of Antipsychotics for Metabolic

Problems, CAMP) carried out between January 2007 to March 2010. This study examined the impact of switching from olanzapine, quetiapine, or risperidone to aripiprazole (flexible dose) on weight and metabolic variables. All subjects in the study participated in a manualized, behaviorally oriented diet and exercise program (once weekly visits for the first month, followed by once monthly visits thereafter). The trial was carried out at 27 clinical research centers affiliated with the Schizophrenia Trials Network in the United States and was 24 weeks in duration.

Overall, the results of this study supported switching to aripiprazole combined with a behavioral health-management program as a useful method for managing weight gain and metabolic problems in individuals with SMI and antipsychotic-related weight gain. Significant group effects were observed for BMI (mean diff = - 1.1, $p < .01$), weight (mean diff = - 2.9 kg, $p < .01$), total cholesterol (mean diff = - 8.8 mg/dl, $p = .02$), and non-HDL cholesterol (mean diff = -9.4 mg/dl, $p = .01$). Stroup et al. (2011) also reported significant intervention effects for health-related quality of life as indicated by the 12-Item Short-Form (SF-12) Health Survey for physical health (mean diff = 3.7, $p < .02$) and the Impact of Weight on Quality of Life-Lite Questionnaire (mean diff = -9.5, $p < .01$), with an advantage on both of these measures for patients who switched to aripiprazole. Serious adverse effects occurred in 16.8 percent of the group who switched to aripiprazole and 13.1 percent of those remaining on their current antipsychotic treatment (p -value not reported).

The biggest limitation of this study was differential attrition, with 47.7 percent of participants who switched medication discontinuing the study for any reason compared with 27.4 percent of those who did not switch. The authors speculated that this was due to clinician detection of clinical worsening in the switch group, which was confirmed in a post-hoc analysis. This highlights the need for careful clinical monitoring following medication switching. Unlike the other two studies included in KQ 4, this study detected significant differential effects on weight and metabolic variables between the study groups. Although this study is informative with regard to medication switching, it did not examine the specific effect of the behavioral intervention, which all participants received. Therefore, we cannot speculate on the impact of this aspect of the lifestyle intervention beyond the effects of the medication.

Summary of Key Question 4

Only three published studies met inclusion criteria for this Key Question. The small number of RCTs and narrow range of interventions preclude drawing strong conclusions about the efficacy or effectiveness of multicondition lifestyle interventions on cardiovascular risk factors or physical health outcomes for adults with SMI. The behavioral component of the identified studies focused on exercise and nutrition only. No studies added components such as medication adherence, smoking cessation, or skills training (e.g., meal planning) that would have constituted a more comprehensive behavioral intervention. Further, no studies evaluated lifestyle interventions in combination with medications for weight loss (e.g., orlistat) or metabolic risk factors such as HMG-CoA reductase inhibitors for hyperlipidemia. The most important signal from these studies is that switching to aripiprazole—in combination with a structured behavioral intervention—is a promising strategy for minimizing adverse metabolic consequences of second-generation antipsychotics, but the tradeoff may be a higher rate of worsening psychiatric status for the individual with SMI. Multicondition interventions demonstrated some promise for impacting health-related quality of life, as indicated by the effects of two out of three included studies.

Discussion

Key Findings and Strength of Evidence

We identified 33 trials that tested a wide array of behavioral and pharmacological interventions to address one or more cardiovascular risk factors in patients with SMI and elevated risk for CVD. Given that CVD is the most prevalent cause of death in this population, it is a surprisingly small number of studies. Further, we identified no peer and family support interventions to address elevated CVD risk, nor did we find any interventions designed specifically to address lipids. No interventions targeted individuals with psychotic depression specifically. Outcomes reported were primarily metabolic outcomes such as glucose control, or weight; effects on physical function and overall CVD risk (e.g., Framingham index) were reported infrequently, and all-cause mortality was not reported.

Table 11 presents a brief overview of key findings by intervention as well as the strength of evidence (SOE) by Key Question for major outcomes. Our drug classes sometimes include drugs with diverse mechanisms of action. When results varied by drug, we assigned separate SOE. Publication bias was difficult to assess because only one comparison had sufficient studies for statistical analysis. For adverse effects, we considered discontinuation due to adverse effects and worsening of psychiatric status as the key outcomes when rating SOE. When the majority of studies reported only one of these outcomes, we considered the evidence for adverse effects incomplete and rated the limited evidence as indirect. In brief, evidence was insufficient for most intervention strategies, and there were too few studies to conduct quantitative synthesis for all outcomes of interest, except for weight.

Table 11. Overview of treatment effects and SOE by intervention and key outcomes

Intervention	(KQ 1) Weight	(KQ 2) Diabetes (HbA1c)	(KQ 3) Lipids ^a	Overall CVD risk and Other Outcomes
Behavioral	Small benefit (-3.1 kg) Moderate SOE	Insufficient SOE	No important effect from weight control interventions Low SOE	1 study assessed health-related quality of life and found no differences Only 2 studies reported discontinuation due to adverse effects Insufficient SOE
Peer or family support	No studies Insufficient SOE	No studies Insufficient SOE	No studies Insufficient SOE	No studies Insufficient SOE
Metformin	Small benefit (-2 to -4.7 kg) Low SOE	Insufficient SOE	No studies Insufficient SOE	Insufficient SOE for CVD risk
Antiseizure medication	Small to moderate benefit (-5.1 kg) Low SOE	Insufficient SOE	Possible benefit with topiramate Insufficient SOE	Insufficient SOE for CVD risk

Intervention	(KQ 1) Weight	(KQ 2) Diabetes (HbA1c)	(KQ 3) Lipids ^a	Overall CVD risk and Other Outcomes
Antihistamine	No benefit Low SOE	Insufficient SOE	Single study did not suggest benefit Insufficient SOE	Insufficient SOE for CVD risk
Other medications	Insufficient SOE	Insufficient SOE	No study suggested possible benefit Insufficient SOE	Insufficient SOE for CVD risk
Antipsychotic switching	Small benefit (-2 to -3 kg) with aripiprazole Moderate SOE	Insufficient SOE	Possible benefit with aripiprazole Insufficient SOE	Insufficient SOE for CVD risk Possible higher rate of mental health worsening; low SOE
Multicomponent lifestyle	Insufficient SOE	Insufficient SOE	Insufficient SOE	Two studies suggested benefit for health-related QOL 1 study reported no benefit on CVD risk score Insufficient SOE

^aNo studies of lipid-focused interventions.

Abbreviations: CVD=cardiovascular disease; SOE=strength of evidence

Key Question 1: Weight Control

The largest number of studies (30 of 33) addressed weight control. We found moderate SOE that behavioral interventions are associated with small decreases in weight (about 3 kg) compared with controls (Table 12). We found low SOE that switching to or adding adjunctive aripiprazole, adding the antiseizure medications topiramate and zonisamide, or adding metformin yield small to moderate weight loss. Nizatidine, an antihistamine, did not show any consistent effect on weight (low SOE). The SOE was insufficient for all other interventions.

The findings for behavioral interventions and metformin are consistent with a recent review that examined treatments for obesity relevant to primary care.¹¹⁷ No studies evaluated orlistat, an FDA-approved medication for the treatment of obesity that is also available without prescription at a lower dose. Orlistat is associated with approximately a 3-kg weight reduction over 12 to 18 months, but it must be used in conjunction with a low-fat diet.

Table 12. Summary SOE for KQ 1: Interventions for weight control

Outcome	Number of Studies (Subjects)	SOE Domains: Risk of Bias (ROB) Consistency	SOE Domains: Directness Precision	SOE and Effect Estimate
Psychotropic medications: atomoxetine, fluoxetine, ramelteon				
Weight	4 (268)	Moderate ROB NA	Direct Imprecise	Insufficient SOE; single studies showing no effect for atomoxetine, fluoxetine, ramelteon; small effects for amantadine
Physical function/ HRQOL	1 (207)	Low ROB NA	Direct Imprecise	Insufficient SOE; 1 study showing no positive effect
Adverse effects	1 (207)	Low ROB NA	Direct Imprecise	Insufficient SOE; 1 study reporting discontinuation due to adverse effects reported
Antiseizure medications: topiramate, zonisamide				
Weight	3 (158)	Moderate ROB Consistent	Direct Imprecise	Low SOE; mean difference -5.1 kg (95% CI, -9.8 to -0.7)
Physical function/ HRQOL	1 (67)	Moderate ROB NA	Direct Imprecise	Insufficient SOE; positive effects on multiple scales for topiramate in a single study
Adverse effects	1 (42)	Low ROB NA	Indirect Imprecise	Insufficient SOE; Only discontinuation due to adverse effect reported
Metformin				
Weight	3 (388)	Moderate ROB Consistent	Direct Imprecise	Low SOE; range of mean differences -2.1 to -4.7 kg
Physical function/ HRQOL	0	NA	NA	Insufficient SOE
Adverse effects	3 (388)	Low ROB NA	Indirect Imprecise	Insufficient SOE; inconsistent reporting of major adverse effect of interest
Antihistamine: nizatidine				
Weight	4 (286)	Moderate ROB Inconsistent	Direct Precise	Low SOE; mean difference -0.5 (95% CI, -1.3 to 0.3)
Physical function/ HRQOL	No studies	NA	NA	Insufficient SOE
Adverse effects	1 (54)	Low ROB NA	Indirect Imprecise	Insufficient SOE; inconsistent reporting of major adverse effect of interest
Antipsychotic switching				
Weight-aripiprazole	3 (595)	Low ROB Consistent	Direct Imprecise	Moderate SOE; range of mean difference -2 to -3 kg when used as adjunct or switch and compared to placebo or behavioral intervention alone
Weight-olanzapine	2 (1070)	Moderate ROB Consistent	Direct Imprecise	Insufficient SOE for oral disintegrating and injectable olanzapine; single studies
Physical function/ HRQOL-aripiprazole	2 (422)	Low ROB Inconsistent	Direct Imprecise	Insufficient SOE; 1 study found small, clinically insignificant improvements in physical function; 1 found no effect on HRQOL
Physical function/ HrQOL-olanzapine	1 (149)	Low ROB NA	Direct Imprecise	Insufficient SOE; 1 study found no difference with oral disintegrating olanzapine

Outcome	Number of Studies (Subjects)	SOE Domains: Risk of Bias (ROB) Consistency	SOE Domains: Directness Precision	SOE and Effect Estimate
Adverse effects- aripiprazole	3 (595)	Moderate ROB Consistent	Indirect Imprecise	Insufficient SOE; possible higher rate of clinical worsening
Adverse effects- olanzapine	2 (1070)	Moderate ROB Consistent	Direct Imprecise	Insufficient SOE
Behavioral interventions				
Weight	11 (792)	Moderate ROB Consistent	Direct Precise	Moderate SOE Mean difference -3.1kg (-4.2 to -2.1)
Physical function/ HRQOL	1 (48)	High ROB NA	Direct Imprecise	Insufficient SOE
Adverse effects	2 (199)	Moderate ROB Consistent	Direct Imprecise	Insufficient SOE
Peer or family support interventions				
All outcomes	No studies	NA	NA	Insufficient SOE

Abbreviations: CI=confidence interval; CVD=cardiovascular disease; HRQOL=health-related quality of life; kg=kilogram; NA=not applicable; OR=odds ratio; RCT=randomized controlled trial; ROB=risk of bias; SOE=strength of evidence

Key Question 2: Diabetes Control

We identified only seven trials that assessed the impact of behavioral and pharmacological interventions to address glucose control as measured by HbA1c in patients with SMI and elevated risk for CVD. Of these, only one study assessed patients with diabetes and glucose control directly;¹⁰¹ the other six studies assessed HbA1c as a secondary outcome. Overall, we found insufficient evidence for all interventions (Table 13). Among populations without SMI who have diabetes, disease management programs¹¹⁸ and metformin have been effective, as have lifestyle interventions for improving glucose control in persons with diabetes or at risk of developing diabetes. Further, metformin is associated with decreased cardiovascular events compared with no treatment.¹¹⁹ These interventions may also translate to populations with SMI and warrant exploration.

Table 13. Summary SOE for KQ 2: Interventions for diabetes control (glucose)

Outcome	Number of Studies (Subjects)	SOE Domains: Risk of Bias (ROB) Consistency	SOE Domains: Directness Precision	SOE and Effect Estimate
Psychotropic medication: ramelteon				
A1c	1 (20)	Moderate ROB NA	Direct Imprecise	Insufficient SOE; 1 small study with small reduction in A1c
Physical function/ HRQOL	No studies	NA	NA	Insufficient SOE
Adverse effects	No studies	NA	NA	Insufficient SOE
Antiseizure medications				
All outcomes	No studies	NA	NA	Insufficient SOE
Metformin				
A1c	2 (260)	High ROB Inconsistent	Direct Imprecise	Insufficient SOE; 2 studies, 1 using metformin with other medications in a treatment algorithm yielded small reductions in A1c

Outcome	Number of Studies (Subjects)	SOE Domains: Risk of Bias (ROB) Consistency	SOE Domains: Directness Precision	SOE and Effect Estimate
Physical function/ HRQOL	No studies	NA	NA	Insufficient SOE
Adverse effects	2 (260)	High ROB NA	Direct Imprecise	Insufficient SOE
Antipsychotic switching: olanzapine to quetiapine, aripiprazole, or oral-disintegrating olanzapine				
A1c	3 (497)	Low ROB Consistent	Direct Precise	Moderate SOE; range of mean difference 0 to -0.1
Physical function/ HRQOL	1 (215)	Low ROB NA	Direct Imprecise	Insufficient SOE; 1 study showed improvements in physical functioning
Adverse effects	3 (497)	Low ROB Consistent	Direct Imprecise	Low SOE; switching strategies had higher discontinuations, often due to psychiatric adverse effects
Behavioral interventions				
A1c	2 (117)	Moderate ROB Inconsistent	Direct Imprecise	Insufficient SOE; range of mean difference -0.6 to 0
Physical function/ HRQOL	No studies	NA	NA	Insufficient SOE
Adverse effects	1 (64)	Moderate ROB NA	Direct Imprecise	Insufficient SOE
Peer or family support interventions				
All outcomes	No studies	NA	NA	Insufficient SOE

Abbreviations: CI=confidence interval; CVD=cardiovascular disease; HRQOL=health-related quality of life; NA=not applicable; OR=odds ratio; RCT=randomized controlled trial; ROB=risk of bias; SOE=strength of evidence

Key Question 3: Lipid Control

No studies evaluated an intervention specifically designed to target lipid levels in patients with SMI who have dyslipidemia or are at risk for dyslipidemia. We found low SOE that behavioral interventions focusing on weight loss or diabetes management have no substantial effects on lipids (Table 14). The SOE was insufficient for all other interventions. However, small benefits were seen when aripiprazole was used as an adjunct or as an antipsychotic-switching strategy, and single studies suggested possible benefit with rimegepant or topiramate. In contrast, low to moderate doses of statins are associated with a 20 to 40 percent reduction in LDL cholesterol.^{120,121}

Table 14. Summary SOE for KQ 3: Interventions for lipid control

Outcome	Number of Studies (Subjects)	SOE Domains: Risk of Bias (ROB) Consistency	SOE Domains: Directness Precision	SOE and Effect Estimate
Psychotropic medications: atomoxetine, rimegepant				
Total cholesterol	1 (25)	Moderate ROB NA	Direct Imprecise	Insufficient SOE; 1 study showing benefit on total cholesterol for rimegepant, 1 study showing no effect on LDL cholesterol for atomoxetine
LDL cholesterol	2 (62)			
Physical function/ HRQOL	1 (207)	NA	NA	Insufficient SOE; 1 study showing no benefit
Adverse effects	No studies	NA	NA	Insufficient SOE

Outcome	Number of Studies (Subjects)	SOE Domains: Risk of Bias (ROB) Consistency	SOE Domains: Directness Precision	SOE and Effect Estimate
Antiseizure medications: topiramate, zonisamide				
Total cholesterol	1 (42)	Low ROB NA	Direct Imprecise	Insufficient SOE; 1 study showing moderate benefit (mean difference 10.2 mg%) with topiramate on LDL; 1 study showing no effect with zonisamide
LDL cholesterol	2 (114)	Moderate ROB Inconsistent	Direct Imprecise	
Physical function/ HRQOL	No studies	NA	NA	Insufficient SOE
Adverse effects	No studies	NA	NA	Insufficient SOE
Other medications: amantadine, nizatidine				
Total cholesterol LDL cholesterol	2 (75) 2 (75)	Low to High ROB NA	Direct Imprecise	Insufficient SOE; single studies for amantadine and nizatidine showing no effect
Physical function/ HRQOL	No studies	NA	NA	Insufficient SOE
Adverse effects	No studies	NA	NA	Insufficient SOE
Antipsychotic switching				
Total cholesterol	4 (1376)	Moderate ROB Inconsistent	Direct Imprecise	Insufficient SOE; results varied by switching strategy. Only a switch to aripiprazole improved lipid values; switch to injectable olanzapine increased lipid values
LDL cholesterol	4 (1376)			
Physical function/ HRQOL	1 (149)	Low ROB NA	Direct Imprecise	Insufficient SOE
Adverse effects	3 (1243)	Moderate ROB Consistent	Indirect Imprecise	Low SOE for no moderate to large differences in serious adverse events or discontinuations due to adverse events Insufficient SOE for risk of psychiatric worsening
Behavioral interventions				
Total cholesterol	2 (99)	Moderate ROB Consistent	Direct Imprecise	Insufficient SOE Low SOE; mean difference=1.9 mg/dl (-6.1 to 9.9)
LDL cholesterol	3 (156)			
Physical function/ HRQOL	0 0	NA NA	NA NA	Insufficient SOE
Adverse effects	1 (49)	High ROB NA	Indirect Imprecise	Insufficient SOE
Peer or family support interventions				
All outcomes	No studies	NA	NA	Insufficient SOE

Abbreviations: CI=confidence interval; CVD=cardiovascular disease; HRQOL=health-related quality of life; NA=not applicable; OR=odds ratio; RCT=randomized controlled trial; ROB=risk of bias; SOE=strength of evidence

Key Question 4: Multicondition Lifestyle Interventions

Few studies evaluated multicondition interventions, and these studies evaluated only a limited number of components. Two studies evaluated multicomponent lifestyle interventions alone and one evaluated switching from one of three second-generation antipsychotic medications to aripiprazole in combination with a structured diet and exercise program. None of these studies evaluated lifestyle interventions in combination with medications that directly address weight (e.g., orlistat), glucose (e.g., metformin), or lipids (e.g., statins). Studies reported each outcome separately without reporting an overall CVD risk such as the Framingham score. As described above, when adding or switching to aripiprazole, there is low SOE for a small benefit on weight, but the evidence is insufficient for overall CVD risk. The two multicomponent behavioral interventions did not have a positive effect on the individual CVD risk factors, although one of the two studies showed a large positive effect on health-related QOL.

Table 15. Summary SOE for KQ 4: Multicondition lifestyle interventions

Outcome	Number of Studies (Subjects)	SOE Domains: Risk of Bias (ROB) Consistency	SOE Domains: Directness Precision	SOE and Effect Estimate
Multicondition interventions				
CVD Risk	1 (41)	Moderate NA	Direct Imprecise	Insufficient SOE; 1 study showed no positive effects
Physical function/ HRQOL	2 (245)	Low ROB Inconsistent	Direct Imprecise	Insufficient SOE; Two studies showing no effect of multicomponent behavioral intervention but positive effects with switch to aripiprazole plus behavioral intervention
Adverse effects	1 (215)	Low ROB NA	Direct Imprecise	Insufficient SOE; greater discontinuation due to adverse effects and greater serious adverse effects in aripiprazole plus behavioral intervention

Abbreviations: HRQOL=health-related quality of life; NA = not applicable; ROB=risk of bias; SOE = strength of evidence

Findings in Relation to What is Already Known

A number of high-quality systematic reviews have evaluated the comparative benefits and harms of antipsychotic medications.^{122,123} However, these reviews focused on mental health outcomes and adverse effects, including adverse metabolic consequences, but not strategies for managing the adverse metabolic effects. Other reviews have identified effective treatments for cardiovascular risk factors such as obesity, tobacco use, and hyperlipidemia in *general populations* or *adults at increased risk for CVD*.^{117,124,125} We specifically excluded from our review evaluations of general health advice, smoking cessation interventions, and models to provide integrated mental health–general medical care because these topics had been the subject of recent high-quality reviews in patients with SMI.³¹⁻³⁵ Tsoi et al.^{31,32} found that bupropion more than doubled the rate of smoking abstinence in smokers with schizophrenia without jeopardizing their mental state. There were few studies of other smoking cessation treatments. In contrast, Tosh et al.³³ found a small number of RCTs evaluating general physical health advice for patients with SMI, and no clear benefit on health outcomes. Bradford et al.³⁵ found moderately strong evidence that integrated mental health and general medical care improves preventive services but limited and inconsistent effects on physical functioning.

Our results complement prior reports by examining a broad array of interventions for patients at increased risk for worsening health outcomes due to cardiovascular risk factors such as obesity, hyperlipidemia, diabetes mellitus, or chronic administration of antipsychotic medication that negatively impact metabolic parameters. Earlier narrative and systematic reviews have focused primarily on behavioral interventions for weight control in patients with schizophrenia or who were on antipsychotic medications.^{72,73,126} The conclusions of these reviews were largely consistent with our findings in that behavioral interventions were associated with small improvements in weight. Our review builds on these findings by identifying clear omissions in treatments known to be effective in non-SMI populations, including guideline-concordant care, and promising treatment strategies such as aripiprazole, metformin, and topiramate, which deserve further investigation.

Applicability

The positive effects of interventions do not always translate well to usual practice, where clinician training, clinical setting, system resources, and patient characteristics may vary importantly from trial conditions. In our review, only 15 of 33 trials were conducted in the United States, and most studies (n=20) were classified as efficacy studies and were relatively short in duration. Studies typically enrolled midlife adults; none specifically enrolled older adults. Women, as well as racial minorities, were well represented. Most were conducted in mental health outpatient settings, typical of the principal locus of medical care for patients with SMI; none were conducted in patient-centered medical homes or in settings that integrated mental health and general medical services. None were classified as effectiveness studies, but for many interventions, initial studies are justifiably designed to answer the question, Can it work under ideal conditions?—before moving to a test of effectiveness. Probably the most important constraint on applicability is the inconsistent reporting of the CVD-related outcomes of interest and the nearly total lack of reporting (only reported in one study) for overall CVD risk indices (e.g., Framingham Risk Score). Understanding intervention effects on overall CVD risk would, arguably, be reported as effects on CVD risk indices, CVD events (e.g., stroke, myocardial infarction) or CVD-related mortality—all of which were missing from the included trials except for one that reported CVD risk indices.¹¹⁵

Implications for Clinical and Policy Decisionmaking

The U.S. Preventive Services Task Force makes recommendations for CVD screening in adults, including blood pressure¹²⁷ and tobacco use,¹²⁸ screening for diabetes in patients with elevated blood pressure,¹²⁹ and lipid screening in midlife adults or young adults at increased risk for CVD.¹³⁰ Increasing guideline-concordant care for individuals with SMI—given the current lack of evidence for SMI-specific interventions—could be considered a starting point for minimizing CVD risk in patients with SMI. These guidelines for the general population should then be modified to consider the special risks for patients with SMI. In 2004, the American Diabetes Association and American Psychiatric Association issued consensus guidelines¹³¹ for screening and monitoring of patients taking antipsychotic drugs. These guidelines recommended baseline monitoring to include a family history, BMI, waist circumference, blood pressure, fasting plasma glucose, and fasting lipid profile as well as followup monitoring of weight, fasting glucose, lipid levels, and blood pressure. Diabetes screening guidelines have since been updated to include the HbA1c as an appropriate measure to screen for diabetes mellitus.¹³² Although

screening and monitoring are addressed well by current guidelines, the American Psychiatric Association guidelines for schizophrenia provide only general advice for managing adverse effects of antipsychotic medication, such as helping the patient tolerate the adverse effect, treating the comorbid condition, or considering a change in the psychotropic medication to an alternative with less potential to induce side effects.

Our review, together with other reviews on interventions to decrease CVD risk in patients with or without SMI, suggests a few actionable strategies and others requiring further study. For weight control, moderate evidence supports behavioral interventions and more limited evidence supports metformin, topiramate, or aripiprazole as an adjunctive or antipsychotic-switching strategy. All of these interventions yield small to moderate effects, and the benefits must be weighed against the potential harms, including the small risk of lactic acidosis and need for monitoring renal function with metformin. Data are much more limited for effects on average glucose control or lipid levels in patients at increased risk. The antihistamine nizatidine was not effective for any CVD risk factor and is unlikely to be a useful treatment. Other reviews identify bupropion as the best supported treatment for smoking cessation;^{31,32} nicotine replacement therapy is effective in non-SMI populations but has not been adequately studied in patients with schizophrenia, bipolar disorder or psychotic depression. Other reviews identified tailored mood management in patients with depressive symptoms^{133,134} and behavioral support interventions in individuals with mental illness as potentially effective.¹³⁵ Although the evidence is limited, the meta-finding is that, of the interventions tested in SMI populations to date, effects on intermediate outcomes (e.g., weight) are similar to the effects found in the general population.

Physicians take an oath of *primum non nocere*: First do no harm. The American Psychiatric Association's 2004 guidance follows this principle, recommending a response to adverse medication effects by considering a change in the psychotropic medication to an alternative with less potential to induce side effects. When treating emergent metabolic abnormalities that temporally follow medication treatment, this approach is rational, but existing data show only small improvements in the cardiovascular outcomes of interest. Other high-quality systematic reviews have addressed the comparative efficacy of antipsychotics and identified few differences in short-term efficacy between second-generation antipsychotics; clozapine reduced suicides and suicidal behavior, and clozapine and olanzapine had lower rates of discontinuation. Olanzapine resulted in greater weight gain and increased risk of new onset diabetes.¹²³ In patients who have responded well to psychotropic medication, a change in treatment carries the risk of symptom-worsening, an outcome not consistently reported in the studies reviewed. Further, antipsychotic-switching strategies have not been tested directly against treatments that target the metabolic abnormality directly (e.g., statin for hyperlipidemia) or multimodal strategies that include medication switching and lifestyle interventions. Although one would expect standard treatments such as statins to have similar benefits in patients with SMI, potential lower treatment adherence or poorer tolerability of side effects could diminish effectiveness. For some medications, interactions with psychotropic medications (e.g., lithium) may limit effectiveness. Despite these cautions, and in the absence of direct evidence in patients with SMI, treatments established as effective in non-SMI populations are a logical choice to treat risk factors for CVD in SMI populations until better evidence is available.

Studies of guideline adherence show significant gaps between current practice and recommendations for cardiovascular risk screening and followup.¹³⁶ Studies show screening rates ranging from about 10 to 26 percent for lipids and 22 to 52 percent for glucose.¹³⁷⁻¹⁴⁰ Data on monitoring of these risk factors in patients treated with second-generation antipsychotics are

more limited but also show gaps between guidelines and practice. Assessment and monitoring is only a first step. When abnormalities are detected, they must be addressed, either by the mental health professional or by a general medicine clinician. Integrated mental health–general medical care has shown promise as the optimal way to deliver this care, and the current move to medical homes has the potential to make this type of care more readily available. Unfortunately, few medical home models to date have explicitly included mental health care.¹⁴¹ Until integrated care is better established and more readily available, there are a number of implementation strategies to consider when a change to a metabolically more neutral antipsychotic is not sufficient to address elevated CVD risk factors. When patients have access to both mental health specialty care and general medical care, it is important that these clinicians coordinate care across issues that may impact both physical and mental health. For example, general medical providers may be aware of the adverse metabolic effects of some psychotropics but are appropriately hesitant to adjust these medications. Coordinating care with the mental health professional about roles and specific strategies for addressing cardiovascular risk factors has the potential to improve care and clinical outcomes.

When general medical care is unavailable, one pragmatic strategy to consider is an expanded role for psychiatrists. Weight and blood pressure screening and monitoring are low-cost measures, requiring minimal time and office equipment. For patients without access to general medical care, psychiatrists could incorporate these activities into their usual clinical practice. Treating hyperlipidemia with statins is only slightly more difficult. The FDA and guidelines groups have recently revised recommendations; periodic transaminase monitoring is no longer recommended. In addition, some authors have made a strong case for fixed-dose statins that would further decrease the need for ongoing monitoring of lipid levels.¹⁴² Thus, psychiatrists would need only to follow NCEP-III guidelines for when to initiate treatment (and readily available Web and smartphone-based applications facilitate quick access to these guidelines) and consider potential drug-drug interactions, which are relatively few.

Limitations of the Comparative Effectiveness Review Process

Our study has a number of strengths, including a protocol-driven review, a comprehensive search, careful quality assessment, and rigorous synthesis methods. Our report, and the literature, also has limitations. There were substantial limitations in the literature. First, the number of studies is small, many had design limitations affecting the validity of findings, and the range of interventions evaluated was limited. Further, descriptions of the interventions were often inadequate to permit replication. Second, there were few studies in certain populations of high interest (e.g., depression with psychosis, bipolar disorder). Third, the range of outcomes was limited, including infrequent reporting of overall cardiovascular risk, physical functioning, and outcomes related to worsening of psychiatric status. Limitations in the number and reporting of studies precluded any analyses of variability in treatment effects by patient characteristics.

Our review methods also had limitations. Our study was limited to English-language publications. However, the likelihood of identifying relevant data unavailable from English-language sources is low. Also, only one study was specifically designed to address diabetes, and no studies directly targeted dyslipidemia. Thus, results for those cardiovascular risks were culled from secondary outcome assessments of primarily weight management interventions. If a trial provided information on weight, glucose, and lipid control, these results were organized for the

outcomes across KQ 1 through KQ 3 to reduce redundancy of reporting. However, we reported on adverse events and health-related quality of life for each study or class of intervention in each chapter. We excluded studies whose primary goal was to control psychiatric symptoms, thus, potentially excluding some antipsychotic trials that had relevant outcomes information, particularly related to adverse events. However, the recent DERP report¹²³ and AHRQ report¹²² on the comparative effectiveness of antipsychotics provide a robust review of these outcomes as they pertain to adverse events of these treatments. Although we attempted to evaluate the impact of effectiveness versus efficacy studies, the small number of studies overall and lack of effectiveness studies made this analysis unfeasible.

Research Gaps

We used the framework recommended by Robinson et al.¹⁴³ to identify gaps in evidence and classify why these gaps exist. This approach considers PICOTS (population, intervention, comparator, outcomes, timing, and setting) to identify gaps and classifies gaps as due to (1) insufficient or imprecise information, (2) biased information; (3) inconsistency or unknown consistency, and (4) not the right information. In addition, we considered studies in progress identified from ClinicalTrials.gov when making recommendations for future research. Gaps and recommendations are presented in Table 16. Although we recommend multicenter RCTs to address some evidence gaps, we are aware that there are particular challenges to conducting RCTs in this population. Recruitment and retention is an important issue for all trials and may be particularly challenging in patients with SMI. Symptoms of mental illness and effects on cognition along with substantial rates may make it difficult for patients with SMI to fully participate in planned interventions. Some important outcomes, such as cardiovascular events, may take large sample sizes and long followup periods to evaluate.

Table 16. Evidence gaps and future research for SMI

Evidence Gap	Reason	Type of Studies to Consider
Patients		
Limited data for patients with conditions other than schizophrenia	Insufficient information	Single and multisite RCTs
No data in older adults who have more comorbid medical illness	Insufficient information	Single and multisite RCTs
Few studies of ethnic and racial minorities	Insufficient information	Single and multisite RCTs
Interventions		
No interventions evaluating peer and family support interventions	Insufficient information	Single and multisite RCTs
No studies on the effects of the most recently approved second-generation antipsychotics such as paliperidone, iloperidone, asenapine and lurasidone	Insufficient information	Single and multisite RCTs
Limited evidence about the benefits and harms of switching from one antipsychotic to another on metabolic parameters	Insufficient information	Secondary analyses of existing studies such as the CATIE trial or large observational datasets

Evidence Gap	Reason	Type of Studies to Consider
No studies comparing optimized antipsychotic management (e.g., start with or switch to drugs with more favorable metabolic profiles) vs. continuing current antipsychotics in responders and treating adverse metabolic effects directly using treatments (e.g., statins) with known efficacy	Insufficient information	Single and multisite RCTs
Few multimodal interventions	Insufficient information	Single and multisite RCTs
Uncertainty about the details of the intervention	Not the right information	Provide manuals to promote replication/implementation of successful interventions
Interventions to improve guideline concordant care	Insufficient information	Single and multisite RCTs
Comparators		
Few studies comparing two active interventions	Insufficient information	Single and multisite RCTs comparing effective treatments
Outcomes		
Uncertain effects on overall cardiovascular risk or cardiovascular events	Insufficient information	Use risk indices (e.g., Framingham) and/or cardiovascular events as outcome measures
Intervention adherence	Insufficient information	Improve study reporting
Uncertainty about adverse effects on mental health status	Insufficient information	Define and report proportion of patients who mental health status worsens
Timing		
Few studies with outcomes measured beyond 6 months	Insufficient information	RCTs with longer term followup and/or quasi experimental or observational studies
Setting		
Lack of studies designed to evaluate “real world” effects of the intervention (effectiveness studies)	Insufficient information	RCTs or quasi experimental studies with broad inclusion criteria, conducted in community practices, with long term follow up and that include clinically important outcomes such as physical functioning, cardiovascular events and adverse events. Improve reporting of efficacy–effectiveness characteristics

Abbreviations: CATIE=Clinical Antipsychotic Trials in Intervention Effectiveness; RCT=randomized controlled trial

Conclusions

In summary, patients with SMI are at risk for increased CVD—in part due to health behaviors (tobacco use, physical inactivity), possibly due to direct effects of the illness (e.g., changes in the neuroendocrine system that are associated with atherosclerosis), and due to adverse effects from some treatments (e.g., increased metabolic syndrome from antipsychotics). Surprisingly few studies addressed one or more cardiovascular risk factors in patients with SMI and most studies were skewed towards efficacy trials. Behavioral interventions, switching to or adding adjunctive aripiprazole, adding antiseizure medications topiramate and zonisamide, or adding metformin yield small to moderate weight loss compared to controls. We found insufficient evidence to support any strategy to control glucose. We found limited support of behavioral interventions focusing on weight loss or diabetes management on lipid control; SOE was insufficient for all other interventions. We found no studies testing a number of important interventions (e.g., orlistat, statins) known to be effective in non-SMI populations. Comparative effectiveness trials are needed that test multimodal strategies, known effective agents in non-SMI

population (e.g., statins), and antipsychotic management strategies. However, in the absence of evidence for SMI-specific interventions, guideline-concordant care for individuals with SMI may help mitigate the unequal burden of CVD that SMI populations sustain.

References

1. National Institute of Mental Health. Statistics. Available at: <http://www.nimh.nih.gov/statistics/index.shtml> Accessed June 22, 2012.
2. National Institute of Mental Health. Statistics. Schizophrenias. Available at: <http://www.nimh.nih.gov/statistics/1SCHIZ.shtml>. Accessed June 22, 2012.
3. Epstein J., Barker P, Vorburger M, et al. Serious mental illness and its co-occurrence with substance use disorders, 2002 (DHHS Publication No. SMA 04-3905, Analytic Series A-24). Rockville, MD: Substance Abuse and Mental Health Services Administration, Office of Applied Studies. Available at: <http://www.samhsa.gov/data/CoD/CoD.pdf>. Accessed June 22, 2012. 2004.
4. Chang C-K, Hayes R, Broadbent M, et al. All-cause mortality among people with serious mental illness (SMI), substance use disorders, and depressive disorders in southeast London: a cohort study. *BMC Psychiatry*. 2010;10(1):77. PMID: 20920287.
5. Brown AS, Birthwhistle J. Excess mortality of mental illness. *Br J Psychiatry*. 1996;169(3):383-4. PMID: 8879735.
6. Hsu JH, Chien IC, Lin CH, et al. Incidence of diabetes in patients with schizophrenia: a population-based study. *Can J Psychiatry*. 2011;56(1):19-26. PMID: 21324239.
7. Dixon L, Weiden P, Delahanty J, et al. Prevalence and correlates of diabetes in national schizophrenia samples. *Schizophr Bull*. 2000;26(4):903-12. PMID: 11087022.
8. van Winkel R, De Hert M, Van Eyck D, et al. Prevalence of diabetes and the metabolic syndrome in a sample of patients with bipolar disorder. *Bipolar Disord*. 2008;10(2):342-8. PMID: 18271914.
9. Bresee LC, Majumdar SR, Patten SB, et al. Prevalence of cardiovascular risk factors and disease in people with schizophrenia: a population-based study. *Schizophr Res*. 2010;117(1):75-82. PMID: 20080392.
10. Weiner M, Warren L, Fiedorowicz JG. Cardiovascular morbidity and mortality in bipolar disorder. *Ann Clin Psychiatry*. 2011;23(1):40-7. PMID: 21318195.
11. Miller BJ, Paschall CB, 3rd, Svendsen DP. Mortality and medical comorbidity among patients with serious mental illness. *Psychiatr Serv*. 2006;57(10):1482-7. PMID: 17035569.
12. Fagiolini A, Goracci A. The effects of undertreated chronic medical illnesses in patients with severe mental disorders. *J Clin Psychiatry*. 2009;70 Suppl 3:22-9. PMID: 19570498.
13. Ryan MC, Collins P, Thakore JH. Impaired fasting glucose tolerance in first-episode, drug-naive patients with schizophrenia. *Am J Psychiatry*. 2003;160(2):284-9. PMID: 12562574.
14. Kupfer DJ. The increasing medical burden in bipolar disorder. *JAMA*. 2005;293(20):2528-30. PMID: 15914754.
15. McCreadie RG. Diet, smoking and cardiovascular risk in people with schizophrenia: descriptive study. *Br J Psychiatry*. 2003;183:534-9. PMID: 14645025.
16. McElroy SL. Obesity in patients with severe mental illness: overview and management. *J Clin Psychiatry*. 2009;70 Suppl 3:12-21. PMID: 19570497.
17. Fountoulakis KN, Siamouli M, Panagiotidis P, et al. Obesity and smoking in patients with schizophrenia and normal controls: a case-control study. *Psychiatry Res*. 2010;176(1):13-6. PMID: 20079934.
18. Brown S, Birtwistle J, Roe L, et al. The unhealthy lifestyle of people with schizophrenia. *Psychol Med*. 1999;29(3):697-701. PMID: 10405091.
19. Newcomer JW. Metabolic considerations in the use of antipsychotic medications: a review of recent evidence. *J Clin Psychiatry*. 2007;68 Suppl 1:20-7. PMID: 17286524.

20. Desai MM, Rosenheck RA, Druss BG, et al. Receipt of nutrition and exercise counseling among medical outpatients with psychiatric and substance use disorders. *J Gen Intern Med.* 2002;17(7):556-60. PMID: 12133146.
21. Druss BG, Rosenheck RA, Desai MM, et al. Quality of preventive medical care for patients with mental disorders. *Med Care.* 2002;40(2):129-36. PMID: 11802085.
22. Green JL, Gazmararian JA, Rask KJ, et al. Quality of diabetes care for underserved patients with and without mental illness: site of care matters. *Psychiatr Serv.* 2010;61(12):1204-10. PMID: 21123404.
23. Frayne SM, Halanych JH, Miller DR, et al. Disparities in diabetes care: impact of mental illness. *Arch Intern Med.* 2005;165(22):2631-8. PMID: 16344421.
24. Mitchell AJ, Lord O. Do deficits in cardiac care influence high mortality rates in schizophrenia? A systematic review and pooled analysis. *J Psychopharmacol.* 2010;24(4 Suppl):69-80. PMID: 20923922.
25. McGuire J, Gelberg L, Blue-Howells J, et al. Access to primary care for homeless veterans with serious mental illness or substance abuse: a follow-up evaluation of co-located primary care and homeless social services. *Administration and Policy in Mental Health.* 2009;36(4):255-64. PMID: 19280333.
26. Druss BG, Rohrbaugh RM, Levinson CM, et al. Integrated medical care for patients with serious psychiatric illness: a randomized trial. *Arch Gen Psychiatry.* 2001;58(9):861-8. PMID: 11545670.
27. Warner CH, Morganstein J, Rachal J, et al. Perceptions and practices of graduates of combined family medicine-psychiatry residency programs: a nationwide survey. *Acad Psychiatry.* 2007;31(4):297-303. PMID: 17626192.
28. Bradford DW, Kim MM, Braxton LE, et al. Access to medical care among persons with psychotic and major affective disorders. *Psychiatr Serv.* 2008;59(8):847-52. PMID: 18678680.
29. Druss BG, Zhao L, von Esenwein SA, et al. The Health and Recovery Peer (HARP) Program: a peer-led intervention to improve medical self-management for persons with serious mental illness. *Schizophr Res.* 2010;118(1-3):264-70. PMID: 20185272.
30. Peck MC, Scheffler RM. An analysis of the definitions of mental illness used in state parity laws. *Psychiatr Serv.* 2002;53(9):1089-95. PMID: 12221306.
31. Tsoi DT, Porwal M, Webster AC. Interventions for smoking cessation and reduction in individuals with schizophrenia. *Cochrane Database Syst Rev.* 2010(6):CD007253. PMID: 20556777.
32. Tsoi DT, Porwal M, Webster AC. Efficacy and safety of bupropion for smoking cessation and reduction in schizophrenia: systematic review and meta-analysis. *Br J Psychiatry.* 2010;196(5):346-53. PMID: 20435957.
33. Tosh G, Clifton A, Bachner M. General physical health advice for people with serious mental illness. *Cochrane Database Syst Rev.* 2011;2:CD008567. PMID: 21328308.
34. Tosh G, Clifton A, Mala S, et al. Physical health care monitoring for people with serious mental illness. *Cochrane Database Syst Rev.* 2010(3):CD008298. PMID: 20238365.
35. Bradford DW, Slubicki MN, McDuffie JR, et al. Effects of care models to improve general medical outcomes for individuals with serious mental illness. VA-ESP Project #09-010; [In press.].
36. Agency for Healthcare Research and Quality. *Methods Guide for Effectiveness and Comparative Effectiveness Reviews.* Rockville, MD: Agency for Healthcare Research and Quality. Available at: <http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=318>. Accessed June 12, 2012.
37. Moher D, Liberati A, Tetzlaff J, et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med.* 2009;6(7):e1000097. PMID: 19621072.

38. Anonymous. Evidence-based Practice Center Systematic Review Protocol. Project Title: Strategies To Improve Cardiovascular Risk Factors in People With Serious Mental Illness: A Comparative Effectiveness Review. Available at: <http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=933&pageaction=displayproduct>. Accessed June 22, 2012
39. Agius M, Davis A, Gilhooley M, et al. What do large scale studies of medication in schizophrenia add to our management strategies? *Psychiatr Danub*. 2010;22(2):323-8. PMID: 20562774.
40. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry*. 1999;156(11):1686-96. PMID: 10553730.
41. Alvarez-Jimenez M, Hetrick SE, Gonzalez-Blanch C, et al. Non-pharmacological management of antipsychotic-induced weight gain: systematic review and meta-analysis of randomised controlled trials. *Br J Psychiatry*. 2008;193(2):101-7. PMID: 18669990.
42. Banham L, Gilbody S. Smoking cessation in severe mental illness: what works? *Addiction*. 2010;105(7):1176-89. PMID: 20491721.
43. Barkhof E, Meijer CJ, de Sonnevile LM, et al. Interventions to improve adherence to antipsychotic medication in patients with schizophrenia-A review of the past decade. *Eur Psychiatry*. 2011. PMID: 21561742.
44. Beynon S, Soares-Weiser K, Woolacott N, et al. Pharmacological interventions for the prevention of relapse in bipolar disorder: a systematic review of controlled trials. *J Psychopharmacol*. 2009;23(5):574-91. PMID: 18635701.
45. Bradshaw T, Lovell K, Harris N. Healthy living interventions and schizophrenia: a systematic review. *J Adv Nurs*. 2005;49(6):634-54. PMID: 15737224.
46. Bushe CJ, Bradley AJ, Doshi S, et al. Changes in weight and metabolic parameters during treatment with antipsychotics and metformin: do the data inform as to potential guideline development? A systematic review of clinical studies. *Int J Clin Pract*. 2009;63(12):1743-61. PMID: 19840151.
47. Bushe CJ, Leonard BE. Blood glucose and schizophrenia: a systematic review of prospective randomized clinical trials. *J Clin Psychiatry*. 2007;68(11):1682-90. PMID: 18052561.
48. Cabassa LJ, Ezell JM, Lewis-Fernandez R. Lifestyle interventions for adults with serious mental illness: a systematic literature review. *Psychiatr Serv*. 2010;61(8):774-82. PMID: 20675835.
49. Citrome L, Holt RI, Walker DJ, et al. Weight gain and changes in metabolic variables following olanzapine treatment in schizophrenia and bipolar disorder. *Clin Drug Investig*. 2011;31(7):455-82. PMID: 21495734.
50. Citrome L. A review of aripiprazole in the treatment of patients with schizophrenia or bipolar I disorder. *Neuropsychiatr Dis Treat*. 2006;2(4):427-43. PMID: 19412492.
51. Ellinger LK, Ipema HJ, Stachnik JM. Efficacy of metformin and topiramate in prevention and treatment of second-generation antipsychotic-induced weight gain. *Ann Pharmacother*. 2010;44(4):668-79. PMID: 20233913.
52. Faulkner G, Cohn T, Remington G. Interventions to reduce weight gain in schizophrenia. *Cochrane Database Syst Rev*. 2007(1):CD005148. PMID: 17253540.
53. Karagianis J, Hoffmann VP, Arranz B, et al. Orally disintegrating olanzapine and potential differences in treatment-emergent weight gain. *Hum Psychopharmacol*. 2008;23(4):275-81. PMID: 18338426.
54. Komossa K, Rummel-Kluge C, Schmid F, et al. Quetiapine versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2010(1):CD006625. PMID: 20091600.
55. Komossa K, Rummel-Kluge C, Hunger H, et al. Sertindole versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2009(2):CD006752. PMID: 19370652.
56. Kreyenbuhl J, Buchanan RW, Dickerson FB, et al. The Schizophrenia Patient Outcomes Research Team (PORT): updated treatment recommendations 2009. *Schizophr Bull*. 2010;36(1):94-103. PMID: 19955388.

57. Leucht S, Kissling W, Davis JM. Second-generation antipsychotics for schizophrenia: can we resolve the conflict? *Psychol Med.* 2009;39(10):1591-602. PMID: 19335931.
58. Lipkovich I, Jacobson JG, Caldwell C, et al. Early predictors of weight gain risk during treatment with olanzapine: analysis of pooled data from 58 clinical trials. *Psychopharmacol Bull.* 2009;42(4):23-39. PMID: 20581791.
59. Mukundan A, Faulkner G, Cohn T, et al. Antipsychotic switching for people with schizophrenia who have neuroleptic-induced weight or metabolic problems. *Cochrane Database Syst Rev.* 2010(12):CD006629. PMID: 21154372.
60. Prahara SK, Jana AK, Goyal N, et al. Metformin for olanzapine-induced weight gain: a systematic review and meta-analysis. *Br J Clin Pharmacol.* 2011;71(3):377-82. PMID: 21284696.
61. Rege S. Antipsychotic induced weight gain in schizophrenia: mechanisms and management. *Aust N Z J Psychiatry.* 2008;42(5):369-81. PMID: 18473255.
62. Rummel-Kluge C, Komossa K, Schwarz S, et al. Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: a systematic review and meta-analysis. *Schizophr Res.* 2010;123(2-3):225-33. PMID: 20692814.
63. Lee YJ, Jeong JH. A systematic review of metformin to limit weight-gain with atypical antipsychotics. *J Clin Pharm Ther.* 2011;36(5):537-545.
64. Verhaeghe N, De Maeseneer J, Maes L, et al. Effectiveness and cost-effectiveness of lifestyle interventions on physical activity and eating habits in persons with severe mental disorders: A systematic review. *Int J Behav Nutr Phys Act.* 2011;8.
65. Bjorkhem-Bergman L, Asplund AB, Lindh JD. Metformin for weight reduction in non-diabetic patients on antipsychotic drugs: A systematic review and meta-analysis. *J Psychopharmacol.* 2011;25(3):299-305.
66. Alvarez-Jimenez M. Tackling the physical consequences of psychosis and its treatment. *Early Interv Psychiatry.* 2010;4:17.
67. Strassnig M, Ganguli R. Weight loss interventions for patients with schizophrenia. *Clin Schizophr Relat Psychoses.* 2007;1(1):43-53.
68. Chue P, Stip E, Remington G, et al. Switching atypical antipsychotics: A review. *Acta Neuropsychiatrica.* 2004;16(6):301-313.
69. Bushe C, Leonard B. Association between atypical antipsychotic agents and type 2 diabetes: Review of prospective clinical data. *Br J Psychiatry.* 2004;184(SUPPL. 47):s87-s93.
70. Compton MT, Daumit GL, Druss BG. Cigarette smoking and overweight/obesity among individuals with serious mental illnesses: a preventive perspective. *Harv Rev Psychiatry.* 2006;14(4):212-22. PMID: 16912007.
71. Faulkner G, Soundy AA, Lloyd K. Schizophrenia and weight management: a systematic review of interventions to control weight. *Acta Psychiatr Scand.* 2003;108(5):324-32. PMID: 14531752.
72. Loh C, Meyer JM, Leckband SG. A comprehensive review of behavioral interventions for weight management in schizophrenia. *Ann Clin Psychiatry.* 2006;18(1):23-31. PMID: 16517450.
73. Gabriele JM, Dubbert PM, Reeves RR. Efficacy of behavioural interventions in managing atypical antipsychotic weight gain. *Obes Rev.* 2009;10(4):442-55. PMID: 19389059.
74. Newcomer JW, Haupt DW. The metabolic effects of antipsychotic medications. *Can J Psychiatry.* 2006;51(8):480-91. PMID: 16933585.
75. Faulkner G, Cohn T, Remington G. Interventions to reduce weight gain in schizophrenia. *Schizophr Bull.* 2007;33(3):654-6. PMID: 17449900.
76. Khan AY, Macaluso M, McHale RJ, et al. The adjunctive use of metformin to treat or prevent atypical antipsychotic-induced weight gain: a review. *J Psychiatr Pract.* 2010;16(5):289-96. PMID: 20859106.

77. Zimmermann U, Kraus T, Himmerich H, et al. Epidemiology, implications and mechanisms underlying drug-induced weight gain in psychiatric patients. *J Psychiatr Res.* 2003;37(3):193-220. PMID: 12650740.
78. Ganguli R. Behavioral therapy for weight loss in patients with schizophrenia. *J Clin Psychiatry.* 2007;68 Suppl 4:19-25. PMID: 17539696.
79. Gartlehner G, Hansen RA, Nissman D, et al. A simple and valid tool distinguished efficacy from effectiveness studies. *J Clin Epidemiol.* 2006;59(10):1040-8. PMID: 16980143.
80. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine.* 2002;21(11):1539-58. PMID: 12111919.
81. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics.* 1994;50(4):1088-101. PMID: 7786990.
82. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: Grading the strength of a body of evidence when comparing medical interventions--Agency for Healthcare Research and Quality and the Effective Health-Care Program. *J Clin Epidemiol.* 2010;63(5):513-23. PMID: 19595577.
83. Atkins D, Chang SM, Gartlehner G, et al. Assessing applicability when comparing medical interventions: AHRQ and the Effective Health Care Program. *J Clin Epidemiol.* 2011;64(11):1198-207. PMID: 21463926.
84. Alvarez-Jimenez M, Gonzalez-Blanch C, Vazquez-Barquero JL, et al. Attenuation of antipsychotic-induced weight gain with early behavioral intervention in drug-naive first-episode psychosis patients: A randomized controlled trial. *J Clin Psychiatry.* 2006;67(8):1253-60. PMID: 16965204.
85. Assuncao SS, Ruschel SI, Rosa Lde C, et al. Weight gain management in patients with schizophrenia during treatment with olanzapine in association with nizatidine. *Rev Bras Psiquiatr.* 2006;28(4):270-6. PMID: 17242805.
86. Atmaca M, Kuloglu M, Tezcan E, et al. Nizatidine for the treatment of patients with quetiapine-induced weight gain. *Hum Psychopharmacol.* 2004;19(1):37-40. PMID: 14716710.
87. Ball MP, Warren KR, Feldman S, et al. Placebo-controlled trial of atomoxetine for weight reduction in people with schizophrenia treated with clozapine or olanzapine. *Clin Schizophr Relat Psychoses.* 2011;5(1):17-25. PMID: 21459735.
88. Borba CP, Fan X, Copeland PM, et al. Placebo-controlled pilot study of ramelteon for adiposity and lipids in patients with schizophrenia. *J Clin Psychopharmacol.* 2011;31(5):653-8. PMID: 21869685.
89. Brar JS, Ganguli R, Pandina G, et al. Effects of behavioral therapy on weight loss in overweight and obese patients with schizophrenia or schizoaffective disorder. *J Clin Psychiatry.* 2005;66(2):205-12. PMID: 15705006.
90. Brown C, Goetz J, Hamera E. Weight loss intervention for people with serious mental illness: a randomized controlled trial of the RENEW program. *Psychiatr Serv.* 2011;62(7):800-2. PMID: 21724796.
91. Deberdt W, Lipkovich I, Heinloth AN, et al. Double-blind, randomized trial comparing efficacy and safety of continuing olanzapine versus switching to quetiapine in overweight or obese patients with schizophrenia or schizoaffective disorder. *Ther Clin Risk Manag.* 2008;4(4):713-20. PMID: 19209252.
92. Elmslie JL, Porter RJ, Joyce PR, et al. Carnitine does not improve weight loss outcomes in valproate-treated bipolar patients consuming an energy-restricted, low-fat diet. *Bipolar Disord.* 2006;8(5 Pt 1):503-7. PMID: 17042889.
93. Evans S, Newton R, Higgins S. Nutritional intervention to prevent weight gain in patients commenced on olanzapine: a randomized controlled trial. *Aust N Z J Psychiatry.* 2005;39(6):479-86. PMID: 15943650.

94. Fleischhacker WW, Heikkinen ME, Olie JP, et al. Effects of adjunctive treatment with aripiprazole on body weight and clinical efficacy in schizophrenia patients treated with clozapine: a randomized, double-blind, placebo-controlled trial. *Int J Neuropsychopharmacol*. 2010;13(8):1115-25. PMID: 20459883.
95. Gillhoff K, Gaab J, Emini L, et al. Effects of a multimodal lifestyle intervention on body mass index in patients with bipolar disorder: a randomized controlled trial. *Prim Care Companion J Clin Psychiatry*. 2010;12(5). PMID: 21274359.
96. Graham KA, Gu H, Lieberman JA, et al. Double-blind, placebo-controlled investigation of amantadine for weight loss in subjects who gained weight with olanzapine. *Am J Psychiatry*. 2005;162(9):1744-6. PMID: 16135638.
97. Hoffmann VP, Case M, Jacobson JG. Assessment of treatment algorithms including amantadine, metformin, and zonisamide for the prevention of weight gain with olanzapine: a randomized controlled open-label study. *J Clin Psychiatry*. 2011. PMID: 21672497.
98. Karagianis J, Grossman L, Landry J, et al. A randomized controlled trial of the effect of sublingual orally disintegrating olanzapine versus oral olanzapine on body mass index: the PLATYPUS Study. *Schizophr Res*. 2009;113(1):41-8. PMID: 19535229.
99. Kwon JS, Choi JS, Bahk WM, et al. Weight management program for treatment-emergent weight gain in olanzapine-treated patients with schizophrenia or schizoaffective disorder: A 12-week randomized controlled clinical trial. *J Clin Psychiatry*. 2006;67(4):547-53. PMID: 16669719.
100. Littrell KH, Hilligoss NM, Kirshner CD, et al. The effects of an educational intervention on antipsychotic-induced weight gain. *J Nurs Scholarsh*. 2003;35(3):237-41. PMID: 14562491.
101. McKibbin CL, Patterson TL, Norman G, et al. A lifestyle intervention for older schizophrenia patients with diabetes mellitus: a randomized controlled trial. *Schizophr Res*. 2006;86(1-3):36-44. PMID: 16842977.
102. Newcomer JW, Campos JA, Marcus RN, et al. A multicenter, randomized, double-blind study of the effects of aripiprazole in overweight subjects with schizophrenia or schizoaffective disorder switched from olanzapine. *J Clin Psychiatry*. 2008;69(7):1046-56. PMID: 18605811.
103. Wu RR, Zhao JP, Jin H, et al. Lifestyle intervention and metformin for treatment of antipsychotic-induced weight gain: a randomized controlled trial. *JAMA*. 2008;299(2):185-93. PMID: 18182600.
104. McDonnell DP, Kryzhanovskaya LA, Zhao F, et al. Comparison of metabolic changes in patients with schizophrenia during randomized treatment with intramuscular olanzapine long-acting injection versus oral olanzapine. *Hum Psychopharmacol*. 2011;26(6):422-433.
105. Bustillo JR, Lauriello J, Parker K, et al. Treatment of weight gain with fluoxetine in olanzapine-treated schizophrenic outpatients. *Neuropsychopharmacology*. 2003;28(3):527-9. PMID: 12629532.
106. Atmaca M, Kuloglu M, Tezcan E, et al. Nizatidine treatment and its relationship with leptin levels in patients with olanzapine-induced weight gain. *Hum Psychopharmacol*. 2003;18(6):457-61. PMID: 12923824.
107. Cavazzoni P, Tanaka Y, Roychowdhury SM, et al. Nizatidine for prevention of weight gain with olanzapine: a double-blind placebo-controlled trial. *Eur Neuropsychopharmacol*. 2003;13(2):81-5. PMID: 12650950.
108. Nickel MK, Nickel C, Muehlbacher M, et al. Influence of topiramate on olanzapine-related adiposity in women: a random, double-blind, placebo-controlled study. *J Clin Psychopharmacol*. 2005;25(3):211-7. PMID: 15876898.
109. Khazaal Y, Fresard E, Rabia S, et al. Cognitive behavioural therapy for weight gain associated with antipsychotic drugs. *Schizophr Res*. 2007;91(1-3):169-77. PMID: 17306507.
110. Mauri M, Simoncini M, Castrogiovanni S, et al. A psychoeducational program for weight loss in patients who have experienced weight gain during antipsychotic treatment with olanzapine. *Pharmacopsychiatry*. 2008;41(1):17-23. PMID: 18203047.

111. McElroy SL, Winstanley E, Mori N, et al. A randomized, placebo-controlled study of zonisamide to prevent olanzapine-associated weight gain. *J Clin Psychopharmacol*. 2012;32(2):165-72. PMID: 22367654.
112. Carrizo E, Fernandez V, Connell L, et al. Extended release metformin for metabolic control assistance during prolonged clozapine administration: a 14 week, double-blind, parallel group, placebo-controlled study. *Schizophr Res*. 2009;113(1):19-26. PMID: 19515536.
113. Narula PK, Rehan HS, Unni KE, et al. Topiramate for prevention of olanzapine associated weight gain and metabolic dysfunction in schizophrenia: a double-blind, placebo-controlled trial. *Schizophr Res*. 2010;118(1-3):218-23. PMID: 20207521.
114. Stroup TS, McEvoy JP, Ring KD, et al. A randomized trial examining the effectiveness of switching from olanzapine, quetiapine, or risperidone to aripiprazole to reduce metabolic risk: comparison of antipsychotics for metabolic problems (CAMP). *Am J Psychiatry*. 2011;168(9):947-56. PMID: 21768610.
115. Forsberg KA, Bjorkman T, Sandman PO, et al. Physical health--a cluster randomized controlled lifestyle intervention among persons with a psychiatric disability and their staff. *Nord J Psychiatry*. 2008;62(6):486-95. PMID: 18843564.
116. Skrinar GS, Huxley NA, Hutchinson DS, et al. The role of a fitness intervention on people with serious psychiatric disabilities. *Psychiatr Rehabil J*. 2005;29(2):122-7. PMID: 16268007.
117. Leblanc ES, O'Connor E, Whitlock EP, et al. Effectiveness of primary care-relevant treatments for obesity in adults: a systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2011;155(7):434-47. PMID: 21969342.
118. Zaza S, Briss PA, Harris KW, et al. *The guide to community preventive services : what works to promote health?* New York: Oxford University; 2005.
119. Lamanna C, Monami M, Marchionni N, et al. Effect of metformin on cardiovascular events and mortality: a meta-analysis of randomized clinical trials. *Diabetes Obes Metab*. 2011;13(3):221-8. PMID: 21205121.
120. The Medical Letter. Drugs for Lipids. Treatment Guidelines from The Medical Letter. Issue 66. February 2008.
121. Thavendiranathan P, Bagai A, Brookhart MA, et al. Primary prevention of cardiovascular diseases with statin therapy: a meta-analysis of randomized controlled trials. *Arch Intern Med*. 2006;166(21):2307-13. PMID: 17130382.
122. Anonymous. Evidence-based Practice Center Systematic Review Protocol. Project Title: Comparative Effectiveness of First and Second Generation Antipsychotics in the Adult Population. Available at: <http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=583> Accessed. June 22, 2012
123. McDonagh M, Peterson K, Carson S, et al. Drug Effectiveness Review Project. Drug Class Review: Atypical Antipsychotic Drugs. Final Update 3. Oregon Evidence-based Practice Center. July 2010. Available at: <http://derp.ohsu.edu/about/final-document-display.cfm>. Accessed June 15, 2012. PMID: 21348048.
124. Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database of Systematic Reviews*. 2011(2). PMID: ISI:000288616600005.
125. Anonymous. Evidence-based Practice Center Systematic Review Protocol. Project Title: Comparative Effectiveness of Approaches to Weight Maintenance in Adults. Available at: <http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=824&pageaction=displayproduct>. Accessed June 22, 2012.
126. Wildes JE, Marcus MD, Fagiolini A. Obesity in patients with bipolar disorder: a biopsychosocial-behavioral model. *J Clin Psychiatry*. 2006;67(6):904-15. PMID: 16848650.

127. U.S. Preventive Services Task Force. Screening for High Blood Pressure: U.S. Preventive Services Task Force Reaffirmation Recommendation Statement. AHRQ Publication No. 08-05105-EF-2, December 2007. First published in *Ann Intern Med* 2007;147-783-786. Available at: <http://www.uspreventiveservicestaskforce.org/uspstf07/hbp/hbprs.htm>. Accessed June 15, 2012.
128. U.S. Preventive Services Task Force. Counseling to Prevent Tobacco Use and Tobacco-Caused Disease Recommendation Statement. Available at: <http://www.uspreventiveservicestaskforce.org/3rduspstf/tobaccoun/tobcounrs.htm>. Accessed June 15, 2012. 2003.
129. Norris SL, Kansagara D, Bougatsos C, et al. Screening for Type 2 Diabetes: Update of 2003 Systematic Evidence Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 61. AHRQ Publication No. 08-05116-EF-1. Rockville, Maryland: Agency for Healthcare Research and Quality. June 2008. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK33981/>. Accessed June 15, 2012.
130. Helfand M, Carson S. Screening for Lipid Disorders in Adults: Selective Update of 2001 U.S. Preventive Services Task Force Review. Evidence Synthesis No. 49. Rockville, MD: Agency for Healthcare Research and Quality, April 2008. AHRQ Publication no. 08-05114-EF-1. Available at <http://www.ncbi.nlm.nih.gov/books/NBK33494/>. Accessed June 15, 2012.
131. American Diabetes Association. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care*. 2004;27(2):596-601. PMID: ISI:000188739900043.
132. Standards of Medical Care in Diabetes-2012. *Diabetes Care*. 2012;35(1):S11-S63. PMID: ISI:000298772200002.
133. Gierisch JM, Bastian LA, Calhoun PS, et al. Smoking cessation interventions for patients with depression: a systematic review and meta-analysis. *J Gen Intern Med*. 2012;27(3):351-60. PMID: 22038468.
134. Gierisch JM, Bastian LA, Calhoun PS, et al. Comparative Effectiveness of Smoking Cessation Treatments for Patients With Depression: A Systematic Review and Meta-analysis of the Evidence. VA-ESP Project #09-010; 2010.
135. Bryant J, Bonevski B, Paul C, et al. A systematic review and meta-analysis of the effectiveness of behavioural smoking cessation interventions in selected disadvantaged groups. *Addiction*. 2011;106(9):1568-85. PMID: 21489007.
136. Mitchell AJ, Delaffon V, Vancampfort D, et al. Guideline concordant monitoring of metabolic risk in people treated with antipsychotic medication: systematic review and meta-analysis of screening practices. *Psychol Med*. 2012;42(1):125-47. PMID: 21846426.
137. Haupt DW, Rosenblatt LC, Kim E, et al. Prevalence and predictors of lipid and glucose monitoring in commercially insured patients treated with second-generation antipsychotic agents. *Am J Psychiatry*. 2009;166(3):345-53. PMID: 19147694.
138. Morrato EH, Newcomer JW, Kamat S, et al. Metabolic screening after the American Diabetes Association's consensus statement on antipsychotic drugs and diabetes. *Diabetes Care*. 2009;32(6):1037-42. PMID: 19244091.
139. Morrato EH, Druss B, Hartung DM, et al. Metabolic testing rates in 3 state Medicaid programs after FDA warnings and ADA/APA recommendations for second-generation antipsychotic drugs. *Arch Gen Psychiatry*. 2010;67(1):17-24. PMID: 20048219.
140. Morrato EH, Druss BG, Hartung DM, et al. Small area variation and geographic and patient-specific determinants of metabolic testing in antipsychotic users. *Pharmacoepidemiol Drug Saf*. 2011;20(1):66-75. PMID: 21182154.
141. Williams JW, Jackson GL, Powers BJ, et al. Closing the Quality Gap Series: Revisiting the State of the Science. The Patient-Centered Medical Home. (Prepared by the Duke Evidence-based Practice Center under Contract No. 290-2007-10066-I.) Rockville, MD. Agency for Healthcare Research and Quality. [in press].

142. Hayward RA, Hofer TP, Vijan S. Narrative review: lack of evidence for recommended low-density lipoprotein treatment targets: a solvable problem. *Ann Intern Med*. 2006;145(7):520-30. PMID: 17015870.
143. Robinson KA, Saldanha IJ, Mckoy NA. Frameworks for Determining Research Gaps During Systematic Reviews. *Methods Future Research Needs Report No. 2*. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. HHS A 290-2007-10061-I.) AHRQ Publication No. 11-EHC043-EF. Rockville, MD: Agency for Healthcare Research and Quality. June 2011. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed May 22, 2012.

Abbreviations

AHRQ	Agency for Healthcare Research and Quality
CI	confidence interval
CVD	cardiovascular disease
df	degrees of freedom
HR	hazard ratio
HRQOL	health-related quality of life
kg	kilogram
KQ	Key Question
MI	myocardial infarction
NA	not available
NR	not reported
OR	odds ratio
PICOTS	population, intervention, comparator, outcomes, timing, setting
QOL	quality of life
RCT	randomized controlled trial
ROB	risk of bias
RR	risk ratio
SMI	serious mental illness
SOE	strength of evidence
TEP	Technical Expert Panel