Comparative Effectiveness Review
Number 105

Effective Health Care Program

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

Executive Summary

Background

Serious mental illness (SMI) is defined generally as a major mental or behavioral disorder, causing substantial impairment in multiple areas of daily functioning. SMI affects about 4 to 8 percent of adults[1-3] and includes disorders such as schizophrenia and bipolar disorder but not isolated substance abuse or developmental disorders. 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 diabetes[6-8] and cardiovascular disease (CVD).[9-11] Among patients using the public mental health system, heart disease was the leading cause of death.[12] This excess of 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.[13-15] Modifiable CVD risk factors, such as smoking,[16] obesity,[17,18] and physical inactivity[19,20] are highly prevalent among adults with

Effective Health Care Program

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**.

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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.[21] Lower socioeconomic status is more common in individuals with SMI[22,23] and may limit access to healthy food, opportunities for physical exercise (e.g., walkable neighborhoods and access to fitness facilities), and high-quality medical care. Numerous studies have demonstrated disparities in the quality of general medical care provided to individuals with SMI.[24-28] 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[24,25] and less frequent guideline-concordant treatment to manage chronic physical illnesses such as diabetes[26,27] and CVD.[28] Given these issues, identifying intervention strategies that address CVD 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 CVD risk factors in adults with SMI. SMI has been defined variously by different groups over time.[29] 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 CVD risk factors in individuals with SMI and consulted with our Key Informants. Because we identified recent high-quality reviews of general health advice, interventions for smoking cessation, and models to provide integrated mental health–general medical care, we elected not to cover these interventions again in our review.[30-34] We included randomized controlled trials (RCTs) of the pharmacological and patient-focused behavioral strategies 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. Major outcomes of interest for this report are primary CVD risk factors (excluding tobacco use, as explained above), physical functioning or health-related quality of life, adverse effects, and all-cause mortality.

Key Questions

With input from our Technical Expert Panel (TEP), 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?

Analytic Framework

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

Methods

The methods for this comparative effectiveness review follow those suggested in the AHRQ "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (available at www.effectivehealthcare.ahrq.gov/methodsguide.cfm; hereafter referred to as the Methods Guide).[35]

During the topic refinement stage, we solicited input from Key Informants representing clinicians, 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 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 Web site.[36]

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. Exact search strings and dates are included in the appendix to the main report. 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 reviewed and cross-referenced against our library of search results, and additional potentially relevant citations were retrieved for screening. All citations were imported into an electronic database (EndNote® X4; Thomson Reuters, Philadelphia, PA).

We used two approaches to identify relevant gray 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.

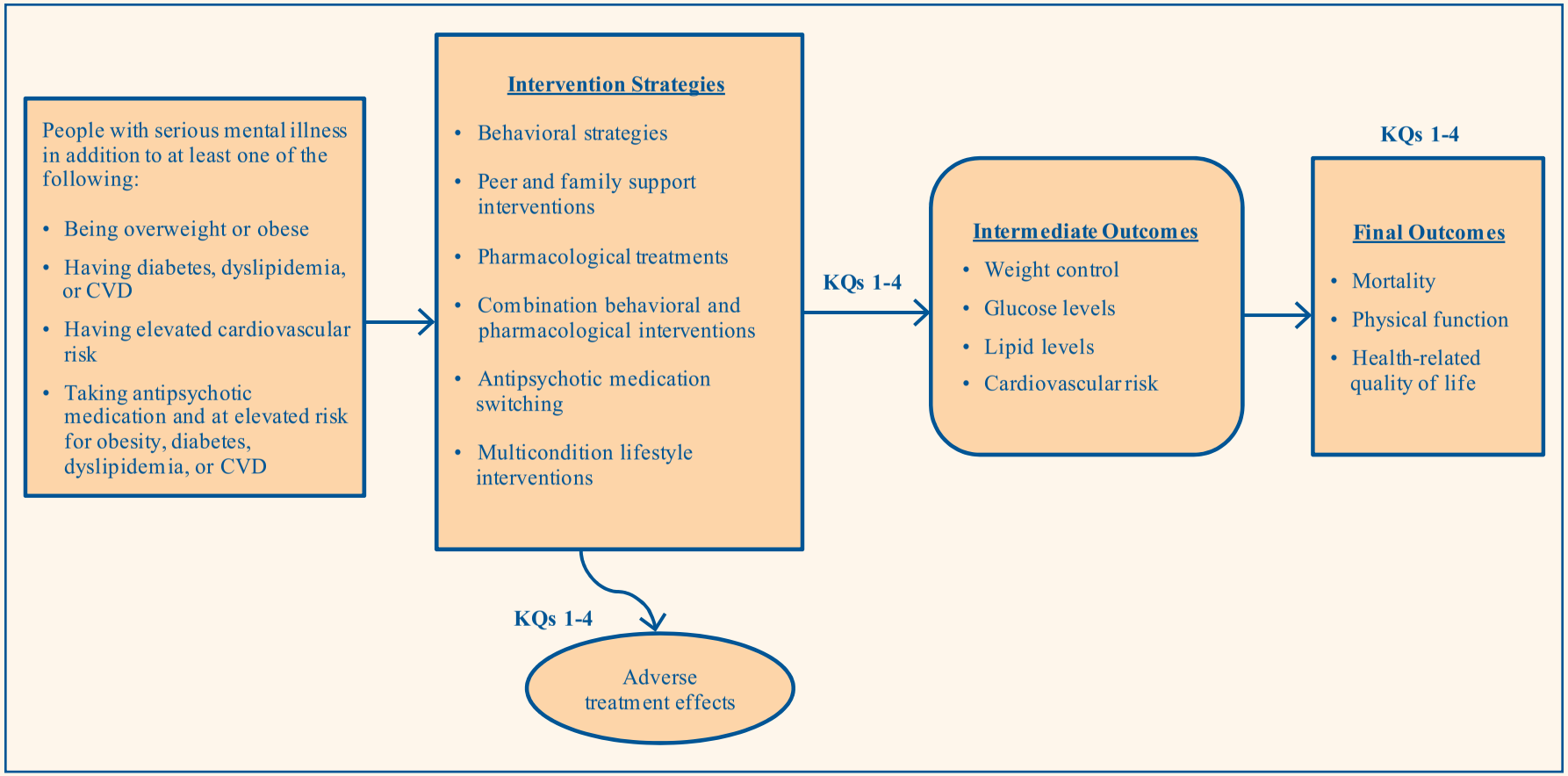
Inclusion and Exclusion Criteria

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 CVD risk profile among adults with SMI at elevated risk of CVD. We excluded articles describing studies that: (1) had as their primary goal improving psychiatric outcomes, (2) assessed only mass media strategies, (3) evaluated pharmacological agents not currently available on the U.S. market, or (4) 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); CVD risk profile (e.g., Framingham CVD scores) or multiple individual components of modifiable CVD 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 described in Table 2 of the full report, 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

Figure A. Analytical framework



CVD = cardiovascular disease; KQ = Key Question

for manual searching of references and cross-referencing against the library of citations identified through electronic database searching. For citations retrieved by searching the gray 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,[35] were also abstracted. 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.[35] Criteria of interest included methods of randomization and allocation concealment, 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, and conflicts of interest.

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 Key Question. 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. 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 KQs, 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 also reported effects on glucose and lipid parameters—was described in each relevant KQ. When a study was designed to intervene on more than one CVD risk factor (e.g., metabolic syndrome), it was summarized in KQ 4. 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.[37] 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.[37] 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.[35,38] 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.[35,39] 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 with 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 5,769 citations, 756 of which were duplicate citations. Manual searching identified 213 additional citations, for a total of 5,226 citations. After applying inclusion/exclusion criteria at the title-and-abstract level, 179 full-text articles were retrieved and screened. Of these, 139 were excluded at the full-text screening stage, leaving 40 articles (representing 35 unique studies) for data abstraction. No additional information was found through our gray literature search.

Overall, we included 35 studies, some of which were relevant to more than one KQ: 32 studies were relevant to KQ 1, 7 to KQ 2, 15 to KQ 3, and 3 to KQ 4. Studies were conducted in Europe (23%); Asia (14%); the United States (37%); Australia/New Zealand (6%); and South America (6%); or multiple continents (14%). Sixty-three percent of included studies enrolled individuals with schizophrenia or schizoaffective disorder, 11 percent recruited individuals with schizophrenia, schizoaffective disorder, or bipolar disorder, 20 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 (80%); only one study was designed to target diabetes management, and no studies were designed to target dyslipidemia.

The most common comparisons were between behavioral interventions and control (26% of comparisons), followed by neurologics (13%), and psychotropics or antihistamines compared with control (10% for each comparison). 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.

Key Question 1. Effectiveness of Weight-Management Interventions

Key points are:

- Of the 32 studies identified, most were specifically designed to control weight gain for individuals with SMI.
- Behavioral interventions were found in a meta-analysis to have a significant advantage over control conditions. We found moderate strength of evidence (SOE) that behavioral interventions are associated with small decreases in weight (about 3 kg) compared with controls.
- Switching to or adding adjunctive aripiprazole, adding the anticonvulsant medications topiramate and zonisamide, or adding metformin yielded small to moderate weight loss (low SOE).
- There was no advantage in favor of nizatidine compared with placebo for the management of weight gain among patients with SMI (low SOE).
- No studies evaluated the weight loss medication orlistat in this population.
- Few studies reported effects on physical functioning or health-related quality of life, and no studies reported all-cause mortality.

We identified 32 RCTs encompassing 3,473 participants that assessed the effects of weight-management strategies among adults with SMI. Most studies (n=19) were rated fair quality, with 9 studies rated good quality and 4 poor quality. In total, 22 studies targeted weight control, 6 obesity prevention, 3 antipsychotic metabolic effects, and 1 diabetes management. Of the 3,473 participants across the 32 included studies, most were male and white.

We had sufficient studies to perform three meta-analyses: behavioral interventions, the anticonvulsant medications topiramate and zonisamide, and the antihistamine nizatidine compared with placebo control. 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 anticonvulsant medications topiramate and zonisamide (mean difference, -5.11 kg; CI, -9.48 to -0.74), or adding metformin (mean difference, -4.13 kg; 95% CI, 6.58 to -1.68) yield small to moderate weight loss. Nizatidine, an antihistamine, did not show any consistent effect on weight (mean difference, -0.496 kg; 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

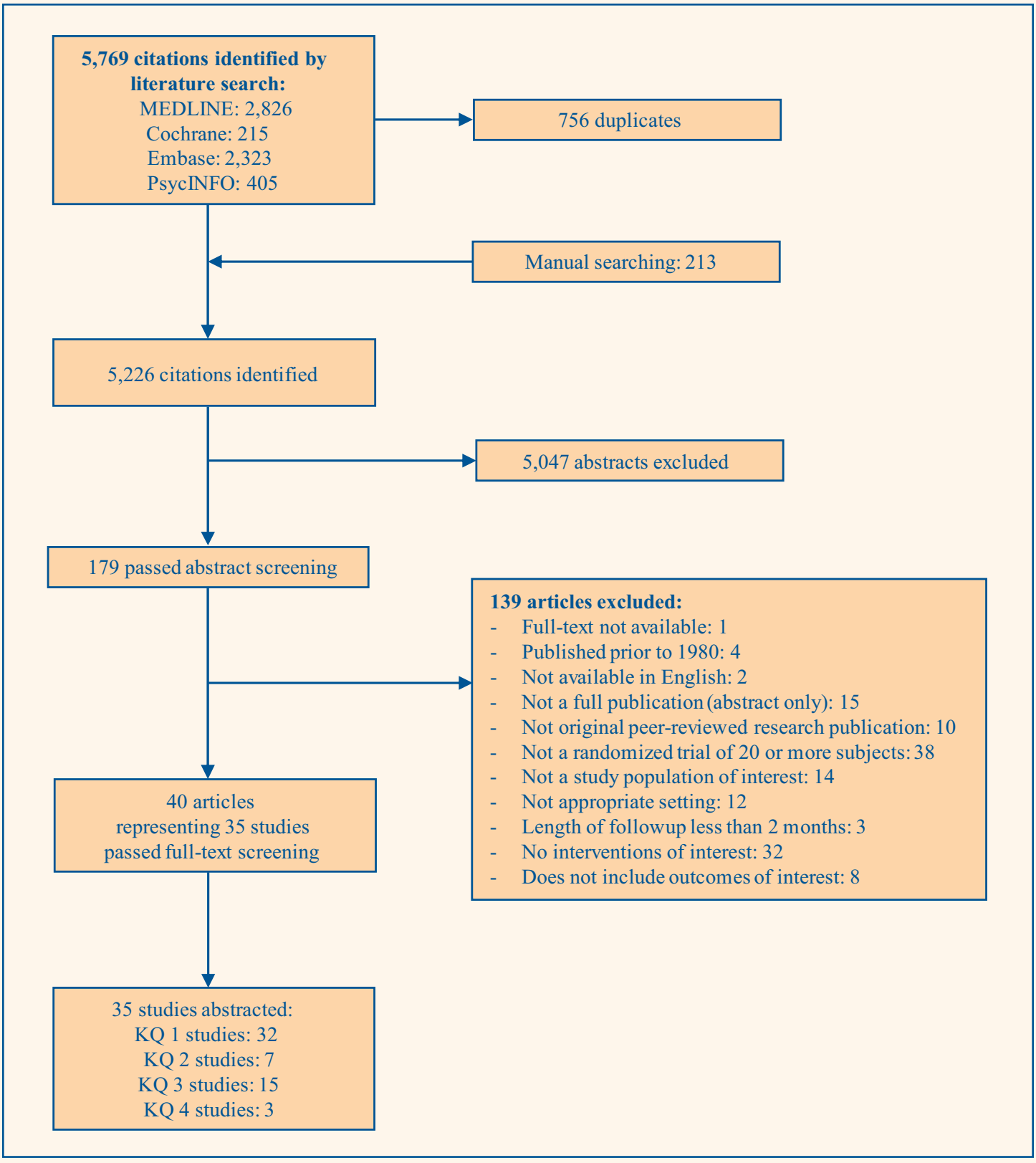
Key points are:

- Overall, we found insufficient evidence to support any strategy to control glucose. Of the seven studies identified, only one evaluated an intervention specifically designed to target glucose control in individuals with SMI who have diabetes. Two additional 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 interventions represented in these seven studies were ramelteon, antipsychotic switching, metformin, amantadine, and behavioral interventions.
- Just two of the trials found significant advantages for the intervention in controlling HbA1c, with both of these studies involving the use of metformin. Improvements in HbA1c were small.
- Health-related quality of life and serious adverse events were inconsistently reported in the seven trials. Only one study reported effects on physical functioning or health-related quality of life, and no studies reported CVD mortality.

We identified 7 RCTs encompassing 681 participants that assessed the effects of diabetes-management strategies among adults with SMI. Of these studies, one was rated good quality, five fair quality, and one poor quality. Only one study enrolled patients with diabetes and addressed glucose control directly; the other six studies assessed HbA1c as a secondary outcome.

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.

Figure B. Literature flow diagram



KQ = Key Question

Key Question 3. Effectiveness of Dyslipidemia-Management Interventions

Key points are:

- Lipid levels have not been a primary target for interventions studied in individuals with SMI. While 15 RCTs reported lipid levels as a secondary outcome (the studies included in this section), no studies evaluated an intervention specifically designed to target lipid levels in individuals with SMI who have or are at risk for dyslipidemia. Hence, the strength of evidence for this KQ 3 is insufficient.
- Interventions known to be effective for managing dyslipidemia, such as medications (e.g., HMG-CoA reductase inhibitors) or dietary interventions, have not been studied in SMI populations. It seems that such interventions should be considered for clinical use, but direct evidence in SMI populations is lacking.
- Behavioral interventions were found in a meta-analysis to have no advantage over usual care for managing low-density lipoprotein (LDL) levels, but this analysis consisted of three small, 3- to 12-month studies aimed primarily at either weight or diabetes management.
- 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.
- Lipid levels improved modestly in two studies of aripiprazole—one that added aripiprazole to chronic clozapine and one that switched patients from olanzapine to aripiprazole. 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 2,322 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 four studies rated good quality, and three 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. 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). Small benefits were seen when aripiprazole was used as an adjunct or as an antipsychotic-switching strategy, and single studies suggested possible benefit with ramelteon or topiramate. However, SOE was insufficient for all interventions; no strategies were designed to target lipid levels.

Key Question 4. Effectiveness of Multicondition Lifestyle Interventions

Key points are:

- Only three studies evaluated lifestyle interventions. Lifestyle interventions consisted primarily of dietary and exercise components. One study offered additional provisions such as heart rate monitors and financial subsidies to support the exercise component.
- One study reported small to moderate beneficial 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 benefits of multicondition lifestyle interventions for self-reported health-related quality of life.
- Studies included in KQ 4 varied substantially on methodological rigor and quality variables.
- Overall, the evidence is insufficient to estimate the effects of multicondition lifestyle interventions.

We identified 1 good and 2 fair-quality studies involving 286 patients that assessed the effects of lifestyle interventions on CVD 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. Adding or switching to aripiprazole results in a small benefit on weight (low SOE), 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 quality of life.

Discussion

Key Findings and Strength of Evidence

We identified 35 trials that tested a wide array of pharmacological and behavioral interventions to address one or more CVD risk factors in adults with SMI who have elevated risk for CVD. Given that CVD is the most prevalent cause of death in this population, this 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 Risk Score) 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 KQ for major outcomes. The drug classes in our review sometimes included drugs with diverse mechanisms of action. When results varied by drug, we assigned separate SOE. Publication bias was difficult to assess because only a few comparisons 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.

Prior reviews have identified effective treatments for CVD risk factors such as obesity, tobacco use, and hyperlipidemia in *general populations* or in *adults at increased risk for CVD*.[40-42] We specifically excluded from our review evaluations of general health advice, smoking cessation interventions, and models that provide integrated mental health–general medical care because these topics had been the subject of recent high-quality reviews in patients with SMI.[30-34] Tsoi et al.[30,31] 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 (including nicotine replacement therapy) and no evidence of benefit for these other treatments. In contrast, Tosh et al.[32] 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.[34] found moderately strong evidence that integrated mental health–general medical care improves preventive services, including CVD screening, but limited and inconsistent effects on physical functioning and CVD risk factors.

Our results complement prior reports by examining a broad array of interventions for patients at increased risk for worsening health outcomes due to CVD risk factors such as obesity, hyperlipidemia, diabetes mellitus, or chronic administration of antipsychotic medication that negatively impacts 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.[43-49] These reviews used differing eligibility criteria, with some including observational designs. Despite the differences in methods, the conclusions of these reviews are largely consistent with our findings that behavioral interventions are associated with small improvements in weight. Our review builds on these findings by identifying clear omissions in treatments that are 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

In our review, only 15 of 35 trials were conducted in the United States, and most studies (n=21) were classified as efficacy studies and were relatively short in duration.

Table A. Overview of treatment effects and SOE by intervention and major outcomes[a]				
Intervention	**KQ 1: Weight**	**KQ 2: Diabetes (HbA1c)**	**KQ 3: Lipids[b]**	**Overall CVD Risk and Other Outcomes**
Behavioral	Small benefit (-3.1 kg)[a] Moderate SOE[a]	Insufficient SOE	No important effect from weight control interventions Insufficient 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 (-4.1 kg)[a] Low SOE[a]	Insufficient SOE	No studies Insufficient SOE	Insufficient SOE for CVD risk
Topiramate, zonisamide	Small to moderate benefit (-5.1 kg)[a] Low SOE[a]	Insufficient SOE	Possible benefit with topiramate Insufficient SOE	Insufficient SOE for CVD risk
Antihistamine	No benefit[a] Low SOE[a]	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 or adjunctive use	Low SOE for small benefit (-2 to -3 kg) with switching to aripiprazole or adjunctive aripiprazole[a] Insufficient SOE from single studies that found no effect with switching to quetiapine or parenteral olanzapine	Insufficient SOE	Possible benefit with adjunctive or switching to aripiprazole[a] Low SOE[a]	Insufficient SOE for CVD risk Low SOE for possible higher rate of mental health worsening with switching[a]
Multicomponent lifestyle	Insufficient SOE	Insufficient SOE	Insufficient SOE	2 studies suggested benefit for health-related quality of life 1 study reported no benefit on CVD risk score Insufficient SOE

CVD = cardiovascular disease; KQ = Key Question; SOE = strength of evidence
[a]Shaded cells highlight SOE ratings that are above insufficient.
[b]No studies of lipid-focused interventions.

Studies typically enrolled midlife adults; none specifically enrolled older adults. Women, as well as racial minorities, were well represented overall but underrepresented for some specific comparisons. Most studies 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 with 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 pressure[50] and tobacco use,[51] screening for diabetes in patients with elevated blood pressure,[52] and lipid screening in midlife adults or young adults at increased risk for CVD.[53] 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. Because only limited data on harms were reported in the trials examined, data from non-SMI populations should be incorporated into decisionmaking. 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;[30,31] 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[54,55] and behavioral support interventions in individuals with mental illness as potentially effective.[56] 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 CVD risk screening and followup.[57] Studies show screening rates ranging from about 10 to 26 percent for lipids and 22 to 52 percent for glucose.[58-61] 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.[62] 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 CVD risk factors has the potential to improve care and clinical outcomes.

Research Gaps

We considered 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.[63] Gaps and recommendations are presented in Table B.

Table B. Evidence gaps and future research for adults with SMI			
PICOTS	**Evidence Gap**	**Reason**	**Type of Studies To Consider**
Patients	Limited data for patients with conditions other than schizophrenia	Insufficient information	Single and multisite RCTs Quasi-experimental or clinical records-based observational studies
	No data in older adults who have more comorbid medical illness	Insufficient information	Single and multisite RCTs Quasi-experimental or clinical records-based observational studies
	Few studies of ethnic and racial minorities	Insufficient information	Single and multisite RCTs Quasi-experimental or clinical records-based observational studies
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 Quasi-experimental or clinical records-based observational studies
	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) with 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 Quasi-experimental studies
	Few multimodal interventions (e.g., robust behavioral and pharmacological treatments) and few multicondition interventions (interventions that address multiple CVD risk factors)	Insufficient information	Single and multisite RCTs
	Few evaluations of smoking cessation interventions other than bupropion[a]	Insufficient information	Single and multisite RCTs Quasi-experimental or clinical records-based observational studies
	Few studies evaluating integrated mental health and general medical care[a]	Insufficient information	Single and multisite RCTs Quasi-experimental or clinical records-based observational studies
	Uncertainty about the key characteristics of successful behavioral interventions (e.g., tailoring, dose, duration, delivery mode, individual vs. group)	Insufficient information Not the right information	Improved intervention reporting Single and multisite RCTs Systematic reviews
	Uncertainty about the details of the intervention	Not the right information	Manuals provided to promote replication/ implementation of successful interventions
	Interventions to improve guideline concordant care	Insufficient information	Single and multisite RCTs Quasi-experimental studies

Table B. Evidence gaps and future research for adults with SMI (continued)			
PICOTS	**Evidence Gap**	**Reason**	**Type of Studies To Consider**
Comparators	Few studies comparing two active interventions	Insufficient information	Single and multisite RCTs comparing effective treatments Quasi-experimental or clinical records-based observational studies
Outcomes	Uncertain effects on overall CVD risk or cardiovascular events	Insufficient information	Risk indices (e.g., Framingham Risk Score) and/or cardiovascular events used as outcome measures
	Intervention adherence	Insufficient information	Improved study reporting
	Uncertainty about adverse effects on mental health status and other serious adverse effects, specifically in individuals with SMI	Insufficient information	Studies that define and report the proportion of patients for whom mental health status worsens Improved reporting of adverse effects
Timing	Few studies with outcomes measured beyond 6 months	Insufficient information	RCTs with longer term followup 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 followup and which include clinically important outcomes such as physical functioning, cardiovascular events, and adverse events Improved reporting of efficacy–effectiveness characteristics

CATIE = Clinical Antipsychotic Trials in Intervention Effectiveness; CVD = cardiovascular disease; PICOTS = patients, interventions, comparators, outcomes, timing, setting; RCT = randomized controlled trial; SMI = serious mental illness.
[a]Research gaps from prior high-quality systematic reviews that were identified during the topic refinement phase of this review and are described briefly in this report.

Because the list of gaps in evidence is extensive, we suggest general principles for prioritizing research as applied to the population of adults with SMI. Most groups[64] advocate input from multiple stakeholders and consideration of issues such as the burden of disease, the availability of existing treatment options, the likelihood that the new intervention will substantially improve outcomes, practice variation and health disparities, and the feasibility of implementing effective interventions with existing resources. Specific research questions can be evaluated quantitatively, using value-of-information analysis, which employs Bayesian methods to estimate the potential benefits of gathering more information through research.[65] A recent AHRQ white paper used a multiple-stakeholder consensus process to identify patient-centered outcomes research priorities for serious mental illness,[66] and prioritized comparative effectiveness studies of interventions targeting modifiable risk factors such as tobacco abuse, physical exercise, and nutrition.

We also considered the most appropriate research designs for the research gaps. We suggest that observational designs may be particularly appropriate for these applications: (1) evaluating interventions proven effective in non-SMI populations, (2) testing the *effectiveness* of interventions demonstrated efficacious in tightly controlled trials, and (3) formulating hypotheses to be tested in RCTs. RCTs may be particularly useful for interventions specifically tailored for SMI populations and for drugs, or drug strategies (e.g., antipsychotic switching), that are used primarily in this population. Although we recommend multicenter RCTs to address some evidence gaps, we are aware that there are particular challenges to conducting RCTs in this population. For example, individuals with SMI have been routinely excluded from large cardiovascular trials—limiting opportunities to participate in research. Also, behavioral interventions may be affected by limited access to healthy foods or opportunities for exercise because many individuals with SMI are in lower

socioeconomic status groups. Some important outcomes, such as cardiovascular events, may take large sample sizes and long followup periods to evaluate.

Conclusions

In summary, individuals with SMI are at risk for increased CVD—in part due to health behaviors, direct effects of the illness, and adverse effects from some treatments. Prior reviews identified bupropion as effective for smoking cessation, and integrated general medical and mental health care as effective for CVD screening. In our review, surprisingly few studies addressed one or more CVD risk factors in patients with SMI, and most studies were skewed toward efficacy trials. Behavioral interventions, switching to or adding adjunctive aripiprazole, adding anticonvulsant medications topiramate and zonisamide, or adding metformin yield small to moderate weight loss compared with 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 or 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.

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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

Full Report

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