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

Amendment Date(s):

Amendment 1 – January 20, 2012

Amendment 2 – February 10, 2012

Amendment 3 – April 18, 2012

(Amendment Details–see Section VII)

I. Background and Objectives for the Systematic Review

Individuals with serious mental illness (SMI) have shortened life expectancies relative to the general population to an extent that is not explained by suicide and accidents alone.[1,2] This population experiences higher rates of morbidity from multiple general medical conditions, including diabetes[3-5] and cardiovascular disease (CVD).[6,7] Modifiable cardiovascular risk factors for poor health, such as smoking,[8] obesity,[9,10] and physical inactivity,[11] are highly prevalent among individuals with SMI. Numerous studies have demonstrated disparities in the quality of general medical care provided to individuals with SMI; they receive fewer preventive medical services[12,13] and less frequent guideline-concordant treatment to manage chronic illnesses such as diabetes[14,15] and CVD.[16] 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.[17] Care for individuals with SMI is costly; care for individuals with schizophrenia, for example, costs $62.7 billion annually in the United States.[18] Given these issues, identifying approaches that avoid early morbidity and mortality by addressing cardiovascular risk in individuals with SMI is a pressing priority.

SMI has been defined variously by different groups over time.[19] For the purposes of this evidence review, people with SMI are individuals who currently have (or at any time during the past year had): (1) schizophrenia or schizoaffective disorder (or other related primary psychotic disorder), (2) bipolar disorder, (3) psychotic depression, or (4) no specified diagnosis but are classified as having SMI or severe and persistent mental illness (SPMI). (Note: Excluded from this definition are individuals with a primary diagnosis of substance abuse, dementia, personality disorder, or mental retardation.)

Current Standard of Care

Managing CVD risk in individuals with SMI include standard pharmacological treatments and behavioral interventions used in the general population, as well as some 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 (i.e., pharmacotherapy) may be used to manage cardiovascular risk factors in individuals with SMI. In addition, peer and family support interventions are helpful for improving mental health outcomes and may be helpful to improve general medical outcomes.[20] 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 is expected to be similar in patients with SMI when compared to general populations, but the potential for higher or more severe adverse effects may be greater in individuals with SMI than in general populations for some medications (e.g., varenicline). It is possible for health behavior interventions to be tailored to individuals with SMI. However, complex behavioral treatments that require more intense monitoring may be differentially *effective* in patients with SMI when compared to the general population. For behavioral interventions, direct effects of SMI and the limited social and economic support systems often available to these individuals may decrease *effectiveness*. Furthermore, it is unclear what the optimal strategies are to manage adverse effects of antipsychotics used to treat SMI. Table 1 provides a summary of selected pharmacological treatments and behavioral strategies available to optimize adherence and address comorbid risk factors for general medical conditions among individuals with SMI.

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

Comorbid Risk Factors in People With SMI	Pharmacological Treatments	Patient-Focused 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
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
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
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

Rationale for the Review

As shown in Table 1, many pharmacological treatments and patient-focused behavioral strategies exist to manage cardiovascular risk factors for people with SMI. To assess gaps in the literature and inform selection of relevant strategies, we examined eight relevant systematic reviews that summarized pharmacological treatments and behavioral strategies related to cardiovascular risk factors among individuals with SMI. Our conclusions from this assessment are as follows:

- Based on existing clinical studies, the current review literature provides adequate coverage for the topics of smoking cessation[21,22] and general health advice.[23,24]
- The current review literature on weight-management interventions for people with SMI is outdated, not of good quality, or inconclusive.[25-27]
- The current review literature on pharmacological treatments and patient-focused behavioral strategies does not adequately address multiple high-prevalence medical conditions (e.g., CVD, diabetes) for individuals with SMI.
- Beyond weight-management interventions, the current review literature on nonpharmacological approaches (e.g., behavioral interventions) to managing cardiovascular risk in people with SMI is lacking.
- The current review literature provides little guidance on the management of adverse effects of antipsychotics used to treat SMI and whether switching antipsychotics or medically managing side effects optimizes CVD outcomes.
- The only existing review of multicondition lifestyle interventions to address general health outcomes in people with SMI is not of good quality and did not include a meta-analysis because the eligible studies included variable interventions and populations, which precluded overarching conclusions from this literature.[28]

II. The Key Questions

The draft Key Questions (KQs), which were developed during Topic Refinement, were available for public comment from October 28, 2011, to November 28, 2011. The comments received led to the following changes in the KQs and analytic framework:

- Added peer and family support interventions to the strategies examined for each KQ
- Added the phrase "to an antipsychotic with a low or neutral impact" to KQs 1–3.
- Added a separate KQ on dyslipidemia (KQ 3)
- Deleted two KQs (previously KQs 4 and 5) based on public comments that stated cancer screening and HIV risk-reduction interventions are of lower relevance to this population than other conditions related to CVD risk and on the need to limit the scope due to the additions listed above.

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?

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?

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?

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?

PICOTS (Population, Intervention, Comparator, Outcome, Timing, Setting) Criteria

Population(s):

- KQs 1–4: Adults ≥18 years of age with SMI, defined as individuals who currently have (or at any time during the past year had):
    - Schizophrenia or schizoaffective disorder (or other related primary psychotic disorder)
    - Bipolar disorder
    - Psychotic depression
    - No specified diagnosis but are classified as having SMI or SPMI. Individuals with SMI or SPMI are defined as people who currently have, or at any time during the past

year had, a diagnosable mental, behavioral, or emotional disorder of sufficient duration to meet diagnostic criteria specified within the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*)[29] or its ICD-9-CM[30] equivalent (and subsequent revisions) and who experience functional impairment that substantially interferes with or limits one or more major life activities. Excluded from this definition are 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.

Individuals with SMI must also meet one or more of the following population criteria for each KQ:

- KQ 1:
  - Individuals who are overweight or obese
  - Individuals who are taking antipsychotics and consequently at increased risk for obesity
- KQ 2:
  - Individuals who have diabetes
  - Individuals who are taking antipsychotics and consequently at risk for elevated glucose levels
- KQ 3:
  - Individuals who have dyslipidemia
  - Individuals who are taking antipsychotics and consequently at risk for elevated lipid levels
- KQ 4:
  - Individuals who have CVD or elevated cardiovascular risk (e.g., hyperlipidemia, hypertension, metabolic syndrome)
  - Individuals who are taking antipsychotics and consequently at increased risk for CVD

Interventions:

- KQs 1–3:
  - Patient-focused behavioral interventions, peer or family support interventions, pharmacological treatments, or combinations thereof targeting weight control, glucose levels, lipid level, or cardiovascular risk profile (see Table 1 for specific examples of patient-focused behavioral interventions and pharmacological treatments)

- Antipsychotic switching to manage side effects related to weight control, glucose levels, lipid level, or elevated cardiovascular risk (e.g., from atypical to typical antipsychotic medication)

- KQ 4:

  - Multicondition lifestyle interventions (e.g., combinations of smoking cessation, physical activity, nutrition counseling with or without medication management) for elevated cardiovascular risk

Comparators:

- KQs 1–4:

  - Comparison of the intervention treatments with each other
  - Usual care
  - Placebo
  - Other control (e.g., attention control)

Outcome Measures:

- KQ 1: Weight control (i.e., weight loss or maintenance of current weight)

- KQ 2: Glucose level (e.g., hemoglobin A_{1c})

- KQ 3: Lipid level (e.g., change in low-density lipoprotein)

- 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)

- KQs 1–4:

  - Health-related quality of life
  - CVD mortality
  - Adverse effects (e.g., discontinuation due to adverse effects or serious adverse effects as defined by FDA at www.fda.gov/safety/medwatch/howtoreport/ucm053087.htm

Timing:

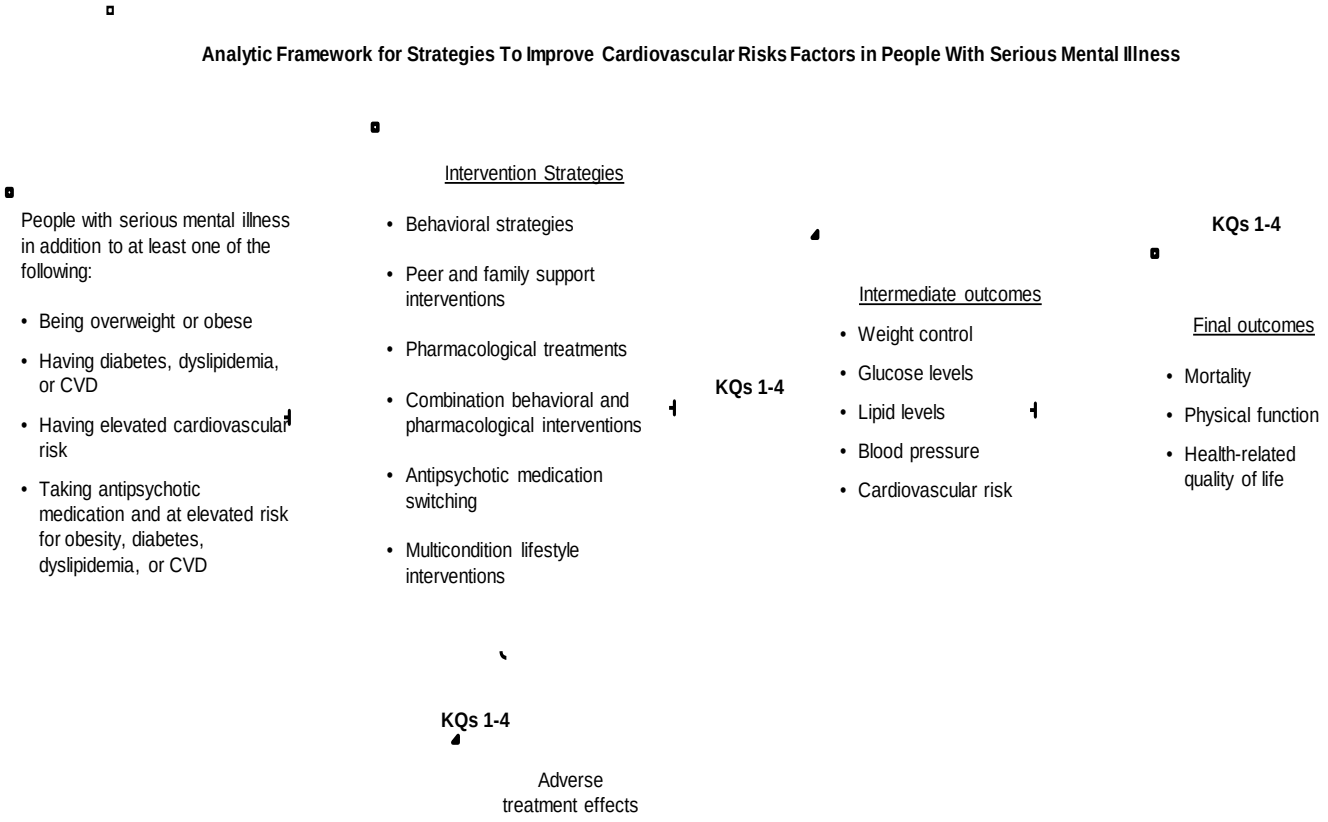
- KQs 1–4: Outcomes must be measured at $\geq$ 90 days from randomization

Settings:

- KQs 1–4:

- Outpatient mental health and outpatient general medical settings
- Community settings

III. Analytic Framework



Abbreviations: CVD = cardiovascular disease; KQ = key question

IV. Methods

In developing this comprehensive review, we will apply the rules of evidence and evaluation of strength of evidence recommended by the Agency for Healthcare Research and Quality in its *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter referred to as the *Methods Guide*).[31] When appropriate, we will solicit feedback regarding conduct of the work (such as development of search strategies) from the Task Order Officer and the Technical Expert Panel. We will follow the methodology recommended to the Evidence-based Practice Centers for literature search strategies, inclusion/exclusion of studies in our review, abstract screening, data abstraction and management, assessment of methodological quality of individual studies, data synthesis, and grading of evidence for each KQ.

A. Criteria for Inclusion/Exclusion of Studies in the Review

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Population	KQs 1–4: According to standardized diagnostic criteria (e.g., *DSM-IV*, ICD), people ≥18 years of age who currently have (or at any time during the past year had) one of the following: • Schizophrenia or schizoaffective disorder (or other related primary psychotic disorder) • Bipolar disorder • Psychotic depression • No specified diagnosis but are classified as having SMI or SPMI (see PICOTS for further description). 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.	KQs 1–4: • People <18 years of age • Individuals 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
	In addition to these population criteria: KQ 1: • Individuals who are overweight or obese *or* • Individuals who are taking antipsychotics and consequently at increased risk for obesity KQ 2: • Individuals who have diabetes *or* • Individuals who are taking antipsychotics and consequently at risk for elevated glucose levels KQ 3: • Individuals who have dyslipidemia *or* • Individuals who are taking antipsychotics and consequently at risk for elevated lipid levels KQ 4: • Individuals who have CVD or elevated cardiovascular risk (e.g., hyperlipidemia, hypertension, metabolic syndrome) *or* • Individuals who are taking antipsychotics and consequently at increased risk for CVD	

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Interventions[a]	KQs 1–4: • 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 *or* elevated glucose levels or cardiovascular risk KQ 4: Multicondition lifestyle interventions (e.g., combinations of smoking cessation, physical activity, nutrition counseling with or without medication management) for elevated cardiovascular risk	KQs 1–4: • Studies with the primary goal of improving psychiatric outcomes • Mass media strategies KQ 4: Interventions that use multiple strategies (e.g., physical activity, medication changes, and nutrition counseling) to improve one condition (e.g., diabetes mellitus as measured by hemoglobin A_{1c}; weight change). (These interventions will be allocated to KQ 1–3, if eligible.)
Comparators	KQ 1–4: • Usual care • Placebo • Other control (e.g., attention control) KQs 1–4: • 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 KQ 4: Multicondition lifestyle interventions (e.g., combinations of smoking cessation, physical activity, nutrition counseling with or without medication management) for elevated cardiovascular risk	None

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Outcomes	KQ 1: Weight control (i.e., weight loss or maintenance of current weight) KQ 2: Glucose level (e.g., hemoglobin A_{1c}) KQ 3: Lipid level (e.g., change in low-density lipoprotein) 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) KQ 1–4: • Health-related quality of life • All-cause mortality	None
Timing	≥ 90 days	< 90 days
Setting	• Outpatient mental health and outpatient general medical settings • Community settings	Hospital inpatient setting
Study design	Randomized trials	• Not a clinical study (e.g., editorial, nonsystematic review, letter to the editor, case series) • Prospective and retrospective observational studies • N ≤20
Publications	• 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]

[a]Studies will be classified by primary study goal (i.e., weight management, diabetes management, CVD management). To meet criteria for KQ 4, the study must state a goal to improve more than one condition related to cardiovascular risk.
[b]1980 was the year the *DSM-III* was introduced.
[c]Given the high volume of English-language publications (including the majority of known important studies), non–English-language articles will be excluded. It is the opinion of the investigators that the resources required to translate non–English-language articles would not be justified by the low potential likelihood of identifying relevant data unavailable from English-language sources.
Abbreviations: CVD = cardiovascular disease; KQ = key question

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions

To identify the relevant published literature, we will search MEDLINE®, PsycINFO®, EMBASE®, and the Cochrane Database of Systematic Reviews, limiting the search to studies conducted in adults. Where possible, we will use existing validated search filters (such as the Clinical Queries Filters in PubMed®). An experienced search librarian will guide all searches (Appendix 1). We will supplement the electronic searches with a manual search of citations from a set of key primary and review articles. The reference list for identified pivotal articles will be manually hand-searched and cross-referenced against our library, and additional manuscripts will be retrieved. All citations will be imported into an electronic database (EndNote X4®). As a mechanism to ascertain publication bias, we will search www.clinicaltrials.gov to identify completed but unpublished studies. While the draft report is under peer review, we will update the search and include any eligible studies in the final report. To identify relevant gray literature, we will request scientific information packets submitted to relevant pharmaceutical manufacturers.

For MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews, two reviewers, using prespecified inclusion/exclusion criteria, will review titles/abstracts for potential relevance to the research questions. We will track the number of articles excluded based on language criteria and report this result in the final report. Articles included by either reviewer will undergo full-text screening. At the full-text screening stage, two independent reviewers must agree on a final inclusion/exclusion decision. Articles meeting eligibility criteria will be included for data abstraction. All results will be tracked in the DistillerSR data synthesis software program (Evidence Partners Inc., Manotick, ON, Canada).

C. Data Abstraction and Data Management

The research team will create data abstraction forms for the KQs that will be programmed in the DistillerSR software. Based on their clinical and methodological expertise, a pair of researchers will be assigned to abstract data from each of the eligible articles. One researcher will abstract the data, and the second will read the article and the accompanying abstraction to check for accuracy and completeness. Disagreements will be resolved by consensus or by obtaining a third reviewer's opinion if consensus cannot be reached. Guidance documents will be drafted and provided to the researchers to aid both reproducibility and standardization of data collection.

We will design 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 will pay 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*,[31] will also be abstracted. Before they are used, abstraction-form templates will be pilot-tested with a sample of included articles to ensure that all relevant data elements are captured and that there is consistency/reproducibility between abstractors. Forms will be revised as necessary before full abstraction of all included articles.

D. Assessment of Methodological Quality of Individual Studies

The included studies will be assessed on the basis of the quality of their reporting of relevant data. We will evaluate the quality of individual studies by using the approach described in the *Methods Guide*.[31] To assess quality, we will employ the strategy to (1) classify the study design, (2) apply predefined criteria for quality and critical appraisal, and (3) arrive at a summary judgment of the study's quality. To evaluate methodological quality, we will apply criteria for each study type derived from the core elements described in the *Methods Guide* (selection, performance, attrition, detection, and reporting bias). To indicate the summary judgment of the quality of the individual studies, we will use the summary ratings of good, fair, and poor based on their adherence to well-accepted standard methodologies and adequate reporting. Grading will be outcome-specific; thus, a given study may be graded to be of different quality for two individual outcomes reported within that study.

We will use data abstracted on population studied, intervention strategies and comparators, outcomes measured, study settings, and timing of assessments to identify specific issues that may limit the applicability of individual studies or a body of evidence as recommended in the *Methods Guide*.[31] We will use these data to evaluate the applicability to clinical practice, paying special attention to study eligibility criteria, demographic features of the enrolled population (disease severity, age, ethnicity, and sex) in comparison with the target population, characteristics of the intervention used in comparison with interventions currently in use, and clinical relevance and timing of the outcome measures. We will summarize issues of applicability qualitatively.

E. Data Synthesis

We will begin by summarizing key features of the included studies for each KQ. To the degree that data are available, we will abstract information on study design; patient characteristics; clinical settings; interventions; and intermediate, final, and adverse events outcomes. We will then determine the feasibility of completing a quantitative synthesis (i.e., meta-analysis). Feasibility depends on the volume of relevant literature, conceptual homogeneity of the studies, and completeness of the reporting of results. When a meta-analysis is appropriate, we will use random-effects models to quantitatively synthesize the available evidence. We will test for statistical heterogeneity using graphical displays and test statistics (Q and I^2 statistics), while recognizing that the ability of statistical methods to detect clinical heterogeneity may be limited. We will present summary estimates, standard errors, and confidence intervals. We anticipate that intervention effects may be heterogeneous. We hypothesize that the methodological quality of individual studies, study-effectiveness characteristics, characteristics of comparator, and patients' specific mental illness (i.e., bipolar disorder vs. schizophrenia), or patient baseline risk (e.g., at risk of obesity versus overweight versus obese) will be associated with the intervention effects. If there are sufficient studies, we will perform subgroup analyses and/or meta-regression analyses to examine variability in treatment effects by subgroups. We will summarize binary or categorical outcomes (e.g., smoking status) by weighted effect measure for proportions (e.g., risk ratio). We will summarize continuous variables (e.g., body mass index, hemoglobin A_{1c}),

by using a weighted average of the effect estimates from the different studies; for continuous measures using different scales, we will use standard mean differences.

F. Grading the Evidence for Each Key Question

We will grade the strength of evidence for each outcome assessed; thus, a given study may be graded to be of different quality for two individual outcomes reported within that study. The strength of evidence will be assessed by using the approach described in the *Methods Guide*.[31,32] In brief, the approach requires assessment of four domains: risk of bias, consistency, directness, and precision. Additional domains are to be used when appropriate: dose-response association, impact of plausible residual confounders, strength of association (magnitude of effect), and publication bias. These domains will be considered qualitatively, and a summary rating of "high," "moderate," or "low" strength of evidence will be assigned after discussion between two reviewers. In some cases, high, moderate, or low ratings will be impossible or imprudent to make—for example, when no evidence is available or when evidence on the outcome is too weak, sparse, or inconsistent to permit any conclusion). In these situations, a grade of "insufficient" will be assigned. The four levels of this rating scale are defined as follows:

- 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.

G. Assessing Applicability

We will assess applicability across our KQs with the method described in the *Methods Guide*.[31,33] In brief, this latter method uses the PICOTS (population, intervention, comparator, outcome, timing, and setting) 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 will use a checklist to guide the assessment of applicability. We will use 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 will summarize issues of applicability qualitatively.

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VI. Abbreviations

CVD	cardiovascular disease
KQ	key question
SMI	serious mental illness
SPMI	severe and persistent mental illness

VII. Summary of Protocol Amendments

Date	Section	Original Protocol	Revised Protocol	Rationale
1/20/2012	II. Key Questions	KQs 1–4: Outcomes must be measured at ≥ 90 days	KQs 1–4: Outcomes must be measured at ≥ 2 months	We have shortened the required followup period in order to avoid being overly restrictive of relevant studies that report outcomes of interest with a shorter followup period.
1/20/2012	IV. Methods (Timing)	Inclusion Criteria: ≥ 90 days	Inclusion Criteria: ≥ 2 months	We have shortened the required followup period in order to avoid being overly restrictive of relevant studies that report outcomes of interest with a shorter followup period.
1/20/2012	IV. Methods (Timing)	Exclusion Criteria: < 90 days	Exclusion Criteria: < 2 months	We have shortened the required followup period in order to avoid being overly restrictive of relevant studies that report outcomes of interest with a shorter followup period.
2/10/2012	IV. Methods (Criteria for Inclusion/ Exclusion)	KQs 1–4: Studies with the primary goal of improving psychiatric outcomes	KQs 1–4: Studies with the primary goal of improving psychiatric outcomes	We have clarified that pharmacological agents that are not currently on the US market will be excluded.

		Mass media strategies	Mass media strategies Studies of pharmacological agents that are not currently on the US market	
4/18/2012	II. PICOTS (Outcomes)	Outcome of interest: Adverse effects (e.g., discontinuation due to adverse effects or serious adverse effects as defined by FDA)	Adverse effect outcome of interest further specified as follows: Data abstracted will include all-cause mortality, significant worsening of psychiatric status, and discontinuations due to serious or non-serious adverse effects	We have explicitly clarified the adverse effect measures for data abstraction.
4/18/2012	IV. Methods and PICOTS (Outcomes)	Inclusion criterion: KQ 1–4: • Health-related quality of life • All-cause mortality	Inclusion criterion: KQ 1–4: • Health-related quality of life • All-cause mortality • Physical function	We have explicitly specified physical function as an outcome of interest within these two sections of the protocol to be consistent with the analytic framework diagram.
4/18/2012	IV. Methods (Outcomes)	Exclusion criterion: None	Exclusion criterion: Article reports physical function/ health-related quality of life outcomes only; does not also include CV risk measures of interest	We have clarified the requirement for articles presenting physical function/ health-related quality of life outcomes to also provide data for a CV risk measure of interest in order to ensure the relevance of the included studies to the KQs.

VIII. Review of Key Questions

For all EPC reviews, key questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, for Comparative Effectiveness reviews, the key questions were posted for public comment and finalized by the EPC after review of the comments.

IX. Key Informants

Key Informants are the end-users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Individuals are invited to serve as Key Informants because of their role as end-users; therefore, those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts comprise a multidisciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Individuals are invited to serve as Technical Experts because of their unique clinical or content expertise; therefore, those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published three months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC team disclosures

The EPC has no conflicts of interest to disclose.

XIII. Role of the Funder

This project was funded under Contract No. 290-2007-10066-I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements, including the objectivity and independence of the research process and the methodological quality of the report. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Appendix 1. Literature Search Strategy (12/14/2011)

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?

Set #	Terms	Results
#1	Schizophrenia[tiab] OR schizophrenia[mesh] OR bipolar disorder[mesh:noexp] OR "bipolar disorder"[tiab] OR "psychotic disorders"[tiab] OR schizoaffective[tiab] OR mania[ti] OR manic[ti] OR "bipolar affective disorder"[tiab] OR "serious mental illness"[tiab] OR "severe mental illness"[tiab] OR "severe psychiatric illness"[tiab] OR ("depressive disorder"[mesh] AND psychotic[tiab]) OR "affective disorders, psychotic"[mesh] OR "psychotic disorders"[mesh]	146177
#2	overweight[mesh] OR overweight[tiab] OR obesity[mesh] OR obesity[tiab] OR obese[tiab] OR weight[tiab] OR Body weights and measures[mesh] OR "body mass index"[tw] OR bmi[tw]	824293
#3	chlorpromazine[MeSH] OR chlorpromazine[tw] OR thorazine[tw] OR fluphenazine[MeSH] OR fluphenazine[tw] OR haloperidol[MeSH] OR haloperidol[tw] OR haldol[tw] OR iloperidone[Supplementary Concept] OR iloperidone[tw] OR fanapt[tw] OR loxapine[MeSH] OR loxapine[tw] OR loxitane[tw] OR molindone[MeSH] OR molindone[tw] OR moban[tw] OR chlorpromazine[MeSH] OR chlorpromazine[tw] OR thorazine[tw] OR perphenazine[MeSH] OR perphenazine[tw] OR pimozide[MeSH] OR pimozide[tw] OR orap[tw] OR thioridazine[MeSH] OR thioridazine[tw] OR thiothixene[MeSH] OR thiothixene[tw] OR navane[tw] OR trifluoperazine[MeSH] OR trifluoperazine[tw] OR stelazine[tw] OR clozapine[MeSH] OR clozapine[tw] OR clozaril[tw] OR risperidone[MeSH] OR risperidone[tw] OR risperidal[tw] OR olanzapine[Supplementary Concept] OR olanzapine[tw] OR zyprexa[tw] OR quetiapine[Supplementary Concept] OR quetiapine[tw] OR seroquel[tw] OR ziprasidone[Supplementary Concept] OR ziprasidone[tw] OR geodon[tw] OR aripiprazole[Supplementary Concept] OR aripiprazole[tw] OR abilify[tw] OR 9-hydroxy-risperidone[Supplementary Concept] OR "9-hydroxy-risperidone"[tw] OR paliperidone[tw] OR invega[tw] OR antipsychotic agents[mh] OR antipsychotic agents[pharmacological action] OR antipsychotic[tiab] OR antipsychotics[tiab]	130495
#4	#1 AND (#2 OR #3)	37641
#5	orlistat[Supplementary Concept] OR orlistat[tw] OR topiramate[Supplementary Concept] OR topiramate[tw] OR metformin[MeSH] OR metformin[tw] OR amantadine[MeSH] OR amantadine[tw] OR "Appetite Depressants"[Mesh] OR "Appetite Depressants" [Pharmacological Action] OR "Anti-Obesity Agents"[Mesh] OR "Anti-Obesity Agents" [Pharmacological Action]	26757

Set #	Terms	Results
#6	"Nutrition Therapy"[Mesh] OR "Exercise"[Mesh] OR "Exercise Therapy"[Mesh] OR "Exercise Movement Techniques"[Mesh] OR “diet therapy”[mesh] OR exercise[tiab] OR "physical activity"[tiab] OR diet[tiab] OR diets[tiab] OR “weight management”[tiab] OR "Behavior Therapy"[Mesh] OR health education[mesh] OR health promotion[mesh] OR counsel*[tiab] OR counseling[mesh] OR “disease management”[mesh] OR “cognitive behavioral therapy”[tiab] OR “lifestyle modification”[tiab] OR (“life style”[mesh] AND modification[tiab]) OR "Patient Compliance"[Mesh] OR adher*[tiab] OR “self-monitoring”[tiab] OR "Recurrence/prevention and control"[Mesh] OR “relapse prevention”[tiab] OR “skills training”[tiab] OR “motivational interviewing”[tiab] OR educat*[tiab]	1111731
#7	social support[mesh] OR family[tiab] OR peer[tiab]	526071
#8	Drug substitution[mesh] OR substitut*[tw] switch[tiab] OR switched[tiab] OR switching[tiab] OR change[tiab] OR changed[tiab] OR changing[tiab] OR replace[tiab] OR replaced[tiab] OR replacing[tiab] OR replacement[tiab] OR abandon*[tiab]	1089259
#9	#5 OR #6 OR #7 OR #8	2539863
#10	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT humans[mh]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp])	1394319
#11	#4 AND #9 AND #10, Limits: English	2249

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?

Set #	Terms	Results
#1	Schizophrenia[tiab] OR schizophrenia[mesh] OR bipolar disorder[mesh:noexp] OR "bipolar disorder"[tiab] OR “psychotic disorders”[tiab] OR schizoaffective[tiab] OR mania[ti] OR manic[ti] OR "bipolar affective disorder"[tiab] OR "serious mental illness"[tiab] OR “severe mental illness”[tiab] OR “severe psychiatric illness”[tiab] OR (“depressive disorder”[mesh] AND psychotic[tiab]) OR “affective disorders, psychotic”[mesh] OR “psychotic disorders”[mesh]	**146177**
#2	Diabetes mellitus[mesh] OR diabetes[tiab]	**368280**

Set #	Terms	Results
#3	chlorpromazine[MeSH] OR chlorpromazine[tw] OR thorazine[tw] OR fluphenazine[MeSH] OR fluphenazine[tw] OR haloperidol[MeSH] OR haloperidol[tw] OR haldol[tw] OR iloperidone[Supplementary Concept] OR iloperidone[tw] OR fanapt[tw] OR loxapine[MeSH] OR loxapine[tw] OR loxitane[tw] OR molindone[MeSH] OR molindone[tw] OR moban[tw] OR chlorpromazine[MeSH] OR chlorpromazine[tw] OR thorazine[tw] OR perphenazine[MeSH] OR perphenazine[tw] OR pimozide[MeSH] OR pimozide[tw] OR orap[tw] OR thioridazine[MeSH] OR thioridazine[tw] OR thiothixene[MeSH] OR thiothixene[tw] OR navane[tw] OR trifluoperazine[MeSH] OR trifluoperazine[tw] OR stelazine[tw] OR clozapine[MeSH] OR clozapine[tw] OR clozaril[tw] OR risperidone[MeSH] OR risperidone[tw] OR risperidal[tw] OR olanzapine[Supplementary Concept] OR olanzapine[tw] OR zyprexa[tw] OR quetiapine[Supplementary Concept] OR quetiapine[tw] OR seroquel[tw] OR ziprasidone[Supplementary Concept] OR ziprasidone[tw] OR geodon[tw] OR aripiprazole[Supplementary Concept] OR aripiprazole[tw] OR abilify[tw] OR 9-hydroxy-risperidone[Supplementary Concept] OR "9-hydroxy-risperidone"[tw] OR paliperidone[tw] OR invega[tw] OR antipsychotic agents[mh] OR antipsychotic agents[pharmacological action] OR antipsychotic[tiab] OR antipsychotics[tiab]	**130495**
#4	#1 AND (#2 OR #3)	**36725**
#5	"exenatide"[Supplementary Concept] OR Byetta[tiab] OR exenatide[tiab] OR "pramlintide"[Supplementary Concept] OR Symlin[tiab] OR *pramlintide* [tiab] OR "sitagliptin"[Supplementary Concept] OR Januvia[tiab] OR sitagliptin[tiab] OR glargine[supplementary concept] OR Lantus[tiab] OR “insulin glargine”[tiab] OR "saxagliptin"[Supplementary Concept] OR Onglyza[tiab] OR saxagliptin[tiab] OR "miglitol"[Supplementary Concept] OR Glyset[tiab] OR miglitol[tiab] OR "rosiglitazone"[Supplementary Concept] OR Avandia[tiab] OR rosiglitazone[tiab] OR "pioglitazone"[Supplementary Concept] OR Actos[tiab] OR pioglitazone[tiab] OR "repaglinide"[Supplementary Concept] OR Prandin[tiab] OR repaglinide[tiab] OR "nateglinide"[Supplementary Concept] OR Starlix[tiab] OR nateglinide[tiab] OR "glyburide"[MeSH] OR Diabeta[tiab] OR glyburide[tiab] OR "glimepiride"[Supplementary Concept]OR Amaryl[tiab] OR glimepiride[tiab] OR "metformin"[MeSH] OR Glumetza[tiab] OR metformin[tiab] OR Riomet[tiab] OR Fortamet[tiab] OR "BI 1356"[Supplementary Concept] OR Tradjenta[tiab] OR linagliptin[tiab] OR "liraglutide"[Supplementary Concept]OR Victoza[tiab] OR liraglutide[tiab] OR "colesevelam"[Supplementary Concept] OR WelChol[tiab] OR colesevelam[tiab] OR "bromocriptine"[MeSH] OR Cycloset[tiab] OR bromocriptine[tiab] OR Parlodel[tiab] OR "Hypoglycemic Agents"[Mesh] OR "Hypoglycemic Agents" [Pharmacological Action]	**189599**
#6	"Diabetes Mellitus/prevention and control"[Mesh] OR “diabetes management”[tiab] OR "Behavior Therapy"[Mesh] OR health education[mesh] OR health promotion[mesh] OR counsel*[tiab] OR counseling[mesh] OR “disease management”[mesh] OR “cognitive behavioral therapy”[tiab] OR “lifestyle modification”[tiab] OR (“life style”[mesh] AND modification[tiab]) OR "Patient Compliance"[Mesh] OR adher*[tiab] OR “self-monitoring”[tiab] OR "Recurrence/prevention and control"[Mesh] OR “relapse prevention”[tiab] OR “skills training”[tiab] OR “motivational interviewing”[tiab] OR educat*[tiab]	**683034**
#7	social support[mesh] OR family[tiab] OR peer[tiab]	**526071**

Set #	Terms	Results
#8	Drug substitution[mesh] OR substitut*[tw] switch[tiab] OR switched[tiab] OR switching[tiab] OR change[tiab] OR changed[tiab] OR changing[tiab] OR replace[tiab] OR replaced[tiab] OR replacing[tiab] OR replacement[tiab] OR abandon*[tiab]	**1089259**
#9	#5 OR #6 OR #7 OR #8	**2309228**
#10	#4 AND #9	**6818**
#11	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT humans[mh]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp])	**1394319**
#12	#10 AND #11, Limits: English	**2116**

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?

Set #	Terms	Results
#1	Schizophrenia[tiab] OR schizophrenia[mesh] OR bipolar disorder[mesh:noexp] OR "bipolar disorder"[tiab] OR “psychotic disorders”[tiab] OR schizoaffective[tiab] OR mania[ti] OR manic[ti] OR "bipolar affective disorder"[tiab] OR "serious mental illness"[tiab] OR “severe mental illness”[tiab] OR “severe psychiatric illness”[tiab] OR (“depressive disorder”[mesh] AND psychotic[tiab]) OR “affective disorders, psychotic”[mesh] OR “psychotic disorders”[mesh]	**146177**
#2	"Dyslipidemias"[Mesh] OR "Hyperlipidemias"[Mesh] OR dyslipidemia[tiab] OR dyslipidemias[tiab] OR hyperlipidemia[tiab] OR hyperlipidemias[tiab]	**70190**

Set #	Terms	Results
#3	chlorpromazine[MeSH] OR chlorpromazine[tw] OR thorazine[tw] OR fluphenazine[MeSH] OR fluphenazine[tw] OR haloperidol[MeSH] OR haloperidol[tw] OR haldol[tw] OR iloperidone[Supplementary Concept] OR iloperidone[tw] OR fanapt[tw] OR loxapine[MeSH] OR loxapine[tw] OR loxitane[tw] OR molindone[MeSH] OR molindone[tw] OR moban[tw] OR chlorpromazine[MeSH] OR chlorpromazine[tw] OR thorazine[tw] OR perphenazine[MeSH] OR perphenazine[tw] OR pimozide[MeSH] OR pimozide[tw] OR orap[tw] OR thioridazine[MeSH] OR thioridazine[tw] OR thiothixene[MeSH] OR thiothixene[tw] OR navane[tw] OR trifluoperazine[MeSH] OR trifluoperazine[tw] OR stelazine[tw] OR clozapine[MeSH] OR clozapine[tw] OR clozaril[tw] OR risperidone[MeSH] OR risperidone[tw] OR risperidal[tw] OR olanzapine[Supplementary Concept] OR olanzapine[tw] OR zyprexa[tw] OR quetiapine[Supplementary Concept] OR quetiapine[tw] OR seroquel[tw] OR ziprasidone[Supplementary Concept] OR ziprasidone[tw] OR geodon[tw] OR aripiprazole[Supplementary Concept] OR aripiprazole[tw] OR abilify[tw] OR 9-hydroxy-risperidone[Supplementary Concept] OR "9-hydroxy-risperidone"[tw] OR paliperidone[tw] OR invega[tw] OR antipsychotic agents[mh] OR antipsychotic agents[pharmacological action] OR antipsychotic[tiab] OR antipsychotics[tiab]	**130495**
#4	#1 AND (#2 OR #3)	**35977**
#5	"Hypolipidemic Agents"[Mesh] OR "Hypolipidemic Agents" [Pharmacological Action] OR "Hydroxymethylglutaryl-CoA Reductase Inhibitors"[Mesh] OR "Hydroxymethylglutaryl-CoA Reductase Inhibitors" [Pharmacological Action] OR statins[tiab] OR statin[tiab] OR "Simvastatin"[Mesh] OR simvastatin[tiab] OR "Lovastatin"[Mesh] OR lovastatin[tiab] OR "atorvastatin" [Supplementary Concept] OR atorvastatin[tiab] OR "Pravastatin"[Mesh] OR pravastatin[tiab] OR "fluvastatin" [Supplementary Concept] OR fluvastatin[tiab] OR "pitavastatin" [Supplementary Concept] OR pitavastatin[tiab] OR "ezetimibe" [Supplementary Concept] OR Ezetimibe[tiab] OR "Niacin"[Mesh] OR niacin[tiab] OR "Fenofibrate"[Mesh] OR fenofibrate[tiab] OR "Fibric Acids"[Mesh] OR "fibric acid"[tiab] OR "fibric acids"[tiab] OR fibrates[tiab] OR fibrate[tiab] OR "Gemfibrozil"[Mesh] OR gemfibrozil[tiab] OR "Colestipol"[Mesh] OR "Cholestyramine Resin"[Mesh] OR Colestipol[tiab] OR Cholestyramine[tiab] OR "colesevelam" [Supplementary Concept] OR colesevelam[tiab]	**102074**
#6	"Nutrition Therapy"[Mesh] OR "Exercise"[Mesh] OR "Exercise Therapy"[Mesh] OR "Exercise Movement Techniques"[Mesh] OR “diet therapy”[mesh] OR exercise[tiab] OR "physical activity"[tiab] OR diet[tiab] OR diets[tiab] OR “weight management”[tiab] OR "Behavior Therapy"[Mesh] OR health education[mesh] OR health promotion[mesh] OR counsel*[tiab] OR counseling[mesh] OR “disease management”[mesh] OR “cognitive behavioral therapy”[tiab] OR “lifestyle modification”[tiab] OR (“life style”[mesh] AND modification[tiab]) OR "Patient Compliance"[Mesh] OR adher*[tiab] OR “self-monitoring”[tiab] OR "Recurrence/prevention and control"[Mesh] OR “relapse prevention”[tiab] OR “skills training”[tiab] OR “motivational interviewing”[tiab] OR educat*[tiab]	**1111731**
#7	social support[mesh] OR family[tiab] OR peer[tiab]	**526071**
#8	Drug substitution[mesh] OR substitut*[tw] switch[tiab] OR switched[tiab] OR switching[tiab] OR change[tiab] OR changed[tiab] OR changing[tiab] OR replace[tiab] OR replaced[tiab] OR replacing[tiab] OR replacement[tiab] OR abandon*[tiab]	**1089259**
#9	#5 OR #6 OR #7 OR #8	**2602062**

Set #	Terms	Results
#10	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT humans[mh]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp])	**1394319**
#11	#4 AND #9 AND #10, Limits: English	**2093**

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?

Set #	Terms	Results
#1	Schizophrenia[tiab] OR schizophrenia[mesh] OR bipolar disorder[mesh:noexp] OR "bipolar disorder"[tiab] OR “psychotic disorders”[tiab] OR schizoaffective[tiab] OR mania[ti] OR manic[ti] OR "bipolar affective disorder"[tiab] OR "serious mental illness"[tiab] OR “severe mental illness”[tiab] OR “severe psychiatric illness”[tiab] OR (“depressive disorder”[mesh] AND psychotic[tiab]) OR “affective disorders, psychotic”[mesh] OR “psychotic disorders”[mesh]	**146177**
#2	"Cardiovascular Diseases"[Mesh] OR "Hyperlipidemias"[Mesh] OR hypertension[tiab] OR ((cardiovascular[tiab] OR heart[tiab] OR coronary[tiab]) AND (disease[tiab] OR diseases[tiab] OR risk[tiab]))	**1879632**
#3	chlorpromazine[MeSH] OR chlorpromazine[tw] OR thorazine[tw] OR fluphenazine[MeSH] OR fluphenazine[tw] OR haloperidol[MeSH] OR haloperidol[tw] OR haldol[tw] OR iloperidone[Supplementary Concept] OR iloperidone[tw] OR fanapt[tw] OR loxapine[MeSH] OR loxapine[tw] OR loxitane[tw] OR molindone[MeSH] OR molindone[tw] OR moban[tw] OR chlorpromazine[MeSH] OR chlorpromazine[tw] OR thorazine[tw] OR perphenazine[MeSH] OR perphenazine[tw] OR pimozide[MeSH] OR pimozide[tw] OR orap[tw] OR thioridazine[MeSH] OR thioridazine[tw] OR thiothixene[MeSH] OR thiothixene[tw] OR navane[tw] OR trifluoperazine[MeSH] OR trifluoperazine[tw] OR stelazine[tw] OR clozapine[MeSH] OR clozapine[tw] OR clozaril[tw] OR risperidone[MeSH] OR risperidone[tw] OR risperidal[tw] OR olanzapine[Supplementary Concept] OR olanzapine[tw] OR zyprexa[tw] OR quetiapine[Supplementary Concept] OR quetiapine[tw] OR seroquel[tw] OR ziprasidone[Supplementary Concept] OR ziprasidone[tw] OR geodon[tw] OR aripiprazole[Supplementary Concept] OR aripiprazole[tw] OR abilify[tw] OR 9-hydroxy-risperidone[Supplementary Concept] OR "9-hydroxy-risperidone"[tw] OR paliperidone[tw] OR invega[tw] OR antipsychotic agents[mh] OR antipsychotic agents[pharmacological action] OR antipsychotic[tiab] OR antipsychotics[tiab]	**130495**
#4	#1 AND (#2 OR #3)	**38686**

Set #	Terms	Results
#5	atorvastatin[Supplementary Concept] OR cholestyramine resin[MeSH] OR colesevelam[Supplementary Concept] colestipol[MeSH] OR ezetimibe[Supplementary Concept] OR fenofibrate[MeSH] OR fluvastatin[Supplementary Concept] OR lovastatin[MeSH] OR pitavastatin[Supplementary Concept] OR pravastatin[MeSH] OR rosuvastatin[Supplementary Concept] OR simvastatin[MeSH] OR acebutolol[Mesh] OR aliskiren[Supplementary Concept] OR amiloride[Mesh] OR amlodipine[Mesh] OR atenolol[Mesh] OR "2-ethoxy-1-((2'-(5-oxo-2,5-dihydro-1,2,4-oxadiazol-3-yl)-biphenyl-4-yl)methyl)-1H-benzimidazole-7-carboxylic acid"[Supplementary Concept] OR benazepril[Supplementary Concept] OR betaxolol[Mesh] OR bisoprolol[Mesh] OR candesartan[Supplementary Concept] OR carvedilol[Supplementary Concept] OR chlorothiazide[Mesh] OR chlorthalidone[Mesh] OR clonidine[Mesh] OR diltiazem[Mesh] OR irbesartan[Supplementary Concept] OR isradipine[Mesh] OR labetalol[Mesh] OR lisinopril[Mesh] OR losartan[Mesh] OR metolazone[Mesh] OR metoprolol[Mesh] OR moexipril[Supplementary Concept] OR nebivolol[Supplementary Concept] OR nicardipine[Mesh] OR nifedipine[Mesh] OR nisoldipine[Mesh] OR olmesartan[Supplementary Concept] OR penbutolol[Mesh] OR perindopril[Mesh] OR pindolol[Mesh] OR prazosin[Mesh] OR propranolol[Mesh] OR quinapril[Supplementary Concept] OR ramipril[Mesh] OR telmisartan[Supplementary Concept] OR torsemide[Supplementary Concept] OR trandolapril[Supplementary Concept] OR valsartan[Supplementary Concept] OR verapamil[Mesh] OR Lipitor[tiab] OR atorvastatin[tiab] OR Caduet[tiab] OR Prevalite[tiab] OR cholestyramine[tiab] OR Questran[tiab] OR WelChol[tiab] OR colesevelam[tiab] OR Colestid[tiab] OR colestipol[tiab] OR Zetia[tiab] OR	**(see next page)**

Set #	Terms	Results
#5 (cont.)	ezetimibe[tiab] OR Tricor[tiab] OR fenofibrate[tiab] OR Lescol[tiab] OR fluvastatin[tiab] OR Mevacor[tiab] OR lovastatin[tiab] OR Livalo[tiab] OR pitavastatin[tiab] OR Pravachol[tiab] OR pravastatin[tiab] OR Crestor[tiab] OR rosuvastatin[tiab] OR Zocor[tiab] OR simvastatin[tiab] OR Sectral[tiab] OR Acebutolol[tiab] OR Tekturna[tiab] OR Aliskiren[tiab] OR Tekamlo[tiab] OR Valturna[tiab] OR Midimor[tiab] OR Amiloride[tiab] OR Norvasc[tiab] OR Amlodipine[tiab] OR Caduet[tiab] OR Lotrel[tiab] OR Tenormin[tiab] OR Atenolol[tiab] OR Tenoretic[tiab] OR Edarbi[tiab] OR Azilsartan[tiab] OR Lotensin[tiab] OR Benazepril[tiab] OR Kerlone[tiab] OR Betaxolol[tiab] OR Zebeta[tiab] OR Bisoprolol[tiab] OR Atacand[tiab] OR Candesartan[tiab] OR Coreg[tiab] OR Carvedilol[tiab] OR Diuril[tiab] OR Chlorothiazide[tiab] OR Thalitone[tiab] OR Chlorthalidone[tiab] OR Clorpres[tiab] OR Catapres[tiab] OR Clonidine[tiab] OR Cardizem[tiab] OR diltiazem[tiab] OR Cartia[tiab] OR Dilacor[tiab] OR Dilt[tiab] OR Diltia[tiab] OR Matzim[tiab] OR Taztia[tiab] OR Tiamate[tiab] OR Tiazac[tiab] OR Avapro[tiab] OR irbesartan[tiab] OR Dynacirc[tiab] OR isradipine[tiab] OR Trandate[tiab] OR labetalol[tiab] OR Prinivil[tiab] OR lisinopril[tiab] OR Zestril[tiab] OR Cozaar[tiab] OR losartan[tiab] OR Zaroxloyn[tiab] OR metolazone[tiab] OR Lopressor[tiab] OR metoprolol[tiab] OR Toprol[tiab] OR Univasc[tiab] OR moexipril[tiab] OR Corgard[tiab] OR nadalol[tiab] OR Bystolic[tiab] OR nebivolol[tiab] OR Cardene[tiab] OR nicardipine[tiab] OR Procardia[tiab] OR nifedipine[tiab] OR Sular[tiab] OR nisoldipine[tiab] OR Benicar[tiab] OR olmesartan[tiab] OR Levitol[tiab] OR penbutolol[tiab] OR Aceon[tiab] OR perindopril[tiab] OR Pindolol[tiab] OR pindolol[tiab] OR Minipress[tiab] OR prazosin[tiab] OR Inderal[tiab] OR propranolol[tiab] OR Accupril[tiab] OR quinapril[tiab] OR Altace[tiab] OR ramipril[tiab] OR Micardis[tiab] OR telmisartan[tiab] OR Demadex[tiab] OR torsemide[tiab] OR Mavik[tiab] OR trandolapril[tiab] OR Diovan[tiab] OR valsartan[tiab] OR Calan[tiab] OR verapamil[tiab] OR Covera[tiab] OR Isoptin[tiab] OR Verelan[tiab] OR "Antihypertensive Agents"[Mesh] OR "Antihypertensive Agents" [Pharmacological Action] OR "Hypolipidemic Agents"[Mesh] OR "Nicotinic Agonists"[Mesh] OR "Nicotinic Agonists" [Pharmacological Action] OR "Cardiovascular Agents"[Mesh] OR "Cardiovascular Agents" [Pharmacological Action] OR "Heparin"[Mesh] OR "Heparin, Low-Molecular-Weight"[Mesh] OR "Warfarin"[Mesh] OR heparin[tiab] OR warfarin[tiab] OR bupropion[tiab] OR "Bupropion"[Mesh]	**1123991**
#6	Smoking cessation[mesh] OR smoking[tiab] OR tobacco[tiab] OR "Nutrition Therapy"[Mesh] OR "Exercise"[Mesh] OR "Exercise Therapy"[Mesh] OR "Exercise Movement Techniques"[Mesh] OR diet therapy[mesh] OR exercise[tiab] OR "physical activity"[tiab] OR diet[tiab] OR diets[tiab] OR "Behavior Therapy"[Mesh] OR health education[mesh] OR health promotion[mesh] OR counsel*[tiab] OR counseling[mesh] OR “disease management”[mesh] OR “cognitive behavioral therapy”[tiab] OR “lifestyle modification”[tiab] OR (“life style”[mesh] AND modification[tiab]) OR "Patient Compliance"[Mesh] OR adher*[tiab] OR “self-monitoring”[tiab] OR "Recurrence/prevention and control"[Mesh] OR “relapse prevention”[tiab] OR “skills training”[tiab] OR “motivational interviewing”[tiab] OR educat*[tiab]	**1239185**
#7	social support[mesh] OR family[tiab] OR peer[tiab]	**526071**
#8	Drug substitution[mesh] OR substitut*[tw] switch[tiab] OR switched[tiab] OR switching[tiab] OR change[tiab] OR changed[tiab] OR changing[tiab] OR replace[tiab] OR replaced[tiab] OR replacing[tiab] OR replacement[tiab] OR abandon*[tiab]	**1089259**
#9	#5 OR #6 OR #7 OR #8	**3591401**

Set #	Terms	Results
#10	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT humans[mh]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp])	**1394319**
#11	#4 AND #9 AND #10, Limits: English	**2466**