Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Interventions To Improve Cardiovascular Risk Factors in People With Serious Mental Illness*

Draft review available for public comment from July 19, 2012, to August 17, 2012.

Research Review Citation: Gierisch JM, Nieuwsma JA, Bradford DW, Wilder CM, Mann-Wrobel MC, McBroom AJ, Wing L, Musty MD, Chobot MM, Hasselblad V, Williams JW Jr. Interventions To Improve Cardiovascular Risk Factors in People With Serious Mental Illness. Comparative Effectiveness Review No. 105. (Prepared by the Duke Evidence-based Practice Center under Contract No. 290-2007-10066-I.) AHRQ Publication No. 13-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. April 2013. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Commentator & Affiliation	Section	Comment	Response
Stephen Hansen, M.D.	Executive Summary	It's mostly about tobacco use prevention/cessation	We agree that tobacco use prevention and cessation is an important factor in reducing CVD in patients with SMI. The results of a recent high-quality systematic review are summarized in the Discussion section. In addition, we have added smoking cessation interventions as a research priority.
National Institute of Mental Health (NIMH)	Executive Summary and Introduction/Scope of the Review	The scope of the report could have been broadened to cover mood and anxiety disorders rather than SMI alone. A review of the broader scientific literature on comorbid depression and CVD, as well as health behavior change, would inform future research on CVD outcomes in SMI. (pp. ES-2–ES-5; pp. 1-5)	Thank you. The NIMH's interest in a broader review is noted and will be communicated to AHRQ.
National Institute of Mental Health (NIMH)	Executive Summary and Introduction/Scope of the Review	The exclusion of studies of interventions for smoking cessation may severely limit the report conclusions, especially because of the high rate of smoking in those with SMI and the frequent use of tobacco by smokers to control weight. NIMH staff suggested noting this exclusion; expanding the rationale for omitting such studies; and discussing the implications for conclusions drawn in the report analyses. (p. ES-2; p. 3)	We have clarified in our Introduction that recent high-quality systematic reviews of smoking cessation have already been completed and, therefore, including this issue would have been redundant.
Peer Reviewer 1	Introduction Page 3, lines 33 and 42	"..individuals with SMI...": state that you mean adults with SMI. It sounds like you are also including children.	This statement has been modified to specify adults.
Peer Reviewer 2	Introduction	Excellent and concise	Thank you.
Peer Reviewer 3	Introduction	Clear and issues well described	Thank you.
Peer Reviewer 4	Introduction	The introduction is clear and describes the risk for cardiovascular disease in those with SMI clearly. Context of care, while important, is not an area of focus and comes up briefly in the discussion in the section on applicability, therefore does not warrant a section in this introduction.	We retained the section on context of care. Even though we did not directly evaluate organizational interventions, care context is important when considering the applicability of the interventions.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 6	Introduction	A good summary of the issues with respect to cardiovascular risk factors. Only major omission is the impact of low socioeconomic status on other determinants of health including poor access to healthy foods and good nutrition, and less access to opportunities for physical exercise (walkable neighborhoods, access to gyms, fitness facilities etc. The impact of smoking (and prevalence) does not seem to be adequately emphasized as a major risk factor. Also, the issue of cardiorespiratory fitness (independent of weight loss) is also something that could be more clearly addressed as both a risk factor and goal.	We added comments on the impact of low socioeconomic status on cardiovascular risk factors. Smoking is not emphasized in this report due to the existence of recent high-quality reviews covering this topic. See response to NIMH comment in General section.
Peer Reviewer 7	Introduction	The introduction is concise yet thorough and clearly written.	Thank you.
TEP Member 1	Introduction	The introduction cites some articles from 10 years ago or review articles that do not involve empirical data. The introduction could benefit from updated citations on prevalence of specific comorbidities in SMI, gaps in quality of care, and health behaviors. Some examples of the more recent literature in these areas are presented below- e.g.,: Kilbourne AM, Morden NE, Austin K, Ilgen M, McCarthy JF, Dalack G, Blow FC. Excess heart-disease-related mortality in a national study of patients with mental disorders: identifying modifiable risk factors. Gen Hosp Psychiatry. 2009 Nov-Dec;31(6):555-63. Epub 2009 Aug 27. Kilbourne AM, Rofey DL, McCarthy JF, Post EP, Welsh D, Blow FC. Nutrition and exercise behavior among patients with bipolar disorder. Bipolar Disord. 2007 Aug;9(5):443-52. Kilbourne AM, Brar JS, Drayer RA, Xu X, Post EP. Cardiovascular disease and metabolic risk factors in male patients with schizophrenia, schizoaffective disorder, and bipolar disorder. Psychosomatics. 2007 Sep-Oct;48(5):412-7.	We have added citations for two studies that were more recent or provided additional key information (Kilbourne 2009 and Kilbourne 2007a).

Commentator & Affiliation	Section	Comment	Response
TEP Member 1	Introduction (continued)	Kilbourne AM, Cornelius JR, Han X, Haas GL, Salloum I, Conigliaro J, Pincus HA. General-medical conditions in older patients with serious mental illness. Am J Geriatr Psychiatry. 2005 Mar;13(3):250-4. Kilbourne AM, Pirraglia PA, Lai Z, Bauer MS, Charns MP, Greenwald D, Welsh DE, McCarthy JF, Yano EM. Quality of general medical care among patients with serious mental illness: does colocation of services matter? Psychiatr Serv. 2011 Aug;62(8):922-8. Kilbourne AM, Welsh D, McCarthy JF, Post EP, Blow FC. Quality of care for cardiovascular disease-related conditions in patients with and without mental disorders. J Gen Intern Med. 2008 Oct;23(10):1628-33. Epub 2008 Jul 15.	(Response goes with cell above.)

Commentator & Affiliation	Section	Comment	Response
TEP Member 2	Introduction	The background usefully reviews the topic of morbidity and mortality in persons with SMI. The analytic framework is well organized and reviews how an intervention study in the population might be associated with improved outcomes, although there isn't anything about how the categories of interventions were chosen or how the framework would lead to be able to identify research gaps. For instance, it is unclear why is peer and family support a separate category --this seems like an issue of who is delivering a particular type of intervention, not a difference in the intervention is being delivered.	The analytic framework is designed to show a simple graphical description of the literature considered and the logic chain. It is not intended to be a conceptual model that would incorporate multiple moderators and contextual factors. We agree that peer intervention may only differ from other types of behavioral interventions by who delivered the content. However, it is not uncommon to classify behavior change approached by interventionist if the context and position of the interventionist is seen as a key element of the intervention approach (e.g., lay health advisors, health care provider-delivered reminders). After consultation with the TEP, we included peer interventions as a separate class of interventions and operationalized this class of interventions as interventions led by peer support specialist/educators who had (or have) a history of SMI. We defined family support interventions as strategies that targeted both the patient and family members. These approaches were seen as conceptually different from other types of behavioral interventions delivered by professional physical or mental health providers.
TEP Member 3	Introduction	The target population and the key questions are both well defined.	Acknowledged
TEP Member 4	Introduction	Well done	Thank you.
TEP Member 5	Introduction	ok	Acknowledged
TEP Member 6	Introduction	Background is succinct and clearly identifies the need for this review. On page ES-1, line 36 you might consider adding the prevalence to "affects about 4 to 8 percent of adults," so readers (especially policymakers) have an idea of impact of the problem.	4-8% refers to the prevalence of SMI in the general population.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 1	Methods	I have 2 methodological criticisms with respect to this report: 1) Authors limited RCTs to those with an n greater of 20. For qualitative analyses this is defensible because very small studies rarely add anything to the strength of evidence. In quantitative analyses, however, this is frowned upon because small studies have little weight in meta-analyses models. I don't think including small studies will change anything but if possible I would go back and include them. 2) I was surprised that you did not include observational studies for the assessment of harms. Rare but serious adverse events are rarely captured by RCTs.	1) We excluded very small studies (n<20) because these studies are often pilots, where blinding and other design features may not be as rigorous as larger, Phase III trials. Further, very small studies are more likely to introduce publication bias and may distort the results of meta-analyses (Nuesch E et al. BMJ 2010;341:c3515). 2) After consultation with the TEP, we excluded observational studies in order to obtain the highest quality evidence on treatment effects. Further, adverse effects of antipsychotic drugs have been thoroughly summarized in existing systematic reviews, which are cited in the discussion (McDonagh et al. 2010; Anonymous 2012). Finally, our results are consistent with studies that have included observational studies.
Peer Reviewer 1	Methods Page 12, Quality Assessment	You need to state how you have handled high risk of bias (poor) studies. Currently it is unclear whether you included/excluded them. For meta-analyses one would expect sensitivity analyses with/without poor studies.	Studies with high risk of bias were included in both qualitative and quantitative analyses. For meta-analyses, we conducted sensitivity analyses (by quality rating) on a limited basis since most empirical studies show no association between study quality and treatment effects in RCTs (Emerson JD et al. Controlled Clin Trials 1990;11:339, Verhagen AP et al. Int J Technol Assess Health Care 2002;18:11 and Juni P et al. JAMA 1999; 282:1054).
Peer Reviewer 2	Methods	My main question re the analysis is the rationale for excluding studies that had improving psychiatric symptoms as a primary outcome. Since psychiatric symptom reduction may be necessary for some individuals to begin to use therapies that can reduce CVD risk, wouldn't it be helpful to look at studies where symptom reduction occured either before or at the same time as CVD risk reduction strategies? At the very least it would be helpful to identify how many studies were excluded because they had psychiatric symptoms as a primary outcome and CVD measures as a secondary outcome.	We excluded studies with interventions that were designed to improve psychiatric outcomes; we did not exclude studies designed to decrease CVD risk, even if the primary outcome was a mental health outcome. The text has been revised to clarify this point.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 3	Methods	Limiting to RCT is unavoidable, given the nature of the report but in such complex issues, RCTs may not answer the question.	Acknowledged; we have addressed the potential for observational studies to address some gaps in evidence in the Research Gaps section of the Discussion.
Peer Reviewer 4	Methods	The methods are solid and well described. The approach is synthetic rather than statistical which is appropriate given the relatively low number of studies.	Acknowledged
Peer Reviewer 5	Methods	Search strategies were stated and logical although I believe several important weight management studies were not included and have been listed below. Articles that were overlooked that should have been included: Jean-Baptiste M, Tek C, et al. A pilot study of a weight management program with food provision in schizophrenia. Schizophr Res.2007;96:198-205. Weber M, Wyne K. A cognitive/behavioral group intervention for weight loss in patients treated with atypical antipsychotics. Schizophr Res.2006;83:95-101. Melamed Y, Stein-Reisner O, et al. Multi-modal weight control intervention for people with persistent mental disorders. Psychiatr Rehabil J.2008;31:194-200. Menza M, Vreeland B, et al. Managing atypical antipsychotic-associated weight gain: 12-month data on a multimodal weight control program. J Clin Psychiatry.2004;65:471-7. Vreeland B, Minsky S, et al. A program for managing weight gain associated with atypical antipsychotics. Psychiatr Serv.2003;54:1155-7.	Each citation has been reviewed and was identified in our search and appropriately excluded as follows: Jean-Baptiste M, Tek C, et al: n<20 Weber M, Wyne K. et al.: n<20 Melamed Y et al.: ineligible setting (long-term psychiatric hospitalization) Menza M et al: not an RCT Vreeland B et al.: not an RCT
Peer Reviewer 6	Methods	The inclusion and exclusion criteria are justifiable.	Acknowledged

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 6	Methods	There are two primary concerns with respect to the methods: 1) KQ 4 is not clearly defined and difficult to fully understand. What is a "multi-condition" lifestyle intervention. What are the multiple conditions? The examples that follow are not of conditions-- but of combinations of interventions (e.g. smoking cessation, physical activity, and nutrition counseling, with or without medication management.) I think that what is intended is "multi-modality" of multi-intervention". OR is the major factor here the combination of a behavioral and a pharmacological intervention. If so, this narrow definition would be useful and highlights a major need in the research literature-- namely-- what do we know about the efficacy of combined behavioral and pharmacological interventions for weight loss in SMI, diabetes, and hyperlipidemia. BUT suggesting that the combination of physical activity and nutrition counseling is eligible for this group is confusing as MOST weight loss interventions consist of this combination. Hence there is confusion about how studies might be sorted into KQ 1 vs. KQ 4	Our research team discussed this recommendation extensively and decided to keep the current structure. The multicondition/multi-intervention studies differ importantly from studies in the other KQs. The multicondition studies have less rigid exclusion criteria, and interventions designed to address more than one condition. We have revised the methods and KQ 4 to make this distinction clearer and provide a better rationale for this grouping.
Peer Reviewer 7	Methods	The methods used are excellent, as would be expected given that they have been developed and refined over many years by AHRQ and used in many other EHR's.	Thank you.
Peer Reviewer 7	Methods, Table 2	On page 32, blood pressure is listed as an intermediate outcome, but besides here I don't see where this outcome was investigated further (e.g., not included in Table 2 or elsewhere).	Blood pressure was not intended as a separate outcome and has been deleted from the analytic framework. Blood pressure outcomes, when reported with other CVD risk factors, were an intended outcome for KQ 4, and the results have been updated with the blood pressure results.

Commentator & Affiliation	Section	Comment	Response
TEP Member 1	Methods	It was unclear why studies with primary psychiatric outcomes were excluded - many behavioral interventions (eg., Druss PCARE) are designed to improve both medical and psychiatric outcome- the distinction seems artificial and may inappropriately exclude studies designed to address both but because of the need for conservative sample size estimates deem their "primary" outcomes as psychiatric	We excluded studies with interventions that were designed to improve psychiatric outcomes; we did not exclude studies designed to decrease CVD risk, even if the primary outcome was a mental health outcome. The text has been revised to clarify this point.
TEP Member 2	Methods	Criteria are clearly stated. In general, the narrow framing of the inclusion population may lead to the potential for "false negatives," cases in which there is relevant evidence that was excluded from the review. For instance, there are a large number of interventions tested in persons with major depression (which is often included in definitions of SMI) that could probably be implemented in persons with other mental illnesses without the need for designing new intervention studies	Consistent with the definition of SMI and stated in the Introduction and Methods sections, we include studies of severe MDD. After consultation with the TEP, we operationalized severe MDD as depression with psychotic features. Our eligibility criteria also allowed for studies that enrolled adults with SMI or severe and persistent mental illness, but did not further provide specific diagnoses. This latter approach would also have included studies that enrolled patients with severe MDD.
TEP Member 3	Methods	Are the inclusion and exclusion criteria justifiable? Yes Are the search strategies explicitly stated and logical? Yes	Acknowledged
TEP Member 4	Methods	The methodologies for defining the target populations, outcomes, inclusion/exclusion of studies and statistical analyses are clearly explained and appropriately applied.	Acknowledged
TEP Member 5	Methods	ok	Acknowledged
TEP Member 6	Methods	Methods are appropriate - search strategies, selection criteria, data extraction, quality rating are explicit and logical. Would re-order the criteria used for quality assessment on page ES-5 (lines 51-57) putting methods of randomization and allocation concealment up front since they are key criteria.	Acknowledged. The methods of randomization and allocation concealment have been moved to the first criteria.
Stephen Hansen, M.D.	Methods	See policy at Smoking Cessation Leadership Center,UCSF	We reviewed the suggested website and agree that it is useful resource.
Peer Reviewer 1	Results	Some sections of the results could use a bit more synthesis. Often you just list findings of studies and make the reader do the work to figure out the overall message is.	The results have been reviewed and revised to better synthesize the findings and summarize the main message.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 1	Results	Throughout the report the use of "control" was confusing. Most of the time, I think, you meant "inactive control", sometimes, however, I was not sure. Please be specific.	The results have been revised to clarify control, distinguishing between inactive controls (e.g. placebo) and usual care
Peer Reviewer 1	Results Page 25, Fig 5	In the text you use the word "control" and it is unclear whether you mean inactive or active control. Also, could the heterogeneity be explained by varying treatment durations?	For behavioral interventions, control conditions consisted of waitlist, no intervention, and usual care plus information. These control group conditions were combined in the meta-analysis, as participants in waitlist and no intervention conditions were allowed to continue receiving usual care. We have clarified this in the text. It is possible that effects varied by duration. For behavioral interventions, we conducted exploratory analysis by treatment intensity, with duration of intervention as a key domain of intensity, and found no significant differences in effects.
Peer Reviewer 1	Results Page 28, line 54	"translates into less THAN 3%.."	We have made this correction.
Peer Reviewer 1	Results Page 32, line 4.	Please add citations of the studies directly to the good/fair/ poor. It is hard to figure out which one is the poor study.	The Results sections have been revised to include citations as requested.
Peer Reviewer 1	Results Page 32, Fig 7	You combine 3 fair or good studies with one poor study. In the text you should also present results of a sensitivity analysis without the poor study.	All meta-analyses have been revised to conduct the requested sensitivity analysis when appropriate. However, we note that a substantial literature suggests that sensitivity analysis by study quality is uninformative.
Peer Reviewer 1	Results Page 35, line 28	What is a mixed efficacy-effectiveness study?	A “mixed efficacy-effectiveness” study was intended to refer to studies assessed to have scores of 3 to 5 on the efficacy-effectiveness scale. The scores corresponding to efficacy, mixed, or effectiveness are defined in Table 8. Based on this comment, we have changed the wording to “…three studies assessed in the mixed range on the efficacy–effectiveness continuum.”

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 1	Results Page 38	Metformin. I think you put too much emphasis on a poor trial (Hoffman). After all, poor means that you have serious doubts about the validity of these results. In addition, you have a fair trial on metformin that provides more reliable results.	Thank you for this comment. Though the Hoffman et al. study was assessed to be of poor quality, the more complex protocol and number of reported results required more text than for some of the other studies. Study elements were consistently reported regardless of study quality. Study quality is taken into account in later strength of evidence determinations.
Peer Reviewer 1	Results Page 43, Fig 8	You combine studies with active (usual care) and inactive (waitlist, no intervention) controls in a meta-analysis which is a bit questionable. You should state why you think this can be done.	We combined these studies because patients assigned to wait list and no intervention continue to get usual medical care
Peer Reviewer 1	Results Page 48, line 57	You state that Stroup et al was a good quality trial. On the next page, however, you report that it had a high attrition and a differential attrition of 20 percentage points. I am not sure if such a study can be considered good quality. I would reconsider the rating.	We reviewed our quality rating for this study and confirmed it meets criteria for a "good" trial. We added the following text to explain our rating: "Despite the high rate of attrition, we rated the study as being of good quality since the authors thoroughly examined and accounted for incomplete data and the study rated highly on many other aspects of quality (e.g., performance bias, detection bias)."
Peer Reviewer 2	Results	Level of detail is appropriate and well-laid out.	Acknowledged
Peer Reviewer 3	Results	Well done	Thank you.
Peer Reviewer 4	Results	The results are clear and comprehensive. This reviewer did not identify any studies that were overlooked in the report. Tables and figures are clear and useful, supplement the text nicely.	Acknowledged
Peer Reviewer 6	Results	Detail is adequate and characteristics of studies and figures generally clear.	Thank you.
Peer Reviewer 6	Results	Not clear is the extent to which the authors carefully reviewed prior systematic reviews/meta-analyses to ensure that all relevant studies are included (though it appears that this was probably done). For example, the number of RCTs included (n=10) for behavioral interventions focused on weight management in SMI appears to be slightly lower than the number in a series of four prior systematic reviews. This might be due to more stringent criteria... but it would be helpful to see a separate list (group of citations) of the systematic reviews that were used to cross check for comprehensiveness.	We cite the articles and systematic reviews examined for relevant studies in the Methods section under literature search strategy. This includes 26 narrative and systematic reviews.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 7	Results	On page 29, in the 1st sentence of the 4th paragraph, '(5-20mg/day)' seems to be a typo.	We deleted this phrase.
TEP Member 1	Results	The results section was well-written	Thank you.
TEP Member 2	Results	Results are clearly reported.	Thank you.
TEP Member 3	Results	Is the amount of detail presented in the results section appropriate? Yes Are the characteristics of the studies clearly described? Yes Are the key messages explicit and applicable? Yes Are figures, tables and appendices adequate and descriptive? Yes	Acknowledged
TEP Member 4	Results	The organization of the result sis well done. The summary narratives with substantial supporting tables and figures are highly reader friendly, permitting readers to quickly gather the main findings and then examining the detailed reults	Acknowledged
TEP Member 5	Results	Why is the CAMP study (Stroup et al. 2011) not included in the switching antipsychotics for weight loss section?	The Stroup study was included in KQ 4 because it used a multicomponent intervention (antipsychotic switching and behavioral intervention) for multiple conditions (multiple metabolic effects).
TEP Member 6	Results	The results are clearly presented in bullet points in the executive summary, but in a few places the text is a bit harder to follow. -There is a disconnect between the bullet points and text for KQ1 on page ES-9. Given that behavioral interventions had moderate SOE, I was expecting to see a bullet point and it isn't there. The bullet points should follow from the meta-analysis first, I would think. The orlistat bullet point should be near the end.	We revised all bullet points to enhance clarity and focus on the key messages of the review.
TEP Member 6	Results	-delete the 2nd "that" on page ES-9, line44 -The last 2 sentences (ES-10, lines 35-38) are confusing. We found just two intervention studies and both used metformin, an FDA-approved drug for treatment of type 2 diabets. These trials found significant advantages for the intervention in..." -ES-10, line 52 is confusing. How about "Meta-analysis of three small, 3- to 12-month..."	We revised this text in the ES to enhance clarity.
TEP Member 6	Results	-I believe a bullet is missing on page ES-11 line 10 for "Switching from oral to injectable.."	The sentence is meant to be part of the same bullet key point and not a separate bullet.

Commentator & Affiliation	Section	Comment	Response
TEP Member 6	Results	-I wonder if shading or color for the cells in Table A might draw attention to the areas where there is enough evidence to rate its overall SOE. They get lost in all the cells were we just don't know anything.	We have added highlights where the evidence is Low or Moderate.
Peer Reviewer 2	Summary/Discussion/Conclusion	Discussion is appropriate and consistent with the review findings with the exception of comment noted above re relationship of psychiatric symptom reduction in relation to CVD risk reduction.	Acknowledged
Peer Reviewer 3	Summary/Discussion/Conclusion	Few implications due to paucity of studies and difficulties in assessing interventions and long term effectiveness	Acknowledged
Peer Reviewer 4	Summary/Discussion/Conclusion	Discussion is good, nicely summarizes present knowledge in this area. All KG's well covered. The future research section (Research Gaps) is rather short given the report generally tells us that the findings of the present research are encouraging but much more work is needed. This section could be expanded, using the findings of the report as a means of providing a roadmap for further inquiry.	The Research Gaps section has been revised and expanded to more fully discuss the research gaps and a process for prioritizing the identified gaps.
Peer Reviewer 5	Summary/Discussion/Conclusion	It would be good to have a section discussing if and how the psychosocial weight programs were tailored for this population. This would be key to understanding why or why not these programs were effective and also would be important for implementing these programs.	We have added details on how behavioral interventions were customized for persons with SMI.
Peer Reviewer 5	Summary/Discussion/Conclusion	It would be good to have a mention of the fact that getting providers to switch medications to one with less weight gain potential is very difficult outside of a study. This implementation issue should be mentioned.	We are unaware of any research that evaluates whether or how willing providers are to switch medications to ones causing less weight gain, therefore it is difficult to comment on this as an implementation issue.
Peer Reviewer 6	Summary/Discussion/Conclusion	1) A major strength of this review is a very good review of pharmacological interventions and the potential implications for clinical care and research. The discussion of the clinical implications and potential areas for future research in behavioral (non-pharmacological) interventions is less well developed and more limited. In general, the report could be better balanced.	The Research Gaps section has been revised and expanded to more fully discuss the research gaps, including consideration of behavioral interventions.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 6	Summary/Discussion/Conclusion	2) As previously stated (see intro comments) there could be more attention to discussing the clinical significance of the findings to date. The authors appropriately state that there are few studies that use aggregate indicators (eg Framingham index) as outcomes to assess if the intervention has had a meaningful impact. At the same time, there are potential benchmarks for clinically meaningful reductions in weight (e.g.) 5% or more of body weight, that could be used to assess the clinical significance of interventions either in aggregate (mean changes) or with respect to proportions (eg the % of subjects in the intervention vs. control achieving a 5% or greater reduction). Similar metrics might be considered for achieving a threshold of glucose or A1c, lipid control or physical fitness.	We have taken the approach of comparing effects achieved in the SMI population with non-SMI populations and with other interventions. For example, we note the 20–40% LDL reduction achieved with statins and the average 1% reduction in A1c achieved with an oral hypoglycemic.
Peer Reviewer 6	Summary/Discussion/Conclusion	3) A major point missed in the discussion is the issue of heterogeneity of outcomes that might be explained by patient level variables vs. intervention efficacy. For example, it may be that the very modest mean outcomes of most of the interventions for obesity (with or without SMI) have to do with a failure to be able to match or individually tailor interventions to different etiological or subtypes --due to a multiplicity of patient level factors--eg genetics, motivation, symptom severity, readiness for change, diagnostic characteristics etc etc. For example, embedded in the primary data of most research in this area are individuals who have been adequately exposed to interventions that have highly significant responses (eg high weight loss) and also individuals who have none, and also those who gain weight despite participation). In brief, there may be a problem with assuming that any single or specific combination of treatments might have a robust mean outcome for all individuals who have a heterogeneous disorder such as "obesity". How do we better match (individually tailor) specific interventions with different subtypes?	Matching/tailoring interventions is a generic issue to most interventions and populations.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 7	Summary/Discussion/ Conclusion	Under Key Points for Key Question 3 (page ES-10, page 40), it is noted that "no studies examined a drug (e.g., HMG CoA reductase inhibitors) or dietary intervention known to be effective for managing dyslipidemia in non-SMI populations". Later on page 58 the following is stated, "Although one would expect standard treatments such as statins to have similar benefits in patients with SMI, potential lower treatment adherence or poorer tolerability of side effects could diminish effectiveness." There are no references provided to support these assertions, and on the contrary, there is a growing literature indicating that individuals with SMI and e.g., Type 2 diabetes exhibit as good as or better adherence to hypoglycemic medications than diabetes patients without SMI (Kreyenbuhl et al., 2011 Psychiatry Research; Kreyenbuhl et al., 2010 Schizophrenia Bulletin). And, why would individuals with SMI be less tolerable of side effects? Regardless, are the authors of the review calling for studies of the efficacy or effectiveness of e.g., statins to be conducted only in SMI populations? Who would fund such a study?	Thank you. There is a growing literature suggesting that adherence to diabetic and hyperlipidemia medication in SMI is qualitatively different from adherence to antipsychotics. Poor adherence to antipsychotic medication is extremely well documented and well recognized in the literature. However, with respect to diabetic, hypertension, hyperlipidemia, nonpsychiatric medications, it seems that individuals with SMI are at least as adherent, or *more* adherent, to these medications than patients without SMI in the general population. We have deleted the sentence suggesting poor adherence may be a problem leading to differential treatment effects in this population.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 7	Summary/Discussion/ Conclusion	Further, it is noted throughout the review that intervention effects on overall CVD risk, CVD events, and mortality in those with SMI were reported rarely in the studies reviewed. First, have studies of the behavioral interventions (in particular) that were the focus of this review but that were conducted in general population samples examined such long term, distal outcomes (e.g., changes in cardiovascular risk/Framingham scores or mortality)? If not, why should studies in individuals with SMI be held to such lofty standards? Second, the types of studies required to examine such effects, in terms of size, duration, resources required to follow people, etc. would require substantial resources that this reviewer doubts will ever be provided by typical (federal) funders. Yet, there are repeated calls in this review for these types of studies. It seems that highlighting the gaps in the evidence and calling for many large RCTs such as in Table 16 needs to be greatly tempered by funding realities. For example, NIMH in particular has wavered numerous times over the years on whether studies examining physical (rather than mental) health outcomes in individuals with mental illnesses/SMI should be within their purview. This is a major barrier to furthering this area of research (i.e., not just that its 'hard' to do these studies in people with SMI).	Our analytic model includes intermediate outcomes (e.g., Framingham CV risk) and final outcomes (e.g., physical function, mortality). This is consistent with a recent report prioritizing patient-centered outcomes for individuals with SMI that called for studies examining health outcomes. We do not think this is a higher standard but, rather, a typical standard for interventions. However, we have expanded the Research Gaps section, adding guidance on prioritizing research and when RCTs or other designs might be appropriate.
TEP Member 1	Summary/Discussion/Conclusion: Pg 57 and Figure 16	Adequate- but on page 57 it says that studies adequately included racial/ethnic minorities but in Table 16 it also says that more studies involving racial/ethnic minorities are needed	We have clarified in the Discussion that racial/ethnic minorities are well represented overall but underrepresented for certain treatment comparisons.
TEP Member 2	Summary/Discussion/Conclusion	As described above, it is not clear that the section prioritizing needs for new research fully follows from the review strategy or conceptual framework.	Our report provides an analytic framework, rather than a more comprehensive conceptual framework. We considered PICOTS as described in our Methods when developing research priorities. These priorities have been reexamined and updated for the final report.
TEP Member 3	Summary/Discussion/Conclusion	Are the implications of the major findings clearly stated? Yes Are the limitations of the review/studies described adequately? Yes Is the future research section clear and easily translated into new research? Yes	Acknowledged

Commentator & Affiliation	Section	Comment	Response
TEP Member 4	Summary/Discussion/Conclusion	A major strength of this report is the identification of the limited nature of existing evidence and the need for future research.	Acknowledged
TEP Member 5	Summary/Discussion/Conclusion	ok	Acknowledged
TEP Member 6	Summary/Discussion/Conclusion	The implications and limitations of the repart are clearly stated.	Thank you.
TEP Member 6	Summary/Discussion/Conclusion	-I would define what you mean by "guideline-concordant care (ES-14, line 8)" when you first use the term. This doesn't happen until the discussion of the USPSTF recommendations.	Guideline-concordant care is a commonly used term to mean care that is consistent with current guidelines for care.
TEP Member 6	Summary/Discussion/Conclusion	-Under applicability, I believe there is a missing "not" in line 17, ES-14. I think it should read "Women, as well as racial minorities, were NOT well represented."	The statement now reads: “Women, as well as racial minorities, were well represented overall but underrepresented for some specific comparisons.”
TEP Member 7	Summary/Discussion/Conclusion	On p. 58, about line 10, there is mention of the potential harms of metformin such as lactic acidosis, however the document does not discuss potential harms of other agents such as topiramate, which commonly is associated with cognitive dulling and which also has been associated with hyperchloremic, non-anionic gap metabolic acidosis (‘Dear Healthcare Professional’ letter from Ortho-McNeil Pharmaceutical Inc, 18 December 2003. Available from URL: http://www.fda.gov). 4.	The general issue, which we have described, is that this literature provides limited evidence about harms. A broader literature in the general population provides a more robust evaluation of harms (e.g., metformin, topiramate). We have drawn on systematic reviews to address harms for drugs with more adverse effects such as antipsychotics, metformin and topiramate.
TEP Member 7	Summary/Discussion/Conclusion	Also on p. 58, towards the end of the 2nd paragraph, it states that “For some medications, interactions with psychotropic medications (e.g., lithium) may limit effectiveness.” It is not clear what this sentence is referring to either in terms of the general principle or the specific example of lithium.	The sentence was intended to illustrate the general principle. We have modified the example to improve clarity.

Commentator & Affiliation	Section	Comment	Response
TEP Member 7	Summary/Discussion/Conclusion	At the bottom of p. 58, the document discusses recommendations for cardiovascular risk screening and followup. Available screening guidelines do a good job of advising about risk screening in the general population and in suggesting an initial screening for individuals who are already taking a second generation antipsychotic. To my knowledge, however, they are less informative about lipid monitoring in the context of antipsychotic initiation and followup. For example, a psychiatrist sees a new patient. If the patient's age is less than the recommended ages for routine lipid screening, should lipids be done if antipsychotic treatment is planned? If lipid screening tests are done and lipid levels are currently normal, at what time points should lipid testing be repeated if antipsychotic treatment is begun? If normal after 3 months of treatment, should they be repeated every year? every 5 years? If a higher lipid level is found, do the LDL targets differ for individuals on a second generation antipsychotic independent of the other reasons for using a lower LDL target (e.g., CHD, CHD risk equivalents).	The ADA/APA guidelines (Diabetes Care 2004;27:596) do make recommendations regarding some of the specific situations described. For example, a fasting lipid panel is recommended for all patients initiating an antipsychotic medication at baselines, at 3-month followup, and then annually.
TEP Member 7	Summary/Discussion/Conclusion	In terms of the evidence gaps (pp. 60-61), several have been alluded to in the comments above. Another specific gap is determining whether the weight-loss associated medications must be continued indefinitely to maintain the weight loss. An additional question is whether the weight loss properties of these drugs are associated with particular side effects (e.g., nausea) or seem to relate to a general appetite suppressing property. There are certainly many other gaps in our knowledge of this important problem.	We have modified one gap to include better reporting of adverse events and added an additional research priority to identify the characteristics of successful interventions, including dose and duration.

Commentator & Affiliation	Section	Comment	Response
NIMH	Summary/Discussion/Conclusion	Regarding the following quote: "Surprisingly few studies addressed one or more cardiovascular risk factors in patients with SMI and most studies were skewed towards efficacy trials…Comparative effectiveness studies are needed to test multimodal strategies, agents known to be effective in non-SMI populations, and antipsychotic-management strategies." (pp. 61-62) NIMH staff noted that a major reason for the lack of health outcomes data in people with SMI is that mental illness has long been an exclusion criterion in clinical trials focused on other health conditions such as CVD and diabetes. It appears that the report does not address the exclusion of people with SMI from such clinical trials.	Good point. We have added this issue to the Discussion.
Peer Reviewer 1	General: Quality of the Report	Good	Acknowledged
Peer Reviewer 1	General	This is a well written and well structured report. Congratulations to the authors, the report is an important contribution.	Thank you.
Peer Reviewer 1	General	I was surprised that the key questions do not mention risk of harms. The authors clearly assessed harms in the report, the first impression that someone reading the KQs would get, however, would be that the focus is just on effectiveness.	Not all outcomes are explicitly listed in the KQs; however, adverse effects and other outcomes are explicitly listed in Methods and the analytic framework figure.
Peer Reviewer 1	General: Clarity/Usability	Key points could be a bit crisper and more to the point. Often you talk about the number of studies that you found regarding a particular outcome but you don't summarize the main message. I also think it would be informative for readers if you stated the strength of evidence in your key points.	All key points and results have been reviewed and revised where needed to emphasize the main message. We have presented the SOE rating with the key point when relevant.
Peer Reviewer 2	General: Quality of the Report	Superior	Thank you.
Peer Reviewer 2	General	The report is clinically meaningful and will inform and guide clinicians in treatment planning. Researchers will appreciate the careful summary and will find the report to be very helpful in better understanding where the gaps in science exist.	Acknowledged
Peer Reviewer 2	General: Clarity/Usability	Clarity and usability are excellent. I believe this has the potential to be a widely read and often-cited paper.	Thank you.
Peer Reviewer 3	General: Quality of the Report	Superior	Thank you.
Peer Reviewer 3	General	Well done, clinically meaningful. paucity of relevant studies	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 3	General: Clarity/Usability	I have little comment regarding this review. Cardiovascular risk is a complex construct with many interacting variables. and it is difficult to draw conclusions regaring overall risk while isolating individual risk factors. It may well be that, in this population, specific combinations of risk factors may be more important than in other populations. The bottom line in the conclusions is cannot be overemphasized. We have every reason to believe that interventions that are effective in the general population are also effective in the population suffering from SMI. Success in these interventions is more difficult due to the effects of the illness on behavior as well as the medications necessary to control symptoms. We know of no substitute for provision of necessary healthcare services, including behavioral approaches to reduce risk, such as smoking cessation, weight control, diet and exercise. It may well be that, as the authors suggest, the most promising studies in the future will be those that enhance the receipt of holistic primary care preventive services, whether through integrated care programs or enhanced coordination of care.	Acknowledged
Peer Reviewer 4	General: Quality of the Report	Good	Acknowledged
Peer Reviewer 4	General	This is a comprehensive review of a still emerging area of interest on a well defined population at increased cardiovascular risk. The report is definitely clinically relevant. The key questions are appropriate and explicit. Given the relatively limited number of studies, the report's utility to the reader is actually more with respect to what more needs to be done rather than provide clarity as to present clinical care.	Acknowledged
Peer Reviewer 4	General: Clarity/Usability	The report is well structured and organized. As stated above, the utility of the report seems to be mainly in giving direction to future research.	Acknowledged
Peer Reviewer 5	General: Quality of the Report	Good	Acknowledged
Peer Reviewer 5	General	This review has clinical relevance as cardiovascular risk has become a major concern in serious mental illness. Key questions are explicitly stated and target population is defined.	Acknowledged

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 5	General: Clarity/Usability	Policy and practice decisions (that is, implementing the findings) would be helped by the comments made regarding the discussion section.	Acknowledged
Peer Reviewer 6	General: Quality of the Report	Good	Thank you.
Peer Reviewer 6	General	The target population is explicitly defined-- though the definition of serious mental illness (SMI) does not fully coincide with that generally used. Most applications of this definition describe SMI as consisting of schizophrenia, schizoaffective disorder, bipolar disorder and major depression with persistent impairment in multiple areas of functioning. This review substitutes "major depression with psychotic features" for "major depression with persistent impairment in multiple areas of functioning." It should be acknowledged that this distinction is not a major concern-- yet some of the studies reviewed likely include major depression within mixed samples-- though it is entirely appropriate to exclude studies that exclusively focus on major depression.	Our definition of SMI is consistent with those definitions most commonly used in the literature. The inclusion and exclusion criteria we used are clearly defined in the introduction and methods. In the discussion section, we note that our operational definition (MDD with psychosis) was necessary since there was no practical method to search specifically for MDD with persistent impairment in multiple areas of functioning (as described in most definitions of SMI).
Peer Reviewer 6	General	The definition of the target population also states "but not substance abuse or developmental disorders" This should more clearly be followed with the qualifier "as the primary diagnosis". Almost half of persons with SMI have a secondary dx of substance use disorder at some time in the course of the illness.	We modified this definition to clarify that SMI does not include individuals who only have a substance abuse disorder.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 6	General: Clarity/Usability	Instead, I would suggest that the review a) Be explicitly titled: "Pharmacological and Combined Pharmacological and Behavioral Strategies to Improve Cardiovascular Risk Factors in People with Serious Mental Illness" b) Consider explicitly focusing the methods and questions on this focus making the KQs on Pharmacological and Combined Pharmacological and behavioral interventions for weight management, diabetes, and lipid control c) Eliminate the confusing category of "multiconditon and wrap relevant studies into the other sections d) Add a KQ specifically of pharmacological and combined pharmacological and behavioral interventions for smoking cessation	a) We have revised the title to “Pharmacological and Behavioral Interventions to Improve Cardiovascular Risk Factors in People with Serious Mental Illness.” b) The research questions were developed in collaboration with stakeholders during a topic development process and address the recommended content areas. c) Our research team discussed this recommendation extensively and decided to keep the current structure. The multicondition/multi-intervention studies differ importantly from studies in the other KQs. The multicondition studies have less rigid exclusion criteria and interventions designed to address more than one condition. We have revised KQ 4 to make this distinction clearer and provide a better rationale for this grouping. d) Smoking interventions were not considered in this review. The Introduction and Discussion give the rationale; that is, a recent high-quality review already summarized this literature.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 6	General: Clarity/Usability	e) briefly summarize (in the discussion) the take home conclusions from other reviews on health promotion/health behavior change interventions and refer the reader to these much more extensive and detailed reviews. These include the following: 1. Bartels SJ, Desilets R. Health Promotion Programs for Persons with Serious Mental Illness (Prepared by the Dartmouth Health Promotion Research Team for SAMHSA-HRSA Center for Integrated Health Solutions, Washington DC). 2012. http://www.integration.samhsa.gov/health-wellness/wellnesswhitepaper. 2. Happell B, Davies C, Scott D. Health behaviour interventions to improve physical health in individuals diagnosed with a mental illness: A systematic review. International Journal of Mental Health Nursing. 2012;21(3):236-247. 3. Verhaeghe N, De Maeseneer J, Maes L, Van Heeringen C, Annemans L. Effectiveness and cost-effectiveness of lifestyle interventions on physical activity and eating habits in persons with severe mental disorders: A systematic review. Int J Behav Nutr Phys Act. 2011;8:28. 4. Cabassa LJ, Ezell JM, Lewis-Fernandez R. Lifestyle interventions for adults with serious mental illness: a systematic literature review. Psychiatr Serv. Aug 2010;61(8):774-782. 5. Alvarez-Jimenez M, Hetrick SE, Gonzalez-Blanch C, Gleeson JF, McGorry PD. Non-pharmacological management of antipsychotic-induced weight gain: systematic review and meta-analysis of randomised controlled trials. Br J Psychiatry. Aug 2008;193(2):101-107.	Thank you. All listed citations were reviewed. Of these, five were cited in the draft report. We have added to the Discussion the two new reviews (Bartels 2012, Happell 2012) that were published after our literature search. We also note that, although the methods of these reviews and number of eligible studies vary substantially, the key findings are consistent.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 6	General: Clarity/Usability (continued)	6. Lowe T, Lubos E. Effectiveness of weight management interventions for people with serious mental illness who receive treatment with atypical antipsychotic medications. A literature review. J Psychiatr Ment Health Nurs. Dec 2008;15(10):857-863. 7. Faulkner G, Cohn T, Remington G. Interventions to reduce weight gain in schizophrenia. Cochrane Database Syst Rev. 2007(1):CD005148. 8. Loh C, Meyer JM, Leckband SG. A comprehensive review of behavioral interventions for weight management in schizophrenia. Ann Clin Psychiatry. Jan-Mar 2006;18(1):23-31.	(Response goes with cell above.)
Peer Reviewer 7	General: Quality of Report	Superior	Thank you.
Peer Reviewer 7	General	Overall, I think this is a worthwhile topic of investigation for an Effective Healthcare Review, given the substantial cardiovascular disease-related morbidity and mortality in individuals with SMI. The target population (SMI) was clearly defined and the rationale for including the disorders that were considered to be serious mental illnesses was supported by the literature. The key questions were appropriate and clearly/explicitly stated.	Acknowledged
Peer Reviewer 7	General	In the abstract (and elsewhere), I would be careful using the more general term 'anti-seizure medications' when discussing the two agents that have been investigated for weight loss (topiramate, zonisamide) in individuals with SMI, as there are other anti-seizure medications (e.g., valproate) that are associated with significant amounts of weight gain in this population.	We have revised the document to emphasize the specific drugs evaluated within classes, paying particular attention to anticonvulsants, antipsychotics, and neurologic agents.
Peer Reviewer 7	General: Clarity/Usability	The report is very clearly written and well organized. The main points are clearly presented. Given the paucity of research in the area reviewed, it is unclear how much the results of the review will be able to inform policy and/or practice decisions (but that is not the fault of the authors).	Acknowledged
TEP Member 1	General: Quality of the report	Quality of the Report: Good	Thank you.
TEP Member 1	General	This was a very thorough review of the literature and it covered both pharmacotherapy and behavioral therapies.	Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP Member 1	General: Clarity/Usability	In recommending future research, it would be helpful to discuss why specific strategies for SMI are need-especially with behavioral interventions. What is unique about SMI that precludes evidence-based programs such as the Diabetes Prevention Program from benefitting this group? What is the likelihood that the available evidence-based programs can be sustainable for persons with SMI who may have limited access to general medical services?	This issue was addressed in the Introduction section titled "Current Treatment Approaches," and we briefly refer to potential barriers to effective interventions in the Discussion section called "Research Gaps."
TEP Member 2	General: Quality of the Report	Quality of the Report: Good	Thank you.
TEP Member 2	General	This manuscript reviews 33 studies of differing approaches to address cardiovascular risk factors in persons with serious mental illness. Overall the review is well-written and organized. The main concern is the section around priorities for future research, which does not appear to follow clearly from the conceptual framework or study findings. Addressing this more complicated issue would require more consideration about the larger pool of studies available about this topic in the general literature, and issues of generalizability. For instance: Do all types of interventions shown effective in general medical populations need to be replicated in populations with SMI? If not, then what are the priority areas and why? If an intervention is shown to be effective in patients with one diagnosis (e.g. schizophrenia or depression) then is it necessary to also test its effectiveness in patients with other diagnoses? If particular approaches (e.g. behavioral interventions, medications) are shown to be effective, then why (or in what cases) is it important to test multimodal interventions that combine two or more? Addressing these questions may go beyond the scope of the review; if so, the review might focus to a greater extent on what was found (which seems to be the focus of K1-K4) than on recommendations for further research (e.g. the final sentence of the abstract, conclusions section of the text).	This report uses an analytic framework rather than a conceptual framework. Analytic frameworks are not intended to represent a comprehensive model of the factors that may affect outcomes. However, the Research Gaps section was revised to provide a general framework for prioritizing research and to identify when existing research in general populations may not be generalizable to the SMI population.
TEP Member 2	General: Clarity/Usability	Report is well written and well organized.	Thank you.
TEP Member 3	General: Quality of the Report	Good	Acknowledged

Commentator & Affiliation	Section	Comment	Response
TEP Member 3	General	The reports greatest value is the clear case it makes to fund futher clinical trials.	Acknowledged
TEP Member 3	General: Clarity/Usability	Is the report well structured and organized? Yes Are the main points clearly presented? Yes Can the conclusions be used to inform policy? Yes The following statement might appear subjective "Recruitment and retention is an important issue for all trials and may be particularly challenging in patients with SMI. Symptoms of mental illness and effects on cognition along with substantial rates may make it difficult for patients with SMI to fully participate in planned interventions." at the same time documenting that there are few opportunities for the SMI population to participate in comparative effectiveness studies.	Acknowledged Thank you. The Research Gaps section has been revised extensively to describe a framework for prioritizing research, some of the barriers to participation, and issues of particular relevance to the SMI population.
TEP Member 4	General: Quality of the Report	Superior	Thank you.
TEP Member 4	General	The report addresses a highly significant public health problem among persons with serious mental illnesses. The purpose of the report and the key questions are clear and important.	Acknowledged
TEP Member 4	General: Clarity/Usability	Excellent	Thank you.
TEP Member 5	General: Quality of the Report	Good	Thank you.
TEP Member 5	General	Nice job overall. Yes to all these questions.	Thank you.
TEP Member 5	General	The first- vs. second-generation antipsychotic distinction is not valid and should be purged from the document.	The distinction between first- and second-generation antipsychotics is used throughout the literature we reviewed; therefore, we elected to maintain this terminology in our review.
TEP Member 5	General	More than once the document complains that authors did not report a global measure of risk such as the Framingham risk score. This sounds reasonable but are short-term changes in this valid?	Thank you. This is an interesting point. Composite measures such as these have certainly been used as outcome measures in cardiovascular trials. Further, changes in risk (even short-term) may drive clinical decisionmaking. For example, a 52-year-old man who smokes and has mild hypertension and moderate cholesterol values would decrease 10-year CVD risk by >50% with a 10-point improvement in systolic blood pressure together with smoking cessation.
TEP Member 5	General: Clarity/Usability	ok	Acknowledged
TEP Member 6	General: Quality of Report	Good	Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP Member 6	General: Clarity/Usability	The ES is clear and can be used to inform practice and policy, given the lack of evidence. I found the laundry list of areas that need study useful as a catalog of what needs to be done, but I wondered if the authors might prioritize this list in the text. As a funder or policymaker, I would want to know where should I put money first to have the best chance at having an impact on care for a very difficult and disadvantaged population.	The Research Gaps section has been revised and expanded. Although it is beyond the scope of this report to explicitly prioritize the research gaps, we present a general framework to help policymakers complete their own prioritization.
TEP Member 7	General	Overall, this is an impressive document that is well-written and that a rigorous, well defined systematic review methodology.	Thank you.
TEP Member 7	General	As a practicing psychiatrist, I didn't find much in the way of "take-home" messages from the review that would help me improve my management of individuals with metabolic syndrome or weight issues in the context of serious mental illness. Perhaps this is the job of guideline developers but the way that the findings are summarized, makes it hard to draw clinical inferences from the review. As one example, the structured abstract (p. iv.) notes "Compared with controls, behavioral interventions (mean difference [MD] -3.13 kg; 95% CI, -4.21 to -2.05), antiseizure medications (MD -5.11kg; 95% CI, -9.48 to -0.74), adjunctive or antipsychotic switching to aripiprazole, and metformin improved weight control. However, aripiprazole-switching may be associated with higher rates of treatment failure."	The key points have been revised for clarity and clinically actionable information when possible.

Commentator & Affiliation	Section	Comment	Response
TEP Member 7	General	Given the clear heterogeneity in the types of interventions that were studied, I found the description of the findings to be unclear and potentially misleading. For example, in stating that antiseizure medications are beneficial, a reader may (erroneously) infer that this is a drug class effect when topiramate and zonisamide were the only agents studied. In addition, in looking at the later tables and discussion, I had a hard time figuring out what the actual benefits were for topiramate vs. zonisamide. It would be clearer to list the specific interventions that showed benefits or no change rather than lumping multiple diverse interventions into a single category. As another example, atomoxetine, ramelteon, and fluoxetine are quite different in their indications and pharmacology though they are grouped together here as psychotropics. Amantadine seems to be listed as a psychotropic in some sections and a neurological drug in others, yet it can also be used as an antiviral agent. Discussing it in terms of any specific drug class rather than simply using the name amantadine	We have revised the key points, results, and SOE table to emphasize the specific drugs evaluated within classes. We also reviewed the document to ensure consistency in how drugs were classified. We acknowledge that some drugs are not readily classified or could be classified in more than one category.
TEP Member 7	General	It would also be useful to know that typical starting weights of the patients in the studies. Particularly in a short term study, individuals who have a greater initial weight often show a more sizeable initial weight drop (e.g., with calorie restriction) due to the greater number of calories/day needed to support a large body mass. Thus, a fairly small weight loss in a morbidly obese individual may have a different implication that the same weight loss in a mildly overweight individual in terms of health benefits or quality of life.	We revised the results for all KQs to add the baseline values for the outcome of interest per intervention approach.

Commentator & Affiliation	Section	Comment	Response
TEP Member 7	General	The above sentence also seems to equate adjunctive use of aripiprazole with switching to aripiprazole. Clinically, an increasing number of individuals are receiving more than one antipsychotic medication with no clear evidence of benefits for efficacy in symptom control. Use of two antipsychotics also has the potential for increasing side effects, drug interactions and cost. It would be important to include the comparable weight loss statistics for adjunctive aripiprazole, switching to aripiprazole and metformin so that the reader can compare these options to the behavioral interventions and to topiramate and zonisamide. (These additional details are also needed in other parts of the document such as the last paragraph of page ES-9.)	The results and strength of evidence tables have been revised to clearly distinguish between switching and adjunctive use.
TEP Member 7	General	It is not clear why the term “anti-seizure” is used throughout the document rather than “anticonvulsant”	Although both terms are acceptable (according to our pharmacologist), we have used anticonvulsant throughout the document.
TEP Member 7	General	On p. ES-9, about line 15, the following sentence seemed unclear “However, there were few studies of antiseizure agents with small samples sizes.” This may be better phrased as “There were only a few studies of antiseizure agents and available studies had small sample sizes.”	We have revised the Key Points, including this sentence.
TEP Member 7	General	On p. E-14, about line 16, it says that minorities and women were well represented but elsewhere in the document it says that the majority of subjects were middleaged white males and that there are few studies of ethnic and racial minorities (p. 60). These statements seem contradictory.	We revised the discussion to clarify that minorities and women were well represented overall but underrepresented for some specific comparisons.
National Institute of Mental Health (NIMH)	General	This report addresses an important component of the health concerns facing individuals with SMI: cardiovascular risk. Overall, NIMH staff found the report to be well organized and well written but had comments about specific elements of the report.	Acknowledged

Comments received after reviewer response deadline—not addressed above

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 6	Methods	2) Where do studies that specifically focus only on smoking cessation fit in? Are these all encompassed under KQ 4? Or did the authors only include studies that were "multicondition" interventions? As smoking (by itself) is highly prevalent and an important cardiovascular risk factor, the report should have had a specific subanalysis (KQ) of smoking cessation interventions in SMI	We appreciate this comment. Unfortunately as it was received after the reviewer response deadline, the time constraints of the final stages of report production precluded expanding our revisions to address it.
Peer Reviewer 6	Summary/Discussion/Conclusion	4) There are a myriad of issues that could be addressed in the discussion of the health promotion research literature that are not addressed but covered in other systematic reviews (see below)	We appreciate this comment. Unfortunately as it was received after the reviewer response deadline, the time constraints of the final stages of report production precluded expanding our revisions to address it.
TEP Member 6	Summary/Discussion/Conclusion	-Adding in the discuss about integrating mental health and primary care is important but as written feels a bit out of place. One way to better tie this in would be to use the USPSTF comments (and the fact that they guide primary care clinicians) as the tie in. I'm not sure statements about the medical home are accurate. The literature may be behind what is happening with federal and state policy for the ACA. The discussion now is on how to implement "health homes" were mental health and social services are integrated into the medical home.	We appreciate this comment. Unfortunately as it was received after the reviewer response deadline, the time constraints of the final stages of report production precluded expanding our revisions to address it.

Commentator & Affiliation	Section	Comment	Response
TEP Member 7	Summary/Discussion/Conclusion	On p. 59, the document gives a pragmatic suggestion for a greater role for psychiatrists in screening and monitoring of measures such as weight and blood pressure and a potentially increase role in statin therapy. This does seem like a potential way to enhance delivery of needed screening and interventions to reduce the risk of cardiovascular disease among those with serious mental illness. On the other hand, many psychiatric settings are not currently configured to do such assessments as part of the workflow. For example, office-based psychiatrists in private practice would rarely have nursing staff who could take such measurements. In terms of prescribing statins, this would currently fall outside of the scope of a psychiatrists' specialty training from a medicolegal standpoint. As a result, it will not always be possible or appropriate for psychiatrists to take on these added primary care functions.	We appreciate this comment. Unfortunately as it was received after the reviewer response deadline, the time constraints of the final stages of report production precluded expanding our revisions to address it.
TEP Member 7	Summary/Discussion/Conclusion	Another item that may be worth considering in the discussion is that using an additional medication that affords a statistically significant but fairly minor weight loss (e.g., topiramate) also carries added financial costs (of the drug) and an added risk of drugdrug interactions (with one or more additional medications that the patient is taking). These risks are hard to quantify and may not be apparent from measures of side effects or treatment dropout but can be clinically important.	We appreciate this comment. Unfortunately as it was received after the reviewer response deadline, the time constraints of the final stages of report production precluded expanding our revisions to address it.
Peer Reviewer 6	General	The report is clinically meaningful-- though it misses the opportunity to definitively anchor the interpretation of results (e.g. weight loss) in the context of clinical significance-- generally accepted as 5% or more of body weight.	We appreciate this comment. Unfortunately as it was received after the reviewer response deadline, the time constraints of the final stages of report production precluded expanding our revisions to address it.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 6	General: Clarity/Usability	1) This is an excellent review of pharmacological and combined pharmacological and behavioral interventions for weight loss, diabetes, and hyperlipidemia. This focus is well represented and can be used to inform policy, practice and research. 2) However- it is less in depth and detailed in addressing smoking cessation-- this should be improved (particularly with respect to pharmacological and combined pharmacological/behavioral interventions and given its own KQ.	We appreciate this comment. Unfortunately as it was received after the reviewer response deadline, the time constraints of the final stages of report production precluded expanding our revisions to address it.
Peer Reviewer 6	General: Clarity/Usability	3) The health promotion/behavioral intervention component and review is superficial and unbalanced with respect to the pharmacological. I would suggest that this could be addressed by highlighting and identifying the focus and strength of this review, and not attempting to be overly ambitious and comprehensive.	We appreciate this comment. Unfortunately as it was received after the reviewer response deadline, the time constraints of the final stages of report production precluded expanding our revisions to address it.
TEP Member 6	General	The report is clinically meaningful, but the results are disappointing in that there are so few studies addressing CV risk factors in individuals with SMI. The KQ are appropriate and explicit.	We appreciate this comment. Unfortunately as it was received after the reviewer response deadline, the time constraints of the final stages of report production precluded expanding our revisions to address it.
TEP Member 7	General	In presenting the results, it is often clinically useful to know the patient's weight change when expressed in terms of the proportion of body mass as well as knowing the absolute amount of weight lost (as noted here). Many of the studies that have looked at cardiovascular and metabolic benefits of weight loss have analyzed the data in terms of percent of body mass so this may allow different inferences to be made about potential benefits of the intervention in an individual patient.	We appreciate this comment. Unfortunately as it was received after the reviewer response deadline, the time constraints of the final stages of report production precluded expanding our revisions to address it.

Commentator & Affiliation	Section	Comment	Response
TEP Member 7	General	In the detailed discussion of the studies, it would be useful to have a clearer impression of the approach used when making the switch from another antipsychotic to aripiprazole and to specify in the abstract what the switch entailed and the way in which it was achieved. (Switching from a drug such as olanzapine or clozapine that has a high weight gain risk would seem much more likely to lead to benefits than switching to aripiprazole from other agents. Switching rapidly with no cross-taper would seem more likely to lead to symptom relapse than switching more slowly with a cross-taper.)	We appreciate this comment. Unfortunately as it was received after the reviewer response deadline, the time constraints of the final stages of report production precluded expanding our revisions to address it.