



Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: Treatments for Schizophrenia in Adults: A Systematic Review

Draft review available for public comment from February 9, 2017 to March 8, 2017.

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Comments to Research Review

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Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

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.



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Executive Summary	I see that the authors considered other options but "ability to maintain treatment" is an awkward locution that seems to make treatments actors. Other options: duration of treatment, time on treatment, retention in treatment, time to treatment discontinuation.	Yes, we agree. We have decided to return to the most commonly used terminology in the literature, which is "treatment discontinuation."
Peer Reviewer #3	Executive Summary	On p. ES-9, Perphenazine was not inferior to olanzapine on the primary outcome of the CATIE trial (ref 146). If this is about some other outcome then that outcome should be specified.	Thank you for pointing this out. The full text of the report does a better job of describing these findings, and we have made the Executive Summary more consistent with that text.
Peer Reviewer #3	Executive Summary	Table C. A table organized according to the treatments studied would be preferred to one organized by outcome (or would be a nice addition).	Yes, determining the best way to display the evidence is complex and depends not only on the evidence itself, but also the reader's context. We have added tables that present the findings on outcomes for specific comparisons, which may be helpful.
Peer Reviewer #3	Executive Summary	On p. ES-15 the following statement seems inconsistent with the cited previous work: "Our findings on FGAs versus SGAs are entirely consistent with the pre-existing review: for most outcomes the SGAs are superior to the FGAs." The authors of the previous report concluded there were few meaningful differences: "In summary, data on the comparative effectiveness of individual FGAs and SGAs precluded drawing firm conclusions for outcomes that are directly relevant to front-line clinical decisions. Overall, there were few significant differences of clinical importance. Outcomes potentially important to patients were rarely assessed. Finally, data on long-term safety are lacking and urgently needed."	We appreciate this comment and agree that this was an oversimplification of the findings. We have revised these conclusions to better reflect the nuances in the findings—that it mainly focused on haloperidol, with few differences for other outcomes.
TEP Reviewer #2	Executive Summary	p. 11 line 11 - see above in terms of use of the phrase "mental health illness"	Thank you for this comment. We have taken your advice and modified this sentence.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Executive Summary	p. 11 line 20 -- I'd suggest either eliminating this sentence or making it less detailed. For example "Ongoing research is attempting to define risk factors for schizophrenia and possible mechanisms of treatment but the underlying basis of this disorder is not yet clear and means of prevention remain lacking." As written, I think it overstates our knowledge of some of the risks and focuses on neurocognitive aspects rather than other aspects of the disorder.	Thank you for this comment. We have taken your advice and modified this sentence.
TEP Reviewer #2	Executive Summary	p. 11 line 24 -- the phrases "affective psychosis" and "substance abuse" are outmoded, at least in terms of DSM wording. Would suggest rewording "The differential diagnosis is broad and includes mood disorders (bipolar disorder or major depressive disorder) with psychotic features and substance/medication-induced psychotic disorder."	Thank you for this comment. We have taken your advice and modified this sentence.
TEP Reviewer #2	Executive Summary	p. 11 line 26 -- It may be preferable to emphasize the importance of both approaches without giving extra weight to antipsychotics. For example, "Antipsychotic medication and non-pharmacological treatments are typically used together when treating individuals with schizophrenia. Each approach can result in meaningful improvements...."	Thank you for this comment. We have taken your advice and modified this sentence.
TEP Reviewer #2	Executive Summary	p. 11 line 33 -- Throughout the text, search for "substance abuse" and "substance dependence" and make appropriate substitutions to be consistent with DSM-5, if possible. Here, for example, it would be appropriate to say "co-occurring substance use" whereas in other portions of the text the phrase "substance use disorder" may be more appropriate.	Thank you for pointing this out. We have corrected the text.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Executive Summary	<p>"p. 11 line 36 -- I'm not sure that the poor prognosis necessarily follows from the lack of understanding; I think the first part of the sentence can be deleted. There is some debate, especially in the recovery focused literature, about the actual prognosis. It may be preferable to phrase this in terms of the data or variability of outcomes rather than using the specific phrase ""prognosis remains poor"".</p> <p>Relevant text from DSM-5 notes: The predictors of course and outcome are largely unexplained, and course and outcome may not be reliably predicted. The course appears to be favorable in about 20% of those with schizophrenia, and a small number of individuals are reported to recover completely. However, most individuals with schizophrenia still require formal or informal daily living supports, and many remain chronically ill, with exacerbations and remissions of active symptoms, while others have a course of progressive deterioration.... Schizophrenia is associated with significant social and occupational dysfunction.""</p> <p>Consider adding info on course/prognosis right after line 25, for example ""The course of schizophrenia varies but the majority of individuals will experience some degree of social and occupational difficulty and chronic illness is common."" "</p>	Thank you for this comment. In consultation with our team's content experts, we have revised this section of the report.
TEP Reviewer #2	Executive Summary	p. 11 line 44 -- there was also the hope of improving negative symptoms.	Thank you for this comment. We have taken your advice and modified this sentence.
TEP Reviewer #2	Executive Summary	p. 11 line 48 -- the comment about the need for consistent definitions and valid ascertainment seems out of place since the rest of the information on the page and in the paragraph relates to clinical aspects rather than aspects of study design. Would suggest moving these latter two items to a new sentence at the end of the paragraph. For example, "The evidence base also needs to be strengthened by the use of consistent definitions and valid ascertainment methods when designing and conducting research."	This is a good point, and we have moved the mention of definitions and validity to later in the text as suggested.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Executive Summary	p. 16 line 41 lurasidone is misspelled	Thank you for pointing this out. We have corrected the text.
TEP Reviewer #2	Executive Summary	p. 17 line 19 -- suggest moving "for core illness symptom improvement" from this line to the preceding line just after the word "other". Sentence is a bit confusing as written.	Thank you. We have modified this sentence as suggested.
TEP Reviewer #2	Executive Summary	p. 17 line 44 ff Is there a way to split up this sentence into two or more parts? For example, put a period after "(moderate strength evidence)" and then say "Low strength evidence also suggests no difference in the overall risk of adverse events for quetiapine ER versus...."	Thank you for this comment. We have taken your advice and modified the sentence as suggested.
TEP Reviewer #2	Executive Summary	p. 18 line 17 -- I believe the FDA training materials now refers to this as severe neutropenia rather than agranulocytosis although clinicians will still know it as the latter. Nonetheless, it may be appropriate to include both terminologies.	Thank you for this comment. We have taken your advice and modified this sentence.
TEP Reviewer #2	Executive Summary	p. 18 line 20 -- the prior page said there wasn't enough data on remission. Double check this sentence for accuracy. Also, the sentence is somewhat confusing due to its length and multiple modifying phrases. Consider splitting it up into 2 or more sentences.	Thank you for noting this—the statement about remission not being reported should have indicated that there was evidence in the subgroup of studies of patients with first-episode schizophrenia, but that this was not consistently reported in other studies.
TEP Reviewer #2	Executive Summary	p. 22 line 47 There is a word missing here. Also, the bullet in the right column is not aligned correctly.	Thank you for pointing this out. We have corrected the text.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Executive Summary	<p>p. 25 lines 25 ff The first part of the first paragraph is a little confusing although I understand what's being said. Would suggest rephrasing as follows:</p> <p>With regard to drug therapy, the findings of our review are generally consistent with prior systematic reviews that make comparisons among the SGAs and between SGAs and FGAs.6-11 Although we incorporated the most relevant of these systematic reviews in our report, our findings differ to some extent from previous reviews because we consider outcomes prioritized by technical experts, incorporate newer evidence and the most recently approved drugs, and include three updated network meta-analyses.</p>	Thank you for this comment. We have taken your advice and modified this sentence.
TEP Reviewer #2	Executive Summary	p. 25 line 34 throughout the document, the word "while" is used when the word "whereas" is preferable. At other places in the document, "while" is used at the beginning of sentences when the word "Although" would be preferable. If the document is not being copyedited before publication, consider searching/replacing as appropriate.	Thank you for pointing this out. We have revised the text as appropriate.
TEP Reviewer #2	Executive Summary	p. 19 line 35 -- here and elsewhere in the document the phrase "not different to" is used, which sounds odd. Suggest changing to "not different from" throughout the document. Also note that in some places (e.g., Table A), the phrase that is used is "not found different to" which should be replaced with "not different from".	Thank you for pointing this out. We have corrected the text.
TEP Reviewer #2	Executive Summary	p. 20 line 43 -- the difference between global function (for example in line 38) and scale-assessed global function is not immediately apparent. These wording differences (and apparent distinctions) are also mentioned elsewhere in the document and require clarification throughout.	Thank you for this comment; we have addressed this throughout the report. There are instances where the scale assesses functional skill or has not been validated, but in general we did not mean to imply a meaningful difference in the terms.
TEP Reviewer #2	Executive Summary	p. 25 line 49 Suggest changing to "A single comprehensive review is available and serves as the basis of our report, with nine new trials included."	Thank you for this comment. We have taken your advice and modified this sentence.
TEP Reviewer #2	Executive Summary	p. 27 line 44 suggest change to "Reflect real-life practice by using a minimum study duration of..."	Thank you for this comment. We have taken your advice and modified this sentence.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Executive Summary	p. 27 line 48 Suggest change to "Enroll subjects who reflect..."	Thank you for this comment. We have taken your advice and modified this sentence.
TEP Reviewer #2	Executive Summary	p. 27 line 51 -- It seems fairly clear that no additional studies are needed of haloperidol as compared to newer medications but it's not clear to me that additional studies of other FGAs (e.g., perphenazine) would not be useful. The negative health effects of the most effective SGAs (olanzapine, clozapine, risperidone) are considerable in terms of metabolic syndrome, weight gain, diabetes, etc. The social consequences of obesity are also considerable. Although the FGAs also had some weight gain liability, it does not seem to be as significant as with the SGAs. I don't think we know enough about treatment resistant illness in the modern era to know whether individuals who don't respond to multiple SGAs are now more likely to respond to an FGA (due to a possibly different mechanism).	Yes, we agree with this comment and were overly inclusive in the previous statement in an effort to be succinct in the summary. We have modified the text to reflect the evidence on haloperidol, and not the other two drugs as much. The discussion of weight gain implications has been modified to reflect the uncertainty noted here.
TEP Reviewer #2	Executive Summary	p. 28 line 14 Suggest change to "Interventions should be clearly defined and categorized before new trials are conducted."	Thank you for this comment. We have taken your advice and modified these sentences.
TEP Reviewer #2	Executive Summary	p. 28 line 17 Suggest change to the following: Additional well-designed long-term studies are needed because most individuals with chronic psychotic illnesses such as schizophrenia require lifetime engagement with mental health services to have good outcomes. The long-term benefits versus costs and risks of treatments for these illnesses remain unclear, particular for individuals whose illnesses are resistant or only partially responsive to treatment.	Thank you for this comment. We have taken your advice and modified these sentences.
TEP Reviewer #2	Executive Summary	p. 28 line 34 See prior comment. Would help to clarify that this is primarily because the studies haven't been done.	We agree, and we have added this to the discussion here.
TEP Reviewer #2	Executive Summary	p. 28 line 35 olanzapine is spelled incorrectly	Thank you for pointing this out. We have corrected the text.



Public Reviewer #6: American Psychological Association Task Force on Serious Mental Illness/ Severe Emotional Disturbance, Mary A. Jansen	Introduction	<p>First, I appreciate the Agency's attention to this important health disorder. In order to assist those with serious mental illnesses, knowledge of reliable treatments and their recommendations are critical. As a reviewer, I also recognize the difficulty of conducting a review such as this one. However, despite the resources that must have gone into this effort, it is unfortunate that this Research Review does not meet the high standard needed to produce a quality and useful product. Instead this Research Review does a dis-service to AHRQ, the many researchers in this field, treating professionals, and most importantly, individuals with this and similar disorders and their families who could benefit from a competent review of the research. The authors of this Research Review do not appear to have the background knowledge of much of the work that has been done in this area and, in my opinion have either failed to consider or have excluded from consideration, many of the most important and well conducted studies and reviews produced over the past decades. The rules for rating the characteristics and quality of the literature seem to have been determined by individuals who do not know the literature well and appear to not understand the multiple variables that impact on the conduct of research in the field. This apparent lack of knowledge and understanding has resulted in an arbitrary set of rules that excluded some of the best conducted studies and RCTs resulting in conclusions that are erroneous, have the potential to erode confidence in AHRQ and reverse the very positive treatment advances made over the past two decades. Detailed comments are contained in the attached document. [Attachment A below]</p>	<p>We appreciate the reviewer taking time to comment in depth on our review. We have undertaken work to clarify and take a more granular look at some of the clinical issues noted in further comments (Attachment A), including analysis of older reviews that came to differing conclusions. Our review team included clinicians with expertise in schizophrenia (two psychologists and one psychiatrist) and those with expertise in the methodology and practice of conducting high quality systematic reviews and outcomes research methodology. In addition, the scope of this work was guided by a group of key informants and a technical expert panel (see report for details). In order to apply the consistency of a systematic review framework within budgetary and time limitations to the numerous and diverse interventions, the review scope was focused in a few specific ways. These were: limiting to studies in outpatient and U.S.-relevant settings (to make the findings more applicable to typical ambulatory treatment in the U.S.), requiring at least 12 weeks follow up (to allow time for meaningful changes in outcomes), and for psychosocial interventions, studies needed to have at least 50 patients (to avoid spurious findings), and have a comparison with usual care.</p>
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Commentator & Affiliation	Section	Comment	Response
Public Reviewer #12: Mental Illness Policy Org, DJ Jaffe	Introduction	The report fails to incorporate the extensive evidence that outpatient commitment (AOT) is an effective treatment. The AHRQ 2015 Report, "Management Strategies to Reduce Psychiatric Hospitalizations" was clear on this point. Citation: Gaynes BN, Brown C, Lux LJ, Ashok M, Coker-Schwimmer E, Hoffman V, Sheitman B, Viswanathan M. Management Strategies To Reduce Psychiatric Readmissions. Technical Brief No. 21. (Prepared by the RTI-UNC Evidence-based Practice Center under Contract No. 290-2012-00008-I.) AHRQ Publication No.15-EHC018-EF. Rockville, MD: Agency for Healthcare Research and Quality. May 2015. www.effectivehealthcare.ahrq.gov/reports/final.cfm . (See http://effectivehealthcare.ahrq.gov/ehc/products/596/2082/psychiatric-readmissions-report-150521.pdf).	We appreciate these comments and the reference on outpatient commitment therapy. We identified the included psychosocial and other non-drug interventions through consultation with a group of key informants, including a patient representative, and a technical expert panel. We also posted our protocol on the AHRQ website and the PROSPERO systematic review registry. This treatment was not selected to be included in this review, not because it was deemed unimportant, but because our clinical expert advisors felt these were mechanisms to get patients into treatment, rather than a treatment themselves.
Peer Reviewer #1	Introduction	Page 6 of PDF: Results. The sentence beginning with "Clozapine is superior to other older SGAs..." is missing something as it is unclear which medications improved core illness symptoms. (lines 37-38) Lines 46-47- Does the statement about benefits apply to all treatments or just the psychosocial/ non pharm most recently summarized?	We have improved the clarity of this text.



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Introduction	Page 20 of PDF: Key Question 2 Would be helpful to have definition of "usual care."	Yes, while the specific care received by patients as usual care in individual studies was not reported, we have some description of the potential treatments, as they were reported in the studies or reviews. We have added discussion of issues related to usual care controls to the discussion and future research sections of the report.
Peer Reviewer #2	Introduction	The introduction is not especially informative, but does not contain significant errors.	Noted; see our responses to specific comments.
Peer Reviewer #2	Introduction	The specific questions raised for the scope of the review are reasonable.	Thank you for taking the time to review our report. We appreciate your feedback.
Peer Reviewer #3	Introduction	I do not quite follow the distinction between "ability to maintain treatment" and "all-cause treatment discontinuation". If these are different then it would be good to explain.	We agree that the terms are similar and have revised the text for Key Question 1 to refer to treatment discontinuation.
Peer Reviewer #4	Introduction	Abstract is well synthesized and contains key information from the review.	Thank you for taking the time to review our report. We appreciate your feedback.
Peer Reviewer #4	Introduction	Would consider rewording sentence starting with word "Clozapine on line 34 of page 6 (per top page number) to increase clarity around which drugs are associated with improvement in which outcome.	Please see the revisions made to the text to improve clarity.
Peer Reviewer #4	Introduction	Appreciate list of "older SGAs."	Thank you for taking the time to review our report. We appreciate your feedback.
Peer Reviewer #4	Introduction	Consider adding a brief list of newer SGAs to increase clarity of conclusion statement on line 53 of page 6.	Please see the revised text.
Peer Reviewer #4	Introduction	Olanzapine is misspelled on line 35 of page 28.	This typo has been corrected.



Commentator & Affiliation	Section	Comment	Response
Public Reviewer #19: Team Daniel Running For Recovery From Mental Illness, Robert Laitman	Introduction	Robert Laitman 3:50pm Mar 4 Once again I am very underwhelmed. I found the report to be a hodgepodge of incomplete information citing poorly done and often industry influenced studies. Schizophrenia is such a spectrum of illnesses and the course of treatment varies tremendously with the duration of untreated psychosis. The study that needs to be done is Optimal clozapine plus RAISE vs RAISE. Sorry but I found this report of little value.	Thank you for taking the time to comment. We appreciate the suggestion for future research. We note that the issue of industry funding, for the pharmaceutical studies, is mentioned in the Limitations of the Evidence Base section of the report – over 80% of the drug studies had some form of support from the manufacturer of one of the drugs being studied.
TEP Reviewer #2	Introduction	The introduction is appropriate and gives a brief overview of the importance of the topic, the public health implications of schizophrenia and its impact on families and individuals. (See also detailed comments for suggestions on wording and phrasing.)	Thank you for taking the time to review our report. We appreciate your feedback.
TEP Reviewer #2	Introduction	p. 32 Throughout this section, please refer to my comments on the parallel sections in the earlier portion of the document. I am not repeating each of those comments below.	We have addressed these comments and suggestions throughout the report.
TEP Reviewer #2	Introduction	p. 32 line 36 suggest changing "effective" to "acting" since we don't really know why these drugs work	Thank you for this comment. We have taken your advice and modified this sentence.
TEP Reviewer #2	Introduction	p. 32 line 49 This sentence is somewhat confusing. May be able to split this into 2 sentences and make it seem less convoluted. I don't think that symptom reduction is actually of unclear clinical relevance -- plenty of patients are very bothered by hallucinations and/or delusions and actively want to reduce them -- but the changes in the magnitude of these symptoms is fairly small in many clinical studies, albeit statistically significant.	Thank you for this comment. We did not intend to say that symptom improvement is not clinically relevant per se; we meant to say that small differences between drugs in changes in symptoms, while often statistically significant, often have little or unclear clinical importance. We have revised this section.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Introduction	<p>p. 32 line 55 Suggest change to:</p> <p>""Historically, the wide array of antipsychotic drug treatments has had a mixed impact on long-term outcomes, such as the ability to have consistent employment, engage in successful interpersonal relationships, and maintain independent living. Serious concerns exist about adverse effects....""</p>	Thank you for this comment. We have taken your advice and modified this sentence.
TEP Reviewer #2	Introduction	<p>p. 33 line 27 Suggest changing "differ from" to "require a different approach than"</p>	Thank you for this suggestion. Please see the revised text.
TEP Reviewer #2	Introduction	<p>p. 33 line 30-37 These sentences seem as if they could be worded better. For example, it's not clear what's meant by aggressive treatment early in the disease -- is this initiating treatment when symptoms are first noted to reduce the duration of untreated psychosis or is this treating with a multi-component approach or something else. Presumably in the second half of the sentence, "aggressive" is referring to high doses. In the next sentence, the phrase "in these patients" (line 34) presumably refers to any patient with co-occurring substance use disorder not just those with onset of use early on. It's not clear why the metabolic effects are of concern only in middle-age and older patients and it's not clear if the statement is referring to metabolic syndrome per se or to drug metabolism (e.g., with reduced creatinine clearance with age or renal impairment from other causes). Finally, it's not clear if the metabolic effects due to disease are implying that these effects are due to schizophrenia per se or to other disease processes.</p>	Thank you for this comment. We were meaning to discuss the relationship between both age and comorbidities (that increase with age, typically) and decisions around specific treatments, particularly adverse effects. In consultation with our team's content experts, we have revised this section of the report.
TEP Reviewer #2	Introduction	<p>p. 32 line 49 This sentence is somewhat confusing. May be able to split this into 2 sentences and make it seem less convoluted. I don't think that symptom reduction is actually of unclear clinical relevance -- plenty of patients are very bothered by hallucinations and/or delusions and actively want to reduce them -- but the changes in the magnitude of these symptoms is fairly small in many clinical studies, albeit statistically significant.</p>	Thank you for this comment. We did not intend to say that symptom improvement is not clinically relevant per se, we meant to say that small differences between drugs in changes in symptoms, while often statistically significant, often have little or unclear clinical importance. We have revised this section.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Introduction	p. 33 line 39 Similar to the comment just above, this sentence seems a bit unclear. Older patients in general have increased mortality just because they are older, but it's not clear if this is intending to refer to the shortened lifespan of individuals with schizophrenia noted in the sentence on epidemiologic findings or if it's referring to the data on mortality with antipsychotics in individuals with dementia (though it's not clear whether that data is relevant to those with non-dementia diagnoses). The info on a need for possible changes in antipsychotic dosing would seem to fit better with information on changes in drug metabolism with age.	Thank you for this comment. We were meaning to discuss the relationship between both age and comorbidities (that increase with age, typically) and decisions around specific treatments, particularly adverse effects. In consultation with our team content experts, we have revised this section of the report.
TEP Reviewer #2	Introduction	p. 33 line 55 suggest changing to read "the review scope has been limited to the most commonly used"	Thank you for this suggestion. Please see the revised text.
TEP Reviewer #2	Introduction	p. 34 line 4 The phrase "one-off" is used here and elsewhere in the document. I'm not sure what it's trying to signify. I suspect that investigators whose intervention was mentioned in this context might be miffed but beyond that I wonder if there is a different way to phrase this that would be clearer to readers.	We appreciate the concern that using this phrase may undermine the value of these interventions. We have changed the wording to "unique," to better indicate that these were interventions with a single study, where it was certain to result in a strength of evidence rating of insufficient.
TEP Reviewer #2	Introduction	p. 34 line 6 Suggest splitting sentence in two and start the second sentence with the word "Unlike.." On line 8, there is a word missing "are limited to in order to..."	Thank you for this suggestion. Please see the revised text.
TEP Reviewer #2	Introduction	p. 34 line 9 Suggest changing to "we limited the outcomes that are included in this review in two ways. Rehospitalization" Can probably delete the phrase "it is considered a flawed outcome measure" as the subsequent info is self-explanatory.	Thank you for this suggestion. Please see the revised text.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Introduction	<p>p. 34 line 12 Suggest rewording as follows:</p> <p>1) there is important variation in the indications for and length of psychiatric hospitalizations across time, in different localities and with different financial contexts, and 2) there is important variation across trials in how rehospitalization is measured/evaluated, which may confound study interpretation. Changes in neurocognitive test results were viewed as an intermediate outcome and are excluded. Instead, we have prioritized measures of functioning that include neurocognition as part of a broader patient-centered health outcome.</p>	Thank you for this suggestion. Please see the revised text.
TEP Reviewer #2	Introduction	<p>p. 35 line 48 Change population specific to diagnosis-specific</p>	Thank you for this suggestion. Please see the revised text.
TEP Reviewer #3	Introduction	<p>ES line 37: Here and again in the Introduction (line 48) there is a sentence stating that 80% of patients continue to require “social support” throughout their lives, and that “prognosis remains poor.” It is not clear where this fact comes from or what “social support” means. I find this overly pessimistic and in general the document does little to instill hope about available treatments.</p>	We appreciate the need for clarity here and have revised the introduction.
TEP Reviewer #3	Introduction	<p>The language throughout the review is surprisingly not very recovery-oriented, especially given the SAMSHA focus on disseminating the recovery model and principles of recovery. For example, there is outdated use of terms like “illness management” and focus on maintenance rather than discussing treatment options to promote recovery (or “functional recovery”).</p>	We appreciate the need for introducing and having more emphasis on recovery and have revised the introduction.
TEP Reviewer #3	Introduction	<p>The selection of several functioning outcomes for the review is focused on functional recovery more than prior reviews, which typically focused more on symptom management or remission, but the review does not include much recovery language which comes in large part from SAMSHA itself.</p>	The list of included outcomes was developed with input from a Key Informant group, and further refined and prioritized with input from the Technical Expert Panel. We included response, remission, and functional improvement outcomes.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #4	Introduction	The structured abstract (page vi) is unclear as to the results for clozapine. In the Results section, the sentence, “Clozapine is superior to other older SGAs in reducing the risk of suicide outcomes, olanzapine and risperidone had better symptom response rates than quetiapine, clozapine, olanzapine, risperidone and paliperidone ER improved core illness symptoms more than other older SGAs, and risperidone LAI and olanzapine had less withdrawal due to adverse events” is hard to understand, and would be clearer if broken into two or three sentences. As it is, it seems to be saying that olanzapine and risperidone had “better symptom response rates” than clozapine. But in the following Conclusions section (repeated on page ES-18), it is stated that “clozapine, olanzapine, and risperidone oral and LAI had superiority on more outcomes than other SGAs.”	Please see the revised abstract.
Peer Reviewer #1	Methods	Yes.	Thank you for taking the time to review our report. We appreciate your feedback.



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Methods	The inclusion/exclusion criteria are not reasonable. Ruling out studies with active comparators is a particular problem.	The decision to focus Key Question 2 on comparisons with usual care was made as part of a set of decisions required to reduce the scope of the project. After identifying a large body of evidence for Key Question 2, we determined that the available funding and timeline required a reduction in scope. We first decided to use systematic reviews as the primary evidence, with subsequently published trials included as well. In examining those, we saw that most reviews mixed active and attention controls, and even usual care sometimes. Many, however, reviewed usual care comparisons separately, or exclusively. Therefore, within the systematic reviews, usual care was the most commonly reported comparison group. In the end, we included well over 200 studies of the 12 psychosocial interventions that made comparisons to usual care.
Peer Reviewer #2	Methods	Diagnostic criteria for selection of studies (> 90% for pharmacological; > 50% for psychosocial treatments) are reasonable.	Thank you for taking the time to review our report. We appreciate your feedback.
Peer Reviewer #2	Methods	Sample size of N > 50 may be unnecessarily limited.	Only a small number of studies were excluded for this reason (N = 17).
Peer Reviewer #2	Methods	Inattention to targets of specific studies is problematic, and results in combining effect sizes for outcomes that were targeted in some studies, but not others, resulting in underestimation of effect sizes.	We agree that targets of an intervention are important, and have added notation of targets where they were reported.



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Methods	There is a fundamental flaw in the literature and in this review that, if corrected, would be extremely valuable in this important report. Leucht et al have demonstrated and argued that the FGA vs. SGA distinction is of questionable validity, confusing and should not be perpetuated. There is considerable evidence of great heterogeneity in both of these groups with regard to pharmacology, efficacy, and adverse effects. The fact that haloperidol accounts for almost all of the data reviewed and therefore counts for an entire "class" is troubling.	We agree that the categorization of the antipsychotic drugs into generations may be artificial and too confining. We are maintaining this structure because this is how much of the literature is published, and the two reviews we included were organized in this way. However, we have clarified that the bulk of the comparisons were with haloperidol, and that the findings apply mainly to this drug.
Peer Reviewer #4	Methods	Methodology for review is appropriate. Level of description of methodology is fantastic both in summary and in full. Inclusion and exclusion criteria are both reasonable and justifiable. Search strategies are well defined and appropriate. No recommendations for change. Outcome measures (including diagnostic criteria) are appropriate. Patient characteristics are well defined and reasonable. Statistical methods are commendable. Population applicability for each Key Question is well defined. SOE definitions were reasonable. Key outcomes are well organized.	Thank you for taking the time to review our report. We appreciate your feedback.
TEP Reviewer #2	Methods	The methods are rigorous, the statistical methods and outcome measures are appropriate and the search strategies are explicit and logical. The inclusion and exclusion criteria are justifiable. Where decisions have been made to restrict the scope of the review, they seem reasonable and strike a balance between the work effort required and the amount of additional information that would be gained.	Thank you for taking the time to review our report. We appreciate your feedback.
TEP Reviewer #2	General	p. 6 line 53 -- It may be worth pointing out that there is a paucity of head-to-head trials with the newer SGAs that makes it hard to determine whether they are associated with differences on any outcomes. As worded, the text could imply that studies were available and that the newer SGAs weren't superior.	Yes, this is true and we added notation of this to the text.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Methods	p. 37 line 11 It's not clear why ClinicalTrials.gov wouldn't be relevant for medication trials as well.	Yes, the Drug Effectiveness Review Project report on second generation antipsychotics that we included searched ClinicalTrials.gov already, so we did not need to search it again. We clarified the text on this.
TEP Reviewer #2	Methods	p. 37 line 25 suggest change from population-specific to diagnosis-specific	Thank you for this suggestion. Please see the revised text.
TEP Reviewer #2	Methods	p. 37 line 49 It's not clear why Zyprexa Zydys wasn't mentioned here -- I assume it's an oversight since the other oral dissolving formulations are noted.	Thank you for catching this error. We have corrected it.
TEP Reviewer #2	Methods	p. 39 line 18 ff See prior suggestions on wording	Thank you for the suggestions. Please see the revised text.
TEP Reviewer #2	Methods	p. 40 line 49 Suggest specifically mentioning funding source as noted above.	Thank you for this suggestion. Please see the revised text.
TEP Reviewer #2	Methods	p. 41 Other AHRQ reviews that we've used for prior guidelines have focused on (and reported) studies as having high, medium and low risk of bias. Here, the focus is on study quality which has an inverse relationship with risk of bias. Since both terms are being used in the title of the section and since the methods guide refers to "assessing risk of bias", it may be worth noting these distinctions explicitly and editing the last sentence of the 1st paragraph to note that the terms good and a poor are referring to study quality.	We have added some additional details to this paragraph to explain the relationship between study quality and study risk of bias ratings, both of which are acceptable under the AHRQ methods guidance.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Methods	As described in the Results box (d), the findings for this review contrast with many others. The contrasting findings for this review might be due to the very high number of studies excluded in the psychosocial interventions review. For psychosocial studies, 2,686 references were reviewed, and only 43 were included (1.6%). The entire review for 14 psychosocial interventions is based on only 43 articles. The vast majority of the literature, therefore, was excluded for this review, especially if one considers the few studies reviewed per each psychosocial intervention. It is not clear why so many reviews and RCTs were excluded. Most guidelines and other reviews are based on much more of the available data. What can be concluded from only a few studies per each intervention?	Due to a high volume of literature available on psychosocial interventions, we included systematic reviews when possible and supplemented these with randomized controlled trials published subsequent to the reviews' search dates. When there were no systematic reviews available, we included all trials meeting inclusion criteria. Among the publications included for psychosocial interventions, 13 were systematic reviews that included 271 studies of over 20,000 patients. To this we added another 27 trials. Please see Tables 1 through 4 for more details. We also clarified the numbers of trials included in the systematic reviews in the literature flow diagram figures.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #4	Methods	<p>The Methods are carefully described and seem quite reasonable. Two comments: (1) I wonder whether "sedation" should be considered a major adverse effect worthy of individual consideration. In particular, two SGAs (quetiapine and olanzapine) are often preferentially prescribed specifically to benefit from their strong sedating properties, while some patients have difficulty tolerating them if the sedation is too strong. (2) A strength of the Methods is the use of the ClinicalTrials.gov Web site to identify nonpharmacological intervention studies that have been completed but not yet published; wouldn't that same logic apply to pharmacotherapy trials? Related to that, and to the larger issue that most of the cited published literature deals with studies funded by pharmaceutical company sponsors, is there a change over time in the completeness of the available literature? That is, are manufacturers now required to be more "transparent" about their funded trials, for example posting them on ClinicalTrials.gov or related sites, as opposed to the traditional "selective publication" of only positive trials of their own products?</p>	<p>Sedation is likely an important outcome, however, it was not specifically called out or prioritized during our scoping processes with our experts. In addition, we were limited by the systematic reviews we used and what they reported on sedation, which was very limited. With regard to searching ClinicalTrials.gov for evidence on drug treatments, our draft text was unclear. The Drug Effectiveness Review Project report that we included on second generation antipsychotics had already searched this database, so we did not need to search it again. This is a standard part of our searches for drug treatments, due to the FDA requirements for registering studies in ClinicalTrials.gov; while only NIH funded studies of psychosocial interventions are required to register (although anyone can register a study). We wanted to note that we had gone the extra mile and searched it for nonpharmacological treatments as well. We clarified the text on this.</p>



<p>Public Reviewer #12: Mental Illness Policy Org, DJ Jaffe</p>	<p>Results</p>	<p>In May, 2015, the Agency for Healthcare Research and Quality (AHRQ), located within HHS, released Management Strategies to Reduce Psychiatric Hospitalizations focused on reducing readmission and Length of Stay (LOS) in psychiatric hospitals for adults over 18 with two or more previous psychiatric hospital admissions or who were at high risk of readmission.FN 1 The report evaluated Assisted Outpatient Treatment (AOT), referred to as Outpatient Commitment (OPC) and Compulsory Community Treatment Orders (CTOs). They often lumped them together. The report showed AOT to be an effective treatment. EXCERPTS OPC [AOT], as it is known in the United States, and CTO, as it is known in the United Kingdom, Canada, New Zealand, and Australia, are based on the principle that people with severe mental disorders who are at risk of becoming dangerous or gravely disabled without treatment and reluctant or unable to follow through with community-based treatment, can be required to engage in outpatient treatment as the less restrictive long-term approach for reducing inpatient rehospitalization. The literature implies that some individuals may need involuntary treatment to prevent readmission because of the high prevalence of anosognosia (i.e., lack of insight as part of the disease process) with severe and persistent mental illness.(71,72) OPC laws in the US require a judge s order, supported by clinician input, and generally do not allow patients to be given medications forcibly. CTOs can often be implemented by a clinician, without the need for court involvement, and in some countries, such as Australia and Canada, the administration of intramuscular forced medication is allowed. STUDIES Eighteen studies assessed its effectiveness 10 were labeled as an OPC(67,72,84,88,98,100,112,113,116,117) and 8 (in 11 articles) were labeled CTOs. (66,69-71,74,108 ,114,115,120-122) Of the 18 studies, 3 were RCTs,(66,72,117) 3 (reported in 6 articles) were a retrospective cohort design,(74,84,114,115, 120-122) 3 were a case control design,(69,71,100) and 9 were pre-post testing of the same group.(67,70,88,98,108,112-114,116) OPC/CTO was generally designed to target individuals with serious mental illness (as opposed to the general psychiatric population) and, accordingly, is most frequently used for patients with primary psychotic disorders. This approach is supported by data that OPC/CTOs may be most effective for individuals with nonaffective psychoses(72) and/or individuals without insight or with severe functional impairment.67 RESULTS After being placed under an OPC, patients experienced</p>	<p>Thank you for the summary of this work. These interventions were not included in our review because we were focusing on the most common psychosocial and non-pharmacological interventions used in US practices. In addition, our team’s clinical experts felt that these programs are a mechanism to get patients into treatment, rather than a treatment in and of themselves. We have screened the suggested reference for studies that might be eligible for our review, and have added a notation of this evidence in our discussion of the limitations of our review.</p>
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		<p>reductions in numbers of readmissions,(67,98,108,112-114,116) readmission rates,(70,114) and LOS.67,108,112 ,113,114,116) One study was able to demonstrate that involuntary outpatient commitment decreased homelessness during the 4-month period following hospital discharge for participants with severe functional impairment at baseline.(73) Another study reported that patients with extended OPC/CTO and a prior history of multiple hospitalizations and prior arrests/violent behavior (180 days) had a lower probability of arrest than before OPC/CTO(.86) In yet another study, patients receiving OPC/CTO and long-acting injectables demonstrated a higher adherence rate and lower readmission rate than patients receiving OPC/CTO and oral medications.(74) Because the comparison group did not experience the same effect, the authors suggested that OPC/CTO may be particularly advantageous when combined with long-acting injectable medications.(74) Additionally, two included studies identified increased engagement in community treatment during the course of the order as a positive, albeit predictable, outcome of OPC/CTO(.84,87 Finally, one study suggested that OPC/CTO was associated with decreased episodes of seclusion and restraint in addition to decreased episodes of hospitalization(.88) One study compared the combination of Assertive Community Treatment (ACT) and OPC/CTO with the combination of Intensive Case Management (ICM) and OPC/CTO and with ACT alone(.84) Aside from the interventions effects on hospitalization, patients receiving either combined intervention were more engaged in outpatient services as rated by case managers than patients receiving ACT alone. (Note: This shows that it is not the provisioning of services, but the presence of the court order that helps. MIPO) In Iowa, the State code allows a person who had been committed to inpatient treatment to be transferred to OPC upon written petition documenting the absence of being gravely disabled. Compliance with a set schedule of followup treatment visits determines whether the patient can remain out of the hospital.(87) Massachusetts has a similar involuntary outpatient treatment procedure with distinct eligibility criteria and treatment plan ordered by the court.(100 These programs improve adherence with outpatient treatment⁸⁷ and have been shown to lead to significantly fewer emergency commitments,(98) hospital admissions,(87) and hospital days(100) as well as a reduction in arrests and violent behavior.)⁸ 1 For study and footnote references included in Excerpts Section, see actual study at</p>	
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Commentator & Affiliation	Section	Comment	Response
		http://effectivehealthcare.ahrq.gov/ehc/products/596/2082/psychiatric-readmissions-report-150521.pdf .	
Peer Reviewer #1	Results	Yes, the main points are well structured and clearly presented. However, the issue most relevant to practice decisions is just how much treatment a person needs and for how long. One of the dilemmas in the presentation of the findings (which most likely stems from the limitations of the research articles) is less clarity regarding how long an intervention is and what kind of care a person received post study (none, TAU (not defined), other care, continuation of care provided in study, etc.)	Most of the studies did not directly address this question, but we have added more depth of assessment and synthesis where possible.
Peer Reviewer #1	Results	Page 26: Timing It would be helpful to know if the duration of treatment is at all linked to outcomes. Perhaps this is addressed further in the document but as worded, it appears that there is not evidence linking outcomes to longer treatment. Does this mean that outcomes are realized relatively quickly with pharmacological treatment? Does continued pharmacological treatment maintain outcomes or is there no evidence of benefit with longer treatment (the person returns to baseline levels)? Or, is the person discontinued from medication by follow up? Unclear as presented briefly in lines 37-39. Similar questions are relevant to the discussion related to timing for the nonpharmacological interventions also.	The studies of antipsychotics that were eligible for this review did not examine the effect of discontinuing medications. If patients stopped taking a drug during the course of study, an assessment of their outcomes was not reported separately. Whether treatment effects differ by duration of treatment is also not clear from this evidence. We have added this to our recommendations for future research.
Peer Reviewer #1	Results	The tables on page 48 and 49 are helpful as they provide some information about the duration of the intervention and duration of followup and a quick scan suggests for psychosocial interventions that these may be the same length for some interventions, although it is unclear.	Thank you for taking the time to review our report. We appreciate your feedback.



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Results	This is a very important question that needs to be adequately addressed and prominently featured. The crux of the question is whether intervention must continue for any benefit to be realized and sustained. We know in the depression literature that individuals who receive some types of psychotherapy show gains at the end of treatment and sometimes demonstrate even greater gains at follow up EVEN IF THEY HAVE NOT HAD FURTHER PSYCHOTHERAPY. Does this hold for people with schizophrenia? We also know that for some people treated for depression solely with medications, when medications are discontinued, they relapse. See the following article for one explication of this issue in the depression literature.	We agree, and have added more details and stratified by duration of treatment versus duration of follow up in relation to results where we could. Most of the studies did not report on follow up after treatment ended (other than cognitive behavioral therapy).
Peer Reviewer #1	Results	Cuijpers, P., Hollon, S. D., van Straten, A., Bockting, C., Berking, M., & Andersson, G. Does cognitive behaviour therapy have an enduring effect that is superior to keeping patients on continuation pharmacotherapy? A meta-analysis. <i>BMJ Open</i> . 2013 Apr 26;3(4).	This publication was excluded due to the population not having at least 50% of the patients diagnosed with schizophrenia.
Peer Reviewer #1	Results	A question facing clinicians and policy makers is whether to continue an intervention? This question arises after reasonable gains have been made and it also arises when someone appears to be stable but perhaps not functioning as well as would be desirable or still have active symptoms that are not responding to treatment. Could it be that keeping someone in the intervention is staving off possible relapse or other losses? It is very important to understand this but the data, as reported in the review, do not clarify these questions.	Thank you for these comments; we have added discussion of the duration of therapy versus duration of follow up in relation to results in the section.
Peer Reviewer #1	Results	Page 63 of 469 The discussion of drug discontinuation and time to discontinuation is helpful but would benefit from slightly more clarification. As I understand it, "discontinuation" is the patient or provider deciding to take the person off the medication and typically this occurred because the drug was not producing desired outcomes or the adverse events were too great. While the discussion is precisely conveyed in the document, translating it to meaningful language for consumers is critical.	We have edited the wording for clarity. The key messages are written in plain language, but not specifically for patients/consumers. We do plan to submit manuscripts to key journals to further disseminate our findings.



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Results	Page 67 (page number 36) of the PDF, lines 55-57: It would be helpful to know whether patients were maintained on the medication dose through follow up.	In the drug studies, patients were maintained on their drug unless they withdrew from the study, but the dose varied within the dosing range depending on response and adverse effects. Although most studies reported the mean dose received by patients during the study period, dose through follow up was not generally reported.
Peer Reviewer #2	Results	Numerous studies were overlooked or excluded, including many randomized controlled trials (RCTs) of studies with > 50 participants and > 50% schizophrenia-spectrum, resulting in a fraction of the studies in some areas being included.	We appreciate the concern and looked for suggested studies in the further comments from this reviewer. We feel that many of the studies referred to were included in the systematic reviews we used as the primary sources of evidence.
Peer Reviewer #2	Results	Poor documentation as to which studies were excluded and why--many studies missing from the list of studies excluded.	As noted in our methods, we used good quality, recent, comprehensive systematic reviews where possible, adding new studies if they existed. As a result, studies included in these reviews were not individually cited as being included. Our excluded studies list denotes those that we screened separately. Publications excluded as abstracts are not listed on the excluded studies list. However, we would note that in the systematic reviews included in Key Question 2, there were 271 unique randomized controlled trials (with >20,000 patients) included and considered in this review.



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Results	Results of systematic reviews of research are often given the same weight as individual RCTs.	Thank you for the opportunity to clarify. We draw your attention to the numbers of studies identified in the data tables, which is not to be construed as a weight. We have updated meta-analyses presented in the included reviews where possible, giving each study its own weight. Where no meta-analyses were conducted, we presented information on the results of the review, including the number of trials, and the findings of newer studies. Similarities and differences in findings are then discussed in the context of the volume and quality of studies in and not in the reviews.
Peer Reviewer #3	Results	Page 37: the comparator in reference 268 is paliperidone, which is not listed in the text.	Thank you for pointing this out, we have corrected the text.
Peer Reviewer #4	Results	Amount of detail in results section is appropriate and well documented. Study characteristics are well described. Key messages are explicit and applicable. Figures, tables, etc. are adequate, not over or under done and provide enhancement to the review. They are adequately descriptive.	Thank you for taking the time to review our report. We appreciate your feedback.
Peer Reviewer #4	Results	Could Appendix G-1 (page 398) be better represented?	Thank you for the comment, but this is the best and most concise format that we can think of for presenting this dense and complex information on the second generation antipsychotic versus second generation antipsychotic network meta-analysis.
Peer Reviewer #4	Results	There are no relevant studies that I am aware of that have been overlooked in this review. All studies included are considered relevant based on the selection and review criteria.	Thank you for taking the time to review our report. We appreciate your feedback.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Results	Please see my comments on the section regarding the study results in the attachment [comments added below the disposition table].	Thank you for taking the time to review our report. We appreciate your feedback.
TEP Reviewer #2	Results	p. 47 line 32 Insert line break after the number 87	Thank you for pointing this out. We have corrected the text.
TEP Reviewer #2	Results	p. 48 See specific comments on table formatting embedded in pdf file	Thank you. We have reviewed the comments and made changes accordingly.
TEP Reviewer #2	Results	p. 48 line 9 Add range of sample sizes	We have added this information.
TEP Reviewer #2	Results	p. 48 line 11 delete "Range"	Thank you for pointing this out. We have corrected the text.
TEP Reviewer #2	Results	Total N (range of sample sizes)	Thank you for pointing this out. We have corrected the text.
TEP Reviewer #2	Results	Is this just the new included trials? If so, this should be specified (in the title).	Thank you for pointing this out. We have corrected the title.
TEP Reviewer #2	Results	p. 50 line 9 insert "from one another"	Thank you for pointing this out. We have corrected the text.
TEP Reviewer #2	Results	p. 50 line 9 Is this with each of the older SGAs? If so, it may be helpful to state this explicitly.	Yes, thank you for noting this. Please see the revised text.
TEP Reviewer #2	Results	p. 51 line 10 Insert "was"	Thank you for pointing this out. We have corrected the text.
TEP Reviewer #2	Results	p. 53 line 12 Was this because they didn't wish to be on clozapine? If so, do we know whether they were concerned about side effects, didn't want to have blood drawn frequently or some other reason? It would be helpful to state specifically, if known, given the importance of patient preferences in crafting guideline recommendations.	No, there was no information in the original publication on the reasons; however, it is possible that one of the numerous secondary publications from this trial did include more information on the reasons.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Results	p. 53 line 16 It's not clear what "of this" is referring to in terms of the "full implications". Consider revising the sentence to be more specific.	Thank you for pointing this out. We have corrected the text.
TEP Reviewer #2	Results	p. 52 line 52 Need to clarify what "midpoint" refers to. Is this the midpoint of the range of FDA approved doses, typically used doses or something else?	Thank you for noting that this was unclear. We describe this elsewhere, but have not repeated it here. The process for identifying the "midpoint" dose range is based largely on the PORT 2009 publication (for the older drugs) and based on the suggested dosing range in the product label for newer drugs.
TEP Reviewer #2	Results	p. 54 line 51 It's not clear how what figures are being averaged to get a mean value as a percent reporting employment. If there was no difference in employment rates among treatment groups, it would seem preferable to report employment (as a percent) for the sample as a whole.	As we tried to describe, the way employment was measured and reported was complicated, with 18% being the mean across the medication groups. An overall proportion was not reported. We could report the percentage for each drug group, or the range instead.
TEP Reviewer #2	Results	p. 55 line 25 The phrase "pooled estimate of RCTs" sounds incorrect. Presumably there is a specific scale or measurement for which the pooled estimate is calculated based on values from multiple RCTs.	We have edited this text to clarify that we were referring to the Global Assessment of Functioning (GAF) scale.
TEP Reviewer #2	Results	p. 56 line 12 -- the phrase "these findings" seems unclear. Is it possible to clarify what is meant?	Thank you for this suggestion. Please see the revised text.
TEP Reviewer #2	Results	p. 56 line 55 The sentence is somewhat unclear as written. In particular, it seems to imply that the lack of inconsistency indicates a low SOE which seems backwards. Presumably, the sentence is trying to suggest that the network meta-analysis data is low SOE.	Yes, you are correct. The comment has been revised to clarify both issues.
TEP Reviewer #2	Results	p. 59 line 14 The sentence that begins "Studies like these..." is confusing.	Thank you. We have clarified the sentence.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Results	p. 59 line 43 The statement that begins "The other patients ... " is confusing as written.	Thank you. We have clarified the sentence.
TEP Reviewer #2	Results	<p>p. 60 line 13 Should say ""all of the drugs in the network...""</p> <p>This point, from the placebo-controlled trial data, is an important one in terms of guideline development and is worth emphasizing in the document (e.g., abstract, conclusions). Since the systematic review of antipsychotics excluded placebo-controlled trials, it is difficult to judge whether to recommend an antipsychotic at all. When two drugs have equal efficacy in a head-to-head trial, both could be effective or both could be ineffective. Thus, one might recommend both or one might recommend neither.</p> <p>We had agreed that placebo-controlled studies were outside the scope of the review, but this is still an important point in my opinion.</p>	We have added additional notation of this, but would also point out that for antipsychotic drugs, the FDA approval process addresses the "does it work" question, and all of these have been approved specifically for treating schizophrenia. The approvals are based almost entirely on improvement of core illness symptoms and review of the adverse effect profiles.
TEP Reviewer #2	Results	<p>p. 61 line 42 Sentence is hard to read especially with long string of reference footnotes. Suggest changing as follows:</p> <p>A network meta-analysis assessed discontinuation rates due to adverse events using data from 89 head-to-head trials of greater than 6-weeks duration (76 two arm studies, 8 three arm studies, 3 four arm studies and 2 five arm studies; N=29,678). 37,39-41,43-45,48-50,54,56,59,136,146-149,157-159,161,168,172,174-180,182,184,185,187-190,192-196,198,200-203,205,209,211-213,217,222,225,227,229-231,234,236,238,239,241-244,246,247,249-266</p>	Agreed. We have edited the sentence as suggested.
TEP Reviewer #2	Results	p. 63 line 29 Change to "Few studies of newer drugs exist, suggesting that these findings should be interpreted cautiously."	Thank you for this suggestion. Please see the revised text.
TEP Reviewer #2	Results	p. 63 line 57 Consider adding citation here and on subsequent pages discussing adverse events, unless they are all reported and analyzed in a single publication.	These observational studies were all included and reviewed in the Drug Effectiveness Review Project report that we included, so the individual studies were not separately evaluated here. We have revised the text to indicate this.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Results	p. 64 line 48 Table 7 is fine but it's not clear why EPS warrants a separate table whereas other discussions of adverse effects do not.	The table comes from the Drug Effectiveness Review Project report that we included, and it seems that the volume and complexity of evidence was greater for EPS than the other adverse events given the multiple ways to define, identify, and report it.
TEP Reviewer #2	Results	p. 65 line 22 ff Would suggest moving sections on Weight Gain and Metabolic Syndrome so that they are contiguous with the section on Diabetes.	Agreed. Please see the revised text.
TEP Reviewer #2	Results	p. 65 line 41 A more general point is question of whether patients are more (or less) likely to gain weight with a particular drug if they have already gained a significant amount of weight with a prior drug. (In other words, is there some sort of threshold effect on total weight gain so that a second or subsequent drug would appear to cause less weight gain or even weight loss relative to the initial drug.)	Yes, we agree that this would be good to know. While there are a few studies that clearly evaluate this, most report a mix of prior exposure and weight gain experience. The evidence on the patients with first episodes are helpful regarding those with little or no prior experience, but as noted, the evidence on prior experience with specific drugs is less robust.
TEP Reviewer #2	Results	p. 65 line 49 Is it possible to express this in the same format as the first sentence? (i.e., Olanzapine had a significantly greater risk of metabolic syndrome than aripiprazole....)	Thank you for this suggestion. Please see the revised text.
TEP Reviewer #2	Results	p. 66 line 15 Change to "with the other drugs currently available."	Thank you for this suggestion. Please see the revised text.
TEP Reviewer #2	Results	p. 66 line 52 This is somewhat confusing as written. Consider revising as: Reductions in core illness symptoms were greater with older SGAs than with haloperidol.	Thank you for this suggestion. Please see the revised text.
TEP Reviewer #2	Results	p. 68 line 12 Change to "Two trials limited enrollment to participants..."	Thank you for this suggestion. Please see the revised text.
TEP Reviewer #2	Results	p. 68 line 47 It may be helpful to define what MANSAs means since I believe this is its first use in the document.	Thank you for pointing this out. We have corrected the text.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Results	p. 70 line 35 It may help the reader to mention briefly what CGI-S and CGI-I are related to (as compared to the CGI). For example, CGI-S scores, as a measure of illness severity, were marginally better....	Thank you for this suggestion. Please see the revised text.
TEP Reviewer #2	Results	p. 71 line 18 This section seems to imply that olanzapine is better than haloperidol, which is comparable to clozapine in terms of reducing negative symptoms. (i.e., olanzapine would be better than clozapine.) This may not be a fair conclusion without head-to-head olanzapine to clozapine data but it contrasts with usual clinical experience in which clozapine seems to be better than the other medications for negative symptoms.	Yes, these are the findings of the studies in the Alberta AHRQ review that we included — the reason for not finding clozapine superior to haloperidol, and likely better than the other second generation antipsychotics, is almost surely related to the much smaller sample size (184) for those studies compared with thousands of patients in the studies of other second generation antipsychotics versus haloperidol.
TEP Reviewer #2	Results	p. 72 line 39 See prior comment about weight gain in the context of prior antipsychotic	Yes, this is an important issue that was not adequately studied in the two systematic reviews we used to address this outcome, primarily due to a lack of good studies reporting on this issue.
TEP Reviewer #2	Results	p. 74 line 42 Not clear was specific risk is being referred to in terms of quetiapine vs. olanzapine.	Thank you for this suggestion. Please see the revised text.
TEP Reviewer #2	Results	p. 75 line 6 Double check the actual comparison here. The bullet points under the results column refer to ziprasidone and not to risperidone	Thank you. We have corrected this.
TEP Reviewer #2	Results	p. 75 line 26 The statement that 20-30% of patients with schizophrenia are treatment resistant seems at odds with the statement earlier in the document that 80% have significant persistent impairment. Perhaps this simply depends on the definition of treatment resistance and lack of response (vs. lack of remission).	This is a good point, and the persistent impairment statement has been removed from the introduction because it was possibly out of date and also not well defined. The definition of treatment resistant has been clarified.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Results	<p>p. 76 line 28 Suggest changing sentence as follows:</p> <p>These 66 patients were followed for an additional 3 years and no significant differences in long-term adherence to olanzapine (65%) or risperidone (56%) were found although efficacy outcomes were not available.²⁸⁸</p>	Thank you for pointing this out. We have corrected the text.
TEP Reviewer #2	Results	p. 77 line 11 Fix typo "Black" rather than "back"	Thank you for pointing this out. We have corrected the text.
TEP Reviewer #2	Results	<p>p. 79 line 3 Sentence needs to be reworded. I presume it's the dose that was lower than recommended and not the injection location. But this needs clarification. Also, it would be helpful to know why the location of the injection would influence the results. Issues of dosing in individuals with obesity also deserve attention and are typically not well studied or addressed in registration trials or subsequent head-to-head trials, despite the increasing prevalence of obesity.</p>	Thank you for this comment. We have revised the wording to clarify the problem.
TEP Reviewer #2	Results	<p>p. 81 line 56 Were these analyses adequately corrected for factors related to study enrollment or to attrition? For example, did they all have to be in stable housing at the beginning of the trial? In terms of applicability, most patients who receive ACT in the community nowadays are quite ill and already have long histories of poor treatment adherence with multiple relapses/readmissions. It would be helpful to know (here or elsewhere in the document) whether the ACT study populations are similar or different from that patient profile. Is having a lower likelihood of not living independently the same as having a higher likelihood of living independently? (It seems less confusing to phrase in the latter fashion.) Is independent living defined as truly independent or would living with parents count as independent? (Again, the relates to applicability and implications of the findings.)</p>	Across the studies, there was not consistency in reporting or requiring these characteristics at enrollment. We have added text to describe the populations included in these studies to the extent possible.
TEP Reviewer #2	Results	p. 93 line 52 Suggest change to "One other RCT in veterans, which was rated as poor quality,..."	Thank you for pointing this out. We have corrected the text.
TEP Reviewer #2	Results	p. 93 line 52 Delete "of veterans"	Thank you for pointing this out. We have corrected the text.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Results	p. 93 line 56 Delete "were"	Thank you for pointing this out. We have corrected the text.
TEP Reviewer #2	Results	p. 94 line 34 Suggest change to "due to a high number of study limitations"	Thank you for pointing this out. We have corrected the text.
TEP Reviewer #2	Results	p. 99 line 5 Since none of the other outcomes showed a change with ICM, is there any information in the studies that is not reported here that would suggest any benefits to patients of having less loss to followup. The presumption is generally that staying in treatment is good with an intuitive sense that if you stay in treatment you should do better. Are the ICM subjects actually maintaining treatment or just maintaining ICM but not necessarily adhering to medications or psychiatric followup?	The outcome measure here is actually about maintaining or discontinuing the Intensive Case Management (ICM) treatment, and not others. We did not report other outcomes, but do not think that there is data reported across the studies on outcomes with low or high loss to follow up.
TEP Reviewer #2	Results	p. 105 line 9 Since usual care typically includes some sort of supportive therapy, it's somewhat difficult to understand how the two conditions differed. If this was discussed in the papers, it may be useful to mention in another sentence or two. The description of the study intervention as "generally aimed at maintaining current functioning" doesn't really describe what was done in the therapy to achieve that goal.	We agree that the description of the intervention was vague—but this was what was reported in the study. The description of usual care has been added to the text, but it was also vague.
TEP Reviewer #2	Results	p. 106 line 52 Is this percent the difference between CSC and usual care or the absolute value of people who were working or in school with CSC interventions?	Yes, that is correct. This represents the percent difference between the intervention and usual care. This section has been revised; please see the new text.
TEP Reviewer #2	Results	p. 107 line 14 Insert "who received"	Thank you for pointing this out. We have corrected the text.
TEP Reviewer #2	Results	p. 107 line 23 It's not clear how integrated ACT differs from ACT.	There should not be something called "integrated ACT". This has been corrected.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Results	p. 107 line 28 Do these studies take into account differences in first-episode vs. multi-episode or treatment resistant patients between the subgroups being compared? Were there any baseline differences in the groups? The reason that I'm especially curious is that women tend to have a later age of onset and less disabling functional impairments so age and gender effects could introduce additional bias if not controlled for. In addition, younger individuals would be more likely to be experiencing a first episode, which could affect their relative response to treatment.	Study inclusion criteria did not take into account duration of illness, other than limiting to only those who had not been given antipsychotic drugs for more than 12 weeks of continuous treatment. Unfortunately, these are simple stratifications of the subgroups. Analyses evaluating differences at baseline or controlling for these factors were not reported. We have added notation about the need for this in the future research section.
TEP Reviewer #2	Results	p. 108 line 38 It would be helpful to know what the comparison group is here. Ordinarily, living in supported housing would not be as positive an outcome as living independently, yet the sentence says the finding was "in favor of the team based CSC approach".	The comparison group was standard community mental health center treatment (i.e., contact with a physician, a community mental health nurse, and access to a social worker). Staff-to-client ratio was 1:20 and 1:30. Outside of standard office hours, clients could self-refer to the psychiatric emergency room. This study examined non-institutional versus institutional living.
TEP Reviewer #2	Results	p. 109 line 7 If they reported the number of actual suicides in the groups, it would be helpful to include or the total number/percent of suicide deaths for the entire sample, since no difference was reported between the groups.	Agreed. We have added these data. One person from each group died by suicide in the first year of the study (n=506, RR 0.93, CI 0.06 to 14.81).
TEP Reviewer #2	Results	p. 109 line 28 In some places in the document, the word "sex" is used whereas in others, the word "gender" is used. Without going into the whole debate about which is preferable, I'd simply suggest to pick one and use it consistently.	Thank you for noting this.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Results	p. 109 line 28 I thought the team-based CDC studies were with patients with new/recent onset illness, so I wouldn't expect them to have prior psychotic episodes.	This study also included participants who had presented once but had subsequently disengaged without treatment from routine community services.
TEP Reviewer #2	Results	p. 109 line 31 insert CSC after team-based	We changed the term from "CSC" to "team-based multi-component treatment program." The latter was inserted in this sentence.
TEP Reviewer #2	Results	p. 109 line 32 It may help to include the study duration since one might expect significant attrition in a lengthy study.	The text currently includes 12- to 18-months for the first cited study. We added two-year duration for the second cited study.
TEP Reviewer #2	Results	p. 110 line 43 It would help to be explicit that this information refers to individuals with a substance use disorder and another co-occurring psychiatric diagnosis. Otherwise, it's not clear why ICM would be a non-integrated approach.	Yes, correct; we have edited this sentence to remove "integrated."
TEP Reviewer #2	Results	p. 111 line 7 There are a number of places such as this one where the superscript is not formatted correctly. You may want to do a search/replace with formatting for I ² .	Thank you for pointing this out. We have corrected the text.
TEP Reviewer #2	Results	p. 111 line 36 Change "the effect size for men" to "had an effect size for men that"	Thank you for pointing this out. We have corrected the text.



TEP Reviewer #3	Results	<p>The primary concern is that the results and conclusions of this review with regard to psychosocial and nonpharmacologic interventions are in sharp contrast to other reviews and published guidelines; often the exact opposite. The discussion states that the findings of the review are consistent with prior reviews, but this is only true for some of the selected reviews included, which are primarily Cochrane reviews. For example, with regard to CBT, greater benefits have been found at 6-month to 5-year follow-ups than at end of treatment (Gould et al., 2001; Sarin et al., 2011; Turkington et al., 2008; Zimmerman et al., 2005), but the review concludes the opposite. In general, the review is in sharp contrast to the 2010 PORT guidelines, which concluded 1) CBT should be offered for positive symptoms (this review concludes that the benefits are transient); 2) SE promotes work (this review concludes it does not); 3) there is insufficient evidence to recommend cognitive remediation (this review recommends CR for long-lasting improvements in several outcomes); 4) that psychoeducation promotes long-lasting improvement in functioning and relapse prevention (most experts would probably say that other interventions like SST, CBT and SE were developed because of the lack of long-lasting meaningful benefits for psychoeducation alone). There are many findings that are not consistent with other reviews. The statement that this review does not change the conclusions of other reviews is not accurate.</p>	<p>We have considered each of these citations, and found that they did not provide better evidence than the reviews and RCTs included in our review. Specifically, the PORT Guideline is an important document, and our review adds newer evidence and methods of evaluating the strength of evidence. We have included the 2010 PORT Guidelines in our discussion of how our review findings compare to previous findings. Likewise, the Zimmerman and Sarin reviews were older, and included different types of evidence than included in this report. Turkington 2008 is a report of a small group of patients who had participated in a prior trial of Cognitive Behavior Therapy (CBT) who were evaluated 5 years later and evaluated post hoc. While it provides interesting findings, they are valuable only for hypothesis generation, rather than hypothesis proving. The Gould citation is a meta-analysis of a limited number of CBT studies, and has methodological flaws. We have added more discussion of differences in findings between our review and others to the discussion section. We find that there are many areas of agreement, and a few differences due to the comparison groups used (i.e., usual care in our review, and mixed comparators in some other reviews). Other reasons for differences may be due to the</p>
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Commentator & Affiliation	Section	Comment	Response
			<p>inclusion of newer studies and the methodology used in our review. Our review follows the most up-to-date methods recommended by the AHRQ, the Institute of Medicine, Cochrane, and others. Some of the reviews noted here were not systematic, and in some cases outcomes were based on measurement tools that are no longer widely used. We feel that our findings on CBT are not discordant—we also find that CBT is beneficial. The evidence does not show a benefit over longer follow up times when using better studies and review methodology, and focusing on comparisons with usual care. However, more studies and better studies could find such a difference.</p>



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Results	The negative findings for Supported Employment (SE) are particularly surprising, given that PORT concluded: "RCTs have consistently demonstrated the effectiveness of SE in helping persons with schizophrenia to achieve competitive employment, work more hours, and earn more wages than persons who did not receive SE" (citing 9 RCT and meta-analysis references). In contrast, this review concluded SE provided no benefit (citing only 1 review and 2 poor to fair RCTs). It is not clear how these conclusions could be so different. The PORT findings are based on the superiority of SE over other models like clubhouse and pre-training vocational rehabilitation approaches, and it is not clear whether studies of these other models are included in the present review. If so, the term "supported employment" should not be used to refer to this. Or better, the review should only focus on SE, which is widely viewed as one of the most effective psychosocial treatments for schizophrenia.	We appreciate this comment and have removed interventions that were not specifically Supported Employment (SE). The comparison of interest for our review was usual care, and limiting to SE versus usual care, we ultimately only had one trial to include; this study found benefit with SE. We have reviewed the studies cited in the reviews mentioned here and found no other studies comparing SE to usual care. In addition, according to our "best evidence" approach, we added evidence from a systematic review of 14 RCTs with vocational training comparisons, and a large RCT (N=1,273) with both usual care and vocational training comparisons. We did so because this intervention had only 1 trial with a usual care comparison group (unlike the other interventions).
TEP Reviewer #4	Results	The Results are clearly presented. There are unavoidable handicaps presented by the lack of high-quality evidence available and the simple fact that the literature represents a unplanned assortment of studies and comparisons of greatly uneven quality and quantity. Very important questions, such as whether clozapine reduces the risk of self-harm, frustratingly is represented mainly by a "low strength of evidence" - so comparing this potential asset of clozapine to the risk of agranulocytosis for a given patient seems impossible on an evidence basis; this is not a fault of the authors of this review, but a reflection on the wholly incomplete data base available to the field.	Thank you for taking the time to review our report. We appreciate your feedback.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #4	Results	It might be helpful to note that medication formulations that require more face-to-face interaction with healthcare professionals might indirectly augment the pharmacologic actions of the drugs in question with "nonspecific" support, encouragement, and even structure to the daily or weekly schedule. This could apply to clozapine, given the requirement for regular blood cell count monitoring, and long-acting injectable forms of medications, requiring regular clinic visits for administration of the medication.	We have added some text to the discussion to introduce this concept with regard to clozapine.
TEP Reviewer #4	Results	A minor clarification needed in Table A, page ES-12: In the last row ("Overall Adverse Events" the entry under "Moderate Strength of Evidence" includes the phrase "between and olanzapine". I believe that should read "between ASENAPINE and olanzapine." Similarly, on page E-14, under "Inclusion Criteria" I think it is safe to assume that "DSM-VI" (which does not yet exist!) should be "DSM-IV".	Thank you for pointing this out. We have revised the text to correct this.
Public Reviewer #12: Mental Health Policy Org, DJ Jaffe	Discussion/ Conclusion	In addition to AHRQ's own conclusions that AOT helps, there is extensive other evidence from SAMHSA, DOJ and research in the published literature. I am uploading Appendix D of Insane Consequences: How the Mental Health Industry Fails the Mentally Ill by DJ Jaffe, (Prometheus Books, April 2017) which contains just some of the conclusions of those studies. Copyright, 2017, Mental Illness Policy Org. The diagnosis of those served in NY studies are at and are overwhelmingly schizophrenics. http://bi.omh.ny.gov/aot/characteristics?p=diagnosis-diagnosis	Thank you for the summary of this work. These interventions were not included in our review because we were focusing on the most common psychosocial and non-pharmacological interventions used in U.S. practices. In addition, our team's clinical experts felt that these programs are a mechanism to get patients into treatment, rather than a treatment in and of themselves. We have screened the suggested reference for studies that might be eligible for our review, and have added a notation of this evidence in our discussion of the limitations of our review.



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Discussion/Conclusion	Page 119 PDF (beginning on numbered page 88)- Similar to the discussion for medications, it is important to know whether individuals continue receiving the psychosocial intervention at follow up. It is much more likely that individuals with schizophrenia have longer term interventions or are transitioned from an intense intervention to some sort of supported situation. It would be helpful to know what "usual care" consists of although suspect this is variable from one study to another. Regardless, these are often individuals with a lot of services and it is really important to know how much of what kind of care really makes a difference in both the short and long term. For instance, page 120, lines 22-26- how long did individuals receive family interventions? Had they just completed care at 18 months but had not received any family intervention between 18 and 36 months? Or was the family intervention much briefer and provided some protection against relapse for a period of time but not indefinitely?	We have added details of the duration of therapy versus duration of follow up in relation to the outcomes to the Cognitive Behavioral Therapy and family intervention sections, in particular. We have no information on what treatments were received during the follow up period, except that they were not pre-specified. We recognize the complexity in which people receive real-world treatment; they may get multiple interventions with varying duration, making trial evidence less generalizable to real world experience.
Peer Reviewer #1	Discussion/Conclusion	Page 128, lines 49-53 This is exactly my concern! Well stated here, just would be clearer in the report to indicate as much as possible length of treatment relative to follow up and what if any other care is provided post studied intervention. This may not be possible because this information is not reported but this information is very valuable.	Thank you for these comments; we have added discussion of the duration of therapy versus duration of follow up in relation to results for interventions where we had this information (e.g., Cognitive Behavioral Therapy, family and employment interventions).
Peer Reviewer #1	Discussion/Conclusion	Your research recommendations are critical. We would also add that there needs to be better attention to reporting possible harms of interventions within the psychosocial intervention literature.	Thank you for pointing out this omission. We have added this to the future research section.
Peer Reviewer #2	Discussion/Conclusion	The discussion of the findings is not illuminating, nor does it point the field in useful new directions.	Please see the revised discussion text, which includes topics noted in further comments from this reviewer.
Peer Reviewer #3	Discussion/Conclusion	The non-pharmacologic results seem right.	Thank you for your comment.



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Discussion/Conclusion	The authors' main SGA vs. FGA conclusions do not really seem to capture the key points and lack nuance--there is a great deal of heterogeneity among the drugs. More emphasis is needed on the fact that most FGA comparisons involve haloperidol. I would conclude that drugs need to be considered on their own merits rather than as FGAs or SGAs, as suggested by Leucht et al (2013) in reference 219. The entire section on FGA vs SGA could be eliminated and haloperidol and maybe perphenazine included in a single section comparing all of the antipsychotics of interest.	We appreciate the somewhat arbitrary segregation of these groups of drugs and have revised the text in the discussion and introduction to introduce these concepts. The Leucht analysis is included in our review.
Peer Reviewer #3	Discussion/Conclusion	Future needs: information on adjunctive treatments, beyond the scope of this.	Noted.
Peer Reviewer #4	Discussion/Conclusion	Discussion of mortality is highly valued.	Thank you for taking the time to review our report. We appreciate your feedback.
Peer Reviewer #4	Discussion/Conclusion	The authors do not recommend additional studies of FGAs versus SGAs--do they feel that the studies comparing SGAs to haloperidol reasonably represent FGAs as a class?	It is not clear that the haloperidol evidence is sufficient to draw conclusions about the group of drugs called first generation antipsychotics. We have modified this text to refer to haloperidol only.
Peer Reviewer #4	Discussion/Conclusion	I would highly value additional findings from SGAs compared to perphenazine.	Thank you for this suggestion. We have added this to the future research suggestions.
Peer Reviewer #4	Discussion/Conclusion	I also believe there should be additional research specifically looking at long-term harms (most notably impact of metabolic changes and tardive dyskinesia).	Thank you for this suggestion. We have added this to the future research suggestions.
Peer Reviewer #4	Discussion/Conclusion	Would there be additional value from comparative trials of long-acting injectables? I do agree with the discussion and conclusion that is presented--I do wonder about the value of additional research, however.	Thank you for this suggestion. We have added this to the future research suggestions.
TEP Reviewer #2	Discussion/Conclusion	Most of these points are already addressed in comments on the results section. Specific comments about possible additions to the new research section are included in my detailed remarks [added to the disposition table]. The investigators do a good job of discussing the limitations of the available research and the possible limitations of the review (e.g., based on the scope).	Thank you for taking the time to review our report. We appreciate your feedback.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Discussion/Conclusion	p. 112 line 34 It's not clear whether the initial phrase refers to the prioritized outcome (in which case there are more than several) or whether it's referring to something else. The initial phrase may not even be needed.	We agree that the first part of the sentence is not necessary and have removed it. There were seven prioritized outcomes, so we left it as several.
TEP Reviewer #2	Discussion/Conclusion	p. 112 line 44 lurasidone is spelled incorrectly	Thank you for pointing this out. We have corrected the text.
TEP Reviewer #2	Discussion/Conclusion	p. 112 line 48 Was ziprasidone superior on any outcome? If not, it may be worth mentioning here as well.	Good point. We have added text on this.
TEP Reviewer #2	Discussion/Conclusion	p. 113 line 22 Suggest change to: Olanzapine and risperidone were not significantly different in treating core illness symptoms compared with each other, and both were superior to the other SGAs, except for paliperidone ER and clozapine.	Thank you for this suggestion. Please see the revised text.
TEP Reviewer #2	Discussion/Conclusion	p. 113 line 34 Consider using semicolons to divide out the comparisons here. It's a bit confusing as written.	Thank you for pointing this out. We have corrected the text.
TEP Reviewer #2	Discussion/Conclusion	p. 113 line 48 This sentence is also a bit difficult to read in terms of figuring out the actual comparisons and findings.	Thank you for this suggestion. Please see the revised text.
TEP Reviewer #2	Discussion/Conclusion	p. 114 line 6 asenapine is spelled incorrectly	Thank you for pointing this out. We have corrected the text.
TEP Reviewer #2	Discussion/Conclusion	p. 114 line 19 Consider splitting into two sentences or eliminating the first half. Patient characteristics could still influence outcomes even if differences did exist for SGAs overall.	Thank you for this suggestion. Please see the revised text.
TEP Reviewer #2	Discussion/Conclusion	p. 114 line 27 Put a period after ER, delete "and" and capitalize "Most".	Thank you for pointing this out. We have corrected the text.
TEP Reviewer #2	Discussion/Conclusion	p. 114 line 28 Put a period after "scales," delete "except that" and insert "Although".	Thank you for pointing this out. We have corrected the text.
TEP Reviewer #2	Discussion/Conclusion	p. 114 line 30 Delete "but"	Thank you for pointing this out. We have corrected the text.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Discussion/Conclusion	p. 114 line 32 It's not clear what "These findings" refers to.	Thank you for this suggestion. Please see the revised text.
TEP Reviewer #2	Discussion/Conclusion	p. 114 line 44 This can probably be deleted as it was already noted above.	Thank you for pointing this out. We have corrected the text.
TEP Reviewer #2	Discussion/Conclusion	p. 115 line 7 olanzapine is misspelled	Thank you for pointing this out. We have corrected the text.
TEP Reviewer #2	Discussion/Conclusion	p. 116 line 12 It's not clear what drug is being compared with risperidone here. If comparison is with olanzapine, it may be clearer to write "but improvement in core illness symptoms was comparable for olanzapine and risperidone."	Thank you for this suggestion. Please see the revised text.
TEP Reviewer #2	Discussion/Conclusion	p. 117 line 34 insert the word "was" between "PANSS" and "greater"	Thank you for pointing this out. We have corrected the text.
TEP Reviewer #2	Discussion/Conclusion	p. 120 line 3 This sentence is confusing as written.	We have revised the sentence for better clarity; please see the revised text.
TEP Reviewer #2	Discussion/Conclusion	p. 120 line 13 If team-based coordinated specialty care interventions have not been studied in other individuals (non-first episode), this may be worth stating explicitly and including in areas for future research.	Thank you for this suggestion. Similar team-based multi-component interventions have been studied with other populations, including multi-episode (Assertive Community Treatment) and people with co-occurring substance use disorders.
TEP Reviewer #2	Discussion/Conclusion	p. 120 line 48 Was this corrected for baseline differences (if any) between men and women given the typical finding of greater social dysfunction in men than women?	No, these analyses did not undertake any correction for differences at baseline.
TEP Reviewer #2	Discussion/Conclusion	p. 121 line 16 Since unemployment is not a housing function, you may want to have a new row related to effects of ACT on employment.	Thank you for this suggestion.
TEP Reviewer #2	Discussion/Conclusion	p. 122 line 5 It seems surprising that an effect size of 0.18 would be significant whereas an effect size of 0.17 would not. Is it clear that the effect of cognitive remediation is clinically significant regardless of its statistical significance?	The difference is almost surely related to the difference in sample sizes between the two meta-analyses noted here.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Discussion/Conclusion	p. 122 line 18 Should this be split off into a new row for school/work function?	Thank you for this suggestion.
TEP Reviewer #2	Discussion/Conclusion	p. 122 line 44 Split off into new row for housing function	Thank you for this suggestion.
TEP Reviewer #2	Discussion/Conclusion	p. 125 line 20 fix punctuation	Thank you for pointing this out. We have corrected the text.
TEP Reviewer #2	Discussion/Conclusion	p. 125 line 49 Should be "we" instead of "be"	Thank you for pointing this out. We have corrected the text.
TEP Reviewer #2	Discussion/Conclusion	p. 126 line 11 This sentence is confusing as written.	We have revised the sentence for better clarity; please see the revised text.
TEP Reviewer #2	Discussion/Conclusion	p. 126 line 48 Even though the inclusion of some inpatient studies were not part of the precise clinical questions of the systematic review, it seems as if this would actually increase the generalizability of the findings in terms of their clinical use.	Since the intent was to focus on outpatient (and therefore exclude inpatient) settings, we see this as a disadvantage, unless the results were stratified by setting (in patient versus outpatient settings).
TEP Reviewer #2	Discussion/Conclusion	p. 127 line 36 Although this was previously defined, it may be worth being more specific. Even if you spelled out scientific information packet here, I'm not sure people would be able to infer what was meant. TEP may also be worth spelling out again.	Good point. We have revised this text.
TEP Reviewer #2	Discussion/Conclusion	p. 127 line 39 Change "a" to "are"	Thank you for pointing this out. We have corrected the text.
TEP Reviewer #2	Discussion/Conclusion	p. 128 line 6 Consider whether sentence can be edited for clarity	We have revised the sentence for better clarity; please see the revised text.
TEP Reviewer #2	Discussion/Conclusion	p. 128 line 22 Change "low versus high" to "low dose of one drug versus high dose of comparator"	Thank you for this suggestion.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Discussion/Conclusion	p. 128 line 25 Was this supposed to be FGA given the shift to lower doses of FGAs in more recent decades?	This actually applied to both first generation and second generation antipsychotic drugs, where dosing was generally lower in more recent studies, except for clozapine and quetiapine where early studies used doses lower than typically used today. We have removed second generation antipsychotic from the sentence so that it applies to all of the drugs.
TEP Reviewer #2	Discussion/Conclusion	p. 128 line 37 These sentences are somewhat confusing. Variance implies a statistical concept; variability may be a better word choice. It's not clear what is meant by "how outcomes are reported". It's also not clear how the method of outcome reporting (whatever that means) relates to the finding of small statistically significant changes that may lack clinical significance.	We have revised the sentence for better clarity; please see the revised text.
TEP Reviewer #2	Discussion/Conclusion	p. 129 line 5 It may be helpful to clarify that these recommendations relate to research for clinical trials and do not include research needed to enhance our understanding of the epidemiology of schizophrenia, the basic and translational underpinnings of the neurobiology of schizophrenia and its treatments, or research into health services delivery or qualitative improvement methods to improve the care and outcomes of schizophrenia. These recommendations also are restricted to primary treatments for schizophrenia and do not include recommendations that may relate to use of adjunctive medications to treat side effects of primary treatment (e.g., interventions to reduce weight gain or EPSE associated with antipsychotics).	Good point. We have revised this text.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Discussion/Conclusion	p. 129 line 10 Given the significant number of individuals who do not have even a partial response to existing pharmacotherapy, research is needed to develop drugs with new mechanisms. There is also a considerable amount of polypharmacy that occurs in the "real world." However, few research studies have actually looked at the use of more than one antipsychotic, either in an effort to target more than one mechanism (e.g., combining an FGA and an SGA) or in an effort to address differing aspects of the patient's symptomatology (e.g., control psychosis with minimal daytime sedation with one agent, assist with sleep without potential for tolerance or misuse using another more sedating antipsychotic).	Thank you for this suggestion.
TEP Reviewer #2	Discussion/Conclusion	p. 129 line 14 Should be "ensure" not "insure"	Thank you for pointing this out. We have corrected the text.
TEP Reviewer #2	Discussion/Conclusion	p. 129 line 14 Delete "s" at end of "titrations"	Thank you for pointing this out. We have corrected the text.
TEP Reviewer #2	Discussion/Conclusion	p. 129 line 18 It's not clear what an actual measure of functioning would be as compared to a rating scale report of functioning.	We agree that there are not standard measures for real-world functioning, but ideally that is what we would measure rather than relying on a scale, which is subjective in nature.
TEP Reviewer #2	Discussion/Conclusion	p. 129 line 29 For some subgroups such as older individuals or patients with severe disease, it may be preferable to have an individual trial but for other subgroups, such as men vs. women, it may actually be preferable to include both groups and have analyses that are specified a priori that examine differences between men and women. For studies of minorities, a mixed sample may also be beneficial with a sampling format that optimizes a sufficient number of minority individuals. Obviously for all such studies, data needs to be reported in a way that differences based on sex or minority status can be determined.	Thank you for this suggestion.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Discussion/Conclusion	p. 129 line 31 Given the brief lengths of inpatient stays for most individuals and the lack of funding for inpatient based research protocols, it is highly unlikely that one could conduct an inpatient trial that's of sufficient duration to be meaningful for a chronic condition such as schizophrenia. For those individuals who are hospitalized on a long-term basis, they would typically be too severely ill to provide informed consent, even if funding were available.	Noted. We have revised this text.
TEP Reviewer #2	Discussion/Conclusion	p. 129 line 32 See prior comment on p. 27	Thank you for this suggestion.
TEP Reviewer #2	Discussion/Conclusion	p. 129 line 44 For some complex, multi-component interventions, "unbundling" studies may be warranted to attempt to define the "active ingredients" of a particular intervention.	Thank you for this suggestion.
TEP Reviewer #2	Discussion/Conclusion	p. 129 line 49 Incomplete sentence	Thank you for pointing this out. We have corrected the text.
TEP Reviewer #2	Discussion/Conclusion	p. 129 line 53 Is there a reason that the illness management and recovery scale has been singled out? If so, it may help to explain why this one is so crucial for further investigation.	We have revised the future research section and noted more generally that studies should identify what constitutes clinically meaningful change in scale scores.
TEP Reviewer #2	Discussion/Conclusion	p. 130 line 22 olanzapine is misspelled	Thank you for pointing this out. We have corrected the text.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Discussion/ Conclusion	In addition to the comments in the Results box (d), the issue of pseudospecificity is not addressed. The primary target of an intervention is important to consider. If the intervention targets positive symptoms but not functioning or negative symptoms (e.g., most CBT interventions), it may not be expected to improve other outcomes. Also, secondary outcomes may improve as a result of improvement in the primary target (e.g., a patient who goes back to work because his voices stop telling him his coworkers are dangerous), which indicates the intervention is not specifically effective for the secondary outcome. This should be considered in evaluating trials to include for different outcomes and drawing conclusions about the efficacy for specific outcomes.	We have added notation of the targets for each intervention in the description of study sections where the studies clearly identified them. We have added some comments on this issue in the discussion. As described in our methods, the selection and prioritization of outcomes was based on the clinically most important outcomes (i.e., improvement in function), with input from the Key Informants and the Technical Expert Panel. While an intervention may be primarily aimed at improving symptoms, improved symptoms may also lead to improved function, etc. Therefore, examining other highly prioritized outcomes is important.
TEP Reviewer #3	Discussion/ Conclusion	The conclusions are well-stated, given the tremendous limitations of the data available. Quite honestly, the phrase "evidence is insufficient" appears repeatedly, and frustratingly, a reflection of the state of the field, not of this report. Gaps in studies done, contradictory results, and many examples of "apples and oranges" abound, e.g. "No two studies used the same definition of relapse" (page 31).	Thank you for taking the time to review our report. We appreciate your feedback.
TEP Reviewer #3	Discussion/ Conclusion	"Additional areas of promising future research are recommended: • Ongoing research related to optimizing the safety of clozapine, specifically aimed at mitigating the risk of agranulocytosis. This includes pending FDA updates to the Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program (https://www.fda.gov/Drugs/DrugSafety/ucm467560.htm) and studies in progress to better assess the actual risk and possible modification of monitoring requirements for people of African descent with Benign Ethnic Neutropenia (BEN) (https://clinicaltrials.gov/ct2/show/NCT02404155)."	Thank you for these suggestions. Please see the revised future research section.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Discussion/Conclusion	<ul style="list-style-type: none"> The role of nonpharmacological, device-based somatic treatments, including electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS). These are not included in the present review, and several references are noted to be “excluded for wrong intervention.” The de Jesus (2011) reference on a TMS trial is said to be “excluded for inadequate duration,” but the distinction between this and other TMS trials which are described as “wrong intervention” is not clear. 	Thank you for these suggestions. The intent of the review was to focus on the most commonly used interventions and therefore electroconvulsive therapy and transcranial magnetic stimulation were excluded. Please see the revised future research section.
TEP Reviewer #3	Discussion/Conclusion	On the other hand, one of the best recent trials of electroconvulsive therapy (ECT) in schizophrenia, an NIH-funded controlled trial of ECT augmentation in clozapine-resistant patients by Petrides et al. (2015) was in fact, too short (8 weeks) to meet the review’s minimum duration criterion of 12 weeks. On the other hand, perhaps this work is worth citing as “pilot data” for a longer, more definitive trial appropriate for future research. It is noteworthy that this methodology is analogous to the antipsychotic-augmentation trials cited on page E-17 for patients responding inadequately to clozapine monotherapy.	Thank you for these suggestions. The intent of the review was to focus on the most commonly used interventions and therefore electroconvulsive therapy was excluded. Please see the revised future research section.
TEP Reviewer #3	Discussion/Conclusion	<ul style="list-style-type: none"> Another area of promising future research that is attracting a lot of attention in the field is the issue of people, mainly adolescents and young adults, felt to be at “clinical high risk” of developing psychosis. Ongoing work, both nationally and internationally, is aimed at identifying such individuals and studying various treatments, in this case “preventive interventions” aimed at staving off progression to full-blown schizophrenia. One example from the published literature: Liu CC, Demjaha A. Antipsychotic interventions in prodromal psychosis: Safety issues. <i>CNS Drugs</i> 2013; 27(3):197-205. doi: 10.1007/s40263-013-0046-1. 	Thank you for pointing out this citation. It is not eligible for our review since it was not a systematic review, but please see the revised future research section.
TEP Reviewer #3	Discussion/Conclusion	<ul style="list-style-type: none"> Given the previously-noted heterogeneity of the patient samples, future treatment research might consider use or analysis of results with the NIMH RDoC or other transdiagnostic “disaggregation of symptoms” approach, rather than grouping subjects by entire syndromes. 	Thank you for these suggestions. Please see the revised future research section.



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Clarity/ Usability	Yes, the main points are well structured and clearly presented. However, the issue most relevant to practice decisions is just how much treatment a person needs and for how long. One of the dilemmas in the presentation of the findings (which most likely stems from the limitations of the research articles) is less clarity regarding how long an intervention is and what kind of care a person received post study (none, TAU (not defined), other care, continuation of care provided in study, etc.)	We agree with these comments in general, and we would like to have addressed them in our report. The questions for the review did not include this issue, specifically, and the studies themselves were not clearly designed to answer these questions, precluding drawing conclusions. However, this clearly identifies a significant area for future research (including systematic reviews).
Peer Reviewer #1	Clarity/ Usability	And small copy editing points: Page 22: Table A Last box- overall adverse events- something is missing for the statement regarding moderate evidence	Thank you for pointing this out—we have corrected this.
Peer Reviewer #1	Clarity/ Usability	Page 59 of 469- line 38- not limited is repeated (sorry I can't help but find typos!)	Thank you for pointing this out—we have corrected this.
Peer Reviewer #1	Clarity/ Usability	Page 77, line number 7 Remove the comma between white, patients	Thank you for pointing this out—we have corrected this.
Peer Reviewer #1	Clarity/ Usability	Page 81, line 34 You need a word between trials and review	Thank you for pointing this out—we have corrected this.
Peer Reviewer #1	Clarity/ Usability	Page 125 (94) line 49- Do not think it should be "be" after KQ2.	Thank you for pointing this out—we have corrected this.
Peer Reviewer #1	Clarity/ Usability	Page 126, lines 11-12 are unclear	Thank you for pointing this out—we have corrected this.
Peer Reviewer #1	Clarity/ Usability	Page 127, line 39- there ARE several (not a)	Thank you for pointing this out—we have corrected this.
Peer Reviewer #1	Clarity/ Usability	Page 129, line 30- trial should be plural	Thank you for pointing this out—we have corrected this.



Comment ator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Clarity/ Usability	No, the report is not usefully structured, and the lack of important findings are attributed to problems in the research literature, despite the hundreds of studies conducted, with little consideration of the method employed to review the research.	We understand that the reviewer wishes we had a broader scope in our systematic review. We were not able to expand the scope to include all studies (e.g., comparisons to other active treatments) within the confines of the timeline and budget allowed for this work.
Peer Reviewer #3	Clarity/ Usability	Please do not perpetuate the FGA vs SGA distinction in light of considerable evidence of great heterogeneity within these "classes" and inconsistencies in their pharmacology and side effect profiles. The conclusion that SGAs are better than FGAs in effect relegates some very useful drugs, e.g., haloperidol and perphenazine, and perhaps inadvertently assumes advantages of some newer ones of unknown comparative effectiveness.	We can see the reviewer's point. The evidence, however, currently does separate out these groupings, particularly the systematic reviews on which we based our analysis where there was no new evidence.
Peer Reviewer #4	Clarity/ Usability	The report is extremely well structure and organized. It is a timely topic and this will provide an outstanding resource for multiple interested parties. The main points are clearly presented and related well to the Key Questions. The conclusions are relevant to clinical practice and to policy makers--without being too prescriptive. Although most findings are not new--knowing that the research has been thorough vetted and updated is a key contribution to current understanding of this important topic.	Thank you for taking the time to review our report. We appreciate your feedback.
TEP Reviewer #3	Clarity/ Usability	The review is well structured and organized and generally well written. The pharmacologic review is relevant and may inform practice decisions and policy/guidelines. As noted in other sections of this review, I have serious concerns about the psychosocial interventions review and whether it adds new information or understanding.	Thank you for taking the time to review our report. We appreciate your feedback. Please see the revised "Findings in Relationship to What is Already Known" section, where our results are discussed in the context of the findings of other, older reviews.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Clarity/ Usability	Minor points to improve clarity are listed below: There may be some confusion about what “ACT” stands for -- Assertive Community Treatment or Acceptance and Commitment Therapy – especially early in the document. The reference to Assertive Community Treatment is made often in the detailed summary, but not in the Executive Summary. Maybe clarify more often throughout the document or just always spell out and not use “ACT.”	Thank you for this comment—we have used the complete definition at the beginning of each new section where it is discussed.
TEP Reviewer #3	Clarity/ Usability	Abstract line 37-38: This sentence seems to say risperidone has better symptom outcome than risperidone	Please see revised abstract
TEP Reviewer #3	Clarity/ Usability	ES line 12 and 17 and 30: There is some inconsistency here about the number of studies included. Line 12 says 285 studies included but the line before says 29 + 2 reviews were included; then line 33 discusses 33 trials when 29 are described above. Would help to clarify.	Thank you for pointing this out. We have corrected the numbers so that they are now consistent.
TEP Reviewer #3	Clarity/ Usability	ES line 48: “...difference in adverse effects between _____(missing) and olanzapine.”	Thank you for pointing this out. We have corrected this error.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #4	Clarity/ Usability	<p>The report is well-structured and organized, with the main points presented clearly. The strengths and weaknesses of the trials cited are described carefully and dispassionately. The conclusions are relevant to policy and practice but due to the extreme limitations of the underlying data must be narrowly drawn, limiting their potential value. As one example, the risk of metabolic syndrome associated with the use of SGAs has been a concern of the field for years, yet the only definitive data available for this report concerns two comparative trials involving olanzapine and two other SGAs; otherwise, "Evidence for other comparisons was too limited to draw conclusions" (page 34). Needless to say, this is both informative as far as it goes (and an accurate reporting of the published literature), but wholly inadequate for the purpose of clinical decision-making. Even more frustrating are the multiple examples presented (e.g. EPS adverse events in Asian patients, page 46) of two similar studies addressing the same question -- that reach opposite conclusions! Again, this is by no means a failing of the present report; it is a limitation of the dearth of well-designed and -conducted clinical research.</p>	<p>Thank you for taking the time to review our report. We appreciate your feedback.</p>
Public Reviewer #5: Allergan, Gavin Corcoran	General	[Attachment B below]	<p>We reviewed the suggested studies and found one trial of cariprazine to be eligible for the review (Nemeth et al, 2017). This study has been included. The other did not meet our inclusion criteria due to its duration being less than 12 weeks.</p>



Commentator & Affiliation	Section	Comment	Response
Public Reviewer #6: American Psychological Association Task Force on Serious Mental Illness/Severe Emotional Disturbance, Mary A. Jansen	General	[Attachment A below]	We have undertaken work to clarify and take a more granular look at some of the clinical issues noted in further comments (attached below), including analysis of older reviews that came to differing conclusions. We have noted targets (population and outcome) of specific interventions, analyzed duration of treatment in relation to duration of follow up and outcomes/results (where possible), and stratified analyses according to differing intervention specifics (e.g., targets) where possible. Please see the revised final report full text.



Public Reviewer #7: APA Task Force, Susan A. Pickett, Marcia Hunt, and Sandra G. Resnick	General	[Attachment C below]	<p>We thank the members of the American Psychological Association Task Force on Serious Mental Illness/Severe Emotional Disturbance for their comments on our report. We note that our inclusion criteria were initially outlined by the nomination from the American Psychiatric Association, and then further refined with input from a group of Key Informants. Subsequently, a Technical Expert Panel provided in-depth input on the criteria. The Key Informants and the Technical Expert Panel included psychologists and representatives of the American Psychological Association. As a part of measures taken to limit the scope of the project, we limited to studies with usual care comparators. This led to only one study being included for Supported Employment. As a result, according to our “best evidence” approach, we added evidence from a systematic review of 14 RCTs with vocational training comparisons, and a large RCT (N=1,273) with both usual care and vocational training comparisons because this intervention had only 1 trial with a usual care comparison group (unlike the other interventions). We have included text in the discussion regarding our findings in the context of other reviews. Please see this revised text. We appreciate the comments on the tone of the introduction and</p>
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Commentator & Affiliation	Section	Comment	Response
			revised it to incorporate the concept of recovery.
Public Reviewer #8: Courtenay Harding	General	[Attachment D below]	We appreciate the comments and the viewpoint. We have revised the introduction and discussion to view schizophrenia in a context of recovery-based objectives and to acknowledge the heterogeneity of conditions captured under the title schizophrenia.
Public Reviewer #9: David Pickar	General	The piece seriously misses the point that the only antipsychotic with "proven" efficacy over other antipsychotics is clozapine, as determined by the FDA. None of the newer antipsychotics attempted (nor found) superiority over any other antipsychotic. CATIE brings home this truth emphatically - and olanzapine is not superior in a meaningful way from CATIE. It is important to do meta-analyses, etc, but not all trials have the same controlled methods and examinations in comparison to FDA registration studies. Until a company wishes to take on the question of superiority, it's all sort of "fake" news. The importance of pharmacological interention an maintenance of treatment is the overwhelmingly most import part of managing patients with schizophrenia. Psychosocial treatments are well, intended and important, but compliance is overwhelmingly #1.	Thank you for your comments on our review. We have evaluated the methodological quality and risk of bias of each study included in the report. We agree that the CATIE trial was very well done and its findings are important. Many of the currently approved antipsychotic drugs were not included (or available) in that study, such that assessing evidence on them is important.
Public Reviewer #10: Freses	General	[Copy of publication was submitted.]	Thank you for this publication. It did not meet the inclusion criteria for this report, in that it was a correlation study rather than a treatment study.
Public Reviewer #11: Janssen	General	[Copy of publication was submitted.]	We have reviewed the suggested studies and found none that were eligible for this review. We appreciated the suggestions for improvement in wording in the report.



Commentator & Affiliation	Section	Comment	Response
Public Reviewer #12: Mental Illness Policy Org, DJ Jaffe	General	There are no studies done in well over 10 years that show AOT doesn't work. A study before then (Bellevue) was a pilot program not taken statewide until problems were fixed. Another report before then (Rand) said that at that time, the studies weren't controlled well enough, something future studies addressed. Community Treatment Orders in England do not require a court and have little resemblance to use of AOT in US. It would be cruel to those with schizophrenia who have anosognosia or other reasons for refusing care to not report what AHRQ already concluded and extensive other evidence shows: AOT can help them.	Thank you for the summary of this work. These interventions were not included in our review because we were focusing on the most common psychosocial and non-pharmacological interventions used in U.S. practices. Our team's clinical experts felt that these programs are a mechanism to get patients into treatment, rather than a treatment in and of themselves. We have screened the suggested reference for studies that might be eligible for our review, and have added a notation of this evidence in our discussion of the limitations of our review.



Public Reviewer #12: Mental Illness Policy Org, DJ Jaffe	General	<p>References for other studies showing Assisted Outpatient Treatment is an effective treatment modality. Substance Abuse and Mental Health Services Administration, Assisted Outpatient Treatment, National Registry of Evidence-Based Programs and Practices (SAMHSA-NREPP), 2015, Agency for Healthcare Research and Quality (AHRQ), Management Strategies to Reduce Psychiatric Readmissions (May 2015). Department of Justice, Program Profile: Assisted Outpatient Treatment (AOT), 2012, Bruce Link, Matthew Epperson, Brian Perron, et al., Arrest Outcomes Associated with Outpatient Commitment in New York State, Psychiatric Services 62, no. 5 (2011): 504 508, Allison Gilbert, Lorna Mower, Richard Van Dorn, et al., Reductions in Arrest Under Assisted Outpatient Treatment in New York, Psychiatric Services 61, no. 10 (2010): 996 99, Marvin Swartz, Christine Wilder, Jeffrey Swanson, et al., Assessing Outcomes for Consumers in New York s Assisted Outpatient Treatment Program, Psychiatric Services 61, no. 10 (2010): 976 81. New York State Office of Mental Health, Kendra s Law: Final Report on the Status of Assisted Outpatient Treatment (Albany: New York State, 2005), p. 60, Jeffrey Swanson, Richard Van Dorn, Marvin Swartz, et. al., The Cost of Assisted Outpatient Treatment: Can it Save States Money? American Journal of Psychiatry 170 (2013): 1423 32, Alisa Busch, Christine Wilder, Richard Van Dorn, et. al., Changes in Guideline-Recommended Medication Possession after Implementing Kendra s Law in New York, Psychiatric Services 61, no. 10 (2010): 1000 1005, Jeffrey Swanson, Richard Van Dorn, Marvin Swartz, et. al., Robbing Peter to Pay Paul: Did New York State s Outpatient Commitment Program Crowd Out Voluntary Service Recipients? Psychiatric Services 61, no. 10 (2010): 988 95, Marvin Swartz, Christine Wilder, Jeffrey Swanson, et al., Assessing Outcomes for Consumers in New York s Assisted Outpatient Treatment Program, Psychiatric Services 61, no. 10 (2010): 976 81, ; Marvin Swartz, Jeffrey Swanson, Henry Steadman, et al., New York State Assisted Outpatient Treatment Program Evaluation, Office of Mental Health, June 30, 2009, Richard Van Dorn, Jeffrey Swanson, Marvin Swartz, et al., Continuing Medication and Hospitalization Outcomes after Assisted Outpatient Treatment in New York, Psychiatric Services 61, no. 10 (2010): 982 87, Michael Heggarty, The Nevada County Laura s Law Experience, Behavioral Health Department, November 15, 2011, Marvin Southard, Assisted Outpatient Treatment Program Outcomes Report, Department of Mental Health, February 24, 2011, Virginia</p>	<p>Thank you for this list of citations, but they are of an intervention that was not included in the review, as discussed above.</p>
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Commentator & Affiliation	Section	Comment	Response
		<p>Hiday and Teresa Scheid-Cook, The North Carolina Experience with Outpatient Commitment: a Critical Appraisal, International Journal of Law and Psychiatry 10, no. 3 (1987): 215 32, Mark Munetz, Thomas Grande, Jeffrey Kleist, et. al., The Effectiveness of Outpatient Civil Commitment, Psychiatric Services 47, no. 11 (1996): 1251 53. Robert Van Putten, Jose Santiago, Michael Berren, Involuntary Outpatient Commitment in Arizona: A Retrospective Study, Hospital and Community Psychiatry 39, no. 9 (1988): 953 58. Barbara Rohland, The Role of Outpatient Commitment in the Management of persons with Schizophrenia, Iowa Consortium for Mental Health Services, 1998, h Treatment Advocacy Center, Success of AOT in New Jersey Beyond Wildest Dreams, September 2, 2014, Virginia Hiday, Marvin Swartz, Jeffrey Swanson, et al., Impact of Outpatient Commitment on Victimization of People with Severe Mental Illness, American Journal of Psychiatry 159, no. 8 (2002): 1403 11, Jeffrey Swanson, Marvin Swartz, Richard Van Dorn, et. al., Racial Disparities in Involuntary Outpatient Commitment: Are They Real? Health Affairs 28, no. 3 (2009): 816 26, Copyright, 2017, Mental Illness Policy Org. Appendix D of Insane Consequences: How the Mental Health Industry Fails the Mentally Ill by DJ Jaffe, (Prometheus Books, April 2017).</p>	



<p>Public Reviewer #13: NEOMED (Northeast Ohio Medical University), Frederick Frese</p>	<p>General</p>	<p>Thank you for sending this systematic review on Treatments for adults with schizophrenia . I have two comments: 1. Recently there have been two RCT studies from Europe indicating that schizophrenia patients followed over extended periods of time often do better when they are not on antipsychotic medications. These studies, which are not referenced in the paper, are important and should not be ignored. These papers are: o Wunderink et al., 2013 o L. Wunderink, et al. o Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation or maintenance treatment strategy: long-term follow-up of a 2-year randomized clinical trial o JAMA Psychiat. (Chicago, Ill.), 70 (9) (2013), pp. 913 920 o [SD-008] And Antipsychotic medication and remission of psychotic symptoms 10 years after a first-episode psychosis Regitze S lling Wils, MD, , 1 , , Ditte Resendal Gotfredsen, MD, 1 , , Carsten Hjorth j, MSci, PhD, c , , Stephen F. Austin, MSci, PhD, b , , Nikolai Albert, MD, , Rikke Gry Secher, MSci, PhD, , Anne Amalie Elgaard Thorup, MD, PhD, , Ole Mors, MD, PhD, c , Merete Nordentoft, MD, PhD, Dr. Med.Sci.b, c, Show more http://dx.doi.org/10.1016/j.schres.2016.10.030</p> <p style="text-align: right;">Abstract</p> <p>Background Several national guidelines recommend continuous use of antipsychotic medication after a psychotic episode in order to minimize the risk of relapse. However some studies have identified a subgroup of patients who obtain remission of psychotic symptoms while not being on antipsychotic medication for a period of time. This study investigated the long-term outcome and characteristics of patients in remission of psychotic symptoms with no use of antipsychotic medication at the 10-year follow-up. Methods The study was a cohort study including 496 patients diagnosed with schizophrenia spectrum disorders (ICD 10: F20 and F22 29). Patients were included in the Danish OPUS Trial and followed up 10 years after inclusion, where patient data was collected on socio-demographic factors, psychopathology, level of functioning and medication. Findings 61% of the patients from the original cohort attended the 10-year follow up and 30% of these had remission of psychotic symptoms at the time of the 10-year follow up with no current use of antipsychotic medication. This outcome was associated with female gender, high GAF-F score, participation in the labor market and absence of substance abuse. Conclusion Our results describe a subgroup of patients who obtained remission while not being on antipsychotic medication at the 10-year follow-up.</p>	<p>This is very interesting—thank you for providing these references. While the question of the impact of stopping medications was not posed as a review question, we are addressing this issue in the discussion of the report and have cited these there.</p>
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Commentator & Affiliation	Section	Comment	Response
		<p>The finding calls for further investigation on a more individualized approach to long-term treatment with antipsychotic medication. 2. I find no references to publications by mental health professionals who have actually experienced schizophrenia. As is well known, the mantra of the consumer advocacy movement is Nothing about us without us . I strongly feel that the words of those in recovery should not be ignored. Drs. Ed Knight, Elyn Saks, and I have produced an article naming some ten psychologists, psychiatrists and other doctoral level mental health professionals who have themselves been diagnosed with schizophrenia and cite some of their publications reflecting their views on treatment. I followed this with another publication identifying some 33 such individuals who have experienced psychotic episodes. These publications are: *Frese, F., Knight, E. L., & Saks, E. (2009). Recovery from schizophrenia: With views of psychiatrists, psychologists, and others diagnosed with this disorder. Schizophrenia Bulletin, 35(2): 370-380. Frese, F. (2015). Advocacy, stigma, and self-disclosure: A personal perspective. In E. J. Bromet, (Ed.). Long Term Outcomes in Psychopathology Research: Rethinking the Scientific Agenda. (pp. 227- 237). New York: Oxford University Press. There are of course many similar publications by persons in recovery from schizophrenia and similar serious mental illnesses. I am hopeful that the authors of the systematic review will acknowledge the two items that I have mentioned above. Thank you for any consideration you may give to these comments.</p>	



Commentator & Affiliation	Section	Comment	Response
Public Reviewer #14: Oregon State Hospital, Jessica Murakami-Brundage	General	I understand the purpose of this document and appreciate all of the work and thoughtful analyses that went into it. That said, I do have questions about the general tone of the document and the following statement on pg. ES1: Consistent with limited understanding of the causes and best treatments of schizophrenia, prognosis remains poor, with nearly 80 percent of patients continuing to require varying forms of social support throughout their lives. This is not consistent with long-term studies of individuals diagnosed with schizophrenia, where the majority of people recover. See the following review: https://cpr.bu.edu/wp-content/uploads/2011/11/harding2003.pdf The long-term studies reviewed in this chapter are notable, because the definition of recovery was defined through the lens of the medical model (functioning well in the community, lack of symptoms, etc.) rather than the disability model, and is consistent with the lens that was used to conceptualize AHRQ's draft report. Also, I think it would be worthwhile to include the answer to the question of "How effective are these treatments?" (rather than "How effective are they compared to treatment as usual?"). If treatments are somewhat more effective than fairly effective treatments, that is different than if treatments are somewhat more effective than fairly ineffective treatments. Thank you for your consideration.	<p>We appreciate these suggestions and the concern over the tone of the introduction. We have revised the document in various places to emphasize the concept of recovery in patients with schizophrenia. We have considered the cited review in our revision of the introduction. Please see the revised text.</p> <p>We also appreciate your thoughts on the Key Questions. Unfortunately, at this stage of the review the questions cannot be altered.</p>
Peer Reviewer #1	General	The report is clinically meaningful but will require some "translation" to be useful for most individuals. The results are presented in a detailed, straight facts format with little interpretation or even aggregation of related information. It thus requires a clinician to hold much information and weigh small pieces of information against one another to try and determine best paths.	Thank you for taking the time to review our report. We appreciate your feedback.
Peer Reviewer #1	General	It is unclear how much input consumers had into this review-involving them in the translation of this report will be valuable.	Thank you. In accordance with AHRQ methods, we included a patient representative in our Key Informant group.
Peer Reviewer #1	General	The target population and key questions are appropriate and clearly stated.	Thank you for taking the time to review our report. We appreciate your feedback.
Peer Reviewer #2	General	My page numbers refer to the numbers for the overall document (top of page).	Noted.



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General	please see my attached review, which covers all of the areas required below in considerably greater detail. [Comments have been added to the disposition table.]	Thank you for taking the time to review our report. We appreciate your feedback.
Peer Reviewer #2	General	This review is extremely flawed, with problems ranging from the methods taken to the specification of critical outcomes, the review of the extant literature (most of which is excluded for one reason or another), and the conclusions drawn. Central to the problem of the review is that there appears to be a lack of expertise in schizophrenia and its treatment, and familiarity with the treatment literature, among the primary team of individuals who conducted the review. An informed review of the research literature requires some knowledge of treatments and research, and understanding of research on the treatment of schizophrenia. Consultation with experts in the area is not a substitute for inexperience and lack of knowledge among the review team if they don't know how to use the expertise available to them. The use of somewhat arbitrary rules for rating the characteristics of research studies (such as methodological rigor quality of evidence) does not result in a rigorous and useful review if it is not informed by an understanding of the purposes of specific research studies.	We would naturally like for the reviewer to find this systematic review useful and have undertaken work to clarify and take a more granular look at some of the clinical issues noted in further comments, including analysis of older reviews that came to somewhat differing conclusions. Our review team included clinicians with expertise in schizophrenia (2 psychologists and 1 psychiatrist) and those with expertise in the methodology and practice of conducting high quality systematic reviews and outcomes research methodology, using methods derived and approved by the AHRQ. We are confident that these methods are sound and well informed. We also engaged Key Informants and Technical Experts while developing the scope of the report.



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General	In the specific points below, examples of major problems in the review are highlighted. However, it would not be possible or worth the time to compile an exhaustive list of the problems. Overall, this review is a disservice to both the field of researchers in schizophrenia, where significant progress in treatment has been made over the past several decades, and the public, which has a right to know what treatments for schizophrenia have been shown to be effective.	The methods used in this review are the currently applied standards in evaluating effectiveness of treatments, and may differ from those used in older reviews. Additionally, new evidence was added, which may also have affected prior findings. We have undertaken additional stratification of our analyses based on duration of treatment, intervention variation, and population characteristics as suggested in other comments, have added notation of the targets of interventions, and a thorough analysis of the findings of other, older, reviews that came to differing conclusions to this review (see revised results and discussion).



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General	<p>Treatment Priorities:</p> <p>1. Problems with the review team are immediately apparent when inspecting the prioritization of the key outcomes for the pharmacological and psychosocial outcomes (pp. 42-43). For both areas, “health related quality of life” is the second priority, which generally refers to subjective ratings of satisfaction with different areas of one’s life, including physical health. However, subjective quality of life ratings in schizophrenia tend to be very stable over time (influenced only by dramatic life circumstances such as hospitalization, incarceration, or homelessness) and are only modestly related to more objective indicators of functioning. People with mood disorders consistently have worse self-rated quality of life than people with schizophrenia, despite the fact that they have less severe symptoms and functional impairment. Quality of life ratings in schizophrenia tend to be trait-like, are not especially sensitive to the effects of interventions, and while of concern they belong lower on the list of priority outcomes.</p>	<p>The list of outcomes was created with input from Key Informants and a Technical Expert Panel. The perspective of the review was the patient – how do the interventions affect the outcomes that are most important to them? While the interventions may have had a smaller impact on some of these highly prioritized patient-centered outcomes, they may be effective for the targeted purpose. Depending on the target, these outcomes are addressed in the report as well, but with lower priority. However, some outcomes were not included in the review, such as positive symptoms, because they were not prioritized – presumably because most interventions included in our report have some beneficial effect on these outcomes. During our discussions with the experts, there was no controversy over including quality of life as an outcome, and our experts judged it to be highly important.</p>



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General	<p>2. Functioning is listed as the most important outcome for evaluating the effects of both types of intervention. However, the primary effects of medications are on reducing symptom severity and preventing symptom relapses. Reducing symptoms is listed as 6th out of 8 outcomes, and relapse prevention isn't even included for pharmacological treatments! Of course, improving functioning is the primary goal of treatment, but the evaluation of interventions needs to be mindful of what the target of the intervention is, and focus on the evaluation of those targets. If someone had an infection that caused high fever, nausea, and diarrhea, which prevented the person from going to work, it would make sense to evaluate a medication primarily in terms of its effects on those immediate signs of the infection rather than the person's ability to work.</p>	<p>The list of outcomes was created with input from Key Informants and a Technical Expert Panel. Improvements in function were prioritized as the most important patient-centered outcome. The perspective of the review was the patient – how do the interventions affect the outcomes that are most important to them? While the interventions may have had a smaller impact on some of these highly prioritized patient-centered outcomes, they may be effective for the targeted purpose. Depending on the target, these outcomes are addressed in the report as well, but with lower priority. However, some outcomes were not included in the review, such as positive symptoms, because they were not highly prioritized – presumably because most interventions included in our report have some beneficial effect on these outcomes.</p>
Peer Reviewer #2	General	<p>The reviewers would benefit from attention to the concept of “proximal” vs. “distal” targets of an intervention, in which immediate focus of an intervention is expected to have the strongest effect (i.e., on the most proximal outcomes), and to have weaker effects on less immediate (or distal) outcomes, which can be influenced by a greater range of non-treatment related intervening variables. Reducing symptoms and preventing relapses are clearly the most proximal targets of pharmacological treatment, and should be listed as the primary outcomes of interest.</p>	<p>We agree with this concept. This is why we focus our analysis of intervention effectiveness on randomized controlled trials, and is also the reason that intention-to-treat analyses are preferred and given a higher quality rating when used. We have added notation of the target of specific interventions (population and outcome) to specific intervention sections.</p>



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General	3. "Rates of response and/or remission" are listed as the 3rd most important outcome for pharmacological treatments and 4th for psychosocial treatments. However, the definitions of response and remission are almost always based on symptom measures (sometimes in combination with functioning), they involve the application of somewhat arbitrary rules to clinical data, and they are less frequently measured across different studies. It is difficult to see why this outcome was given the priority it was.	The list of outcomes was created with input from Key Informants and a Technical Expert Panel, the latter of which also assisted with prioritizing the outcomes. While the definition of response is certainly acknowledged to be a potential problem, it is regarded as a meaningful outcome for patients.
Peer Reviewer #2	General	4. Reduction in self-harm, suicide, and suicide attempts are the 3rd priority for psychosocial treatments and 5th for pharmacological treatments. However, these events are relatively low probability events for a given treatment episode, and it doesn't make sense that their prevention would be considered more important than reducing symptom severity and preventing relapses, which we know are related quality of life, psychosocial functioning, and self-injurious behavior.	The list of outcomes was created with input from Key Informants and a Technical Expert Panel. The perspective of the review was the patient – how do the interventions affect the outcomes that are most important to them? In this context, self-harm, including suicide outcomes, are highly important outcomes for patients and their families. Certainly because the incidence is low, interventions may have a smaller impact, but any beneficial impact was considered important. It is also the perspective of comparative effectiveness reviews that the distal, health outcomes are the most important. If the reduction in symptoms and improvement in functioning lead to reductions in self-harm, we would like to see studies that focus on the most distal, most important health outcome; in this case suicide outcomes.



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General	5. "Ability to maintain treatment" (listed 6th for psychosocial treatments) would not be considered by most people in the field to be a valuable outcome on its own.	The list of outcomes was created with input from Key Informants and a Technical Expert Panel, the latter of which also assisted with prioritizing the outcomes. We agree that for psychosocial interventions, it is less clear how this outcome is best measured, and what it means in the context of interventions that are not all intended to be applied long-term. For simplicity, we have changed the wording to "treatment discontinuation" as recommended by other reviewers.



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General	6. While improving functioning is the primary focus of many psychosocial interventions, the specific focus of treatment may vary from one intervention to the next, and even within intervention. For example, many family interventions have targeted relapse prevention, and many cognitive behavioral therapy (CBT) studies have targeted severity of psychotic symptoms. Thus, stating that improving functioning is the primary outcome of interest for all psychosocial interventions fails to take into account the specific nature and target of the psychosocial treatment (a problem that comes up in other ways in the review; see points #15 and 23 below).	As noted, the prioritization of the list of included outcomes was based on input from the Technical Expert Panel, which included many experts in the field. We also note that the primary outcome of a study (the target outcome) is important, but not to the exclusion of other outcomes, particularly those that are patient-centered. The list of outcomes and their prioritization was created from the perspective of how important the outcomes are to the patient and the clinician treating them, not to the researcher designing a study. Function was considered to be the most important outcome to patients, and therefore we want to know if each intervention has an impact on this outcome, regardless of whether it was a primary (target) or secondary outcome per the trial methods. We have highlighted the target of the intervention in the revised text.



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General	7. Rehospitalization was ruled out as a “flawed” outcome (e.g., many factors affect rehospitalizations other than relapses and symptom severity), but despite its limitations it is important and deserves consideration. Psychiatric hospitalization is often correlated with symptom relapses, but it is easier to measure (i.e., it doesn’t require symptom monitoring over time) and arguably it has a more disruptive effect on the community functioning of patients than relapses. Both assertive community treatment (ACT) and family interventions have explicitly targeted reduction in hospitalizations, and excluding this outcome leads to a less useful summary of the literature on these approaches.	We agree that the implications and reasons for hospitalization are a proxy for serious negative outcomes for both patient and family, but it was ultimately decided that the lack of generalizability of this outcome across studies, time, and setting made it not useful in making comparisons of treatment outcomes. Even within studies, individual patients and providers may have different thresholds for hospitalization, for example depending on the patient’s social network and resources. Other reviewers have raised this issue as well. We note that the list of outcomes was created with input from Key Informants and a Technical Expert Panel. We have edited the report include rehospitalization for ACT, where this outcome is in fact the target of the intervention for specific populations at higher risk of rehospitalization. For family interventions, relapse was the identified target and sometimes included rehospitalization as a proxy for relapse.



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General	8. Cognitive functioning is not included as an outcome, which is consistent with many previous reviews, but probably deserves reconsideration. There is widespread agreement that impaired cognitive functioning is a critical component of schizophrenia, with reductions in cognitive functioning usually preceding onset of psychotic symptoms, and poor cognitive functioning associated with impaired psychosocial functioning. Symptoms are widely considered to be an important target of treatments, and thus there is some inconsistency in excluding cognitive functioning as an important outcome on its own.	We certainly agree with the reviewer that cognitive functioning is impaired in many patients with schizophrenia and would be an important outcome if we had valid and reliable methods to assess it in terms of real world improvements, rather than intermediate or surrogate outcomes typically reported.



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General	<p>Methodology:</p> <p>9. The reviewers ruled out RCTs of psychosocial treatments with an active comparator group, but the rationale for this and its implications were not discussed. This would probably have the strongest effect on the review of research on CBT for psychosis (which has often used active comparator interventions), vocational rehabilitation (which has typically compared supported employment with other vocational programs), and social skills training. While the nature of the control group is of interest when reviewing treatment research, simply ruling out all studies that had active comparators can lead erroneous conclusions, as appears to be the case especially for supported employment.</p>	<p>The decision to focus Key Question 2 on comparisons with usual care was made as part of a set of decisions required to reduce the scope of the project. After identifying a large body of evidence for Key Question 2, we determined that the funding and timeline required a reduction in scope. We first decided to use systematic reviews as the primary evidence, with subsequently published trials included as well. In examining those, we saw that most reviews mixed active and attention controls, even mixing with usual care sometimes. Many, however, reviewed usual care comparisons separately, or exclusively. Therefore, within the systematic reviews, usual care was the most commonly reported comparison group. In the end, we included well over 200 studies of the 12 psychosocial interventions that made comparisons to usual care. We agree that assessing the comparative effectiveness of two interventions might come to different conclusions than our review, but we note that there were several trials of, for example, Cognitive Behavioral Therapy versus usual care. We have added discussion of this issue to the applicability section of the discussion.</p>



Peer Reviewer #2	General	10. Overly generalized descriptors are used to summarize computed indices that are intended to summarize the methodological quality of a study and the evidence supporting treatment effects. However, these descriptors are neither informative nor helpful. For example, what are readers to make of the statement that only about 10% of the RCTs reviewed were of “good” quality, or that no study of a psychosocial intervention had “high strength evidence” for any outcome of interest (pp. 20, 112)?	The methodology used to assess individual study quality and the strength of evidence for a given outcome associated with an intervention are well developed and described in the AHRQ Evidence-based Practice Center Program Methods Guide. This methodology has been used many times in reviewing psychosocial interventions. We refer the reviewer to the quality and strength of evidence ratings of the pharmacological therapies in this report where similar proportions of studies were “good,” “fair,” and “poor” and where the majority of the bodies of evidence were judged to be low strength of evidence (several were moderate in Key Question 2). These ratings reflect the fact that even well-designed trials can have some risk of bias through imperfect execution. This does not mean the evidence is useless, but does mean that the reader should understand the level of potential bias. In rating the strength of evidence, high strength means that there is essentially no room for change in the results with new studies. This is a very high bar and requires multiple large studies with consistent results and low risk of bias. Across reviews of various types of interventions, this is uncommon.
Peer Reviewer #2	General	The use of these descriptors paints a bleak picture of the current state of research on the treatment of schizophrenia, and the overriding message to readers is that not much can be concluded about	The methodology used to assess individual study quality and the strength of evidence for a given



Commentator & Affiliation	Section	Comment	Response
		<p>anything from the abundant research conducted in the field. The rules used for these descriptions are of questionable validity and utility (especially to the extent that they are drawn from other areas of medicine), and there is little discussion as to what the methodological limitations are of most studies reviewed (how serious are they?) and the limits of the evidence for interventions (e.g., psychosocial treatments need to demonstrate persistence of effects after treatment, but how reasonable a requirement is this?). The general impression is one of imposing impossibly “high” standards on the field, without grappling with the relevance, importance, and reasonableness of those standards.</p>	<p>outcome associated with an intervention are well developed and described in the AHRQ Evidence-based Practice Center Program Methods Guide. This methodology has been used many times in reviewing psychosocial interventions. We refer the reviewer to the quality and strength of evidence ratings of the pharmacological therapies in this report and also in any random selection of AHRQ reports to see that psychosocial interventions in this report have very similar range and weight of quality and strength of evidence ratings.</p>
Peer Reviewer #2	General	<p>11. Throughout the review, the results of entire literature reviews are often given the same level of importance as specific studies published since the reviews were completed. There is a lack of balance in weighing the evidence from the reviews with research published since.</p>	<p>We disagree and feel that the reviewer may have misunderstood our methods in this review. The prior reviews served as the primary source for evidence, with newer studies added. We synthesized the evidence, not as “1 review plus 2 new studies”, but “1 review of 22 trials plus 2 new trials—24 trials total.” In many cases we updated meta-analyses conducted in these reviews (where possible and appropriate).</p>



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General	<p>Assertive Community Treatment:</p> <p>12. There is a lack of recognition that the ACT program was developed to address the problem of frequent hospitalizations and poor functioning in a subgroup of patients who fail to utilize community-based services. Most (but not all) of the studies have focused on this population, with more questionable benefits associated with ACT for patients who use lower levels of services.</p>	<p>We have added notation that the target of Assertive Community Treatment is rehospitalizations in this specific population of patients and have added this as a reported outcome for this intervention.</p>
Peer Reviewer #2	General	<p>13. The Pederson et al. (2005) study added to the review of RCTs on ACT (p. 82) was really an evaluation of the OPUS first episode psychosis program, which in addition to ACT-based services also included social skills training and family psychoeducation. It is not really an ACT study proper, and does not target the usual population targeted by ACT.</p>	<p>Thank you for pointing out this error. We have removed this study from the section on Assertive Community Treatment, and is now presented along with the other OPUS study results in the section now called team-based multi-component treatment.</p>
Peer Reviewer #2	General	<p>Petersen, L., Jeppesen, P., Thorup, A., Abel, M. B., Øhlenschlaeger, J., Christensen, T. Ø., Krarup, G., Jørgensen, P., & Nordentoft, M. (2005). A randomised multicentre trial of integrated versus standard treatment for patients with a first episode of psychotic illness. <i>British Medical Journal</i>, 331.</p>	<p>Thank you for pointing out this error. We have removed this study from the section on Assertive Community Treatment, and it is now presented along with the other OPUS study results in the section now called team-based multi-component treatment.</p>
Peer Reviewer #2	General	<p>Cognitive Behavioral Therapy (CBT):</p> <p>14. It is stated that “Control groups among the trials included in the reviews varied, although all were an approximation of usual care” *(p. 85), this isn’t really accurate. Many of the RCTs in this area had active control groups that were not a reflection of usual care, which were in many cases designed to control for non-specific factors, such as “befriending” or supportive therapy. There is evidence of modest effects of supportive therapy, and there is a difference between a study comparing CBT to usual care with one comparing it to an active control group.</p>	<p>Thank you for this comment. After discussion with our team, including our content and methodological experts, we had decided to include some interventions as comparators that were considered to have minimal effect (e.g., befriending), as has previously been done in other reviews. We have taken your comment into consideration and stratified the evidence according to true “usual care” and these other, few interventions.</p>



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General	15. A more fundamental problem with the review of CBT studies is that it does not take into account what the target of the intervention was. CBT is a therapeutic tool that can be used to address problems in a wide range of different areas, such as psychotic symptoms, negative symptoms, or psychosocial functioning, and patients are typically selected based on symptoms or impairments in the areas targeted by the treatment. In many of the earlier studies, the target of the CBT program was persistent psychotic symptoms. Over time, the focus of the target broadened and shifted to other domains, such as negative symptoms and psychosocial functioning. For example, studies of CBT that focused primarily on psychotic symptoms selected patients with persistent psychotic symptoms (e.g., studies by Garrety, Tarrrier, Sensky/Kingdon/Turkington, Birchwood), whereas those that focused on psychosocial impairment and lower overall functioning (or a specific area of functioning such as work) selected patients based on those impairments (e.g., Granholm, Grant, Lysaker).	Thank you for this comment. We have added notation of the target of the Cognitive Behavioral Therapy in the trials or reviews we included and stratified the results where there were very different targets (e.g., employment versus symptoms, positive versus negative symptoms). Similarly, we re-assessed the characteristics of patients enrolled to look for impact on outcomes/results. Please see the revised Cognitive Behavioral Therapy section in the full text of the report.
Peer Reviewer #2	General	Combining effect sizes for outcomes across different studies that did vs. did not target a particular outcome, which is what all the meta-analyses of CBT for schizophrenia have done, can lead to a reduced estimate of the impact of the intervention on the targeted outcome (e.g., the effect size of CBT for improving psychotic symptoms in studies targeting psychotic symptoms and selecting patients for high and persistent psychotic symptoms would be expected to be higher than in studies targeting poor functioning where many participants might not have flagrant psychotic symptoms). In short, the research literature on CBT for schizophrenia cannot be meaningfully reviewed without taking into consideration the intended target of the CBT program in the study. This issue has been discussed in Mueser and Glynn (2014).	We have read the paper by Dr. Mueser on this topic with interest. In the revised text on Cognitive Behavioral Therapy, we have added an additional discussion of the studies according to target, as well as across targets.
Peer Reviewer #2	General	Mueser, K. T., & Glynn, S. M. (2014). Have the potential benefits of CBT for severe mental disorders been undersold? <i>World Psychiatry</i> , 13, 253-6.	Thank you for this citation. We have read this paper and revised the text accordingly.



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General	16. Sellwood et al. (2001) is a family intervention study, not a CBT study and shouldn't be included as a CBT study (p. 85).	Thank you for your comment. We have added this study to the family intervention section and removed it from the Cognitive Behavioral Therapy section.
Peer Reviewer #2	General	17. The UPSA is included as a measure of functional outcome, but it is actually a skills based measure of the ability of someone to perform a functional skill—not the same as a measure of functioning itself (p. 86), in contrast to the ILSS on the same page.	Yes, we agree. We have added additional text to clarify this point.
Peer Reviewer #2	General	Cognitive Remediation: 18. There is no mention in this section of the fact that 3 prior reviews of cognitive remediation have reported that receipt of adjunctive (or integrated) psychosocial treatment moderates the effects of cognitive remediation on functional outcomes (stronger effects in studies where cognitive remediation was added to a psychosocial treatment program).	Please see the revised text for a discussion of how and why our results differ from the findings of other reviews.
Peer Reviewer #2	General	McGurk, S. R., Twamley, E. W., Sitzer, D. I., McHugo, G. J., & Mueser, K. T. (2007). A meta-analysis of cognitive remediation in schizophrenia. <i>American Journal of Psychiatry</i> , 164, 1791-802.	Thank you for this citation. We have cited it in our section comparing other reviews findings to ours, and note that the Wykes review that we included is actually an update of this older review with new studies added.
Peer Reviewer #2	General	Tan, S., Zou, Y., Wykes, T., Reeder, C., Zhu, X., Yang, F., Zhao, Y., Tan, Y., Fan, F., & Zhou, D. (2016). Group cognitive remediation therapy for chronic schizophrenia: A randomized controlled trial <i>Neuroscience Letters</i> , 626, 106-11.	Thank you for this citation. We excluded this review because the studies are from China, a setting that was determined to not be directly relevant to U.S. healthcare settings for this review.
Peer Reviewer #2	General	Wykes, T., Huddy, V., Cellard, C., McGurk, S. R., & Czobor, P. (2011). A meta-analysis of cognitive remediation for schizophrenia: Methodology and effect sizes. <i>American Journal of Psychiatry</i> , 168, 472-85.	Thank you for this citation. It has been included in the final report both in the results section and in the section comparing our results to those of other reviews. It is also an update of one of the 3 reviews noted in this comment.



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General	<p>Supported Employment: 19. Nowhere is the review more discrepant with what is well established in the literature than on the topic of interventions targeting employment outcomes. The review states “Low strength evidence suggests that supported employment interventions are not associated with improvements in employment outcomes or the ability to maintain treatment” (p. 20). In contrast to these conclusions, there are over 20 RCTs of supported employment, with many studies including over 50% schizophrenia participants, with the overwhelming findings being that supported employment is more effective than usual vocational services or other specific vocational rehabilitation approaches in getting people competitive jobs, and cumulative hours worked and wages earned in competitive jobs over 18-24 months.</p>	<p>This text has been changed by limiting the evidence to only Supported Employment as an intervention. This resulted in changing the conclusions for Supported Employment, to a finding that is consistent with the reviewer’s comment; there is evidence of benefit on multiple employment outcomes. For comparisons with usual care, there was only one trial. As a result, for this particular intervention, we used a best evidence approach and added evidence from a systematic review of 14 RCTs with vocational training comparisons, and a large RCT with both usual care and vocational training comparisons. We have included text in the discussion regarding our findings in the context of other reviews. Please see this revised text. Our findings are now concordant with these reviews for most outcomes.</p>



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General	The problematic conclusions of the review may be attributed to a variety of reasons, including omitting studies that compared supported employment to other vocational programs, and the definition of what supported employment is. Most studies of supported employment have compared it to other vocational programs. To drop the findings of these studies (e.g., skills training, diversified work placement, psychosocial clubhouse), most of which found better competitive work outcomes for supported employment, misses an important trend in this research: supported employment has been found to result in better competitive work outcomes than a broad range of other vocational rehabilitation models.	The decision to limit to usual care comparisons was made due to inability to conduct a broad, comprehensive review that would include head to head comparisons of treatments within our available timeline and budget. Across all of the psychosocial interventions, usual care was the most common comparator used. However, for this particular intervention, to better reflect the literature base, we used a best evidence approach and added indirect evidence from a systematic review of 14 RCTs with vocational training comparisons, and a large RCT with both usual care and vocational training comparisons. We have included text in the discussion regarding our findings in the context of other reviews. Please see this revised text. Our findings are now concordant with these reviews for most outcomes.
Peer Reviewer #2	General	Drake, R. E., Bond, G. R., Goldman, H. H., Hogan, M. F., & Karakus, M. (2016). Individual Placement and Support services boost employment for people with serious mental illnesses, but funding is lacking. <i>Health Affairs</i> , 35, 1098-105.	Thank you for this citation. We have reviewed it and determined it is not a study, but did review the reference list.



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General	20. It states that included in supported employment are interventions which involve prevocational training (p. 93), which is an activity that is clearly inconsistent with the principles of supported employment, as specified by the most standardized version of supported employment, the Individual Placement and Support (IPS) model. Becker, D. R., & Drake, R. E. (2003). <i>A Working Life for People with Severe Mental Illness</i> . New York: Oxford University Press. Drake, R. E., Bond, G. R., & Becker, D. R. (2012). <i>IPS Supported Employment: An Evidence-based Approach</i> . New York: Oxford University Press.	Thank you for pointing out this important differentiation. We have removed the pre-vocational training studies that were included in the Cochrane review and pooled with Supported Employment studies. This section is now focused only on supported employment interventions.
Peer Reviewer #2	General	21. There are numerous IPS studies missing, many that were included in some of the previous reviews, but are not listed specifically as being excluded, with over 50% schizophrenia, such as:	Thank you for this list. We have reviewed the Individual Placement and Support studies identified and determined that one is eligible for our review (Meuser et al.), and it is now included.
Peer Reviewer #2	General	Bond, G. R., Salyers, M. P., Dincin, J., R.E., D., Becker, D. R., Fraser, V. V., & Haines, M. (2007). A randomized controlled trial comparing two vocational models for persons with severe mental illness. <i>Journal of Consulting and Clinical Psychology</i> , 968-82.	Thank you for this citation. This study was included in a systematic review (Kinoshita, 2013) which we have now included in our review.
Peer Reviewer #2	General	Drake, R. E., McHugo, G. J., Bebout, R. R., Becker, D. R., Harris, M., Bond, G. R., & Quimby, E. (1999). A randomized clinical trial of supported employment for inner-city patients with severe mental illness. <i>Archives of General Psychiatry</i> , 56, 627-33.	Thank you for this citation. This study was included in a systematic review (Kinoshita, 2013) which we have now included in our review.
Peer Reviewer #2	General	Mueser, K. T., Clark, R. E., Haines, M., Drake, R. E., McHugo, G. J., Bond, G. R., Becker, D. R., Essock, S. M., Wolfe, R., & Swain, K. (2004). The Hartford study of supported employment for severe mental illness. <i>Journal of Consulting and Clinical Psychology</i> , 72, 479-90.	Thank you for this citation. We have added this study to our report. Please see the revised text.



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General	Family Intervention: 22. Studies from China were excluded from the review but it is unclear what the impact of this exclusion might have been on the findings.	As per our methods, we focused on U.S.-relevant settings. The Cochrane review conducted multiple sensitivity and subgroup analyses to examine the impact of studies from China and determined that they consistently result in higher point estimates than studies from the United States. This is consistent with other research that finds studies from China often overestimate treatment effects. We have added discussion of the findings of the Cochrane sensitivity analyses to our report.
Peer Reviewer #2	General	23. Similar to point #15 above, some studies of family intervention specifically targeted reduced relapses and rehospitalizations, but not others. Distinguishing between such studies could be important, as those focusing on the prevention of relapse typically enrolled patients and relatives in treatment following a relapse or hospitalization, and thus focused on a subgroup of patients at high risk for relapse.	Thank you for this comment. We have added discussion of the target and have re-assessed the characteristics of patients at baseline across the studies. Please see the revised text in the full report.
Peer Reviewer #2	General	24. Inattention to the duration of the family program is another problem with the review. The literature on family intervention has accumulated over more than 30 years, with very clear trends indicating that longer-term family interventions (e.g., 6 months or more) are more effective at reducing relapse/rehospitalization rates than shorter term programs. Discussion of this frequently reported association was missing in the review.	Thank you for this important distinction. We have added analysis of the duration of treatment in relation to outcomes, notation of the target of the intervention, and rehospitalization as a proxy for relapse (as reported in studies).



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General	Pitschel-Walz, G., Leucht, S., Bäuml, J., Kissling, W., & Engel, R. R. (2001). The effect of family interventions on relapse and rehospitalization in schizophrenia: A meta-analysis. <i>Schizophrenia Bulletin</i> , 27, 73-92.	Thank you for this citation. We excluded this review in favor of a more recent systematic review (Pharoah, 2010). The Pharoah review included all the studies in the Pitschel review except one trial with less than five intervention sessions and one trial in hospitalized patients. The Pharoah review also included several more recently published trials not in the Pitschel-Walz review.
Peer Reviewer #2	General	Illness Management and Recovery (IMR): 25. There is a need to describe the nature and focus of each of the psychosocial intervention in order for readers to understand the nature and goals of the intervention. It might be noted that IMR is the name of a specific illness (self) management program for persons with severe mental illness, and that the broader category of interventions reviewed would be considered illness self-management programs.	Thank you for these comments; we have added description of this and other interventions, making it clear that Illness Management and Recovery is a specific form of illness self-management program and referring to this intervention category using the broader term. We have also added more details in the descriptions of other interventions.



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General	<p>Social Skills Training:</p> <p>26. Considering the number of studies that have been conducted on social skills training, inclusion of only 3 RCTs in the review is problematic (e.g., Kurtz & Mueser identified 22 studies in their meta-analysis of schizophrenia). This would appear to be the result, at least in part, of excluding studies with active comparator groups. Again, it is worth reconsidering the inclusion/exclusion criteria for selecting studies when they end up ruling out the majority of RCTs that have been conducted on a type of intervention.</p>	<p>We appreciate the comment that there are many studies making other comparisons for some particular interventions that were not included here. We have added a note about this other literature and cited this review. To add context, we have noted this review in our text of the full report, and noted how the results compare to the results of the three studies included that compared interventions with usual care. We also added a comparison of findings to the discussion section.</p>
Peer Reviewer #2	General	<p>Kurtz, M. M., & Mueser, K. T. (2008). A meta-analysis of controlled research on social skills training for schizophrenia. <i>Journal of Consulting and Clinical Psychology</i>, 76, 491-504.</p>	<p>Thank you for this citation. We discuss this and other reviews in our section on how our findings compare to other, older reviews. In this case, the review used studies that were smaller than 50 patients and shorter than 12 weeks. However, we note that our findings are consistent with this and other prior reviews.</p>
Peer Reviewer #2	General	<p>Conclusions and Other Comments:</p> <p>27. It is likely that ruling out so many of the studies conducted on the treatment of schizophrenia (in many cases, ruling out 50-75% of RCTs with > 50% schizophrenia-spectrum participants) reduced the power of this review to detect and confirm effects. A more informed and nuanced approach to reviewing the research literature is required.</p>	<p>We have included all studies covering 13 psychosocial interventions that compared to usual care and met our other criteria, a total of 271 trials of >20,000 patients. Studies making comparisons with specific other interventions are excluded and would have provided evidence on a different question that was addressed in our review.</p>



Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General	28. The correct name for the Positive and Negative Symptoms Scale (one of the most widely used symptom scales in research on schizophrenia) is the Positive and Negative Syndrome Scale (PANSS) (p. 17).	Thank you; this typographical error has been corrected.
Peer Reviewer #2	General	29. The statement that the findings of this review of psychosocial treatment are similar to other reviews of the area is just plain wrong (p. 25).	Please see our revised text on comparison with other reviews, which has been expanded to include older reviews and specifically reviews with differing findings. We find that most of our conclusions in the revised report are in alignment with these reviews. We point out areas of difference and possible reasons for these differences.
Peer Reviewer #2	General	30. The statement that “Other than CBT, a key limitation of the ability to understand the applicability of the evidence is the lack of clear definitions or variation in definitions, of the interventions and poor reporting of the intervention details” (p. 27). While this certainly applies to some studies, there is much more clarity on most of the published interventions than what the reviewers give credit for, and the statement appears to be more of an excuse for dealing with the weak findings.	We agree that not all studies are unclear, but in a large proportion there was vagueness in description of the specific intervention, and the duration and/or timing of outcomes. We have revised this sentence to be clear on this point.
Peer Reviewer #2	General	31. The recommendations for future research are not especially informative for the field (e.g., clearly define and categorize the interventions) (p. 28).	Based on other reviewer comments, we have revised and updated the future research section.
Peer Reviewer #2	General	Overall, this is a poor review that does not advance the state of understanding about what treatments are effective for schizophrenia.	Please see the revised final report and our responses to comments in this document.
Peer Reviewer #3	General	This comparative effectiveness review is extremely relevant and clinically meaningful. It will be an important update for mental health and primary care providers, hospital systems and both government and Commercial health plans. The key questions are straight forward, explicitly stated and [sentence ends here, cut off]	Thank you for taking the time to review our report. We appreciate your feedback.



Commentator & Affiliation	Section	Comment	Response
Public Reviewer #15: Poetry for Personal Power, Corinna West	General	Look, this whole study is focused on stuff that doesn't even matter to people. Bob Whitaker did a very careful review of the data and found that antipsychotics don't even improve outcomes in the long term. You are asking the wrong questions and using the wrong literature and not even paying attention to what patients need.	We appreciate the reviewer's comments and would like to hear what the more meaningful question and literature are.



<p>Public Reviewer #2, Anonymous</p>	<p>General</p>	<p>I looked forward to this report, but found the draft highly limited and its conclusions misleading. The criteria and outcomes used and the way they was employed were, in my view, not in the service of substantially answering the report s focal questions. I found quite a few questionable details in the report (such as evaluating ACT as if it was a general psychosocial intervention for schizophrenia when it was actually developed to assist a narrow sub-group). However, for brevity I will focus on several larger aspects of it that I found troubling. First, methodologically, I was struck by the lack of inclusion of mixed-methods research and high quality quasi-experimental designs that allow better real life testing of outcomes. I did not see any rationale for this exclusion in the draft. Surely we have advanced beyond seeing RCTs as the only worthwhile evidence? Especially regarding health care and its provision, these other designs and paradigms have their own strengths that compliment RCTs that have been well recognized regarding schizophrenia treatment and more broadly in mental health care, as well as their own limitations. To best guide decision-making we need to integrate them into conclusions as well. Second, I was struck by the exclusion of trials where the control condition was an active intervention. Yes heterogeneity among control conditions is a challenge in reviews, but many psychosocial interventions of interest are routinely tested against active controls because it is a more rigorous test of their effectiveness and gives results that are more practically useful for improving care. This decision excluded a great deal of high quality research in several areas, compromising this review. I am noticed this especially of supported employment and social skills training, but the problem applies to many sections. Third, in the psychosocial intervention sections, I found the use of general functioning overly-generic and worrisome. Most psychosocial treatments focus on specific domains or skills which together enable the person to function better, a la psychiatric rehabilitation programs, and do not target global functioning. This is not a flaw of these programs, it is good clinical effectiveness practice and fosters personalized medicine. Fourth, I noticed that relapse prevention was not even included. This is a puzzling mistake as it is a crucial target for psychiatric meds and some psychosocial interventions due to the highly disruptive (to person, life functioning, community) nature of schizophrenia relapse. Further, relapse is more often accessible to accurate measurement than daily functioning while also factoring centrally in a person s ability to function so it is an important</p>	<p>We appreciate the commenter's thoughts and encourage them to read the final report, which reflects some changes in the evaluation of the psychosocial interventions evidence that address some of these concerns. For example, the target of the intervention (outcome and population) are now highlighted in each intervention section, explicit comparisons to prior reviews with differing findings are made in the discussion, and for Assertive Community Treatment and family interventions, where decreasing relapse and rehospitalizations were the targets, we have added this outcome. As for the study design eligibility, we followed the AHRQ methods guidance and sought input from a group of Key Informants and Technical Experts (see report for details) on these and other issues. We did not receive suggestions to include these study designs. The choice of comparator for psychosocial interventions as usual care was necessary due to the resource and time limitations allowed by the funder. It was determined that usual care was a good place to start, a more real-world comparator, more generalizable, and was the most commonly used comparator. The incidence of relapse was an outcome that we included for the psychosocial interventions, and is reported for several psychosocial interventions (e.g., Cognitive</p>
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Commentator & Affiliation	Section	Comment	Response
		<p>outcome. (I had the same problem with the exclusion of re-hospitalization). My comments are not to be interpreted as implying that there is not room for improvement. Far from it. For example, funding for trials of psychosocial interventions for schizophrenia and other serious mental illnesses has been supremely difficult in recent years hampering our ability to test and replicate and improve intervention potency. But this review does not accurately summarize what IS known, nor the state of the field regarding evidence and quality. I was left with the impression that those preparing the report were doing so as technicians applying criteria developed without thorough knowledge of this area of research and practice, doing so in rote ways not grounded in the strengths and weaknesses of the literature, and then drawing conclusions without crucial context in the field. Treatment of and personal recovery regarding schizophrenia is hugely challenging and complex, both at individual and health system levels, and for research. However there has been a lot more progress, and there is a lot more reason for optimism and determination among people with schizophrenia, their loved ones, and service providers than this report depicts. As a health services researcher in this area, I regrettably cannot avoid concluding that that policy makers; health care system architects and administrators; people with schizophrenia and their health care providers, families, and communities; researchers; and the public will be ill served if this misleading report is released in current form.</p>	<p>Behavioral Therapy and Illness Self-Management and Recovery). For pharmacological interventions, relapse was not prioritized among the top 8 patient-centered outcomes, but was reported under "Other Outcomes" in the full report text.</p>



Public Reviewer #3, Anonymous	General	<p>1) Throughout the manuscript, evidence in support of psychosocial interventions is described as small to moderate. Although the evidence in support of pharmacotherapy included in the manuscript tables also falls under the small to moderate category, these qualifiers are never used to describe pharmacotherapy. This inconsistent use of qualifiers opens up a great risk that the reader will misinterpret the strength of the evidence in support of pharmacotherapy as greater than that of psychosocial interventions.</p> <p>2) Antipsychotic medication is described as the foundation of treatment. Although such medications are effective with certain symptoms, they have little to no effect on functional or cognitive outcomes which comprise the key areas of disability associated with schizophrenia. Medications are a key aspect of treatment. However, describing medications as the foundation of treatment is an overstatement of their role in recovery in schizophrenia.</p> <p>3) In Table C, it appears that the same study of CSC is sometimes describe as moderate quality evidence and sometimes described as low quality evidence. What is the rationale for this inconsistency?</p> <p>4) Given the sheer number of studies excluded from the study, the majority of the evidence-base with regard to treatment of schizophrenia is not utilized in the current study. As this document will likely have large influence on treatment decisions for schizophrenia, exclusion of so much evidence may provide incomplete (at best) and potentially inaccurate (at worst) conclusions with regard to effective treatment of schizophrenia</p>	<p>We thank the commenter for reviewing our report and providing these comments. The evidence is assessed for drug and non-drug interventions using strength of evidence ratings of low, moderate, high or insufficient. We did not apply this methodology or terminology only to describe the psychosocial interventions. These ratings do not depend on the numbers of studies, but on the study limitations, directness evidence, and consistency and precision of the findings of the body of evidence. The comment on Table C can be explained within these methods as well (see the AHRQ Evidence-based Practice Centers Methods Guide) in that each outcome is evaluated separately. The strength of the evidence for one outcome is not necessarily the same as for another. For example, if 12 large, high quality studies report on outcome A, but only 1 fair quality, small study reports on outcome B, the strength of the evidence on outcome B is generally lower—meaning that it is more likely that future studies would change these findings. We were not making direct comparisons of drug and non-drug interventions, but the strength of evidence for psychosocial interventions included more instances of moderate strength evidence (as opposed to low strength of evidence) than the drug therapy</p>
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Commentator & Affiliation	Section	Comment	Response
			evidence did. We did describe the volume of evidence differently because there are numerous, very different, types of psychosocial interventions, each with its own body of evidence.



<p>Public Reviewer #4, Anonymous</p>	<p>General</p>	<p>This ambitious review comprises most of the clinical outcome literature on schizophrenia, focusing on antipsychotic drugs, especially SGAs, and psychosocial treatments and interventions, limited to those in common use. In an attempt to be thorough and rigorous, it has seemingly overlooked data, especially regarding psychosocial interventions, that might paint a more positive picture of outcomes achieved in those studies that were of higher quality. Several of the conclusions stand in contrast to outcomes reported by studies of high quality, suggesting that some studies with lower quality are diminishing the impact in the meta-analyses. In particular, family interventions and supported seem to suffer from this issue. Of the studies known to this reviewer, some of which he conducted, strong efforts were made to control fidelity, blinding of assessments and rigorous cleaning and analysis of many dimensions of outcome data assessed with widely used instruments. Those studies routinely reported outcomes superior to those in the meta-analyses.</p> <p>The review states that outcomes at 36 months for family interventions showed no difference with usual care. However, the number of studies reporting those outcomes is exceedingly small, especially since the stated result suggests that those interventions are ineffective. The implication is that treatments should continue to have effects long after they are discontinued in a very severe and chronic illness, while such an expectation would never be assigned to pharmacologic treatment.</p> <p>Another problem is that the review cites psychosocial interventions as having poor definition. That is the direct result of journals shortening reports to the point that describing these complex treatment models has become impossible in the outcome study articles. The reviewers need to include cited, detailed descriptions of the interventions, which are almost always in other publications, especially books and treatment manuals. Lack of such citations or sources would constitute another evidence for poor quality, which should reduce the impact of those studies on the overall analysis.</p> <p>The most serious problem with this and its cited reviews is not ranking studies of psychosocial interventions based on fidelity measures. The assumption in the review is that these treatments are like drugs—prescribed or not prescribed. The contrary evidence</p>	<p>We appreciate these comments. For the family interventions section, we have revised the text to more clearly show the types of interventions included in each study, highlighting studies that included psychoeducation as a component. We examined the duration of intervention versus the follow up time and results, and reported the impact of studies conducted in China (which we excluded). We also added text on how our review findings compare to other reviews. We note that our findings did not differ substantially from the Cochrane review for the outcomes that were prioritized for our review. Please see the revised text on family interventions. For supported employment, we narrowed the section to only this specific intervention, which meant excluding the Cochrane review we had included previously because it had also included pre-vocational training. For the comparison with usual care, we ultimately included one trial with a usual care comparison, and a systematic review with 14 trials that used vocational training controls, and a large trial that used usual care and vocational training controls. We added a description of supported employment, but the family intervention studies include a range of poorly described interventions, which we have now listed in a table. The issue of fidelity is, of course, meaningful</p>
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		<p>is clear on this issue: for ACT, family interventions and supported employment, and likely for CBT, fidelity determines outcomes. High fidelity begets high impact on outcome, and vice versa. Fidelity in these review is thus treated as equivalent to purity of drug delivered, which is always assumed to be high in outcome studies of those agents. Thus, the review is suspect in including many psychosocial treatment studies in which fidelity was either poor or at least not assessed or reported. A case in point is Cook’s massive and highly rigorous test of supported employment, which documented highly significant and very substantial effects on competitive employment, reaching over 50% in most sites, but which also thoroughly specified the interventions and had internal controls on fidelity. That all but definitive study stands in stark contrast to the review, which finds no effect on employment for this intervention. The same problem applies to the comparator, “usual care”. This is also treated as a unitary controlled intervention, as would be placebo in a drug trial. This also needs specification, which varies widely in psychosocial intervention studies, thereby affecting the apparent efficacy of the test treatment.</p> <p>This review of psychosocial treatment studies could be substantially improved by including quality of study, especially fidelity to the treatment model being tested, and specification of the “usual care” control intervention. The review should then report on outcomes of studies of high quality in contrast to those of lesser quality. A small criticism is that the seemingly grudging admission that some psychosocial interventions might be effective cites CBT as the example, when other interventions have a much deeper evidence base.</p>	<p>and could impact the results of these studies. We did assess and reported the quality of studies, as well as the strength of evidence according the international standards. Unfortunately, the number of studies assessing fidelity was so small, it would eliminate most studies if we limited to these. We have added notation about fidelity if it was reported. The decision to focus Key Question 2 on comparisons with usual care was made as part of a set of decisions required to reduce the scope of the project. After identifying a large body of evidence for Key Question 2 we determined that the funding and timeline required a reduction in scope. We first decided to use systematic reviews as the primary evidence, with subsequently published trials included as well. Examining those we saw that most reviews mixed active and attention controls, even mixing with usual care sometimes. Many, however, reviewed usual care comparisons separately, or exclusively. Therefore, within the systematic reviews, usual care was the most commonly reported comparison group. In the end we included well over 200 studies of the 12 psychosocial interventions that made comparisons to usual care. We agree that what constitutes usual care certainly varied across the studies, and would have preferred more reporting on what</p>
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Commentator & Affiliation	Section	Comment	Response
			treatments patients in these study arms actually received.
Public Reviewer #17: Sonovion, Patel	General	<p>Please review the following publications cited below for consideration for inclusion in this report. These publications, in addition to Meltzer, et al., 2011, established the efficacy and safety of lurasidone for the treatment of adult patients with schizophrenia. Ogasa M, Kimura T, Nakamura M, Guarino J. Lurasidone in the treatment of schizophrenia: a 6-week, placebo-controlled study. <i>Psychopharmacology (Berl)</i>. 2013;225(3):519-530.</p> <p>Nakamura M, Ogasa M, Guarino J, et al. Lurasidone in the treatment of acute schizophrenia: a double-blind, placebo-controlled trial. <i>J Clin Psychiatry</i>. 2009;70(6):829-836.</p> <p>Nasrallah HA, Silva R, Phillips D, et al. Lurasidone for the treatment of acutely psychotic patients with schizophrenia: a 6-week, randomized, placebo-controlled study. <i>J Psychiatr Res</i>. 2013;47(5):670-677.</p> <p>Loebel A, Cucchiaro J, Sarma K, et al. Efficacy and safety of lurasidone 80 mg/day and 160 mg/day in the treatment of schizophrenia: a randomized, double-blind, placebo- and active-controlled trial. <i>Schizophr Res</i>. 2013;145(1-3):101-109.</p>	We have reviewed the suggested studies and found that only the Nemeth 2017 study met our inclusion criteria, and it was added to the report. The other studies were excluded because they either precluded our search dates for second generation antipsychotics, which began in 2013 due to the inclusion of an existing systematic review, and/or because they did not meet eligibility criteria for duration or comparator.
TEP Reviewer #1	General	I have a number of overall comments about the report that don't fit neatly into the categories below. They mostly relate to methods. I have some serious concerns:	Noted. Please see our response to specific concerns.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	General	1) The omission of hospitalization as an outcome of interest is problematic. Yes, there are problems with the outcome of hospitalization, but many outcomes have problems. Hospitalization is a key a priori outcome of ACT and to some extent FPE, and is of tremendous interest to policy makers. Its omission is a big problem in my view.	The outcomes for the review were created with input from Key Informants and a Technical Expert Panel. Overall, the perspective of the outcomes selected for this review were that they be patient-centered. Hospitalization was not included, although it was discussed at stakeholder meetings. We have added information on the target of all of the interventions, and since the target of Assertive Community Treatment is to reduce frequent rehospitalizations in patients with a history or at risk of this outcome, we have reported it for completeness. In reviewing the studies of first episode psychosis, we noted that the studies identified relapse as the target, which was reported in our review.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	General	2) Several of the psychosocial interventions including employment and family intervention, and probably others, grouped a variety of interventions with very different characteristics together. This, I believe, led to erroneous conclusions.	The section on supported employment has been limited to this specific intervention, removing the prevocational training studies. These were pooled together in a Cochrane review we used (their primary analysis) and we mistakenly reported them together. The family intervention section has been revised to evaluate the components of the interventions, with a focus on whether those with family psychoeducation versus those without differ in results. We also evaluated duration of treatment and number of sessions. Please see the revised text. These revisions have led to different, and more nuanced conclusions for both.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	General	3) There were times that international studies were excluded because it was said that they "do not apply." I would like to know the criteria that were used to determine that something does not apply.	As described in the methods, we limited study inclusion to those conducted in the U.S. or U.S.-relevant countries (those listed as "high" or "very high" on the United Nations International Human Development Index) and applicable to current U.S. practices. For example, in the family interventions section, several studies conducted in China were excluded. We felt that the family structure and dynamic in China were importantly different to those in the U.S., even for Chinese immigrants. Additionally, in our analysis and others, Chinese studies appear to over-estimate the effect, and in the Cochrane review's assessment were suspected of not being truly randomized.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	General	4) There was a great deal of focus on whether the impact of psychosocial interventions extended beyond the end of the treatment period. I would like to see greater justification/discussion of whether that is a standard to which all programs should be held. We do not expect that from medication.	The effect of treatment beyond the end of the treatment period was frequently reported in studies of psychosocial interventions, thus we included those results here. This was not a decision on the part of the reviewers, but the way the studies were designed. Other reviewers commented that they would like to see more evidence to inform the best duration of treatment, and how long the effects last (including drugs). We have noted in the revised report that there is interest in evidence on discontinuing drug therapy as well.
TEP Reviewer #1	General	5) Another example of a strange grouping of psychosocial interventions reflecting some lack of understanding of the actual clinical program is the discussion of Coordinated Specialty Care (CSC). CSC is an invention of the NIMH which is its best effort to synthesize the literature. Most of the international literature preceding RAISE did not test CSC (i.e., no IPS) and it doesn't make sense to talk about it that way. It's hard to know what to make of that section.	We appreciate this distinction, and have modified the section to refer to these interventions in more descriptive terms and no longer use the phrase 'Coordinated Specialty Care.'
TEP Reviewer #1	General	6) The inclusion of 3. Directness (direct or indirect) 4. Precision (precise or imprecise) as part of the SOE rating is also of some interest and should be debated. It seems to make assumptions about the importance of context that could be challenged.	We appreciate the reviewer's comments on the complexity of assessing the domains of the strength of evidence (GRADE) rating system. There are numerous publications surrounding these issues, and we suggest the Journal of Clinical Epidemiology series on GRADE.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	General	7) While the overall structure of the document was clear and organized and well written, I found some of these decisions so distracting and problematic that I had trouble reading through it. I also alerted colleagues with more detailed knowledge of some of the study areas to please review this as a number of the findings are strikingly inconsistent with previous review processes.	Thank you for your comments and for asking colleagues to comment. We believe that the report is much improved as a result. The final report reflects the input of the reviewers.



TEP Reviewer #1	General	<p>5. Family Psychoeducation. The reviewer has several concerns about the section on family psychoeducation. First, the reviewers appear to have been very limited in their selection of studies. They based their conclusions predominantly on one Cochrane review (Pharoah F, Mari J, Rathbone J, et al., 2010) without considering other review articles (e.g., McFarlane et al., 2003; Dixon et al., 2000) or even previous Cochrane reviews. Interestingly, a more recent Cochrane review concluded that psychoeducational interventions “significantly reduced relapse and readmission rates, enabled fewer hospital days, increased medication adherence, increased satisfaction with mental health services, and improved quality of life” (Xia, Merinder, and Belgamwar, 2011).</p>	<p>When multiple systematic reviews existed, we included the most recent and/or highest quality review available. The inclusion of multiple systematic reviews for each intervention was not practical, unless reviews focused on different outcomes (e.g., Cognitive Behavioral Therapy). Table 1 from McFarlane, 2003 lists the major outcome trials of family psychoeducation. All of these trials are included in the Cochrane review by Pharoah, with the exception of 2 trials conducted in China (which we would have excluded) and 1 small trial without a usual care arm for comparison. The Pharoah review also included several more recently published trials not in the McFarlane article. This is the benefit of using the most recent good quality review. The studies included in Dixon, 2000 that are not included in the Pharoah review are excluded from our review because they do not provide patient-centered outcomes, do not have a usual care arm, were conducted in China, or had a sample size less than 50. The Pharoah review also included several more recently published trials not in the Dixon article. We agree that the Cochrane review (Xia, Merinder, and Belgamwar, 2011) indicates lower risk of relapse with psychoeducation. However, the intervention of psychoeducation is</p>
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Commentator & Affiliation	Section	Comment	Response
			<p>not limited to the family setting or with family members so not all studies included in this review are relevant to our review of this intervention. Additionally, the review authors expressed concerns about applicability of their findings: "Most trials were undertaken in hospital, whereas the majority of people with schizophrenia are treated in the community. We are unsure that, in the context of well-functioning community services, psychoeducation, as a separate package, has a place. This is the sort of information that would not be difficult to generate. As many of the included trials are conducted in China, the findings of this review are applicable to the Chinese population. Nevertheless, most of the included Chinese trials are also conducted in hospitals, thus raising the same concern that it may be inappropriate to apply the results to community based patients." (Xia, 2011)</p>



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	General	My second issue is the negative spin on the Cochrane review they did use. The Pharoah et al. article has this statement in the Abstract, "Family intervention may decrease the frequency of relapse (n = 2981, 32 RCTs, RR 0.55 CI 0.5 to 0.6, NNT 7 CI 6 to 8) ... reduce hospital admission (n = 481, 8 RCTs, RR 0.78 CI 0.6 to 1.0, NNT 8 CI 6 to 13) and encourage compliance with medication (n = 695, 10 RCTs, RR 0.60 CI 0.5 to 0.7, NNT 6 CI 5 to 9). Family intervention also seems to improve general social impairment and the levels of expressed emotion within the family." That seems quite different from the tone of the AHRQ comparative review.	Our reporting is consistent with the Cochrane review findings, although our review includes some outcomes that the Cochrane review does not report in the abstract, and some of their reported outcomes were not prioritized for this review. For example, we also report that relapse is significantly reduced. We have added rehospitalization where it was explicitly reported as a proxy for relapse for this intervention and note that this was generally one of the targets of the intervention. Our revised text has been clarified on the benefits of family interventions, but the outcomes reported are those prioritized for this report, such that some of those quoted here (e.g., compliance with medication) are not reported in our review.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	General	Third, the rationale was unclear for excluding articles to supplement the findings of the Cochrane review. I did not systematically evaluate this but I did look for our 2012 article in the Archives of General Psychiatry only to discover that it was “excluded for wrong setting”, whatever that means.	We have searched our excluded studies list and were not able to locate this study. We also searched for a 2012 article in Archives of General Psychiatry with this reviewer as an author but were unsuccessful. We would be glad to review this study if the reviewer would like to send it to us, or point out which study it is in our excluded studies list. We excluded studies for “setting” when they were either entirely conducted in inpatients (or had a large proportion of inpatients included), or was conducted in a non-US applicable country. See our inclusion criteria in the methods section.
TEP Reviewer #1	General	Finally, the basis for using the term ‘low strength’ to describe the evidence for the effectiveness of family psychoeducation seems arbitrary. They defined ‘low strength’ as “limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both).” Unfortunately, the AHRQ reviewers did not specify how they arrived at this conclusion (which, in any event, is contradicted by the literature reviews mentioned above). Rather, they just cited the Comparative Effectiveness Research Methods Guide. I looked at the Guide and it does contain five domains (i.e., study limitations, consistency, directness, precision and reporting bias) with some criteria to distinguish low, medium and high strength, but the authors failed to specify how they came to their conclusion based on the selected studies.	We believe the reviewer is referring to the brief description of methods in the executive summary. A more detailed description of our methods is presented in the main report text, and specific intervention-outcome assessments are presented in Appendix H. The strength of evidence methods are fully peer reviewed and based largely on the GRADE methodology.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	General	The level of methodological thoroughness and rigor and the amount of work that went into creating this document and its associated appendices is astronomical. The authors deserve kudos for this massive undertaking! The report is definitely of clinical relevance. For some of the information, particularly that related to pharmacotherapy, it is difficult to grasp the "big picture" of the implications for clinical practice due to the complexities of the available data. The target population is well delineated and the key questions are appropriate and explicit. The audience for the report includes guideline developers and policy makers as well as clinicians and others who are interested in the topic and this is described in the document.	Thank you for these comments. We appreciate the amount of time this reviewer has taken to review our report in detail. We appreciate your feedback.
TEP Reviewer #2	General	p 6 Line 10 -- the phrase "mental health illness" seems oddly worded. The more useful meaning is "mental illness" when referring to disorders.	Thank you for this suggestion.
TEP Reviewer #2	General	p 6 Line 25 -- it would be good to mention funding source since this was included in the evidence tables and is a common source of possible study bias.	We have added notation of this in the abstract.
TEP Reviewer #2	General	p 6 Line 29 -- to my knowledge, there isn't a marketed oral form of paliperidone that is in an immediate release form. I don't think most clinicians realize that the extended release formulation is the oral tablet that most people just know as paliperidone. Also, the long-acting injectable paliperidone includes the 1 month long formulation (Sustenna) and the 3 month long formulation (Trinza). Because both of the latter have the generic name paliperidone palmitate, there is potential for confusion. Ordinarily, we wouldn't suggest using trade names but for this circumstance it may create less potential for confusion to the reader.	This is a good idea; we appreciate this input and have revised the text accordingly and with notation about this when the drugs are introduced in the report.
TEP Reviewer #2	General	p. 6 line 54 -- the comparisons of older SGAs to FGAs were predominantly using haloperidol as the FGA. It may be preferable to state this specifically, unless the data on perphenazine and fluphenazine is sufficiently robust to make this point for FGAs in general.	Thank you for this comment. We have taken your advice and modified this sentence.
TEP Reviewer #2	General	p. 6 line 57 -- some of these benefits of active treatment seemed to extend out for over a year. I'm not sure that I would have viewed that as a short-term benefit.	We agree, and we changed the wording to "during on-going treatment."



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	General	This table is very helpful! Do we have any sense of what a clinically meaningful difference would be for these scales? If so, it would be nice to include. If not, it's still a useful table since one can get a general sense of the spread of the numbers to determine whether a several point change is likely to be important.	Thank you. We also thought that would be great, initially, but found that it was too difficult to find data for clinically meaningful differences that were valid and reliable across all of the scales.
TEP Reviewer #2	General	The amount of detail is important to have and appropriate for purposes of transparency and rigorous methodology and the characteristics of each study are very well described in the appendices. I am unaware of any other studies that should have been included. Due to the nature and scope of the review, placebo controlled trials had to be excluded. However, the review does cite a systematic review of placebo controlled trials that provides sufficient support for antipsychotic pharmacotherapy relative to placebo and helps to justify the decision to focus only on head-to-head trials.	Thank you for taking the time to review our report. We appreciate your feedback.
TEP Reviewer #2	General	Unfortunately, given the complexity of the data and the large number of comparisons, it is difficult to read through the document and derive clear "take home messages" from it that could be used for clinical decision making. The summary tables provide some assistance in making sense of the data and the key points in each section are helpful as well. Nevertheless, even these efforts at summarization produce a fairly complicated set of comparisons.	We appreciate this comment and have endeavored to improve readability.
TEP Reviewer #2	General	The other issue that makes the information a hard for readers to interpret is the emphasis on the strength of the evidence in the discussion as compared to the magnitude of the effect. Although the text includes summary statistics and confidence intervals, readers do not generally have a quick mental construct of what these numbers mean in practice. Including a corresponding estimate of effect size (i.e., no effect, small, medium, large) or number needed to treat (or harm, for adverse effects) would be a helpful addition to the information on the strength of evidence. This information is included in the tables of Appendix H but the numbers are expressed in differing terms (e.g., relative risks, odds ratios, standardized effect sizes). This emphasis on strength of evidence is understandable as an outgrowth of the GRADE approach, but it is one of the aspects of GRADE that creates difficulties for integrating findings into clinically useful guideline recommendations.	This is an excellent comment and we agree with it. Our constraints are that the evidence just is not amenable to conversion to one format to convey magnitude of effect, and most often there is little information to guide us in weighing these magnitudes of effect in terms of clinical relevance.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	General	<p>Consequently, some additional comparison tables would be helpful to crystallize the key points based on specific treatments rather than an organization based on outcomes. For guideline development and for clinical decision making, more broadly, one must weigh the pluses and minuses (e.g., benefits and adverse effects) of one treatment as compared to the pluses and minuses of other treatment options and also determine whether there are specific subgroups of patients for whom benefits or adverse effects may differ based on individual characteristics. Given the huge amount of information in the document, it is difficult to know what the best way would be to display all of the possible comparisons to summarize the findings in a format that would be easy for readers to comprehend.</p>	<p>We agree that in a large and complex review such as this one it is quite difficult to present the information in an easily understandable format. We appreciate the reviewer highlighting some of the difficulties and the needs of the readers. Our Summary of Evidence table, per AHRQ format, is an effort to provide this information, but we understand that it is not ideal.</p>
TEP Reviewer #2	General	<p>One possible suggestion would be to have a table organized as follows: (*see example table).</p> <p>The Drug and Comparator rows should include all possible pairs of drugs, even though such as for the newer SGAs where no data is available. There would need to be BenefitsOutcome columns for each of the possible benefits (1 through N) and similarly for each of the possible harms. The strength of evidence (low, moderate, high) could be represented by the format of the font (italics, underline, bold) and the color of the font could represent the direction of the effect. The wording of the text could describe the magnitude of the effect (i.e., no effect, small, medium, large). Other layouts may also be possible that would convey the same information in a summary format, but that still preserves key information on the presence or absence of studies on a given comparison, the quality of the evidence and the magnitude of the effect.</p>	<p>Thank you very much for the excellent outline and discussion of what would be most useful. We have undertaken a version of this suggestion in our report—please see the final version that is noted in the discussion and included in the final Appendix I.</p>



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	General	Guideline development also requires making hierarchical assessments of which drug should be used before another drug in a treatment sequence or alternatively, whether some drugs should not be use as a first line choice (typically due to excessive risk, but in some instances due to lower efficacy). When selecting one drug over another drug, one has to synthesize the effects across all outcomes, not just those outcomes that have been studied with that drug and not just those outcomes that have been studied and have a moderate or high strength of evidence.	This is an excellent point and most likely is true for other uses of the review as well. We have attempted to create a table that achieves most of these goals, but were not able to accommodate all of the wishes in one table. Please see the new table in the discussion of the complete report text.
TEP Reviewer #2	General	It is conceivable that a treatment may be chosen for it's effect on a particular outcome, depending upon the symptoms, functional impairments or other outcome related factors that a patient is exhibiting. In this context, it may be useful to know whether specific patients are more or less likely to respond based upon their baseline value of a particular outcome measure. For example, if a particular treatment has a moderate strength of evidence and a medium effect size for social functioning, one might be prone to choose it for a patient with low social functioning as compared to a drug with stronger effects on other outcomes. However, it is possible that the treatment works well in improving function for those with moderate to high social functioning at baseline but works much less well for those with very low social functioning at baseline. This is a distinct question from looking at patient subpopulations based on demographic characteristics or diagnostic co-morbidity, but is important if we are to ultimately individualize care to patients. If such information is unavailable, it would be useful to add to the section on future research needs.	Thank you for articulating this idea. We agree that this would be the ideal use of evidence. As the reviewer suspected, we do not have this level of granularity in the currently available evidence to draw such conclusions, outside of the subgroup analyses as noted. This may be an area where decision analysis could play a role, and we have added this to the future research section.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	General	Another table that may be helpful to add, if the information is available, is one that notes the percentage of individuals with a particular outcome (benefit or harm). Patients, families and clinicians often wish to know what their chances are of responding to a particular treatment or experiencing a particular benefit or adverse effect (particularly for serious effects or effects that are of concern to them such as weight gain). Having outcomes available in terms of proportions allows data to be incorporated into patient decision aids more easily. Again, this information may not be readily available as part of the current review, but it could be included as another topic that should be fleshed out in future research.	We certainly agree that for some users this information is useful and would be desirable. In reviewing the evidence we have available to us, after using numerous systematic reviews as our primary source of evidence, we find that we do not have these data across comparisons and outcomes. We have added a note about this in the future research section.
TEP Reviewer #2	General	Finally, not all of the text and tables include citations to the articles that are being referred to. This is important to have for each sentence or table row since we are using the review for development of guidelines. This is especially needed given the new National Guidelines Clearinghouse approach to rating the quality of guidelines, which requires that the references supporting a particular guideline recommendation be explicitly noted if the guideline is to receive the highest quality rating.	Yes, we intended to complete this process in the finalization of the report. These have been added.
TEP Reviewer #3	General	The report is clinically relevant and key questions are appropriate and well stated in detail. The target audience is described to some extent but it is not clear whether this is intended for consumers and family members. It seems intended for researchers and maybe providers. Could be clearer.	Thank you for taking the time to review our report. We appreciate your feedback.
TEP Reviewer #4	General	A striking, if indirect, finding of this review that may be worth highlighting is the extent of heterogeneity of patients falling under the umbrella heading of Schizophrenia. While it is acknowledged that reviewed studies included in some cases subjects with schizoaffective and schizophreniform disorder, it is notable that even within the more narrow Schizophrenia diagnosis, issues such as the relative predominance of positive and negative symptoms could have an effect on responses to various pharmacological and psychosocial interventions.	Thank you for this good point. We have added this to the section on applicability.



Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #4	General	The unique nature of Clozapine might be more explicitly highlighted. On the one hand, clozapine is typically reserved for otherwise treatment-refractory schizophrenia, such that in contrast to other SGAs, clozapine subjects are unlikely to be in a first episode of psychosis or have a relatively short duration of illness; by the time they are in a clozapine trial, they are likely to be suffering from the complications of a chronic psychotic illness well beyond the acute symptoms. On the other hand, the need for routine blood monitoring and other risk mitigation programs ensures a certain amount of regular clinical contact. Presumably, clozapine subjects by definition are adherent to treatment or they will be unable to stay on the drug. And they may benefit from the nonspecific support and structure provided by the risk mitigation programs, beyond the pharmacologic effects of the drug. While hopefully all these effects benefit the patient, they make comparative effectiveness evaluations involving clozapine more complicated.	Thank you for this good point. We have added this to the discussion.
Public Reviewer #20: West, Robert Whitaker	General	[Attachment E below]	We appreciate the commenter taking time to submit comments.
Public Reviewer #1, Anonymous	Introduction	[Redacted]	No comment.
Public Reviewer #1, Anonymous	References	[Redacted]	No comment.
Public Reviewer #1, Anonymous	Abbreviations	[Redacted]	No comment.



*TEP Reviewer #2: Example table

Drug	Comparator	BenefitsOutcome1	BenefitsOutcome2	BenefitsOutcomeN	HarmsOutcome1	HarmsOutcomeN
Drug 1	Drug 2	Insufficient	No effect	Insufficient	<i>Small</i>	No data
Drug 1	Drug 3	No data	<i>Large</i>	<i>Medium</i>	No data	<i>Medium</i>
Drug 1	Drug 4	<i>No effect</i>	No data	<u>Large</u>	<i>No effect</i>	Insufficient
Drug 2	Drug 3	<u>Medium</u>	Insufficient	No data	Insufficient	<i>No effect</i>
Drug 2	Drug 4	Insufficient	<i>Small</i>	No data	<u>Medium</u>	No effect
Drug 3	Drug 4	<i>Large</i>	Insufficient	Medium	<i>Small</i>	No data

Source: <https://www.effectivehealthcare.ahrq.gov/topics/schizophrenia-adult/research-2017>

Published online: October 26, 2017

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Comments on the Agency for Healthcare Research and Quality (AHRQ) Research Review:
Treatments for Adults with Schizophrenia: A Systematic Review
March 7, 2017

First, I appreciate the Agency's attention to this important health disorder. In order to assist those with serious mental illnesses, knowledge of reliable treatments and their recommendations are critical. As a reviewer, I also recognize the difficulty of conducting a review such as this one.

However, despite the resources that must have gone into this effort, it is unfortunate that this Research Review does not meet the high standard needed to produce a quality and useful product. Instead this Research Review does a dis-service to AHRQ, the many researchers in this field, treating professionals, and most importantly, individuals with this and similar disorders and their families who could benefit from a competent review of the research.

The authors of this Research Review do not appear to have the background knowledge of much of the work that has been done in this area and, in my opinion have either failed to consider or have excluded from consideration, many of the most important and well conducted studies and reviews produced over the past decades. The rules for rating the characteristics and quality of the literature seem to have been determined by individuals who do not know the literature well and appear to not understand the multiple variables that impact on the conduct of research in the field. This apparent lack of knowledge and understanding has resulted in an arbitrary set of rules that excluded some of the best conducted studies and RCTs resulting in conclusions that are erroneous, have the potential to erode confidence in AHRQ and reverse the very positive treatment advances made over the past two decades.

Prior to providing detailed comments on some (particularly the psychosocial) aspects of the Research Review, it is worth noting that key reviews and clinical practice guidelines were either not considered or eliminated from consideration. Many offer substantial recommendations for the psychosocial treatments included in this Review and minimally include:

1. The very highly regarded clinical practice guidelines available especially: Psychosis and schizophrenia in adults: prevention and management, from the National Institute for Health and Care Excellence, (available from: <https://www.nice.org.uk/guidance/cg178>)
2. Management of schizophrenia, from Healthcare Improvement Scotland, (available from: <http://www.sign.ac.uk>), along with other similar guidelines all of which have found strong evidence for use of the psychosocial treatments reviewed on and reported on in this report.
3. The latest update of the Schizophrenia Patient Outcomes Research Study (PORT) which is the most comprehensive scholarly review of both pharmacologic and psychosocial treatments

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available and to my knowledge has never been refuted. The references are: Dixon, L. B., Dickerson, F., Bellack, A. S., Bennett, M., et al. (2010). The 2009 schizophrenia PORT psychosocial treatment recommendations and summary statements. *Schizophrenia Bulletin*, 36, 1, 48-70.

Kreyenbuhl, J., Buchanan, R.W., Dickerson, F. B. & Dixon, L. B. (2010). The Schizophrenia Patient Outcomes Research Team (PORT): Updated treatment recommendations 2009. *Schizophrenia Bulletin*, 36, 1, 94-103.

More specific and detailed comments follow but these are only a sampling of what could be provided if time permitted. At the end of the day, this Research Review is so seriously flawed that the Agency is encouraged to have it re-done using experts who actually know the treatments of interest. Anything less risks embarrassing the Agency and doing a dis-service to those with these disorders and the general public.

Major comments include:

Determination of the key outcomes of interest is a major flaw of this Research Review. There are many issues that could be raised related to the outcomes of interest chosen but space and time do not permit an exhaustive discussion of all of these; thus a few examples will suffice.

One of the key outcomes in the pharmacologic section is that of functional improvement. Yet, functional improvement is not an outcome that medication treatments aim to improve. Most pharmacologic treatments are targeted to symptom remission, which may have spillover effects for an individual's functioning, but functional improvement is not the primary target of medical treatment. Given that the authors of this Research Review believe that functional improvement is a critical outcome for pharmacologic treatments, it is difficult to take seriously the notion that the authors have even the most rudimentary knowledge of schizophrenia and its treatments.

With respect to psychosocial treatments, one can only wonder why response rate and remission rate are even considered in a short list of important outcomes. Similarly to the discussion above for pharmacologic treatments, response rates and remission rates are not outcomes that would normally be considered critical for psychosocial interventions that often take a long time to implement, often require considerable support and reinforcement, and which are targeted to functional improvement, not response or remission rates. However, it must be stated that while functional improvement is considered a major outcome for many psychosocial treatments, there are so many nuances of psychosocial interventions that making such a blanket reliance on this one broad outcome difficult to justify. Additionally, as previously mentioned, many psychosocial interventions take considerable time to implement and considerable time for their effects to become apparent, making a simple indicator such as "functional improvement" not reflective of the real world.

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Relatedly, Assertive Community Treatment (ACT) was never designed nor intended to improve functioning. In simple terms, its primary purpose is to help the most severely ill individuals remain out of the hospital. Is this what the authors mean by functional improvement? This simple and overly inclusive attribution of functional improvement to ACT is not warranted and leads to misleading conclusions. In fact, ACT is recognized world-wide as the most widely researched and regarded psychosocial intervention; it is in fact considered the gold standard for helping those with the most severe mental illnesses to remain in treatment in their communities. Like so much in this Research Review, this subtlety seems to have been overlooked or missed.

Regarding the conclusions about Supported Employment (SE), one can only wonder ‘What were they thinking?’ This is because, after years of well-designed research, including multiple RCTs supporting its efficacy and effectiveness, (several of which do not seem to be mentioned), SE is considered one of the cornerstones of recommended interventions for persons who wish to work. As with so much of this Research Review, the criteria for judging the quality of a given review or individual study often do not match the intended target of the intervention. For example, the authors looked at core symptom improvement following SE intervention. However, SE is not designed to improve core symptoms – this fact seems to have eluded the authors. Another problem related to SE is the authors have confounded the Research Review by including studies and reviews that either include or compare traditional vocational rehabilitation approaches such as pre-vocational training. Those with knowledge of SE know that SE does not include any form of pre-vocational training.

Similarly, the conclusions concerning Family Interventions are not supportable. As with ACT and SE, Family Psychoeducation (FP) is one of the most widely researched, supported, and recommended interventions for this population. FP has been shown over many years and in multiple trials in countries all over the world to decrease relapse and re-hospitalization rates, reduce the burden on families and improve self-care and quality of life for individuals with severe mental illnesses. This is particularly the case when FP is continued for longer duration (6 – 9 months). As with other parts of this Research Review, several critical and recent studies and reviews were omitted from consideration.

With respect to Cognitive Remediation (CR), the authors of this Research Review apparently do not know that it is now widely recognized that in addition to CR’s efforts to improve cognitive functioning when used on its own, adding CR to other interventions has shown enhanced outcomes for individuals on measures of improvement for the other intervention(s) under study. Supported Employment is the intervention that has been most often studied in combination with CR, but most of those who are knowledgeable in this area recognize that one of the hallmarks of schizophrenia is poor cognitive functioning, leading to recommendations to

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integrate CR into a range of treatment regimens. There are increasing calls for integrated treatment to include cognitive remediation and social cognition training approaches as a fundamental component. Some have stated that including cognitive remediation “may result in a magnitude of change that exceeds that which can be achieved by targeted treatments alone” (Pinkham & Harvey, 2013, p. 499). As with so many other aspects of this Research Review, the authors seem to lack knowledge of these findings and implications for use of integrated or combinatory approaches. [Pinkham, A. & Harvey, P. D. (2013). Future directions for social cognitive interventions in schizophrenia. *Schizophrenia Bulletin*, 39, 3, 499–500.]

Although comments could be made about just about every aspect of this Research Review, one final comment about CBT seems in order. There is no mention of CTBp (CBT for Psychosis) which was designed expressly for those with psychotic disorders. While some reviews of CBTp have shown mixed results, many studies have demonstrated positive effects. This is curious and leads again to the conclusion that the authors of this Research Review are unfamiliar with the latest developments in the field.

In summary, based on the conclusions of the very highly regarded prior research reviews and clinical practice guidelines cited at the beginning of these comments, it should be apparent that the current authors’ conclusion that the findings of their review are “very consistent with the findings of other reviews” (p. 93) is not supportable. Moreover, the authors’ assertion that “A major contribution of our review is the collection of the most commonly used nonpharmacological interventions in one review” (p. 93) is also completely inaccurate. If the authors were familiar with the comprehensive reviews and clinical practice guidelines mentioned earlier, they would know this – further testament to the fact that they lack knowledge of the existing literature and the nuances of recommended treatments. Finally, the overly negative tone of this Research Review leads one to question the (perhaps unrecognized) bias that may underlie the findings.

As previously stated, at the end of the day, this Research Review is so seriously flawed that the Agency is encouraged to have it completely re-done using experts who actually know the treatments of interest. Anything less risks embarrassing the Agency and doing a dis-service to those with these disorders and to the general public.

Thank you for the opportunity to provide comments.

Mary A. Jansen, Ph.D.

Past Chair and Current Member

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Submitted electronically via <https://www.effectivehealthcare.ahrq.gov>

March 8, 2017

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Task Order Officers
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality
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RE: Treatment for Adults with Schizophrenia: A Systematic Review

Dear Drs. Niebuhr and Gozu:

Allergan appreciates the opportunity to provide comments on the Agency for Health Research and Quality (AHRQ) systematic review of treatments for adults with schizophrenia.¹ Allergan is a unique, global pharmaceutical company focused on developing, manufacturing, and commercializing innovative branded pharmaceuticals, and biological products for patients around the world. Our portfolio includes best-in-class products that provide valuable treatments in central nervous system, women's health, eye care, medical aesthetics, gastroenterology, urology, cardiovascular, and anti-infective therapeutic categories. Allergan is an industry leader in research and development, with one of the broadest development pipelines in the pharmaceutical industry. Allergan is committed to working with AHRQ, physicians, hospitals, and patients to deliver innovative and meaningful treatments that help people around the world live longer, healthier lives. Cariprazine (trade name VRAYLAR®), a second-generation antipsychotic (SGA), is licensed to Allergan and approved for the treatment of schizophrenia in adult patients in the U.S. and Canada. Cariprazine was discovered and co-developed by Gedeon Richter Plc. We appreciate the agency's willingness to review the appropriate management of schizophrenia, a debilitating neuropsychiatric syndrome with a severe and chronic course; however, we request that AHRQ review our recommendations and update the final report accordingly.

I. Background

The lifetime prevalence of schizophrenia in the United States is estimated at approximately 0.3% to 0.7%.² Schizophrenia is associated with considerable functional and social impairment including generalized disability, decreased somatic health and quality of life, comorbid substance abuse, and a marked decrease in life expectancy.³ We commend AHRQ's Effective Health Care Program for recognizing the wide-ranging impact of schizophrenia on patients and their families.

¹ AHRQ, Effective Healthcare Program, Draft Comparative Effectiveness Review. *Treatments for Adults with Schizophrenia: A Systematic Review*, (February, 2017).

² *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. American Psychiatric Association: Washington, DC; 2015.

³ Schaefer J, Giangrande E, Weinberger DR, Dickinson D. The global cognitive impairment in schizophrenia: consistent over decades and around the world. *Schizophr Res* 2013 Oct;150(1):42-50.

Antipsychotic medications, the cornerstone of treatment for schizophrenia, are indicated for nearly all episodes of acute psychosis in patients with schizophrenia. Although antipsychotics are generally effective against the positive symptoms of schizophrenia (eg, hallucinations, delusions), they are generally less effective in the treatment of negative symptoms (eg, anhedonia, blunted affect, avolition). Negative symptoms are intrinsic to schizophrenia pathology and are associated with considerable long-term morbidity and poor functional outcome; therefore, the identification of drugs that are effective on negative symptoms is an important treatment goal. The efficacy of cariprazine was demonstrated in three Phase IIb or Phase III double-blind, placebo-controlled trials in adult patients with acute exacerbation of schizophrenia. In each trial, the difference in change from baseline to week 6 in Positive and Negative Syndrome Scale (PANSS) total scores and Clinical Global Impressions-Severity (CGI-S) scores was statistically significant in favor of once-daily cariprazine versus placebo.^{4,5,6} Risperidone and aripiprazole were each included in one of the pivotal trials as an active control. Dr. Németh et al recently published results from a randomized, 26-week, double-blind, active-controlled trial in stable patients identified as having long-term predominant negative symptoms of schizophrenia; cariprazine was found to be significantly more effective than risperidone in treating negative symptoms and improving patient functioning.⁷ In each of the four trials mentioned above, cariprazine was generally well tolerated.

As discussed in more detail below, we urge AHRQ to incorporate the randomized, controlled pivotal trial of cariprazine that included aripiprazole as an active control and the active-controlled study of cariprazine versus risperidone in the treatment of predominant negative symptoms of schizophrenia in the systematic review. These trials will ensure that the final report include the relevant evidence supporting the use of cariprazine in the medical management of schizophrenia.

a. AHRQ Excluded Two Trials That Demonstrate the Efficacy and Safety of Cariprazine Versus Other Second Generation Antipsychotics (SGAs) in Patients With Schizophrenia

In their *Treatment for Adults with Schizophrenia: A Systematic Review* draft report, AHRQ included one Phase II study of cariprazine in patients with acute exacerbation of schizophrenia, which utilized risperidone as an active control (Durgam et al, 2014).⁴ However, the review failed to include one pivotal Phase III trial of cariprazine in patients with acute exacerbation of schizophrenia (Durgam et al, 2015)⁵ and one Phase III trial of cariprazine in a patient population with predominant negative symptoms of schizophrenia (Németh et al, 2017).⁷ Allergan believes that AHRQ should not release its final report until data from these pivotal trials are reviewed and incorporated. Both studies were randomized controlled trials (RCTs) that provided key efficacy and safety information for cariprazine treatment; as they allowed for the comparison of two SGAs and were published after 2013, they meet the inclusion criteria described in the Methods (p. ES-3).

⁴ Durgam S, Starace A, Li D, et al. An evaluation of the safety and efficacy of cariprazine in patients with acute exacerbation of schizophrenia: a phase II, randomized clinical trial. *Schizophr Res*. 2014;152(2-3):450-457.

⁵ Durgam S, Cutler AJ, Lu K, et al. Cariprazine in acute exacerbation of schizophrenia: A fixed-dose, phase III randomized, double-blind, placebo- and active-controlled trial. *J Clin Psychiatry*. 2015 Dec;76(12):e1574-82.

⁶ Kane JM, Zukin S, Wang Y, et al. Efficacy and safety of cariprazine in acute exacerbation of schizophrenia: results from an international, phase III clinical trial. *J Clin Psychopharmacol*. 2015;35(4):367-373.

⁷ Németh G, Laszlovszky I, Czobor P, et al. Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: a randomised, double-blind, controlled trial. *Lancet*. Published online February 6, 2017; [http://dx.doi.org/10.1016/S0140-6736\(17\)30060-0](http://dx.doi.org/10.1016/S0140-6736(17)30060-0).

The Durgam 2015 study, a 6-week, double-blind, placebo-controlled RCT of cariprazine in acutely exacerbated patients with schizophrenia (NCT01104766), was one of the three pivotal trials that served as the basis for the FDA approval of cariprazine in the treatment of adult patients with schizophrenia. Although the study was designed to compare the efficacy of cariprazine versus placebo, aripiprazole was included as an active control. Efficacy measures included the PANSS, CGI-S, and the Schizophrenia Quality of Life Scale-Revision 4 (SQLS-R4).

The Németh study, a 26-week, double-blind, active-controlled trial, performed a head-to-head comparison of cariprazine versus risperidone in patients with predominant negative symptoms of schizophrenia. Efficacy measures included PANSS-factor score for negative symptoms (PANSS-FSNS), PANSS total score, and Personal and Social Performance (PSP) scale. The study findings were that greater improvement in negative symptoms were observed in cariprazine-treated patients versus risperidone-treated patients.

Recommendation: Based on AHRQ’s own search strategy for systematic reviews, which states that “Library searches will be updated while the draft report is posted for public comment and peer review to capture any new publications”, AHRQ should incorporate data from the Németh and Durgam 2015 studies in its final report. Allergan believes that the incorporation of data from these publications will alter the conclusions of the systematic review, and more accurately reflect the published literature of treatment with SGAs in patients with schizophrenia.

II. ABSTRACT SUMMARY

- a. In the abstract to its draft report, AHRQ concludes that “No single drug was superior on multiple high-priority outcomes, but clozapine, olanzapine, and risperidone oral and LAI had superiority on more outcomes than other SGAs. Newer SGAs were not superior on any outcome.” However, in the Németh study, cariprazine demonstrated superiority to risperidone on multiple outcomes, including improvement in core negative symptoms and social functioning. Therefore, the omission of this trial results in AHRQ drawing a conclusion that is not supported by the published literature.

Recommendation: AHRQ should amend its draft report and include the additional active-controlled Phase III trials (Durgam 2015 and Németh studies) of cariprazine in patients with schizophrenia.

III. RESULTS

- a. Response (p. 25, Appendix p. G-1): In the AHRQ report, cariprazine was shown to be less likely to result in PANSS response than risperidone or aripiprazole. These findings are based on the results from a small, Phase II study of cariprazine, and exclude data from the larger Phase III trials. Allergan believes that inclusion of data from the Németh and Durgam 2015 studies is necessary for a complete picture of the efficacy of cariprazine versus these two SGAs since PANSS total score response was numerically higher with cariprazine than with aripiprazole in the 6-week trial, and PANSS-FSNS response was significantly higher with cariprazine than with risperidone in the 26-week trial.
- b. Improvement in Core Illness Symptoms (ES-7, p. 29): The draft report uses three network meta-analyses to assess improvements in core illness symptoms, as well as a single trial of brexpiprazole and aripiprazole. The report states that in the meta-analyses, “Cariprazine was not included, and the

analysis includes drugs not available in the United States.” In the draft report, AHRQ concludes that *“Olanzapine and risperidone were not significantly different compared with each other, and both were superior to the other SGAs for core illness symptoms improvement, except for paliperidone ER and clozapine.”* In addition, the report states *“A network meta-analysis of negative symptoms also found olanzapine significantly better than the other older SGAs, while response rates and all-cause discontinuations indicated no significant differences among the older SGAs.”* In the Németh study, cariprazine demonstrated significantly greater improvement versus risperidone on negative symptoms, one of the core domains of schizophrenia. As such, Allergan believes that inclusion of data from this study is crucial to provide an accurate picture of the overall efficacy of SGAs versus SGAs on core illness symptoms.

- c. Functional Outcomes (ES-6, p. 23): The draft report indicates that *“For newer SGAs, the review found that evidence from a pooled analysis of patient-level data from three, 6-week placebo-controlled trials of paliperidone ER and a small group assigned to olanzapine was insufficient to draw conclusions.”* Since the Durgam 2014 study that was included in the systematic review did not evaluate the efficacy of cariprazine on functional outcomes, cariprazine was not included in this section of the draft report. However, the Németh study of cariprazine did evaluate efficacy versus risperidone on the PSP scale, and may therefore permit conclusions to be drawn regarding the impact of SGAs on functioning. Additionally, the Durgam 2015 study included quality of life assessments, as measured by the SQLS-R4, and inclusion of this trial would provide further evidence of the effect of newer SGAs on patient quality of life.
- d. Discontinuations (p. 32): Based on data from the included Phase II trial of cariprazine (Durgam 2014), olanzapine and clozapine are described in the draft report as having significantly lower discontinuation rates than cariprazine. The inclusion of this single trial, which utilized cariprazine doses on the low end of the approved dose range, only provides a partial picture of discontinuations due to cariprazine treatment. Discontinuation rates in the Németh study were lower and roughly equal for cariprazine and risperidone; therefore, inclusion of this study may more accurately reflect the true rates of discontinuation with cariprazine in RCTs.

Recommendation: AHRQ should incorporate data from the Németh study in adults with predominant negative symptoms of schizophrenia and the Durgam 2015 study of cariprazine in adults with acute exacerbation of schizophrenia in its report. Allergan believes that incorporating data from these publications may alter the conclusions of the systematic review regarding efficacy on response rates, core illness symptoms and function, as well as the discontinuation rates of cariprazine, thereby more accurately reflecting the efficacy and safety of cariprazine versus other SGAs in patients with schizophrenia.

Conclusion:

Allergan strongly recommends that AHRQ include the Németh and Durgam 2015 studies, which represent two active-controlled, Phase III trials of cariprazine in patients with schizophrenia, in its systematic review. These studies are critical for assessing the entirety of available evidence in relation to the efficacy and safety of cariprazine versus other antipsychotics, and any final report excluding them will not be accurate. These studies included efficacy measures that are utilized throughout the report, as well as additional measures of quality of life and functioning. Additionally, the Németh study demonstrated the efficacy of cariprazine versus another SGA, risperidone, in a predefined head-to-head RCT. Excluding these publications would not accurately reflect the published data on the treatment of adults with schizophrenia, and we stress that AHRQ should not endorse any final report without their inclusion.



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We appreciate the opportunity to provide these comments. If you have any additional questions, please do not hesitate to contact me via email at Gavin.Corcoran@Allergan.com or by phone at (201) 427-8119.

Sincerely,

/s/

Gavin Corcoran, MD FACP
SVP, Chief Medical Officer
Allergan plc.

Enclosure: VRAYLAR® (cariprazine) [package insert]. Allergan, Inc. February 2017.

As stated on the AHRQ website, “Comparative effectiveness research is designed to inform health-care decisions by providing evidence on the effectiveness, benefits, and harms of different treatment options.” Reviews such as the one currently under comment, “Treatments for Adults With Schizophrenia: A Systematic Review,” are designed to provide researchers, providers, family members, and consumers of mental health services with important guidance to help guide decision-making. The impact of such a review is considerable, and therefore we, the members of the American Psychological Association (APA) Task Force for Severe Mental Illness/Severe Emotional Disturbance (SMI/SED) and the APA Division 18 Section on SMI/SED, appreciate the opportunity to review and provide public comment on this important document. The two areas of concerns described below are broad and intended to convey how deeply we are concerned with how the authors’ conclusions are represented.

The first area of concern is related to the broad conclusions drawn by the data. As noted by the authors, the studies included in this review represent only a small proportion of the research on the psychosocial interventions of interest, eliminating studies comparing interventions to active treatment (vs. “usual care”), requiring that 50% of the study sample consist of individuals with schizophrenia, and requiring a minimum of 12 weeks of follow-up. Given that for some interventions, such as supported employment, almost all published studies did not meet criteria for this review, statements such as “Low strength evidence suggests that supported employment interventions are not associated with improvements in employment outcomes or the ability to maintain treatment” are quite misleading. While we recognize that this statement is supported by the methodology, we believe that it is misleading to the point of irresponsibility to draw this conclusion because it is deeply dependent on the particular limitations of the review’s inclusion/exclusion criteria.

The second area of concern relates to multiple statements within the review that appear to represent opinions of the authors. Specifically, we object to statements outside the scope of the review that provide unnecessarily pessimistic statements about individuals with schizophrenia, such as this one from the executive summary: “Since most individuals with chronic psychotic illnesses such as schizophrenia require lifetime engagement with mental health services to have good outcomes, more well-designed long-term studies could help identify the overall benefit versus costs and risks for these illnesses that remain refractory to cure or easy management.” A large body of empirical research, including the work of Dr. Harding and others, show that such statements are patently false. Although the likely intent behind such statements is to ensure that high quality, evidence-based psychosocial treatments are available for individuals with schizophrenia, we believe that a broader review of the psychosocial treatment literature suggests that individuals with schizophrenia do benefit from these treatments, and as a result, may live lives without “lifetime” reliance on mental health services.

We strongly recommend that the authors revise this report. We ask that the authors rethink the way conclusions of this review are stated as well as how other statements outside the scope of the review describe the illness of schizophrenia and the hope and potential future for those who live with this mental health challenge. We call upon the authors to acknowledge the limitations of their review and remove false and stigmatizing statements regarding life-long needs for care. We also ask that the authors acknowledge and address the empirical evidence supporting recovery and the benefits of psychosocial treatments for people living with schizophrenia. It is imperative that the authors of this manuscript, as well as all who contribute to research, literature, education, and training, carefully consider the full implication of the work we do and—in particular—how we present it in writing.

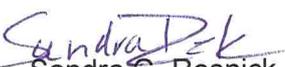
Sincerely,



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RE: Draft AHRQ Report - Treatments for Adults with Schizophrenia: A Systematic Review

Oh, my goodness gracious...I have spent my whole career studying schizophrenia and I suggest that you guys have missed the bigger picture and are bogged down in 120 years of going off on the wrong path. Things are changing though slowly but surely. Treatment has been mostly medications with rehabilitation skill building and other psychological strategies offered as an adjunct only. People have been told they have a lifelong illness. Systems have been set-up for long-term care for all. There has been a reliance on a poorly constructed diagnostic system based on a woeful misunderstanding about schizophrenia. Even the past head of NIMH, Tom Insel, (2012) has admitted that we do not understand that there is no such a thing as schizophrenia; that it doesn't exist as an entity but many entities which are slowly coming into focus. Pretty soon we will throw out the name "schizophrenia" as there emerges a clearer picture of the components of this underlying heterogeneity and produce a name for each. But everything is even more muddled which is why the DSM-5 (2013) has thrown out all the subtypes. Symptom pictures are really much more fluid than we thought and blend into one another over time including schizoaffective and bipolar categories (see Carpenter's editorials on the matter). And now the sturdy psychopharmacologist, Jeff Lieberman (2016) at Columbia and former President of his APA, writing recently how the current medications are very ineffective! All of this means that the findings from all of our studies are significantly skewed because we don't know what works for whom, nor who is who, and we might throw out the baby with the bathwater.

In addition, there are now 11 long-term studies of two and three decades in length that have shown 46-68% of people so labeled have managed to get their life back (very different picture than the 80% for long-term care. (Harding et al, 1987 AJP; Harding, in press) So based on all these assumptions of the past, we might say that rehabilitation strategies should be the first line of defense and medications only a small part of the equation. We might reorganize our treatment centers to be warm places of hope and caring with strong messages of getting better and getting a life back. Activists have explained to us how negative many places are and how important the environment is for helping people get on their feet. And consumers tell us what they want is a home, a job, friends, and a date for Saturday night. We probably have not even a clue about the remaining 30% yet who are really struggling and the meds or programs haven't touched them either. But as for the rest, they talk about disempowering programs and policies, stigma and discrimination, including a sense of internalized stigma and shame. This really says to me that we have not set up very helpful supports! I have been to 30 US states, 11 European countries, 9 Asian (including China) Canada, New Zealand, and Australia looking at many kinds of programs, some pockets of excellence and some that have copied the general approach here in the states. We need to start from scratch, shuffle the deck, and completely *rethink* what we are

doing in most cases. It is really really important that government agencies need to understand that the so-called medical model has not worked and needs overhauling perhaps to a public health one.

Lives are being lived out without remediation. It breaks my heart.

Professor Courtenay Harding

Alexander Gralnick Investigator Award (2004-5) from APA/APF
A former member of the APA Task Force on Serious Mental Illness

A POSSIBLE SCENARIO FOR COMMUNITY CARE

A person walks into the door suffering from great emotional distress and seeks some help. Show him/her around the place and sit down to find out what they want. Sometimes, they start with something different than expected (e.g. How can I get out of the house?") Paying attention to that request or to others seemingly not directly involved with psychological help-seeking makes an entry into that treatment much easier and effective.

If help with emotional distress how about trauma-informed treatment? Or how about Cognitive Behavioral Treatment (both phrased in ordinary English and as classes) or

If hearing voices how about the one of the new U.S. groups of Hearing Voices from the UK where people who do get together and talk about it and how to cope or

Something like the new Open Dialogue from Finland in which clinicians go to the family home and everyone openly talks about the problems and solutions? Work with families and don't hide behind HIPAA. Arrange with the person in most situations to have guidelines as to who you can talk with and who you can't. Explain it will make you a better clinician and be more helpful. Families deserve to be involved whenever possible.

Get the person to identify what is the earliest sign of a relapse, then what is the next warning sign and then the full- fledged all out relapse. Show him/her how to rate status every day and what to do if needed and/or where to go for help. Families and friends often know the early signs better. Then figure out how it feels to feel better in increments and check that out too while preparing for the day.

Help the person find ways to help others or animals. This strategy turns out to be remarkably helpful in restoring a sense of self.

If there is trouble thinking... Well, how about trying cognitive remediation in one form or another and also in preparation for a job?

If the person wants a job, first find out what the person dreamed about for his/her future before the symptoms interfered. Perhaps finishing schooling is a better start and we can help with that. Then there are multiple pathways to start working again. Choose the best fit.

Is it finding a home or friends, or learning some more social skills to get a date?

If financial assistance is needed tell SSA that the person is really looking for 5 years and should be reviewed then and start talking about the Ticket to Work program.

If the symptoms are making the person miserable, find out if there is anxiety or lack of sleep and try a little anxiolytics or Benadryl first before hitting the person with major antipsychotics or antidepressants. This is a new movement in psychiatry, called "slow psychiatry." If already on prescriptions try to back them off to the lowest possible dose and eventually off.

If the person is a danger to self or others then a distinct move is necessary and hopefully there is a hospital that won't make matters worse because you have made linkages with them and sit with its staff to make a cohesive plan for both inside and outside. Use coworkers with the lived experience working side by side and take their suggestions seriously. Many crises are resolved using drop-in centers, a Soteria House nearby or short term beds and living rooms with cups of tea and a quiet talk run with recovered consumers.

If there are co-morbid medical/dental/hearing/limited literacy problems, use a network that you have set-up to help solve these situations. Refocus on health and physical activity as well as setting up quiet places for meditation and yoga. Have classes on cooking, grow a garden, start a music group or an art group with shows.

If there are co-occurring problems with drugs and alcohol, the agency should be tending to these simultaneously. Find out what the payoff for the person is and replace it with something else.

Talk in terms of 2-5 years to solve things and reclaim a life. Not a lifetime. Talk about graduation, getting out of the system eventually but that you will walk a collaborative path with the person and share what you know and learn what he or she knows. Believe it or not there are places that are run like this.

The key thing is to listen to what the person is seeking not that we have a uniform plan for everyone and we think that you have a lifelong illness and will need support all the rest of your life. See how far we have gotten off track?

Set up an environment that is warm and inviting. For example I found one such place, south of San Diego on the Mexican border. It has vibrant colors on its walls, flowers and food and music. Clinicians work with entire families not with just one person in this culture and with local priests and curanderos (local healers). Persons with the lived experience who are on the road to recovery will have some great ideas on how to get a community meeting together to figure out how to jazz the place up with as many people involved as possible. Clinicians and clients work together, eat together, use the same bathrooms, with the work shared inside and outside. This is a very human endeavor not a medical establishment. It is a therapeutic community. It is a healing community.

Anatomy of an Epidemic: Summary of Findings. By Robert Whitaker, robert.b.whitaker@verizon.net**1. Disability Numbers Due to Mental Illness Are Soaring.**

Our society understands that the arrival of Thorazine into asylum medicine in 1955 kicked off a “psychopharmacological revolution,” leading to much better long-term outcomes for people with psychiatric disorders. Yet, the disability rate due to mental illness, as measured by adults under governmental care, has risen from one in every 468 Americans in 1955 to one in 76 today.

The rise in the number of disabled mentally ill has been especially pronounced since 1987, the year that Prozac, the first of the “second-generation” psychiatric drugs, arrived on the market. The number of adults on SSI or SSDI due to mental illness has risen from 1.25 million in 1987 to more than 4 million today. The number of children and youth on SSI due to a serious mental illness has skyrocketed from 16,200 in 1987 to more than 600,000 today.

2. Affective Disorders Run a Much More Chronic Course Today than in the Pre-Drug Era.

The rise in disability numbers is being driven by a sharp increase in the number of people disabled by affective disorders (depression and bipolar illness.) In the pre-drug era, the affective disorders were seen as episodic illnesses, with fairly good long-term outcomes. As George Winokur, a leading expert at Washington University, explained in a 1969 text: “Assurances can be given to a patient and to his family that subsequent episodes of illness after a first mania or even a first depression will not tend toward a more chronic course.” However, affective disorders today run a chronic course, and functional outcomes (employment rates, etc.) are much worse than they were 50 years ago.

For instance, in the pre-drug era, roughly 50% of people hospitalized for first episode of manic-depressive illness were asymptomatic in long follow up studies, and only 15% to 20% became chronically ill. Various long-term studies found that 75% to 90% worked, and people so diagnosed did not show signs of long-term cognitive decline. Today, bipolar patients suffer many more acute episodes of illness and are much more likely to be rapid cyclers; they often suffer low-grade depressive symptoms in the interludes between acute episodes; only about 33% to 40% are regularly employed; and they show long-term cognitive impairment.

Here is how the NIMH’s Carlos Zarate has summed up this deterioration in modern outcomes: “In the era prior to pharmacotherapy, poor outcome in mania was considered a relatively rare occurrence. However, modern outcome studies have found that a majority of bipolar patients evidence high rates of functional impairment.”

3. It Is a Myth that All People With Schizophrenia Need to be On Antipsychotic Medication All Their Lives.

In the decade prior to the introduction of Thorazine, 65% or so first-episode schizophrenia patients admitted to state mental hospitals would be discharged within 18 months, and at the end of five years, 70% to 75% would be living independently in the community. (Employment rates for the men were above 50%.)

This good employment rate continued into the early 1960s. An NIMH study of first-episode patients treated either with an antipsychotic or a placebo upon initial hospitalization found that one year later 58% were employed (or functioning well as “housewives.”) Furthermore, it was the patients treated in the hospital with placebo who were the least likely to be rehospitalized at the end of one year.

Since then, numerous studies have found that there is a subgroup of first-episode schizophrenia patients who can recover and fare well without the use of antipsychotic medications, and that it is this unmedicated subgroup that has the best long-term outcomes. Most recently, in an NIMH-funded study conducted by Martin Harrow at the University of Illinois College of Medicine, 40% of the schizophrenia patients off medication were recovered at the end of 15 years, versus 5% of those on medication. “I conclude that patients with schizophrenia not on

antipsychotic medication for a long period of time have significantly better global functioning than those on antipsychotics,” Harrow reported at the 2008 meeting of the American Psychiatric Association.

In western Lapland in Finland, the psychiatric community has been using antipsychotics in a selective manner since 1992, and today that region has the best outcomes in the Western World. At the end of five years, 80% of first-episode psychotic patients in western Lapland are either working or back in school, and here is their medication use: only 33% have been exposed to antipsychotics, and only 20% are regularly maintained on the drugs.

4. Use of Illicit Drugs and Antidepressants is Fueling the Bipolar Boom

Fifty years ago, bipolar illness was a rare disorder, affecting perhaps one in 3,000 adults. Today, one in every 40 Americans is said to suffer from the disorder. While this increase is being driven in part by an expansion of diagnostic boundaries, it is also being fueled by the widespread use of illicit drugs, and by the use of psychiatric drugs (stimulants and antidepressants.)

In studies of first-episode bipolar patients, roughly one-third suffered their first bout of mania or “mood instability” after they had abused illicit drugs (amphetamines, cocaine, marijuana and hallucinogens are common culprits.)

In patients diagnosed with unipolar depression, treatment with antidepressants more than triples the risk that they will convert to bipolar illness, such that 20% to 40% of long-term users of antidepressants today end up with bipolar diagnosis. In a survey of members of the Depressive and Manic-Depressive Association, 60% of those with a bipolar diagnosis reported that they had turned bipolar after exposure to an antidepressant.

5. The Medicating of Children and Youth for Mental Disorders Is Not Helping Them Thrive Over the Long-Term.

In long-term ADHD studies, the medicated youth have not fared better than the unmedicated group. For instance, in a long-term study conducted by the NIMH (known as the Multisite Multimodal Treatment Study,) medication use at the end of the third year “was a significant marker not of beneficial outcome, but of deterioration.” Furthermore, children treated with stimulants are exposed to significant long-term risks; 10% to 25% convert to bipolar illness, which puts them onto a lifelong path of chronic mental illness.

Twelve of 15 pediatric studies of SSRI antidepressants failed to show even a short-term benefit for the medicated group over placebo. Antidepressants can cause a host of psychiatric and physical side effects in youth; most problematic is that 25% of youth treated with antidepressants convert to bipolar illness within four years.

Prior to the 1980s, which is when the prescribing of stimulants to youth became common, bipolar illness was virtually unknown in prepubertal children. Today, one percent of all American youth are said to be bipolar, and surveys of children so diagnosed have found that more than 65% turned bipolar after treatment with a stimulant or an antidepressant. Long-term outcomes for youth diagnosed with juvenile bipolar disorder are poor; they exhibit symptoms “similar to the clinical picture reported for severely ill, treatment-resistant adults,” researchers have found.

6. Conclusion.

There is evidence that psychiatric medications may be helpful over the short-term, and there are some people who fare well on the drugs long term. However, the outcomes for affective disorders have noticeably worsened during the modern drug era, and there is evidence that a significant percentage of schizophrenia patients can fare well over the long term without the use of antipsychotics. The regular use of psychiatric medications has also fueled an astonishing increase in the number of adults and children diagnosed with bipolar illness.