Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Efficacy and Comparative Effectiveness of Off-Label Use of Atypical Antipsychotics – Update*

Draft review available for public comment January 19, 2011 to February 9, 2011.

Research Review Citation: Maglione M, Ruelaz Maher A, Hu J, Wang Z, Shanman R, Shekelle PG, Roth B, Hilton L, Suttorp MJ, Ewing BA, Motala A, Perry T. Off-Label Use of Atypical Antipsychotics: An Update. Comparative Effectiveness Review No. 43. (Prepared by the Southern California Evidence-based Practice Center under Contract No. HHSA290-2007-10062-1.) Rockville, MD: Agency for Healthcare Research and Quality. September 2011. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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

Peer Reviewer Comments

Reviewer	Comment Section	Page	Comment	Response
Reviewer 1	General	0	The authors are to be commended on a thorough and systematic, even encyclopedic, compilation of information on treatment patterns, efficacy, and safety of off-label use of atypical antipsychotic medications across a wide range of conditions. The field will be well served by their efforts. Organizing the presentation around key questions was helpful.	None needed
Reviewer 1	General	0	The report might be strengthened by making explicit the limitations of combining studies with heterogenous patient populations and appropriately calibrating the overall assessments of the strength of efficacy evidence on the basis of these limitations. An expanded discussion of the clinical implications of the main findings might increase the value of the report to clinical readers.	We have expanded our discussion in response to this suggestion, however it must be kept in mind that the role of the Evidence Report is not to make clinical case recommendations.
Reviewer 2	General		This is a very comprehensive report of an important area. It is clear from both the report and from clinical experience that off-label use of atypicals is not a small part of current practice, and one that has been lacking in evidence. This report fills an important gap. It also shows that more work in this area is needed.	None needed
Reviewer 3	General		The report addresses clinically important questions, and examines important subgroups that include age and sex differences. The key questions are important, clear and stated succinctly.	None needed
Reviewer 4	General		This is a very clearly written report on a clinically meaningful topic. The key questions addressed are appropriate and explicitly stated. As aptly demonstrated in this report, second-generation antipsychotic (SGA) medications are widely prescribed for numerous off-label indications despite a paucity of robust research data for most of them. A key strength of this update is the addition of several off-label indications not reviewed in the initial report. Each of the target populations for each reviewed indication is explicitly defined.	None needed
Reviewer 4	General		A minor quibble I have is the use of the term ‘atypical’ antipsychotics, which I realize was carried over from the initial report. The term atypical is being used less now as it implies that there is something special or unusual about these agents – I prefer the term ‘second-generation’ antipsychotics. I noticed that the term ‘first-generation antipsychotics’ was sometimes used, as was ‘conventional’, and for clarity I would use consistent terminology for these agents (e.g., first-generation) throughout the document.	We now use the term "conventional" antipsychotics throughout the document, rather than "typical" or first-generation. We continue to use the term "atypical."

Reviewer	Comment Section	Page	Comment	Response
Reviewer 5	General		The 847 page report focuses on off-label use of antipsychotic medication in the U.S. A few years ago, these drugs were all off label for autism, depression, augmentation of depression, etc. Now, many have received FDA approval for indications to treatment these disorders. That raises the question: Why focus on off-label use since expanding FDA approval for an approved drug to other indications is a chip shot. [Look at Paxil with 6 indications—even though it is not a good choice for women in their child bearing years (Category D), for youth ('Suicidality'), and for long term use (major withdrawal problems).	We are given our focus by our partners. In this case, the original Evidence Report on off-label uses was requested by State Medicaid Directors, who themselves were responding to the pressure placed on their budgets by the increasing use of atypical antipsychotics for uses other than FDA approved indications. Thus their interest was knowing whether there was evidence to support such prescribing. Their concern continues to the present. And, as our report indicates, in this update there are more "new" off-label indications than there are previous off-label indications that now have FDA approval.
Reviewer 5	General		Another concern is that the data were primarily taken from industry-sponsored clinical trials for one drug for one specific indication (accepting only 15% of possible subjects). Obviously subjects accepted into clinical trials do not reflect community populations who use psychotropic medication. So generalization of the trial findings to community treatment is limited. Furthermore, the trials are loosely based on DSM-IV-TR and a number of diagnostic categories have been substantially modified to meet criteria for the trials, (such as autism, ADHD and bipolar I,II, and NOS disorder).	We have added to the limitations section some text about industry funding.
Reviewer 2	Clarity and Usability		he report is well-structured, however, it is quite long, and a bit cumbersome to navigate. I would consider adding internal hyperlinks so that figures, tables, citations, and internal crossreferences including the table of contents could be directly accessed by clicking on the appropriate link. Also, I'd use chapter and section titles are part of header or footer information to ease navigation, assuming that fits without the style guidelines.	We will pass this suggestion along to AHRQ for consideration for future reports.

Reviewer	Comment Section	Page	Comment	Response
Reviewer 3	Clarity and Usability		the conclusions are clearly stated and accessible in the beginning of the document	None needed
Reviewer 1	Clarity and Usability		The report has the virtue of being exhaustive, but its shear length may detract from the extent to which it is read and referenced. The figures might be moved from main body of the report to the appendix. It might also be possible to shorten the current report by making more extensive use of references to the earlier report.	We agree with this comment. We will summarize the most important points in a journal article. AHRQ will fund brief clinician and consumer guides based on our findings, to help disseminate the message.
Reviewer 4	Clarity and Usability		This report is extremely clear and should be usable by a wide range of stakeholders, including other researchers, clinicians, patients, and policy makers.	None needed
Reviewer 2	Executive Summary	4	I don't understand why augmentation for OCD has been broken into SSRI and then citalopram, which is itself an SSRI. Would it be more accurate to write "SSRI (not citalopram)" if that distinction is needed?	These studies were divided not based on their use of citalopram but rather that one group of papers - possibly all from the same trial - studied treatment-naïve patients with OCD while almost all others, including all in our pooled analysis, studied patients who had already failed to respond adquately to SRI therapy.
Reviewer 1	Introduction	17	The authors do an excellent job of placing their topic in an appropriate clinical and services context. In defining the topic, it is not clear why antipsychotic augmentation for major depressive disorder is included. As the reviewers note, the FDA has approved quetiapine and aripiprazole as augmentation agents for major depressive disorder and the combination of olanzapine/fluoxetine for major depressive disorder. In view of these approvals, these agents and indications might be left out of the current report on off-label use.	We appreciate this comment, but left the data in the report since other atypicals have not been FDA approved for this indication and these provide comparative data. We added text explaining this.
Reviewer 2	Introduction	17, second paragraph, line 9	I don't know what "refractive" means in this context. "Refractory"?	Yes, we have changed to refractory.
Reviewer 2	Introduction	18, Anxiety, line 5	Social phobia isn't a specific phobia.	Reference to social phobia has been removed. Should be "social anxiety."

Reviewer	Comment Section	Page	Comment	Response
Reviewer 3	Introduction		Describes the reasons for the study in accessible, clear language.	None needed
Reviewer 4	Introduction	17, second paragraph	Regarding clozapine, is the intention here that the 'illness' rather than the 'drug' has proven refractive to other treatment?	Corrected.
Reviewer 4	Introduction	17, second paragraph	It wasn't entirely clear to me if there were any instances where a study included in the initial report/meta-analyses was not included in an updated meta-analysis.	All studies that met the current criteria were included. Some publications from the earlier report had been updated, while others had errata published. Others were presented as conference abstracts as of our first report, and were later published in peer reviewed journals. We used the most current information on each study.
Reviewer 1	Methods		The methods are exceptionally clearly laid out from the search strategy to the study seelction, data extraction, assessment of quality and strength of evidence, and approach to data synthesis. The language is easy to follow and coherent. The clarity of methods and defining of key tems is particularly important because many of these terms (efficacy, effectiveness, comparative effectiveness) have taken on several meanings in various literatures.	None needed
Reviewer 2	Methods		No concerns about the methods	None needed
Reviewer 2	Methods	28, line 31-41	The writing here is a bit clumsy and I'd consider rewriting it to clarify the point being made.	We have revised the text.
Reviewer 3	Methods		The clinical descriptions and definitions are clear and accurate. Inclusion and exclusion criteria, outcome measures, and statistical methods are clear.	None needed
Reviewer 4	Methods		The inclusion and exclusion criteria are justifiable. The search strategies were explicitly stated and logical. The definitions/diagnostic criteria for the outcome measures were appropriate, and the statistical methods used were appropriate.	None needed

Reviewer	Comment Section	Page	Comment	Response
Reviewer 4	Methods		Was there any consideration given to stratifying the analyses according to whether studies were drug-company funded or not? I realize this will not be applicable to most of the off-label indications, but this would apply to depression and possibly dementia. I also wondered why depression was covered in this review now that some SGAs have FDA indications for refractory depression.	Regarding depression, see the response to a previous question about this. Regarding the potential effect of industry sponsorships: In general there are too few non-industry sponsored studies to perform a stratified analysis. We now call greater attention to the potential for industry funding to influence the reported outcome of a trial.
Reviewer 1	Results		The rationale for separating depression trials that use MADRS and HAM-D as outcome measures is not clearly articulated. Although some comparative work has been done on the psychometric properties of these two similar instruments, it is not cited as a possible rationale for segregating the studies in this manner.	We kept these outcomes as separate because it facilitated the interpretation of the results. To statistically pool studies using these two outcomes, would require converting all outcomes into unitless "effect sizes", and then back-converting the pooled effect size into a clinically meaningful measure. We have done this in other studies where doing so helped clarify the conclusion. But in this case the studies with HAM-D outcomes and with MADRS outcomes yielded very similar results, so a pooled analysis across both outcomes would not have added substantially to our conclusions.

Reviewer	Comment Section	Page	Comment	Response
Reviewer 1	Results		For several conditions, the authors mix in meta-analyses studies of different populations. For example, the depression analyses mix studies of treatment resistant MDD with studies of MDD without regard to treatment response status. Similarly, the OCD meta-analysis mixes studies of treatment resistant OCD and OCD without regard to treatment response status. A clinical rationale for these decisions should be provided or separate analyses should be presented.	All patients in the studies included in the OCD meta-analysis were tx resistant. We have revised our depression analyses, conducting separate analyses for augmention studies of tx resistant patients, and those receiving monotherapy.
Reviewer 1	Results		For some conditions, the clinical samples are so disparate as to be uncertain value. For example, four ADHD trials are reviewed: two that concern bipolar disorder with comorbid ADHD, one that concerns mental retardation and ADHD, and one that concerns ADHD with treatment resistant aggression. None of these samples readily generalize to the broad range of children with ADHD. Without careful qualification of these clinical populations, the findings may easily be taken out of context.	Patient heterogenity is an issue in most of our analyses. We used clinical opinion to determine when the heterogenity was so great a pooled analysis was not justified, such as in ADHD, and when it was, such as in OCD, GAD, and dementia. We have described our decisions and tried to make clear the limitations.
Reviewer 1	Results	54,55 Table 7	In the GAD table, the inclusion of the Sheehan study, which involved patients with bipolar disorder with lifetime panic or GAD should be reconsidered. According to DSM-IV, GAD is not to be diagnosed when the focus of the anxiety is confined to features of another Axis I disorder. Reliably diagnosing GAD in the presence of bipolar disorder is extremely difficult.	We agree. Study has been rejected.
Reviewer 2	Results		This section is quite detailed, but needs to be so as much material is covered. There are relevant summaries	None needed
Reviewer 2	Results / KQ1	40, utilization, second paragraph	6.8% and 95.9% of what?	We have revised to clarify that the percentage of antipsychotics that were atypical (as opposed to conventional) prescribed to new users grew from 6.8% in 1996 to 95.9% in 2001.

Reviewer	Comment Section	Page	Comment	Response
Reviewer 3	Results		The tables and text include adequate detail. Studies are succintly but adequately described, and the descriptions appear to be accurate (for those studies of which I have knowledge). I did not identify important trials that were overlooked.	None needed
Reviewer 4	Results		The amount of detail presented in the results section is appropriate. The characteristics of the studies are clearly described. The key messages were explicit. Figures, tables and appendices are adequate and descriptive. It does not appear that investigators overlooked any studies that should have been included or included any studies inappropriately.	None needed
Reviewer 1	Discussion / Conclusion		It might also be helpful to briefly discuss the fact that no effort is made to assess the comparative effectiveness of antipsychotic medications vis-à-vis other medication classes for the off-label conditions under study.	We included studies comparing atypicals to other drug classes throughout the report. We can add more to the discussion.
Reviewer 1	Discussion / Conclusion		The report provides a balanced description of the relevant clinical trial literature regarding antipsychotics for off-label conditions. It would be strengthened by an effort to place the results in a context that helps clinicians to evaluate the meaning of the main findings.	These comments are all requesting more direction in the conclusions regarding "What does this mean clinicians should do?" However it is important to recognize that the role of Evidence Reports are to present the evidence. Conclusions about whether or not certain drugs should be recommended for certain indications require nuanced clinical judgement of the type usually used to develop practice guidelines. Practice guidelines are not the role of the Evidence Report, hence we refrain from reaching conclusions about what clinicians "should" do.
Reviewer 1	Discussion / Conclusion		What are prescribing physicians to make of the results, especially in the clinically challenging area of weighing risks and benefits? For conditions with a paucity of clinical trials but substantial community prescribing, is there a role for consensus based algorithms?	
Reviewer 1	Discussion / Conclusion		This point may be important to clinicians and clinical policy makers who are interested to learn where antipsychotic medications should fit in as either first, second, or third line treatments or whether their insufficient information to make any recommendations.	
Reviewer 2	Discussion / KQ1	47	The issue is lack of information, not known disparities.	We revised the text on this point.

Reviewer	Comment Section	Page	Comment	Response
Reviewer 2	Results / KQ2	78,79	Figure 12 appears identical to Figure 13	We have replaced with the correct figure.
Reviewer 2	Discussion / Conclusion		There are some unexpected findings, and I'd consider highlighting them, at least in some small way: (1) aripiprazole was associated with weight gain. (2) quetiapine was associated with EPS.	We have highlighted these and other findings which our psychiatrists deemed unexpected.
Reviewer 3	Discussion / Conclusion		The limitations of the data and of the review are clearly stated. Needs for future research are clear.	None needed
Reviewer 4	Discussion / Conclusion		The implications of the major findings are clearly stated. The limitations of the review are described adequately. The future research section is clear and easily translated into new research.	None needed
Reviewer 4	Discussion / Conclusion		My only substantive concern about this report has to do with the reporting and interpretation of the analyses on dementia. A number of new studies have been published in this area since the last report, which is encouraging. On page 57, however, as in the initial report, the results of the updated meta-analyses are appropriately qualified by stating that the effect sizes are generally considered "small" in magnitude for each of the outcomes analyzed (which I agree with). In Table 22 (p. 106), however, it is made to look as though comparatively, the results for dementia are much more positive and perhaps substantial in magnitude. Further in Table 32 (p. 137), the language about 'small but statistically significant effects' does not appear under the 2010 Findings for dementia as it did under the 2006 Findings. Has the language been removed because there are so many more studies available now? With the newer studies, the data on side effects, particularly CVA, is also stronger. It would seem that the outcome results should be more strongly qualified by the updated side effects data i.e., some comment on risk-benefit of the use of these agents in the elderly seems warranted.	We acknowledge this concern. Table 22 (now Table 23) lists symbols for the strength of evidence, which should not be confused with the magnitude of the benefit. We have now added a footnote making this point. Also, in Table 32 (now called Table 33) we have added to the 2011 findings that the size of effects were small.

Reviewer	Comment Section	Page	Comment	Response
Reviewer 1	Future Research	147	In the last paragraph of the report, the investigators state: “Newer agents, such as asenapine, iloperidone and paliperidone cannot be assumed to have efficacy and harms similar to the older atypical antipsychotics, since the evidence to date does not support that there is a general “class effect” in terms of either efficacy or harm for most off label indications.” The summary table makes clear that the strength of efficacy evidence varies across drugs for different conditions. Yet the computation of the overall effects in several of the meta-analyses, which may be one of the most widely cited aspects of this report, makes the assumption that class effects can be summed across drugs within disease conditions. In the methods, it might be helpful to briefly discuss the decision to aggregate the meta-analyses within drug class.	Actually, we refrained from doing pooled analyses across, drugs in response to reviewers comments on our original report (that had included such "across drugs" analyses) that each drug needed to be considered seperately. Similarly, our summary table of benefits (Table 1) lists each drug seperately for each indication. So, we think the report is suitably restrained on drawing conclusions across drugs. However, this point and the earlier point about class effects have led us to discuss in greater detail the challenge of drawing conclusions in the "class effect" versus "individual drug" debate.
Reviewer 5	Other		In the trials covered by the reviews, statistical significance is often used, not effect size.	We have tried to address effect size at the end of each section, and in the discussion section.
Reviewer 5	Other		The Cochrane reviews are far more selective, concise and readable.	We appreciate these two comments. This report follows the AHRQ required format. Note, however, that AHRQ supports development of brief clinical guides and consumer guides to help disseminate the findings.
Reviewer 5	Other		The review is obsessive in detail. Not much can be gleaned from the mountains of detail, unless the important findings are organized for pertinence and framed within major diagnostic categories.	

Reviewer	Comment Section	Page	Comment	Response
Reviewer 5	Other		Symptom decrease in the (industry-sponsored) efficacy trials are presented, not functional changes in effectiveness.	We acknowledge that most of the included trials do not report those measures, and we encourage further research in that area.
Reviewer 5	Other		Future research efforts need to focus less on industry-sponsored, symptom-focused, clinical trials and focus more on effectiveness and the overwhelming degree of concomitant treatment.	We agree, and have highlighted this more.
Reviewer 5	Other		The report only touches on the benefit/risk ratio, but this is the very heart of good clinical judgment. For example, olanzapine is on-label for a number of indications, but it presents serious potential problems for >65% of adult and adolescent subjects—even though it is on-label. I don't think that the Rand Corporation is at fault for the conception of the study. They just bid and got the contract from AHRQ.	We appreciate this comment. We have tried our best to highlight the evidence and the issues, but recognize it is not the role of the Evidence Report to provide clinicians recommendations for clinical care. This requires knowing the evidence about benefits, harms and applicability, and using clinical judgment to balance these given patients' desires for certain outcomes.

Public Comments

Reviewer	Comment Section	Page	Comment	Response
BMS	General		Aripiprazole (and quetiapine) data for MDD is provided in the report. As these drugs are approved for use in MDD, rationale for inclusion of the data in the report should be clarified.	We have added the rationale to the methods section.
BMS	Executive Summary - Table B	ES-5	With respect to the efficacy of atypicals for use in SSRI augmentation for the treatment of MDD, it may be more useful to describe the strength of evidence (Table 2) as not two but three levels (high – which would include those compounds with FDA approval, medium – which would include those with RCT based evidence, and low).	We need to use the strength of evidence criteria used by the AHRQ Effective Healthcare program. However, we have added a new designation in the table to identify those drugs / indications that are FDA approved.
BMS	Executive Summary - Table B	ES-5	In that same section under 2010 findings, it should probably be reemphasized that aripiprazole and quetiapine were adjunctive to SSRI/SNRIs.	In revising the report, we conducted separate analyses for monotherapy and augmention of SSRI/SNRIs, so this distinction is now made more clearly.
BMS	Executive Summary - Table C	ES-11	Table 3 does not summarize EPS for younger patients. Should these be included?	We found only one trial that reported EPS in children; 32% of patients on aripiprazole reported EPS compared to 83% of placebo patients. We did not feel this was sufficiently important to include in the executive summary, but these data are in the main body of the report.

Reviewer	Comment Section	Page	Comment	Response
BMS	Executive Summary - Remaining Issues	ES-14	In the "remaining issues" section on page 14, it is mentioned that "It would facilitate assessments of comparative effectiveness if future studies contained a standardized list of assessed side effects". Beyond the use of MedDRA terms for reporting adverse events and standardized measures of EPS, what specifically is meant by "standardized list"? A scale such at the UKU or PAERS?	Too clarify, many studies mention only a handful of side effects. It is unclear if other side effects were just not assessed, or if they were tracked but zero occurred.
BMS	Introduction / Background		Among antipsychotics with approvals since the last report, the approval for aripiprazole in the treatment of irritability associated with autistic disorder was not mentioned.	This was added.
BMS	Results - KQ1	40	On page 40, it is mentioned for the Cooper study that new users of antipsychotics nearly doubled from 1996 to 2001; new users of atypicals increased from 6.8% in 1996 to 95.9% in 2001. Is this figure correct?	We have revised to clarify that the percentage of antipsychotics that were atypical (as opposed to conventional) prescribed to new users grew from 6.8% in 1996 to 95.9% in 2001.
BMS	Results - KQ1		Two recent studies that have assessed the off-label use of atypical antipsychotics (Key Question 1) have not been included in the analysis: a. Leslie D et al. Off label use of antipsychotic medications in the department of VA health care systems. Psychiatric Services 60:1175–1181, 2009. This study provides rate of off-label use of antipsychotics from a 2007 VA dataset. b. Alexander et al. Increasing off-label use of antipsychotic medications in the United States, 1995– 2008. Pharmacoepidemiology and drug safety (2011) DOI: 10.1002/pds.2082 The study results indicated 75% off-label use of antipsychotics in 1995 and 60% off-label use in 2008 (both estimates based on FDA approvals through 2008). Additionally, with respect to Key Question 1, it might be useful if the review would explore/discuss variations in the rates of off-label use among different atypical antipsychotics	These studies have been added to our section on prescribing patterns.

Reviewer	Comment Section	Page	Comment	Response
David L Shern	General		MHA commends you for the thoroughness and comprehensiveness of the review, as well as the expanded list of conditions examined relative to the 2006 review. We know that individuals with the conditions considered in this report – anxiety, attention-deficit hyperactivity disorder, dementia, major depressive disorder, eating disorders, insomnia, obsessive compulsive disorder, post traumatic stress disorder, personality disorders, substance abuse, and Tourette's syndrome – experience variability in their tolerance for and effectiveness of available treatments, and for some conditions the pharmacologic treatment options are few. Therefore, this review of the evidence is vital for helping individuals and practitioners to identify the potential off-label uses for medications. To this end, MHA encourages AHRQ to disseminate the findings of the review in ways that are accessible to patients, family members, and providers, so those living with these conditions can make informed decisions regarding their treatment options. AHRQ has been committed to effective dissemination and implementation of research evidence. Providing this information in patient and provider friendly formats will advance these efforts substantially. Any materials that are developed to promote the dissemination of findings from this review should consider the great variability in health literacy among individuals with these conditions. Treatment and prescribing issues are complicated. The accessibility of patient information is critically important.	None needed
David L Shern	General		MHA is committed to promoting patient involvement in all areas of the health care system, including in research development and utilization, and especially in shared decision making during the clinical experience. We would be happy to assist AHRQ in any way to advance the evidence that has been compiled in this review and promote its application in clinical settings by disseminating information to patients and providers, and promoting health literacy among individuals who live with these various conditions. Please feel free to contact us as you develop your outreach materials for patients and providers. Thank you for the opportunity to present our views	We have brought this to the attention of the AHRQ-funded Eisenberg Center, which develops materials for clinicians and consumers.
Jeni Bastean	Tables		Table 20. Adjust treatments column to include risperidone long-acting injection 25 mg every two weeks. Risperidone 1-2 mg oral daily was utilized only during initation of risperidone longacting injection (weeks 0-3).	Revised

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Kathleen Gans-Brangs	Executive Summary - Table A	ES-4	Table 1; Depression-MDD augmentation of SSRI / SNRI. Recommend that the chart reflect where indications have been approved since the time of the initial request (e.g., aripiprazole and quetiapine XR – now approved for use in Depression-MDD augmentation of SSRI / SNRI). Executive Summary, p. 4; Table 1;	These approvals are mentioned in the introduction. The drugs are still included in the chart for comparative purposes.
Kathleen Gans-Brangs	Executive Summary - Table A	ES-4	Depression-MDD: Monotherapy. There are 5 trials of quetiapine XR as monotherapy for MDD but Table 1 indicates that there are none. Please see the following studies in this area: • Weisler R, Joyce M, McGill L, et al. Extended release quetiapine fumarate monotherapy for major depressive disorder: results of a double-blind, randomized, placebo-controlled study. CNS Spectr. 2009;14(6):299-313. • Cutler AJ, Montgomery SA, Feifel D, et al. Extended release quetiapine fumarate monotherapy in major depressive disorder: a placebo- and duloxetine-controlled study. J Clin Psychiatry. 2009;70(4):526-539. • Bortnick B, El-Khalili N, Banov M, et al. Efficacy and tolerability of extended release quetiapine fumarate (quetiapine XR) monotherapy in major depressive disorder: a placebo-controlled, randomized study [published online ahead of print August 9, 2010]. J Affect Disord. 2010. doi:10.1016/j.jad.2010.06.031. • Earley W, McIntyre A, Wang G, et al. Double-blind study of the efficacy and tolerability of extended release quetiapine fumarate (quetiapine XR) monotherapy in patients with major depressive disorder (MDD) [poster]. Presented at: 8th International Forum on Mood and Anxiety Disorders; November 12-14, 2008; Vienna, Austria. • Liebowitz M, Lam RW, Lepola U, et al. Efficacy and tolerability of extended release quetiapine fumarate monotherapy as maintenance treatment of major depressive disorder: a randomized, placebo-controlled trial. Depress Anxiety. 2010;27:964-976.	We have added these studies to our report and conducted a meta-analysis on quetiapine XR as monotherapy for MDD.
Kathleen Gans-Brangs	Executive Summary - Table B	ES-5	Executive Summary, p. 6; Table 2; Depression-MDD augmentation of SSRI / SNRI. Recommend including that quetiapine XR and aripiprazole are approved for this use.	These approvals are mentioned in the introduction. The drugs are still included in the chart for comparative purposes.

Reviewer	Comment Section	Page	Comment	Response
Kathleen Gans-Brangs	Executive Summary - Table B	ES-7	Executive Summary, p. 7; Table 2; Post traumatic stress disorder. There are no quetiapine trials mentioned. Please see the following studies in this area: • Ozdemir AC, Kocabasoglu N, Yargic I. Quetiapine/sertraline combination in PTSD [poster]. Presented at: 159th Annual Meeting of the American Psychiatric Association; May 20-25, 2006; Toronto, Canada. • Hamner M, Robert S, Canive J, et al. Quetiapine monotherapy in chronic posttraumatic stress disorder: A randomized, double-blind, placebo-controlled trial [abstract]. Euro Neuropsychopharmacol. 2009;19(suppl 3): S591-S692. Abs P.4.a.011.	We have added these studies to our report.
Kathleen Gans-Brangs	Executive Summary - Table B	ES-9	Executive Summary, p. 9; Table 2; Substance abuse - alcohol. Please see the following studies in this area: • Brown ES, Garza M, Carmody TJ. A randomized, double-blind, placebocontrolled add-on trial of quetiapine in outpatients with bipolar disorder and alcohol use disorders. J Clin Psychiatry. 2008;69(5):701-705. • Pettinati HM, Stedman M, Brown ES, et al. A double-blind, placebo-controlled study of quetiapine adjunct therapy with traditional mood stabilizers in bipolar I patients with alcohol dependence [abstract]. Alcohol Clin Exp Res. 2008;32(6 suppl 1):260A. Abs 998. • Guardia J, Roncero C, Galan JL, et al. Efficacy and tolerability of quetiapine, combined with naltrexone, in the treatment of alcohol dependence [abstract]. Eur Neuropsychopharm. 2007;17(suppl 4):S545-S546.Abs. P.6.a.013. Executive Summary, p. 9; Table 2; Substance abuse - cocaine. Please see the following study in this area: • Brown ES, Gabrielson B, Gu P. A randomized, double-blind, placebo-controlled pilot study of quetiapine in outpatients with bipolar disorder and cocaine dependence [abstract]. Bipolar Disord. 2009;11(suppl 1):25. Abs.P32.	Patients with bipolar disorder are beyond the scope of this report, regardless of co-occuring disorders. Thus, the three studies by Brown were excluded. We have now included this study by Guardia.

Reviewer	Comment Section	Page	Comment	Response
Kathleen Gans-Brangs	Results	37	Chapter 3, p. 53-56; Anxiety. Please see the following studies in this area: • Khan A, Joyce M, Eggens I, et al. Extended release quetiapine fumarate (quetiapine XR) monotherapy in the treatment of patients with generalized anxiety disorder (GAD) [poster]. Presented at: Anxiety Disorders Association of America Congress; March 6-9, 2008; Savannah, GA. • Merideth C, Cutler A, Neijber A, et al. Efficacy and tolerability of extended release quetiapine fumarate (quetiapine XR) monotherapy in the treatment of generalized anxiety disorder (GAD) [poster]. Presented at: 21st Congress of the European College of Neuropsychopharmacology; August 30-September 3, 2008; Barcelona, Spain. • Bandelow B, Chouinard G, Bobes J, et al. Extended-release quetiapine fumarate (quetiapine XR): a once-daily monotherapy effective in generalized anxiety disorder. data from a randomized, double-blind, placebo- and active-controlled study. Int J Neuropsychopharmacol. 2010;13(3):305-320. • Montgomery S, Locklear J, Svedsater H, et al. Efficacy of extendedrelease quetiapine fumarate: pooled analysis in patients with generalized anxiety disorder [abstract]. Int J Psychiatry Clin Pract. 2009;13(suppl 1):39. Abs P40. • Katzman MA, Brawman-Mintzer O, Reyes EB, et al. Extended release quetiapine fumarate (quetiapine XR) monotherapy as maintenance treatment for generalized anxiety disorder: a long-term, randomized, placebo-controlled trial. Int Clin Psychopharmacol. 2011;26(1):11-24. • Svedater H, Endicott J, Locklear J. Effects of extended release quetiapine fumarate (Quetiapine XR) on patient-reported outcomes in patients with generalized anxiety disorder (GAD) [abstract]. Int J Psychiatry Clin Pract. 2009;13(suppl 1):44. Abs P51. • Khan A, Atkinson S, Mezhebovsky I, et al. Efficacy and safety of once-daily extended release quetiapine fumarate (quetiapine XR) as an adjunct therapy in patients with treatment non-responsive generalized anxiety disorder (GAD) [poster]. Presented at: 49th Annual New Clinical Drug Evaluation Unit Meeting, June 29–July 2, 2009; Hollywood, FL.	These studies have been screened for inclusion. Several were duplicates of unpublished studies we had already included in our draft report, as they had been sent by the manufacturer. Others were journal publications of studies that had already been included as conference abstracts. The net result is that we updated the reference list, but there were no new studies in this group.
Rebecca Swift	Methods		Looks like the study treated any major conflicts internally, as well as a variety of factors affecting test patients. Also, a variety of disorders were covered separately and with the various pharmeceuticals. Extensive.	None needed
Rebecca Swift	Tables		Liked the table in Introduction which mapped the drugs and their uses in atypical case studies.	None needed

Reviewer	Comment Section	Page	Comment	Response
Ryan Carnahan	Executive Summary	ES-1,2	Page 4 in executive summary: As described previously, the evidence for quetiapine in dementia is almost all negative. The pooled results do not show a significant benefit, nor do individual trials. It seems much more appropriate to place this in the category of little to no evidence or mixed results. It could almost be categorized as having moderate to high evidence of inefficacy. It is misleading to state that there is moderate to high evidence of efficacy for this drug in dementia.	We have revised to downgrade the strength of evidence for quetiapine.
Ryan Carnahan	Results	57	page 57: States that for total/global scores in dementia trials, each drug studied was superior to placebo. This is not true for quetiapine. In addition, it shows a trend towards worsening psychosis with this drug. I can't reconcile the fact that this is placed in the "moderate evidence for efficacy" category with the rest of the drugs when the evidence presented does not support it. Not a single study showed a significant benefit in pooled results, and neither did the metaanalysis. One study showed a benefit at 200 mg in some but not all subscales, but that's hardly even a moderately conclusive finding given all the negative studies.	We have added several new studies to the dementia analyses, removed a duplicate study, and rewritten this section. We have downgraded the strength of evidence for quetiapine.

TEP Comments

Reviewer	Comment Section	Page	Comment	Response
TEP #2	General		This review has been an focused and intensive exercise in resilience in the past three days. I cannot find any major critique. There are minor changes which are not needed for immediate correction. This is fine by my perspective. Thank you for giving me the opportunity to be part of the process.	None needed
TEP #3	Executive Summary		With the exception of clozapine, every atypical antipsychotic has been associated with extrapyramidal symptoms and tardive dyskinesia. These harms should be assumed for the newer agents as well. There is a "class effect" of these harms for almost every d2 blocking agent.	By stating that we found no trials or large observational studies of these drugs for off-label uses, we do not wish to imply that there is no risk of these harms. There is simply a lack of evidence; the potential for harms (as well as benefits) still exists.
TEP #4	Dosages and Timing		Dosages and timing -- this is a very important element for providers and highlighting the lack of data here is very useful. I hope this will stimulate researchers to focus on these questions.	None needed
TEP #4	Methods	12	Source of funding -- I noted in the methods section that source of funding was an element of quality assessment, but it wasn't clear to me that it was included in the quantitative scale. I believe the source of funding for any potential conflict of interest is an important piece of information for any reader in evaluating the quality of a study. I would find helpful more information regarding the source of funding as well as potential conflicts of interest for authors, even though we do not yet have good measures for these.	We have added text to the discussion about the role of industry funding. Identifying potential conflicts of interest among the authors of all included studies is beyond our means.
TEP #1	Methods	25	p 25 - analytic framework - list "depression" but in other areas of the report you list MDD.	Added
TEP #4	Results	Publication Bias, 107	Publication bias -- I appreciate the discussion on page 107 and in the Limitations section, however publication bias remains a problem for the field as well as the strength of recommendations from a report such as this. I hope this report will spur more work in this area.	We agree.

Reviewer	Comment Section	Page	Comment	Response
TEP #4	Results	KQ 3, 92	Key question number 3 -- I have concern regarding the applicability of this information to the treatment of populations of individuals with severe mental illness, particularly in urban, diverse communities. Unfortunately the authors find little information specific for treatment decision-making with individuals of varying ethnicities and backgrounds. I found useful the authors notation that even though investigators included individuals from different ethnic backgrounds or genders, they rarely published subgroup analyses. I also appreciated the comments in the Limitations section regarding the applicability.	None needed
TEP #1	Results	19?	p 35 - 1st paragraph - when will the articles being retreived be added?	The articles were added to the final version of the report.
TEP #1	Results	21?	p37 - define API?	AP1 refers to our original report on this topic, completed in December 2006, and is indicated in the footnote.
TEP #1	Results	?	p.56 - the use of "&" is not intuitive in how this is written. I had to read it twice to understand.	Change to "and"
TEP #1	Results	58?	p.74 - last paragraph - for the nonstatistician please explain why "continuous outcomes" were not included?	We have added the explanation to the text.
TEP #1	Results	64 Table 12	P 80 - Table 12 - later in the text there is explanation as to why AZ is listed as an author, but it is strange to read this in a table. Suggest listing it as Anon with a bracket for sponsorship by AZ?	This study was sent to us directly from Astra Zeneca. No authors were named. We judged it is more informative to list Astra Zeneca as the author than "anonymous"
TEP #1	Results	87	p103 - YGTSS? what is this?	Yale Global Tic Severity Scale, and it is defined in its first use.
TEP #1	Results	95	p111 - suggest listing the specific anticholinergic effects.	Anticholinergic effects were reported in only one trial. In the article, the specific effects are not listed.

Reviewer	Comment Section	Page	Comment	Response
TEP #1	Results	99 Table 24	p115 - second line, 95CI NNH, "44,NC" - can you have a lower but an NC upper limit?	We have corrected.
TEP #1	Results	101	p117 - text notes that the CI are "very wide" - I'm not sure a CI of 6-11 is "very wide".	The "very wide" refers to these studies: Bystritsy, 2004, Atmaca, 2002, and Hollander, 2003. Each has a upper confidence interval of at least 90.
TEP #1	Results	101	p117 - "pulmonary adverse events" - give details of what this is?	Includes pneumonia and unspecified events labeled "respiratory" in several studies.
TEP #1	Results	109	p125 - "a handful of trials" - give actual # of trials.	We have corrected. The text now indicates 2 quetiapine, 3 olanzapine, and 1 risperidone trial.
TEP #1	Results	111	p127 - list "urinary symptoms" - not incl to any extent earlier in the report.	Includes enuresis, urinary tract infection, urinary urgency, and acute retention of urine.
TEP #1	Results	115	p131 - "1.43 (CI1.25 - 163) - should be 1.63?	Correct, this has been revised.
TEP #3	Discussion	127	The strength of evidence may be low, but magnitude of the reported difference is large. Typical antipsychotics have Tardive dyskinesia rates of 7% per year of exposure, while atypicals range around 1-2%. We need more studies assessing this, but these data are consistent with clinical experience as well.	We agree that more studies are needed, and have called for better studies of potential adverse events in our Future Research section.

Reviewer	Comment Section	Page	Comment	Response
TEP #1	References		some refs are "in press" but from 2007 (e.g. ref 147) - need to footnote this as to why it's still not in press 4 years later	"In press" was stamped on several unpublished studies we received from Astra Zeneca, the manufacturer of quetiapine. Since our draft report was circulated, several of these studies have been published in journals. However, others have not yet been published. We have changed the designation of such studies to "unpublished", rather than "in press".

Grammar-Editing Typos

Reviewer	Comment Section	Page	Comment	Response
Reviewer 2	Executive Summary	5 and 137	It would be nice of the column headings of the table carried over to subsequent pages.	corrected
Kathleen Gans-Brangs	Introduction	ES-1	There should be a space between “quetiapine” and “XR”. Executive Summary, p. 4;	corrected
Reviewer 2	Background	23	consentional is a typo	corrected
TEP #1	Results	22?	P 38 - 4th line - "there is little reported off-label..." - isn't it "nothing reported"?	corrected
TEP #1	Results	31	p. 47 - "another issue which arose..." - another issue which was noted?	sentence has been deleted
TEP #1	Results	68	p 84 - 3rd paragraph - "0.004"? or 0.04?	.004 is correct as stated
TEP #1	Results	71	p.87 - Y-BOCS vs YBOCS? hyphen?	hyphen has been inserted every time
TEP #1	Results	82	p.98 - "four trials" - now says trails	corrected
TEP #1	Results	75,76	p 91, 92 - different tenses used - e..g "we thought it was worth mentioning"... "we would not condut meta-analysis..."	corrected
TEP #1	Results	96	p113 - "odds of GI.." - GI adverse effects?	yes, added
TEP #1	Results	110	p 126 - "critiqued" - criticized?	corrected
Kathleen Gans-Brangs	Results	108	Chapter 3, p. 124; 3rd line above Table 3. Abbreviation for extrapyramidal side effects should be EPS, not EBS.	corrected
Kathleen Gans-Brangs	Results	111	Chapter 3, p. 127; line 3. “The CATIE-AD trial concluded that EPS are more common with olanzapine and risperidone that quetiapine.” Please change “that quetiapine” to “than with quetiapine.”	corrected
Reviewer 2	Substance Abuse	104	Table 19 should be "Table 22"	re-numbered
Reviewer 4	KQ5	113	should the term be ‘salivation’ rather than ‘salvation’?	corrected

Reviewer	Comment Section	Page	Comment	Response
TEP #1	Summary and Discussion	124	p 140 - suggest changing "eating disorder patients" to "patients with eating disorder"	corrected