

AHRQ Systematic Review Surveillance Program

CER #43: Off-label Use of Atypical Antipsychotics: An Update

Original Release Date: September 2011

Surveillance Report: August 2014

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Summary of Key Findings from Surveillance Report:

- Key Question 1: While the conclusions in the original review related to utilization trends are likely current, the scope related to new off label uses is likely out of date. The original review limited inclusion to specific conditions, and excluded studies examining conditions not on the list (ie, delirium). The current and prior assessments identified numerous off-label indications for atypical antipsychotics that were not included in the original systematic review. Experts suggest updating the review to include new indications, particularly delirium.
- Key Question 2: Conclusions related to dementia, anxiety, schizotypal personality disorder, attention deficit hyperactivity disorder (ADHD), eating disorders, insomnia, and substance abuse are likely current. However, while the original review's conclusions related to the effectiveness of the identified atypical antipsychotics for major depressive disorder (MDD), obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and Tourette's syndrome are likely current as well, new evidence examining atypical antipsychotics not identified in the original review (ie, ziprasidone, aripiprazole, paliperidone, and asenapine) may render the scope of the review for these conditions out of date.
- Key Question 3: Original systematic review conclusions are likely current.
- Key Question 4: Conclusions related to weight gain, endocrine/diabetes, and mortality are likely current. However, while the original review's conclusions related to the effectiveness of the identified atypical antipsychotics for extrapyramidal symptoms (EPS) and tardive dyskinesia are likely current as well, we identified new evidence examining atypical antipsychotics not identified in the original review (ie, ziprasidone and aripiprazole) that may render the scope of the review for these conditions out of date. We also identified new evidence examining potential harms for which no conclusions

- were determined in the original review (ie, blood pressure, heart rate, treatment-related suicidal ideation, sexual dysfunction, and somnolence).
- Key Question 5: The conclusions of insufficient evidence related to timing and dose are likely still current. However, we identified new evidence examining the use of atypical antipsychotics for conditions not included in the original review (ie, dose: quetiapine for borderline personality disorder, ziprasidone for MDD; timing: examined timing for augmentation for OCD, risperidone for Alzheimer’s disease).
 - A new atypical antipsychotic, lurasidone, was approved after the publication of the original systematic review. No identified studies in the prior or current assessment examined off-label use.

Signal Assessment: The signals examined in this surveillance assessment suggest that portions of the original systematic review may not be current.

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Conflict of Interest:

None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

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Introduction

The purpose of the surveillance process for the Evidence-based Practice Center (EPC) Program is to determine whether the conclusions of a systematic review are current. The surveillance process examines the conclusions to the key questions as written, and does not evaluate the currency of the original scope (ie, key questions and included interventions). A limited number of systematic reviews are selected for surveillance annually based on popularity, use in obtaining continuing medical education certificates, potential impact for changing the field, and use in clinical practice guidelines.

Comparative Effectiveness Review (CER) #43 titled, *Off-Label Use of Atypical Antipsychotics: An Update*, was published in September 2011.¹

The key questions for the original systematic review are as follows:

Key Question 1. What are the leading off-label uses of atypical antipsychotics in utilization studies? How have trends in utilization changed in recent years, including inpatient versus outpatient use? What new uses are being studied in trials?

Key Question 2. What does the evidence show regarding the efficacy and comparative effectiveness of atypical antipsychotics for off-label indications?

- **Sub-Key Question 2.** How do atypical antipsychotic medications compare with other drugs, including first-generation antipsychotics, for treating off-label indications?

Key Question 3. What subset of the population would potentially benefit from off-label uses? Do effectiveness and harms differ by race/ethnicity, gender, and age group? By severity of condition and clinical subtype?

Key Question 4. What are the potential adverse effects and/or complications involved with off-label prescribing of atypical antipsychotics? How do they compare within the class and with other drugs used for the conditions?

Key Question 5. What is the effective dose and time limit for off-label indications?

Our surveillance assessment began in March 2016. We conducted an electronic search for literature published since the end date of the most recent surveillance report search date. After completing a scan of this literature to identify evidence potentially related to the key questions in this systematic review, we contacted experts involved in the original systematic review to request their opinions as to whether the conclusions had changed.

Methods

Prior Surveillance

A surveillance report for the original systematic review was released in August 2014, and included a search for relevant literature published between January 2011 and June 2014, expert opinion, and a search of U.S. Food and Drug Administration (FDA). The findings from this report are included in our assessment.

Literature Searches

We conducted a literature search of PubMed covering June 2014 to March 2016 using the identical search strategy used for the original review¹ and searching for studies published since the end date of the most recent surveillance search.

The search was conducted to assess the currency of conclusions using journals from among the top 10 journals from relevant specialty subject areas and among those most highly represented among the references for the original review. We included the journals searched in the previous surveillance assessment. The included journals were eight high-impact general medical interest journals (Annals of Internal Medicine, Archives of Internal Medicine, The BMJ, Cochrane Database of Systematic Reviews, JAMA, Lancet, New England Journal of Medicine, and PLOS Medicine) and six specialty journals (American Journal of Psychiatry, Archives of General Psychiatry, International Clinical Psychopharmacology, Journal of Clinical Psychiatry, Journal of Clinical Psychopharmacology, and Neuropsychopharmacology).

Study Selection

Using the same inclusion and exclusion criteria as the original systematic review (see Appendix B), one investigator reviewed the titles and abstracts of the 14 high-impact journal search results (Appendix C). We included systematic reviews and meta-analyses, whether or not they were included (as a study design) in the original systematic review. For systematic reviews and meta-analyses, we considered findings only if all included studies met criteria that a) all studies were not included or excluded from the original systematic review, b) all studies were not included in a prior surveillance report (if applicable), and c) all studies met inclusion criteria for the original systematic review. Reviews for which one or more study did not meet our criteria were used to identify potentially relevant primary research. Reviews of systematic reviews were not included.

Expert Opinion

We shared the conclusions of the original systematic review and most recent surveillance assessment, findings from the literature analysis, and the newly identified studies with 12 experts in the field (seven original peer reviewers and five technical expert panel members [TEP]) to request their assessment of the currency of the original review conclusions and their recommendations of any relevant new studies. Three subject matter experts responded to our request. Appendix D shows the form experts were asked to complete.

FDA Black Box Warnings

We searched the FDA MedWatch online database website for black box warnings relevant to the key questions in this systematic review.

Check for Qualitative Signals

The authors of the original systematic review conducted qualitative and quantitative analysis of off-label use of atypical antipsychotics, including utilization trends, studies of new off-label uses, efficacy and comparative effectiveness to other pharmacological interventions, subgroup analysis, adverse events, and dose and time limits. We compared the conclusions of the included abstracts to the conclusions of the original systematic review and surveillance

report(s), and assessed expert input, and FDA alert information to identify qualitative signals about the currency of conclusions.

Compilation of Findings and Conclusions

For this assessment we constructed a summary table (Appendix E) that includes the key questions and conclusions from the original systematic review, findings of the new literature search, FDA black box warnings, and the expert assessments pertaining to each key question. We categorized the currency of conclusions using a 3-category scheme:

- Original conclusion is still valid and this portion of the systematic review is likely current
- Original conclusion is possibly out of date and this portion of the systematic review may not be current
- Original conclusion is out of date.

We considered the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the systematic review conclusion as still valid, we classified the systematic review conclusion as likely current.
- If we found some new evidence that might change the systematic review conclusion, and /or a minority of responding experts assessed the systematic review conclusion as having new evidence that might change the conclusion, then we classified the systematic review conclusion as possibly not current.
- If we found new evidence that rendered the systematic review conclusion out of date or no longer applicable, we classified the systematic review conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, etc.

Signal Assessment for Currency of the Systematic Review

We used the following considerations in our assessment of currency of the systematic review:

- **Strong signal:** A report is considered to have a strong signal if new evidence is identified that clearly renders conclusions from the original systematic review out of date, such as the addition or removal of a drug or device from the market or a new FDA boxed warning.
- **Medium signal:** A report is considered to have a medium signal when new evidence is identified which may change the conclusions from the original systematic review. This may occur when abstract review and expert assessment indicates that some conclusions from the original systematic review may not be current, or when it is unclear from abstract review how new evidence may impact the findings from the original systematic review.
- **Weak signal:** A report is considered to have a weak signal if no new evidence is identified that would change the conclusions from the original systematic review. This may occur when no new evidence is identified, or when some new evidence is identified but it is clear from abstract review and expert assessment that the new evidence is unlikely to change the conclusions of the original systematic review.

Results

Prior Surveillance

Prior surveillance² of the topic included 43 studies and consultation with four subject matter experts. The prior surveillance concluded that for Key Question 1, conclusions related to the new off-label uses for atypical antipsychotics may no longer be current. The assessment included the identification of an atypical antipsychotic (lurasidone) approved after the completion of the original systematic review (no studies examining off-label uses were identified). In addition, the assessment identified studies examining off-label uses for atypical antipsychotics (ie, risperidone, aripiprazole, paliperidone, olanzapine, and quetiapine) for conditions that were not specified for inclusion in the original systematic review (ie, Huntington's disease, trichotillomania, somatoform disorder, and fibromyalgia), a study examining asenapine for borderline personality disorder, and a study examining ziprasidone for delirium. Both asenapine and borderline personality disorder were within the scope of the original review, and while ziprasidone was included as an atypical antipsychotic of interest in the original review, delirium was not. For Key Questions 2-5, based on identified studies and expert opinion, the prior surveillance assessment concluded that while the conclusions in the original systematic review were likely still current, the systematic review may be out of date due to a new atypical antipsychotic (lurasidone) and new conditions for which atypical antipsychotics are being studied. The inclusion criteria for the original review allowed for the inclusion of only specific drugs and conditions.

Literature Search

The literature search identified 280 unique titles from the 14 selected high profile general medical and specialty journals (Appendix E). Upon abstract review, 273 studies were rejected because they did not meet the original systematic review inclusion criteria (see Appendix B). The remaining seven studies³⁻⁹ were examined for potential to change the results of the original systematic review. One study was a systematic review.³

A 2016 systematic review of 56 studies,³ which examined atypical antipsychotics for anxiety, somatoform, and trauma-related disorders included 46 studies that were included in the original systematic review¹ (which was an update to a 2007 review), the 2007 review,¹⁰ the 2014 surveillance report,² was identified in the current literature search, or did not meet inclusion criteria. For social anxiety disorder, one of the two studies¹¹ included was included in the original systematic review (one study was examined).¹² For panic disorder, of the four included studies,¹³⁻¹⁶ two were included in the original systematic review.^{14,16} Two studies^{13,15} were excluded because participants were diagnosed with comorbid bipolar disorder, for which atypical antipsychotics are approved. No studies were examined. For generalized anxiety disorder, eleven^{14,17-26} of the fourteen^{13,14,17-28} included studies were included in the original systematic review^{14,17-19,21,23-26} or the prior surveillance assessment.^{20,22} One study¹³ was excluded due to comorbid bipolar disorder. Two studies^{27,28} were examined for the potential to affect the currency of review conclusions. Of the 23²⁹⁻⁵¹ studies examining augmentation to selective serotonin reuptake inhibitors (SSRIs) for treatment resistant obsessive-compulsive disorder (OCD), 16^{29,33,36-39,41-48,50,51} were included in the original review,^{29,38,39,42} the 2007 review,^{33,37,41,43-48,50} or the prior surveillance assessment,^{36,51} and one study⁴⁹ was excluded because it did not specify the type of antipsychotic (six studies were examined).^{30-32,34,35,40} Of the

studies examining post-traumatic stress disorder (PTSD), all but one⁴⁶ of the 11 studies^{6,52-61} were included in the original systematic review,^{55,60} the 2007 review,^{53,54,56-59} the previous surveillance,⁶¹ or identified in the current literature search⁶ (one study was examined⁵²). Ten studies^{12,27,28,30-32,34,35,40,52} identified in the review were examined for the potential to change report conclusions.

We identified one additional study⁶² examining aripiprazole for Tourette's syndrome while searching for primary studies in the systematic review. In total, we examined 18 studies to evaluate the currency of the conclusions in the original systematic review.^{3-9,12,27,28,30-32,34,35,40,52,62}

FDA Black Box Warnings

We identified no FDA black box warnings issued since the prior surveillance assessment.

Expert Opinion

We shared the conclusions of the original review with 12 experts in the field (seven original peer reviewers and five TEP members) to request their assessment of the currency of report conclusions and their recommendations of any relevant new studies. Three subject matter experts responded. Note, one study,⁴⁰ examining time to relapse after discontinuation of an antipsychotic as an adjunct to a SSRI for OCD was presented to experts as applicable to Key Question 2; however, it was later re-classified as applicable to Key Question 5. None of the expert comments were specific to this study or related findings.

All three experts agreed that the conclusions for all key questions are likely current. However, for Key Question 1, one expert felt that off-label uses identified since the original review should be added, and another expert felt that there has been an increase in the use of antipsychotics for delirium, possibly triggered by the American Geriatrics Society guidelines for postoperative delirium, published since the original review. For Key Question 5, one expert commented that the intention of the question in the original review was to present the results of dose-finding and time-limit studies, and not to extrapolate from current studies that the study duration was appropriate timing. The expert suggested that the question be reworded for clarity. A second expert suggested two studies related to mortality associated with atypical antipsychotic use for dementia^{63,64} and suggested that the conclusions should be adjusted to include the findings.

For Key Question 1, one expert recommended three studies.⁶⁵⁻⁶⁷ One study⁶⁷ was excluded because it did not differentiate between first generation antipsychotics (FGAs) and second generation antipsychotics (SGAs). For Key Question 2, one expert suggested a meta-analysis examining SGAs for dementia.⁶⁸ All but one of the 16 studies in the meta-analysis were included in the original review. The study was a randomized controlled trial (RCT) (n=40) that compared quetiapine to placebo in individuals with dementia/Alzheimer's and comorbid Parkinson's disease or parkinsonism. There was no difference between groups on the Brief Psychiatric Rating Scale (BPRS), Mini Mental Status Exam (MMSE), Neuropsychiatric Inventory (NPI), or the Alzheimer's Disease Cooperative Study Clinical Global Impression of Change (ADCS-CGIC).⁶⁹ For Key Question 3, one expert provided a Canadian Agency for Drugs and Technologies in Health (CADTH) rapid review of reviews focused on antipsychotic use in pediatric populations;¹³ however, reviews of reviews are not included as a study design in our assessment of currency, and it was thus excluded. For Key Question 4, one expert suggested one study,⁷⁰ and another expert suggested two studies.^{63,64} One study was excluded because it did not stratify results by antipsychotic generation.⁶³ For Key Question 5, one expert suggested

two studies,^{71,72} one of which⁷² was excluded because it did not stratify antipsychotics by generation (see Appendix E for more detail).

Identifying Qualitative Signals

Appendix E shows the original key questions, the conclusions of the original systematic review and the most recent surveillance report, the results of the literature search, FDA boxed warnings, expert opinion, and the assessment of the currency of the systematic review.

For Key Question 1, while the conclusions related to utilization trends are likely current, the scope related to new off-label uses for atypical antipsychotics is likely out of date. The original systematic review¹ limited inclusion to a list of off-label uses for *specific conditions* and to atypical antipsychotics that were approved by the FDA at the time of publication (see Appendix B). Three atypical antipsychotics were relatively new at the time of publication (ie, asenapine, iloperidone, and paliperidone), and no studies for off-label indications were identified. Of the conditions and atypical antipsychotics of included in the original review, the prior surveillance assessment identified a study examining asenapine for borderline personality disorder, and we identified a study examining paliperidone for obsessive-compulsive disorder.³⁰ In addition, the prior surveillance assessment identified studies examining off-label uses for conditions that were *not specified* (thus excluded) in the original systematic review (ie, Huntington's disease, trichotillomania, somatoform disorder, and fibromyalgia).² We identified studies examining additional off-label uses: Parkinson's disease,⁹ other movement disorders,⁹ sleep disorders (other than insomnia),⁹ dizziness and vertigo,⁹ pain, nausea and vomiting,⁹ metastatic tumor disorders,⁹ arachnophobia,³ somatoform disorders,³ irritable bowel syndrome,³ and functional abdominal pain syndrome.³ Finally, the prior assessment identified an atypical antipsychotic (lurasidone), approved after publication of the original review. Neither the prior surveillance, nor the current assessment identified studies examining off-label use of lurasidone.

For Key Question 2, conclusions related to dementia, anxiety, schizotypal personality disorder, attention deficit hyperactivity disorder (ADHD), eating disorders, insomnia, and substance abuse are likely current. Studies identified in both the prior² and current assessment^{5,12,27,28} were congruent with findings in the original review. The conclusions related to the effect of the identified atypical antipsychotics on all other conditions are likely current as well; however, there is new evidence examining atypical antipsychotics not identified in the original review (ie, ziprasidone, aripiprazole, paliperidone, and asenapine) that may render the scope of the original review for these conditions out of date. The original review identified no studies examining ziprasidone as monotherapy for major depressive disorder (MDD). A RCT identified in the prior surveillance² found ziprasidone to be beneficial as monotherapy for symptom reduction. For OCD, no studies in the original review examined aripiprazole as an adjunct to SSRIs. We identified three small studies^{31,32,35} that found aripiprazole to be more effective than placebo³⁵ no significant difference as compared to quetiapine,³² and that aripiprazole was less effective than risperidone on Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score reduction.³⁴ In addition, the original review did not include any studies examining paliperidone. We identified one study³⁰ examining paliperidone as an adjunct to SSRIs (none identified in the original review) that found no difference in symptom reduction as compared to placebo. For PTSD, no studies examined aripiprazole as an adjunct to antidepressants. A pilot study identified in the prior surveillance assessment² found that aripiprazole was effective in reducing PTSD symptoms; however, we identified another pilot study that found no associated significant improvement.⁶ For borderline personality disorder, no studies in the original review examined aripiprazole. The prior assessment² identified one case series that found associated symptom improvement. For Tourette's syndrome, no studies examined in the original review examined

aripiprazole. Both a case series identified in the prior surveillance² assessment and a study identified in the current assessment found aripiprazole to be effective in symptom improvement.⁶²

For Key Question 3, the conclusion of insufficient evidence related to clinical and demographic subpopulations are likely current. The prior surveillance identified a study that found that fewer failed serotonin reuptake inhibitor (SRI) trials and higher Y-BOCS score were predictors of response to quetiapine for OCD.² We identified a study comparing quetiapine XR to placebo in older adults and found that participants ≤75 experienced a significant reduction in symptoms by the end of week 1; however, those over 75 did not.²⁷

For Key Question 4, conclusions related to weight gain, endocrine/diabetes, and mortality are likely current. Studies identified in the prior² and current assessment^{4-6,8,12,27,28,31,52,64,70} were congruent with the findings in the original review. For extrapyramidal symptoms (EPS), no studies included in the original review examined EPS-related adverse events associated with ziprasidone. *While conclusions in the original review related to the identified atypical antipsychotics are likely current*, we identified one study comparing ziprasidone to placebo that found higher rates of self-reported treatment-emergent akathisia and muscle twitching associated with ziprasidone.⁸ For tardive dyskinesia, no studies in the original review examined aripiprazole. *While conclusions in the original review related to the identified atypical antipsychotics are likely current*, we identified one RCT³ examining aripiprazole that found no increase in risk as compared to placebo. Finally, while they do not change the findings of the original review (no conclusions determined) we identified studies that found no difference in blood pressure reduction or increased heart rate as compared to placebo, associated with quetiapine⁴, no evidence of treatment-emergent suicidal ideation associated with aripiprazole⁵ or quetiapine,²⁸ no reports of sexual dysfunction associated with quetiapine XR,^{27,28} more reports of decreased libido associated with risperidone, as compared to cognitive behavioral therapy (CBT) or placebo,³¹ a higher rate of insomnia associated with risperidone³¹ and quetiapine XR,²⁸ as compared to placebo, and a higher rate of somnolence associated with quetiapine XR^{27,28} as compared to placebo, and risperidone as compared to CBT or placebo.³¹

For Key Question 5, the original review concluded that the evidence was insufficient from which to draw conclusions.¹ The prior surveillance assessment identified a review reporting effective quetiapine doses for MDD and generalized anxiety disorder, and a study that found no consistent effective quetiapine dose for OCD.² We identified one study that found better outcomes associated with 150 mg/day of quetiapine vs 300 mg/day for borderline personality disorder,⁴ and another study that found no significant difference in dose between the responders (96 mg) and remitters (96.9 mg).⁸ No studies examining quetiapine dose for borderline personality disorder or ziprasidone for MDD were included in the original review or prior assessment. In addition, no studies in the original review or prior surveillance examined timing for augmentation for OCD, or risperidone for Alzheimer's disease. We identified one study that found that of individuals who had responded to, then discontinued antipsychotic use for OCD, of the 15 participants receiving an atypical antipsychotic, 12 relapsed within four weeks, with one additional participant relapsing at week 50.¹⁰ Another study found that among individuals responding to risperidone for Alzheimer's disease, then randomized to continuation or placebo, placebo was associated with an increased risk of relapse at both 16 and 32 weeks.⁷¹

Signal Assessment

The Scientific Resource Center (SRC) conclusions based on the results of the prior surveillance assessment, literature published since the original report, FDA black box warnings, and expert assessment are that:

- Key Question 1: While the conclusions in the original review related to utilization trends are likely current, the scope related to new off label uses is likely out of date. The original review limited inclusion to specific conditions, and excluded studies examining conditions not on the list (ie, delirium). The current and prior assessments identified numerous off-label indications for atypical antipsychotics that were not included in the original systematic review. Experts suggest updating the review to include new indications, particularly delirium.
- Key Question 2: Conclusions related to dementia, anxiety, schizotypal personality disorder, attention deficit hyperactivity disorder (ADHD), eating disorders, insomnia, substance abuse are likely current. However, while the original review's conclusions related to the effectiveness of the identified atypical antipsychotics for major depressive disorder (MDD), obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and Tourette's syndrome are likely current as well, new evidence examining atypical antipsychotics not identified in the original review (ie, ziprasidone, aripiprazole, paliperidone, and asenapine) may render the scope of the review for these conditions out of date.
- Key Question 3: Original systematic review conclusions are likely current.
- Key Question 4: Conclusions related to weight gain, endocrine/diabetes, and mortality are likely current. However, while the original review's conclusions related to the effectiveness of the identified atypical antipsychotics for extrapyramidal symptoms (EPS) and tardive dyskinesia are likely current as well, we identified new evidence examining atypical antipsychotics not identified in the original review (ie, ziprasidone and aripiprazole) that may render the scope of the review for these conditions out of date. We also identified new evidence examining potential harms for which no conclusions
- Key Question 5: The conclusions of insufficient evidence related to timing and dose are likely still current. However, we identified new evidence examining the use of atypical antipsychotics for conditions not included in the original review (ie, dose: quetiapine for borderline personality disorder, ziprasidone for MDD; timing: examined timing for augmentation for OCD, risperidone for Alzheimer's disease).
- A new atypical antipsychotic, lurasidone, was approved after the publication of the original systematic review. No identified studies in the prior or current assessment examined off-label use.

The signal for this report is medium, suggesting that some of the conclusions in the original systematic review are out of date.

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Appendices

Appendix A: Search Strategy

Appendix B: Inclusion and Exclusion Criteria from Original Systematic Review

Appendix C: Literature Search Results

Appendix D: Questionnaire Sent to Expert Reviewers

Appendix E: Summary Table

Appendix A. Search Strategy

Medline searched via PubMed March 17, 2016 by Rose Relevo

Original Search String : Drug Utilization	((atypical antipsychotic* OR atypical anti - psychotic* OR olanzapine OR quetiapine OR risperidone OR ziprasidone OR aripiprazole OR paliperidone OR iloperidone OR asenapine OR Risperidone"[MeSH] OR "olanzapine"[Substance Name] OR "quetiapine"[Substance Name] OR "aripiprazole"[Substance Name] OR "ziprasidone"[Substance Name])) AND (drug utilization OR pharmacoepidemiolog* OR utiliz*[tiab] OR utilis* OR use[ti] OR uses[ti] OR off - label OR "off-label" OR offlabel)
Journal Limits	AND ((((("The American journal of psychiatry "[Journal]) OR "Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology"[Journal])) OR "The New England journal of medicine"[Journal]) OR (((("lancet"[Journal]) OR "jama"[Journal]) OR "PLoS medicine"[Journal]) OR " Annals of internal medicine"[Journal])) OR (((("bmj"[Journal]) OR "Archives of internal medicine"[Journal]) OR "The Cochrane database of systematic reviews"[Journal]) OR "Journal of clinical psychiatry"[Journal]) OR "Journal of clinical psychopharmacology"[Journal]) OR "Archives of general psychiatry"[Journal])) OR "International clinical psychopharmacology"[Journal])
Date Limits	AND ("2014/06/01"[Date - Entrez] : "3000"[Date - Entrez])
N=5	http://www.ncbi.nlm.nih.gov/sites/myncbi/r.relevo.1/collections/49867564/public/
Original Search String : Insomnia	((“Antipsychotic Agents”[MeSH] OR “Antipsychotic Agents”[Pharmacological Action] OR aripiprazole OR olanzapine OR quetiapine OR risperidone OR ziprasidone))) AND ("Sleep Initiation and Maintenance Disorders"[Mesh] OR insomni*[tiab] OR sleep*[tiab])
Journal Limits	AND ((((("The American journal of psychiatry "[Journal]) OR "Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology"[Journal])) OR "The New England journal of medicine"[Journal]) OR (((("lancet"[Journal]) OR "jama"[Journal]) OR "PLoS medicine"[Journal]) OR " Annals of internal medicine"[Journal])) OR (((("bmj"[Journal]) OR "Archives of internal medicine"[Journal]) OR "The Cochrane database of systematic reviews"[Journal]) OR "Journal of clinical psychiatry"[Journal]) OR "Journal of clinical psychopharmacology"[Journal]) OR "Archives of general psychiatry"[Journal])) OR "International clinical psychopharmacology"[Journal])
Date Limits	AND ("2014/06/01"[Date - Entrez] : "3000"[Date - Entrez])
N=3	http://www.ncbi.nlm.nih.gov/sites/myncbi/r.relevo.1/collections/49867578/public/
Original Search String : Autism	((“Antipsychotic Agents”[MeSH] OR “Antipsychotic Agents”[Pharmacological Action] OR aripiprazole OR olanzapine OR quetiapine OR risperidone OR ziprasidone))) AND (autism OR autistic)

Journal Limits	AND ((((("The American journal of psychiatry "[Journal]) OR "Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology"[Journal])) OR "The New England journal of medicine"[Journal]) OR (((("lancet"[Journal]) OR "jama"[Journal]) OR "PLoS medicine"[Journal]) OR " Annals of internal medicine"[Journal])) OR ((((("bmj"[Journal]) OR "Archives of internal medicine"[Journal]) OR "The Cochrane database of systematic reviews"[Journal]) OR "Journal of clinical psychiatry"[Journal]) OR "Journal of clinical psychopharmacolog y"[Journal]) OR "Archives of general psychiatry"[Journal])) OR "International clinical psychopharmacology"[Journal])
Date Limits	AND ("2014/06/01"[Date - Entrez] : "3000"[Date - Entrez])
N=0	

Original Search String : ADHD	((("Antipsychotic Agents"[MeSH] OR "Antipsychotic Agents"[Pharmacological Action] OR aripiprazole OR olanzapine OR quetiapine OR risperidone OR ziprasidone))) AND ("Attention Deficit Disorder with Hyperactivity"[Mesh] OR attention deficit disorder[tiab] OR adhd)
Journal Limits	AND ((((("The American journal of psychiatry "[Journal]) OR "Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology"[Journal])) OR "The New England journal of medicine"[Journal]) OR (((("lancet"[Journal]) OR "jama"[Journal]) OR "PLoS medicine"[Journal]) OR " Annals of internal medicine"[Journal])) OR ((((("bmj"[Journal]) OR "Archives of internal medicine"[Journal]) OR "The Cochrane database of systematic reviews"[Journal]) OR "Journal of clinical psychiatry"[Journal]) OR "Journal of clinical psychopharmacolog y"[Journal]) OR "Archives of general psychiatry"[Journal])) OR "International clinical psychopharmacology"[Journal])
Date Limits	AND ("2014/06/01"[Date - Entrez] : "3000"[Date - Entrez])
N=1	http://www.ncbi.nlm.nih.gov/sites/myncbi/r.relev.1/collections/49867605/public/

Original Search String : Eating Disorders	((("Antipsychotic Agents"[MeSH] OR "Antipsychotic Agents"[Pharmacological Action] OR aripiprazole OR olanzapine OR quetiapine OR risperidone OR ziprasidone))) AND ("Anorexia Nervosa"[Mesh] OR "Anorexia"[Mesh] OR ("Bulimia"[Mesh] OR "Bulimia Nervosa"[Mesh]) OR anorexi*[tiab] OR bulimi*[tiab]))
Journal Limits	AND ((((("The American journal of psychiatry "[Journal]) OR "Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology"[Journal])) OR "The New England journal of medicine"[Journal]) OR (((("lancet"[Journal]) OR "jama"[Journal]) OR "PLoS medicine"[Journal]) OR " Annals of internal medicine"[Journal])) OR ((((("bmj"[Journal]) OR "Archives of internal medicine"[Journal]) OR "The Cochrane database of systematic reviews"[Journal]) OR "Journal of clinical psychiatry"[Journal]) OR "Journal of clinical psychopharmacolog y"[Journal]) OR "Archives of general psychiatry"[Journal])) OR "International clinical psychopharmacology"[Journal])

Date Limits	AND ("2014/06/01"[Date - Entrez] : "3000"[Date - Entrez])
N=0	

Original Search String : Tourette Syndrome	((("Antipsychotic Agents"[MeSH] OR "Antipsychotic Agents"[Pharmacological Action] OR aripiprazole OR olanzapine OR quetiapine OR risperidone OR ziprasidone))) AND ("Tourette Syndrome"[Mesh] OR tourette*[tiab])
Journal Limits	AND ((((("The American journal of psychiatry "[Journal]) OR "Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology"[Journal])) OR "The New England journal of medicine"[Journal]) OR (((("lancet"[Journal]) OR "jama"[Journal]) OR "PLoS medicine"[Journal]) OR " Annals of internal medicine"[Journal])) OR (((("bmj"[Journal]) OR "Archives of internal medicine"[Journal]) OR "The Cochrane database of systematic reviews"[Journal]) OR "Journal of clinical psychiatry"[Journal]) OR "Journal of clinical psychopharmacology"[Journal]) OR "Archives of general psychiatry"[Journal])) OR "International clinical psychopharmacology"[Journal])
Date Limits	AND ("2014/06/01"[Date - Entrez] : "3000"[Date - Entrez])
N=0	

Original Search String : Substance Abuse	((("Antipsychotic Agents"[MeSH] OR "Antipsychotic Agents"[Pharmacological Action] OR aripiprazole OR olanzapine OR quetiapine OR risperidone OR ziprasidone))) AND (substance abuse* OR drug abuse* OR alcohol abuse OR addict* OR drug dependen* OR cocaine OR heroin OR "Substance - Related Disorders"[Mesh])
Journal Limits	AND ((((("The American journal of psychiatry "[Journal]) OR "Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology"[Journal])) OR "The New England journal of medicine"[Journal]) OR (((("lancet"[Journal]) OR "jama"[Journal]) OR "PLoS medicine"[Journal]) OR " Annals of internal medicine"[Journal])) OR (((("bmj"[Journal]) OR "Archives of internal medicine"[Journal]) OR "The Cochrane database of systematic reviews"[Journal]) OR "Journal of clinical psychiatry"[Journal]) OR "Journal of clinical psychopharmacology"[Journal]) OR "Archives of general psychiatry"[Journal])) OR "International clinical psychopharmacology"[Journal])
Date Limits	AND ("2014/06/01"[Date - Entrez] : "3000"[Date - Entrez])
N=16	http://www.ncbi.nlm.nih.gov/sites/myncbi/r.relevo.1/collections/49867623/public/

Original Search String : Personality Disorders	((("Antipsychotic Agents"[MeSH] OR "Antipsychotic Agents"[Pharmacological Action] OR aripiprazole OR olanzapine OR quetiapine OR risperidone OR ziprasidone))) AND ("Obsessive - Compulsive Disorder"[Mesh] OR " Obsessive Behavior"[Mesh] OR "Stress Disorders, Post - Traumatic"[Mesh] OR "Personality Disorders"[Mesh] OR "Dementia"[Mesh] OR "Depressive Disorder,
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	Major"[Mesh] OR obsessive*[tiab] OR posttraumatic stress[tiab] OR post-traumatic stress[tiab] OR post traumatic stress[tiab] OR ptsd[tiab] OR personality disorder*[tiab] OR dementia[tiab] OR major depress*[tiab])
Journal Limits	AND ((((("The American journal of psychiatry "[Journal]) OR "Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology"[Journal])) OR "The New England journal of medicine"[Journal]) OR (((("lancet"[Journal]) OR "jama"[Journal]) OR "PLoS medicine"[Journal]) OR " Annals of internal medicine"[Journal])) OR (((("bmj"[Journal]) OR "Archives of internal medicine"[Journal]) OR "The Cochrane database of systematic reviews"[Journal]) OR "Journal of clinical psychiatry"[Journal]) OR "Journal of clinical psychopharmacology"[Journal]) OR "Archives of general psychiatry"[Journal])) OR "International clinical psychopharmacology"[Journal])
Date Limits	AND ("2014/06/01"[Date - Entrez] : "3000"[Date - Entrez])
N=21	http://www.ncbi.nlm.nih.gov/sites/myncbi/r.relevo.1/collections/49867643/public/

Original Search String : Anxiety	((("Antipsychotic Agents"[MeSH] OR "Antipsychotic Agents"[Pharmacological Action] OR aripiprazole OR olanzapine OR quetiapine OR risperidone OR ziprasidone))) AND ("Anxiety"[Mesh] OR "Anxiety Disorders"[Mesh] OR "Anti - Anxiety Agents"[Mesh] OR "Anti - Anxiety Agents "[Pharmacological Action]) OR anxiety[tiab] OR anxious*[tiab] OR anti - anxiety[tiab] OR antianxiety[tiab])
Journal Limits	AND ((((("The American journal of psychiatry "[Journal]) OR "Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology"[Journal])) OR "The New England journal of medicine"[Journal]) OR (((("lancet"[Journal]) OR "jama"[Journal]) OR "PLoS medicine"[Journal]) OR " Annals of internal medicine"[Journal])) OR (((("bmj"[Journal]) OR "Archives of internal medicine"[Journal]) OR "The Cochrane database of systematic reviews"[Journal]) OR "Journal of clinical psychiatry"[Journal]) OR "Journal of clinical psychopharmacology"[Journal]) OR "Archives of general psychiatry"[Journal])) OR "International clinical psychopharmacology"[Journal])
Date Limits	AND ("2014/06/01"[Date - Entrez] : "3000"[Date - Entrez])
N=244	http://www.ncbi.nlm.nih.gov/sites/myncbi/r.relevo.1/collections/49867655/public/

Appendix B. Inclusion and Exclusion Criteria from Original Systematic Review

Each article retrieved was reviewed with a brief screening form (see below) that collected data on medication, psychiatric condition, study design, population, sample size, and study duration. Only studies on humans were included. Studies that did not report any outcomes of efficacy, effectiveness, safety/adverse events, or utilization patterns were excluded. As single dose or short term trials (less than six weeks in length) are common for several of the new uses, we decided, at the TEP's suggestion, not to limit inclusion by study duration. Clinical trials were used to review efficacy outcomes. In the case that no clinical trials were found for a given condition or drug of interest, we turned to observational studies.

All reported side effects and adverse events were abstracted from clinical trials, even if the trial did not report efficacy or effectiveness results. We also included large observational studies of adverse events. Reports of utilization and prescribing patterns were accepted if they discussed use in the United States since 1995.

SCEPC Atypical Anti-Psychotic Drug Review Update Article Screener FINAL 12/11/2009

Article ID:

Citation:

1. Research topic (s):

- Aripiprazole
- Asenapine
- Iloperidone
- Olanzapine
- Quetiapine
- Paliperidone
- Risperidone
- Ziprasidone
- Entire class
- None of the above (STOP)

Check all that apply

2. Condition(s) studied:

- Anxiety
- Dementia/severe geriatric agitation
- Depression
- Insomnia
- Obsessive-compulsive disorder
- Personality disorders (DSM IV)
- PTSD
- Substance abuse
- Eating disorder (incl children 17 & under)
- ADHD (incl children 17 & under)
- Tourette's (incl children 17 & under)
- None of the above (STOP)

Check all that apply

3. Study population: "

- Human included
- Only animal or cell lines

Circle one

- 1
 - 2 (STOP)
- Circle one**

4. Study design:

- Descriptive (historical, editorial etc.)
- Non-systematic review
- Systematic review / meta-analysis
- Case report
- Case series
- Cohort
- Case control
- RCT *only*
- CCT *only*
- Trial + Open label extension
- Other design

- 1 (STOP)
- 2 (STOP)
- 3 (STOP)
- 4 (STOP)
- 5
- 6
- 7
- 8
- 9
- 10
- 11

5. Was a placebo used in this study?

- Yes
- No

Circle one

- 1
- 2

6. Total sample size entering study. If not reported then total completing sample size:

Enter # or 999 if no sample reported

Check all that apply

7. Does article report on the following:

- Efficacy
- Safety / Adverse events

Utilization / Prescribing patterns

None of the above (STOP)

8. Total duration of study:

For Duration enter # or 999 if not reported. \$
For Units enter code from below. \$

Duration	Units		
	01. Hour	03. Week	05. Year
	02. Day	04. Month	99. NR

9. Language of article:

- English **Circle one**
- Other
- Specify: _____

10. Do you think that this article might be a duplicate or include the same data as another study?

- No **Circle one**
- Yes
- If YES, ID#: _____

11. Do you think that this article might be part of a large or named trial?

- No **Circle one**
- Yes
- If YES, trial name: _____

12. Is there a reference that needs to be ordered?

- No **Circle one**
- Yes
- If YES, Ref #: _____

NOTES:

Appendix C. Literature Search Results

1. Abbass AA, Kisely SR, Town JM, et al. Short-term psychodynamic psychotherapies for common mental disorders. *The Cochrane database of systematic reviews*. 2014;7:CD004687.
2. Agorastos A, Demiralay C, Stiedl O, Muhtz C, Wiedemann K, Kellner M. Metabotropic glutamate2/3 receptor agonism facilitates autonomic recovery after pharmacological panic challenge in healthy humans. *International clinical psychopharmacology*. Jan 8 2016.
3. Albert U, Carmassi C, Cosci F, et al. Role and clinical implications of atypical antipsychotics in anxiety disorders, obsessive-compulsive disorder, trauma-related, and somatic symptom disorders: a systematized review. *International clinical psychopharmacology*. Mar 11 2016.
4. Alldred SK, Guo B, Takwoingi Y, et al. Urine tests for Down's syndrome screening. *The Cochrane database of systematic reviews*. 2015;12:CD011984.
5. Altieri SC, Yang H, O'Brien HJ, et al. Perinatal vs genetic programming of serotonin states associated with anxiety. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. May 2015;40(6):1456-1470.
6. Amos T, Stein DJ, Ipser JC. Pharmacological interventions for preventing post-traumatic stress disorder (PTSD). *The Cochrane database of systematic reviews*. 2014;7:CD006239.
7. Aoyama Y, Toriumi K, Mouri A, et al. Prenatal Nicotine Exposure Impairs the Proliferation of Neuronal Progenitors, Leading to Fewer Glutamatergic Neurons in the Medial Prefrontal Cortex. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. Jan 2016;41(2):578-589.
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Appendix D. Questionnaire Sent to Expert Reviewers

AHRQ Systematic Review Surveillance Program

Reviewer Form

Title of Original Systematic Review: Off-label use of atypical antipsychotics: An update
[Original Systematic Review](#)

Prior Surveillance Published: August 2014
[Surveillance Report](#)

Name of Reviewer: _____

Instructions:

The AHRQ Scientific Resource Center (SRC) periodically conducts surveillance of published AHRQ systematic reviews to assess the currency of review conclusions. The goal of this process is to identify signals that a report may be out of date. One part of this process includes soliciting expert review of our synthesis of recently published literature.

The original systematic review was published in September 2011. The original systematic review search dates went through May 2011. A prior surveillance assessment was conducted in August 2014 with the search extending through June 2014. We conducted a bridged literature search of select high impact journals from June 2014 to March 2016 and identified evidence potentially related to the key questions of the original systematic review.

The table below highlights the conclusions from the original systematic review, the findings and assessment of the prior surveillance assessment and a summary of the relevant recently published literature. Abstracts from relevant literature are included at the end of the document. If you would like a list of our full search results, please let us know.

Please review the table and provide responses to the questions for each key question below. The primary goal of this review is to identify any important new studies, drugs, interventions, or devices you know of that we may have missed in our literature search and to understand if any new evidence exists which may alter the conclusions of the original systematic review.

Key Question 1:

What are the leading off-label uses of atypical antipsychotics in utilization studies? How have trends in utilization changed in recent years, including inpatient versus outpatient use? What new uses are being studied in trials?

Prior Surveillance Assessment (August 2014):

- The original review conclusion is possibly out of date with regard to new off-label uses of atypical antipsychotics.
- The assessment included the identification of an atypical antipsychotic (lurasidone) approved after the completion of the original systematic review (no studies examining off-label uses were identified).
- The assessment identified studies examining off-label uses for atypical antipsychotics (ie, risperidone, aripiprazole, paliperidone, olanzapine, and quetiapine) for conditions that were not included as conditions of interest in the original systematic review (ie, Huntington's disease, trichotillomania, somatoform disorder, and fibromyalgia), a study examining asenapine for borderline personality disorder, and a study examining ziprasidone for delirium. Both asenapine and borderline personality disorder were within the scope of the original review, and while ziprasidone was included as an atypical antipsychotic of interest in the original review, delirium was not.

Current Literature Analysis:

- We identified no studies related to utilization trends, and two studies reporting new uses.
- New off-label use for conditions of interest in the original systematic review included the use of paliperidone for obsessive-compulsive disorder, and risperidone for panic disorder.¹
- The studies included a wide range of off-label atypical antipsychotic use for conditions that were not of interest in the original review: Parkinson's disease,² other movement disorders,² sleep disorders (other than insomnia),² dizziness and vertigo,² pain, nausea and vomiting,² metastatic tumor disorders,² arachnophobia,¹ somatoform disorders,¹ irritable bowel syndrome,¹ and functional abdominal pain syndrome.¹

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

[Check here to enter text.](#)

2. Are there any published or unpublished studies that you know of that we may have overlooked?

[Click here to enter text.](#)

Key Question 2:

What does the evidence show regarding the efficacy and comparative of atypical antipsychotics for off-label indications?

- How do atypical antipsychotic medications compare with other drugs, including first-generation antipsychotics, for treating off-label indications?

Prior Surveillance Assessment (August 2014):

- Likely current for all included off-label antipsychotics and conditions; however, lurasidone was approved after the publication of the original review.

Current Literature Analysis:

- We identified no studies examining dementia.
- We identified two RCTs,^{3,4} one examining aripiprazole, and the other examining ziprasidone, as an adjunct to a SNRI/SSRI for major depressive disorder. Consistent

with the original review, both studies found that participants augmented with an atypical antipsychotic experienced a greater reduction in symptoms, and that augmentation was associated with higher rates of remission. We identified no studies examining atypical antipsychotic monotherapy for major depressive disorder.

- We identified a systematic review that included six studies⁵⁻¹⁰ examining augmentation to an SSRI for obsessive-compulsive disorder (OCD) which met inclusion criteria and were not included in the original review or prior surveillance.
 - Results related to risperidone were inconsistent. One study found risperidone to be associated with significant obsessive, compulsive, and depressive symptom improvement, and a greater reduction in obsessive symptoms than aripiprazole;⁶ however, another study found no difference from placebo and a significantly lower reduction in obsessive, compulsive, and depressive symptoms than CBT.⁵
 - Results related to aripiprazole were also mixed. Two studies found aripiprazole to be associated with a significant improvement in obsessive,^{6,8} compulsive,^{6,8} and depressive symptoms,⁸ with one reporting a significantly greater reduction in symptoms than placebo,⁶ and the other reporting no difference in compulsive and depressive symptom, but a lower reduction in obsessive symptoms as compared to risperidone.⁸ A third study found only a partial improvement in symptoms.⁹
 - One study examined paliperidone and found that while paliperidone was associated improvements in obsessive and compulsive symptoms, differences from placebo were not significant.⁷
 - One study found that quetiapine was associated with a significant improvement in symptoms at week 12, but not at weeks four and 8.⁹
 - A retrospective cohort study found that of 15 individuals who discontinued atypical antipsychotic use after achieving a significant reduction in obsessive and compulsive symptoms, 12 relapsed within the first month.¹⁰
- For post-traumatic stress disorder (PTSD), we identified two studies. One study, a pilot RCT,¹¹ compared aripiprazole to placebo and found that aripiprazole was associated with non-significant improvement. The second study¹² was identified through a systematic review,¹ and found that as compared to placebo, participants in the olanzapine group experienced a significantly greater improvement.
- For borderline personality disorder, we identified a RCT¹³ comparing low of quetiapine to placebo. Result indicated that that significant Zanarini scale total score improvement was associated with a low, but not a moderate dose of quetiapine, as compared to placebo, and a moderate, but not a low dose was associated with better Young Mania Rating Scale (YMRS) and SCL-90-R general severity index (differences between doses were not significant). Time to treatment response, affective and cognitive disturbance, disturbed relationships, verbal and physical aggression, and work/school days lost due to symptoms were significantly better for both quetiapine groups as compared to placebo.
- We identified one study¹⁴ examining Tourette's syndrome. Results indicated that aripiprazole was associated with significantly improvement.
- We identified two studies included in a systematic review,¹ which had not been included or excluded from prior reviews/assessments examining quetiapine XR for generalized anxiety disorder. One study¹⁵ found that in adults 66 or older, quetiapine XR monotherapy was associated with greater symptom reduction than placebo. The second study¹⁶ found that as compared to placebo, quetiapine XR as an adjunct to an SNRI/SSRI was associated with greater symptom improvement at week one, but not at week eight.

- For social anxiety disorder, one study,¹⁷ included in the systematic review,¹ a pilot RCT comparing olanzapine monotherapy to placebo, met inclusion criteria and was not included in a previous review or assessment. Results indicated greater improvement associated with olanzapine.
- We identified no studies examining eating disorders, insomnia, or substance abuse.

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

[Click here to enter text.](#)

2. Are there any published or unpublished studies that you know of that we may have overlooked?

[Click here to enter text.](#)

Key Question 3:

What subset of the population would potentially benefit from off-label uses? Do effectiveness and harms differ by race/ethnicity, gender, and age group? By severity of condition and clinical subtype?

Prior Surveillance Assessment (August 2014):

- Likely current; however, lurasidone was approved after the publication of the original review.

Current Literature Analysis:

- One study in the systematic review¹ examined subgroup differences, met inclusion criteria for the original review and was not included in a prior review or surveillance. An RCT¹⁵ comparing quetiapine XR monotherapy to placebo in adults ≥ 66 years, found that significantly better efficacy was demonstrated in week one in participants ≤ 75 , but not >75 . Incidence of adverse events related to EPS and somnolence were higher in participants >75 .

Reviewer Questions:

1. "Are the original report conclusions still supported by the current evidence?"

[Click here to enter text.](#)

2. Are there any published or unpublished studies that you know of that we may have overlooked?

[Click here to enter text.](#)

Key Question 4:

What are the potential adverse effects and/or complications involved with off-label prescribing of atypical antipsychotics? How do they compare within the class and with other drugs used for the conditions?

Prior Surveillance Assessment (August 2014):

- Likely current; however, lurasidone was approved after the publication of the original review.

Current Literature Analysis:

- Our literature search identified three RCTs,^{3,4,13} and five additional studies^{5,12,15-17} included in a systematic review¹ (not included/excluded from previous reviews/assessments) reporting on adverse events related to weight gain.
 - Three studies^{13,15,16} compared quetiapine to placebo (two examined quetiapine XR). Two studies^{15,16} found no significant difference in weight gain as compared to placebo. The third study¹⁶ found that 4.9% of the quetiapine XR group experienced a 7% or greater increase in body weight, vs. 1% of participants receiving placebo.
 - Two studies^{12,17} examined weight gain associated with olanzapine. One study¹² found that all participants receiving olanzapine reported weight gain, with 43% in the olanzapine group gaining 6-10 kg (none in placebo). The second study¹⁷ reported a mean weight gain of 1.4 lbs. for olanzapine and 2.2 lbs. for placebo.
 - One study³ comparing aripiprazole to placebo in older adults found no increase in the amount or percentage of body fat associated with aripiprazole.
 - One study⁴ comparing ziprasidone to placebo found that while there was no significant difference between groups, fewer participants receiving ziprasidone reported weight gain.
 - One study compared risperidone to CBT and placebo for OCD and found that 45% receiving risperidone and 19% receiving CBT reported > 1 kg/m² weight gain (none in placebo).
- We identified two RCTs^{3,11} in our literature search and an additional two RCTs^{15,16} in a systematic review¹ examining endocrine/diabetes related adverse events.
 - Two studies^{3,11} found no significant increase in glucose associated with aripiprazole.
 - Two studies^{15,16} examined quetiapine XR and found no significant difference in shift in fasting glucose as compared to placebo.
- For EPS-related adverse events, we identified five studies^{3,4,11,13,14} through our literature search, and an additional three studies^{5,15,16} through a systematic review.¹
 - Three studies examined aripiprazole. One RCT³ of older adults found a higher proportion of participants in the aripiprazole group patients with akathisia (generally mild and transient) as compared to placebo, and that aripiprazole was also associated with Parkinsonism and complaints of tremor. The second,¹⁴ a retrospective cohort study found that 3/20 individuals receiving aripiprazole reported akathisia, and the third study,¹¹ a pilot RCT found no associated treatment-emergent akathisia associated with aripiprazole.
 - Three studies^{13,15,16} compared quetiapine to placebo (two examined quetiapine XR).^{15,16} One study¹⁵ found EPS related AEs reported by 5.4% of older adults receiving quetiapine XR (monotherapy; 2.2% placebo), and a second study¹⁶ found EPS related adverse events reported by 3.8% of participants (adjunct to SNRI/SSRI; 2% placebo). The third study¹³ found no significant differences between quetiapine and placebo over 11 weeks.
 - One study⁴ compared ziprasidone to placebo and found that significantly more participants receiving ziprasidone reported muscle twitching (11.2% vs. 1.4%).
 - One study⁵ compared risperidone to Cognitive Behavioral Therapy (CBT) and placebo and found no difference in reported akathisia.
- One study³ found no increased risk of Tardive dyskinesia associated with aripiprazole as compared to placebo over 24 weeks.

- A RCT¹³ found 150 mg/day of quetiapine to be associated with a significant decrease in systolic blood pressure; however, there was no significant difference as compared to placebo.
- A RCT¹³ found 300 mg/day of quetiapine to be associated with a significant increase in heart rate; however, there was no significant difference as compared to placebo.
- One study³ identified in our literature search and another¹⁶ identified through a systematic review¹ examined treatment emergent suicidal ideation and found no evidence of treatment emergent suicidal ideation associated with aripiprazole in older adults,³ and no suicide related adverse events associated with quetiapine XR.¹⁶
- Three studies^{5,15,16} identified through a systematic review¹ examined sexual dysfunction and found no sexual dysfunction^{15,16} associated with quetiapine XR, and that 27% of participants receiving risperidone reported decreased libido, as compared to 16% of participants receiving CBT and 6% placebo.⁵
- Two studies^{5,16} identified through a systematic review¹ examined sleep related adverse events and found that 7.2% of participants receiving quetiapine vs. 1.5% of participants receiving placebo reported insomnia,¹⁶ and that 21% of participants receiving risperidone group reported insomnia, as compared to 13% receiving CBT and 17%.⁵
- Three studies^{5,15,16} identified through a systematic review¹ examined somnolence and found quetiapine XR to be associated with more reported somnolence as compared to placebo,^{15,16} with no difference in somnolence associated with risperidone as compared to CBT or placebo.⁵

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?
2. Are there any published or unpublished studies that you know of that we may have overlooked?

Key Question 5:

What is the effective dose and time limit for off-label indications?

Prior Surveillance Assessment (August 2014):

- Likely current; however, lurasidone was approved after the publication of the original review.

Current Literature Analysis:

- We identified three studies examining effective dose limits.
 - For borderline personality disorder, as compared to placebo, a low but not a moderate dose of quetiapine was associated with Zanzarini scale total improvement, and that a moderate but not a low dose was associated with better YMRS and SCL-90-R general severity index (differences between doses were not significant). In general, the low dose group “bested” the moderate dose group on outcomes related to efficacy (most group differences by dose were not reported). Compared to the low dose group, sedation, change in appetite, dry mouth, and dizziness were more common in the moderate dose group.¹³
 - For quetiapine as an adjunct to an antidepressant for major depressive disorder (MDD), the mean treatment duration was approximately six months and the mean time to the first increase of the was approximately one week. The mean initial and maintenance doses of quetiapine were 23.6 and 40.7mg/day. The mean use of quetiapine was 150 days.¹⁸

- For ziprasidone as an adjunct to escitalopram for MDD, mean daily doses of ziprasidone for responders and remitters were 96.0 mg (SD=32.6) and 96.9 mg (SD=32.3) respectively.⁴

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?
2. Are there any published or unpublished studies that you know of that we may have overlooked?

Original Systematic Review Conclusions and Literature Analysis

Title of Original Systematic Review: Off-label use of atypical antipsychotics: an update

Original Systematic Review Published: September 2011

Original Systematic Review Search Dates: Database inception or 2008 (varied by key question and condition) to May 2011.

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Surveillance Report Published: April 2015 (completed August 2014)

Surveillance Report Search Dates: January 2011 to June 2014

Current Literature Search Dates: June 2014 to March 2016

The conclusions from the original systematic review, the findings and assessment of the prior surveillance assessment, and a summary of the relevant recently published literature are outlined below. Abstracts are provided at the end of the document.

Table 1. Key Question 1: What are the leading off-label uses of atypical antipsychotics in utilization studies? How have trends in utilization changed in recent years, including inpatient versus outpatient use? What new uses are being studied in trials?

Conclusions from Original Systematic Review Link to Review	Findings and Assessment from Prior Surveillance Assessment (August 2014) Link to Report	Literature Analysis (March 2016)
<p>Leading off-label uses of atypical antipsychotics: Atypicals have been studied as off-label treatment for the following conditions: ADHD, anxiety, dementia in elderly patients, depression, eating disorders, insomnia, OCD, personality disorder, PTSD, substance use disorders, and Tourette’s syndrome.</p> <p>Utilization trends: Off-label use of atypical antipsychotics in various settings has increased rapidly since their introduction in the 1990s; risperidone, quetiapine, and olanzapine are the most common atypicals prescribed for off-label use. Included studies examined utilization trends through 2008. More utilization studies on off-label use were identified for dementia,</p>	<p>Assessment: The original review conclusion is possibly out of date with regard to new off-label uses of atypical antipsychotics.</p> <p>Leading off-label uses of atypical antipsychotics: No new research was found.</p> <p>Utilization trends: Three studies examined utilization trends. One study found that antipsychotic prescriptions increased for anxiety disorders from 10.6% (1996-1999) to 21.3% (2004-2007) with the largest increase in panic disorder. One study found that antipsychotic use increased from 25.9% to 41.9% among Medicaid enrollees (1996-2006). One study found that atypical antipsychotic use for dementia declined after</p>	<p>We identified two studies relevant to Key Question 1.</p> <p>Utilization trends: We identified no studies examining utilization trends.</p> <p>New uses: A retrospective cohort study² of German older adults examined antipsychotic use. Results indicated that atypical antipsychotics were used off-label for depression and anxiety disorders (including OCD), Parkinson’s disease, other movement disorders, sleep disorders, dizziness and vertigo, pain, nausea and vomiting, metastatic tumor disorder, dementia, and generally patients in residential care. Parkinson’s disease, other movement</p>

Conclusions from Original Systematic Review Link to Review	Findings and Assessment from Prior Surveillance Assessment (August 2014) Link to Report	Literature Analysis (March 2016)
<p>depression, PTSD and anxiety than for insomnia, eating disorders, and OCD, with more studies in older adults than other populations.</p> <p>Limited evidence suggests that males and Whites are more likely to receive off-label atypical prescriptions. One study indicated that 2005 FDA and Health Canada regulatory warnings were associated with decreases in overall use of atypical antipsychotics, especially among older adults with dementia.</p> <p>New uses: No off-label use of the newly approved atypicals (asenapine, iloperidone, and paliperidone) was reported in the utilization literature.</p>	<p>the black box warning in 2005. No studies examined trends after 2007.</p> <p>New uses: Four studies examined new off-label uses for previously approved atypicals (risperidone, aripiprazole, paliperidone and quetiapine): Huntington’s disease, trichotillomania, somatoform disorder, and fibromyalgia. One review included a study of olanzapine use for trichotillomania.</p> <p>One study examined off-label use of asenapine for borderline personality disorder.</p>	<p>disorders, sleep disorders (other than insomnia), dizziness and vertigo, pain, nausea and vomiting, metastatic tumor disorders, and residential care, were not included as conditions/situations of interest in the original systematic review.</p> <p>A systematic review¹ of 56 studies examined the use of atypical antipsychotics for anxiety disorders, trauma-related and somatoform disorders. The review identified studies examining paliperidone for obsessive-compulsive disorder and somatoform disorder, and risperidone for panic disorder. Off-label antipsychotic use for conditions that were not of interest in the original systematic review includes arachnophobia, somatoform disorders, irritable bowel syndrome, and functional abdominal pain syndrome.</p>

Abbreviations: ADHD=Attention Deficit Hyperactivity Disorder; FDA=Food and Drug Administration; OCD=Obsessive-Compulsive Disorder; PTSD=Post-Traumatic Stress Disorder

Table 2. Key Question 2: What does the evidence show regarding the efficacy and comparative of atypical antipsychotics for off-label indications? How do atypical antipsychotic medications compare with other drugs, including first-generation antipsychotics, for treating off-label indications?

Conclusions from Original Systematic Review Link to Review	Findings and Assessment from Prior Surveillance Assessment (August 2014) Link to Report	Literature Analysis (March 2016)
<p>Dementia (SOE: High): Aripiprazole, olanzapine, and risperidone have efficacy as treatment for behavioral symptoms of dementia.</p>	<p>Assessment: Current Two randomized trials reported efficacy of risperidone in improving behavioral symptoms of dementia. One randomized trial reported worsening cognitive function with olanzapine, quetiapine or risperidone treatment compared with placebo. One review reported efficacy of atypical antipsychotics in behavioral and psychotic symptoms of dementia.</p>	<p>No studies were identified.</p>
<p>Depression- MDD: Augmentation of</p>	<p>Assessment: Current</p>	<p>Depression – MDD: Augmentation of</p>

Conclusions from Original Systematic Review Link to Review	Findings and Assessment from Prior Surveillance Assessment (August 2014) Link to Report	Literature Analysis (March 2016)
<p>SSRI/SNRI (SOE: Moderate - risperidone, aripiprazole, quetiapine; SOE: Low - olanzapine, ziprasidone) Aripiprazole, quetiapine, and risperidone have efficacy as augmentation to SSRIs/SNRIs for major depressive disorder. Olanzapine and ziprasidone may also have efficacy.</p> <p>Depression- MDD: Monotherapy (SOE: Moderate) Olanzapine does not have efficacy as monotherapy for major depressive disorder. Quetiapine has efficacy as monotherapy for major depressive disorder.</p>	<p>Depression- MDD: Augmentation of SSRI/SNRI: One review reported efficacy of aripiprazole, quetiapine, and risperidone as augmentation to SSRIs/SNRIs. A meta-analysis examined aripiprazole, risperidone, quetiapine, and the combination of olanzapine and fluoxetine (OFC) and found that all four had a significant effect on remission rates, severity measures. All but OFC had a significant effect on response rates.</p> <p>Depression- MDD: Monotherapy Four studies (two pooled analyses of RCTs, one post-hoc analysis of RCT, one RCT reported efficacy of quetiapine for MDD. One RCT reported potential efficacy of ziprasidone for MDD.</p>	<p>SSRI/SNRI: An RCT³ (n=181) compared the use of aripiprazole (n=91) to placebo (n=90) as augmentation to venlafaxine for treatment resistant MDD in adults 60 or older. Significantly more participants receiving aripiprazole achieved remission, and aripiprazole was associated with a significantly faster time to improvement, and a larger decrease on Ham-D and MADRS scores.</p> <p>An RCT⁴ (n=139) compared ziprasidone (n=71) to placebo (n=68) as an adjunct to escitalopram for MDD. Results indicated that more participants receiving ziprasidone had a 50% or larger reduction in score on the Ham-D, the QIDS-SR, and the Ham-A, and more participants receiving ziprasidone achieved remission, according to the QIDS-SR, and the Ham-A. In addition the ziprasidone group experienced greater reductions on the Ham-D, the QIDS-SR, CGI-S, and the Ham-A. There were no differences between groups on change in VAS-Pain scores, or on the CGI-I at the end of the study.</p>
<p>Obsessive-compulsive disorder: augmentation of SSRI (SOE: Moderate - risperidone; SOE: Low- olanzapine) Risperidone has efficacy in improving OCD symptoms when used as an adjunct to SSRI in treatment refractory patients. Olanzapine may also have efficacy. Quetiapine is more efficacious than ziprasidone and clomipramine for this purpose.</p> <p>Obsessive-compulsive disorder: augmentation of citalopram (SOE: Low-</p>	<p>Assessment: Current</p> <p>Obsessive-compulsive disorder: augmentation of SSRI: One RCT reported quetiapine-fluoxetine is inefficacious in improving OCD symptoms compared to fluoxetine-clomipramine or fluoxetine-placebo. One RCT reported efficacy of aripiprazole in improving OCD symptoms as an adjunct to SSRIs. One review reported no consistent effect of quetiapine for OCD symptoms.</p>	<p>A systematic review¹ of 56 studies examined the use of atypical antipsychotics for anxiety disorders, trauma-related and somatoform disorders. Six studies⁵⁻¹⁰ examining augmentation to SSRIs for treatment resistant OCD met inclusion criteria and were not included in a prior review or assessment.</p> <ul style="list-style-type: none"> The first study⁵ was a RCT comparing pill placebo (n=20), risperidone augmentation (n=40), and CBT consisting of exposure and ritual prevention (EX/RP; n=40). Results indicated a significantly lower reduction in Y-

Conclusions from Original Systematic Review Link to Review	Findings and Assessment from Prior Surveillance Assessment (August 2014) Link to Report	Literature Analysis (March 2016)
<p>quetiapine; SOE: Very Low – risperidone) Quetiapine and risperidone may be efficacious as augmentation to citalopram in OCD patients.</p>	<p>One reviewer suggested a meta-analysis that found that risperidone improved OCD symptoms as augmentation to SSRIs.</p> <p>Obsessive-compulsive disorder: augmentation of citalopram: No new research was found.</p>	<p>BOCS, Ham-D, and BABS scores associated with risperidone augmentation at eight weeks as compared to EX/RP, with no difference from placebo.</p> <ul style="list-style-type: none"> • The second study⁶ was a RCT comparing aripiprazole (n=18) to placebo (n=21) for SSRI resistant OCD. Aripiprazole was associated with a significantly greater reduction on the Y-BOCS at 8-weeks and (non-significantly) better sexual functioning. • The third study,⁷ a pilot RCT (n=34) comparing paliperidone augmentation found that while paliperidone was associated with a significant reduction in Y-BOCS score, differences from placebo were not significant. • The fourth study⁸ compared risperidone to aripiprazole augmentation to a high dose SSRI for SSRI refractory OCD. Both groups experienced significant reductions on the Y-BOCS and the HAM-D at eight and 20 weeks, with significantly greater reductions on the Y-BOCS total and obsession scales associated with risperidone, with no significant differences on the Y-BOCS compulsion scale or the HAM-D. • The fifth study⁹ compared aripiprazole (n=22) to quetiapine (n=22) augmentation in fluvoxamine non-responders and found partial improvement in both groups (weeks 4, 8, 12) with a significant improvement in only participants receiving quetiapine at week 12 (no significant difference between groups only at week 12). <p>The sixth study¹⁰ was a retrospective cohort study (n=18) of individuals receiving an antipsychotic, who had a significant reduction</p>

Conclusions from Original Systematic Review Link to Review	Findings and Assessment from Prior Surveillance Assessment (August 2014) Link to Report	Literature Analysis (March 2016)
		<p>in Y-BOCS score (14/18 atypical) associated with augmentation to SRIs and discontinued antipsychotic use. Results indicated that of the 15 participants receiving an atypical antipsychotic, 12 relapsed within four weeks, with one additional participant relapsing at week 50.</p>
<p>Post-traumatic stress disorder (SOE: Moderate- risperidone; SOE: Low - olanzapine; SOE: Very Low- quetiapine) Risperidone is efficacious in reducing combat-related PTSD symptoms when used as an adjunct to primary medication.</p>	<p><u>Assessment: Current</u></p> <p>One pilot study reported efficacy of aripiprazole in improving PTSD symptoms. One randomized trial reported no reduction in PTSD symptoms with risperidone treatment as an adjunct to primary medication in patients with SRI-resistant symptoms. One review reported positive treatment effects for risperidone and quetiapine.</p>	<p>A pilot RCT¹¹ compared aripiprazole (n=7) to placebo (n=7) as an adjunct to an antidepressant for antidepressant resistant combat-related PTSD. Aripiprazole was associated with non-significant reductions on the CAPS, the PANSS, the PCL, and the BDI-II.</p> <p>A systematic review¹ of 56 studies examined the use of atypical antipsychotics for anxiety disorders, trauma-related and somatoform disorders. One RCT¹² examining olanzapine monotherapy for non-combat resistant PTSD (n=14) met inclusion criteria and was not included in a previous review or assessment. As compared to placebo, participants in the olanzapine group experienced a significantly greater improvement on the Clinician Administered PTSD Scale.</p>
<p>Personality disorders: borderline (SOE: Low- aripiprazole; SOE: very low - quetiapine, olanzapine) Olanzapine had mixed results in seven trials, aripiprazole was found efficacious in two trials, quetiapine was found efficacious in one trial, and ziprasidone was found not efficacious in one trial.</p> <p>Personality disorders: schizotypal (SOE: Low)</p>	<p><u>Assessment: Current</u></p> <p>Personality disorders: borderline: One non-randomized trial reported efficacy of olanzapine. One case-series reported improved symptoms with asenapine treatment. One meta-analysis found improved symptoms with antipsychotic treatment.</p> <p>One reviewer suggested review reported some efficacy of atypical antipsychotics.</p>	<p>A RCT¹³ (n=95) compared low (150 mg/day; n=33) and moderate doses (300 mg/day; n=33) of quetiapine to placebo (n=29) for borderline personality disorder, and found that significant Zanarini scale total score improvement was associated with a low, but not a moderate dose of quetiapine, as compared to placebo, and a moderate, but not a low dose was associated with better YMRS and SCL-90-R general severity index (differences between doses were not</p>

Conclusions from Original Systematic Review Link to Review	Findings and Assessment from Prior Surveillance Assessment (August 2014) Link to Report	Literature Analysis (March 2016)
Risperidone had mixed results when used to treat schizotypal personality disorder in two small trials.	Personality disorders: schizotypal: No new research was found.	significant). In general, the low dose group “bested” the moderate dose group on outcomes related to efficacy (most group differences by dose were not reported). Time to treatment response, affective and cognitive disturbance, disturbed relationships, verbal and physical aggression, and work/school days lost due to symptoms were significantly better for both quetiapine groups as compared to placebo.
Tourette’s Syndrome (SOE: Low) Risperidone is at least efficacious as pimozide or clonidine for Tourette’s Syndrome.	Assessment: Current One case-series reported improvement in Tourette’s Syndrome symptoms with aripiprazole treatment.	A retrospective cohort study ¹⁴ (n=20) of individuals with Tourette’s syndrome receiving aripiprazole. When comparing individuals with low vs. high Yale Global Tourette Severity Scale (YGTSS) scores, results indicated that aripiprazole was associated with significantly lower scores for both groups, with a significantly greater reduction in individuals with high YGTSS scores at baseline.
Anxiety (SOE: Moderate) Quetiapine has efficacy as treatment for Generalized Anxiety Disorder. Three studies also examined Social Anxiety Disorder (no SOE noted).	Assessment: Current Five studies (one pooled analysis of three RCTs, four RCTs) reported efficacy of quetiapine as treatment for Generalized Anxiety Disorder. One review reported reduced anxiety score with olanzapine augmentation but not for quetiapine augmentation. One review reported efficacy of quetiapine for anxiety.	A systematic review ¹ of 56 studies examined the use of atypical antipsychotics for anxiety disorders, trauma-related and somatoform disorders included two studies ^{15,16} examining generalized anxiety disorder that met inclusion criteria for the original review and were not included in a prior review or surveillance. <ul style="list-style-type: none"> • One study¹⁵ was an RCT comparing quetiapine XR monotherapy (n=223) to placebo (n=227) in adults ≥66 years, which found a significantly greater reduction in Ham-A scores associated with quetiapine XR for both participants ≤75 and >75, and that significantly better efficacy was demonstrated in week one overall, and for participants ≤75, but not >75. • The second study¹⁶ examined quetiapine XR as an adjunct to an SRNI/SSRI (n=209) vs.

Conclusions from Original Systematic Review Link to Review	Findings and Assessment from Prior Surveillance Assessment (August 2014) Link to Report	Literature Analysis (March 2016)
		<p>placebo + SRNI/SSRI (n=200). Results indicated a greater reduction in Ham-A scores associated with quetiapine XR as compared to placebo at week one, but not at week 8.</p> <p>One study¹⁷ included in the systematic review, a pilot RCT comparing olanzapine (n=7) monotherapy to placebo (n=5) for social anxiety disorder, met inclusion criteria and was not included in a previous review or assessment. Results indicated greater improvement on the BPRS and the SPIN associated with olanzapine.</p>
<p>Attention deficit/hyperactivity disorder: no co-occurring disorders (SOE: Low) Risperidone may be efficacious in treating children with ADHD with no serious co-occurring disorders.</p> <p>Attention deficit/hyperactivity disorder: mentally retarded children (SOE: Low) Risperidone may be superior to methylphenidate in treating ADHD symptoms in mentally retarded children.</p> <p>Attention deficit/hyperactivity disorder: bipolar children (SOE: Low) Aripiprazole is inefficacious in reducing ADHD symptoms in children with bipolar disorder.</p>	<p><u>Assessment: Current</u></p> <p>One review reported efficacy of risperidone in treating children with ADHD.</p>	<p>No studies were identified</p>
<p>Eating disorders (SOE: Moderate-olanzapine; SOE: Low- quetiapine) Olanzapine and quetiapine have no efficacy in increasing body mass in eating disorder patients.</p>	<p><u>Assessment: Current</u></p> <p>No new research was found.</p>	<p>No studies were identified</p>
<p>Insomnia (SOE: Very Low) Quetiapine may be inefficacious in treating insomnia.</p>	<p><u>Assessment: Current</u></p> <p>One non-randomized pilot study reported</p>	<p>No studies were identified</p>

Conclusions from Original Systematic Review Link to Review	Findings and Assessment from Prior Surveillance Assessment (August 2014) Link to Report	Literature Analysis (March 2016)
	potential efficacy of quetiapine for sleep continuity.	
<p>Substance abuse: alcohol (SOE: Moderate-aripiprazole; SOE: Low- quetiapine) Aripiprazole is inefficacious in treating alcohol abuse/ dependence. Quetiapine may also be inefficacious.</p> <p>Substance abuse: cocaine (SOE: Low) Olanzapine is inefficacious in treating cocaine abuse/dependence. Risperidone may also be inefficacious.</p> <p>Substance abuse: methamphetamine (SOE: Low) Aripiprazole is inefficacious in treating methamphetamine abuse/dependence.</p> <p>Substance abuse: methadone clients (SOE: Low) Risperidone is an inefficacious adjunct to methadone maintenance.</p>	<p>Assessment: Current</p> <p>No new research was found.</p>	No studies were identified

Abbreviations: ADHD= Attention Deficit Hyperactivity Disorder; BABS= Brown Assessment of Beliefs Scale; BDI-II= Beck Depression Inventory-II; BPRS= Brief Social Phobia Scale; CAPS= Clinician-Administered PTSD Scale; CBT= Cognitive Behavioral Therapy; CGI-I= Clinical Global Impressions Scale Improvement Subscale; CGI-S= Clinical Global Impressions Scale Severity Subscale; EX/RP= Exposure and Ritual Prevention; HAM-A= Hamilton Anxiety Rating Scale; HAM-D= Hamilton Depression Rating Scale; MADRS= Montgomery-Asberg Depression Rating Scale; MDD= Major Depressive Disorder; OCD= Obsessive Compulsive Disorder; PANSS= Positive and Negative Syndrome Scale; PCL= PTSD Checklist; PTSD= Post-Traumatic Stress Disorder; QIDS-SR= Quick Inventory of Depressive Symptomology Self-Rated; RCT= Randomized Controlled Trial; SCL-90-R= Symptom Checklist-90-Revised; SNRI= Selective Norepinephrine Reuptake Inhibitor; SOE= Strength of Evidence; SPIN= Society Phobia Inventory; SRI= Serotonin Reuptake Inhibitor; SSRI= Selective Serotonin Reuptake Inhibitor; VAS-Pain= Visual Analog Scale for Pain; Y-BOCS= Yale-Brown Obsessive Compulsive Scale; YGTSS= Yale Global Tourette Severity Scale; YMRS= Young Mania Rating Scale

Table 3. Key Question 3: What subset of the population would potentially benefit from off-label uses? Do effectiveness and harms differ by race/ethnicity, gender, and age group? By severity of condition and clinical subtype?

Conclusions from Original Systematic Review Link to Review	Findings and Assessment from Prior Surveillance Assessment (August 2014) Link to Report	Literature Analysis (March 2016)
<p>SOE: Insufficient There are insufficient data regarding efficacy, effectiveness, and harms to determine what subset of the population would potentially benefit from off-label uses of atypicals.</p>	<p>Assessment: Current One study reported predictors of severity of OCD in response to antipsychotic augmentation of SRIs.</p>	<p>A systematic review¹ of 56 studies examined the use of atypical antipsychotics for anxiety disorders, trauma-related and somatoform disorders included one study examining subgroup differences that met inclusion criteria for the original review and was not included in a prior review or surveillance.</p> <p>A RCT¹⁵ comparing quetiapine XR monotherapy (n=223) to placebo (n=227) in adults ≥66 years, which found a significantly greater reduction in Ham-A scores associated with quetiapine XR for both participants ≤75 and >75, and that significantly better efficacy was demonstrated in week one for participants ≤75, but not >75. Incidence of adverse events related to EPS and somnolence were higher in participants >75.</p>

Abbreviations: HAM-A= Hamilton Anxiety Rating Scale; OCD= Obsessive Compulsive Disorder; RCT= Randomized Controlled Trial; SOE= Strength of Evidence; SRI= Serotonin Reuptake Inhibitor

Table 4. Key Question 4: What are the potential adverse effects and/or complications involved with off-label prescribing of atypical antipsychotics? How do they compare within the class and with other drugs used for the conditions?

Conclusions from Original Systematic Review Link to Review	Findings and Assessment from Prior Surveillance Assessment (August 2014) Link to Report	Literature Analysis (March 2016)
<p>Weight gain (SOE: High - risperidone) Olanzapine is associated with more weight gain than placebo, conventional antipsychotics, or other atypical antipsychotics.</p> <p>Some evidence for other atypical antipsychotics. Risperidone, quetiapine and aripiprazole are associated with more weight gain compared with placebo.</p> <p>Endocrine/diabetes (SOE: Low)</p>	<p>Assessment: Current</p> <p>Weight gain One randomized trial reported weight gain more common with risperidone compared to placebo. One review reported weight gain with risperidone use among children with ADHD. One review reported weight gain associated with aripiprazole, quetiapine, risperidone, and the combination of olanzapine and fluoxetine. One review reported weight gain with</p>	<p>Weight gain A RCT¹³ (n=95) comparing low (150 mg/day; n=33) and moderate doses (300 mg/day; n=33) of quetiapine to placebo (n=29) found that the mean weight gain was one pound for placebo (SD=4.4) and the low dose (SD=7.2), and three pounds for the moderate dose (SD=9.2), with no significant differences between groups.</p> <p>A RCT³ (n=181) compared the use of</p>

Conclusions from Original Systematic Review Link to Review	Findings and Assessment from Prior Surveillance Assessment (August 2014) Link to Report	Literature Analysis (March 2016)
<p>Olanzapine associated with higher risk of diabetes than risperidone.</p> <p>Mortality Atypical antipsychotics associated with increased risk of death in elderly patients compared with placebo. (SOE: High)</p> <p>Conventional antipsychotics associated with higher rate of death compared with atypical antipsychotics. (SOE: Moderate)</p> <p>EPS (SOE: Moderate) Aripiprazole and risperidone are associated with an increase in extrapyramidal signs or symptoms compared to quetiapine.</p> <p>Tardive dyskinesia (SOE: Low) Atypical antipsychotics are associated with less tardive dyskinesia than are high doses of haloperidol.</p>	<p>risperidone, quetiapine and aripiprazole. One review reported weight gain with quetiapine use.</p> <p>Endocrine/diabetes One RCT reported worsening glucose metabolism factors with olanzapine compared to placebo in healthy controls. One review reported abnormal metabolic laboratory results with quetiapine.</p> <p>Mortality Two cohort studies reported increased risk of death with haloperidol treatment compared to risperidone. One cohort study reported no association between antipsychotic use and death after adjustment for psychiatric symptoms. One review reported increased risk of death with atypical antipsychotic treatment for dementia.</p> <p>EPS No new research was found.</p> <p>Tardive dyskinesia No new research was found.</p> <p>Akathisia One review reported increased risk of akathisia associated with aripiprazole.</p> <p>Venous thromboembolism: One case-control study reported increased risk of venous thromboembolism in new users of antipsychotics compared to nonusers.</p>	<p>aripiprazole (n=91) to placebo (n=90) as augmentation to venlafaxine for treatment resistant MDD in adults 60 or older, and found no increase in the amount or percentage of body fat associated with aripiprazole.</p> <p>A RCT⁴ (n=139) compared ziprasidone (n=71) to placebo (n=68) as an adjunct to escitalopram for MDD. Fewer participants receiving ziprasidone reported weight gain (no significant difference between groups).</p> <p>A systematic review¹ of 56 studies examined the use of atypical antipsychotics for anxiety disorders, trauma-related and somatoform disorders included five studies reporting weight gain.</p> <ul style="list-style-type: none"> • The first study, a RCT¹² (n=14) comparing olanzapine monotherapy to placebo for PTSD found that all participants receiving olanzapine reported weight gain, with 57% of the olanzapine group gaining 1-5 kg (33% of placebo), and 43% in the olanzapine group gaining 6-10 kg (none in placebo). • The second study,¹⁷ a pilot RCT (n=12) comparing olanzapine monotherapy to placebo for social anxiety reported a mean weight gain of 1.4 lbs. for olanzapine and 2.2 lbs. for placebo. • The third study,¹⁶ an RCT (n=409), compared quetiapine XR to placebo as an adjunct to SNRI/SSRI for GAD. 4.9% of the quetiapine XR group experienced a 7% or greater increase in body weight, vs. 1% of participants receiving placebo. • The fourth study,¹⁵ was an RCT comparing quetiapine XR monotherapy (n=223) to

Conclusions from Original Systematic Review Link to Review	Findings and Assessment from Prior Surveillance Assessment (August 2014) Link to Report	Literature Analysis (March 2016)
		<p>placebo (n=227) in adults ≥66 years, and found no significant weight gain in either group.</p> <ul style="list-style-type: none"> The fifth study⁵ was a RCT comparing pill placebo (n=20), risperidone augmentation (n=40), and CBT consisting of exposure and ritual prevention (EX/RP; n=40) for OCD. 62% in the risperidone group, 42% in the CBT group, and 8% in the placebo group reported > 0.5 kg/m² weight gain, and 45% in the risperidone group and 19% in the CBT group reported > 1 kg/m² weight gain (0% in placebo). <p>Endocrine/diabetes</p> <p>An RCT³ (n=181) compared the use of aripiprazole (n=91) to placebo (n=90) as augmentation to venlafaxine for treatment resistant MDD in adults 60 or older. Aripiprazole was not associated with an increase in fasting glucose or insulin.</p> <p>A pilot RCT¹¹ compared aripiprazole (n=7) to placebo (n=7) as an adjunct to an antidepressant for antidepressant resistant combat-related PTSD. Aripiprazole was not associated with a significant change in glucose.</p> <p>A systematic review¹ of 56 studies examined the use of atypical antipsychotics for anxiety disorders, trauma-related and somatoform disorders included two studies reporting endocrine/diabetes related adverse events.</p> <ul style="list-style-type: none"> The first study,¹⁶ an RCT (n=409), compared quetiapine XR to placebo as an adjunct to SNRI/SSRI for GAD. 3% of participants

Conclusions from Original Systematic Review Link to Review	Findings and Assessment from Prior Surveillance Assessment (August 2014) Link to Report	Literature Analysis (March 2016)
		<p>receiving quetiapine XR experienced a clinically relevant shift in fasting glucose, as compared to 5% receiving placebo.</p> <ul style="list-style-type: none"> The second study,¹⁵ was an RCT comparing quetiapine XR monotherapy (n=223) to placebo (n=227) in adults ≥66 years, and found no significant difference in fasting glucose or fasting glucose shifts between groups. <p>EPS</p> <p>An RCT¹³ (n=95) comparing low (150 mg/day; n=33) and moderate doses (300 mg/day; n=33) of quetiapine to placebo (n=29) found no significant differences in extrapyramidal symptoms over an 11 week period.</p> <p>An RCT³ (n=181) compared the use of aripiprazole (n=91) to placebo (n=90) as augmentation to venlafaxine for treatment resistant MDD in adults 60 or older. There were a higher proportion of participants in the aripiprazole group patients with akathisia; however, akathisia was generally mild and transient. Aripiprazole was also associated with parkinsonism and complaints of tremor.</p> <p>A pilot RCT¹¹ compared aripiprazole (n=7) to placebo (n=7) as an adjunct to an antidepressant for antidepressant resistant combat-related PTSD. Aripiprazole was not associated with treatment-emergent akathisia.</p> <p>An RCT⁴ (n=139) compared ziprasidone (n=71) to placebo (n=68) as an adjunct to escitalopram for MDD. Higher rates of self-reported treatment-emergent akathisia were</p>

Conclusions from Original Systematic Review Link to Review	Findings and Assessment from Prior Surveillance Assessment (August 2014) Link to Report	Literature Analysis (March 2016)
		<p>associated with ziprasidone. Significantly more participants receiving ziprasidone reported muscle twitching (11.2% vs. 1.4%).</p> <p>In a retrospective cohort study¹⁴ (n=20) of individuals receiving aripiprazole for Tourette's syndrome 3/20 participants reported akathisia.</p> <p>A systematic review¹ of 56 studies examined the use of atypical antipsychotics for anxiety disorders, trauma-related and somatoform disorders included three studies reporting EPS related adverse events.</p> <ul style="list-style-type: none"> • The first study,¹⁶ an RCT (n=409), compared quetiapine XR to placebo as an adjunct to SNRI/SSRI for GAD. EPS related AEs were reported in 3.8% of the quetiapine XR group, and 2% in participants receiving placebo. • The second study,¹⁵ was an RCT comparing quetiapine XR monotherapy (n=223) to placebo (n=227) in adults ≥66 years, and found 5.4% of participants receiving quetiapine XR and 2.2% of those receiving placebo reported EPS related AEs. • The third study⁵ was a RCT comparing pill placebo (n=20), risperidone augmentation (n=40), and CBT consisting of exposure and ritual prevention (EX/RP; n=40) for OCD. One participant in the risperidone group, and one receiving placebo reported akathisia. <p>Tardive dyskinesia</p> <p>An RCT³ (n=181) compared the use of aripiprazole (n=91) to placebo (n=90) as augmentation to venlafaxine for treatment resistant MDD in adults 60 or older. There was no increased risk of Tardive dyskinesia</p>

Conclusions from Original Systematic Review Link to Review	Findings and Assessment from Prior Surveillance Assessment (August 2014) Link to Report	Literature Analysis (March 2016)
		<p>associated with aripiprazole as compared to placebo over 24 weeks.</p> <p>Blood pressure An RCT¹³ found 150 mg/day of quetiapine to be associated with a significant decrease in systolic blood pressure; however, there was no significant difference as compared to placebo.</p> <p>Heart rate An RCT¹³ found 300 mg/day of quetiapine to be associated with a significant increase in heart rate; however, there was no significant difference as compared to placebo.</p> <p>Treatment-emergent suicidal ideation An RCT³ (n=181) compared the use of aripiprazole (n=91) to placebo (n=90) as augmentation to venlafaxine for treatment resistant MDD in adults 60 or older. There was no evidence of treatment-emergent suicidal ideation associated with aripiprazole.</p> <p>A systematic review¹ of 56 studies examined the use of atypical antipsychotics for anxiety disorders, trauma-related and somatoform disorders included one study reporting suicide related adverse events.</p> <ul style="list-style-type: none"> • The first study,¹⁶ an RCT (n=409), compared quetiapine XR to placebo as an adjunct to SNRI/SSRI for GAD. No suicide related adverse events were reported for either group. <p>Sexual Dysfunction</p> <p>A systematic review¹ of 56 studies examined</p>

Conclusions from Original Systematic Review Link to Review	Findings and Assessment from Prior Surveillance Assessment (August 2014) Link to Report	Literature Analysis (March 2016)
		<p>the use of atypical antipsychotics for anxiety disorders, trauma-related and somatoform disorders included three studies reporting sexual dysfunction.</p> <ul style="list-style-type: none"> • The first study,¹⁶ an RCT (n=409), compared quetiapine XR to placebo as an adjunct to SNRI/SSRI for GAD. 2.9% of participants receiving quetiapine XR reported AEs related to sexual dysfunction. No sexual dysfunction related AEs were reported by participants receiving placebo. • The second study,¹⁵ was an RCT comparing quetiapine XR monotherapy (n=223) to placebo (n=227) in adults ≥66 years. No participants reported sexual dysfunction. • The third study⁵ was a RCT comparing pill placebo (n=20), risperidone augmentation (n=40), and CBT consisting of exposure and ritual prevention (EX/RP; n=40) for OCD. 27% in the risperidone group, 16% in the CBT group, and 6% in the placebo group reported decreased libido. <p>Sleep-related</p> <p>A systematic¹ review of 56 studies examined the use of atypical antipsychotics for anxiety disorders, trauma-related and somatoform disorders included two studies reporting sleep related adverse events.</p> <ul style="list-style-type: none"> • The first study,¹⁶ an RCT (n=409), compared quetiapine XR to placebo as an adjunct to SNRI/SSRI for GAD. 7.2% of participants receiving quetiapine vs. 1.5% of participants receiving placebo reported insomnia. • The second study⁵ was a RCT comparing pill placebo (n=20), risperidone augmentation (n=40), and CBT consisting of

Conclusions from Original Systematic Review Link to Review	Findings and Assessment from Prior Surveillance Assessment (August 2014) Link to Report	Literature Analysis (March 2016)
		<p>exposure and ritual prevention (EX/RP; n=40) for OCD. 21% in the risperidone group, 13% in the CBT group, and 17% in the placebo group reported insomnia.</p> <p>Somnolence A systematic review¹ of 56 studies examined the use of atypical antipsychotics for anxiety disorders, trauma-related and somatoform disorders included three studies reporting somnolence.</p> <ul style="list-style-type: none"> • The first study,¹⁶ an RCT (n=409), compared quetiapine XR to placebo as an adjunct to SNRI/SSRI for GAD. 25.5% of participants receiving quetiapine XR vs. 12% of participants receiving placebo reported somnolence. • The second study¹⁵ was an RCT comparing quetiapine XR monotherapy (n=223) to placebo (n=227) in adults ≥66 years, and found 26% of the quetiapine XR group and 8.4% of the placebo group reported somnolence. More participants >75 reported experiencing somnolence. <p>The third study⁵ was a RCT comparing pill placebo (n=20), risperidone augmentation (n=40), and CBT consisting of exposure and ritual prevention (EX/RP; n=40) for OCD. 21% in the risperidone group, 18% in the CBT group, and 22% in the placebo group reported somnolence.</p>

Abbreviations: ADHD= Attention Deficit Hyperactivity Disorder; AE= Adverse Events; CBT=Cognitive Behavioral Therapy; EPS= Extrapyramidal Signs/Symptoms; EX/RP= Exposure and Ritual Prevention; GAD= General Anxiety Disorder; MDD= Major Depressive Disorder; PTSD= Post-Traumatic Stress Disorder; RCT= Randomized Controlled Trial; SNRI= Selective Norepinephrine Reuptake Inhibitor; SOE= Strength of Evidence; SSRI= Selective Serotonin Reuptake Inhibitor

Table 5. Key Question 5: What is the effective dose and time limit for off-label indications?

Conclusions from Original Systematic Review Link to Review	Findings and Assessment from Prior Surveillance Assessment (August 2014) Link to Report	Literature Analysis (March 2016)
<p>SOE: Insufficient There are too few studies comparing doses of atypical antipsychotic medications to draw a conclusion about a minimum dose needed.</p>	<p>Assessment: Current</p> <p>One review reported effective doses for quetiapine for depression generalized anxiety disorder and no consistent effective dose for quetiapine for OCD treatment.</p>	<p>A RCT¹³ (n=95) compared low (150 mg/day; n=33) and moderate doses (300 mg/day; n=33) of quetiapine to placebo (n=29) and found that significant Zanzarini scale total score improvement was associated with a low, but not a moderate dose of quetiapine, as compared to placebo, and a moderate, but not a low dose was associated with better YMRS and SCL-90-R general severity index (differences between doses were not significant). In general, the low dose group “bested” the moderate dose group on outcomes related to efficacy (most group differences by dose were not reported). Compared to the low dose group, sedation, change in appetite, dry mouth, and dizziness were more common in the moderate dose group.</p> <p>A retrospective cohort study¹⁸ (n=977) examined the use of quetiapine as an adjunct to an antidepressant (most often paroxetine and venlafaxine for MDD). The mean treatment duration was approximately six months and the mean time to the first increase was approximately one week. The mean initial and maintenance doses of quetiapine were 23.6 and 40.7mg/day. The mean use of quetiapine was 150 days.</p> <p>A RCT⁴ (n=139) compared ziprasidone (n=71) to placebo (n=68) as an adjunct to escitalopram for MDD. Mean daily doses of ziprasidone for responders and</p>

Conclusions from Original Systematic Review Link to Review	Findings and Assessment from Prior Surveillance Assessment (August 2014) Link to Report	Literature Analysis (March 2016)
		remitters were 96.0 mg (SD=32.6) and 96.9 mg (SD=32.3) respectively.

Abbreviations: MDD= Major Depressive Disorder; OCD= Obsessive Compulsive Disorder; RCT= Randomized Controlled Trial; SCL-90-R= Symptom Checklist-90-Revised; SOE= Strength of Evidence; YMRS= Young Mania Rating Scale

Abstracts from Relevant Literature/References

Studies identified in our literature search:

1. Albert U, Carmassi C, Cosci F, et al. Role and clinical implications of atypical antipsychotics in anxiety disorders, obsessive-compulsive disorder, trauma-related, and somatic symptom disorders: a systematized review. *International clinical psychopharmacology*. Mar 11 2016.

Atypical antipsychotics (AAs) may play a role in the treatment of anxiety disorders, obsessive-compulsive disorder (OCD), and trauma-related disorders. No reviews on their differential use in these different disorders have been performed recently. The aim of this systematized review was to obtain data on efficacy and comparative effectiveness of AAs as a treatment of anxiety disorders, OCD, and trauma-related disorders to provide guidance for clinicians on when and which AA to use. We searched on PubMed, Psychnet, and Cochrane Libraries from inception to July 2015. Search results were limited to randomized, placebo-controlled trials of adult patients. Evidence of efficacy was considered the presence of positive results in two or more double-blind placebo-controlled studies. Our systematized search identified 1298 papers, of which 191 were subjected to a full-text review and 56 were included. Quetiapine extended-release showed a role in both acute and maintenance treatment of uncomplicated generalized anxiety disorder, whereas more studies are needed before drawing practical recommendations on the use of olanzapine and risperidone; aripiprazole and risperidone are effective in resistant OCD as augmentation treatments. Risperidone and olanzapine add-on may have a role in resistant or chronic post-traumatic stress disorder patients, although only risperidone addition can be recommended on the basis of the criterion of two or more positive placebo-controlled trials. This systematized review supports the evidence that only a few AAs are effective in only a minority of the off-label conditions in which they are currently used and confirms that AAs are not all the same. Their use should be on the basis of a balance between efficacy and side effects, and the characteristics as well as the preference of the patient.

13. Black DW, Zanarini MC, Romine A, Shaw M, Allen J, Schulz SC. Comparison of low and moderate dosages of extended-release quetiapine in borderline personality disorder: a randomized, double-blind, placebo-controlled trial. *The American journal of psychiatry*. Nov 1 2014;171(11):1174-1182.

OBJECTIVE: The authors compared the efficacy and tolerability of low and moderate dosages of extended-release quetiapine in adults with borderline personality disorder. **METHOD:** Ninety-five participants with DSM-IV borderline personality disorder were randomly assigned to receive 150 mg/day of quetiapine (the low-dosage group; N=33), 300 mg/day of quetiapine (the moderate-dosage group; N=33), or placebo (N=29). Total score over time on the clinician-rated Zanarini Rating Scale for Borderline Personality Disorder ("Zanarini scale") was analyzed in a mixed-effects model accounting for informative dropout. **RESULTS:** Participants in the low-dosage quetiapine group had significant improvement on the Zanarini

scale compared with those in the placebo group. Time to response (defined as a reduction of 50% or more on the Zanzarini scale total score) was significantly shorter for both the low-dosage quetiapine group (hazard ratio=2.54, p=0.007) and the moderate-dosage quetiapine group (hazard ratio=2.37, p=0.011) than for the placebo group. Among participants who completed the study, 82% in the low-dosage quetiapine group were rated as "responders," compared with 74% in the moderate-dosage group and 48% in the placebo group. Treatment-emergent adverse events included sedation, change in appetite, and dry mouth. The overall completion rate for the 8-week double-blind treatment phase was 67% (67% for the low-dosage quetiapine group, 58% for the moderate-dosage quetiapine group, and 79% for the placebo group). Participants who experienced sedation were more likely to drop out. CONCLUSIONS: Participants treated with 150 mg/day of quetiapine had a significant reduction in the severity of borderline personality disorder symptoms compared with those who received placebo. Adverse events were more likely in participants taking 300 mg/day of quetiapine.

3. Lenze EJ, Mulsant BH, Blumberger DM, et al. Efficacy, safety, and tolerability of augmentation pharmacotherapy with aripiprazole for treatment-resistant depression in late life: a randomised, double-blind, placebo-controlled trial. *Lancet (London, England)*. Dec 12 2015;386(10011):2404-2412.

BACKGROUND: Treatment-resistant major depression is common and potentially life-threatening in elderly people, in whom little is known about the benefits and risks of augmentation pharmacotherapy. We aimed to assess whether aripiprazole is associated with a higher probability of remission than is placebo. METHODS: We did a randomised, double-blind, placebo-controlled trial at three centres in the USA and Canada to test the efficacy and safety of aripiprazole augmentation for adults aged older than 60 years with treatment-resistant depression (Montgomery Asberg Depression Rating Scale [MADRS] score of ≥ 15). Patients who did not achieve remission during a pre-trial with venlafaxine extended-release (150-300 mg/day) were randomly assigned (1:1) to the addition of aripiprazole (target dose 10 mg [maximum 15 mg] daily) or placebo for 12 weeks. The computer-generated randomisation was done in blocks and stratified by site. Only the database administrator and research pharmacists had knowledge of treatment assignment. The primary endpoint was remission, defined as an MADRS score of 10 or less (and at least 2 points below the score at the start of the randomised phase) at both of the final two consecutive visits, analysed by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00892047. FINDINGS: From July 20, 2009, to Dec 30, 2013, we recruited 468 eligible participants, 181 (39%) of whom did not remit and were randomly assigned to aripiprazole (n=91) or placebo (n=90). A greater proportion of participants in the aripiprazole group achieved remission than did those in the placebo group (40 [44%] vs 26 [29%] participants; odds ratio [OR] 2.0 [95% CI 1.1-3.7], p=0.03; number needed to treat [NNT] 6.6 [95% CI 3.5-81.8]). Akathisia was the most common adverse effect of aripiprazole (reported in 24 [26%] of 91 participants on aripiprazole vs 11 [12%] of 90 on placebo). Compared with placebo, aripiprazole was also associated with more Parkinsonism (15 [17%] of 86 vs two [2%] of 81 participants), but not with treatment-emergent suicidal ideation (13 [21%] of 61 vs 19 [29%] of 65 participants) or other measured safety variables. INTERPRETATION: In adults aged 60 years or older who do not achieve remission from depression with a first-line antidepressant, the addition of aripiprazole is effective in achieving and sustaining remission. Tolerability concerns include the potential for akathisia and Parkinsonism. FUNDING: National Institute of Mental Health, UPMC Endowment in Geriatric Psychiatry, Taylor Family Institute for Innovative Psychiatric Research, National Center for Advancing Translational Sciences, and the Campbell Family Mental Health Research Institute.

11. Naylor JC, Kilts JD, Bradford DW, et al. A pilot randomized placebo-controlled trial of adjunctive aripiprazole for chronic PTSD in US military Veterans resistant to antidepressant treatment. *International clinical psychopharmacology*. May 2015;30(3):167-174.

Many individuals with post-traumatic stress disorder (PTSD) experience persistent symptoms despite pharmacological treatment with antidepressants. Several open-label monotherapy and adjunctive studies have suggested that aripiprazole (a second-generation antipsychotic) may have clinical utility in PTSD. However, there have been no randomized placebo-controlled trials of aripiprazole use for PTSD. We thus conducted a pilot randomized controlled trial of adjunctive aripiprazole versus placebo among Veterans with chronic PTSD serving in the US military since 11 September 2001 to assess the feasibility, safety, tolerability, and therapeutic potential of aripiprazole. Sixteen Veterans were randomized, and 14 completed at least 4 weeks of the study; 12 completed the entire 8-week trial. Outcome measures included the Clinician-Administered PTSD Scale (CAPS), PTSD Checklist, Beck Depression Inventory, Second Edition, and Positive and Negative Syndrome Scale scores. Aripiprazole was well-tolerated in this cohort, and improvements in CAPS, PTSD Checklist, Beck Depression Inventory, Second Edition, and Positive and Negative Syndrome Scale scores were as hypothesized. Although CAPS change scores did not reach statistical significance, aripiprazole outperformed placebo by 9 points on the CAPS in the last observation carried forward analysis compared with the placebo group (n = 7 per group), and by 20 points in the group randomized to aripiprazole that completed the entire study (n = 5) compared with the placebo group (n = 7). Results suggest promise for aripiprazole as an adjunctive strategy for the treatment of PTSD.

18. Pae CU, Wang SM, Han C, Lee SJ, Patkar AA, Masand PS. Quetiapine augmentation for depression: dosing pattern in routine practice. *International clinical psychopharmacology*. Jan 2015;30(1):54-58.

This study investigated the dosing patterns of quetiapine augmentation (QA) for major depressive disorder (MDD) in routine practice. Between 1 January 2009 and 31 May 2013, patients with a diagnosis of MDD who were receiving QA in conjunction with an ongoing antidepressant were recruited into this study. The electronic medical records and clinical data for a total of 977 patients were reviewed up to a year. Almost half the patients maintained QA treatment for more than 3 months. The mean duration of QA was approximately 6 months, and the mean initial and maintenance doses were 23.6 and 40.7 mg/day, respectively (range=12.5-400 mg/day). The most frequent adverse events observed were somnolence, followed by dry mouth and lethargy. Our results indicate that the actual doses of QA for MDD in routine practice should be lower than the doses used in placebo-controlled clinical trials and those recommended by a regulatory agency. Adequately powered and well-controlled prospective studies are needed to better understand the exact role of low doses of QA in the treatment of MDD, particularly in routine practice.

4. Papakostas GI, Fava M, Baer L, et al. Ziprasidone Augmentation of Escitalopram for Major Depressive Disorder: Efficacy Results From a Randomized, Double-Blind, Placebo-Controlled Study. *The American journal of psychiatry*. Dec 1 2015;172(12):1251-1258.

OBJECTIVE: The authors sought to test the efficacy of adjunctive ziprasidone in adults with nonpsychotic unipolar major depression experiencing persistent symptoms after 8 weeks of open-label treatment with escitalopram. **METHOD:** This was an 8-week, randomized, double-blind, parallel-group, placebo-controlled trial conducted at three academic medical centers. Participants were 139 outpatients with persistent symptoms of major depression after an 8-week open-label trial of escitalopram (phase 1), randomly assigned in a 1:1 ratio to receive adjunctive ziprasidone (escitalopram plus ziprasidone, N=71) or adjunctive placebo (escitalopram plus placebo, N=68), with 8 weekly follow-up assessments. The primary outcome measure was clinical response, defined as a reduction of at least 50% in score on the 17-item Hamilton Depression Rating Scale (HAM-D). The Hamilton Anxiety Rating scale (HAM-A) and Visual Analog Scale for Pain were defined a priori as key secondary outcome measures. **RESULTS:** Rates of clinical response (35.2% compared with 20.5%) and mean improvement in HAM-D total scores (-6.4 [SD=6.4] compared with -3.3 [SD=6.2]) were significantly greater for the escitalopram plus ziprasidone group. Several secondary measures of antidepressant efficacy also favored adjunctive ziprasidone. The escitalopram plus ziprasidone group also showed significantly greater

improvement on HAM-A score but not on Visual Analog Scale for Pain score. Ten (14%) patients in the escitalopram plus ziprasidone group discontinued treatment because of intolerance, compared with none in the escitalopram plus placebo group. CONCLUSIONS: Ziprasidone as an adjunct to escitalopram demonstrated antidepressant efficacy in adult patients with major depressive disorder experiencing persistent symptoms after 8 weeks of open-label treatment with escitalopram.

2. Schmedt N, Jobski K, Kollhorst B, et al. Treatment patterns and characteristics of older antipsychotic users in Germany. *International clinical psychopharmacology*. Feb 11 2016.

The aim of this study was to investigate the characteristics and treatment patterns of older antipsychotic (AP) users in Germany. We carried out a cohort study in the German Pharmacoepidemiological Research Database and identified new AP users aged at least 65 years between 2005 and 2011. Possible indications, comedication, and information on persistence and adherence, concurrent multiple use, and switch of APs were assessed. Overall, 298 847 individuals were included in the cohort. Almost 70% entered the cohort with a typical antipsychotic (TAP). Melperone (23.4%) was used most frequently, followed by promethazine (18.3%), sulpiride (11.0%), and risperidone (10.3%). AP users had a low prevalence of schizophrenia and bipolar disorders in contrast to dementia. Initiators of atypical antipsychotics had more treatment episodes compared with TAPs (median 3 vs. 2), but lower median persistence (14 vs. 22 days). Persistence was also lower in patients with, rather than without, dementia. The overall percentage of concurrent multiple use and switch to other APs was low with 5.6%, but higher in patients with, rather than without, dementia. In conclusion, APs were used for a broad range of indications, mostly other than schizophrenia and bipolar disorders. Low persistence and a high number of treatment episodes suggest frequent 'as-needed' treatment, especially in dementia patients.

Primary studies included in Albert et al. (2016) meeting inclusion criteria, and not included in a previous AHRQ review or surveillance report, or identified in our literature search:

17. Barnett SD, Kramer ML, Casat CD, Connor KM, Davidson JR. Efficacy of olanzapine in social anxiety disorder: a pilot study. *Journal of psychopharmacology (Oxford, England)*. Dec 2002;16(4):365-368.

Based on evidence suggesting anxiolytic properties of the atypical antipsychotic olanzapine, this study was conducted to evaluate whether olanzapine may be efficacious in treating social anxiety disorder (SAD). This study was an 8-week, double-blind, placebo-controlled evaluation of olanzapine as monotherapy in which 12 patients with the DSM-IV diagnosis of SAD were randomized to either olanzapine (n = 7) or placebo (n = 5). An initial dose of 5 mg/day was titrated to a maximum of 20 mg/day. Baseline to endpoint scores from the Brief Social Phobia Scale (BSPS), Social Phobia Inventory (SPIN), Liebowitz Social Anxiety Scale and Sheehan Disability Scale, as well as Clinical Global Impression-Improvement ratings, were compared for olanzapine versus placebo. Seven subjects completed all 8 weeks of the study, four in the olanzapine group and three in the placebo group. In the intent-to-treat analysis, olanzapine yielded greater improvement than placebo on the primary measures: BSPS (p = 0.02) and SPIN (p = 0.01). Both treatments were well tolerated, although the olanzapine group had more drowsiness and dry mouth. Olanzapine and placebo were both associated with negligible weight gain. Olanzapine was superior to placebo on the primary outcome measures in this preliminary study of SAD. Additional studies of olanzapine as a treatment for SAD are warranted.

12. Carey P, Suliman S, Ganesan K, Seedat S, Stein DJ. Olanzapine monotherapy in posttraumatic stress disorder: efficacy in a randomized, double-blind, placebo-controlled study. *Human psychopharmacology*. Jul 2012;27(4):386-391.

OBJECTIVES: Although there have been important advances in the treatment of posttraumatic stress disorder (PTSD), many patients fail to respond to first-line pharmacotherapy. Limited evidence suggests that second generation antipsychotics may have a role to play as monotherapy in PTSD. **METHODS:** We undertook a randomized, placebo-controlled study using flexible-dose olanzapine monotherapy for 8 weeks in 28 adult male and female participants (mean age: 40.75 +/- 11.59 years) with non-combat related chronic PTSD. Data were analysed with repeated measures analysis of variance, using an intention to treat, last observation carried forward approach. **RESULTS:** The olanzapine group (n = 14) demonstrated significantly greater improvement on the Clinician Administered PTSD Scale from baseline to endpoint than the placebo group (n = 14) (F = 5.71, p = 0.018). Olanzapine was generally well tolerated, with no serious adverse events recorded. Substantial weight gain (6-10 kg) was, however, reported in 6/14 participants in the olanzapine group. **CONCLUSIONS:** To our knowledge, this is the first controlled evidence of the efficacy of olanzapine monotherapy in an exclusively non-combat related chronic PTSD group. Despite the small sample size, these data suggest that olanzapine may have a role in the treatment of PTSD. These findings warrant replication in a larger sample.

16. Khan A, Atkinson S, Mezhebovsky I, She F, Leathers T, Pathak S. Extended-release quetiapine fumarate (quetiapine XR) as adjunctive therapy in patients with generalized anxiety disorder and a history of inadequate treatment response: a randomized, double-blind study. *Annals of clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists*. Feb 2014;26(1):3-18.

BACKGROUND: For many patients with generalized anxiety disorder (GAD), first-line treatment does not lead to remission. This study investigated the efficacy and tolerability of adjunctive extended-release quetiapine fumarate (quetiapine XR) in patients with GAD and an inadequate response to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). **METHODS:** Patients were randomized to quetiapine XR or placebo adjunctive to SSRI/SNRIs in an 11-week study. The primary endpoint was change from randomization to week 8 in Hamilton Anxiety Rating Scale (HAM-A) total score. Secondary variables were HAM-A psychic/somatic clusters, response, and remission, and Clinical Global Impression-Severity of Illness (CGI-S) score. **RESULTS:** A total of 409 patients received quetiapine XR (n=209) or placebo (n=200). The week 8 mean change in HAM-A total score was not statistically significant for quetiapine XR (-10.74; P=.079) vs placebo (-9.61). Secondary variables were generally consistent with the primary analysis, except for a significant reduction in HAM-A total score (week 1) and significant improvements in HAM-A psychic cluster and CGI-S total scores (week 8). Adverse events included dry mouth, somnolence, sedation, headache, and dizziness. **CONCLUSIONS:** In patients with GAD and an inadequate response to SSRI/SNRIs, adjunctive quetiapine XR did not show a statistically significant effect for the primary endpoint at week 8, although some secondary endpoints were statistically significant vs placebo. Quetiapine XR was generally well tolerated.

10. Maina G, Albert U, Ziero S, Bogetto F. Antipsychotic augmentation for treatment resistant obsessive-compulsive disorder: what if antipsychotic is discontinued? *International clinical psychopharmacology*. Jan 2003;18(1):23-28.

The aim of the present study was to retrospectively review the charts of obsessive-compulsive disorder (OCD) patients who responded to the addition of an antipsychotic to the serotonin reuptake inhibitor (SRI), and who subsequently discontinued the antipsychotic, in order to evaluate whether antipsychotic discontinuation resulted in a relapse of the disorder. Charts of patients with a principal diagnosis of OCD (DSM-IV) treated with pharmacotherapy were reviewed in order to select patients who: (i) did not respond to a trial with a first-line drug (clomipramine or a selective SRI); (ii) received an antipsychotic at low doses (haloperidol, pimozide, risperidone or olanzapine) in order to potentiate the SRI; (iii) responded to this augmentation strategy; and (iv) discontinued the antipsychotic drug for any reason while continuing the SRI at the same dose. Relapse was

defined as a worsening of Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) total score $\geq 35\%$ with respect to last evaluation before antipsychotic discontinuation or, for patients with a Y-BOCS < 16 at the end of the combination period, as a Y-BOCS total score ≥ 16 at any time after antipsychotic discontinuation. According to our definition of relapse, 15 patients out of 18 (83.3%) relapsed after antipsychotic discontinuation, with a mean worsening of symptoms of 6.6 \pm 1.7 points in the Y-BOCS total score. Thirteen patients out of the 15 who relapsed did so by week 8 after discontinuation. Two subjects relapsed at the end of the 1-year study. Although retrospective, our study provides initial evidence that antipsychotic augmentation has to be maintained for patients who respond to this strategy, because the vast majority of subjects who discontinue the antipsychotic relapse within 2 months.

15. Mezhebovsky I, Magi K, She F, Datto C, Eriksson H. Double-blind, randomized study of extended release quetiapine fumarate (quetiapine XR) monotherapy in older patients with generalized anxiety disorder. *International journal of geriatric psychiatry*. Jun 2013;28(6):615-625.

OBJECTIVE: The objective of the study was to evaluate once-daily extended release quetiapine fumarate (quetiapine XR) monotherapy in older patients with generalized anxiety disorder (GAD). METHODS: An 11-week (9-week treatment; 2-week posttreatment), randomized, double-blind, placebo-controlled study (D1448C00015) of flexibly-dosed quetiapine XR (50-300 mg/day) or placebo conducted at 47 sites (Estonia, Poland, Russia, Ukraine, and USA) between September 2006 and April 2008. Patients (≥ 66 years) with DSM-IV diagnosis of GAD, Hamilton Anxiety Rating Scale (HAM-A) total score of ≥ 20 with item 1 (anxious mood) and 2 (tension) scores of ≥ 2 , Clinical Global Impressions-Severity of Illness (CGI-S) score of ≥ 4 , and Montgomery Asberg Depression Rating Scale (MADRS) total score of ≤ 16 were eligible for inclusion. Primary endpoint: week 9 change from randomization in HAM-A total score. RESULTS: Patients were randomized to quetiapine XR (n = 223) or placebo (n = 227). At week 9, quetiapine XR significantly reduced HAM-A total score versus placebo (least squares mean -14.97 versus -7.21; p < 0.001); symptom improvement with quetiapine XR versus placebo was significant at week 1 (p < 0.001). At week 9, quetiapine XR demonstrated significant benefits over placebo for HAM-A response and remission rates, HAM-A psychic and somatic cluster, MADRS total, CGI-S, Pittsburgh Sleep Quality Index global, pain visual analog scale, and Quality of Life, Enjoyment and Satisfaction Questionnaire short form % maximum total scores and Clinical Global Impressions-Improvement (% patients with a score of 1/2) (all p < 0.001). Adverse events ($>5\%$ in either treatment group) included somnolence, dry mouth, dizziness, headache, and nausea. CONCLUSIONS: Quetiapine XR (50-300 mg/day) monotherapy is effective in the short term in improving symptoms of anxiety in older patients with GAD, with symptom improvement seen as early as week 1. Tolerability findings were generally consistent with the known profile of quetiapine.

6. Sayyah M, Sayyah M, Boostani H, Ghaffari SM, Hoseini A. Effects of aripiprazole augmentation in treatment-resistant obsessive-compulsive disorder (a double blind clinical trial). *Depression and anxiety*. Oct 2012;29(10):850-854.

BACKGROUND: Obsessive-compulsive disorder (OCD) is a chronic disorder with unknown etiology. Failure in OCD treatment compulsive is common and finding effective augmentations in treatment of OCD will benefit patients. Antipsychotic augmentation is a common strategy for treatment resistant OCD. This trial evaluated the efficacy of adding aripiprazole in patients whose OCD was insufficiently responsive to an adequate SSRI treatment. METHODS: Thirty-nine adult outpatients, who met the DSM-IV-TR criteria for OCD and had treatment resistant OCD were evaluated in a double-blind randomized clinical trial. The patients received either aripiprazole 10 mg/day or placebo, for 12 weeks. Data were analyzed using intention-to-treat analysis with last observation carried forward. All statistical tests were two-sided, and were considered statistically significant at P < 0.05. RESULTS: A significant reduction in total scores of Y-BOCS (P < 0.0001) was found in the aripiprazole group. Aripiprazole was generally well tolerated. There was no significant difference between the two groups in terms of observed side effects.

CONCLUSION: Results of the present study indicate that aripiprazole could be an effective augmentation medicine in treatment resistant OCD.

8. Selvi Y, Atli A, Aydin A, Besiroglu L, Ozdemir P, Ozdemir O. The comparison of aripiprazole and risperidone augmentation in selective serotonin reuptake inhibitor-refractory obsessive-compulsive disorder: a single-blind, randomised study. *Human psychopharmacology*. Jan 2011;26(1):51-57.

OBJECTIVE: To investigate the comparative efficacy of aripiprazole and risperidone as augmenting agents in the treatment of obsessive-compulsive disorder (OCD) patients who did not show a $\geq 35\%$ decrease in the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) after 12-week monotherapy with selective serotonin reuptake inhibitors (SSRIs). METHODS: The study consists of two different periods of treatment: a 12-week prospective period to determine resistance to SSRI treatment and an 8-week single-blind addition period for refractory patients only. Ninety patients were randomly assigned to receive one of the SSRI treatments. Sixty-nine patients (76.6%) completed the 12-week SSRI monotherapy period. Forty-one patients (59.4%) were considered refractory and were randomised to receive either risperidone (20 patients, 3 mgr daily) or aripiprazole (21 patients, 15 mgr daily) as augmentation to SSRI treatment. Sixteen patients (76.2%) in the aripiprazole group and 18 patients (84%) in the risperidone group completed the 8-week treatment period. RESULTS: Eight patients (50%) in aripiprazole and 13 patients (72.2%) in risperidone group met response criteria of Y-BOCS decrease $\geq 35\%$ at the end of the study. The risperidone group showed a significant improvement in Y-BOCS obsession scores compared with aripiprazole. CONCLUSIONS: The present findings suggest that risperidone may be more effective than aripiprazole.

9. Shoja Shafti S, Kaviani H. Aripiprazole versus quetiapine in treatment-resistant obsessive-compulsive disorder: a double-blind clinical trial. *Therapeutic advances in psychopharmacology*. Feb 2015;5(1):32-37.

INTRODUCTION: Around 40-60% of the patients with obsessive-compulsive disorder (OCD) remain unimproved by serotonin reuptake inhibitors (SRIs). Goal of this study was to compare the efficiency and safety of aripiprazole versus quetiapine, in patients with OCD, who did not respond effectively to fluvoxamine. METHOD: A total of 44 female inpatients with OCD, who did not respond successfully to fluvoxamine at maximum dose (300 mg/day) and duration (12 weeks), were assigned randomly, in a double-blind trial, to receive aripiprazole (n = 22) or quetiapine (n = 22), in addition to their SRI, for 12 weeks. Treatment response was assessed by the Yale-Brown Obsessive-Compulsive Scale (YBOCS), as primary outcome measure, and Clinical Global Impressions-Severity Scale (CGI-S), as a secondary outcome measure. RESULTS: A total of 27.27% of the cases in the aripiprazole group (n = 6) and 54.54% of them in the quetiapine cluster (n = 12) responded moderately to the aforesaid augmentation. The mean +/- SD baseline YBOCS score of 33.27 +/- 3.90 dropped to a mean of 30.72 +/- 4.67 (p = 0.06) in the aripiprazole group, and from 31.18 +/- 4.93 to 27.97 +/- 3.71 (p = 0.01) in the quetiapine group, at the end of the evaluation. There was no significant change with respect to CGI-S in either of the aforesaid groups. CONCLUSION: This study shows that treatment-resistant OCD patients may benefit more from addition of quetiapine in comparison with aripiprazole, to their ongoing SRI therapy.

5. Simpson HB, Foa EB, Liebowitz MR, et al. Cognitive-behavioral therapy vs risperidone for augmenting serotonin reuptake inhibitors in obsessive-compulsive disorder: a randomized clinical trial. *JAMA psychiatry*. Nov 2013;70(11):1190-1199.

IMPORTANCE: Obsessive-compulsive disorder (OCD) is one of the world's most disabling illnesses according to the World Health Organization.

Serotonin reuptake inhibitors (SRIs) are the only medications approved by the Food and Drug Administration to treat OCD, but few patients achieve minimal symptoms from an SRI alone. In such cases, practice guidelines recommend adding antipsychotics or cognitive-behavioral therapy consisting of exposure and ritual prevention (EX/RP). OBJECTIVE: To compare the effects of these 2 SRI augmentation strategies vs pill placebo for the first time, to our knowledge, in adults with OCD. DESIGN, SETTING, AND PARTICIPANTS: A randomized clinical trial (conducted January 2007-August 2012) at 2 academic outpatient research clinics that specialize in OCD and anxiety disorders. Patients (aged 18-70 years) were eligible if they had OCD of at least moderate severity despite a therapeutic SRI dose for at least 12 weeks prior to entry. Of 163 who were eligible, 100 were randomized (risperidone, n = 40; EX/RP, n = 40; and placebo, n = 20), and 86 completed the trial. INTERVENTIONS: While continuing their SRI at the same dose, patients were randomized to the addition of 8 weeks of risperidone (up to 4 mg/d), EX/RP (17 sessions delivered twice weekly), or pill placebo. Independent assessments were conducted every 4 weeks. MAIN OUTCOME AND MEASURE: The Yale-Brown Obsessive Compulsive Scale (Y-BOCS) to measure OCD severity. RESULTS: Patients randomized to EX/RP had significantly greater reduction in week 8 Y-BOCS scores based on mixed-effects models (vs risperidone: mean [SE], -9.72 [1.38]; $P < .001$ vs placebo: mean [SE], -10.10 [1.68]; $P < .001$). Patients receiving risperidone did not significantly differ from those receiving placebo (mean [SE], -0.38 [1.72]; $P = .83$). More patients receiving EX/RP responded (Y-BOCS score decrease $\geq 25\%$: 80% for EX/RP, 23% for risperidone, and 15% for placebo; $P < .001$). More patients receiving EX/RP achieved minimal symptoms (Y-BOCS score ≤ 12 : 43% for EX/RP, 13% for risperidone, and 5% for placebo; $P = .001$). Adding EX/RP was also superior to risperidone and placebo in improving insight, functioning, and quality of life. CONCLUSIONS AND RELEVANCE: Adding EX/RP to SRIs was superior to both risperidone and pill placebo. Patients with OCD receiving SRIs who continue to have clinically significant symptoms should be offered EX/RP before antipsychotics given its superior efficacy and less negative adverse effect profile. TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00389493.

7. Storch EA, Goddard AW, Grant JE, et al. Double-blind, placebo-controlled, pilot trial of paliperidone augmentation in serotonin reuptake inhibitor-resistant obsessive-compulsive disorder. *The Journal of clinical psychiatry*. Jun 2013;74(6):e527-532.

OBJECTIVE: This pilot study explored the efficacy and tolerability of paliperidone augmentation of serotonin reuptake inhibitors (SRIs) in adults with treatment-resistant obsessive-compulsive disorder (OCD). METHOD: Thirty-four patients aged 24-67 years (mean = 43.7 years, SD = 11.4) who met DSM-IV criteria for OCD and remained symptomatic following 2 or more past adequate SRI trials (including their current medication) were enrolled from May 2008 to March 2012. Participants were treated for 8 weeks in a double-blind study with either paliperidone (up to 9 mg/d) or matching placebo in addition to their SRI. Blinded raters conducted outcome assessments. The primary outcome, obsessive-compulsive symptom severity, was assessed using the Yale-Brown Obsessive Compulsive Scale (YBOCS). Secondary outcomes included the Clinical Global Impressions-Severity of Illness and -Improvement scales. RESULTS: Paliperidone administration resulted in significant baseline-to-posttreatment reductions in obsessive-compulsive symptoms as measured by the YBOCS ($P < .01$, $d = 0.66$), although placebo administration also resulted in medium-sized, trend-level significant YBOCS changes ($P = .05$, $d = 0.53$). In exploratory analyses examining between-group differences, tests for paliperidone superiority relative to placebo were not significant ($P = .14$, $d = 0.34$); however, a numerical trend toward significant between-group differences was found, with a reduction of 7.98 points on the YBOCS for the paliperidone group compared to a reduction of 4.02 points for the placebo group. Paliperidone was generally well tolerated and not associated with significant weight gain (mean [SD] weight: paliperidone, pretreatment 84.70 [27.08] kg, posttreatment 84.84 [18.99] kg; vs placebo, pretreatment 77.50 [25.33] kg, posttreatment 77.43 [19.90] kg; $P = .21$). CONCLUSIONS: These results suggest that paliperidone augmentation is well tolerated and has potential efficacy in the short-term treatment of some patients with SRI-resistant OCD. Well-powered, randomized, controlled studies are necessary to more definitively address the efficacy of this treatment strategy. TRIAL REGISTRATION: ClinicalTrials.gov identifier: NCT00632229.

One additional study identified:

14. Neuner I, Nordt C, Schneider F, Kawohl W. Effectiveness of aripiprazole in the treatment of adult Tourette patients up to 56 months. *Human psychopharmacology*. Jul 2012;27(4):364-369.

OBJECTIVE: Tourette Syndrome (TS) is characterized by motor and vocal tics. Its pharmacological treatment is often a challenge because of the so-called tachyphylactic effects. Aripiprazole has been reported to be effective in small case series with short follow-up periods. METHODS: In a retrospective analysis, we assessed the effect of off-label treatments with aripiprazole in 20 adult patients (mean age 27.4) divided in a group of severely [67 Yale Global Tourette Severity Scale (YGTTS)-total] and moderately (43.3 YGTTS-total) affected patients. TS patients were treated with aripiprazole (mean 11.8 mg daily) and followed for up to 56 months. RESULTS: Applying a random coefficient model, we found a significant benefit resulting from treatment with aripiprazole. This effect was larger in the severely affected patient group in comparison with the moderately affected patient group. The effect was stable over a time period up to 56 months. CONCLUSION: Aripiprazole, a neuroleptic drug of the third generation with a partial D(2) -agonism is effective in moderately and severely affected adult Tourette patients. We add to the current knowledge through our data extending the follow-up interval up to a maximum of 56 months. All available clinical data strongly support the initiation of a double-blind placebo or other neuroleptic substance controlled trial.

Appendix E. Summary Table*

*No relevant FDA boxed warnings/recalls identified.

Table 1. Key Question 1: What are the leading off-label uses of atypical antipsychotics in utilization studies? How have trends in utilization changed in recent years, including inpatient versus outpatient use? What new uses are being studied in trials?

Conclusions from the Original Systematic Review Link to Report	Findings and Conclusions from Prior Surveillance Assessment (August 2014) Link to Report	Current Literature Search (Date)	Expert Opinion	Surveillance Assessment
<p>Leading off-label uses of atypical antipsychotics: Atypicals have been studied as off-label treatment for the following conditions: ADHD, anxiety, dementia in elderly patients, depression, eating disorders, insomnia, OCD, personality disorder, PTSD, substance use disorders, and Tourette's syndrome.</p> <p>Utilization trends: Off-label use of atypical antipsychotics in various settings has increased rapidly since their introduction in the 1990s; risperidone, quetiapine, and olanzapine are the most common atypicals prescribed for off-label use. Included studies</p>	<p>Assessment: The original review conclusion is possibly out of date with regard to new off-label uses of atypical antipsychotics.</p> <p>Leading off-label uses of atypical antipsychotics: No new research was found.</p> <p>Utilization trends: Three studies examined utilization trends. One study found that antipsychotic prescriptions increased for anxiety disorders from 10.6% (1996-1999) to 21.3% (2004-2007) with the largest increase in panic disorder. One study found that antipsychotic use increased from 25.9% to 41.9% among Medicaid enrollees (1996-2006). One study</p>	<p>We identified two studies relevant to Key Question 1.</p> <p>Utilization trends: We identified no studies examining utilization trends.</p> <p>New uses: A retrospective cohort study² of German older adults examined antipsychotic use. Results indicated that atypical antipsychotics were used off-label for depression and anxiety disorders (including OCD), Parkinson's disease, other movement disorders, sleep disorders, dizziness and vertigo, pain, nausea and vomiting, metastatic tumor disorder, dementia, and generally patients in residential care. Parkinson's disease, other movement disorders, sleep disorders (other than insomnia), dizziness and vertigo, pain, nausea and</p>	<p>All three experts believed that the conclusions were current; however, one expert felt that off-label uses identified since the original review should be added, and another expert felt that there has been an increase in the use of antipsychotics for delirium, possibly triggered by the American Geriatrics Society guidelines for postoperative delirium, published since the original review.¹⁹</p> <p>The third expert recommended three studies.²⁰⁻²² One study²² was excluded because it did not differentiate between FGAs and SGAs.</p> <p>One retrospective cohort study (7167 admissions; time series analysis) of a large hospital in the UK between 2005 and 2011 evaluated rates of SGA prescriptions for dementia to evaluate the effect of</p>	<p>The conclusions in the original systematic review are likely current. However, new uses have been identified since the original review.</p>

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<p>examined utilization trends through 2008. More utilization studies on off-label use were identified for dementia, depression, PTSD and anxiety than for insomnia, eating disorders, and OCD, with more studies in older adults than other populations.</p> <p>Limited evidence suggests that males and Whites are more likely to receive off-label atypical prescriptions. One study indicated that 2005 FDA and Health Canada regulatory warnings were associated with decreases in overall use of atypical antipsychotics, especially among older adults with dementia.</p> <p>New uses: No off-label use of the newly approved atypicals (asenapine, iloperidone, and paliperidone) was reported in the</p>	<p>found that atypical antipsychotic use for dementia declined after the black box warning in 2005. No studies examined trends after 2007.</p> <p>New uses: Four studies examined new off-label uses for previously approved atypicals (risperidone, aripiprazole, paliperidone and quetiapine): Huntington’s disease, trichotillomania, somatoform disorder, and fibromyalgia. One review included a study of olanzapine use for trichotillomania.</p> <p>One study examined off-label use of asenapine for personality disorder.</p>	<p>vomiting, metastatic tumor disorders, and residential care, were not specified for inclusion as conditions/situations in the original systematic review.</p> <p>A systematic review¹ of 56 studies examined the use of atypical antipsychotics for anxiety disorders, trauma-related and somatoform disorders. The review identified studies examining paliperidone for obsessive-compulsive disorder and somatoform disorder, and risperidone for panic disorder. Off-label antipsychotic use for conditions that were not of specified for inclusion in the original systematic review includes arachnophobia, somatoform disorders, irritable bowel syndrome, and functional abdominal pain syndrome.</p>	<p>a 2009 MHRA warning related to cerebrovascular adverse events in older adults. Results indicated that the rate of SGA prescriptions fell significantly after 2009 (1.9% per month, 95% CI 0.4 – 3.5%, p= 0.015).²⁰</p> <p>A cross-sectional survey (n=15,591) of claims data in Japan from 2002-2010 examined trends for psychopharmacologic use as an adjunct to cholinesterase inhibitors in older adults with dementia. Results indicated that utilization of SGAs increased from 5.0% in 2002 to 12.0% in 2010 (OR 2.95, 95% CI 2.44–3.59). The use of quetiapine increased from 1.3% to 5.6% (OR 4.78, 95% CI 3.45–6.82), and the use of risperidone increased from 3.1% to 4.5% (OR 1.80, 95% CI 1.41–2.32).²¹</p>	

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utilization literature.				

Abbreviations: ADHD=Attention Deficit Hyperactivity Disorder; CI=Confidence Interval; FDA=Food and Drug Administration; FGA=First Generation Antipsychotics; MHRA= Medicines and Healthcare Products Regulatory Agency; OCD=Obsessive-Compulsive Disorder; PTSD=Post-Traumatic Stress Disorder; SGA=Second Generation Antipsychotics; UK=United Kingdom

Table 2. Key Question 2: What does the evidence show regarding the efficacy and comparative of atypical antipsychotics for off-label indications? How do atypical antipsychotic medications compare with other drugs, including first-generation antipsychotics, for treating off-label indications?

Conclusions from the Original Systematic Review Link to Report	Findings and Conclusions from Prior Surveillance Assessment (August 2014) Link to Report	Current Literature Search (Date)	Expert Opinion	Surveillance Assessment
Dementia (SOE: High): Aripiprazole, olanzapine, and risperidone have efficacy as treatment for behavioral symptoms of dementia.	Assessment: Current Two randomized trials reported efficacy of risperidone in improving behavioral symptoms of dementia. One randomized trial reported worsening cognitive function with olanzapine, quetiapine or risperidone treatment compared with placebo. One review reported efficacy of atypical antipsychotics in behavioral and psychotic symptoms of dementia.	No studies were identified.	All three experts believed the conclusions in the original review to be current. One expert suggested a meta-analysis examining SGAs for dementia. ²³ All but one of the 16 studies in the MA were included in the original review. The study was a RCT (n=40) that compared quetiapine to placebo in individuals with dementia/Alzheimer's and comorbid Parkinson's Disease or parkinsonism. There was no difference between groups on the BPRS, MMSE, NPI, or the ADCS-CGIC. ²⁴	This portion of the original systematic review is likely current.
Depression- MDD: Augmentation of	Assessment: Current	Depression – MDD:	All three experts believed the	This portion of the original

Conclusions from the Original Systematic Review Link to Report	Findings and Conclusions from Prior Surveillance Assessment (August 2014) Link to Report	Current Literature Search (Date)	Expert Opinion	Surveillance Assessment
<p>SSRI/SNRI (SOE: Moderate - risperidone, aripiprazole, quetiapine; SOE: Low - olanzapine, ziprasidone) Aripiprazole, quetiapine, and risperidone have efficacy as augmentation to SSRIs/SNRIs for major depressive disorder. Olanzapine and ziprasidone may also have efficacy.</p> <p>Depression- MDD: Monotherapy (SOE: Moderate) Olanzapine does not have efficacy as monotherapy for major depressive disorder. Quetiapine has efficacy as monotherapy for major depressive disorder.</p>	<p>Depression- MDD: Augmentation of SSRI/SNRI: One review reported efficacy of aripiprazole, quetiapine, and risperidone as augmentation to SSRIs/SNRIs. A meta-analysis examined aripiprazole, risperidone, quetiapine, and the combination of olanzapine and fluoxetine (OFC) and found that all four had a significant effect on remission rates, severity measures. All but OFC had a significant effect on response rates.</p> <p>Depression- MDD: Monotherapy Four studies (two pooled analyses of RCTs, one post-hoc analysis of RCT, one RCT reported efficacy of quetiapine for MDD. One RCT reported potential efficacy of ziprasidone for MDD.</p>	<p>Augmentation of SSRI/SNRI: An RCT³ (n=181) compared the use of aripiprazole (n=91) to placebo (n=90) as augmentation to venlafaxine for treatment resistant MDD in adults 60 or older. Significantly more participants receiving aripiprazole achieved remission, and aripiprazole was associated with a significantly faster time to improvement, and a larger decrease on Ham-D and MADRS scores.</p> <p>An RCT⁴ (n=139) compared ziprasidone (n=71) to placebo (n=68) as an adjunct to escitalopram for MDD. Results indicated that more participants receiving ziprasidone had a 50% or larger reduction in score on the</p>	<p>conclusions in the original review to be current.</p>	<p>systematic review is likely current. Evidence identified in the current and prior surveillance assessments may strengthen the strength of evidence related to the effectiveness of ziprasidone as an adjunct.</p>

Conclusions from the Original Systematic Review Link to Report	Findings and Conclusions from Prior Surveillance Assessment (August 2014) Link to Report	Current Literature Search (Date)	Expert Opinion	Surveillance Assessment
		<p>Ham-D, the QIDS-SR, and the Ham-A, and more participants receiving ziprasidone achieved remission, according to the QIDS-SR, and the Ham-A. In addition, the ziprasidone group experienced greater reductions on the Ham-D, the QIDS-SR, CGI-S, and the Ham-A. There were no differences between groups on change in VAS-Pain scores, or on the CGI-I at the end of the study.</p>		
<p>Obsessive-compulsive disorder: augmentation of SSRI (SOE: Moderate - risperidone; SOE: Low- olanzapine) Risperidone has efficacy in improving OCD symptoms when used as an adjunct to SSRI in treatment refractory patients. Olanzapine may also have efficacy. Quetiapine is more efficacious than ziprasidone and clomipramine for this</p>	<p>Assessment: Current Obsessive-compulsive disorder: augmentation of SSRI: One RCT reported quetiapine-fluoxetine is ineffective in improving OCD symptoms compared to fluoxetine-clomipramine or fluoxetine-placebo. One</p>	<p>A systematic review¹ of 56 studies examined the use of atypical antipsychotics for anxiety disorders, trauma-related and somatoform disorders. Five studies⁵⁻⁹ examining augmentation to SSRIs for treatment resistant OCD met inclusion criteria for this key question</p>	<p>All three experts believed the conclusions in the original review to be current.</p>	<p>The conclusions in this portion of the original systematic review are likely current; however new evidence is available related to the use of aripiprazole as an adjunct to SSRIs for OCD (no studies identified in either the original review or the previous assessment). We identified three small studies that</p>

Conclusions from the Original Systematic Review Link to Report	Findings and Conclusions from Prior Surveillance Assessment (August 2014) Link to Report	Current Literature Search (Date)	Expert Opinion	Surveillance Assessment
<p>purpose.</p> <p>Obsessive-compulsive disorder: augmentation of citalopram (SOE: Low- quetiapine; SOE: Very Low – risperidone) Quetiapine and risperidone may be efficacious as augmentation to citalopram in OCD patients.</p>	<p>RCT reported efficacy of aripiprazole in improving OCD symptoms as an adjunct to SSRIs. One review reported no consistent effect of quetiapine for OCD symptoms.</p> <p>One reviewer suggested a meta-analysis that found that risperidone improved OCD symptoms as augmentation to SSRIs.</p> <p>Obsessive-compulsive disorder: augmentation of citalopram: No new research was found.</p>	<p>and were not included in a prior review or assessment.</p> <ul style="list-style-type: none"> The first study⁵ was a RCT comparing pill placebo (n=20), risperidone augmentation to SSRI (n=40), and CBT consisting of exposure and ritual prevention (EX/RP; n=40). Results indicated a significantly lower reduction in Y-BOCS, Ham-D, and BABS scores associated with risperidone augmentation at eight weeks as compared to EX/RP, with no difference from placebo. The second study⁶ was a RCT comparing aripiprazole (n=18) to placebo (n=21) for SSRI resistant OCD. Aripiprazole was associated with a significantly greater reduction on the Y-BOCS at 		<p>found aripiprazole to be more effective than placebo⁶ no significant difference as compared to quetiapine,⁹ and that aripiprazole was less effective than risperidone on Y-BOCS score reduction. In addition, the original review did not include any studies examining paliperidone. We identified one study examining paliperidone as an adjunct to SSRIs that found no difference in symptom reduction as compared to placebo.</p>

Conclusions from the Original Systematic Review Link to Report	Findings and Conclusions from Prior Surveillance Assessment (August 2014) Link to Report	Current Literature Search (Date)	Expert Opinion	Surveillance Assessment
		<p>8-weeks and (non-significantly) better sexual functioning.</p> <ul style="list-style-type: none"> • The third study,⁷ a pilot RCT (n=34) comparing paliperidone augmentation to SSRI found that while paliperidone was associated with a significant reduction in Y-BOCS score, differences from placebo were not significant. • The fourth study⁸ compared risperidone to aripiprazole augmentation to a high dose SSRI for SSRI refractory OCD. Both groups experienced significant reductions on the Y-BOCS and the HAM-D at eight and 20 weeks, with significantly greater reductions on the Y-BOCS total and obsession scales associated with 		

Conclusions from the Original Systematic Review Link to Report	Findings and Conclusions from Prior Surveillance Assessment (August 2014) Link to Report	Current Literature Search (Date)	Expert Opinion	Surveillance Assessment
		risperidone, with no significant differences on the Y-BOCS compulsion scale or the HAM-D. • The fifth study ⁹ compared aripiprazole (n=22) to quetiapine (n=22) augmentation in fluvoxamine non-responders and found partial improvement in both groups (weeks 4, 8, 12) with a significant improvement in only participants receiving quetiapine at week 12 (there was no significant difference between groups at week 12).		
Post-traumatic stress disorder (SOE: Moderate-risperidone; SOE: Low - olanzapine; SOE: Very Low-quetiapine) Risperidone is efficacious in reducing combat-related PTSD symptoms when used	Assessment: Current One pilot study reported efficacy of aripiprazole in improving PTSD symptoms. One randomized trial reported no reduction in PTSD	A pilot RCT ¹¹ compared aripiprazole (n=7) to placebo (n=7) as an adjunct to an antidepressant for antidepressant resistant combat-related PTSD.	All three experts believed the conclusions in the original review to be current.	The conclusions in this portion of the original systematic review are likely current; however new evidence is available related to the use of aripiprazole as an adjunct to antidepressants

Conclusions from the Original Systematic Review Link to Report	Findings and Conclusions from Prior Surveillance Assessment (August 2014) Link to Report	Current Literature Search (Date)	Expert Opinion	Surveillance Assessment
as an adjunct to primary medication.	symptoms with risperidone treatment as an adjunct to primary medication in patients with SRI-resistant symptoms. One review reported positive treatment effects for risperidone and quetiapine.	<p>Aripiprazole was associated with non-significant reductions on the CAPS, the PANSS, the PCL, and the BDI-II.</p> <p>A systematic review¹ of 56 studies examined the use of atypical antipsychotics for anxiety disorders, trauma-related and somatoform disorders. One RCT¹² examining olanzapine monotherapy for non-combat resistant PTSD (n=14) met inclusion criteria and was not included in a previous review or assessment. As compared to placebo, participants in the olanzapine group experienced a significantly greater improvement on the Clinician Administered PTSD Scale.</p>		for PTSD (no studies identified in the original review). A pilot study identified in the prior surveillance assessment found that aripiprazole was effective in reducing PTSD symptoms; however, we identified another pilot study that found no associated significant improvement. ¹¹
Personality disorders: borderline (SOE: Low- aripiprazole; SOE: very low -	<u>Assessment: Current</u> Personality disorders:	A RCT ¹³ (n=95) compared low (150 mg/day; n=33) and moderate doses	All three experts believed the conclusions in the original review to be current.	The conclusions in this portion of the original systematic review are likely

Conclusions from the Original Systematic Review Link to Report	Findings and Conclusions from Prior Surveillance Assessment (August 2014) Link to Report	Current Literature Search (Date)	Expert Opinion	Surveillance Assessment
<p>quetiapine, olanzapine) Olanzapine had mixed results in seven trials, aripiprazole was found efficacious in two trials, quetiapine was found efficacious in one trial, and ziprasidone was found not efficacious in one trial.</p> <p>Personality disorders: schizotypal (SOE: Low) Risperidone had mixed results when used to treat schizotypal personality disorder in two small trials.</p>	<p>borderline: One non-randomized trial reported efficacy of olanzapine. One case-series reported improved symptoms with asenapine treatment. One meta-analysis found improved symptoms with antipsychotic treatment.</p> <p>One reviewer suggested a review that reported some efficacy of atypical antipsychotics.</p> <p>Personality disorders: schizotypal: No new research was found.</p>	<p>(300 mg/day; n=33) of quetiapine to placebo (n=29) for borderline personality disorder, and found that significant Zanarini scale total score improvement was associated with a low, but not a moderate dose of quetiapine, as compared to placebo, and a moderate, but not a low dose was associated with better YMRS and SCL-90-R general severity index (differences between doses were not significant). In general, the low dose group “bested” the moderate dose group on outcomes related to efficacy (most group differences by dose were not reported). Time to treatment response, affective and cognitive disturbance, disturbed relationships,</p>		<p>current; however new evidence is available related to the use of asenapine for borderline personality disorder (no studies identified in the original review). The prior assessment identified one case series that found associated symptom improvement.</p>

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		verbal and physical aggression, and work/school days lost due to symptoms were significantly better for both quetiapine groups as compared to placebo.		
<p>Tourette's Syndrome (SOE: Low) Risperidone is at least efficacious as pimozide or clonidine for Tourette's Syndrome.</p>	<p><u>Assessment: Current</u> One case-series reported improvement in Tourette's Syndrome symptoms with aripiprazole treatment.</p>	<p>A retrospective cohort study¹⁴ (n=20) of individuals with Tourette's syndrome receiving aripiprazole. When comparing individuals with low vs. high Yale Global Tourette Severity Scale (YGTSS) scores, results indicated that aripiprazole was associated with significantly lower scores for both groups, with a significantly greater reduction in individuals with high YGTSS scores at baseline.</p>	<p>All three experts believed the conclusions in the original review to be current.</p>	<p>The conclusions in this portion of the original systematic review are likely current; however new evidence is available related to the use of aripiprazole for Tourette's syndrome (no studies identified in the original review). Both a case series identified in the prior surveillance assessment and a study identified in the current assessment found aripiprazole to be effective in symptom improvement.¹⁴</p>
<p>Anxiety (SOE: Moderate) Quetiapine has efficacy as treatment for Generalized Anxiety Disorder.</p>	<p><u>Assessment: Current</u> Five studies (one pooled analysis of three</p>	<p>A systematic review¹ of 56 studies examined the use of atypical antipsychotics</p>	<p>All three experts believed the conclusions in the original review to be current.</p>	<p>This portion of the original systematic review is likely current.</p>

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<p>Three studies also examined Social Anxiety Disorder (no SOE noted).</p>	<p>RCTs, four RCTs) reported efficacy of quetiapine as treatment for Generalized Anxiety Disorder. One review reported reduced anxiety score with olanzapine augmentation but not for quetiapine augmentation. One review reported efficacy of quetiapine for anxiety.</p>	<p>for anxiety disorders, trauma-related and somatoform disorders included two studies^{15,16} examining <u>generalized anxiety disorder</u> that met inclusion criteria for the original review and were not included in a prior review or surveillance.</p> <ul style="list-style-type: none"> • One study¹⁵ was an RCT comparing quetiapine XR monotherapy (n=223) to placebo (n=227) in adults ≥66 years, which found a significantly greater reduction in Ham-A scores associated with quetiapine XR for both participants ≤75 and >75, and that significantly better efficacy was demonstrated in week one overall, and for participants ≤75, but not >75. • The second study¹⁶ 		

Conclusions from the Original Systematic Review Link to Report	Findings and Conclusions from Prior Surveillance Assessment (August 2014) Link to Report	Current Literature Search (Date)	Expert Opinion	Surveillance Assessment
		<p>examined quetiapine XR as an adjunct to an SRNI/SSRI (n=209) vs. placebo + SRNI/SSRI (n=200). Results indicated a greater reduction in Ham-A scores associated with quetiapine XR as compared to placebo at week one, but not at week 8.</p> <p>One study¹⁷ included in the systematic review, a pilot RCT comparing olanzapine (n=7) monotherapy to placebo (n=5) for <u>social anxiety disorder</u>, met inclusion criteria and was not included in a previous review or assessment. Results indicated greater improvement on the BPRS and the SPIN associated with olanzapine.</p>		
Attention deficit/hyperactivity disorder: no co-occurring disorders (SOE: Low) Risperidone may be	<u>Assessment: Current</u> One review reported efficacy of risperidone in	No studies were identified	All three experts believed the conclusions in the original review to be current.	This portion of the original systematic review is likely current.

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<p>efficacious in treating children with ADHD with no serious co-occurring disorders.</p> <p>Attention deficit/hyperactivity disorder: mentally retarded children (SOE: Low) Risperidone may be superior to methylphenidate in treating ADHD symptoms in mentally retarded children.</p> <p>Attention deficit/hyperactivity disorder: bipolar children (SOE: Low) Aripiprazole is ineffective in reducing ADHD symptoms in children with bipolar disorder.</p>	<p>treating children with ADHD.</p>			
<p>Eating disorders (SOE: Moderate-olanzapine; SOE: Low- quetiapine) Olanzapine and quetiapine have no efficacy in increasing body mass in eating disorder patients.</p>	<p>Assessment: Current</p> <p>No new research was found.</p>	<p>No studies were identified</p>	<p>All three experts believed the conclusions in the original review to be current.</p>	<p>This portion of the original systematic review is likely current.</p>
<p>Insomnia (SOE: Very Low) Quetiapine may be ineffective in treating insomnia.</p>	<p>Assessment: Current</p> <p>One non-randomized pilot study reported potential efficacy of quetiapine for sleep continuity.</p>	<p>No studies were identified</p>	<p>All three experts believed the conclusions in the original review to be current.</p>	<p>This portion of the original systematic review is likely current.</p>
<p>Substance abuse: alcohol (SOE: Moderate-aripiprazole; SOE: Low- quetiapine)</p>	<p>Assessment: Current</p> <p>No new research was</p>	<p>No studies were identified</p>	<p>All three experts believed the conclusions in the original review to be current.</p>	<p>This portion of the original systematic review is likely current.</p>

Conclusions from the Original Systematic Review Link to Report	Findings and Conclusions from Prior Surveillance Assessment (August 2014) Link to Report	Current Literature Search (Date)	Expert Opinion	Surveillance Assessment
<p>Aripiprazole is inefficacious in treating alcohol abuse/ dependence. Quetiapine may also be inefficacious.</p> <p>Substance abuse: cocaine (SOE: Low) Olanzapine is inefficacious in treating cocaine abuse/dependence. Risperidone may also be inefficacious.</p> <p>Substance abuse: methamphetamine (SOE: Low) Aripiprazole is inefficacious in treating methamphetamine abuse/dependence.</p> <p>Substance abuse: methadone clients (SOE: Low) Risperidone is an inefficacious adjunct to methadone maintenance.</p>	<p>found.</p>			

Abbreviations: ADCS-CGIC= Alzheimer's Disease Cooperative Study Clinical Global Impression of Change; ADHD= Attention Deficit Hyperactivity Disorder; BABS= Brown Assessment of Beliefs Scale; BDI-II= Beck Depression Inventory-II; BPRS= Brief Social Phobia Scale; CAPS= Clinician-Administered PTSD Scale; CBT= Cognitive Behavioral Therapy; CGI-I= Clinical Global Impressions Scale Improvement Subscale; CGI-S= Clinical Global Impressions Scale Severity Subscale; EX/RP= Exposure and Ritual Prevention; HAM-A= Hamilton Anxiety Rating Scale; HAM-D= Hamilton Depression Rating Scale; MA=Meta-Analysis; MADRS= Montgomery-Asberg Depression Rating Scale; MDD= Major Depressive Disorder; MMSE=Mini Mental Status Exam; NPI=Neuropsychiatric Inventory; OCD=Obsessive Compulsive Disorder; PANSS= Positive and Negative Syndrome Scale; PCL= PTSD Checklist; PTSD= Post-Traumatic Stress Disorder; QIDS-SR= Quick Inventory of Depressive Symptomology Self-Rated; RCT= Randomized Controlled Trial; SCL-90-R= Symptom Checklist-90-Revised; SNRI= Selective Norepinephrine Reuptake Inhibitor; SOE= Strength of Evidence; SPIN= Society Phobia Inventory; SRI= Serotonin Reuptake Inhibitor; SSRI= Selective Serotonin Reuptake Inhibitor; VAS-Pain= Visual Analog Scale for Pain; Y-BOCS= Yale-Brown Obsessive Compulsive Scale; YGTSS= Yale Global Tourette Severity Scale; YMRS= Young Mania Rating Scale

Table 3. Key Question 3: What subset of the population would potentially benefit from off-label uses? Do effectiveness and harms differ by race/ethnicity, gender, and age group? By severity of condition and clinical subtype?

Conclusions from the Original Systematic Review Link to Report	Findings and Conclusions from Prior Surveillance Assessment (August 2014) Link to Report	Current Literature Search (Date)	Expert Opinion	Surveillance Assessment
<p>SOE: Insufficient There are insufficient data regarding efficacy, effectiveness, and harms to determine what subset of the population would potentially benefit from off-label uses of atypicals.</p>	<p>Assessment: Current One study reported predictors of severity of OCD in response to antipsychotic augmentation of SRIs.</p>	<p>A systematic review¹ of 56 studies examined the use of atypical antipsychotics for anxiety disorders, trauma-related and somatoform disorders included one study examining subgroup differences that met inclusion criteria for the original review and was not included in a prior review or surveillance. The study was a RCT¹⁵ comparing quetiapine XR monotherapy (n=223) to placebo (n=227) in adults ≥66 years, which found a significantly greater reduction in Ham-A scores associated with quetiapine XR for both participants ≤75 and >75, and that significantly better efficacy was demonstrated in week one for participants ≤75, but not >75. Incidence of adverse events related to EPS and somnolence were higher in participants >75.</p>	<p>All experts believed the original review's conclusions to be current. One expert provided a CADTH rapid review of reviews focused on antipsychotic use in pediatric populations.²⁵ Reviews of reviews are not included in our assessment of currency.</p>	<p>This portion of the original systematic review is likely current.</p>

Abbreviations: CADTH=Canadian Agency for Drugs and Technologies in Health; HAM-A= Hamilton Anxiety Rating Scale; OCD= Obsessive Compulsive Disorder; RCT= Randomized Controlled Trial; SOE= Strength of Evidence; SRI= Serotonin Reuptake Inhibitor

Table 4. Key Question 4: What are the potential adverse effects and/or complications involved with off-label prescribing of atypical antipsychotics? How do they compare within the class and with other drugs used for the conditions?

Conclusions from the Original Systematic Review Link to Report	Findings and Conclusions from Prior Surveillance Assessment (August 2014) Link to Report	Current Literature Search (Date)	Expert Opinion	Surveillance Assessment
<p>Weight gain (SOE: High - risperidone) Olanzapine is associated with more weight gain than placebo, conventional antipsychotics, or other atypical antipsychotics.</p> <p>Some evidence for other atypical antipsychotics. Risperidone, quetiapine and aripiprazole are associated with more weight gain compared with placebo.</p> <p>Endocrine/diabetes (SOE: Low) Olanzapine associated with higher risk of diabetes than risperidone.</p> <p>Mortality Atypical antipsychotics associated with increased risk of death in elderly patients compared with placebo. (SOE: High) Conventional antipsychotics</p>	<p>Assessment: Current</p> <p>Weight gain One randomized trial reported weight gain more common with risperidone compared to placebo. One review reported weight gain with risperidone use among children with ADHD. One review reported weight gain associated with aripiprazole, puetiapine, risperidone, and the combination of olanzebine and fluoxetine. One review reported weight gain with risperidone, quetiapine and aripiprazole. One review reported weight gain with quetiapine use.</p> <p>Endocrine/diabetes One RCT reported worsening glucose metabolism factors with olanzapine compared to placebo in healthy controls. One review reported</p>	<p>Weight gain A RCT¹³ (n=95) comparing low (150 mg/day; n=33) and moderate doses (300 mg/day; n=33) of quetiapine to placebo (n=29) found that the mean weight gain was one lb for placebo (SD=4.4) and the low dose (SD=7.2), and three pounds for the moderate dose (SD=9.2), with no significant differences between groups.</p> <p>A RCT³ (n=181) compared the use of aripiprazole (n=91) to placebo (n=90) as augmentation to venlafaxine for treatment resistant MDD in adults 60 or older, and found no increase in the amount or percentage of body fat associated with aripiprazole.</p> <p>A RCT⁴ (n=139) compared ziprasidone (n=71) to placebo (n=68) as an adjunct to escitalopram for</p>	<p>All experts believed the original review conclusions to be current. One expert suggested a study examining the risk of mortality associated with antipsychotic use among individuals with dementia.²⁶ Another expert suggested one study related to the risk of mortality,²⁷ and a second study related to the risk of diabetes,²⁸ which was excluded because it did not stratify results by antipsychotic generation.</p> <p>Mortality Using VA registry data, a retrospective cohort study (n=33,604) examined the association between antipsychotic</p>	<p>Weight gain: This portion of the original systematic review is likely current.</p> <p>Endocrine/diabetes: This portion of the original systematic review is likely current.</p> <p>Mortality: The conclusions in the original systematic review are likely current.</p> <p>EPS: The conclusions in this portion of the original systematic review are likely current; however new evidence is available related to EPS related risks associated with ziprasidone⁴ (no studies identified in the original review or prior surveillance assessment). We identified one study comparing ziprasidone to placebo that found higher rates of self-reported treatment-emergent akathisia and muscle twitching associated with ziprasidone.⁴</p>

Conclusions from the Original Systematic Review Link to Report	Findings and Conclusions from Prior Surveillance Assessment (August 2014) Link to Report	Current Literature Search (Date)	Expert Opinion	Surveillance Assessment
<p>associated with higher rate of death compared with atypical antipsychotics. (SOE: Moderate)</p> <p>EPS (SOE: Moderate) Aripiprazole and risperidone are associated with an increase in extrapyramidal signs or symptoms compared to quetiapine.</p> <p>Tardive dyskinesia (SOE: Low) Atypical antipsychotics are associated with less tardive dyskinesia than are high doses of haloperidol.</p>	<p>abnormal metabolic laboratory results with quetiapine.</p> <p>Mortality Two cohort studies reported increased risk of death with haloperidol treatment compared to risperidone. One cohort study reported no association between antipsychotic use and death after adjustment for psychiatric symptoms. One review reported increased risk of death with atypical antipsychotic treatment for dementia.</p> <p>EPS No new research was found.</p> <p>Tardive dyskinesia No new research was found.</p> <p>Akathisia One review reported increased risk of akathisia associated with aripiprazole.</p> <p>Venous thromboembolism : One case-control study reported</p>	<p>MDD. Fewer participants receiving ziprasidone reported weight gain (no significant difference between groups).</p> <p>A systematic review¹ of 56 studies examined the use of atypical antipsychotics for anxiety disorders, trauma-related and somatoform disorders included five studies reporting weight gain.</p> <ul style="list-style-type: none"> The first study, a RCT¹² (n=14) comparing olanzapine monotherapy to placebo for PTSD found that all participants receiving olanzapine reported weight gain, with 57% of the olanzapine group gaining 1-5 kg (33% of placebo), and 43% in the olanzapine group gaining 6-10 kg (none in placebo). The second study,¹⁷ a pilot RCT (n=12) comparing olanzapine monotherapy to placebo for social anxiety reported a mean weight gain 	<p>use and mortality in patients 65 and older with dementia.²⁵ Results indicated that 6-month mortality rates were 12.6% for olanzapine, 12.5% for risperidone, and 8.8% for quetiapine. Among SGAs, 180-day mortality adjusted RRs were highest for risperidone (reference), then olanzapine (RR 0.99, 95% CI 0.89–1.10), and quetiapine (RR 0.73, 95% CI 0.67–0.80). Mortality risk differences were highest in the first 120 days, then declined over the next 60 days. There were a larger percentage of individuals with comorbid PD receiving quetiapine. Sensitivity analysis found a higher rate of mortality among individuals with PD receiving</p>	<p>Tardive dyskinesia: The conclusions in this portion of the original systematic review are likely current; however new evidence is available related to tardive dyskinesia associated with aripiprazole (no studies identified in the original review or prior surveillance assessment). We identified one RCT¹ that found no increase in risk as compared to placebo.</p> <p>While they do not change the conclusions in the original review (no conclusions determined), new evidence is available on other potential harms.</p>

Conclusions from the Original Systematic Review Link to Report	Findings and Conclusions from Prior Surveillance Assessment (August 2014) Link to Report	Current Literature Search (Date)	Expert Opinion	Surveillance Assessment
	<p>increased risk of venous thromboembolism in new users of antipsychotics compared to nonusers.</p>	<p>of 1.4 lbs. for olanzapine and 2.2 lbs. for placebo.</p> <ul style="list-style-type: none"> • The third study,¹⁶ an RCT (n=409), compared quetiapine XR to placebo as an adjunct to SNRI/SSRI for GAD. 4.9% of the quetiapine XR group experienced a 7% or greater increase in body weight, vs. 1% of participants receiving placebo. • The fourth study,¹⁵ was an RCT comparing quetiapine XR monotherapy (n=223) to placebo (n=227) in adults ≥66 years, and found no significant weight gain in either group. • The fifth study⁵ was a RCT comparing pill placebo (n=20), risperidone augmentation (n=40), and CBT consisting of exposure and ritual prevention (EX/RP; n=40) for OCD. 62% in the risperidone group, 42% in the CBT group, and 8% in the placebo group reported > 0.5 	<p>quetiapine (RR 1.39, 95% CI 1.18– 1.64, p< 0.001).²⁶</p> <p>A retrospective case controlled study²⁶ of VHA data of adults 65 and older with dementia from 1998 to 2009 (n=90,786) examined mortality risk increase and the number needed to harm (NNH), and found that compared with matched non-users, risperidone had a 3.7% increased risk of mortality (95% CI, 2.2%-5.3%; P < .01) with an NNH of 27 (95% CI, 19-46); olanzapine had a 2.5% increased risk (95% CI, 0.3%-4.7%; P = .02) with an NNH of 40 (95% CI, 21-312); and there was a 2.0% increase in risk of mortality associated with quetiapine (95% CI, 0.7%-3.3%; P < .01) with an NNH of</p>	

Conclusions from the Original Systematic Review Link to Report	Findings and Conclusions from Prior Surveillance Assessment (August 2014) Link to Report	Current Literature Search (Date)	Expert Opinion	Surveillance Assessment
		<p>kg/m² weight gain, and 45% in the risperidone group and 19% in the CBT group reported > 1 kg/m² weight gain (0% in placebo).</p> <p>Endocrine/diabetes</p> <p>An RCT³ (n=181) compared the use of aripiprazole (n=91) to placebo (n=90) as augmentation to venlafaxine for treatment resistant MDD in adults 60 or older. Aripiprazole was not associated with an increase in fasting glucose or insulin.</p> <p>A pilot RCT¹¹ compared aripiprazole (n=7) to placebo (n=7) as an adjunct to an antidepressant for antidepressant resistant combat-related PTSD. Aripiprazole was not associated with a significant change in glucose.</p> <p>A systematic review¹ of 56 studies examined the use of atypical antipsychotics for anxiety disorders, trauma-related and somatoform disorders included two studies</p>	<p>50 (95% CI, 30-150).²⁷</p> <p>A retrospective cohort study (7167 admissions; time series analysis),²⁰ suggested by an expert for Key Question 1, of a large hospital in the UK between 2005 and 2011, examined the relationship between a SGA prescription for dementia and later diagnosis of cerebrovascular disease. No significant relationship was identified (OR 1.19, 95% CI 0.92 – 1.54, p= 0.18).</p>	

Conclusions from the Original Systematic Review Link to Report	Findings and Conclusions from Prior Surveillance Assessment (August 2014) Link to Report	Current Literature Search (Date)	Expert Opinion	Surveillance Assessment
		<p>reporting endocrine/diabetes related adverse events.</p> <ul style="list-style-type: none"> • The first study,¹⁶ an RCT (n=409), compared quetiapine XR to placebo as an adjunct to SNRI/SSRI for GAD. 3% of participants receiving quetiapine XR experienced a clinically relevant shift in fasting glucose, as compared to 5% receiving placebo. • The second study,¹⁵ was an RCT comparing quetiapine XR monotherapy (n=223) to placebo (n=227) in adults ≥66 years, and found no significant difference in fasting glucose or fasting glucose shifts between groups. <p>EPS An RCT¹³ (n=95) comparing low (150 mg/day; n=33) and moderate doses (300 mg/day; n=33) of quetiapine to placebo (n=29) found no significant differences in extrapyramidal symptoms over an</p>		

Conclusions from the Original Systematic Review Link to Report	Findings and Conclusions from Prior Surveillance Assessment (August 2014) Link to Report	Current Literature Search (Date)	Expert Opinion	Surveillance Assessment
		<p>11 week period.</p> <p>An RCT³ (n=181) compared the use of aripiprazole (n=91) to placebo (n=90) as augmentation to venlafaxine for treatment resistant MDD in adults 60 or older. There was a higher proportion of participants in the aripiprazole group patients with akathisia; however, akathisia was generally mild and transient. Aripiprazole was also associated with Parkinsonism and complaints of tremor.</p> <p>A pilot RCT¹¹ compared aripiprazole (n=7) to placebo (n=7) as an adjunct to an antidepressant for antidepressant resistant combat-related PTSD. Aripiprazole was not associated with treatment-emergent akathisia.</p> <p>An RCT⁴ (n=139) compared ziprasidone (n=71) to placebo (n=68) as an adjunct to escitalopram for MDD. Higher rates of self-reported treatment-emergent akathisia were</p>		

Conclusions from the Original Systematic Review Link to Report	Findings and Conclusions from Prior Surveillance Assessment (August 2014) Link to Report	Current Literature Search (Date)	Expert Opinion	Surveillance Assessment
		<p>associated with ziprasidone. Significantly more participants receiving ziprasidone reported muscle twitching (11.2% vs. 1.4%).</p> <p>In a retrospective cohort study¹⁴ (n=20) of individuals receiving aripiprazole for Tourette's syndrome 3/20 participants reported akathisia.</p> <p>A systematic review¹ of 56 studies examined the use of atypical antipsychotics for anxiety disorders, trauma-related and somatoform disorders included three studies reporting EPS related adverse events.</p> <ul style="list-style-type: none"> • The first study,¹⁶ an RCT (n=409), compared quetiapine XR to placebo as an adjunct to SNRI/SSRI for GAD. EPS related AEs were reported in 3.8% of the quetiapine XR group, and 2% in participants receiving placebo. • The second study,¹⁵ was an 		

Conclusions from the Original Systematic Review Link to Report	Findings and Conclusions from Prior Surveillance Assessment (August 2014) Link to Report	Current Literature Search (Date)	Expert Opinion	Surveillance Assessment
		<p>RCT comparing quetiapine XR monotherapy (n=223) to placebo (n=227) in adults ≥66 years, and found 5.4% of participants receiving quetiapine XR and 2.2% of those receiving placebo reported EPS related AEs.</p> <ul style="list-style-type: none"> The third study⁵ was a RCT comparing pill placebo (n=20), risperidone augmentation (n=40), and CBT consisting of exposure and ritual prevention (EX/RP; n=40) for OCD. One participant in the risperidone group, and one receiving placebo reported akathisia. <p>Tardive dyskinesia An RCT³ (n=181) compared the use of aripiprazole (n=91) to placebo (n=90) as augmentation to venlafaxine for treatment resistant MDD in adults 60 or older. There was no increased risk of Tardive dyskinesia associated with aripiprazole as compared to</p>		

Conclusions from the Original Systematic Review Link to Report	Findings and Conclusions from Prior Surveillance Assessment (August 2014) Link to Report	Current Literature Search (Date)	Expert Opinion	Surveillance Assessment
		<p>placebo over 24 weeks.</p> <p>Blood pressure An RCT¹³ found 150 mg/day of quetiapine to be associated with a significant decrease in systolic blood pressure; however, there was no significant difference as compared to placebo.</p> <p>Heart rate An RCT¹³ found 300 mg/day of quetiapine to be associated with a significant increase in heart rate; however, there was no significant difference as compared to placebo.</p> <p>Treatment-emergent suicidal ideation An RCT³ (n=181) compared the use of aripiprazole (n=91) to placebo (n=90) as augmentation to venlafaxine for treatment resistant MDD in adults 60 or older. There was no evidence of treatment-emergent suicidal ideation associated with aripiprazole.</p> <p>A systematic</p>		

Conclusions from the Original Systematic Review Link to Report	Findings and Conclusions from Prior Surveillance Assessment (August 2014) Link to Report	Current Literature Search (Date)	Expert Opinion	Surveillance Assessment
		<p>review¹ of 56 studies examined the use of atypical antipsychotics for anxiety disorders, trauma-related and somatoform disorders included one study reporting suicide related adverse events.</p> <ul style="list-style-type: none"> • The first study,¹⁶ an RCT (n=409), compared quetiapine XR to placebo as an adjunct to SNRI/SSRI for GAD. No suicide related adverse events were reported for either group. <p>Sexual Dysfunction</p> <p>A systematic review¹ of 56 studies examined the use of atypical antipsychotics for anxiety disorders, trauma-related and somatoform disorders included three studies reporting sexual dysfunction.</p> <ul style="list-style-type: none"> • The first study,¹⁶ an RCT (n=409), compared quetiapine XR to placebo as an adjunct to SNRI/SSRI for GAD. 2.9% of participants receiving quetiapine XR 		

Conclusions from the Original Systematic Review Link to Report	Findings and Conclusions from Prior Surveillance Assessment (August 2014) Link to Report	Current Literature Search (Date)	Expert Opinion	Surveillance Assessment
		<p>reported AEs related to sexual dysfunction. No sexual dysfunction related AEs were reported by participants receiving placebo.</p> <ul style="list-style-type: none"> • The second study,¹⁵ was an RCT comparing quetiapine XR monotherapy (n=223) to placebo (n=227) in adults ≥66 years. No participants reported sexual dysfunction. • The third study⁵ was a RCT comparing pill placebo (n=20), risperidone augmentation (n=40), and CBT consisting of exposure and ritual prevention (EX/RP; n=40) for OCD. 27% in the risperidone group, 16% in the CBT group, and 6% in the placebo group reported decreased libido. <p>Sleep-related A systematic¹ review of 56 studies examined the use of atypical antipsychotics for anxiety disorders, trauma-related and somatoform disorders included</p>		

Conclusions from the Original Systematic Review Link to Report	Findings and Conclusions from Prior Surveillance Assessment (August 2014) Link to Report	Current Literature Search (Date)	Expert Opinion	Surveillance Assessment
		<p>two studies reporting sleep related adverse events.</p> <ul style="list-style-type: none"> • The first study,¹⁶ an RCT (n=409), compared quetiapine XR to placebo as an adjunct to SNRI/SSRI for GAD. 7.2% of participants receiving quetiapine vs. 1.5% of participants receiving placebo reported insomnia. • The second study⁵ was a RCT comparing pill placebo (n=20), risperidone augmentation (n=40), and CBT consisting of exposure and ritual prevention (EX/RP; n=40) for OCD. 21% in the risperidone group, 13% in the CBT group, and 17% in the placebo group reported insomnia. <p>Somnolence A systematic review¹ of 56 studies examined the use of atypical antipsychotics for anxiety disorders, trauma-related and somatoform disorders included three studies</p>		

Conclusions from the Original Systematic Review Link to Report	Findings and Conclusions from Prior Surveillance Assessment (August 2014) Link to Report	Current Literature Search (Date)	Expert Opinion	Surveillance Assessment
		<p>reporting somnolence.</p> <ul style="list-style-type: none"> • The first study,¹⁶ an RCT (n=409), compared quetiapine XR to placebo as an adjunct to SNRI/SSRI for GAD. 25.5% of participants receiving quetiapine XR vs. 12% of participants receiving placebo reported somnolence. • The second study¹⁵ was an RCT comparing quetiapine XR monotherapy (n=223) to placebo (n=227) in adults ≥66 years, and found 26% of the quetiapine XR group and 8.4% of the placebo group reported somnolence. More participants >75 reported experiencing somnolence. • The third study⁵ was a RCT comparing pill placebo (n=20), risperidone augmentation (n=40), and CBT consisting of exposure and ritual prevention (EX/RP; n=40) for OCD. 21% in the risperidone group, 		

Conclusions from the Original Systematic Review Link to Report	Findings and Conclusions from Prior Surveillance Assessment (August 2014) Link to Report	Current Literature Search (Date)	Expert Opinion	Surveillance Assessment
		18% in the CBT group, and 22% in the placebo group reported somnolence.		

*Abbreviations:*ADHD= Attention Deficit Hyperactivity Disorder; AE= Adverse Events; CBT=Cognitive Behavioral Therapy; CI=Confidence Interval; EPS= Extrapyramidal Signs/Symptoms; EX/RP= Exposure and Ritual Prevention; GAD= General Anxiety Disorder; MDD= Major Depressive Disorder; NNH=Number Needed to Harm; PD=Parkinson’s Disease; PTSD= Post-Traumatic Stress Disorder; RCT= Randomized Controlled Trial; RR=Risk Ratio; SGA=Second Generation Antipsychotics; SNRI= Selective Norepinephrine Reuptake Inhibitor; SOE= Strength of Evidence; SSRI= Selective Serotonin Reuptake Inhibitor; UK=United Kingdom; VA=Veterans’ Affairs; VHA=Veteran’s Health Administration

Table 5. Key Question 5: What is the effective dose and time limit for off-label indications?

Conclusions from the Original Systematic Review Link to Report	Findings and Conclusions from Prior Surveillance Assessment (August 2014) Link to Report	Current Literature Search (Date)	Expert Opinion	Surveillance Assessment
SOE: Insufficient There are too few studies comparing doses of atypical antipsychotic medications to draw a conclusion about a minimum dose needed.	Assessment: Current One review reported effective doses for quetiapine for depression generalized anxiety disorder and no consistent effective dose for quetiapine for OCD treatment.	A RCT ¹³ (n=95) compared low (150 mg/day; n=33) and moderate doses (300 mg/day; n=33) of quetiapine to placebo (n=29) for borderline personality disorder and found that significant Zanarini scale total score improvement was associated with a low, but not a moderate dose of quetiapine, as compared to placebo, and a moderate, but not a low dose was associated with better YMRS and SCL-90-R general severity index (differences between doses were not significant). In	One expert believed the conclusions to be current. A second expert commented that the intention of the question in the original review was to present the results of dose-finding and time-limit studies, and not extrapolating from current studies that the study duration was appropriate timing. The expert suggested that the question be reworded for clarity. The third expert suggested two studies, ^{29,30} and stated that the original review conclusions may need adjustment based on these	The conclusions in this portion of the original systematic review are likely current. However new evidence is available. Dose: No studies examining quetiapine dose for borderline personality disorder or ziprasidone for MDD were included in the original review or prior assessment. We identified one study that found better outcomes associated with 150 mg/day of quetiapine vs 300 mg/day for borderline personality disorder, ¹³ and

Conclusions from the Original Systematic Review Link to Report	Findings and Conclusions from Prior Surveillance Assessment (August 2014) Link to Report	Current Literature Search (Date)	Expert Opinion	Surveillance Assessment
		<p>general, the low dose group “bested” the moderate dose group on outcomes related to efficacy (most group differences by dose were not reported). Compared to the low dose group, sedation, change in appetite, dry mouth, and dizziness were more common in the moderate dose group.</p> <p>A retrospective cohort study¹⁸ (n=977) examined the use of quetiapine as an adjunct to an antidepressant (most often paroxetine and venlafaxine for MDD. The mean treatment duration was approximately six months and the mean time to the first increase was approximately one week. The mean initial and maintenance doses of quetiapine were 23.6 and 40.7mg/day. The mean use of quetiapine was 150 days.</p> <p>A RCT⁴ (n=139) compared ziprasidone (n=71)</p>	<p>studies.</p> <p>One study,³⁰ which examined long-term risk of mortality in individuals with dementia (relevant to Key Question 4, rather than 5) was excluded because it did not stratify antipsychotics by generation.</p> <p>The second study²⁹ (open label/RCT; n=180) was phase A/B study of risperidone for individuals with Alzheimer’s disease and psychosis or agitation-aggression with a 16-week open label phase (phase A). Responders (n=110) were randomized to a) continue risperidone for 32 weeks, b) risperidone for 16 weeks, then placebo for 16 weeks, or c) placebo for 32 weeks. Phase B results indicated that in the first 16 weeks, there was an increased risk of relapse for individuals receiving placebo (group c; 60% vs</p>	<p>another study that found no significant difference in dose between the responders (96 mg) and remitters (96.9 mg).⁴</p> <p>Timing: No studies in the original review or prior surveillance examined timing for augmentation for OCD, or risperidone for Alzheimer’s disease. We identified one study²⁹ that found that of individuals who had responded to, then discontinued antipsychotic use for OCD, of the 15 participants receiving an atypical antipsychotic, 12 relapsed within four weeks, with one additional participant relapsing at week 50.³¹ Another study found that among individuals responding to risperidone for Alzheimer’s disease, then randomized to continuation or placebo, placebo was associated with an increased risk of relapse at</p>

Conclusions from the Original Systematic Review Link to Report	Findings and Conclusions from Prior Surveillance Assessment (August 2014) Link to Report	Current Literature Search (Date)	Expert Opinion	Surveillance Assessment
		<p>to placebo (n=68) as an adjunct to escitalopram for MDD. Mean daily doses of ziprasidone for responders and remitters were 96.0 mg (SD=32.6) and 96.9 mg (SD=32.3) respectively.</p> <p>A systematic review¹ of 56 studies examined the use of atypical antipsychotics for anxiety disorders, trauma-related and somatoform disorders. One study¹⁰ examining augmentation to SSRIs for treatment resistant OCD met inclusion criteria for this key question and was not included in a prior review or assessment. The study¹⁰ was a retrospective cohort study (n=18) of individuals receiving an antipsychotic, who had a significant reduction in Y-BOCS score (14/18 atypical) associated with augmentation to SRIs and discontinued antipsychotic use. Results indicated that of the 15 participants</p>	<p>33%; hazard ratio with placebo=1.94; 95% CI, 1.09 to 3.45; p=0.02). In the second 16 weeks, the individuals switched to placebo (group b) had a higher risk of relapse (hazard ratio with placebo= 4.88; 95% CI, 1.08 to 21.98; p=0.02; 48% vs 15%). There were no significant differences in adverse events among the three groups.²⁹</p>	<p>both 16 and 32 weeks.²⁹</p>

Conclusions from the Original Systematic Review Link to Report	Findings and Conclusions from Prior Surveillance Assessment (August 2014) Link to Report	Current Literature Search (Date)	Expert Opinion	Surveillance Assessment
		receiving an atypical antipsychotic, 12 relapsed within four weeks, with one additional participant relapsing at week 50.		

Abbreviations: CI=Confidence Interval; MDD= Major Depressive Disorder; OCD= Obsessive Compulsive Disorder; RCT= Randomized Controlled Trial; SCL-90-R= Symptom Checklist-90-Revised; SOE= Strength of Evidence; YMRS= Young Mania Rating Scale

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