

# *AHRQ Comparative Effectiveness Review Surveillance Program*

**CER #43:** Off-label use of atypical antipsychotics: an update

**Original Release Date:** September, 2011

**Surveillance Report:** August, 2014

## **Summary of Key Findings:**

- For Key Question 1, a new atypical antipsychotic and new off-label uses for previously examined antipsychotics were identified. Conclusions on new off-label uses of atypical antipsychotics are possibly out of date.
- For Key Questions 2-5 new studies were identified that may meet the inclusion criteria of the original review. Additionally, new off-label uses for previously examined atypical antipsychotics would likely increase the scope for these Key Questions. The original CER conclusions for these Key Questions are possibly out of date.

**Signal Assessment:** The signals examined in this surveillance assessment suggest that the original CER 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 EPC Program is to decide if the findings of a systematic review are current. Approximately 25 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.<sup>1</sup> The CER was selected for surveillance assessment based on popularity, potential impact, and other measures of use collected as of June, 2013.<sup>2</sup>

The key questions for the original CER 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 June, 2014. We conducted an updated electronic search for literature published since the original CER search date. After completing a scan of this literature to identify evidence potentially related to the key questions in this CER, we contacted experts involved in the original CER to request their opinions as to whether the conclusions had changed.

## Methods

### Literature Search

We conducted two literature searches of PubMed and PsycINFO covering January 1, 2011 to June 10, 2014, using the identical search strategy used for the original report<sup>1</sup> and searching for studies published since the end date of the original CER.

The search was conducted to assess the currency of conclusions. This process included selecting journals from among the top 10 journals from relevant specialty subject areas (Appendix A) and among those most highly represented among the references for the original report (Appendix B). The included journals were eight high-impact general medical interest journals (New England Journal of Medicine, Lancet, JAMA, PLOS Medicine, Annals of Internal Medicine, The BMJ, Archives of Internal Medicine and Cochrane Database of Systematic Reviews) and six specialty journals (American Journal of Psychiatry,

Neuropsychopharmacology, Journal of Clinical Psychiatry, Journal of Clinical Psychopharmacology, International Clinical Psychopharmacology, and Archives of General Psychiatry). The search strategy is reported in Appendix C.

## **Study Selection**

Using the same inclusion and exclusion criteria as the original CER (see Appendix D), one investigator reviewed the titles and abstracts of the 14 high-impact journal search results (Appendix E).

## **Expert Opinion**

We shared the conclusions of the original report and the newly identified studies with six experts in the field (original peer reviewers and a local expert) to request their assessment of the currency of report conclusions and their recommendations of any relevant new studies. Four subject matter experts responded to our request. Appendix F shows the form that the experts were asked to complete. Note that systematic reviews were added to the type of included study designs after summaries were shared with expert reviewers. Consequently, expert reviewers did not receive information on the ten systematic reviews<sup>44-53</sup> meeting inclusion criteria.

## **Horizon Scanning**

The AHRQ Healthcare Horizon Scanning System identifies emerging health care technologies and innovations with the potential to impact health care for AHRQ's 14 priority conditions.<sup>3</sup> We reviewed the Depression and Other Mental Health Disorders section to identify new potentially high-impact interventions<sup>4</sup> related to the key questions in this CER. Potentially high impact interventions were considered in the final assessment.

## **FDA Black Box Warnings**

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

## **Check for Qualitative Signals**

The authors of the original CER conducted qualitative and quantitative analysis of off-label use of atypical antipsychotics. We compared the conclusions of the included abstracts to the conclusions of the original CER and assessed expert opinions to identify qualitative signals about the currency of conclusions.

## **Compilation of Findings and Conclusions**

For this assessment we constructed a summary table (Appendix G) that includes the key questions, the conclusions from the original CER, findings of the new literature search, and expert assessments that pertained to each key question. Because we did not find any FDA black box warnings relevant to the key questions in this CER, we did not include a column for this in the summary table. We categorized whether the currency of conclusions using a 3-category scheme:

- Original conclusion is still valid and this portion of the CER is likely current.

- Original conclusion is possibly out of date and this portion of the CER 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 CER conclusion as still valid, we classified the CER conclusion as likely not out of date.
- If we found some new evidence that might change the CER conclusion, and/or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly out of date.
- If we found new evidence that rendered the CER conclusion out of date or no longer applicable, we classified the CER 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 CER**

We used the following considerations in our assessment of the currency of the CER:

- **Strong signal:** A report is considered to have a strong signal if new evidence is identified that clearly renders conclusions from the original report 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 report. This may occur when abstract review and expert assessment indicates that some conclusions from the original report may be out of date, or when it is unclear from abstract review how new evidence may impact the findings from the original report. In this case, full-text review and data abstraction may be needed to more clearly classify a signal.
- **Weak signal:** A report is considered to have a weak signal if little or no new evidence is identified that would change the conclusions from the original report. This may occur when little to 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 report.

## **Results**

### **Literature Search**

The literature search identified a total of 667 unique titles from the 14 selected high profile general medical and specialty journals. A random selection of 200 articles from the 14 selected high profile general medical and specialty journals is provided in Appendix E. Upon abstract review, 624 articles were rejected because they did not meet the original CER inclusion criteria (see Appendix D).

### **Horizon Scanning**

None of the interventions in the horizon scanning report for Priority Area 05: Depression and Other Mental Health Disorders overlapped with the key questions in the original CER. Thus, we did not identify new interventions with high-impact potential for this report.

## **FDA Black Box Warnings**

We did not find any FDA boxed warnings relevant to the key questions in this CER.

## **Expert Opinion**

We shared the conclusions of the original report with six experts in the field (original peer reviewers and a local expert) to request their assessment of the currency of report conclusions and their recommendations of any relevant new studies. Four subject matter experts responded. The four experts were in agreement that most of the conclusions in the original report were up to date. The experts identified potentially relevant studies for Key Questions 1 and 2<sup>37-42</sup> and agreed that the conclusions from Key Questions 3-5 were still valid (see Appendix G).

## **Identifying Qualitative Signals**

Appendix G shows the original key questions, the conclusions of the original report, the results of the literature search, the experts' assessments, and the conclusions of the Scientific Resource Center (SRC) regarding the currency of the CER.

For Key Question 1, a newer atypical antipsychotic, lurasidone, has been approved for schizophrenia and bipolar disorder and was not included in the original CER. Additionally, a few new studies were identified which may meet the inclusion criteria for the original review. Three studies were identified which examined utilization trends<sup>6,9,16</sup>, but no studies examined trends after 2007. We identified four studies examining new off-label uses for the treatment of Huntington's disease, trichotillomania, somatoform disorder, and fibromyalgia.<sup>11,14,26,34</sup> In addition, one expert suggested adding delirium as an off-label use investigated for ziprasidone.<sup>39</sup> Because the original review inclusion criteria were used, these studies were not included as evidence for Key Questions 2-5. We identified one study<sup>21</sup> examining off-label use of asenapine for borderline personality disorder. Off-label use for personality disorders were eligible for inclusion in the original report; however, no off-label uses specific to borderline personality disorder were included in the original CER.<sup>21</sup>

For Key Questions 2 and 4, several new studies<sup>4,5,7,8,10,12,13,15,17-25,27-33,35,36,44-53</sup> were identified which may meet the inclusion criteria for the original CER. However, the new evidence is unlikely to change the conclusions of the original review. One new review was identified for Key Question 3<sup>53</sup> and another for Key Question 5<sup>52</sup>; however, the new evidence is unlikely to change the conclusions of the original CER. While we did not include the identified studies examining newly identified off-label uses<sup>11,14,26,34</sup> for Key Questions 2-5, these studies do provide data for at least one of these key questions, and would likely increase the scope from that of the original CER.

## **Signal Assessment**

In general, the vast majority of the new studies we identified reflected the conclusions of the original CER. A new atypical antipsychotic, lurasidone, has been approved for treatment of schizophrenia and bipolar depression since the original CER was published. Additionally, new off-label use for the treatment of Huntington's disease, trichotillomania, somatoform disorder, delirium, and fibromyalgia for several other atypical antipsychotics have been investigated. We did not identify evidence of off-label use of lurasidone. There was no high-impact potential for this report based on horizon scanning data and no FDA boxed warnings were identified since the original report was published.

The SRC conclusions based on literature published since the original report, FDA boxed warnings, horizon scanning, and expert assessment is that:

- For Key Question 1, a new atypical antipsychotic and new off-label uses for previously examined antipsychotics were identified. Conclusions on new off-label uses of atypical antipsychotics are possibly out of date.
- For Key Questions 2-5 new studies were identified that may meet the inclusion criteria of the original review. Additionally, newly identified off-label use for previously examined atypical antipsychotics would likely increase the scope for these Key Questions. The original CER conclusions for these Key Questions are possibly out of date.

The signal for this report is medium, suggesting that the conclusions in the original CER are possibly out of date.

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# **Appendices**

**Appendix A: Top 10 Journals**

**Appendix B: Most Cited Journals from Original Systematic Review**

**Appendix C: Exact Search Strings**

**Appendix D: Inclusion and Exclusion Criteria from Original Systematic Review**

**Appendix E: Literature Search Results**

**Appendix F: Questionnaire Sent to Expert Reviewers**

**Appendix G: Summary Table**

## Appendix A. Top 10 Journals

In the Journal Citation Reports database, the science and social science sections were searched by subject area discipline(s) for each surveillance reports topic area. For each subject area discipline, the list was constructed by selecting the top 10 journals from the 5 year citation impact factor average list. Selected citations were downloaded in .csv format.

### **Behavioral Sciences:**

1. Behavioral & Brain Sciences
2. Trends in Cognitive Sciences
3. Neuroscience & Biobehavioral Reviews
4. Advances in the Study of Behavior
5. Cognitive, Affective, & Behavioral Neuroscience
6. Frontiers in Behavioral Neuroscience
7. Cortex
8. Autism Research
9. Neuropsychologia
10. Biological Psychology

### **Psychology:**

1. Annual Review of Psychology
2. Psychological Bulletin
3. Annual Review of Clinical Psychology
4. Psychological Review
5. Social Cognitive and Affective Neuroscience
6. Journal of Child Psychology and Psychiatry
7. Psychological Medicine
8. Psychotherapy and Psychosomatics
9. Cognitive Psychology
10. Health Psychology

### **Psychiatry:**

1. Archives of Gen Psychiatry
2. The American Journal of Psychiatry
3. Molecular Psychiatry
4. Biological Psychiatry
5. Schizophrenia Bulletin
6. Neuropsychopharmacology
7. Journal of the American Academy of Child Psychiatry
8. The British Journal of Psychiatry
9. Journal of Psychiatry & Neuroscience
10. World Psychiatry

### **Top 10 General Medical:**

1. New England Journal of Medicine
2. Lancet
3. Journal of the American Medical Association
4. PLoS Medicine
5. Annals of Internal Medicine
6. British Medical Journal
7. Archives of Internal Medicine
8. Canadian Medical Association Journal
9. Cochrane Database of Systematic Reviews
10. BMC Medicine

## Appendix B. Most Cited Journals from Original Systematic Review

Journal	Citations
Journal of Clinical Psychiatry	39
Journal of Clinical Psychopharmacology	13
American Journal of Psychiatry	12
International Clinical Psychopharmacology	12
The American Journal of Geriatric Psychiatry	9
International Journal of Geriatric Psychiatry	7
European Neuropsychopharmacology	6
Neuropsychopharmacology	6
Psychiatric Services	6
Archives of General Psychiatry	5
Biological Psychiatry	5
The BMJ	5
Current Medical Research and Opinion	5
International Journal of Neuropsychopharmacology	5
Psychopharmacology	5
Canadian Journal of Psychiatry	4
Canadian Medical Association Journal	4
Cochrane Database of Systematic Reviews	4
Journal of Psychopharmacology	4
The American Journal on Addictions	3
Archives of Internal Medicine	3
BMC Psychiatry	3
European Neuropsychopharmacology	3
International Journal of Geriatric Psychiatry	3
Progress in Neuro-Psychopharmacology & Biological Psychiatry	3

## Appendix C. Original Search Strategy

### Top Journals used for surveillance of this topic:

- The American journal of psychiatry
- Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology
- The New England journal of medicine
- Lancet
- JAMA
- PLOS Medicine
- Annals of internal medicine
- BMJ
- Archives of internal medicine
- Cochrane database of systematic reviews
- Journal of clinical Psychiatry
- Journal of clinical psychopharmacology
- International clinical psychopharmacology
- Archives of general psychiatry

Run 06/10/2014

Medline via PubMed Searched June 10<sup>th</sup> 2014 Rose Relevo

Original Search String : <b>Drug Utilization</b>	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 Publication date from 2011/01/01 <b>Results=12</b>

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 Publication date from 2011/01/01 <b>Results=22</b>

Original Search String : <b>Autism</b>	“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 psychopharmacology"[Journal]) OR "Archives of general psychiatry"[Journal])) OR "International clinical psychopharmacology"[Journal]
Date Limits	AND Publication date from 2011/01/01 <b>Results=5</b>

Original Search String : <b>ADHD</b>	“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 psychopharmacology"[Journal]) OR "Archives of general psychiatry"[Journal])) OR "International clinical psychopharmacology"[Journal]

	"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 Publication date from 2011/01/01 <b>Results=4</b>

Original Search String : <b>Eating Disorders</b>	"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 psychopharmacology"[Journal]) OR "Archives of general psychiatry"[Journal])) OR "International clinical psychopharmacology"[Journal]
Date Limits	AND Publication date from 2011/01/01 <b>Results=3</b>

Original Search String : <b>Tourette Syndrome</b>	"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 Publication date from 2011/01/01 <b>Results=4</b>

Original Search String : <b>Substance</b>	"Antipsychotic Agents"[MeSH] OR "Antipsychotic Agents"[Pharmacological Action] OR aripiprazole OR olanzapine OR quetiapine OR risperidone OR ziprasidone) AND
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<b>Abuse</b>	substance abuse* OR drug abuse* OR alcohol abuse OR addict* OR drug dependen* OR cocaine OR heroin OR "Substance-Related Disorders"[Mesh]
<b>Journal Limits</b>	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]
<b>Date Limits</b>	AND Publication date from 2011/01/01 <b>Results=34</b>

<b>Original Search String : Personality Disorders</b>	"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, 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]
<b>Journal Limits</b>	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]
<b>Date Limits</b>	AND Publication date from 2011/01/01 <b>Results=97</b>

<b>Original Search String : Anxiety</b>	"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]
<b>Journal</b>	AND

Limits	((((("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 Publication date from 2011/01/01 <b>Results=551</b>

**When the results from each individual search are combined and de-duplicated, there are a total of 667 citations for review.**

## **Appendix D. 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 6 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:		5. Was a placebo used in this study?	<b>Circle one</b>
Citation:		Yes	1
1. Research topic (s):	<b>Check all that apply</b>	No	2
Aripiprazole		6. Total sample size entering study. If not reported then total completing sample size:	
Asenapine		<b>Enter # or 999 if no sample reported</b>	
Iloperidone		7. Does article report on the following:	<b>Check all that apply</b>
Olanzapine		Efficacy	
Quetiapine		Safety / Adverse events	
Paliperidone		Utilization / Prescribing patterns	
Risperidone		None of the above (STOP)	
Ziprasidone		8. Total duration of study:	
Entire class		<b>For Duration enter # or 999 if not reported.</b>	
None of the above (STOP)		<b>For Units enter code from below.</b>	
2. Condition(s) studied:	<b>Check all that apply</b>	_____	_____
Anxiety		<b>Duration</b>	<b>Units</b>
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)			
3. Study population:	<b>Circle one</b>	9. Language of article:	<b>Circle one</b>
Human included	1	English	1
Only animal or cell lines	2 (STOP)	Other	2
4. Study design:	<b>Circle one</b>	Specify: _____	
Descriptive (historical, editorial etc.)	1 (STOP)	10. Do you think that this article might be a duplicate or include the same data as another study?	<b>Circle one</b>
Non-systematic review	2 (STOP)	No	1
Systematic review / meta-analysis	3 (STOP)	Yes	2
Case report	4 (STOP)	If YES, ID#: _____	
Case series	5	11. Do you think that this article might be part of a large or named trial?	<b>Circle one</b>
Cohort	6	No	1
Case control	7	Yes	2
RCT <i>only</i>	8	If YES, trial name: _____	
CCT <i>only</i>	9	12. Is there a reference that needs to be ordered?	<b>Circle one</b>
Trial + Open label extension	10	No	1
Other design	11	Yes	2
		If YES, Ref #: _____	
		NOTES:	

Original inclusion/exclusion criteria extracted from Effective Health Care Program, CER #43, *Off-Label Use of Atypical Antipsychotics: An Update*, p. B-1

## Appendix E. Literature Search Results

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## Appendix F. Questionnaire Sent to Expert Reviewers

# *AHRQ Comparative Effectiveness Review Surveillance Program*

## Reviewer Form

**Title of Original Review:** Off-Label Use of Atypical Antipsychotics: An Update (2011)

[Link to Report](#)

**Name of Reviewer:** \_\_\_\_\_

### **Instructions:**

The AHRQ Scientific Resource Center (SRC) periodically conducts surveillance of published AHRQ reviews to assist with prioritization of reports for updating. One part of this process includes soliciting expert review of our synthesis of recently published literature and FDA black box warnings.

The attached document includes a table highlighting the conclusions from the original report and our synthesis of the recently published literature. Abstracts from relevant literature are included at the end of the attached document. If you would like a list of our full search results, please let us know.

Please review the table in the attached document and provide responses to the questions for each key question below. The primary goal of this review is to identify any missing studies and ensure the accuracy of our synthesis of the recently published literature.

## 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?

### SRC Literature Analysis:

- No new studies examined utilization trends after 2007. Four studies examined new off-label uses for previously approved atypicals. See attached table for details.

### 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 2:

What does the evidence show regarding the efficacy and comparative effectiveness 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?

### SRC Literature Analysis:

- New studies reported efficacy of atypicals for treatment of dementia, depression, obsessive-compulsive disorder, post-traumatic stress disorder, personality disorders, Tourette 's syndrome, anxiety and insomnia. No new research was found for attention deficit/hyperactivity disorder, eating disorders or substance abuse. See attached table for details.

### 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?

#### SRC Literature Analysis:

- No new research was found.

#### 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?

#### SRC Literature Analysis:

- New studies reported adverse events for atypical antipsychotics including weight gain, endocrine/diabetes, mortality, and venous thromboembolism. No new studies reported on extrapyramidal symptoms or tardive dyskinesia. See table for details.

#### 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 5:

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

#### SRC Literature Analysis:

- No new research was found.

**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.

## Original Review Conclusions and Literature Analysis

**Title of Original Review:** Off-Label Use of Atypical Antipsychotics: An Update (2011)

[Link to Report](#)

The conclusions from the original report and an analysis of recent literature identified by the Scientific Resource Center (SRC) are summarized below. Abstracts are provided for included literature at the end of the document.

Conclusions From Original Review (SOE = Strength of Evidence)	SRC Literature Analysis
<b>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?</b>	
<p><b>Leading off-label uses of atypical antipsychotics:</b> 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><b>Utilization trends:</b> 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.</p> <p><b>New uses:</b> No off-label use of the newly approved atypicals (asenapine, iloperidone, and paliperidone) was reported in the utilization literature.</p>	<p><b>Leading off-label uses of atypical antipsychotics:</b> No new research was found.</p> <p><b>Utilization trends:</b> Three studies examined utilization trends (Comer et al. 2011, Kales et al. 2011, Fullerton et al. 2011). No studies examined trends after 2007.</p> <p><b>New uses:</b> Four studies (Potvin et al. 2012, Johnston 2011, White 2011, Huang et al. 2012) examined new off-label uses for previously approved atypicals (risperidone, aripiprazole, paliperidone and quetiapine): Huntington’s disease, trichotillomania, somatoform disorder, and fibromyalgia.</p> <p>One study examined off-label use of asenapine for personality disorder (Martin-Blanco 2014).</p> <p>No off-label use of the newly approved atypical (lurasidone) was reported.</p>
<b>Key Question 2: What does the evidence show regarding the efficacy and comparative effectiveness of atypical antipsychotics for off-label indications?</b>	
<p><b>Dementia (SOE High)</b> Aripiprazole, olanzapine, and risperidone have efficacy as treatment for behavioral symptoms of dementia.</p>	<p>Two randomized trials (Teranishi et al. 2013, Devanand et al. 2012) 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 (Vigen et al. 2011).</p>

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<p><b>Depression – MDD: Augmentation of SSRI/SNRI (SOE Moderate - Risperidone, aripiprazole, quetiapine; SOE Low – olanzapine, ziprasidone)</b> Aripiprazole, quetiapine, and risperidone have efficacy as augmentation to SSRIs/SNRIs for major depressive disorder. Olanzapine and ziprasidone may also have efficacy.</p> <p><b>Depression – MDD: Monotherapy (SOE Moderate)</b> Olanzapine does not have efficacy as monotherapy for major depressive disorder. Quetiapine has efficacy as monotherapy for major depressive disorder.</p>	<p><b>Depression- MDD: Augmentation of SSRI/SNRI:</b> No new research was found.</p> <p><b>Depression- MDD: Monotherapy</b> Four studies (2 pooled analyses of RCTs (Thase et al. 2013, Weisler et al. 2012), 1 post-hoc analysis of RCT (Montgomery et al. 2014), 1 RCT (Sheehan et al. 2012)) reported efficacy of quetiapine for MDD. One RCT reported potential efficacy of ziprasidone for MDD (Jeon et al. 2014).</p>
<p><b>Obsessive-compulsive disorder: augmentation of SSRI (SOE Moderate – risperidone; SOE Low – olanzapine)</b> 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><b>Obsessive-compulsive disorder: augmentation of citalopram (SOE Low – quetiapine; SOE Very Low – risperidone)</b> Quetiapine and risperidone may be efficacious as augmentation to citalopram in OCD patients.</p>	<p><b>Obsessive-compulsive disorder: augmentation of SSRI:</b> One RCT (Diniz et al. 2011) reported quetiapine-fluoxetine is inefficacious in improving OCD symptoms compared to fluoxetine-clomipramine or fluoxetine-placebo. One RCT (Muscatello et al. 2011) reported efficacy of aripiprazole in improving OCD symptoms as an adjunct to SSRIs.</p> <p><b>Obsessive-compulsive disorder: augmentation of citalopram:</b> No new research was found.</p>
<p><b>Post-traumatic stress disorder (SOE Moderate – risperidone; SOE Low – olanzapine; SOE Very Low - quetiapine)</b> Risperidone is efficacious in reducing combat-related PTSD symptoms when used as an adjunct to primary medication.</p>	<p>One pilot study (Youssef et al. 2012) reported efficacy of aripiprazole in improving PTSD symptoms. One randomized trial (Krystal et al. 2011) reported efficacy of risperidone as an adjunct to SSRIs.</p>
<p><b>Personality disorders: borderline (SOE Low – aripiprazole; SOE Very Low – quetiapine, olanzapine)</b> Olanzapine had mixed results in 7 trials, aripiprazole was found efficacious in 2 trials, quetiapine was found efficacious in 1 trial, and ziprasidone was found not efficacious in 1 trial.</p> <p><b>Personality disorders: schizotypal (SOE Low)</b> Risperidone had mixed results when used to treat schizotypal personality</p>	<p><b>Personality disorders: borderline:</b> One non-randomized trial reported efficacy of olanzapine (Zanarini et al. 2012). One case-series reported improved symptoms with asenapine treatment (Martin-Blanco 2014).</p> <p><b>Personality disorders: schizotypal:</b> No new research was found.</p>

<b>Conclusions From Original Review (SOE = Strength of Evidence)</b>	<b>SRC Literature Analysis</b>
disorder in 2 small trials.	
<b>Tourette’s Syndrome (SOE Low)</b> Risperidone is at least efficacious as pimozone or clonidine for Tourette’s Syndrome.	One case-series reported improvement in Tourette’s Syndrome symptoms with aripiprazole treatment (Wenzel et al. 2012).
<b>Anxiety (SOE Moderate)</b> Quetiapine has efficacy as treatment for Generalized Anxiety Disorder.	Five studies (1 pooled analysis of 3 RCTs (Montgomery et al. 2014), 4 RCTs (Altamura et al. 2011, Merideth et al. 2012, Katzman et al. 2011, Khan et al. 2011)) reported efficacy of quetiapine as treatment for Generalized Anxiety Disorder.
<b>Attention deficit/hyperactivity disorder: no co-occurring disorders (SOE Low)</b> Risperidone may be efficacious in treating children with ADHD with no serious co-occurring disorders.  <b>Attention deficit/hyperactivity disorder: mentally retarded children (SOE Low)</b> Risperidone may be superior to methylphenidate in treating ADHD symptoms in mentally retarded children.  <b>Attention deficit/hyperactivity disorder: bipolar children (SOE Low)</b> Aripiprazole is inefficacious in reducing ADHD symptoms in children with bipolar disorder.	No new research was found.
<b>Eating disorders (SOE Moderate – olanzapine; SOE Low – quetiapine)</b> Olanzapine and quetiapine have no efficacy in increasing body mass in eating disorder patients.	No new research was found.
<b>Insomnia (SOE Very Low)</b> Quetiapine may be inefficacious in treating insomnia.	One non-randomized pilot study reported potential efficacy of quetiapine for sleep continuity (Chakravorty et al. 2014).
<b>Substance abuse: alcohol (SOE Moderate – aripiprazole; SOE Low – quetiapine)</b> Aripiprazole is inefficacious in treating alcohol abuse/ dependence. Quetiapine may also be inefficacious.  <b>Substance abuse: cocaine (SOE Low)</b> Olanzapine is inefficacious in treating cocaine abuse/dependence.	No new research was found.

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<p>Risperidone may also be inefficacious.</p> <p><b>Substance abuse: methamphetamine (SOE Low)</b> Aripiprazole is inefficacious in treating methamphetamine abuse/dependence.</p> <p><b>Substance abuse: methadone clients (SOE Low)</b> Risperidone is an inefficacious adjunct to methadone maintenance.</p>	
<p><b>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?</b></p>	
<p>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>No new research was found.</p>
<p><b>Key Question 4: What are the potential adverse effects and/or complications involved with off-label prescribing of atypical antipsychotics? How to they compare within the class and with other drugs used for the conditions?</b></p>	
<p><b>Weight gain</b> Olanzapine is associated with more weight gain than placebo, conventional antipsychotics, or other atypical antipsychotics. (SOE High) Some evidence for other atypical antipsychotics. Risperidone, quetiapine and aripiprazole are associated with more weight gain compared with placebo.</p> <p><b>Endocrine/diabetes (SOE Low)</b> Olanzapine is associated with higher risk of diabetes than risperidone.</p> <p><b>Mortality</b> Atypical antipsychotics are associated with increased risk of death in elderly patients compared with placebo. (SOE High) Conventional antipsychotics are associated with higher rate of death compared with atypical antipsychotics. (SOE Moderate)</p>	<p><b>Weight gain</b> One randomized trial reported weight gain more common with risperidone compared to placebo (Krystal et al. 2011).</p> <p><b>Endocrine/diabetes</b> One RCT reported worsening glucose metabolism factors with olanzapine compared to placebo in healthy controls (Hahn et al. 2013).</p> <p><b>Mortality:</b> Two cohort studies reported increased risk of death with haloperidol treatment compared to risperidone (Kales et al. 2013, Huybrechts et al. 2012). One cohort study reported no association between antipsychotic use and death after adjustment for psychiatric symptoms (Lopez et al. 2013).</p> <p><b>EPS</b> No new research was found.</p>

<b>Conclusions From Original Review (SOE = Strength of Evidence)</b>	<b>SRC Literature Analysis</b>
<p><b>EPS (SOE Moderate)</b> Aripiprazole and risperidone are associated with an increase in extrapyramidal signs or symptoms compared to quetiapine.</p> <p><b>Tardive dyskinesia (SOE Low)</b> Atypical antipsychotics are associated with less tardive dyskinesia than are high doses of haloperidol.</p>	<p><b>Tardive dyskinesia</b> No new research was found.</p> <p><b>Venous thromboembolism:</b> One case-control study reported increased risk of venous thromboembolism in new users of antipsychotics compared to nonusers (Schmedt et al. 2013).</p>
<b>Key Question 5: What is the effective dose and time limit for off-label indications?</b>	
<p>There are too few studies comparing doses of atypical antipsychotic medications to draw a conclusion about a minimum dose needed.</p>	<p>No new research was found.</p>

Legend: ADHD = attention deficit hyperactivity disorder; OCD = obsessive compulsive disorder; PTSD = post-traumatic stress disorder; MDD = major depressive disorder; EPS = extrapyramidal symptoms

## Abstracts from Relevant Literature

*Ahearn, E.P. Juergens, T. Cordes, T. Becker, T. and Krahn, D.*

*A review of atypical antipsychotic medications for posttraumatic stress disorder.*

Posttraumatic stress disorder (PTSD) can be a chronic and disabling illness with a limited response to antidepressant treatment, particularly in the case of combat-induced PTSD. The purpose of this study is to review randomized controlled and open-label trials of atypical antipsychotics for the treatment of PTSD. We conducted PUBMED and PILOTS database searches for clinical trials of atypical antipsychotic medications for PTSD in May 2010. Eighteen clinical trials (10 double-blind placebo-controlled, eight open-label) of atypical antipsychotics for PTSD were found and reviewed. Effect sizes of double-blind placebo-controlled trials were small, but were positive for risperidone and quetiapine. Intrusive and hypervigilance symptom subscales showed the most improvement. We concluded that atypical antipsychotic medications have a modest benefit for the treatment of PTSD. Larger randomized controlled trials are needed to clarify the potential utility of these medications in the treatment of PTSD and more rigorous examination of metabolic side effects is warranted.

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*Altamura, A.C. Serati, M. Buoli, M. and Dell'osso, B. 2011.*

*Augmentative quetiapine in partial/nonresponders with generalized anxiety disorder: a randomized, placebo-controlled study.*

Generalized anxiety disorder (GAD) is a chronic and disabling condition. The aim of this study was to evaluate the effectiveness of low-dose augmentative quetiapine (mean dose=50 mg/day) in patients with GAD and partial/no response to selective serotonin reuptake inhibitors (SSRIs). Twenty patients with GAD and partial/no response to SSRIs were randomized to quetiapine (n=10) or placebo (n=10) for 8 weeks, continuing their treatment with SSRIs. Analyses of variance with repeated measures on Hamilton Anxiety Rating Scale (HAM-A) and Clinical Global Impression (CGIs; severity of illness) were carried out at baseline and after 8 weeks and the number of responders/remitters was computed and compared between the groups. HAM-A scores at baseline were 15.60 (+/- 4.48) in the placebo group and 18.50 (+/- 6.59) in the quetiapine group, and at the end-point, HAM-A scores in the placebo group were 10.40 (+/- 4.88) and 9.20 (+/- 5.86) in the quetiapine group. A significant time-by-treatment effect was found on the HAM-A ( $F=5.19$ ,  $P=0.035$ ) and CGIs scores ( $F=19.60$ ,  $P<0.001$ ) in favor of the quetiapine group. The number of responders was numerically superior in the quetiapine group (60 vs. 30%) without reaching statistical significance ( $\chi^2=1.82$ , degree of freedom=1,  $P=0.37$ ,  $\phi=0.30$ ). Remitters were 40% for the quetiapine group versus 20% for the placebo group ( $\chi^2=0.95$ , degree of freedom=1,  $P=0.63$ ,  $\phi=0.22$ ). Low-dose augmentative quetiapine may be an useful treatment option for patients with GAD and partial/no response to SSRIs. The lack of double-blind conditions and the limited sample size may limit the confidence in the reported results. Larger randomized controlled trials are warranted to confirm these data.

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Carey, P.D. Lochner, C. Kidd, M. Van Ameringen, M. Stein D.J. and Denys, D. 2012.

*Quetiapine augmentation of serotonin reuptake inhibitors in treatment-refractory obsessive-compulsive disorder: Is response to treatment predictable?*

Several studies have examined the predictors of treatment response in obsessive-compulsive disorder (OCD). Only limited information is available on the predictors of response to antipsychotic augmentation of serotonin reuptake inhibitors (SRIs). Data from placebo-controlled studies of augmentation with quetiapine were combined in a best subsets logistic regression to derive a predictive model for Yale-Brown obsessive-compulsive scale (YBOCS) change and the YBOCS endpoint. Data from the YBOCS checklist and a variety of clinical and demographic variables previously shown to predict treatment outcome in OCD were analysed. In univariate analyses, the failure of fewer previous SRI trials was associated with the YBOCS response. In the multivariate model, for YBOCS change, 45% of the variance was attributed to the fact that patients had failed fewer previous SRI treatments, had higher baseline obsession scores, and ordering and arranging compulsions. For the YBOCS endpoint scores, 50% of the variance was attributed to the fact that patients had fewer failed SRI trials, higher baseline compulsion scores, and counting/ordering and arranging compulsions. These data indicate a number of predictors of response to augmentation of SRIs in treatment-refractory OCD. These include fewer previously failed SRI trials and generally higher overall baseline scores for obsessions and compulsions as well as counting/ordering and arranging compulsions. Other factors are, however, also likely to play an important role in predicting outcome.

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Chakravorty, S., Hanlon, A. L., Kuna, S. T., Ross, R. J., Kampman, K. M., Witte, L. M., Perlis, M. L. and Oslin, D. W. 2014.

*The effects of quetiapine on sleep in recovering alcohol-dependent subjects: a pilot study.*

**OBJECTIVE:** The aim of this hypothesis-generating pilot study was to assess prospectively the objective and subjective effects of treatment with quetiapine XR on sleep during early recovery from alcohol dependence (AD). **METHODS:** Recovering subjects with AD and sleep disturbance complaints were treated with quetiapine XR (n = 10) or matching placebo pills (n = 10) for 8 weeks. Polysomnography was used to assess sleep objectively, and the Insomnia Severity Index and Pittsburgh Sleep Quality Index were used to measure subjective insomnia. Other assessment measures included the 10-minute psychomotor vigilance task (for neurobehavioral functioning), the time-line follow-back measure (for alcohol consumption), the Penn Alcohol Craving Scale (for alcohol craving), the Patient Health Questionnaire-9 item scale (for depressive symptoms), and the Beck Anxiety Inventory (for anxiety symptoms). **RESULTS:** Although there was no effect of quetiapine XR on sleep efficiency (time spent asleep/total recording time), there was a pre-to-post reduction in wake after sleep onset time (P = 0.03) and nonsignificant trends for increases in sleep onset latency (SOL) and stage 2 sleep time. A time x drug interaction was seen for the subjective insomnia, such that quetiapine XR-treated

subjects reported greater initial improvement in their subjective insomnia, but the difference was not sustained. There were no differences between treatment groups on other measures or medication compliance. CONCLUSION: Quetiapine XR improves objective sleep continuity and transiently improves subjective insomnia early in recovery from AD.

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*Comer, J.S. Mojtabai, R. and Olfson, M. 2011*

*National trends in antipsychotic treatment of psychiatric outpatients with anxiety disorders.*

OBJECTIVE: The purpose of the present study was to examine patterns and recent trends in the antipsychotic medication treatment of anxiety disorders among visits to office-based psychiatrists in the United States. METHOD: Annual data from the 1996-2007 National Ambulatory Medical Care Survey were analyzed to examine the patterns and trends in antipsychotic medication treatment within a nationally representative sample of 4,166 visits to office-based psychiatrists in which an anxiety disorder was diagnosed. RESULTS: Across the 12-year period, antipsychotic prescriptions in visits for anxiety disorders increased from 10.6% (1996-1999) to 21.3% (2004-2007). Over the study period, the largest increase in antipsychotic prescribing occurred among new patient visits. Antipsychotic prescribing also significantly increased among privately insured visits and visits in which neither antidepressants nor sedative/hypnotics were prescribed. Among the common anxiety disorder diagnoses, the largest increase in antipsychotic medication treatment was observed in visits for panic disorder. Antipsychotic prescribing rose from 6.9% (1996-1999) to 14.5% (2004-2007) among visits for anxiety disorders in which there were no co-occurring diagnoses with an indication approved by the Food and Drug Administration for antipsychotic medications. CONCLUSIONS: Although little is known about their effectiveness for anxiety disorders, antipsychotic medications are becoming increasingly prescribed to psychiatric outpatients with these disorders.

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*Devanand, D. P., Mintzer, J., Schultz, S. K., Andrews, H. F., Sultzer, D. L., De La Pena, D., Gupta, S., Colon, S., Schimming, C., Pelton, G. H. and Levin, B. 2012.*

*Relapse risk after discontinuation of risperidone in Alzheimer's disease.*

BACKGROUND: Among patients with Alzheimer's disease who have had a response to antipsychotic medication for psychosis or agitation-aggression, the risk of a recurrence of symptoms after discontinuation of the medication has not been established. METHODS: Patients with Alzheimer's disease and psychosis or agitation-aggression received open-label treatment with risperidone for 16 weeks. Those who had a response to risperidone therapy were then randomly assigned, in a double-blind fashion, to one of three regimens: continued risperidone therapy for 32 weeks (group 1), risperidone therapy for 16 weeks followed by placebo for 16 weeks (group 2), or placebo for 32 weeks (group 3). The primary outcome was the time to relapse of psychosis or agitation. RESULTS: A total of 180 patients received open-label risperidone (mean dose, 0.97 mg

daily). The severity of psychosis and agitation were reduced, although there was a mild increase in extrapyramidal signs; 112 patients met the criteria for response to treatment, of whom 110 underwent randomization. In the first 16 weeks after randomization, the rate of relapse was higher in the group that received placebo than in the groups that received risperidone (60% [24 of 40 patients in group 3] vs. 33% [23 of 70 in groups 1 and 2];  $P=0.004$ ; hazard ratio with placebo, 1.94; 95% confidence interval [CI], 1.09 to 3.45;  $P=0.02$ ). During the next 16 weeks, the rate of relapse was higher in the group that was switched from risperidone to placebo than in the group that continued to receive risperidone (48% [13 of 27 patients in group 2] vs. 15% [2 of 13 in group 1];  $P=0.02$ ; hazard ratio, 4.88; 95% CI, 1.08 to 21.98;  $P=0.02$ ). The rates of adverse events and death after randomization did not differ significantly among the groups, although comparisons were based on small numbers of patients, especially during the final 16 weeks. CONCLUSIONS: In patients with Alzheimer's disease who had psychosis or agitation that had responded to risperidone therapy for 4 to 8 months, discontinuation of risperidone was associated with an increased risk of relapse. (Funded by the National Institutes of Health and others; ClinicalTrials.gov number, NCT00417482.).

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*Diniz, J. B., Shavitt, R. G., Fossaluza, V., Koran, L., Pereira, C. A. and Miguel, E. C. 2011.*

*A double-blind, randomized, controlled trial of fluoxetine plus quetiapine or clomipramine versus fluoxetine plus placebo for obsessive-compulsive disorder.*

Obsessive-compulsive disorder patients who do not improve sufficiently after treatment with a selective serotonin reuptake inhibitor might improve further if other drugs were added to the treatment regimen. The authors present a double-blind, placebo-controlled trial comparing the efficacy of adding quetiapine or clomipramine to a treatment regimen consisting of fluoxetine. Between May 2007 and March 2010, a total of 54 patients with a primary diagnosis of obsessive-compulsive disorder, as defined by Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, and a current Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score of at least 16, the score having dropped by less than 35% after fluoxetine monotherapy, were allocated to 1 of 3 arms ( $n = 18$  per arm): quetiapine + fluoxetine ( $\leq 200$  and  $\leq 40$  mg/d, respectively), clomipramine + fluoxetine ( $\leq 75$  and  $\leq 40$  mg/d, respectively), or placebo + fluoxetine ( $\leq 80$  mg/d of fluoxetine). Follow-up was 12 weeks. The Y-BOCS scores were the main outcome measure. No severe adverse events occurred during the trial, and 40 patients (74%) completed the 12-week protocol. The Y-BOCS scores (mean [SD]) were significantly better in the placebo + fluoxetine and clomipramine + fluoxetine groups than in the quetiapine + fluoxetine group (final: 18 [7] and 18 [7], respectively, vs 25 [6],  $P < 0.001$ ) (reduction from baseline: -6.7 [confidence interval<sup>43</sup>, -9.6 to -3.8; and -6.5 [CI, -9.0 to -3.9], respectively, vs -0.1 [CI, -2.9 to 2.7],  $P < 0.001$ ; number needed to treat = 2.4). The clomipramine-fluoxetine combination is a safe and effective treatment for fluoxetine nonresponders, especially those who cannot tolerate high doses of fluoxetine. However, the period of monotherapy with the maximum dose of fluoxetine should be extended before a combination treatment strategy is applied.

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*Fullerton, C.A. Busch, A.B. Normand, S.L. McGuire, T.G. and Epstein, A.M. 2011.  
Ten-year trends in quality of care and spending for depression: 1996 through 2005.*

CONTEXT: During the past decade, the introduction of generic versions of newer antidepressants and the release of Food and Drug Administration warnings regarding suicidality in children, adolescents, and young adults may have had an effect on cost and quality of depression treatment. OBJECTIVES: To examine longitudinal trends in health service utilization, spending, and quality of care for depression. DESIGN: Observational trend study. SETTING: Florida Medicaid enrollees, between July 1, 1996, and June 30, 2006. Patients Annual cohorts aged 18 to 64 years diagnosed as having depression. MAIN OUTCOME MEASURES: Mental health care spending (adjusted for inflation and case mix), as well as its components, including inpatient, outpatient, and medication expenditures. Quality-of-care measures included medication adherence, psychotherapy, and follow-up visits. RESULTS: Mental health care spending increased from a mean of \$2802 per enrollee to \$3610 during this period (29% increase). This increase occurred despite a mean decrease in inpatient spending from \$641 per enrollee to \$373 and was driven primarily by an increase in pharmacotherapy spending (up 110%), the bulk of which was due to spending on antipsychotics (949% increase). The percentage of enrollees with depression who were hospitalized decreased from 9.1% to 5.1%, and the percentage who received psychotherapy decreased from 56.6% to 37.5%. Antidepressant use increased from 80.6% to 86.8%, anxiety medication use was unchanged at 62.7% and 64.4%, and antipsychotic use increased from 25.9% to 41.9%. Changes in quality of care were mixed, with antidepressant use improving slightly, psychotherapy utilization fluctuating, and follow-up visits decreasing. CONCLUSIONS: During a 10-year period, spending for Medicaid enrollees with depression increased substantially, with minimal improvements in quality of care. Antipsychotic use contributed significantly to the increase in spending, while contributing little to traditional measures of quality of care.

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*Gareri, P. De Fazio, P. Manfredi, V.G. and De Sarro, G. 2014.  
Use and safety of antipsychotics in behavioral disorders in elderly people with dementia.*

In recent years, the use of antipsychotics has been widely debated for reasons concerning their safety in elderly patients affected with dementia. To update the use of antipsychotics in elderly demented people, a MEDLINE search was conducted using the following terms: elderly, conventional and atypical antipsychotics, adverse events, dementia, and behavioral and psychotic symptoms in dementia (BPSD). Owing to the large amounts of studies on antipsychotics, we mostly restricted the field of research to the last 10 years. Conventional antipsychotics have been widely used for BPSD; some studies showed they have an efficacy superior to placebo only at high doses, but they are associated with several and severe adverse effects. Atypical antipsychotics showed an efficacy superior to placebo in randomized studies in BPSD treatment, with a better tolerability profile

versus conventional drugs. However, in 2002, trials with risperidone and olanzapine in elderly patients affected with dementia-related psychoses suggested the possible increase in cerebrovascular adverse events. Drug regulatory agencies issued specific recommendations for underlining that treatment of BPSD with atypical antipsychotics is "off-label." Conventional antipsychotics showed the same likelihood to increase the risk of death in the elderly as atypical agents, and they should not replace the atypical agents discontinued by Food and Drug Administration warnings. Before prescribing an antipsychotic drug, the following are factors to be seriously considered: the presence of cardiovascular diseases, QTc interval on electrocardiogram, electrolytic imbalances, familiar history for torsades des pointes, concomitant treatments, and use of drugs able to lengthen QTc. Use of antipsychotics in dementia needs a careful case-by-case assessment, together with the possible drug-drug, drug-disease, and drug-food interactions.

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*Hahn, M. K., Wolever, T. M., Arenovich, T., Teo, C., Giacca, A., Powell, V., Clarke, L., Fletcher, P., Cohn, T., McIntyre, R. S., Gomes, S., Chintoh, A. and Remington, G. J. 2013.*

*Acute effects of single-dose olanzapine on metabolic, endocrine, and inflammatory markers in healthy controls.*

Atypical antipsychotics may "directly" influence glucose homeostasis, increasing risk of type 2 diabetes independently of changes in adiposity. Animal models suggest direct effects after even a single dose of certain atypical antipsychotics on glucose dysregulation. Here, we investigated effects of a single-dose olanzapine (OLA) on glucose metabolism in healthy volunteers, thereby minimizing confounding effects of the illness of schizophrenia and adiposity. In a randomized double-blind crossover design, 15 subjects were administered 10 mg of OLA or placebo at 7:00 A.M. on separate study dates. A frequently sampled intravenous glucose tolerance test was initiated 4.25 hours later to assess changes in glucose homeostasis, including an index of insulin sensitivity, disposition index, glucose effectiveness, and acute insulin response to glucose. We also examined effects on cortisol, prolactin, fasting free fatty acids (FFAs), insulin-mediated suppression of FFAs, and adipocytokines (leptin, adiponectin, C-reactive protein, interleukin 6, and tumor necrosis factor alpha). Complete data for both visits were analyzed for 12 subjects. Olanzapine treatment significantly decreased glucose effectiveness ( $P = 0.041$ ) and raised fasting glucose over 4.25 hours ( $P = 0.03$ ) as compared to placebo. Olanzapine was associated with lower serum cortisol ( $P = 0.003$ ), lower fasting FFA ( $P = 0.042$ ), and increased prolactin levels ( $P < 0.0001$ ). We therefore suggest that a single dose of OLA may invoke early changes in some parameters of glucose and lipid metabolism, as well as endocrine indices.

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*Huang, M., Luo, B., Hu, J., Wei, N., Chen, L., Wang, S., Zhou, W., Hu, S. and Xu, Y. 2012.*

*Combination of citalopram plus paliperidone is better than citalopram alone in the treatment of somatoform disorder: results of a 6-week randomized study.*

The objective of this study was to evaluate the effectiveness and tolerability of citalopram versus citalopram plus paliperidone combination therapy in patients with somatoform disorders (SDs). In this 6-week, randomized, fixed-dose study, 60 patients with SD (ICD-10 F45.0), undifferentiated SD (F45.1), and somatoform autonomic dysfunction (F45.3) were randomly assigned to receive citalopram (20 mg/day) with or without paliperidone (3 mg/day). Four scales were used to evaluate effectiveness and tolerability at baseline and at the end of the second, fourth, and sixth week after treatment: Somatoform Disorders Screening Symptoms-7 (SOMS-7), Hamilton Anxiety Scale (HAMA), 17-item Hamilton Depression Scale (HAMD-17), and Treatment Emergent Symptom Scale (TESS). The rater was blinded to the kind of treatment patients received. (i) In the intention-to-treat population (N = 51), the overall response ratio (50% reduction in SMOS-7 scores) was significantly higher in the citalopram-paliperidone group compared with the citalopram group after a 6-week treatment (71.4 vs. 38.10%,  $\chi^2(2) = 4.71$ ,  $P = 0.03$ ). (ii) The SOMS-7 and somatic subscore of the Hamilton Anxiety Scale (HAMA-SOM) total score of the citalopram plus paliperidone group decreased more significantly than that of the citalopram group, and a significant difference could be observed at the end of 4 weeks of treatment. (iii) There was no significant difference between the two groups in adverse effects, and no serious adverse event was reported in both groups. Our findings indicate that a combination with paliperidone is significantly better than monotherapy with citalopram whether synergistic or add-on for patients with SDs. Our results call for future studies with larger sample sizes and a longer duration to draw more definitive conclusions.

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*Huybrechts, K. F., Gerhard, T., Crystal, S., Olfson, M., Avorn, J., Levin, R., Lucas, J. A. and Schneeweiss, S. 2012.*

*Differential risk of death in older residents in nursing homes prescribed specific antipsychotic drugs: population based cohort study.*

**OBJECTIVE:** To assess risks of mortality associated with use of individual antipsychotic drugs in elderly residents in nursing homes. **DESIGN:** Population based cohort study with linked data from Medicaid, Medicare, the Minimum Data Set, the National Death Index, and a national assessment of nursing home quality. **SETTING:** Nursing homes in the United States. **PARTICIPANTS:** 75,445 new users of antipsychotic drugs (haloperidol, aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone). All participants were aged  $\geq 65$ , were eligible for Medicaid, and lived in a nursing home in 2001-5. **MAIN OUTCOME MEASURES:** Cox proportional hazards models were used to compare 180 day risks of all cause and cause specific mortality by individual drug, with propensity score adjustment to control for potential confounders. **RESULTS:** Compared with risperidone, users of haloperidol had an increased risk of mortality (hazard ratio 2.07, 95% confidence interval 1.89 to 2.26) and users of quetiapine a decreased risk (0.81, 0.75 to 0.88). The effects were strongest shortly after the start of treatment, remained after adjustment for dose, and were seen for all causes of death examined. No clinically meaningful differences were observed for the other drugs. There was no evidence that the effect measure modification in those with dementia or behavioural disturbances. There was a dose-response relation for all drugs except quetiapine. **CONCLUSIONS:** Though these findings cannot prove causality, and we cannot rule out the possibility of residual confounding, they provide more evidence of the risk of using these drugs in older patients, reinforcing the concept that they should not be used in the absence of

clear need. The data suggest that the risk of mortality with these drugs is generally increased with higher doses and seems to be highest for haloperidol and least for quetiapine.

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*Ingenhoven T.J. and Duivenvoorden H.J. 2011.*

*Differential effectiveness of antipsychotics in borderline personality disorder: meta-analyses of placebo-controlled, randomized clinical trials on symptomatic outcome domains.*

**OBJECTIVE:** In clinical practice, antipsychotic drugs are widely used in borderline personality disorder (BPD). To evaluate current pharmacological treatment algorithms and guidelines for BPD, the authors reviewed and meta-analyzed studies on the effectiveness of antipsychotics on specific symptom domains in BPD. **METHODS:** The literature was searched for placebo-controlled, randomized clinical trials (PC-RCTs) on the effectiveness of antipsychotics regarding cognitive perceptual symptoms, impulsive behavioral dyscontrol, and affective dysregulation (with subdomains depressed mood, anxiety, anger, and mood lability) in BPD. Studies whose primary emphasis was on the treatment of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition schizotypal personality disorder or Axis I disorders were excluded. **RESULTS:** Meta-analyses were conducted using 11 retrieved studies including 1152 borderline patients. Antipsychotics have a significant effect on cognitive perceptual symptoms (9 PC-RCTs; standardized mean difference [SMD], 0.23) and mood lability (5 PC-RCTs; SMD, 0.20) as well as on global functioning (8 PC-RCTs; SMD, 0.25), but these effects have to be qualified as small. Antipsychotics have a more pronounced effect on anger (9 PC-RCTs; SMD, 0.39). Antipsychotics did not have a significant effect on impulsive behavioral dyscontrol, depressed mood, and anxiety in BPD. **CONCLUSION:** Drug therapy tailored to well-defined symptom domains can have beneficial effects in BPD. At short term, antipsychotics can have significant effects on cognitive-perceptual symptoms, anger, and mood lability, but the wide and long-term use of antipsychotics in these patients remains controversial. The findings from this study raise questions on current pharmacological algorithms and clinical guidelines.

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*Jeon, H. J., Fava, M., Mischoulon, D., Baer, L., Clain, A., Doorley, J., Dipierro, M., Cardoos, A. and Papakostas, G. I. 2014.*

*Psychomotor symptoms and treatment outcomes of ziprasidone monotherapy in patients with major depressive disorder: a 12-week, randomized, double-blind, placebo-controlled, sequential parallel comparison trial.*

The aim of this study was to evaluate efficacy of ziprasidone monotherapy for major depressive disorder (MDD) with and without psychomotor symptoms. In accordance with the sequential parallel comparison design, 106 MDD patients (age 44.0+/-10.7 years; female, 43.4%) were recruited and a post-hoc analysis was carried out on 12-week double-blind treatment with either ziprasidone (40-160 mg/day) or placebo, divided into two

phases of 6 weeks each to the assigned treatment sequences, drug/drug, placebo/placebo, and placebo/drug. Psychomotor symptoms were evaluated on the basis of the Mini-International Neuropsychiatric Interview at baseline. Efficacy assessments, on the basis of the 17-item Hamilton Depression Rating Scale (HDRS-17) and the Quick Inventory of Depressive Symptomatology Scale, Self-Rated (QIDS-SR), were performed every week throughout the trial. In phase I, ziprasidone monotherapy produced significant improvement in patients with psychomotor symptoms compared with placebo on the basis of HDRS-17 ( $F=5.95$ ,  $P=0.017$ ) and QIDS-SR ( $F=5.26$ ,  $P=0.025$ ) scores, whereas no significant changes were found in HDRS-17 ( $F=2.32$ ,  $P=0.15$ ) and QIDS-SR ( $F=3.70$ ,  $P=0.074$ ) scores in patients without psychomotor symptoms. In phase II, ziprasidone monotherapy produced no significant differences compared with placebo. In the pooled analysis, ziprasidone monotherapy showed significance according to QIDS-SR ( $Z=2.00$ ,  $P=0.046$ ) and a trend toward statistical significance according to the HDRS-17 ( $Z=1.66$ ,  $P=0.10$ ) in patients with psychomotor symptoms. Ziprasidone monotherapy may produce significant improvement compared with placebo in MDD patients with psychomotor symptoms.

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*Johnston, T.G. 2011.*

*Risperidone long-acting injection and Huntington's disease: case series with significant psychiatric and behavioural symptoms.*

There is currently no known disease-altering treatment for Huntington's disease (HD). Successful symptomatic treatment often involves antipsychotic medication, including risperidone, yet the evidence base is limited to case reports. Although noncompliance to oral antipsychotic drugs can be a practical problem, especially when significant psychiatric manifestations of HD are present, the effect of depot antipsychotic medication in HD remains largely unknown. A period of nondrug compliance to oral risperidone in five patients with HD, and significant psychiatric and behavioural symptoms, after appearing to show symptomatic improvement, suggested a possible role for risperidone long-acting injection. The patients gave informed consent before receiving a fortnightly injection at a dose of 25 mg. At the end of 2-15 months (mean 1 year) they appeared to show an unexpected sustained symptomatic improvement (chorea, functioning and insight). In conclusion, this case series suggests risperidone long-acting injection may be a viable symptomatic treatment strategy in similar HD patients. If replicated, these findings have the potential to offer an effective strategy to manage some of the most difficult patients with HD to achieve symptomatic relief.

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*Kales, H.C. Zivin, K. Kim, H.M. Valenstein, M. Chiang, C. Ignacio, R.V. Ganoczy, D. Cunningham, F. Schneider, L.S. and Blow, F.C. 2011*  
*Trends in antipsychotic use in dementia 1999-2007.*

CONTEXT: Use of atypical antipsychotics for neuropsychiatric symptoms of dementia increased markedly in the 1990s. Concerns about their use began to emerge in 2002, and in 2005, the US Food and Drug Administration warned that use of atypical antipsychotics in dementia was

associated with increased mortality. **OBJECTIVE:** To examine changes in atypical and conventional antipsychotic use in outpatients with dementia from 1999 through 2007. **DESIGN:** Time-series analyses estimated the effect of the various warnings on atypical and conventional antipsychotic usage using national Veterans Affairs data across 3 periods: no warning (1999-2003), early warning (2003-2005), and black box warning (2005-2007). **SUBJECTS:** Patients aged 65 years or older with dementia (n = 254 564). **MAIN OUTCOME MEASURES:** Outpatient antipsychotic use (percentage of patients, percentage of quarterly change, and difference between consecutive study periods). **RESULTS:** In 1999, 17.7% (95% confidence interval [CI], 17.2-18.1) of patients with dementia were using atypical or conventional antipsychotics. Overall use began to decline during the no-warning period (rate per quarter, -0.12%; 95% CI, -0.16 to -0.07; P < .001). Following the black box warning, the decline continued (rate, -0.26%; 95% CI, -0.34 to -0.18; P < .001), with a significant difference between the early and black box warning periods (P = .006). Use of atypical antipsychotics as a group increased during the no-warning period (rate, 0.23; 95% CI, 0.17-0.30; P < .001), started to decline during the early-warning period (rate, -0.012; 95% CI, -0.14 to 0.11; P = .85), and more sharply declined during the black box warning period (rate, -0.27; 95% CI, -0.36 to -0.18; P < .001). Olanzapine and risperidone showed declining rates and quetiapine showed an increase during the early-warning period, but rates of use for all 3 antipsychotics declined during the black box warning period. In the black box warning period, there was a small but significant increase in anticonvulsant prescriptions (rate, 0.117; 95% CI, 0.08-0.16; P < .001). **CONCLUSIONS:** Use of atypical antipsychotics began to decline significantly in 2003, and the Food and Drug Administration advisory was temporally associated with a significant acceleration in the decline.

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*Kales, H. C., Kim, H. M., Zivin, K., Valenstein, M., Seyfried, L. S., Chiang, C., Cunningham, F., Schneider, L. S. and Blow, F. C. 2012.  
Risk of mortality among individual antipsychotics in patients with dementia.*

**OBJECTIVE:** The use of antipsychotics to treat the behavioral symptoms of dementia is associated with greater mortality. The authors examined the mortality risk of individual agents to augment the limited information on individual antipsychotic risk. **METHOD:** The authors conducted a retrospective cohort study using national data from the U.S. Department of Veterans Affairs (fiscal years 1999-2008) for dementia patients age 65 and older who began outpatient treatment with an antipsychotic (risperidone, olanzapine, quetiapine, or haloperidol) or valproic acid and its derivatives (as a nonantipsychotic comparison). The total sample included 33,604 patients, and individual drug groups were compared for 180-day mortality rates. The authors analyzed the data using multivariate models and propensity adjustments. **RESULTS:** In covariate-adjusted intent-to-treat analyses, haloperidol was associated with the highest mortality rates (relative risk=1.54, 95% confidence interval [CI]=1.38-1.73) followed by risperidone (reference), olanzapine (relative risk=0.99, 95% CI=0.89-1.10), valproic acid and its derivatives (relative risk=0.91, 95% CI=0.78-1.06), and quetiapine (relative risk=0.73, 95% CI=0.67-0.80). Propensity-stratified and propensity-weighted models as well as analyses controlling for site of care and medication dosage revealed similar patterns. The mortality risk with haloperidol was highest in the first 30 days but decreased significantly and sharply thereafter. Among the other agents, mortality risk differences were most significant in the first 120 days and declined in the subsequent 60 days during follow-up. **CONCLUSIONS:** There may be differences in mortality risks among individual antipsychotic agents

used for treating patients with dementia. The use of valproic acid and its derivatives as alternative agents to address the neuropsychiatric symptoms of dementia may carry associated risks as well.

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*Katzman, M.A. Brawman-Mintzer, O. Reyes, E.B. Olausson, B. Liu, S. and Eriksson, H. 2011.*

*Extended release quetiapine fumarate (quetiapine XR) monotherapy as maintenance treatment for generalized anxiety disorder: a long-term, randomized, placebo-controlled trial.*

The objective of this study was to evaluate the efficacy and tolerability of extended release quetiapine fumarate (quetiapine XR) as maintenance monotherapy for patients with generalized anxiety disorder (GAD). Time-to-event (anxiety symptom recurrence; maximum 52 weeks) multicenter, randomized-withdrawal, parallel-group, double-blind, placebo-controlled study of quetiapine XR (50-300 mg/day) following open-label run-in (4-8 weeks) and open-label stabilization ( $\geq 12$  weeks). Primary variable: time from randomization to anxiety event. Secondary variables included: Hamilton Anxiety Rating Scale (HAM-A) total, HAM-A psychic/somatic anxiety factors, Clinical Global Impression-Severity of Illness (CGI-S), and Quality of Life, Enjoyment and Satisfaction Questionnaire (Q-LES-Q) scores; adverse events (AE) reporting. Four hundred and thirty-two patients, stabilized on quetiapine XR, were randomized to continue quetiapine XR (N=216) or switch to placebo (N=216). Risk of anxiety symptom recurrence was significantly reduced by 81% for quetiapine XR versus placebo: hazard ratio=0.19 (95% confidence interval 0.12-0.31;  $P<0.001$ ). Fewer patients receiving quetiapine XR (N=22, 10.2%) than placebo (N=84, 38.9%) experienced anxiety symptom recurrence. Significant differences were observed between quetiapine XR and placebo in: HAM-A total, psychic/somatic, CGI-S (all  $P<0.001$ ) and Q-LES-Q ( $P<0.05$ ) scores. AEs ( $>10\%$ ) during open-label treatment were dry mouth, sedation, somnolence, dizziness, fatigue, and constipation. During randomized treatment, the most common AEs for quetiapine XR were headache and nasopharyngitis. Quetiapine XR monotherapy reduced the risk of anxiety symptom recurrence in patients with GAD stabilized on quetiapine XR, with tolerability results consistent with the known profile of quetiapine.

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*Khan, A. Joyce, M. Atkinson, S. Eggens, I. Baldytcheva, I. and Eriksson, H. 2011.*

*A randomized, double-blind study of once-daily extended release quetiapine fumarate (quetiapine XR) monotherapy in patients with generalized anxiety disorder.*

This study evaluated once-daily, extended-release quetiapine fumarate (quetiapine XR) monotherapy in generalized anxiety disorder (GAD). This was a 10-week (8-week active treatment/2-week posttreatment drug-discontinuation/tapering phase), double-blind, randomized, placebo-controlled study (D1448C00009). Primary end point was change from randomization at week 8 in Hamilton Anxiety Rating Scale (HAM-A) total score.

Overall, 951 patients with GAD were randomized (quetiapine XR: 50 mg/d, n = 234; 150 mg/d, n = 241; 300 mg/d, n = 241; placebo, n = 235). At week 8, HAM-A total scores significantly ( $P < 0.001$ ) improved versus placebo (-11.10) with quetiapine XR 50 mg/d (-13.31) and 150 mg/d (-13.54), but not 300 mg/d (-11.87;  $P = 0.240$ ). At week 1, HAM-A total scores significantly improved versus placebo (-5.94) with quetiapine XR 50 mg/d (-7.47;  $P < 0.01$ ), 150 mg/d (-8.19;  $P < 0.001$ ), and 300 mg/d (-7.23;  $P < 0.01$ ). Versus placebo at week 8, quetiapine XR 50 and 150 mg/d significantly improved HAM-A psychic ( $P < 0.01$  and  $P < 0.001$ , respectively) and somatic ( $P < 0.001$ ;  $P < 0.01$ , respectively) cluster scores, HAM-A response ( $\geq 50\%$  total score reduction;  $P < 0.05$ ), and Clinical Global Impression-Improvement categorical changes ( $P < 0.05$ ). For quetiapine XR 150 mg/d, significant ( $P < 0.05$ ) improvements were seen for HAM-A remission (total score,  $\leq 7$ ) and Clinical Global Impression-Severity of Illness scores. For quetiapine XR 300 mg/d, improvements in these secondary variables were not significantly different versus placebo. Pittsburgh Sleep Quality Index global scores improved with all 3 doses (quetiapine: XR 50 mg/d, -4.07 [ $P < 0.05$ ]; 150 mg/d, -4.38 [ $P < 0.05$ ]; 300 mg/d, -3.97 [ $P < 0.05$ ], versus -3.31 with placebo). Adverse events ( $>10\%$  with quetiapine XR) were dry mouth, somnolence, sedation, dizziness, headache, and fatigue. Quetiapine XR (50/150 mg/d) monotherapy was effective at week 8 in patients with GAD; symptom improvement was seen at week 1 for all doses (50/150/300 mg/d). Safety and tolerability were consistent with the known profile of quetiapine.

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*Krystal, J. H., Rosenheck, R. A., Cramer, J. A., Vessicchio, J. C., Jones, K. M., Vertrees, J. E., Horney, R. A., Huang, G. D. and Stock, C. 2011. Adjunctive risperidone treatment for antidepressant-resistant symptoms of chronic military service-related PTSD: a randomized trial.*

CONTEXT: Serotonin reuptake-inhibiting (SRI) antidepressants are the only FDA-approved pharmacotherapies for the treatment of posttraumatic stress disorder (PTSD). OBJECTIVE: To determine efficacy of the second-generation antipsychotic risperidone as an adjunct to ongoing pharmacologic and psychosocial treatments for veterans with chronic military-related PTSD. DESIGN, SETTING, AND PARTICIPANTS: A 6-month, randomized, double-blind, placebo-controlled multicenter trial conducted between February 2007 and February 2010 at 23 Veterans Administration outpatient medical centers. Of the 367 patients screened, 296 were diagnosed with military-related PTSD and had ongoing symptoms despite at least 2 adequate SRI treatments, and 247 contributed to analysis of the primary outcome measure. INTERVENTION: Risperidone (up to 4 mg once daily) or placebo. MAIN OUTCOME MEASURES: The Clinician-Administered PTSD Scale (CAPS) (range, 0-136). Other measures included the Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Anxiety Scale (HAMA), Clinical Global Impression scale (CGI), and Veterans RAND 36-Item Health Survey (SF-36V). RESULTS: Change in CAPS scores from baseline to 24 weeks in the risperidone group was -16.3 (95% CI, -19.7 to -12.9) and in the placebo group, -12.5 (95% CI, -15.7 to -9.4); the mean difference was 3.74 (95% CI, -0.86 to 8.35;  $t = 1.6$ ;  $P = .11$ ). Mixed model analysis of all time points also showed no significant difference in CAPS score (risperidone: mean, 64.43; 95% CI, 61.98 to 66.89, vs placebo: mean, 67.16; 95% CI, 64.71 to 69.62; mean difference, 2.73; 95% CI, -0.74 to 6.20;  $P = .12$ ). Risperidone did not reduce symptoms of depression (MADRS mean difference, 1.19; 95% CI, -0.29 to 2.68;  $P = .11$ ) or anxiety (HAMA mean difference, 1.16; 95% CI, -0.18 to 2.51;  $P = .09$ ; patient-rated CGI mean difference, 0.20; 95% CI, -0.06 to 0.45;  $P = .14$ ; observer-rated CGI mean difference, 0.18; 95% CI, 0.01 to 0.34;  $P = .04$ ), or increase quality of life (SF-36V physical component mean difference, -1.13,

95% CI, -2.58 to 0.32; P = .13; SF-36V mental component mean difference, -0.26; 95% CI, -2.13 to 1.61; P = .79). Adverse events were more common with risperidone vs placebo, including self-reported weight gain (15.3% vs 2.3%), fatigue (13.7% vs 0.0%), somnolence (9.9% vs 1.5%), and hypersalivation (9.9% vs 0.8%), respectively. CONCLUSION: Among patients with military-related PTSD with SRI-resistant symptoms, 6-month treatment with risperidone compared with placebo did not reduce PTSD symptoms. TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00099983.

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*Lalonde, C.D. and Van Lieshout, R.J. 2011.*

*Treating generalized anxiety disorder with second generation antipsychotics: A systematic review and meta-analysis.*

Most individuals with generalized anxiety disorder (GAD) fail to achieve remission despite standard treatments. As a result, we examined the efficacy and tolerability of second-generation antipsychotics (SGAs) as (a) augmentation or (b) monotherapy for GAD. We searched MEDLINE, EMBASE, PsycINFO, the Cochrane Library, controlled trials databases, and the abstracts of scientific meetings for all trials of GAD treatment with SGAs in adults. Randomized, double-blind, parallel-group trials examining SGA augmentation and monotherapy were meta-analyzed. Five augmentation studies containing 912 adults with refractory GAD indicated that SGA augmentation was not more likely to produce clinical response or remission than placebo and was associated with an increased risk of all-cause discontinuation (relative risk [RR] = 1.43; 95% confidence interval [CI], 1.04-1.96). There was no difference in the Hamilton Anxiety Rating Scale on change from baseline or weight gain between groups. Four SGA monotherapy studies containing 1383 patients with GAD indicated that treatment with 150 mg of quetiapine was more likely to lead to a clinical response (RR = 1.31; 95% CI, 1.20-1.44), remission (RR = 1.44; 95% CI, 1.23-1.68), and a greater decrease in the Hamilton Anxiety Rating Scale score (-3.66; 95% CI, -5.13 to -2.19) than placebo. However, an increased risk of all-cause discontinuation (RR = 1.30; 95% CI, 1.09-1.54) and weight gain (2.2 lb; 95% CI, 1.16-3.24) was observed. Existing data suggest that SGAs are not superior to placebo as augmentation for refractory GAD. Quetiapine monotherapy is more efficacious than placebo for uncomplicated GAD, but issues with adverse effects and tolerability may limit its use.

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*Lopez, O. L., Becker, J. T., Chang, Y. F., Sweet, R. A., Aizenstein, H., Snitz, B., Saxton, J., Mcdade, E., Kamboh, M. I., Dekosky, S. T., Reynolds, C. F., 3rd and Klunk, W. E. 2013.*

*The long-term effects of conventional and atypical antipsychotics in patients with probable Alzheimer's disease.*

OBJECTIVE: The authors sought to determine the effects of conventional and atypical antipsychotic use on time to nursing home admission and time to death in a group of outpatients with mild to moderate probable Alzheimer's disease. METHOD: The authors examined time to nursing

home admission and time to death in 957 patients with the diagnosis of probable Alzheimer's disease who had at least one follow-up evaluation (mean follow-up time, 4.3 years [SD=2.7]; range, 0.78-18.0 years) using Cox proportional hazard models adjusted for age, gender, education level, dementia severity, hypertension, diabetes mellitus, heart disease, extrapyramidal signs, depression, psychosis, aggression, agitation, and dementia medication use. RESULTS: A total of 241 patients (25%) were exposed to antipsychotics at some time during follow-up (conventional, N=138; atypical, N=95; both, N=8). Nursing home admission (63% compared with 23%) and death (69% compared with 34%) were more frequent in individuals taking conventional than atypical antipsychotics. In a model that included demographic and cognitive variables, hypertension, diabetes mellitus, heart disease, incident strokes, and extrapyramidal signs, only conventional antipsychotic use was associated with time to nursing home admission. However, the association was no longer significant after adjustment for psychiatric symptoms. Psychosis was strongly associated with nursing home admission and time to death, but neither conventional nor atypical antipsychotics were associated with time to death. CONCLUSIONS: The use of antipsychotic medications, both conventional and atypical, was not associated with either time to nursing home admission or time to death after adjustment for relevant covariates. Rather, it was the presence of psychiatric symptoms, including psychosis and agitation, which was linked to increased risk of institutionalization and death after adjustment for exposure to antipsychotics.

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*Loy, J.H. Merry, S.N. Hetrick, S.E. and Stasiak, K. 2012.*

*Atypical antipsychotics for disruptive behavior disorders in children and youths.*

BACKGROUND: Disruptive behaviour disorders include conduct disorder, oppositional defiant disorder and disruptive behaviour not otherwise specified. Attention deficit hyperactivity disorder (ADHD) is frequently associated with disruptive behaviour disorders. The difficulties associated with disruptive behaviour disorders are demonstrated through aggression and severe behavioural problems. These often result in presentation to psychiatric services and may be treated with medications such as atypical antipsychotics. There is increasing evidence of a significant rise in the use of atypical antipsychotics for treating disruptive behaviour disorders in child and adolescent populations. OBJECTIVES: To evaluate the effect and safety of atypical antipsychotics, compared to placebo, for treating disruptive behaviour disorders in children and youths. SEARCH METHODS: We searched the following databases in August 2011: CENTRAL (2011, Issue 3), MEDLINE (1948 to August Week 1), EMBASE (1980 to 2011 Week 32), PsycINFO (1806 to August Week 2 2011), CINAHL (1937 to current), ClinicalTrials.gov (searched 15 August 2011), Australian New Zealand Clinical Trials Registry (ANZCTR) (searched 15 August 2011), CenterWatch (searched 15 August 2011) and ICTRP (searched 15 August 2011). SELECTION CRITERIA: We included randomised controlled trials with children and youths up to and including the age of 18, in any setting, with a diagnosis of a disruptive behaviour disorder. We included trials where participants had a comorbid diagnosis of attention deficit hyperactivity disorder, major depression or an anxiety disorder. DATA COLLECTION AND ANALYSIS: Two review authors independently selected the studies and disagreements were resolved by discussion. Two review authors extracted data independently. One review author entered data into Review Manager software and another checked it. We contacted trial authors for information about adverse effects and to provide missing data. MAIN RESULTS: We included eight randomised controlled trials, spanning 2000 to 2008. Seven assessed risperidone and

one assessed quetiapine. Three of the studies were multicentre. Seven trials assessed acute efficacy and one assessed time to symptom recurrence over a six-month maintenance period. We performed meta-analyses for the primary outcomes of aggression, conduct problems and weight changes but these were limited by the available data as different trials reported either mean change scores (average difference) or final/post-intervention raw scores and used different outcome measures. We also evaluated each individual trial's treatment effect size where possible, using Hedges' g. For aggression, we conducted two meta-analyses. The first included three trials (combined n = 238) using mean difference (MD) on the Aberrant Behaviour Checklist (ABC) Irritability subscale. Results yielded a final mean score with treatment that was 6.49 points lower than the post-intervention mean score with placebo (95% confidence interval (CI) -8.79 to -4.19). The second meta-analysis on aggression included two trials (combined n = 57) that employed two different outcome measures (Overt Aggression Scale (modified) (OAS-M) and OAS, respectively) and thus we used a standardised mean difference. Results yielded an effect estimate of -0.18 (95% CI -0.70 to 0.34), which was statistically non-significant. We also performed two meta-analyses for conduct problems. The first included two trials (combined n = 225), both of which employed the Nisonger Child Behaviour Rating Form - Conduct Problem subscale (NCBRF-CP). The results yielded a final mean score with treatment that was 8.61 points lower than that with placebo (95% CI -11.49 to -5.74). The second meta-analysis on conduct problems included two trials (combined n = 36), which used the Conners' Parent Rating Scale - Conduct Problem subscale (CPRS-CP). Results yielded a mean score with treatment of 12.67 lower than with placebo (95% CI -37.45 to 12.11), which was a statistically non-significant result. With respect to the side effect of weight gain, a meta-analysis of two studies (combined n = 138) showed that participants on risperidone gained on average 2.37 kilograms more than those in the placebo group over the treatment period (MD 2.37; 95% CI 0.26 to 4.49). For individual trials, there was a range of effect sizes (ranging from small to large) for risperidone reducing aggression and conduct problems. The precision of the estimate of the effect size varied between trials.

**AUTHORS' CONCLUSIONS:** There is some limited evidence of efficacy of risperidone reducing aggression and conduct problems in children aged 5 to 18 with disruptive behaviour disorders in the short term. For aggression, the difference in scores of 6.49 points on the ABC Irritability subscale (range 0 to 45) may be clinically significant. For conduct problems, the difference in scores of 8.61 points on the NCBRF-CP (range 0 to 48) is likely to be clinically significant. Caution is required due to the limitations of the evidence and the small number of relevant high-quality studies. The findings from the one study assessing impact in the longer term suggest that the effects are maintained to some extent (small effect size) for up to six months. Inadequately powered studies produced non-significant results. The evidence is restricted by heterogeneity of the population (including below average and borderline IQ), and methodological issues in some studies, such as use of enriched designs and risk of selection bias. No study addressed the issue of pre-existing/concurrent psychosocial interventions, and comorbid stimulant medication and its dosage was only partially addressed. There is currently no evidence to support the use of quetiapine for disruptive behaviour disorders in children and adolescents. It is uncertain to what degree the efficacy found in clinical trials will translate into real life clinical practice. Participants in the studies were recruited from clinical services but those who agree to take part in the clinical trials are a subset of the overall population presenting for care. There are no research data for children under five years of age. Further high-quality research is required with large samples of clinically representative youths and long-term follow-up to replicate current findings.

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*Martin-Blanco, A., Patrizi, B., Villalta, L., Gasol, X., Soler, J., Gasol, M. and Pascual, J. C. 2014.*  
*Asenapine in the treatment of borderline personality disorder: an atypical antipsychotic alternative.*

Many individuals with borderline personality disorder (BPD) receive medical treatment in clinical practice, although to date, there are no drugs specifically available for BPD. The recent Cochrane guideline suggests a benefit from using second-generation antipsychotics such as olanzapine or aripiprazole; nevertheless, side effects limit their use. Asenapine is a novel FDA-approved atypical antipsychotic for schizophrenia and bipolar disorder. However, it has not yet been tested for BPD. The goal of this observational open-label study was to assess the safety, tolerability and efficacy of asenapine in a series of cases of patients with BPD. Twelve individuals with BPD were recruited and treated with asenapine during an 8-week period. Eight individuals completed the study; a significant improvement was observed in the CGI-BPD ( $P<0.001$ ) and BSL-23 ( $P<0.048$ ) scales for BPD symptomatology. Besides, there was a significant improvement in the general psychopathology domains (BPRS,  $P<0.004$ ), whereas no significant differences were observed in depressive symptoms. No serious adverse effects were reported and a significant weight reduction was observed ( $P=0.002$ ). Asenapine appears to be a safe and effective agent in the treatment of patients with BPD, especially when other alternatives are not tolerated. These preliminary findings should be replicated in a controlled clinical trial.

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*Merideth, C. Cutler, A.J. She, F. and Eriksson, H. 2012.*

*Efficacy and tolerability of extended release quetiapine fumarate monotherapy in the acute treatment of generalized anxiety disorder: a randomized, placebo-controlled and active-controlled study.*

The main objective of this study was to evaluate efficacy and tolerability of once-daily extended release quetiapine fumarate (quetiapine XR) monotherapy in generalized anxiety disorder (GAD). This was a 8 week randomized, 2-week follow-up, double-blind, placebo-controlled, and active-controlled study. Patients were randomized to quetiapine XR 150 (n=219) or 300 mg/day (n=207); escitalopram, 10 mg/day (n=213); or placebo (n=215). The primary endpoint was the change from randomization at week 8 in Hamilton Anxiety Rating (HAM-A) total score. Week 8 mean HAM-A total score was significantly reduced from randomization with quetiapine XR 150 mg/day (-13.9,  $P<0.001$ ), 300 mg/day (-12.3,  $P<0.05$ ) and escitalopram (-12.3,  $P<0.05$ ) versus placebo (-10.7); significant improvements with quetiapine XR (150 and 300 mg/day) versus placebo ( $P<0.001$ ) were also shown at day 4. At week 8, significant improvements versus placebo were observed in HAM-A psychic [quetiapine XR (both doses) and escitalopram] and somatic (quetiapine XR 150 mg/day and escitalopram) cluster scores and HAM-A response and remission rates (quetiapine XR 150 mg/day). Most common adverse events were dry mouth, somnolence and sedation (quetiapine XR), headache, and nausea (escitalopram). In patients with GAD, quetiapine XR (150 and 300 mg/day) demonstrated significant efficacy at week 8 with symptom improvement as early as day 4. We concluded that quetiapine XR safety and tolerability results were consistent with the known profile of quetiapine.

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Montgomery, S.A. Locklear, J.C. Svedsater, H. and Eriksson, H. 2014.

*Efficacy of once-daily extended release quetiapine fumarate in patients with different levels of severity of generalized anxiety disorder.*

This study is a pooled, post-hoc analysis evaluating once-daily extended release quetiapine fumarate (quetiapine XR) monotherapy in patients with generalized anxiety disorder (GAD). Three previously reported positive, 8-week, randomized, double-blind, placebo-controlled studies evaluated quetiapine XR therapy (50, 150, 300 mg/day) in patients with GAD [Hamilton Anxiety Rating Scale (HAM-A) total score  $\geq 20$ ]. Patients were stratified by baseline severity: HAM-A total score  $\geq 22$ ,  $\geq 24$ ,  $< 26$ ,  $\geq 26$ ,  $\geq 28$ . We report HAM-A total score change, response ( $\geq 50\%$  reduction in HAM-A total score), and remission (HAM-A total score  $\leq 7$  and  $\leq 9$ ). Quetiapine XR significantly improved HAM-A total scores compared with placebo at Weeks 1 and 8 in the HAM-A  $\geq 22$ ,  $\geq 24$ , and  $\geq 26$  cohorts (all doses), at Week 1 (all doses) and Week 8 (quetiapine XR 150 mg/day) in the  $< 26$  cohort, and at Week 1 (all doses) and Week 8 (quetiapine XR 50 and 150 mg/day) in the HAM-A  $\geq 28$  group ( $P < 0.05$ ). Week 8 effect sizes for 50, 150, and 300 mg/day were as follows: 0.29, 0.47, 0.17 (HAM-A  $\geq 22$ ); 0.35, 0.55, 0.22 (HAM-A  $\geq 24$ ); 0.18, 0.32, 0.10 (HAM-A  $< 26$ ); 0.41, 0.59, 0.24 (HAM-A  $\geq 26$ ); 0.60, 0.64, 0.22 (HAM-A  $\geq 28$ ), respectively. Acute quetiapine XR monotherapy significantly improves anxiety compared with placebo in patients with moderate or severe GAD, with symptom improvements seen as early as Week 1.

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Montgomery, S. A., Altamura, A. C., Katila, H., Datto, C., Szamosi, J. and Eriksson, H. 2014.

*Efficacy of extended release quetiapine fumarate monotherapy in elderly patients with major depressive disorder: secondary analyses in subgroups of patients according to baseline anxiety, sleep disturbance, and pain levels.*

This study evaluated extended release quetiapine fumarate (quetiapine XR) monotherapy in elderly patients with major depressive disorder (MDD) according to baseline levels of anxiety, sleep disturbance, and pain. Post-hoc analyses of data from an 11-week (9-week randomized-treatment, 2-week post-treatment phase), double-blind, placebo-controlled study of quetiapine XR (50-300 mg/day) monotherapy in elderly ( $\geq 66$  years) patients ( $n=338$ ) with MDD were carried out. Outcomes included randomization to week 9 change in Montgomery Asberg Depression Rating Scale (MADRS) score and week 9 response ( $\geq 50\%$  MADRS score reduction) rates. Post-hoc analyses were carried out to assess subgroups of patients with MDD according to baseline levels in terms of the following: higher or lower anxiety (Hamilton Rating Scale for Anxiety total score  $\geq 20$  or  $< 20$ , respectively); high or low sleep disturbance [Hamilton Rating Scale for Depression sleep disturbance factor (items 4+5+6) score  $\geq 5$  or  $< 5$ , respectively]; and pain visual analog scale total score 40 mm or higher or less than 40 mm. At week 9, quetiapine XR reduced the MADRS total score compared with placebo in the higher anxiety (least squares mean change -17.8 vs. -8.5;  $P < 0.001$ ) and lower anxiety (-14.8 vs.

-8.8;  $P < 0.001$ ) subgroups. MADRS total score was also reduced with quetiapine XR compared with placebo in the high (-17.6 vs. -8.7;  $P < 0.001$ ) and low (-14.4 vs. -9.2;  $P < 0.001$ ) sleep disturbance subgroups, as well as in the pain visual analog scale subgroups [ $\geq 40$  mm (-16.6 vs. -8.9;  $P < 0.001$ ) and  $< 40$  mm (-15.7 vs. -8.7;  $P < 0.001$ )]. Quetiapine XR response rates were higher than those of placebo in all subgroups analyzed. In this study, quetiapine XR (50-300 mg/day) monotherapy was shown to be effective against depressive symptoms in elderly patients with MDD, irrespective of baseline levels of anxiety, sleep disturbance, and pain.

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*Muscatello, M. R., Bruno, A., Pandolfo, G., Mico, U., Scimeca, G., Romeo, V. M., Santoro, V., Settineri, S., Spina, E. and Zoccali, R. A. 2011. Effect of aripiprazole augmentation of serotonin reuptake inhibitors or clomipramine in treatment-resistant obsessive-compulsive disorder: a double-blind, placebo-controlled study.*

Based on the evidence that aripiprazole added to serotonin reuptake inhibitors (SRIs) or clomipramine in treatment-resistant obsessive-compulsive disorder (OCD) has reported promising results, the present 16-week, double-blind, randomized, placebo-controlled trial had the aim to explore the efficacy of aripiprazole add-on pharmacotherapy on clinical symptoms and cognitive functioning in a sample of treatment-resistant OCD patients receiving SRIs. After clinical and neurocognitive assessments, patients were randomly allocated to receive, in a double-blind design, 15 mg/d of aripiprazole or a placebo. A final sample of 30 patients completed the study. The results obtained indicate that aripiprazole added to stable SRI treatment substantially improved obsessive-compulsive symptoms as measured by changes on the Yale-Brown Obsessive Compulsive Scale total score and subscores (obsessions,  $P = 0.007$ ; compulsions,  $P = 0.001$ ; total score,  $P < 0.0001$ ). Regarding cognitive functions, improvement was observed in some explored areas, such as attentional resistance to interference (Stroop score,  $P = 0.001$ ) and executive functioning (perseverative errors,  $P = 0.015$ ). The findings provide evidence that aripiprazole augmentation of SRIs/clomipramine treatment is well tolerated and may be proposed as an effective therapeutic strategy to improve outcome in treatment-resistant OCD.

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*Potvin, S. Morin, M. Cloutier, C. Gendron, A. Bissonnette, A. and Marchand, S. 2012. Add-on treatment of quetiapine for fibromyalgia: a pilot, randomized, double-blind, placebo-controlled 12-week trial.*

Recently, second-generation antipsychotic drugs have attracted interest in the treatment of chronic pain, including fibromyalgia (FM). Preliminary uncontrolled studies have shown that quetiapine treatment may be helpful for FM patients. In this trial, we sought to examine-for the first time-the efficacy and tolerability of quetiapine as a treatment for FM and its associated psychiatric symptoms. This was a 12-week double-blind, randomized, placebo-controlled trial of quetiapine XR as an add-on treatment for FM syndrome. Fifty-one female FM patients were randomized, and a flexible dosage of 50 to 300 mg/d was used. The primary outcome was the change from baseline to end point in the Fibromyalgia Impact

Questionnaire total score. Secondary outcomes included mood symptoms, sleep disturbances, and tender points. Using a low dose (mean = 132.2 mg) of quetiapine, we observed significant benefits of drug treatment on sleep, uncertain effects on FM and mood symptoms, but no effects on pain, in a small group of polymedicated FM patients. Quetiapine was generally well tolerated.

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*Rothbart, R. Amos, T. Siegfried, N. Ipser, J.C. Fineberg, N. Chamberlain, S.R. and Stein, D.J. 2013.  
Pharmacotherapy for trichotillomania.*

**BACKGROUND:** Trichotillomania (TTM) (hair-pulling disorder) is a prevalent and disabling disorder characterised by recurrent hair-pulling. The effect of medication on trichotillomania has not been systematically evaluated. **OBJECTIVES:** To assess the effects of medication for trichotillomania in adults compared with placebo or other active agents. **SEARCH METHODS:** We searched the Cochrane Central Register of Controlled Trials and the Cochrane Depression, Anxiety and Neurosis Group Register (to 31 July 2013), which includes relevant randomised controlled trials from the following bibliographic databases: The Cochrane Library (all years); EMBASE (1974 to date); MEDLINE (1950 to date) and PsycINFO (1967 to date). Two review authors identified relevant trials by assessing the abstracts of all possible studies. **SELECTION CRITERIA:** We selected randomised controlled trials (RCTs) of a medication versus placebo or active agent for TTM in adults. **DATA COLLECTION AND ANALYSIS:** Two review authors independently performed the data extraction and 'Risk of bias' assessments, and disagreements were resolved through discussion with a third review author. Primary outcomes included the mean difference (MD) in reduction of trichotillomania symptoms on a continuous measure of trichotillomania symptom severity, and the risk ratio (RR) of the clinical response based on a dichotomous measure, with 95% confidence intervals (CIs). **MAIN RESULTS:** We identified eight studies with a total of 204 participants and a mean sample size of 25. All trials were single-centre trials, and participants seen on an outpatient basis. Seven studies compared medication and placebo (n = 184); one study compared medication and another active agent (n = 13). Duration of the studies was six to twelve weeks. Meta-analysis was not undertaken because of the methodological heterogeneity of the trials. The studies did not employ intention-to-treat analyses and were at a high risk of attrition bias. Adverse events were not well-documented in the studies. None of the three studies of selective serotonin reuptake inhibitors (SSRIs) demonstrated strong evidence of a treatment effect on any of the outcomes of interest. The unpublished naltrexone study did not provide strong evidence of a treatment effect. Two studies, an olanzapine study and a N-acetylcysteine (NAC) study, reported statistically significant treatment effects. One study of clomipramine demonstrated a treatment effect on two out of three measures of response to treatment. **AUTHORS' CONCLUSIONS:** No particular medication class definitively demonstrates efficacy in the treatment of trichotillomania. Preliminary evidence suggests treatment effects of clomipramine, NAC and olanzapine based on three individual trials, albeit with very small sample sizes.

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*Samuel, M. Zimovetz, E.A. Gabriel Z. and Beard S.M. 2011.*  
*Efficacy and safety of treatments for refractory generalized anxiety disorder: a systematic review.*

This study systematically collated clinical evidence on refractory generalized anxiety disorder (GAD). Refractory GAD patients are those who have failed to respond adequately to at least one earlier treatment for GAD. MEDLINE, EMBASE, The Cochrane Library and conference proceedings were searched to identify trials. Four placebo-controlled trials (pregabalin, olanzapine, quetiapine, risperidone) and four single-arm studies (aripiprazole, risperidone, quetiapine, ziprasidone) evaluated the add-ons to initial treatment(s) or switch of treatment(s) because of inadequate efficacy. The most robust trial was the pregabalin study, with a study duration of 8 weeks and a largest sample size that consists of 356 patients. A significant reduction in the Hamilton Anxiety Scale (HAM-A) score was found for pregabalin and risperidone augmentation compared with placebo. Olanzapine augmentation resulted in a significantly higher proportion of responders (using HAM-A scores) compared with placebo. Quetiapine augmentation did not result in significantly greater mean reductions in the HAM-A scores compared with placebo. There is a need for effective and safe augmentation treatments for patient's refractory to initial treatments for GAD. This study has located one large robust trial assessing the add-on to pregabalin. All other trials were small and unpowered studies with less than 50 patients. Further high-quality trials of augmentation treatment on refractory GAD are required.

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*Schmedt, N. and Garbe, E. 2013.*  
*Antipsychotic drug use and the risk of venous thromboembolism in elderly patients with dementia.*

The aim of this study was to investigate the association between the use of antipsychotics and the risk of venous thromboembolism (VTE) in elderly patients with dementia. Based on data from the German Pharmacoepidemiological Research Database, a nested case-control study was conducted within a cohort of 72,591 patients with dementia aged at least 65 years at cohort entry. Cases were patients with a hospitalization due to VTE. Up to 4 controls were matched to each case according to age, sex, health insurance, and calendar time of the VTE. Users of antipsychotics were classified into current or former users, and in addition, all current users were categorized as prevalent or new users. For a further analysis, we distinguished between users of either conventional or atypical antipsychotics or concurrent users of both conventional and atypical antipsychotics. Multivariate conditional logistic regression was applied to calculate odds ratios (ORs) of VTE for all user groups compared with nonusers. The case-control data set comprised 1028 VTE cases and 4109 controls. An increased risk of VTE was found for current users (OR, 1.23; 95% confidence interval [CI], 1.01-1.50) and for users of a combination of atypical and conventional antipsychotics (OR, 1.62; 95% CI, 1.15-2.27). In current users, only new use was associated with an increased risk (OR, 1.63; 95% CI, 1.10-2.40). Increased attention to clinical signs of VTE

should be paid during the first 3 months of treatment with antipsychotics and in patients receiving both conventional and atypical agents, especially if other risk factors for VTE exist.

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*Sheehan, D. V., Locklear, J., Svedsater, H. and Datto, C. 2012.*

*Long-term functioning and sleep quality in patients with major depressive disorder treated with extended-release quetiapine fumarate.*

The aim of this study was to assess patients' functioning and sleep quality during extended-release quetiapine fumarate (quetiapine XR) maintenance treatment. A double-blind, randomized-withdrawal maintenance study of quetiapine XR monotherapy was carried out in patients with major depressive disorder. Following 4-8 weeks of open-label quetiapine XR and 12-18 weeks of open-label quetiapine XR stabilization (50, 150, or 300 mg/day), eligible patients were randomized to quetiapine XR (50, 150, or 300 mg/day) or placebo. Secondary variables of the Sheehan Disability Scale (SDS) and the Pittsburgh Sleep Quality Index (PSQI) were used to assess functioning and sleep quality and are reported here. Quetiapine XR significantly maintained functioning versus placebo. Changes in the least squares means (LSM) from randomization in the SDS total scores were as follows: -0.45, quetiapine XR (P<0.05), versus 0.44, placebo. Quetiapine XR significantly maintained SDS domains 'social life/leisure' (-0.19; P<0.05) and 'family life/home responsibilities' (-0.22; P<0.05) versus placebo (0.13 and 0.10, respectively). Quetiapine XR significantly maintained sleep quality (LSM change in PSQI total scores: 0.06, quetiapine XR vs. 1.35, placebo; P<0.001), with five of seven PSQI components being significant for quetiapine XR versus placebo. In conclusion, quetiapine XR (50-300 mg/day) monotherapy better maintains overall functioning and sleep quality than placebo in patients with major depressive disorder.

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*Spielmanns, G.I. Berman, M.I. Linardatos, E. Rosenlicht, N.Z. Perry, A. and Tsai, A.C. 2013.*

*Adjunctive atypical antipsychotic treatment for major depressive disorder: A meta-analysis of depression, quality of life, and safety outcomes.*

**BACKGROUND:** Atypical antipsychotic medications are widely prescribed for the adjunctive treatment of depression, yet their total risk-benefit profile is not well understood. We thus conducted a systematic review of the efficacy and safety profiles of atypical antipsychotic medications used for the adjunctive treatment of depression. **METHODS AND FINDINGS:** We included randomized trials comparing adjunctive antipsychotic medication to placebo for treatment-resistant depression in adults. Our literature search (conducted in December 2011 and updated on December 14, 2012) identified 14 short-term trials of aripiprazole, olanzapine/fluoxetine combination (OFC), quetiapine, and risperidone. When possible, we supplemented published literature with data from manufacturers' clinical trial registries and US Food and Drug Administration New Drug Applications. Study duration ranged from 4 to 12 wk. All four drugs had statistically significant effects on remission, as follows: aripiprazole (odds ratio [OR], 2.01; 95% CI, 1.48-2.73), OFC (OR, 1.42; 95% CI, 1.01-2.0), quetiapine (OR, 1.79; 95% CI, 1.33-2.42), and risperidone (OR,

2.37; 95% CI, 1.31-4.30). The number needed to treat (NNT) was 19 for OFC and nine for each other drug. All drugs with the exception of OFC also had statistically significant effects on response rates, as follows: aripiprazole (OR, 2.07; 95% CI, 1.58-2.72; NNT, 7), OFC (OR, 1.30, 95% CI, 0.87-1.93), quetiapine (OR, 1.53, 95% CI, 1.17-2.0; NNT, 10), and risperidone (OR, 1.83, 95% CI, 1.16-2.88; NNT, 8). All four drugs showed statistically significant effects on clinician-rated depression severity measures (Hedges' g ranged from 0.26 to 0.48; mean difference of 2.69 points on the Montgomery-Asberg Depression Rating Scale across drugs). On measures of functioning and quality of life, these medications produced either no benefit or a very small benefit, except for risperidone, which had a small-to-moderate effect on quality of life ( $g = 0.49$ ). Treatment was linked to several adverse events, including akathisia (aripiprazole), sedation (quetiapine, OFC, and aripiprazole), abnormal metabolic laboratory results (quetiapine and OFC), and weight gain (all four drugs, especially OFC). Shortcomings in study design and data reporting, as well as use of post hoc analyses, may have inflated the apparent benefits of treatment and reduced the apparent incidence of adverse events. **CONCLUSIONS:** Atypical antipsychotic medications for the adjunctive treatment of depression are efficacious in reducing observer-rated depressive symptoms, but clinicians should interpret these findings cautiously in light of (1) the small-to-moderate-sized benefits, (2) the lack of benefit with regards to quality of life or functional impairment, and (3) the abundant evidence of potential treatment-related harm. Please see later in the article for the Editors' Summary.

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*Teranishi, M. Kurita, M. Nishino, S. Takeyoshi, K. Numata, Y. Sato, T. Tateno, A. and Okubo, Y. 2013.*

*Efficacy and tolerability of risperidone, yokukansan, and fluvoxamine for the treatment of behavioral and psychological symptoms of dementia: a blinded, randomized trial.*

The descriptive term behavioral and psychological symptoms of dementia (BPSD) is used to cover a range of noncognitive disturbances including anxiety, depression, irritability, aggression, agitation, eating disorders, and inappropriate social or sexual behaviors. Behavioral and psychological symptoms of dementia are seen in about 90% of patients with dementia. We aimed to compare the efficacy and tolerability of risperidone, yokukansan, and fluvoxamine used for BPSD in elderly patients with dementia. Ninety inpatients with dementia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria were investigated in Sato Hospital, Koutokukai. We conducted an 8-week, rater-blinded, randomized trial, administering flexibly dosed risperidone, yokukansan, or fluvoxamine. Primary outcome measures were Neuropsychiatric Inventory in Nursing Home Version total score and its items. Secondary outcome measures were cognitive function measured by Mini-Mental State Examination and daily life function measured by Functional Independence Measure (FIM). Neurological adverse effects were measured by the Drug-Induced Extra-Pyramidal Symptoms Scale. At the end of the study, we analyzed 76 patients (92.7%). Mean Neuropsychiatric Inventory in Nursing Home Version total score decreased in all 3 drug groups, with no significant between-group differences. Mini-Mental State Examination and Functional Independence Measure scores did not change significantly. Drug-Induced Extra-Pyramidal Symptoms Scale scores did not change in the yokukansan and fluvoxamine groups, but increased significantly in the risperidone group.

Risperidone, yokukansan, and fluvoxamine were equally effective in the treatment of BPSD in elderly patients. However, yokukansan or fluvoxamine for BPSD showed a more favorable profile in tolerability compared with risperidone. This trial is registered at UMIN Clinical Trials Registry (identifier: UMIN000006146).

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*Thase, M. E., Montgomery, S., Papakostas, G. I., Bauer, M., Trivedi, M. H., Svedsater, H., Locklear, J. C., Gustafsson, U., Datto, C. and Eriksson, H. 2013.*

*Quetiapine XR monotherapy in major depressive disorder: a pooled analysis to assess the influence of baseline severity on efficacy.*

The efficacy of quetiapine XR was investigated in patients with major depressive disorder and differing levels of baseline severity. Pooled data from four placebo-controlled monotherapy studies of quetiapine XR (50-300 mg/day) were analyzed. Post-hoc analyses were carried out to assess change from baseline in the Montgomery Asberg Depression Rating Scale (MADRS) total score at endpoint (week 6 or 8) to week 1, and response ( $\geq 50\%$  reduction in MADRS total score) and remission (MADRS total score  $\leq 10$ ) rates at endpoint for all patients and six baseline severity cohorts (MADRS total score  $\geq 24$ ,  $\geq 26$ ,  $\geq 28$ ,  $\geq 30$ ,  $\geq 32$ , and  $\geq 34$ ). In total, 1752 patients (all patients) were evaluated (MADRS score at baseline:  $\geq 24$ , n=1601;  $\geq 26$ , n=1467;  $\geq 28$ , n=1269;  $\geq 30$ , n=1038;  $\geq 32$ , n=745; and  $\geq 34$ , n=500). At endpoint, quetiapine XR reduced MADRS total score in all patients ( $P < 0.001$ ) and each severity cohort ( $\geq 24$ ,  $\geq 26$ ,  $\geq 28$ ,  $\geq 30$ , and  $\geq 32$ ,  $P < 0.001$ ;  $\geq 34$ ,  $P < 0.01$ ) versus placebo. Quetiapine XR also improved MADRS total score at week 1, response rates for each severity cohort, and remission rates in five out of six severity cohorts, versus placebo. Quetiapine XR monotherapy showed antidepressant effects in patients with major depressive disorder across different levels of baseline severity.

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*Vigen, C.L. Mack, W.J. Keefe, R.S. Sano, M. Sultzer, D.L. Stroup, T.S. Dagerman, K.S. Hsiao, J.K. Lebowitz, B.D. Lyketsos, C.G. Tariot, P.N. Zheng L. and Schneider, L.S. 2011.*

*Cognitive effects of atypical antipsychotic medications in patients with Alzheimer's disease: outcomes from CATIE-AD.*

**OBJECTIVE:** The impact of the atypical antipsychotics olanzapine, quetiapine, and risperidone on cognition in patients with Alzheimer's disease is unclear. The authors assessed the effects of time and treatment on neuropsychological functioning during the Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease study (CATIE-AD). **METHOD:** CATIE-AD included 421 outpatients with Alzheimer's disease and psychosis or agitated/aggressive behavior who were randomly assigned to receive masked, flexible-dose olanzapine, quetiapine, risperidone, or placebo. Based on their clinicians' judgment, patients could discontinue the originally assigned medication and receive another randomly assigned medication. Patients were followed for 36 weeks, and cognitive assessments were obtained at baseline and at 12, 24, and 36 weeks.

Outcomes were compared for 357 patients for whom data were available for at least one cognitive measure at baseline and one follow-up assessment that took place after they had been on their prescribed medication or placebo for at least 2 weeks. RESULTS: Overall, patients showed steady, significant declines over time in most cognitive areas, including in scores on the Mini-Mental State Examination (MMSE; -2.4 points over 36 weeks) and the cognitive subscale of the Alzheimer's Disease Assessment Scale (-4.4 points). Cognitive function declined more in patients receiving antipsychotics than in those given placebo on multiple cognitive measures, including the MMSE, the cognitive subscale of the Brief Psychiatric Rating Scale, and a cognitive summary score summarizing change on 18 cognitive tests. CONCLUSIONS: In CATIE-AD, atypical antipsychotics were associated with worsening cognitive function at a magnitude consistent with 1 year's deterioration compared with placebo. Further cognitive impairment is an additional risk of treatment with atypical antipsychotics that should be considered when treating patients with Alzheimer's disease.

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*Weisler, R. H., Montgomery, S. A., Earley, W. R., Szamosi, J. and Lazarus, A. 2012.*

*Efficacy of extended release quetiapine fumarate monotherapy in patients with major depressive disorder: a pooled analysis of two 6-week, double-blind, placebo-controlled studies.*

Prospectively planned pooled analysis evaluating the efficacy of quetiapine extended release (XR) monotherapy in major depressive disorder (MDD). Data were pooled from two 6-week, randomized, double-blind, placebo-controlled studies of quetiapine XR in outpatients with MDD. The primary endpoint was Montgomery-Asberg Depression Rating Scale (MADRS) total score change from randomization at week 6. Other evaluations were MADRS response/remission, Hamilton Rating Scale for Anxiety, and subgroup analyses. A total of 968 patients were randomized to quetiapine XR, 150 mg/day (n=315), 300 mg/day (n=323), or placebo (n=330). The mean MADRS total score reductions from randomization were significant at week 6 with quetiapine XR, 150 mg/day (-14.7; P<0.001) and 300 mg/day (-14.7; P<0.001) versus placebo (-11.1), with significant reductions versus placebo from week 1 onward. Response rates (week 6): 52.7% (P<0.001) quetiapine XR 150 mg/day and 49.5% (P<0.001) quetiapine XR 300 mg/day versus placebo (33.0%). MADRS remission (score  $\leq$  8; week 6): 23.5% (P=0.208) quetiapine XR 150 mg/day and 28.8% (P<0.01) quetiapine XR 300 mg/day versus placebo (19.4%). Quetiapine XR (both doses) significantly improved eight of 10 MADRS items versus placebo at week 6. The therapeutic effect of quetiapine XR was neither limited to nor driven by factors such as sex, age, or severity of depression. In patients with MDD, quetiapine XR (150 and 300 mg/day) monotherapy reduced depressive symptoms, with significant improvements compared with placebo from week 1 onward.

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*Wenzel, C., Kleimann, A., Bokemeyer, S. and Muller-Vahl, K. R. 2012.*

*Aripiprazole for the treatment of Tourette syndrome: a case series of 100 patients.*

**OBJECTIVE:** Aripiprazole is an atypical neuroleptic with agonistic and antagonistic dopaminergic and serotonergic effects. Because preliminary data obtained from uncontrolled studies suggest that aripiprazole may be effective in the treatment of tics, we performed a retrospective study with a large group of patients with Tourette syndrome. **METHODS:** One hundred patients (78 men and 22 women; mean  $\pm$  SD age, 27.1 years ( $\pm$  11.5) years) who had been treated with daily doses of 5 to 45 mg (mean, 17.0  $\pm$  9.6 mg) aripiprazole at our specialized Tourette syndrome outpatient clinic were included. Ninety-five patients with insufficient pretreatment (one or more neuroleptics) were switched to aripiprazole. **RESULTS:** Eighty-two patients exhibited a considerable reduction in tic severity. In 48 patients, effective treatment lasted for more than 12 months. Five patients reported additional beneficial effects on behavioral comorbidities such as depression, anxiety, and autoaggression. Altogether, 31 patients (31%) dropped out of the treatment owing to inefficacy ( $n = 7$ ), adverse effects ( $n = 15$ : drowsiness, agitation, weight gain, and sleep disturbances), both ( $n = 4$ ) or other reasons ( $n = 5$ ). **CONCLUSION:** This is the largest case series on the treatment of tics with aripiprazole so far. Overall, our results corroborate previous data suggesting that aripiprazole is effective and safe in most patients. In particular, our data confirm effectiveness in adult patients and clarify that beneficial effects sustain. However, in contrast to previous data, in 1 of 3 of our highly selected patients, aripiprazole was ineffective or not well tolerated. Optimal dose seems to be individually different and may range from 5 to 45 mg.

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*White, M.P. and Koran, L.M. 2011.*

*Open-label trial of aripiprazole in the treatment of trichotillomania.*

**BACKGROUND:** Serotonin reuptake inhibitors have been disappointing in the treatment of trichotillomania (TTM). Recent evidence suggests that medications that modulate dopamine may be helpful in this disorder. **OBJECTIVE:** To determine if the D2 partial agonist aripiprazole would be effective in the treatment of TTM. **METHODS:** Twelve subjects participated in an 8-week, open-label, flexible-dose study of aripiprazole treatment of TTM. Primary end points were reduction in the Massachusetts General Hospital Hair Pulling Scale (MGHHS) and MGHHS Actual Pulling Subscale (MGHHS-APS). Secondary end points were the Clinical Global Impressions-Improvement Scale, Hamilton Anxiety Scale, Hamilton Depression Scale, Beck Depression Inventory, and Beck Anxiety Inventory. **RESULTS:** Eleven of 12 subjects had 2 or more assessments; one subject dropped out during the first week. For subjects with 2 or more assessments, there was a significant mean reduction in both primary end points, the MGHHS score (mean change, 7.8; SD,  $\pm$  7.8;  $P \leq 0.01$ ) and the MGHHS-APS score (mean change, 3.9; SD,  $\pm$  4.1;  $P \leq 0.02$ ). Seven subjects had a greater than 50% reduction in MGHHS; 7 subjects had an exit Clinical Global Impressions-Improvement Scale of 2 or lower, and 5 participants had absolute exit scores of 3 or lower on the MGHHS and 1 or lower on the MGHHS-APS. There were no significant changes in mood-related secondary end points. The mean aripiprazole dose for all completers ( $N = 11$ ) was 7.5 mg/d ( $\pm$  3.4 mg/d).

CONCLUSIONS: This small open-label study suggests that aripiprazole is a promising treatment for the treatment of trichotillomania. Larger double-blind, placebo-controlled studies are needed to follow up on these findings.

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*Youssef, N. A., Marx, C. E., Bradford, D. W., Zinn, S., Hertzberg, M. A., Kilts, J. D., Naylor, J. C., Butterfield, M. I. and Strauss, J. L. 2012. An open-label pilot study of aripiprazole for male and female veterans with chronic post-traumatic stress disorder who respond suboptimally to antidepressants.*

Emerging data suggest that second-generation antipsychotics such as aripiprazole may be effective in the treatment of post-traumatic stress disorder (PTSD). However, few clinical trials have used aripiprazole in PTSD, and data are limited on its use in Veterans with PTSD. The objective of this pilot trial was to investigate the safety and efficacy of aripiprazole in Veterans with PTSD. Ten individuals (five men and five women) meeting the Diagnostic and statistical manual of mental disorders, 4th ed., PTSD criteria participated in this 12-week, open-label, flexibly dosed monotherapy trial. The dose range of aripiprazole was 5-30 mg/day, titrated to tolerability and clinical response. The primary outcome measure was the Clinician-Administered PTSD Scale. Additional outcomes included the Short PTSD Rating Interview, the Treatment Outcome PTSD Scale (Top-8), the Davidson Trauma Scale, the Positive and Negative Syndrome Scale, the Beck Depression Inventory-Fast Screen, and Clinical Global Impressions-Improvement. Eight participants completed the study, and aripiprazole was generally well tolerated and associated with a significant improvement in PTSD symptoms, as measured by the Clinician-Administered PTSD Scale (primary outcome measure) and by the Short PTSD Rating Interview, the Treatment Outcome PTSD Scale, and the Davidson Trauma Scale. An improvement was also observed on all three Positive and Negative Syndrome Scale subscales and the Beck Depression Inventory-Fast Screen, and the average Clinical Global Impressions-Improvement ratings indicated that patients were 'much improved'. These promising initial results merit further investigation in a larger, randomized-controlled trial.

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*Zanarini, M. C., Schulz, S. C., Detke, H., Zhao, F., Lin, D., Pritchard, M., Deberdt, W., Fitzmaurice, G. and Corya, S. 2012. Open-label treatment with olanzapine for patients with borderline personality disorder.*

This report presents efficacy and safety outcomes for patients with borderline personality disorder (BPD) treated with olanzapine for up to 24 weeks. In 2 concurrent studies, patients received open-label olanzapine for 12 weeks after 12 weeks of double-blind olanzapine or placebo. Open-label dosing started at 2.5 or 5 mg/d and could be increased up to 20 mg/d (study 1) or 15 mg/d (study 2). The primary efficacy measure was open-label baseline-to-endpoint change in Zanarini Rating Scale for BPD (ZAN-BPD) total score. Of 472 patients who completed the double-blind acute phase, 444 entered and 320 (72.1%) completed 12 weeks of open-label extension treatment. Mean ZAN-BPD total scores at the start of the

acute phase were approximately 17, indicating moderate symptom severity. Mean ZAN-BPD total scores ranged from 7.8 to 10.5 at the start of the open-label treatment and decreased to 5.7 to 6.5, indicating mild symptom severity, by the end of the open-label treatment. Patients taking placebo during the acute phase showed increases in weight, prolactin level, and other laboratory values during open-label olanzapine treatment similar in magnitude to increases seen in olanzapine-treated patients during the acute phase. Patients proceeding from olanzapine during the acute phase to open-label olanzapine showed smaller changes in weight and laboratory values. In conclusion, these results suggest that continued therapy with olanzapine may sustain and build upon improvements seen with acute olanzapine treatment of patients with BPD. However, no medication is currently approved for treatment of BPD, and physicians should carefully weigh potential benefits and risks of antipsychotic treatment in this population.

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*Zhornitsky, S. Potvin, S. Moteshafî, H. Dubreucq, S. Rompre, P.P. and Stip, E. 2011.*

*Dose-response and comparative efficacy and tolerability of quetiapine across psychiatric disorders: A systematic review of the placebo-controlled monotherapy and add-on trials.*

The atypical antipsychotic, quetiapine, is frequently prescribed on-label and off-label for the treatment of a variety of psychiatric disorders. As quetiapine has variable affinity for dozens of receptors, its clinical effects should also show a large variation as a function of dose and diagnostic category. This study attempts to elucidate the dose-response and comparative efficacy and tolerability (metabolic data) of quetiapine across psychiatric disorders. A systematic search was carried out in the electronic databases, PubMed and EMBASE, using the keywords 'quetiapine' and 'placebo'. Both monotherapy and add-on studies were included. A total of 41 studies were identified. In unipolar and bipolar depression, studies consistently found quetiapine to be effective versus placebo, at doses of approximately 150-300 and 300-600 mg per day, respectively. In bipolar mania, they consistently found quetiapine to be effective at doses of approximately 600 mg per day. In acute exacerbation of schizophrenia, the majority of studies found quetiapine to be effective at doses of approximately 600 mg per day; however, a few large studies found no difference versus placebo. In contrast, studies consistently found quetiapine to be more effective than placebo for stable schizophrenia. In obsessive-compulsive disorder, studies did not consistently find quetiapine to be effective at doses of approximately 300 mg per day. However, studies may have underestimated the efficacy of quetiapine for obsessive-compulsive disorder due to concomitant administration of antidepressants and the utilization of treatment-refractory patients. In generalized anxiety disorder, studies consistently found quetiapine to be effective at doses of approximately 150 mg per day. Finally, analysis of metabolic tolerability data suggests that even low doses of quetiapine may lead to increase in weight and triglycerides across psychiatric disorders. Interestingly, however, quetiapine-induced elevations in low-density lipoprotein and total cholesterol seem to be restricted to schizophrenia patients.



## Appendix G. Summary Table

Conclusions From CER Executive Summary	SRC Literature Search (June 2014)	Expert Opinion	Conclusion from SRC
<b>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?</b>			
<p><b>Leading off-label uses of atypical antipsychotics:</b></p> <p>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><b>Utilization trends:</b></p> <p>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, 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</p>	<p><b>Leading off-label uses of atypical antipsychotics:</b></p> <p>No new research was found.</p> <p><b>Utilization trends:</b></p> <p>Three studies examined utilization trends.<sup>11-13</sup> 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.<sup>6</sup> One study found that antipsychotic use increased from 25.9% to 41.9% among Medicaid enrollees (1996-2006).<sup>9</sup> One study found that atypical antipsychotic use for dementia declined after the black box warning in 2005.<sup>16</sup> No studies examined trends after 2007.</p> <p><b>New uses:</b></p> <p>Four studies<sup>5-7,9</sup> examined new off-label uses for previously approved atypicals (risperidone, aripiprazole, paliperidone and quetiapine): Huntington’s disease, trichotillomania, somatoform</p>	<p><b>Leading off-label uses of atypical antipsychotics:</b></p> <p>No new research.</p> <p><b>Utilization trends:</b></p> <p>Three suggested studies examined utilization trends.<sup>14-16</sup> These studies examined trends in antipsychotic utilization in timeframes ranging from 2003 to 2010.</p> <p><b>New uses:</b></p> <p>One suggested RCT<sup>8</sup> examined off-label use of ziprasidone for delirium.</p>	<p>The original review conclusion is possibly out of date with regard to new uses of atypical antipsychotics.</p>

<p>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><b>New uses:</b></p> <p>No off-label use of the newly approved atypicals (asenapine, iloperidone, and paliperidone) was reported in the utilization literature.</p>	<p>disorder, and fibromyalgia. One review included a study of olanzapine use for trichotillomania.<sup>46</sup></p> <p>One study examined off-label use of asenapine for personality disorder.<sup>10</sup></p> <p>No off-label use of the newly approved atypical (lurasidone) was reported.</p>		
<p><b>Key Question 2: What does the evidence show regarding the efficacy and comparative of atypical antipsychotics for off-label indications?</b></p> <ul style="list-style-type: none"> <li><b>How do atypical antipsychotic medications compare with other drugs, including first-generation antipsychotics, for treating off-label indications?</b></li> </ul>			
<p><b>Dementia (SOE High):</b></p> <p>Aripiprazole, olanzapine, and risperidone have efficacy as treatment for behavioral symptoms of dementia.</p>	<p>Two randomized trials<sup>17,18</sup> 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.<sup>19</sup> One review reported efficacy of atypical antipsychotics in behavioral and psychotic symptoms of dementia.<sup>48</sup></p>	<p>Original report conclusions still supported by current evidence.</p>	<p>Original report conclusion is still valid and this portion of the original report does not need updating.</p>

<p><b>Depression- MDD: Augmentation of SSRI/SNRI (SOE Moderate - risperidone, aripiprazole, quetiapine; SOE Low - olanzapine, ziprasidone)</b> Aripiprazole, quetiapine, and risperidone have efficacy as augmentation to SSRIs/SNRIs for major depressive disorder. Olanzapine and ziprasidone may also have efficacy.</p> <p><b>Depression- MDD: Monotherapy (SOE Moderate)</b></p> <p>Olanzapine does not have efficacy as monotherapy for major depressive disorder. Quetiapine has efficacy as monotherapy for major depressive disorder.</p>	<p><b>Depression- MDD: Augmentation of SSRI/SNRI:</b></p> <p>One review reported efficacy of aripiprazole, quetiapine, and risperidone as augmentation to SSRIs/SNRIs.<sup>51</sup> 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.<sup>50</sup></p> <p><b>Depression- MDD: Monotherapy</b></p> <p>Four studies (2 pooled analyses of RCTs,<sup>20,21</sup> 1 post-hoc analysis of RCT,<sup>22</sup> 1 RCT<sup>23</sup>) reported efficacy of quetiapine for MDD. One RCT reported potential efficacy of ziprasidone for MDD.<sup>24</sup></p>	<p>Original report conclusions still supported by current evidence.</p>	<p>Original report conclusion is still valid and this portion of the original report does not need updating.</p>
<p><b>Obsessive-compulsive disorder: augmentation of SSRI (SOE Moderate - risperidone; SOE Low- olanzapine)</b> 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><b>Obsessive-compulsive disorder: augmentation of SSRI:</b></p> <p>One RCT<sup>25</sup> reported quetiapine-fluoxetine is ineffective in improving OCD symptoms compared to fluoxetine-clomipramine or fluoxetine-placebo. One RCT<sup>26</sup> reported efficacy of aripiprazole in improving OCD symptoms as an adjunct to SSRIs. One review reported no consistent effect of</p>	<p><b>Obsessive-compulsive disorder: augmentation of SSRI:</b></p> <p>One suggested meta-analysis reported efficacy for risperidone for improving OCD symptoms as augmentation to SSRIs.<sup>27</sup></p> <p>Original report conclusions still supported by current evidence.</p> <p><b>Obsessive-compulsive disorder:</b></p>	<p>Original report conclusion is still valid and this portion of the original report does not need updating.</p>

<p><b>Obsessive-compulsive disorder: augmentation of citalopram (SOE Low- quetiapine; SOE Very Low – risperidone)</b></p> <p>Quetiapine and risperidone may be efficacious as augmentation to citalopram in OCD patients.</p>	<p>quetiapine for OCD symptoms.<sup>32</sup></p> <p><b>Obsessive-compulsive disorder: augmentation of citalopram:</b></p> <p>No new research was found.</p>	<p><b>augmentation of citalopram:</b></p> <p>No new research.</p>	
<p><b>Post-traumatic stress disorder (SOE Moderate- risperidone; SOE Low - olanzapine; SOE Very Low- quetiapine)</b></p> <p>Risperidone is efficacious in reducing combat-related PTSD symptoms when used as an adjunct to primary medication.</p>	<p>One pilot study<sup>28</sup> reported efficacy of aripiprazole in improving PTSD symptoms. One randomized trial<sup>29</sup> 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.<sup>47</sup></p>	<p>Original report conclusions still supported by current evidence.</p>	<p>Original report conclusion is still valid and this portion of the original report does not need updating.</p>
<p><b>Personality disorders: borderline (SOE Low- aripiprazole; SOE very low - quetiapine, olanzapine)</b></p> <p>Olanzapine had mixed results in 7 trials, aripiprazole was found efficacious in 2 trials, quetiapine was found efficacious in 1 trial, and ziprasidone was found not efficacious in 1 trial.</p> <p><b>Personality disorders: schizotypal (SOE Low)</b></p>	<p><b>Personality disorders: borderline:</b></p> <p>One non-randomized trial reported efficacy of olanzapine.<sup>30</sup> One case-series reported improved symptoms with asenapine treatment.<sup>10</sup> One meta-analysis found improved symptoms with antipsychotic treatment.<sup>44</sup></p> <p><b>Personality disorders: schizotypal:</b></p>	<p><b>Personality disorders: borderline:</b></p> <p>One suggested review reported some efficacy of atypical antipsychotics.<sup>31</sup></p> <p>Original report conclusions still supported by current evidence.</p> <p><b>Personality disorders: schizotypal:</b></p> <p>No new research.</p>	<p>Original report conclusion is still valid and this portion of the original report does not need updating.</p>

Risperidone had mixed results when used to treat schizotypal personality disorder in 2 small trials.	No new research was found.		
<b>Tourette's Syndrome (SOE Low)</b> Risperidone is at least efficacious as pimozide or clonidine for Tourette's Syndrome.	One case-series reported improvement in Tourette's Syndrome symptoms with aripiprazole treatment. <sup>32</sup>	Original report conclusions still supported by current evidence.	Original report conclusion is still valid and this portion of the original report does not need updating.
<b>Anxiety (SOE Moderate)</b> Quetiapine has efficacy as treatment for Generalized Anxiety Disorder.	Five studies (1 pooled analysis of 3 RCTs <sup>33</sup> , 4 RCTs <sup>34-37</sup> ) reported efficacy of quetiapine as treatment for Generalized Anxiety Disorder. One review reported reduced anxiety score with olanzapine augmentation but not for quetiapine augmentation. <sup>45</sup> One review reported efficacy of quetiapine for anxiety. <sup>52</sup>	One suggested review <sup>38</sup> reported efficacy of quetiapine as treatment of generalized anxiety.  Original report conclusions still supported by current evidence.	Original report conclusion is still valid and this portion of the original report does not need updating.

<p><b>Attention deficit/hyperactivity disorder: no co-occurring disorders (SOE Low)</b></p> <p>Risperidone may be efficacious in treating children with ADHD with no serious co-occurring disorders.</p> <p><b>Attention deficit/hyperactivity disorder: mentally retarded children (SOE Low)</b></p> <p>Risperidone may be superior to methylphenidate in treating ADHD symptoms in mentally retarded children.</p> <p><b>Attention deficit/hyperactivity disorder: bipolar children (SOE Low)</b></p> <p>Aripiprazole is inefficacious in reducing ADHD symptoms in children with bipolar disorder.</p>	<p>One review reported efficacy of risperidone in treating children with ADHD.<sup>49</sup></p>	<p>No new research.</p>	<p>Original report conclusion is still valid and this portion of the original report does not need updating.</p>
<p><b>Eating disorders (SOE Moderate-olanzapine; SOE Low- quetiapine)</b></p> <p>Olanzapine and quetiapine have no efficacy in increasing body mass in eating disorder patients.</p>	<p>No new research was found.</p>	<p>No new research.</p>	<p>Original report conclusion is still valid and this portion of the original report does not need updating.</p>

<p><b>Insomnia (SOE Very Low)</b></p> <p>Quetiapine may be inefficacious in treating insomnia.</p>	<p>One non-randomized pilot study reported potential efficacy of quetiapine for sleep continuity.<sup>39</sup></p>	<p>Original report conclusions still supported by current evidence.</p>	
<p><b>Substance abuse: alcohol (SOE Moderate- aripiprazole; SOE Low- quetiapine)</b></p> <p>Aripiprazole is inefficacious in treating alcohol abuse/ dependence. Quetiapine may also be inefficacious.</p> <p><b>Substance abuse: cocaine (SOE Low)</b></p> <p>Olanzapine is inefficacious in treating cocaine abuse/dependence. Risperidone may also be inefficacious.</p> <p><b>Substance abuse: methamphetamine (SOE Low)</b></p> <p>Aripiprazole is inefficacious in treating methamphetamine abuse/dependence.</p> <p><b>Substance abuse: methadone clients (SOE Low)</b></p> <p>Risperidone is an inefficacious adjunct to methadone maintenance.</p>	<p>No new research was found.</p>	<p>No new research.</p>	<p>Original report conclusion is still valid and this portion of the original report does not need updating.</p>

<b>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?</b>			
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.	One study reported predictors of severity of OCD in response to antipsychotic augmentation of SRIs. <sup>53</sup>	No new research.	Original report conclusion is still valid and this portion of the original report does not need updating.
<b>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?</b>			
<p><b>Weight gain</b></p> <p>Olanzapine is associated with more weight gain than placebo, conventional antipsychotics, or other atypical antipsychotics. (SOE High)</p> <p>Some evidence for other atypical antipsychotics. Risperidone, quetiapine and aripiprazole are associated with more weight gain compared with placebo.</p> <p><b>Endocrine/diabetes (SOE Low)</b></p> <p>Olanzapine associated with higher risk of diabetes than risperidone.</p>	<p><b>Weight gain</b></p> <p>One randomized trial reported weight gain more common with risperidone compared to placebo.<sup>29</sup> One review reported weight gain with risperidone use among children with ADHD.<sup>49</sup></p> <p>One review reported weight gain associated with aripiprazole, quetiapine, risperidone, and the combination of olanzapine and fluoxetine.<sup>50</sup> One review reported weight gain with risperidone, quetiapine and aripiprazole.<sup>51</sup> One review reported weight gain with quetiapine use.<sup>52</sup></p> <p><b>Endocrine/diabetes</b></p> <p>One RCT reported worsening glucose metabolism factors with olanzapine compared to placebo in healthy controls.<sup>40</sup> One review</p>	<p><b>Weight gain</b></p> <p>Original report conclusions still supported by current evidence.</p> <p><b>Endocrine/diabetes</b></p> <p>Original report conclusions still supported by current evidence.</p> <p><b>Mortality</b></p> <p>Original report conclusions still supported by current evidence.</p> <p><b>EPS</b></p> <p>There may be new research on EPS within trials of newer antipsychotic drugs.</p> <p>Original report conclusions still supported by current evidence.</p>	Original report conclusion is still valid and this portion of the original report does not need updating.

<p><b>Mortality</b></p> <p>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><b>EPS (SOE Moderate)</b></p> <p>Aripiprazole and risperidone are associated with an increase in extrapyramidal signs or symptoms compared to quetiapine.</p> <p><b>Tardive dyskinesia (SOE Low)</b></p> <p>Atypical antipsychotics are associated with less tardive dyskinesia than are high doses of haloperidol.</p>	<p>reported abnormal metabolic laboratory results with quetiapine.<sup>51</sup></p> <p><b>Mortality</b></p> <p>Two cohort studies reported increased risk of death with haloperidol treatment compared to risperidone.<sup>41,42</sup> One cohort study reported no association between antipsychotic use and death after adjustment for psychiatric symptoms.<sup>43</sup> One review reported increased risk of death with atypical antipsychotic treatment for dementia.<sup>48</sup></p> <p><b>EPS</b></p> <p>No new research was found.</p> <p><b>Tardive dyskinesia</b></p> <p>No new research was found.</p> <p><b>Akathisia</b></p> <p>One review reported increased risk of akathisia associated with aripiprazole.<sup>50</sup></p> <p><b>Venous thromboembolism:</b></p> <p>One case-control study reported increased risk of venous thromboembolism in new users of antipsychotics compared to</p>	<p><b>Tardive dyskinesia</b></p> <p>No new research.</p> <p><b>Venous thromboembolism</b></p> <p>Original report conclusions still supported by current evidence.</p>	
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**Key Question 5: What is the effective dose and time limit for off-label indications?**

There are too few studies comparing doses of atypical antipsychotic medications to draw a conclusion about a minimum dose needed.	One review reported effective doses for quetiapine for depression generalized anxiety disorder and no consistent effective dose for quetiapine for OCD treatment. <sup>52</sup>	No new research.	Original report conclusion is still valid and this portion of the original report does not need updating.
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Legend: ADHD = attention deficit hyperactivity disorder; OCD = obsessive compulsive disorder; PTSD = post-traumatic stress disorder; MDD = major depressive disorder; EPS = extrapyramidal symptoms, SRI = serotonin reuptake-inhibitor, SSRI = selective serotonin reuptake inhibitor