

# *AHRQ Comparative Effectiveness Review Surveillance Program*

**CER #63:** First-Generation Versus Second-Generation Antipsychotics in Adults: Comparative Effectiveness

**Original Release Date:** August, 2012

**Surveillance Report:** December, 2014

## **Summary of Key Findings from Surveillance Reports:**

- Key Question 1: Conclusions regarding findings related to the comparative efficacy of FGAs vs. SGAs for core illness symptoms in patients' schizophrenia or schizophrenia-related psychoses and bipolar disorder are out of date due to an SGA approved since the original CER was published with one identified trial comparing it to an FGA. Conclusions related to mania in patients with bipolar disorder are possibly out of date.
- Key Question 2: Report conclusions are still valid.
- Key Question 3: Conclusions regarding findings related to adverse events are out of date due to a new drug (lurasidone) released since the original CER and one study comparing it to an FGA (haloperidol).
- Key Question 4: Report conclusions are still valid.
- Key Question 5: Report conclusions are still valid.

**Signal Assessment:** The signals examined in this surveillance assessment suggest that the original CER is possibly out of date.

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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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## Contents

|   |     |
|---|-----|
| Introduction .....  | 1   |
| Methods .....   | 2   |
| Literature Searches .....   | 2   |
| Study selection.....  | 3   |
| Expert Opinion .....  | 3   |
| Horizon Scanning High-Impact Potential.....                                       | 3   |
| FDA Black Box Warnings.....   | 3   |
| Check for Qualitative Signals.....  | 3   |
| Compilation of Findings and Conclusions .....                                     | 3   |
| Signal Assessment for Updating.....   | 4   |
| Results .....   | 4   |
| Literature Search.....  | 4   |
| Horizon Scanning .....  | 5   |
| FDA Black Box Warnings.....   | 5   |
| Expert Opinion .....  | 5   |
| Identifying Qualitative Signals.....  | 5   |
| Signal Assessment for Updating.....   | 6   |
| References .....  | 7   |
| Appendices .....  | 9   |
| Appendix A. Top 10 Journals.....  | A-1 |
| Appendix B. Most Cited Journals from Original Systematic Review.....              | B-1 |
| Appendix C. Original Search Strategy .....  | C-1 |
| Appendix D. Inclusion and Exclusion Criteria from Original Systematic Review..... | D-1 |
| Appendix E. Literature Search Results.....  | E-1 |
| Appendix F. Questionnaire Sent to Expert Reviewers .....                          | F-1 |
| Appendix G: Summary Table.....  | G-1 |

## 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) #63 titled “First-Generation Versus Second-Generation Antipsychotics in Adults: Comparative Effectiveness” was originally released in August, 2012.<sup>1</sup>

The key questions for the original CER are as follows:

**Key Question 1.** For adults (age 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what are the comparative efficacy and effectiveness of FGAs versus SGAs for improving core illness symptoms? The following core symptoms were considered:

- Schizophrenia or related psychoses: positive (i.e., delusions and hallucinations) and negative (i.e., passive or apathetic social withdrawal and blunted affect) symptoms, general psychopathology (i.e., preoccupation, lack of insight, and motor retardation), and global ratings and total scores.
- Core illness symptoms for bipolar disorder: mood, motor activity or energy, sleep, speech, behavior, and mood stability.

**Key Question 2.** For adults (age 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what is the comparative effectiveness of FGAs versus SGAs for improving functional outcomes and decreasing health care system utilization?

- Functional outcomes include any of the following: employment or personal earnings, social relatedness or functioning, encounters with the legal system, sexual function or dysfunction, functional capacity, and living situation.
- Health care system utilization includes: time to hospitalization or re-hospitalization because of mental illness and all other causes, rates of hospitalization or re-hospitalization, mean hospital bed days, length of hospitalization stay, rates of emergency department visits, attendance in day care programs, and use of ancillary caseworkers.

**Key Question 3.** For adults (age 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, do FGAs and SGAs differ in medication-associated AEs and safety? AEs included:

- Overall AEs
- Specific AEs
- Major: mortality, cerebrovascular disease–related events, development of diabetes mellitus, diabetic ketoacidosis, neuroleptic malignant syndrome, seizures, tardive dyskinesia, cardiomyopathies and cardiac arrhythmias, agranulocytosis, suicide-related behaviors, and death by suicide
- General: extrapyramidal symptoms (EPS), weight changes, agitation, constipation, sedation, elevated cholesterol, AEs related to prolactin elevations, galactorrhea or bloody galactorrhea, hypotension, and metabolic changes (including changes in glucose levels, triglycerides, lipids, and the risk of developing diabetes)

- Study withdrawals and time to withdrawal because of AEs
- Persistence and reversibility of AEs

**Key Question 4.** For adults (age 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what is the comparative effectiveness of FGAs versus SGAs for the following other outcomes:

- Relapse and remission rates
- Medication adherence and persistent use (and associated dosing and time to discontinuation of treatment)
- Patient insight into illness
- Health-related quality of life
- Patient satisfaction
- Comorbidity: endpoints of victimization, homelessness, and substance abuse
- Patient-reported outcomes
- Ability to obtain and retain employment and succeed in job duties
- Concomitant use of other medications, especially those used to treat EPS
- Patient preferences

**Key Question 5.** For adults (age 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what are the comparative effectiveness and risks of FGAs versus SGAs in subgroups defined by the following variables?

- Disorder subtypes
- Sex
- Age group (18-35 years, 36-54 years, and 55-64 years)
- Race
- Comorbidities
- Drug dosage
- Follow-up period
- Treatment of a first episode versus treatment in the context of previous episodes (previous exposure to antipsychotics)
- Treatment resistance

Our surveillance assessment began in August 2014. We conducted an electronic search for literature published since the most recent surveillance report search date. After completing a scan of this literature to identify evidence potentially related to the key questions in this CER, we contacted experts involved in the original CER to request their opinions as to whether the conclusions had changed.

## Methods

### Literature Searches

We conducted two literature searches of PubMed and PsycINFO covering July 1, 2011 to August 30, 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 six high-profile general medical interest journals (Annals of Internal Medicine, British Medical Journal, Cochrane Database of Systematic Reviews, Journal of the American Medical Association, Lancet, and the New England Journal of Medicine) and five specialty journals (Archives of General Psychiatry, American Journal of Psychiatry, Schizophrenia Bulletin, Journal of Clinical Psychiatry, and British Journal of 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 11 high-impact journal search results (see Appendix E).

## **Expert Opinion**

We shared the conclusions of the original report and the newly identified studies with thirteen experts in the field (original peer reviewers, technical expert panel members [TEP] and a local expert) to request their assessment of the currency of report conclusions and their recommendations of any relevant new studies. Two subject matter experts responded. Appendix F shows the form that the experts were asked to complete.

## **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>2</sup> We reviewed the Depression and Other Mental Health Disorders section to identify new potentially high-impact interventions 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 a qualitative and quantitative synthesis of data comparing the effectiveness, harms, and prevalence of first versus second generation 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, the findings of the new literature search, and the 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 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 the 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 23 titles from the 11 selected high profile general medical and specialty journals (Appendix E). Upon abstract review, 22 articles were rejected because they did not meet the original CER inclusion criteria (see Appendix D). The remaining abstract<sup>3</sup> was examined for potential to change the results of the original review.

## Horizon Scanning

We identified one intervention, *Cortisol antagonist (mifepristone, Korlym) for treatment of psychotic depression*. The high impact potential for this intervention is on the lower end of the high-impact-potential range, and is not closely related to any of the key questions for this CER. Thus, we did not identify a relevant high-impact potential intervention for this CER.

## FDA Black Box Warnings

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

## Expert Opinion

We shared the conclusions of the original report with seven experts in the field (original peer reviewers, TEP members and a local expert) to request their assessment of the currency of report conclusions and their recommendations of any relevant new studies. Two subject matter experts responded.

The two experts identified potentially relevant studies related to Key Questions 1<sup>3,7</sup>, 3<sup>6</sup>, and 4<sup>6,9</sup> and agreed that Key Question 5 conclusions were still valid or did not know (see Appendix G).

## Identifying Qualitative Signals

Appendix G shows the original key questions, the conclusions of the original report and the most recent surveillance 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, for adults with schizophrenia, or schizophrenia related psychoses, conclusions are possibly out of date. A review that examined published and unpublished clinical trials<sup>5</sup> reported unpublished findings that haloperidol was significantly more effective than ziprasidone on the BPRS total, BPRS core, CGI-severity, and PANSS total, and more effective than iloperidone (outcome measures not stated). In addition, based on a recommendation by an expert, we searched [clinicaltrials.gov](http://clinicaltrials.gov) for studies comparing FGAs to SGAs. We identified one study comparing lurasidone to haloperidol that found no difference on the MADRS or the CGI-S<sup>6</sup>, and differences favoring haloperidol on the PANSS and BPRS; however, it is unclear whether these differences are statistically significant.

For patients with bipolar disorder experiencing mania, a multiple treatments meta-analysis<sup>3</sup> found haloperidol to be more effective than aripiprazole, asenapine, quetiapine and ziprasidone on the YMRS, add that risperidone and olanzapine had a very similar profile of comparative efficacy, being more effective than valproate, ziprasidone, lamotrigine, topiramate, and gabapentin. In addition, a study identified by one of our experts found that haloperidol was more likely to induce depression switching in patients<sup>7</sup> experiencing mania.

No studies identified by the SRC or experts had the potential to change the conclusions of Key Question 2. For Key Question 3, we identified one study comparing a drug approved since the original CER (lurasidone) compared with haloperidol.<sup>6</sup> While none of the adverse events highlighted in the original CER were included, adverse events were examined. No studies were identified for Key Questions 4 and 5. There were no new high-impact potential interventions for this report based on horizon scanning data, and no FDA boxed warnings were identified since the original report was published.

## Signal Assessment

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

- Key Question 1: Conclusions regarding findings related to the comparative efficacy of FGAs vs. SGAs for core illness symptoms in patients' schizophrenia or schizophrenia-related psychoses and bipolar disorder are out of date due to an SGA approved since the original CER was published with one identified trial comparing it to an FGA. Conclusions related to mania in patients with bipolar disorder are possibly out of date.
- Key Question 2: Report conclusions are still valid.
- Key Question 3: Conclusions regarding findings related to adverse events are out of date due to a new drug (lurasidone) released since the original CER and one study comparing it to an FGA (haloperidol).
- Key Question 4: Report conclusions are still valid.
- Key Question 5: Report conclusions are still valid.

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

## References

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# **Appendices**

**Appendix A: Top 10 Journals**

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

**Appendix C: Original Search Strategy**

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

**Appendix E: Literature Search Results**

**Appendix F: Questionnaire Matrix 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 General 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. The BMJ
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 |
|--|-----------|
| The American Journal of Psychiatry                           | 19        |
| Journal of Clinical Psychiatry                               | 9         |
| Archives of General Psychiatry                               | 8         |
| Schizophrenia Research                                       | 7         |
| International Clinical Psychopharmacology – LWW Journals     | 5         |
| The International Journal of Neuropsychopharmacology         | 5         |
| Acta Psychiatrica Scandinavica                               | 4         |
| The British Journal of Psychiatry                            | 4         |
| Lancet   | 4         |
| Neuropsychopharmacology                                      | 4         |
| Progress in Neuro-Psychopharmacology & Biological Psychiatry | 4         |
| Psychopharmacology (Berl)                                    | 4         |
| European Neuropsychopharmacology                             | 3         |
| Human Psychopharmacology                                     | 3         |
| The New England Journal of Medicine                          | 3         |
| Schizophrenia Bulletin                                       | 3         |
| The British Medical Journal                                  | 2         |
| Clinical Neuropharmacology                                   | 2         |
| Current Opinion in CPNS Investigational Drugs                | 2         |
| Current Therapeutic Research                                 | 2         |
| Indian Journal of Psychiatry                                 | 2         |
| Neuropsychobiology   | 2         |
| PLoS Medicine  | 2         |

## Appendix C. Original Search Strategy

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

- Annals of Internal Medicine
- British Medical Journal
- Cochrane Database of Systematic Reviews
- Journal of the American Medical Association
- Lancet
- The New England Journal of Medicine
- Archives of General Psychiatry
- American Journal of Psychiatry
- Schizophrenia Bulletin
- Journal of Clinical Psychiatry
- British Journal of Psychiatry

| Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) and Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations |    |   |        |
|---|----|---|--------|
| Searched April 30 <sup>th</sup> , 2014 Rose Relevo  |    |   |        |
| Search Strategy from original Search  | 1  | exp Schizophrenia/  | 82827  |
|   | 2  | Schizophrenia, Catatonic/   | 520    |
|   | 3  | Schizophrenia, Disorganized/  | 500    |
|   | 4  | Schizophrenia, Paranoid/  | 3597   |
|   | 5  | Psychotic Disorders/  | 31123  |
|   | 6  | Schizotypal Personality Disorder/   | 2118   |
|   | 7  | schizophreniform.tw.  | 905    |
|   | 8  | (schizoaffective or schizo-affective).tw.   | 4384   |
|   | 9  | schizophren\$.mp.   | 110474 |
|   | 10 | (dementia adj (praecox or precox)).tw.  | 312    |
|   | 11 | (delusional adj2 disorder*).tw.   | 697    |
|   | 12 | ((negative or positive) adj syndrome*).tw.  | 2492   |
|   | 13 | hebephrenia.tw.   | 75     |
|   | 14 | exp Bipolar Disorder/   | 30492  |
|   | 15 | (((bipolar or manic) adj2 (I or II or illness or disorder or psychos?s or depress\$) or mania*).tw. | 26511  |
|   | 16 | (BPD or hypoman\$ or manic-depressive).tw.  | 10084  |
|   | 17 | (BP 1 or BP 2 or BP I or BP II).tw.   | 1203   |
|   | 18 | (cyclothym\$ or euthymic).tw.   | 2494   |
|   | 19 | (acute adj2 mania).tw.  | 827    |
|   | 20 | (acute adj2 mixed adj episode*).tw.   | 17     |
|   | 21 | (rapid-cycling adj5 bipolar).tw.  | 384    |
|   | 22 | (rapid adj2 cycling adj5 bipolar).tw.   | 385    |
|   | 23 | (mixed adj2 state* adj3 bipolar).tw.  | 119    |
|   | 24 | or/1-23   | 166277 |
|   | 25 | exp Antipsychotic Agents/   | 119338 |
|   | 26 | exp Tranquilizing Agents/   | 197439 |
|   | 27 | (neuroleptic adj2 (agent* or drug*)).tw.  | 2989   |
|   | 28 | or/25-27  | 198048 |
|   | 29 | ((first or 1st) adj generation adj antipsychotic*).tw.  | 464    |

|    |  |       |
|----|--|-------|
| 30 | chlorpromazine/  | 15796 |
| 31 | 50-53-3.m.   | 0     |
| 32 | (Aminazin or Aminazine or Ampliactil or BC 135 or Chlorpromazine or Chlorpromazinum or Clorpromazina or Chlor-Promanyl or Chlorpromados or Chlororderazin or Chlorpromazin or Contomin or Elmarin or Esmind or Fenactil or Fenaktyl or HL 5746 or Largactil or Largactilothiazine or Megaphen or Largactyl or Klooripromatsiini or Klorpromazin or 6 Copin or Trinicalm Forte or Diminex Balsamico Juven Tos or Largatrex or Phenactyl or Proma or Promactil or Promazil or Prozil or Psychozine or Sanpron or Thorazine or Torazina or Wintermin).mp. |       |
| 33 | Droperidol/  | 1899  |
| 34 | 548-73-2.m.  | 0     |
| 35 | (Dehydrobenzoperidol or Dehydrobenzperidol or Deidrobenezperidolo or Dridol or Droleptan or Droperidol or Droperidoli or Droperidolis or Droperidolum or Disifelit or Halkan or Inapsin or Inapsine or Inopsin or Thalamonal or Nilperidol or Properidol or Sintodril or Vetkalm).mp.  |       |
| 36 | fluphenazine/  | 2292  |
| 37 | 69-23-8.m.   | 0     |
| 38 | (Dapotum or Elinol or Flufenazina or Fluofenazine or Fluphenazine or Fluorphenazine or Fluphenazinum or Ftorphenazine or Moditen or Pacinol or Sevinol or Siqualon or Triflumethazine or Valamina or Vespazine).mp.  |       |
| 39 | haloperidol/   | 14562 |
| 40 | 52-86-8.m.   | 0     |
| 41 | (Aldo or Aloperidin or Aloperidol or Aloperidolo or Brootopon or Dozic or Einalon S or Eukystol or Fortunan or Galoperidol or Haldol or Halojust or Halopal or Haloperidol or Haloperidoli or Haloperidolis or Haloperidolu or Halopoidol or Serenace or Halopidol or Haloper or Halperon or Keselan or Lealgin or Linton or Mixidol or Peluces or Pernox or Serenace or Serenefl or Sernas or Sernel or Serenase or Ulcolind or Uliolind or Vesalium).mp.   |       |
| 42 | loxapine/  | 253   |
| 43 | 1977-10-2.m.   | 0     |
| 44 | (Cloxazepine or CL 62362 or Dibenzacepin or Dibenzoazepine or Hydrofluoride 3170 or LW 3170 or Lossapina or Loksapiini or Loxapin or Loxapina or Loxapine or Loxapinum or Oxilapine or Loxapac or SUM 3170 or Loxitane or Desconex).mp.  |       |
| 45 | perphenazine/  | 1423  |
| 46 | 58-39-9.m.   | 0     |
| 47 | (Chlorperphenazine or Chlorpiprazine or Decentan or Emesinal or Etaperazin or Etaperazine or Ethaperazine or Etrafon or F-mon or Fentazin or Mutabon or Perfenazin or Perfenazina or Perfenazinas or Perfenazine or Perphenazin or Perphenazine or Perfenazyna or Perphenazinum or Pertriptyl or Sch 3940 or Thilatazin or Tranquisan or Trifarone or Trilafon or Trilifan or Triptafen or Triphenot or Triavil).mp.   |       |
| 48 | Pimozide/  | 1661  |
| 49 | 2062-78-4.m.   | 0     |
| 50 | (Antalon or Opiran or Orap or Pimotsidi or Pimozid or Pimozida or Pimozidas or Pimozide or Pimozidum or Pimozyd).mp.   |       |
| 51 | Prochlorperazine/  | 942   |
| 52 | 58-38-8.m.   | 0     |
| 53 | (Apo-Prochlorazine or Capazine or Chlormeprazine or Compazine or Compro or Dhaperazine or Emelent or Kronocin or Nipodal or Novamin or Nu-Prochlor or Meterazin or Meterazine or Mital or Prochlorpemazine or Prochlorperazinum or Prochlorperazina or Proklooriperatsiini or Prokloorperazin or Prorazin or Phenothiazine or Seratil or Stemetil or Temetil or Temetid).mp.   |       |
| 54 | thiothixene/   | 332   |

|    |  |       |
|----|--|-------|
| 55 | 5591-45-7.rn.  | 0     |
| 56 | (Navane or Navaron or Orbinamon or Thiothixene or Tiotikseeni or Tiotixen or Tiotixeno or Tiotixenum or Thixit or Tiotixene).mp.   | 457   |
| 57 | trifluoperazine/   | 3363  |
| 58 | 117-89-5.rn.   | 0     |
| 59 | (Cuait D or Cuait N or eskazine or flupazine or Jatrosom or Jalonac or Parstelin or Parmodalin or stelazine or Stelabid or Stelapar or Sycot or Terfluzine or Trifluoperazine or Trifluoperazini Hydrochloridum or triftazin or Trinicalm Forte or Trinicalm Plus).mp.   | 4950  |
| 60 | thioridazine/  | 2183  |
| 61 | 50-52-2.rn.  | 0     |
| 62 | (Aldazine or Dazithin or Detril or Elperil or Mallorol or Malloryl or Melleril or Meleril or Mellaril or Mellerets or Mellerette or Melleretten or Melleril or Sonapax or Thioridazin or Thioridazine or Thioridazinum or Tioridatsiini or Tioridazin or Tioridazina or Tioridazinas).mp.  | 2991  |
| 63 | methotrimeprazine/   | 683   |
| 64 | 60-99-1.rn.  | 0     |
| 65 | (Dedoran or Hirnamin or Hirnamine or Levomepromazine or Levomepromazin or Levomepromazina or Levopromazoni or Levomepromazinum or Levoprome or Levotomin or Mepromazine or Methotrimeprazine or Neurocil or Neozine or Nirvan or Nocinan or Momizan or Nozinane or Sinogan or Levoram or Nozinan or Sinogan or Tisercin or Veractil).mp. | 974   |
| 66 | Phenothiazines/ad, to, tu, ct, po, ae  | 2757  |
| 67 | Butyrophenones/ad, to, tu, ct, po, ae  | 633   |
| 68 | Thioxanthenes/ad, to, tu, ct, po, ae   | 405   |
| 69 | Dibenzoxazepines/ad, to, tu, ct, po, ae  | 301   |
| 70 | Indoles/ad, to, tu, ct, po, ae   | 9211  |
| 71 | or/29-70   | 70366 |
| 72 | atypical antipsychotic\$.tw.   | 7315  |
| 73 | ((second or 2nd) adj generation adj antipsychotic*).tw.  | 1698  |
| 74 | ((third or 3rd) adj generation adj antipsychotic*).tw.   | 21    |
| 75 | Asenapine/   | 0     |
| 76 | 65576-45-6.rn.   | 0     |
| 77 | (Asenapine or EINECS 265-829-4).mp.  | 180   |
| 78 | clozapine/   | 6613  |
| 79 | 5786-21-0.rn.  | 0     |
| 80 | (Clozapin or Clozapina or Clozapine or Clozapinum or Clorazil or Clozaril or FazaClo or Lefonex or LX 100-129 or Zaponex).mp.  | 9724  |
| 81 | risperidone/   | 4887  |
| 82 | 106266-06-2.rn.  | 0     |
| 83 | (Apexidone or Psychodal or Risperdal or Risperidona or Risperidone or Risperidonum or Risperin or Risperilept or Rispolin or Spiron).mp.   | 7434  |
| 84 | olanzapine.mp.   | 6625  |
| 85 | 132539-06-1.rn.  | 4336  |
| 86 | (Zyprexa or Olantsapiini or Olanzapin or Olanzapinaor Olanzapinum or Olansek or Zalasta or Zypadhera or Symbyax).mp.   | 115   |
| 87 | quetiapine.mp.   | 3324  |
| 88 | (111974-69-7 or 111974-72-2).rn.   | 0     |
| 89 | (Co-Quetiapine or HSDB 7557 or Seroquel).mp.   | 125   |
| 90 | ziprasidone.mp.  | 1546  |
| 91 | 146939-27-7.rn.  | 0     |
| 92 | (Zeldox or zeldrox or geodon).mp.  | 20    |
| 93 | aripiprazole.mp.   | 2299  |

|     |   |          |          |
|-----|---|----------|----------|
| 94  | 129722-12-9.rn.   | 0        |          |
| 95  | (Abilitat or Abilify or Aripiprazole or Discmelt or OPC 31 or OPC 14597).mp.  |          |          |
|     | 2303  |          |          |
| 96  | paliperidone.mp.  | 401      |          |
| 97  | 144598-75-4.rn.   | 357      |          |
| 98  | (9-Hydroxyrisperidone or Invega or R 76477 or RO76477).mp.  | 209      |          |
| 99  | Iloperidone/  | 0        |          |
| 100 | 133454-47-4.rn.   | 71       |          |
| 101 | (Fanapt or Iloperidone or HP 873 or Zomaril).mp.  |          | 128      |
| 102 | Isoxazoles/ad, to, tu, ct, po, ae   | 2697     |          |
| 103 | Dibenzazepines/ad, to, tu, ct, po, ae   |          | 1401     |
| 104 | Pyrimidinones/ad, to, tu, ct, po, ae  |          | 1483     |
| 105 | Piperidines/ad, to, tu, ct, po, ae  | 10299    |          |
| 106 | Dibenzothiazepines/ct, ad, to, tu, ae, po   | 1865     |          |
| 107 | Piperazines/ad, tu, to, ct, po, ae  | 17640    |          |
| 108 | Pirenzepine/tu, ad, to, ct, po, ae  | 1549     |          |
| 109 | Thiazoles/ad, th, ct, po, to, ae  | 3770     |          |
| 110 | Quinolones/to, po, ct, ad, tu, ae   | 3572     |          |
| 111 | or/72-110   | 61152    |          |
| 112 | and/71,111  | 6941     |          |
| 113 | and/28,71,111   | 5418     |          |
| 114 | or/112-113  | 6941     |          |
| 115 | randomized controlled trial.pt.   | 360172   |          |
| 116 | controlled clinical trial.pt.   | 86981    |          |
| 117 | randomi?ed.ab.  | 335140   |          |
| 118 | placebo*.ab.  | 149301   |          |
| 119 | drug therapy.fs.  | 1651625  |          |
| 120 | randomly.ab.  | 204443   |          |
| 121 | trial.ab.   | 289423   |          |
| 122 | groups.ab.  | 1308375  |          |
| 123 | or/115-122  | 3239830  |          |
| 124 | humans/ not (animals and humans).hw,sh.   |          | 11682399 |
| 125 | 123 and 124   | 2341517  |          |
| 126 | and/24,114,125  | 2340     |          |
| 127 | 126 and (201107* or 201108* or 201109* or 201110* or 201111* or 201112* or 2012* or 2013* or 2014*).dc.   | 242      |          |
| 128 | limit 127 to english language   | 223      |          |
| 129 | limit 127 to english language   | 223      |          |
| 130 | limit 127 to english language   | 223      |          |
| 131 | cohort studies/   | 155492   |          |
| 132 | followup studies/   | 479650   |          |
| 133 | longitudinal studies/   | 80755    |          |
| 134 | prospective studies/  | 351736   |          |
| 135 | Retrospective Studies/  | 471162   |          |
| 136 | (observation\$ or prospectiv\$ or retrospectiv\$ or cohort\$ or control\$ or volunteer\$ or evaluat\$ or compar\$ or longitudinal or long term or long-term or longterm or followup or followup or followup).mp. and (study or studies or trial\$.ti,ab,sh. |          | 3979196  |
| 137 | or/131-136  | 4510892  |          |
| 138 | humans.hw,sh.   | 13091041 |          |
| 139 | and/137-138   | 3302402  |          |
| 140 | meta-analysis.mp.pt.  | 71175    |          |
| 141 | review.pt.  | 1822936  |          |
| 142 | search:.tw.   | 229660   |          |

|                |  |
|----------------|--|
|                | 143 or/140-142 2006834<br>144 and/24,114,139 1623<br>145 and/24,114,143 689  |
| Date Limits    | 146 144 and (201107* or 201108* or 201109* or 201110* or 201111* or 201112* or 2012* or 2013* or 2014*).dc. 190<br>147 limit 146 to english language 183<br>148 145 and (201107* or 201108* or 201109* or 201110* or 201111* or 201112* or 2012* or 2013* or 2014*).dc. 100<br>149 limit 148 to english language 89  |
| Journal Limits | 150 "annals of internal medicine".jn. 29974<br>151 "bmj".jn. 63839<br>152 "The Cochrane database of systematic reviews".jn. 10696<br>153 "jama".jn. 66076<br>154 "lancet".jn 128966<br>155 "the new England journal of medicine".jn. 71152<br>156 "archives of general psychiatry".jn. 8109<br>157 "the American journal of psychiatry".jn. 23751<br>158 "Schizophrenia bulletin".jn. 2388<br>159 "the journal of clinical psychiatry".jn. 9474<br>160 "The British journal of psychiatry".jn. 13933<br>161 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 526498<br>162 161 and 149 16 |

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|--|--|
| Ovid PsycINFO searched April 30 <sup>th</sup> , 2014 |  |
| Search Strategy from original Search                 | 1 exp schizophrenia/ 70824<br>2 exp "fragmentation (schizophrenia)"/ 39<br>3 exp "positive and negative symptoms"/ 2242<br>4 exp schizoaffective disorder/ 2555<br>5 exp schizoid personality disorder/ 599<br>6 exp schizotypal personality disorder/ 1219<br>7 exp psychosis/ 89982<br>8 or/1-7 91914<br>9 schizophren*.mp. 101584<br>10 (schizoaffective or schizo-affective).tw. 5637<br>11 (dementia adj praecox).tw. 1248<br>12 (delusional adj2 disorder*).tw. 952<br>13 ((negative or positive) adj syndrome*).tw. 2487<br>14 hebephrenia.tw. 141<br>15 or/9-14 103732<br>16 or/8,15 120665<br>17 exp Bipolar Disorder/ 18894<br>18 affective psychosis/ 516<br>19 mania/ 4521<br>20 exp affective disorders/ 115843<br>21 or/17-20 116211 |

|    |  |        |
|----|--|--------|
| 22 | ((bipolar or manic) adj2 (I or II or illness or disorder or psychos?s or depress\$)) or mania*).tw.  | 30140  |
| 23 | (BPD or hypoman\$ or manic-depressive).tw.   | 10110  |
| 24 | (BP 1 or BP 2 or BP I or BP II).tw.  | 308    |
| 25 | (cyclothym\$ or euthymic).tw.  | 2471   |
| 26 | (acute adj2 mania).tw.   | 856    |
| 27 | (acute adj2 mixed adj episode*).tw.  | 17     |
| 28 | (rapid-cycling adj5 bipolar).tw.   | 431    |
| 29 | (rapid adj2 cycling adj5 bipolar).tw.  | 432    |
| 30 | (mixed adj2 state* adj3 bipolar).tw.   | 128    |
| 31 | or/22-30   | 34791  |
| 32 | or/21,31   | 127425 |
| 33 | or/16,32   | 230151 |
| 34 | exp Neuroleptic Drugs/   | 24751  |
| 35 | ((first or 1st) adj generation adj antipsychotic*).tw.   | 437    |
| 36 | exp Chlorpromazine/  | 1638   |
| 37 | (Aminazin or Aminazine or Ampliactil or BC 135 or Chlorpromazine or Chlorpromazinum or Clorpromazina or Chlor-Promanyl or Chlorpromados or Chlorderazin or Chlorpromazin or Contomin or Elmarin or Esmind or Fenactil or Fenaktyl or HL 5746 or Largactil or Largactilothiazine or Megaphen or Largactyl or Klooripromatsiini or Klorpromazin or 6 Copin or Trinicalm Forte or Diminex Balsamico Juven Tos or Largatrex or Phenactyl or Proma or Promactil or Promazil or Prozil or Psychozine or Sanpron or Thorazine or Torazina or Wintermin).mp. | 3691   |
| 38 | Droperidol.mp.   | 90     |
| 39 | (Dehydrobenzoperidol or Dehydrobenzperidol or Deidrobenzperidolo or Dridol or Droleptan or Droperidol or Droperidoli or Droperidolis or Droperidolum or Disifelit or Halkan or Inapsin or Inapsine or Inopsin or Thalamonal or Nilperidol or Properidol or Sintodril or Vetkalm).mp.   | 100    |
| 40 | exp Fluphenazine/  | 532    |
| 41 | (Dapotum or Elinol or Flufenazina or Fluofenazine or Fluphenazine or Fluorphenazine or Fluphenazinum or Ftorphenazine or Moditen or Pacinol or Sevinol or Siqualon or Triflumethazine or Valamina or Vespazine).mp.  | 1007   |
| 42 | exp Haloperidol/   | 4463   |
| 43 | (Aldo or Aloperidin or Aloperidol or Aloperidolo or Brootopon or Dozic or Einalon S or Eukystol or Fortunan or Galoperidol or Haldol or Halojust or Halopal or Haloperidol or Haloperidoli or Haloperidolis or Haloperidolu or Halopoidol or Serenace or Halopidol or Haloper or Halperon or Keselan or Lealgin or Linton or Mixidol or Peluces or Pernox or Serenace or Serenefl or Sernas or Sernel or Serenase or Ulcolind or Uliolind or Vesalium).mp.   | 8168   |
| 44 | exp Loxapine/  | 66     |
| 45 | (Cloxazepine or CL 62362 or Dibenzacepin or Dibenzoazepine or Hydrofluoride 3170 or LW 3170 or Lossapina or Loksapiini or Loxapin or Loxapina or Loxapine or Loxapinum or Oxilapine or Loxapac or SUM Sinophenin or Talofen or Talofen or Tomil or Verophen).mp.   | 197    |
| 46 | exp Perphenazine/  | 181    |
| 47 | (Chlorperphenazine or Chlorpiprazine or Decentan or Emesinal or Etaperazin or Etaperazine or Ethaperazine or Etrafon or F-mon or Fentazin or Mutabon or Perfenazin or Perfenazina or Perfenazinas or Perfenazine or Perphenazin or Perphenazine or Perfenazyna or Perphenazinum or Pertriptyl or Sch 3940 or Thilatazin or Tranquisan or Trifaron or Trilafon or Trilifan or Triptafen or Triphenot or Triavil).mp.  | 509    |
| 48 | Pimozide/  | 483    |
| 49 | (Antalon or Opiran or Orap or Pimotsidi or Pimozid or Pimozida or Pimozidas  |        |

|    |  |       |
|----|--|-------|
|    | or Pimozide or Pimozidum or Pimozyd).mp.   | 833   |
| 50 | Prochlorperazine/  | 22    |
| 51 | (Apo-Prochlorazine or Capazine or Chlormepazine or Compazine or Compro or Dhaperazine or Emelent or Kronocin or Nipodal or Novamin or Nu-Prochlor or Meterazin or Meterazine or Mitil or Prochlorpemazine or Prochlorperazinum or Proclorperazina or Prochlorperazine or Proklooriperatsiini or Proklorperazin or Prorazin or Phenothiazine or Seratil or Stemetil or Tementil or Temetid).mp. | 868   |
| 52 | exp Thioridazine/  | 370   |
| 53 | (Aldazine or Dazithin or Detril or Elperil or Mallorol or Malloryl or Melleril or Meleril or Mellaril or Mellerets or Mellerette or Melleretten or Melleril or Sonapax or Thioridazin or Thioridazine or Thioridazinum or Tioridatsiini or Tioridazin or Tioridazina or Tioridazinas).mp.  | 894   |
| 54 | exp Thiothixene/   | 103   |
| 55 | (Navane or Navaron or Orbinamon or Tiotixene or Tiotikseeni or Tiotixen or Tiotixeno or Tiotixenum or Thixit or Tiotixene or Thiothixene).mp.  | 223   |
| 56 | exp Trifluoperazine/   | 133   |
| 57 | (Cuait D or Cuait N or eskazine or flupazine or Jatrosom or Jalonac or Parstelin or Parmodaline or stelazine or Stelabid or Stelapar or Sycot or Terfluzine or Trifluoperazine or Trifluoperazini Hydrochloridum or triftazin or Trinicalm Forte or Trinicalm Plus or Trifluperazine).mp.  | 445   |
| 58 | or/35-57   | 14495 |
| 59 | ((second or 2nd) adj generation adj antipsychotic*).tw.  | 1495  |
| 60 | ((third or 3rd) adj generation adj antipsychotic*).tw.   | 14    |
| 61 | exp Aripiprazole/  | 924   |
| 62 | (Abilitat or Abilify or Aripiprazole or Discmelt or OPC 31 or OPC 14597).mp.   | 1608  |
| 63 | Asenapine.mp.  | 99    |
| 64 | (Blonanserin or AD 5423).mp.   | 37    |
| 65 | Iloperidone.mp.  | 58    |
| 66 | (Fanapt or HP 873 or Zomaril).mp.  | 6     |
| 67 | exp Olanzapine/2859  |       |
| 68 | (Zyprexa or Olantsapiini or Olanzapin or Olanzapina or Olanzapinum or Olansek or Olanzapine or Zalasta or Zypadhera or Symbyax).mp.  | 4963  |
| 69 | paliperidone.tw.   | 254   |
| 70 | (9-Hydroxyrisperidone or Invega or R 76477 or RO76477).mp.   | 84    |
| 71 | exp Quetiapine/  | 1408  |
| 72 | (Co-Quetiapine or HSDB 7557 or Quetiapine or Seroquel).mp.   | 2651  |
| 73 | exp Risperidone/   | 3144  |
| 74 | (Apexidone or Psychodal or Risperdal or Risperidona or Risperidone or Risperidonum or Risperin or Risperilept or Rispolin or Spiron).mp.   | 5552  |
| 75 | ziprasidone.tw.  | 1082  |
| 76 | (Zeldox or zeldrox or geodon).mp.  | 15    |
| 77 | or/59-76   | 11842 |
| 78 | or/34,58,77  | 35737 |
| 79 | or/58,77   | 23748 |
| 80 | or/78-79   | 35737 |
| 81 | randomi?ed controlled trial.tw,pt.   | 9338  |
| 82 | exp Clinical Trials/   | 7255  |
| 83 | controlled clinical trial.tw,pt.   | 937   |
| 84 | randomi?ed.ab.   | 40956 |
| 85 | placebo*.ab.   | 29854 |
| 86 | randomly.ab.   | 49369 |
| 87 | trial.ab.  | 59863 |

|             |     |   |            |      |
|-------------|-----|---|------------|------|
|             | 88  | groups.ab.  | 351883     |      |
|             | 89  | or/81-88  | 463107     |      |
|             | 90  | exp Animals/  | 266845     |      |
|             | 91  | 89 not 90   | 425007     |      |
|             | 92  | and/33,80,91  | 5717       |      |
|             | 93  | limit 92 to english language  | 5382       |      |
|             | 94  | limit 93 to "300 adulthood <age 18 yrs and older>"  |            | 3488 |
|             | 95  | exp Clinical Trials/  | 7255       |      |
|             | 96  | clinical trial:.mp.   | 22843      |      |
|             | 97  | random:.tw.   | 126203     |      |
|             | 98  | placebo:.mp.  | 30509      |      |
|             | 99  | double-blind:.mp.   | 17952      |      |
|             | 100 | or/95-99  | 158177     |      |
|             | 101 | and/33,80,100   | 4593       |      |
|             | 102 | limit 101 to english language   | 4352       |      |
|             | 103 | 102 and (201107* or 201108* or 201109* or 201110* or 201111* or 201112* or 2012* or 2013* or 2014*).up.   | 728        |      |
|             | 104 | limit 103 to "300 adulthood <age 18 yrs and older>"   |            | 457  |
|             | 105 | limit 104 to "0100 journal"   | 457        |      |
|             | 106 | exp Followup Studies/   | 12304      |      |
|             | 107 | exp longitudinal studies/   | 15214      |      |
|             | 108 | exp prospective studies/  | 418        |      |
|             | 109 | exp retrospective studies/  | 336        |      |
|             | 110 | (observation\$ or prospectiv\$ or cohort\$ or longitudinal or long term or long-term or longterm or followup or followup or followup).mp. and (study or studies or trial\$).ti,ab,sh. | 199197     |      |
|             | 111 | or/106-110  | 212691     |      |
|             | 112 | exp Animals/  | 266845     |      |
|             | 113 | 111 not 112   | 201145     |      |
|             | 114 | and/33,80,113   | 2909       |      |
|             | 115 | limit 114 to english language   | 2668       |      |
|             | 116 | 115 and (201107* or 201108* or 201109* or 201110* or 201111* or 201112* or 2012* or 2013* or 2014*).up.   | 491        |      |
|             | 117 | limit 115 to "0100 journal"   | 2598       |      |
|             | 118 | meta-analys?s.mp.   | 16474      |      |
|             | 119 | search:.tw.   | 60247      |      |
|             | 120 | review:.mp.   | 398224     |      |
|             | 121 | or/118-120  | 449813     |      |
|             | 122 | and/33,80,121   | 2942       |      |
|             | 123 | and/33,80   | 20915      |      |
|             | 124 | limit 123 to "0830 systematic review"   |            | 150  |
|             | 125 | or/122,124  | 2947       |      |
|             | 126 | limit 125 to english language   | 2627       |      |
|             | 127 | limit 126 to "300 adulthood <age 18 yrs and older>"   |            | 673  |
|             | 128 | limit 127 to "0100 journal"   | 657        |      |
|             | 129 | adult*.mp.  | 348372     |      |
|             | 130 | 125 and 129   | 183        |      |
|             | 131 | limit 130 to "0100 journal"   | 170        |      |
|             | 132 | 128 or 131  | 772        |      |
| Date Limits | 133 | 132 and (201107* or 201108* or 201109* or 201110* or 201111* or 201112* or 2012* or 2013* or 2014*).up.   | <b>141</b> |      |

## Appendix D. Inclusion and Exclusion Criteria from Original Systematic Review

Our inclusion/exclusion criteria were developed in consultation with the Technical Expert Panel (TEP). Criteria are summarized below.

Study selection was based on an a priori set of inclusion and exclusion criteria for study design, patient population, interventions, comparators, and outcomes. We screened the results of our searches using a two-step process. First, two reviewers independently screened the titles and abstracts (level 1 screening) to determine if an article met the broad inclusion or exclusion criteria for study design, population, interventions, and comparators. We rated each citation as: “include,” “exclude,” or “unclear.” Records rated as “include” or “unclear” were advanced to level 2 screening. For full-text screening (level 2 screening), two reviewers independently reviewed each retrieved study using a standardized screening form that was developed and piloted by the review team. We resolved discrepancies through discussion and consensus or by third-party adjudication. Reviewers were not masked to the study authors, institution, or journal.

We included studies that included at least 80 percent of patients from the adult population (18-64 years). Polypharmacy is common in clinical practice; therefore, we did not exclude studies examining patients taking other medications from the CER. Studies that included both patients with schizophrenia and patients with bipolar disorder, but did not provide separate results for these two conditions, were included only for the AEs section (KQ3). To be included, cohort studies were required to have a follow-up period of at least 2 years and present data on at least one serious adverse event (SAE), as determined by the Technical Expert Panel (i.e., type II diabetes mellitus, mortality, tardive dyskinesia, and major metabolic syndromes).

| <b>Category</b>  | <b>Criteria</b>  |
|------------------|--|
| Publication type | <p><u>Inclusion Criteria:</u></p> <ul style="list-style-type: none"> <li>English language, full-text publications from 1950 to present</li> </ul> <p><u>Exclusion Criteria</u></p> <ul style="list-style-type: none"> <li>Non-English language publications</li> <li>Conference abstracts</li> </ul>   |
| Study design     | <p><u>Inclusion Criteria:</u></p> <ul style="list-style-type: none"> <li>RCTs, nRCTs, and prospective and retrospective cohort studies</li> </ul> <p><u>Exclusion Criteria</u></p> <ul style="list-style-type: none"> <li>Observational study designs with no comparison group (e.g., case reports, case series, and cross-sectional studies) or case-control studies</li> </ul> |
| Participants     | <p><u>Inclusion Criteria:</u></p> <ul style="list-style-type: none"> <li>Adults (age 18 to 64 years) with schizophrenia or related psychoses or bipolar disorder</li> </ul>  |

|               |  |
|---------------|--|
|               | <u>Exclusion Criteria</u> <ul style="list-style-type: none"> <li>• Pediatric population (aged &lt;18 years)</li> <li>• Geriatric population (aged &gt;64 years)</li> </ul>   |
| Interventions | <u>Inclusion Criteria:</u> <ul style="list-style-type: none"> <li>• Any currently available FDA-approved FGA</li> </ul> <u>Exclusion Criteria</u> <ul style="list-style-type: none"> <li>• Currently unavailable or non-FDA-approved FGA or other interventions</li> </ul>   |
| Comparators   | <u>Inclusion Criteria:</u> <ul style="list-style-type: none"> <li>• Any currently available FDA-approved SGA</li> </ul> <u>Exclusion Criteria</u> <ul style="list-style-type: none"> <li>• Currently unavailable or non-FDA-approved SGA, placebo, or other interventions</li> </ul>   |
| Outcomes      | <u>Inclusion Criteria:</u> <ul style="list-style-type: none"> <li>• Outcomes listed in the KQ; cohort studies must report on <math>\geq 1</math> SAE</li> </ul> <u>Exclusion Criteria</u> <ul style="list-style-type: none"> <li>• None of the a priori identified outcomes were available from the trial report or communication with the study's corresponding author</li> </ul> |
| Timing        | <u>Inclusion Criteria:</u> <ul style="list-style-type: none"> <li>• All follow-up periods for trials; cohort studies <math>\geq 2</math> years follow-up</li> </ul> <u>Exclusion Criteria</u> <ul style="list-style-type: none"> <li>• Cohorts with &lt;2 years follow-up</li> </ul>   |
| Setting       | <u>Inclusion Criteria:</u> <ul style="list-style-type: none"> <li>• All settings</li> </ul> <u>Exclusion Criteria</u> <ul style="list-style-type: none"> <li>• NA</li> </ul>   |

FDA  
=

Food and Drug Administration; FGA = first-generation antipsychotic; KQ = key question; NA = not applicable; nRCT = nonrandomized controlled trial; RCT = randomized controlled trial; SAE = serious adverse event; SGA = second-generation antipsychotic

\*Note: Original inclusion/exclusion criteria extracted from Effective Health Care Program, CER #63, *First-Generation Versus Second-Generation Antipsychotics in Adults: Comparative Effectiveness* pps. 10-11.

## Appendix E. Literature Search Results

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16. Leucht S, Helfer B, Hartung B. Perazine for schizophrenia. *The Cochrane Database of Systematic Reviews*. 2014; 1: CD002832.

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## Appendix F. Questionnaire Sent to Expert Reviewers

# *AHRQ Comparative Effectiveness Review Surveillance Program*

### Reviewer Form

**Title of Original Review:** First-Generation Versus Second-Generation Antipsychotics in Adults: Comparative Effectiveness

[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:

For adults (age 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what are the comparative efficacy and effectiveness of FGAs versus SGAs for improving core illness symptoms?

### Schizophrenia/Schizophrenia-Related

#### **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.

### Bipolar Disorder

#### **SRC Literature Analysis:**

- No new primary research was found.

Mood (mania)

- A multiple treatments meta-analysis found that haloperidol had a larger effect than aripiprazole, asenapine, quetiapine and ziprasidone (YMRS) for mood (mania) in bipolar disorder.

#### **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:

For adults (18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what is the comparative effectiveness of FGAs versus SGAs for improving functional outcomes and decreasing health care system utilization?

### 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 3:

For adults (age 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, do FGAs and SGAs differ in medication-associated AEs and safety?

### 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:

For adults (age 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what is the comparative effectiveness of FGAs versus SGAs for the following other outcomes: Relapse and remission rates; medication adherence and persistent use; patient insight into illness; health-related quality of life; patient satisfaction; comorbidity; endpoints of victimization, homelessness, and substance

abuse; patient reported outcomes; ability to obtain and retain employment and succeed in job duties; concomitant use of other medications, especially those used to treat EPS; patient references.

**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 5:**

For adults (age 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what are the comparative effectiveness and risks of FGAs versus SGAs in subgroups defined by: disorder subtypes; sex; age group (18-35; 36-54; 55-64); race; comorbidities; drug dosage; follow-up period; treatment of a first episode versus treatment in the context of previous episodes; treatment resistance.

**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.](#)

**Title of Original Review:** First-Generation Versus Second-Generation Antipsychotics in Adults: Comparative Effectiveness

[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           |
|--|-----------------------------------|
| <p><b>Key Question 1: For adults (age 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what are the comparative efficacy and effectiveness of FGAs versus SGAs for improving core illness symptoms?: Schizophrenia/Schizophrenia-Related</b></p>  |                                   |
| <p><b>Positive Symptoms</b><br/> <b>SOE: Low</b><br/>                     Numerous studies compared haloperidol to SGAs on either the PANSS or SAPS, and found no difference.</p> <ul style="list-style-type: none"> <li>• vs. aripiprazole (2 studies)</li> <li>• vs. clozapine (2 studies)</li> <li>• vs. olanzapine (16 studies)</li> <li>• vs. quetiapine (4 studies)</li> <li>• vs. risperidone (22 studies)</li> </ul> <p><b>SOE: Insufficient (PANSS or SAPS):</b></p> <ul style="list-style-type: none"> <li>• Chlorpromazine vs. clozapine</li> <li>• Fluphenazine vs. olanzapine</li> <li>• Perphenazine vs. olanzapine, quetiapine, risperidone, and ziprasidone</li> <li>• Haloperidol vs. aripiprazole and asenapine</li> </ul> | <p>No new research was found.</p> |
| <p><b>Negative Symptoms</b><br/> <b>SOE: Moderate</b><br/>                     Numerous studies compared haloperidol to SGAs on either the PANSS or SAPS</p> <ul style="list-style-type: none"> <li>• vs. aripiprazole ( 3 studies) favoring aripiprazole</li> <li>• vs. clozapine (4 studies) found no difference</li> <li>• vs. olanzapine (19 studies) favored olanzapine</li> <li>• vs. risperidone (24 studies) favored risperidone</li> </ul> <p><b>SOE: Low</b><br/>                     Seven studies compared haloperidol to SGAs and found no difference on either the PANSS or SAPS</p> <ul style="list-style-type: none"> <li>• vs. clozapine (1 study)</li> </ul>   | <p>No new research was found.</p> |

|   |                            |
|---|----------------------------|
| <ul style="list-style-type: none"> <li>• vs. quetiapine (4 studies)</li> <li>• vs. ziprasidone (2 studies)</li> </ul> <p><b>SOE: Insufficient (PANSS or SAPS)</b></p> <ul style="list-style-type: none"> <li>• Fluphenazine vs. olanzapine</li> <li>• Chlorpromazine vs. clozapine and olanzapine</li> <li>• Haloperidol vs. aripiprazole, asenapine, and quetiapine</li> <li>• Perphenazine vs. olanzapine, quetiapine, risperidone, and ziprasidone</li> </ul>  |                            |
| <p><b>General Psychopathology</b></p> <p><b>SOE: Moderate</b></p> <ul style="list-style-type: none"> <li>• Haloperidol vs. olanzapine ( 9 studies) favored olanzapine (3 HAM-D, 6 MADRS)</li> </ul> <p><b>SOE: Low</b></p> <p>Numerous studies compared haloperidol to SGAs and found no difference across the PANSS, ABS, ACES, CDS-S, HAM-A, YMRS</p> <ul style="list-style-type: none"> <li>• vs. clozapine (2 studies)</li> <li>• vs. olanzapine (19 studies)</li> <li>• vs. quetiapine (6 studies)</li> <li>• vs. risperidone (20 studies)</li> </ul> <p><b>SOE: Insufficient (numerous measures)</b></p> <ul style="list-style-type: none"> <li>• Chlorpromazine vs. clozapine</li> <li>• Fluphenazine vs. olanzapine</li> <li>• Haloperidol vs. aripiprazole, asenapine, clozapine, quetiapine, and ziprasidone</li> </ul> <p>Perphenazine vs. olanzapine, quetiapine, risperidone, and ziprasidone</p>  | No new research was found. |
| <p><b>Global Ratings &amp; Total Scores</b></p> <p><b>SOE: Moderate</b></p> <ul style="list-style-type: none"> <li>• Chlorpromazine vs. clozapine – 2 trials (6 studies) in patients with treatment resistance favored clozapine (BPRS)</li> <li>• Haloperidol vs. olanzapine – 22 studies favored olanzapine (7 CGI-S, 15 PANSS), and quetiapine – 4 studies favored haloperidol (CGI-S)</li> </ul> <p><b>SOE: Low</b></p> <p>Numerous studies compared haloperidol to SGAs and found no difference on the BPRS, CGI-S, CGI-I, PANSS, and the GAF</p> <ul style="list-style-type: none"> <li>• vs. aripiprazole (8 studies)</li> <li>• vs. olanzapine (15 studies)</li> <li>• vs. quetiapine (13 studies)</li> <li>• vs. risperidone (44 studies)</li> <li>• vs. ziprasidone (15 studies)</li> </ul> <p><b>SOE: Insufficient (CGI-I, CGI-S, GAF, PANSS, SANS, BPRS, NOISE-30, SADS-C, SCL-90-R, SWBUN, response rates)</b></p> <ul style="list-style-type: none"> <li>• Chlorpromazine vs. clozapine, olanzapine, quetiapine, and ziprasidone</li> </ul> | No new research was found. |

|   |  |
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| <ul style="list-style-type: none"> <li>• Fluphenazine vs. olanzapine, quetiapine, and risperidone</li> <li>• Haloperidol vs. aripiprazole, asenapine, olanzapine, quetiapine, and risperidone</li> <li>• Perphenazine vs. aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone</li> <li>• Trifluoperazine vs. clozapine</li> </ul>  |  |
| <b>Key Question 1: For adults (age 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what are the comparative efficacy and effectiveness of FGAs versus SGAs for improving core illness symptoms?: Bipolar Disorder</b>   |  |
| <b>Mood (mania)</b><br><b>SOE: Low</b><br>Seven studies compared haloperidol to SGAs and found no difference (YMRS) <ul style="list-style-type: none"> <li>• vs. aripiprazole (2 studies)</li> <li>• vs. olanzapine (2 studies)</li> <li>• vs. risperidone (3 studies)</li> </ul> <b>SOE: Insufficient (YMRS unless noted)</b> <ul style="list-style-type: none"> <li>• Chlorpromazine vs. clozapine</li> <li>• Haloperidol vs. risperidone (CARS-M) and ziprasidone</li> </ul> | No new primary research was found. A multiple treatments meta-analysis found that haloperidol had a larger effect than aripiprazole, asenapine, quetiapine and ziprasidone (YMRS). |
| <b>Mood (depression)</b><br><b>Studies comparing haloperidol to SGAs found no difference (MADRS, HAM-D, PANSS)</b><br><b>SOE: Low</b> <ul style="list-style-type: none"> <li>• vs. aripiprazole (2 studies)</li> </ul> <b>SOE: Insufficient</b> <ul style="list-style-type: none"> <li>• vs. olanzapine and risperidone</li> </ul>  | No new research was found.   |
| <b>Positive Symptoms</b><br><b>SOE: Insufficient (PANSS)</b> <ul style="list-style-type: none"> <li>• Haloperidol vs. aripiprazole and risperidone</li> </ul>   | No new research was found.   |
| <b>Negative Symptoms</b><br><b>SOE: Insufficient (PANSS)</b> <ul style="list-style-type: none"> <li>• Haloperidol vs. aripiprazole and risperidone</li> </ul>   | No new research was found.   |
| <b>Sleep</b><br><b>SOE: Insufficient</b> <ul style="list-style-type: none"> <li>• Haloperidol vs. olanzapine (# of awakenings, sleep efficiency, stage REM, total REM, total sleep time)</li> </ul>   | No new research was found.   |
| <b>Global Ratings &amp; Total Scores (CGI-BP, CGI-I, PANSS, BPRS, response rates)</b><br><b>SOE: Low</b> <ul style="list-style-type: none"> <li>• Haloperidol vs. aripiprazole (2 studies) found no difference</li> </ul> <b>SOE: Insufficient</b> <ul style="list-style-type: none"> <li>• Haloperidol vs. aripiprazole, olanzapine, quetiapine, and risperidone</li> </ul>  | No new research was found.   |
| <b>Key Question 2. For adults (18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what is the comparative effectiveness of FGAs versus SGAs for improving functional outcomes and decreasing health care system utilization?</b>   |  |

|   |                                   |
|---|-----------------------------------|
| <p><b>Functional Outcomes- No significant differences found for the following:</b></p> <ul style="list-style-type: none"> <li>• Fluphenazine vs. quetiapine (sexual dysfunction, treatment improvement) and risperidone (sexual dysfunction, treatment improvement)</li> <li>• Haloperidol vs. olanzapine (urine toxicology, sexual dysfunction), quetiapine (sexual dysfunction), risperidone (economic independence, attitude regarding drugs), and ziprasidone (sexual dysfunction)</li> <li>• Perphenazine vs. quetiapine, risperidone, and ziprasidone (all paid employment)</li> </ul>  | <p>No new research was found.</p> |
| <p><b>Health Care System Use- No significant differences found for the following:</b></p> <ul style="list-style-type: none"> <li>• Chlorpromazine vs. clozapine (rates of hospitalization, re-hospitalization)</li> <li>• Haloperidol vs. clozapine (mean hospital bed days), olanzapine (mean hospital bed days), olanzapine (mean hospital bed days, rates of hospitalization, re-hospitalization), quetiapine (rates of hospitalization, re-hospitalization), risperidone (rates of hospitalization, re-hospitalization), and ziprasidone (rates of hospitalization, re-hospitalization)</li> <li>• Perphenazine vs. olanzapine (rates of hospitalization, re-hospitalization), quetiapine (rates of hospitalization, re-hospitalization), risperidone (rates of hospitalization, re-hospitalization), and ziprasidone (rates of hospitalization, re-hospitalization)</li> </ul> | <p>No new research was found.</p> |
| <p><b>Bipolar Disorder: Functional Outcomes</b></p> <ul style="list-style-type: none"> <li>• Haloperidol vs. olanzapine – 1 study favored olanzapine (number of active workers working for pay). No difference found for household or work activities impairment</li> </ul>   | <p>No new research was found.</p> |
| <p><b>Key Question 3: For adults (age 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, do FGAs and SGAs differ in medication-associated AEs and safety?</b></p>  |                                   |
| <p><b>Mortality</b><br/> <b>SOE: Low – No differences found</b></p> <ul style="list-style-type: none"> <li>• Chlorpromazine vs. clozapine (2 studies) - at 52 and 208 weeks</li> <li>• Haloperidol vs. aripiprazole (2 studies) - 24 hour follow up</li> </ul> <p><b>SOE: Insufficient</b></p> <ul style="list-style-type: none"> <li>• Chlorpromazine vs. ziprasidone</li> <li>• Haloperidol vs. risperidone</li> <li>• Thioridazine vs. clozapine and risperidone</li> </ul>  | <p>No new research was found.</p> |
| <p><b>Metabolic Syndrome</b><br/> <b>SOE: Low – No differences found</b></p> <ul style="list-style-type: none"> <li>• Haloperidol vs. olanzapine (2 studies) - 6 &amp; 12 week follow up</li> </ul> <p><b>SOE: Insufficient</b></p> <ul style="list-style-type: none"> <li>• Haloperidol vs. clozapine</li> <li>• Perphenazine vs. olanzapine, quetiapine, risperidone, and ziprasidone</li> </ul>  | <p>No new research was found.</p> |
| <p><b>Diabetes Mellitus</b><br/> <b>SOE: Insufficient</b></p> <ul style="list-style-type: none"> <li>• Haloperidol vs. olanzapine</li> <li>• Perphenazine vs. olanzapine, quetiapine, risperidone, and ziprasidone</li> </ul>   | <p>No new research was found.</p> |
| <p><b>Tardive Dyskinesia</b></p>  | <p>No new research was found.</p> |

|   |                                   |
|---|-----------------------------------|
| <p><b>SOE: Insufficient</b></p> <ul style="list-style-type: none"> <li>• Chlorpromazine vs. clozapine and ziprasidone</li> <li>• Haloperidol vs. clozapine, olanzapine, quetiapine, and ziprasidone</li> </ul>  |                                   |
| <p><b>Key Question 4: For adults (age 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what is the comparative effectiveness of FGAs versus SGAs for the following other outcomes: Relapse and remission rates; medication adherence and persistent use; patient insight into illness; health-related quality of life; patient satisfaction; comorbidity: endpoints of victimization, homelessness, and substance abuse; patient reported outcomes; ability to obtain and retain employment and succeed in job duties; concomitant use of other medications, especially those used to treat EPS; patient references.</b></p>   |                                   |
| <p><b>Schizophrenia</b></p> <ul style="list-style-type: none"> <li>• Results for other outcomes were available for 19 head-to-head comparisons in studies of patients with schizophrenia or schizophrenia-related psychoses.</li> <li>• Few significant differences were found across the comparisons and outcomes examined.</li> <li>• For most significant findings, the SGA was preferred. The most commonly reported other outcome was response rate. A significant difference in response rates based on three studies was found favoring clozapine compared with chlorpromazine. Olanzapine was favored over haloperidol for remission (3 trials) and response rates (14 trials).</li> <li>• Significant differences were found favoring aripiprazole over haloperidol for caregiver satisfaction (1 trial) and patient satisfaction (1 trial).</li> <li>• Risperidone was favored over haloperidol for relapse rates (6 trials).</li> <li>• Olanzapine was favored over perphenazine for time to all cause medication discontinuation (1 trial).</li> <li>• Health-related quality of life was evaluated for the following comparisons, and no significant differences were found: haloperidol versus olanzapine, quetiapine, risperidone, and ziprasidone (1 trial each); olanzapine, quetiapine, risperidone, and ziprasidone (1 trial each).</li> <li>• There was a significant difference in HRQoL for perphenazine over aripiprazole (1 trial).</li> </ul> <p><b>Bipolar Disorder</b></p> <ul style="list-style-type: none"> <li>• Results for other outcomes were available for three head-to-head comparisons in studies of patients with bipolar disorder.</li> <li>• Significant differences were found for health-related quality of life in one trial comparing haloperidol versus olanzapine: haloperidol was favored for the mental summary score, and olanzapine was favored for the physical summary score. One study showed a significant difference favoring haloperidol compared with ziprasidone for response rates.</li> </ul> | <p>No new research was found.</p> |
| <p><b>Key Question 5: For adults (age 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what are the comparative effectiveness and risks of FGAs versus SGAs in subgroups defined by: disorder subtypes; sex; age group (18-35; 36-54; 55-64); race; comorbidities; drug dosage; follow-up period; treatment of a first episode versus treatment in the context of previous episodes; treatment resistance.</b></p>   |                                   |
| <p><b>Schizophrenia</b></p> <ul style="list-style-type: none"> <li>• A total of 41 studies compared outcomes for predefined subgroups. Among the studies of patients with</li> </ul>  | <p>No new research was found.</p> |

|   |  |
|---|--|
| <p>schizophrenia and schizophrenia-related psychoses, data were most often available for race and treatment resistance.</p> <ul style="list-style-type: none"> <li>• The race most often examined was Asian. No notable differences were observed for the subgroups compared to the overall findings.</li> </ul> <p><b>Bipolar Disorder</b></p> <ul style="list-style-type: none"> <li>• The only subgroup available for analysis in studies of patients with bipolar disorder was disorder subtype, specifically bipolar I and bipolar II.</li> <li>• The results were consistent with the overall findings. A significant difference favored haloperidol compared with ziprasidone for core illness symptoms (YMRS) in patients with bipolar I disorder.</li> </ul> |  |
|---|--|

## Abstract from Relevant Literature

*Cipriani A, Barbui C, Salanti G. 2011.*

*Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis.*

**BACKGROUND:** Conventional meta-analyses have shown inconsistent results for efficacy of pharmacological treatments for acute mania. We did a multiple-treatments meta-analysis, which accounted for both direct and indirect comparisons, to assess the effects of all antimanic drugs. **METHODS:** We systematically reviewed 68 randomised controlled trials (16,073 participants) from Jan 1, 1980, to Nov 25, 2010, which compared any of the following pharmacological drugs at therapeutic dose range for the treatment of acute mania in adults: aripiprazole, asenapine, carbamazepine, valproate, gabapentin, haloperidol, lamotrigine, lithium, olanzapine, quetiapine, risperidone, topiramate, and ziprasidone. The main outcomes were the mean change on mania rating scales and the number of patients who dropped out of the allocated treatment at 3 weeks. Analysis was done by intention to treat. **FINDINGS:** Haloperidol (standardised mean difference [SMD] -0.56 [95% CI -0.69 to -0.43]), risperidone (-0.50 [-0.63 to -0.38]), olanzapine (-0.43 [-0.54 to -0.32]), lithium (-0.37 [-0.63 to -0.11]), quetiapine (-0.37 [-0.51 to -0.23]), aripiprazole (-0.37 [-0.51 to -0.23]), carbamazepine (-0.36 [-0.60 to -0.11]), asenapine (-0.30 [-0.53 to -0.07]), valproate (-0.20 [-0.37 to -0.04]), and ziprasidone (-0.20 [-0.37 to -0.03]) were significantly more effective than placebo, whereas gabapentin, lamotrigine, and topiramate were not. Haloperidol had the highest number of significant differences and was significantly more effective than lithium (SMD -0.19 [95% CI -0.36 to -0.01]), quetiapine (-0.19 [-0.37 to 0.01]), aripiprazole (-0.19 [-0.36 to -0.02]), carbamazepine (-0.20 [-0.36 to -0.01]), asenapine (-0.26 [-0.52 to 0.01]), valproate (-0.36 [-0.56 to -0.15]), ziprasidone -0.36 [-0.56 to -0.15]), lamotrigine (-0.48 [-0.77 to -0.19]), topiramate (-0.63 [-0.84 to -0.43]), and gabapentin (-0.88 [-1.40 to -0.36]). Risperidone and olanzapine had a very similar profile of comparative efficacy, being more effective than valproate, ziprasidone, lamotrigine, topiramate, and gabapentin. Olanzapine, risperidone, and quetiapine led to significantly fewer discontinuations than did lithium, lamotrigine, placebo, topiramate, and gabapentin. **INTERPRETATION:** Overall, antipsychotic drugs were significantly more effective than mood stabilisers. Risperidone, olanzapine, and haloperidol should be considered as among the best of the available options for the treatment of manic episodes. These results should be considered in the development of clinical practice guidelines.

## Appendix G: Summary Table

| Conclusions From CER Executive Summary   | SRC Literature Search (April 2014) | Expert Opinion<br>EPC Investigator Other Experts  | SRC Conclusion   |
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| <b>Key Question 1: For adults (age 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what are the comparative efficacy and effectiveness of FGAs versus SGAs for improving core illness symptoms?: Schizophrenia/Schizophrenia-Related</b>   |                                    |   |  |
| <p><b>Positive Symptoms</b><br/><b>SOE: Low</b><br/>Numerous studies compared haloperidol to SGAs on either the PANSS or SAPS, and found no difference.</p> <ul style="list-style-type: none"> <li>• vs. aripiprazole (2 studies)</li> <li>• vs. clozapine (2 studies)</li> <li>• vs. olanzapine (16 studies)</li> <li>• vs. quetiapine (4 studies)</li> <li>• vs. risperidone (22 studies)</li> </ul> <p><b>SOE: Insufficient (PANSS or SAPS):</b></p> <ul style="list-style-type: none"> <li>• Chlorpromazine vs. clozapine</li> <li>• Fluphenazine vs. olanzapine</li> <li>• Perphenazine vs. olanzapine, quetiapine, risperidone, and ziprasidone</li> <li>• Haloperidol vs. aripiprazole and asenapine</li> </ul> | No new research was found.         | One expert did not know of any additional studies, and believed the original report to be up to date. The other reviewer suggested 9 missed studies included in a review by Turner et al. <sup>5</sup> Published studies included within Turner et al. were within the date range of the original CER. Turner et al. reports unpublished findings that ziprasidone was statistically inferior to haloperidol on the BPRS total, BPRS core, CGI-severity, and PANSS total. Iloperidol is reported as inferior to haloperidol; however, outcome measures are not mentioned. This reviewer also recommended examining FDA medical review reports. All reports except for lurasidone were published prior to the original CER. We identified only one trial comparing lurasidone to an FGA (vs. haloperidol), <sup>6</sup> which found haloperidol to be more effective (PANSS); however, it is unclear if these results are statistically significant. | This conclusion is possibly out of date with regard to findings related to haloperidol vs. ziprasidone, and haloperidol vs. iloperidone, and out of date with regard to a comparative study examining lurasidone to a FGA. |
| <p><b>Negative Symptoms</b><br/><b>SOE: Moderate</b><br/>Numerous studies compared haloperidol to SGAs on either the PANSS or SAPS</p> <ul style="list-style-type: none"> <li>• vs. aripiprazole ( 3 studies) favoring aripiprazole</li> <li>• vs. clozapine (4 studies) found no difference</li> <li>• vs. olanzapine (19 studies) favored</li> </ul>   | No new research was found.         | One expert did not know of any additional studies, and believed the original report to be up to date. The other reviewer suggested 9 missed studies included in a review by Turner et al. <sup>5</sup> Published studies included within Turner et al. were within the date range of the original CER. Turner et al. reports unpublished findings that Iloperidol is  | This conclusion is possibly out of date with regard to findings related to haloperidol vs. iloperidone, and out of date with regard to a comparative study examining lurasidone to a FGA.                                  |

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| <p>olanzapine</p> <ul style="list-style-type: none"> <li>vs. risperidone (24 studies) favored risperidone</li> </ul> <p><b>SOE: Low</b></p> <p>Seven studies compared haloperidol to SGAs and found no difference on either the PANSS or SAPS</p> <ul style="list-style-type: none"> <li>vs. clozapine (1 study)</li> <li>vs. quetiapine (4 studies)</li> <li>vs. ziprasidone (2 studies)</li> </ul> <p><b>SOE: Insufficient (PANSS or SAPS)</b></p> <ul style="list-style-type: none"> <li>Fluphenazine vs. olanzapine</li> <li>Chlorpromazine vs. clozapine and olanzapine</li> <li>Haloperidol vs. aripiprazole, asenapine, and quetiapine</li> <li>Perphenazine vs. olanzapine, quetiapine, risperidone, and ziprasidone</li> </ul>  |                                   | <p>inferior to haloperidol; however, outcome measures are not mentioned. In addition the reviewer referred to data comparing aripiprazole vs. haloperidol, published prior to the original CER. This reviewer also recommended examining FDA medical review reports. All reports except for lurasidone were published prior to the original CER. We identified only one trial comparing lurasidone to an FGA (vs. haloperidol),<sup>6</sup> which found haloperidol to be more effective (PANSS); however, it is unclear if these results are statistically significant.</p>  |   |
| <p><b>General Psychopathology</b></p> <p><b>SOE: Moderate</b></p> <ul style="list-style-type: none"> <li>Haloperidol vs. olanzapine (9 studies) favored olanzapine (3 HAM-D, 6 MADRS)</li> </ul> <p><b>SOE: Low</b></p> <p>Numerous studies compared haloperidol to SGAs and found no difference across the PANSS, ABS, ACES, CDS-S, HAM-A, YMRS</p> <ul style="list-style-type: none"> <li>vs. clozapine (2 studies)</li> <li>vs. olanzapine (19 studies)</li> <li>vs. quetiapine (6 studies)</li> <li>vs. risperidone (20 studies)</li> </ul> <p><b>SOE: Insufficient (numerous measures)</b></p> <ul style="list-style-type: none"> <li>Chlorpromazine vs. clozapine</li> <li>Fluphenazine vs. olanzapine</li> <li>Haloperidol vs. aripiprazole, asenapine, clozapine, quetiapine, and ziprasidone</li> </ul> | <p>No new research was found.</p> | <p>One expert did not know of any additional studies, and believed the original report to be up to date. The other reviewer suggested 9 missed studies included in a review by Turner et al.<sup>5</sup> Published studies included within Turner et al. were within the date range of the original CER. Turner et al. reports unpublished findings that ziprasidone was statistically inferior to haloperidol on the BPRS total, BPRS core, CGI-severity, and PANSS total. Haloperidol is reported as inferior to haloperidol; however, outcome measures are not mentioned. This reviewer also recommended examining FDA medical review reports. All reports except for lurasidone were published prior to the original CER. We identified only one trial comparing lurasidone to an FGA (vs. haloperidol),<sup>6</sup> which found no</p> | <p>This conclusion is possibly out of date with regard to findings related to haloperidol vs. ziprasidone, and haloperidol vs. iloperidone, and out of date with regard to a comparative study examining lurasidone to a FGA.</p> |

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| <ul style="list-style-type: none"> <li>Perphenazine vs. olanzapine, quetiapine, risperidone, and ziprasidone</li> </ul>   |                            | difference on the MADRS.  |  |
| <p><b>Global Ratings &amp; Total Scores</b><br/> <b>SOE: Moderate</b></p> <ul style="list-style-type: none"> <li>Chlorpromazine vs. clozapine – 2 trials (6 studies) in patients with treatment resistance favored clozapine (BPRS)</li> <li>Haloperidol vs. olanzapine – 22 studies favored olanzapine (7 CGI-S, 15 PANSS), and quetiapine – 4 studies favored haloperidol (CGI-S)</li> </ul> <p><b>SOE: Low</b><br/> Numerous studies compared haloperidol to SGAs and found no difference on the BPRS, CGI-S, CGI-I, PANSS, and the GAF</p> <ul style="list-style-type: none"> <li>vs. aripiprazole (8 studies)</li> <li>vs. olanzapine (15 studies)</li> <li>vs. quetiapine (13 studies)</li> <li>vs. risperidone (44 studies)</li> <li>vs. ziprasidone (15 studies)</li> </ul> <p><b>SOE: Insufficient (CGI-I, CGI-S, GAF, PANSS, SANS, BPRS, NOISE-30, SADS-C, SCL-90-R, SWBUN, response rates)</b></p> <ul style="list-style-type: none"> <li>Chlorpromazine vs. clozapine, olanzapine, quetiapine, and ziprasidone</li> <li>Fluphenazine vs. olanzapine, quetiapine, and risperidone</li> <li>Haloperidol vs. aripiprazole, asenapine, olanzapine, quetiapine, and risperidone</li> <li>Perphenazine vs. aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone</li> <li>Trifluoperazine vs. clozapine</li> </ul> | No new research was found. | One expert did not know of any additional studies, and believed the original report to be up to date. The other reviewer suggested 9 missed studies included in a review by Turner et al. <sup>5</sup> Published studies included within Turner et al. were within the date range of the original CER. Turner et al. reports unpublished findings that ziprasidone was statistically inferior to haloperidol on the BPRS total, BPRS core, CGI-severity, and PANSS total. Iloperidol is reported as inferior to haloperidol; however, outcome measures are not mentioned. The other reviewer recommended examining FDA medical review reports. All reports except for lurasidone were published prior to the original CER. We identified only one trial comparing lurasidone to an FGA (vs. haloperidol) <sup>6</sup> and found no difference on the CGI-Severity, and a difference favoring haloperidol (BPRS); however it is unclear whether these differences are statistically significant. | This conclusion is possibly out of date with regard to findings related to haloperidol vs. ziprasidone, and haloperidol vs. iloperidone, and out of date with regard to a comparative study examining lurasidone to a FGA. |

| <b>Key Question 1: For adults (age 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what are the comparative efficacy and effectiveness of FGAs versus SGAs for improving core illness symptoms?: Bipolar Disorder</b>  |   |   |  |
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| <p><b>Mood (mania)</b><br/> <b>SOE: Low</b><br/>           Seven studies compared haloperidol to SGAs and found no difference (YMRS)</p> <ul style="list-style-type: none"> <li>vs. aripiprazole (2 studies)</li> <li>vs. olanzapine (2 studies)</li> <li>vs. risperidone (3 studies)</li> </ul> <p><b>SOE: Insufficient (YMRS unless noted)</b></p> <ul style="list-style-type: none"> <li>Chlorpromazine vs. clozapine</li> <li>Haloperidol vs. risperidone (CARS-M) and zipasidone</li> </ul> | <p>No new primary research was found. A multiple treatments meta-analysis found that haloperidol had a larger effect than aripiprazole, asenapine, quetiapine and ziprasidone (YMRS).<sup>3</sup> Risperidone and olanzapine had a very similar profile of comparative efficacy, being more effective than valproate, ziprasidone, lamotrigine, topiramate, and gabapentin.</p> | <p>One expert identified a meta-analysis<sup>7</sup> that found that haloperidol was more likely (42%) to induce switching to depression in manic patients treated than SGAs, and felt that the meta-analysis identified by the SRC deserved mention and questions the findings of the original CER.<sup>3</sup> The other expert believed the report was up to date or did not know.</p> | <p>This conclusion is possibly out of date with regard to findings that haloperidol was more likely to induce switching to depression in manic patients than SGAs, and findings that haloperidol had a larger effect than aripiprazole, asenapine, quetiapine and ziprasidone on the YMRS.</p> |
| <p><b>Mood (depression)</b><br/>           Studies comparing haloperidol to SGAs found no difference (MADRS, HAM-D, PANSS)<br/> <b>SOE: Low</b></p> <ul style="list-style-type: none"> <li>vs. aripiprazole (2 studies)</li> </ul> <p><b>SOE: Insufficient</b></p> <ul style="list-style-type: none"> <li>vs. olanzapine and risperidone</li> </ul>  | <p>No new research was found.</p>   | <p>The two experts did not know of any additional studies, and either believed the original report to be up to date or did not know.</p>  | <p>Original conclusion is still valid and this portion of the original report does not need updating.</p>  |
| <p><b>Positive Symptoms</b><br/> <b>SOE: Insufficient (PANSS)</b></p> <ul style="list-style-type: none"> <li>Haloperidol vs. aripiprazole and risperidone</li> </ul>   | <p>No new research was found.</p>   | <p>The two experts did not know of any additional studies, and either believed the original report to be up to date or did not know.</p>  | <p>Original conclusion is still valid and this portion of the original report does not need updating.</p>  |
| <p><b>Negative Symptoms</b><br/> <b>SOE: Insufficient (PANSS)</b></p> <ul style="list-style-type: none"> <li>Haloperidol vs. aripiprazole and risperidone</li> </ul>   | <p>No new research was found.</p>   | <p>The two experts did not know of any additional studies, and either believed the original report to be up to date or did not know.</p>  | <p>Original conclusion is still valid and this portion of the original report does not need updating.</p>  |
| <p><b>Sleep</b><br/> <b>SOE: Insufficient</b></p> <ul style="list-style-type: none"> <li>Haloperidol vs. olanzapine (# of awakenings, sleep efficiency, stage REM, total REM, total sleep time)</li> </ul>   | <p>No new research was found.</p>   | <p>The two experts did not know of any additional studies, and either believed the original report to be up to date or did not know.</p>  | <p>Original conclusion is still valid and this portion of the original report does not need updating.</p>  |

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| <p><b>Global Ratings &amp; Total Scores (CGI-BP, CGI-I, PANSS, BPRS, response rates)</b><br/> <b>SOE: Low</b></p> <ul style="list-style-type: none"> <li>Haloperidol vs. aripiprazole (2 studies) found no difference</li> </ul> <p><b>SOE: Insufficient</b></p> <ul style="list-style-type: none"> <li>Haloperidol vs. aripiprazole, olanzapine, quetiapine, and risperidone</li> </ul>   | <p>No new research was found.</p> | <p>The two experts did not know of any additional studies, and either believed the original report to be up to date or did not know.</p> | <p>Original conclusion is still valid and this portion of the original report does not need updating.</p> |
| <p><b>Key Question 2. For adults (18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what is the comparative effectiveness of FGAs versus SGAs for improving functional outcomes and decreasing health care system utilization?</b></p>   |                                   |  |   |
| <p><b>Functional Outcomes- No significant differences found for the following:</b></p> <ul style="list-style-type: none"> <li>Fluphenazine vs. quetiapine (sexual dysfunction, treatment improvement) and risperidone (sexual dysfunction, treatment improvement)</li> <li>Haloperidol vs. olanzapine (urine toxicology, sexual dysfunction), quetiapine (sexual dysfunction), risperidone (economic independence, attitude regarding drugs), and ziprasidone (sexual dysfunction)</li> <li>Perphenazine vs. quetiapine, risperidone, and ziprasidone (all paid employment)</li> </ul> | <p>No new research was found.</p> | <p>The two experts did not know of any additional studies, and either believed the original report to be up to date or did not know.</p> | <p>Original conclusion is still valid and this portion of the original report does not need updating.</p> |
| <p><b>Health Care System Use- No significant differences found for the following:</b></p> <ul style="list-style-type: none"> <li>Chlorpromazine vs. clozapine (rates of hospitalization, rehospitalization)</li> <li>Haloperidol vs. clozapine (mean hospital bed days), olanzapine (mean hospital bed days), olanzapine (mean hospital bed days, rates of hospitalization, rehospitalization), quetiapine (rates of hospitalization, rehospitalization), risperidone (rates of hospitalization, rehospitalization),</li> </ul>  | <p>No new research was found.</p> | <p>The two experts did not know of any additional studies, and either believed the original report to be up to date or did not know.</p> | <p>Original conclusion is still valid and this portion of the original report does not need updating.</p> |

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| <ul style="list-style-type: none"> <li>and ziprasidone (rates of hospitalization, rehospitalization)</li> <li>Perphenazine vs. olanzapine (rates of hospitalization, rehospitalization), quetiapine (rates of hospitalization, rehospitalization), risperidone (rates of hospitalization, rehospitalization), and ziprasidone (rates of hospitalization, rehospitalization)</li> </ul>   |                            |  |  |
| <p><b>Bipolar Disorder: Functional Outcomes</b></p> <ul style="list-style-type: none"> <li>Haloperidol vs. olanzapine – 1 study favored olanzapine (number of active workers working for pay). No difference found for household or work activities impairment</li> </ul>  | No new research was found. | The two experts did not know of any additional studies, and either believed the original report to be up to date or did not know.  | Original conclusion is still valid and this portion of the original report does not need updating. |
| <p><b>Key Question 3: For adults (age 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, do FGAs and SGAs differ in medication-associated AEs and safety?</b></p>   |                            |  |  |
| <p><b>Mortality</b></p> <p><b>SOE: Low – No differences found</b></p> <ul style="list-style-type: none"> <li>Chlorpromazine vs. clozapine (2 studies) - at 52 and 208 weeks</li> <li>Haloperidol vs. aripiprazole (2 studies) - 24 hour follow up</li> </ul> <p><b>SOE: Insufficient</b></p> <ul style="list-style-type: none"> <li>Chlorpromazine vs. ziprasidone</li> <li>Haloperidol vs. risperidone</li> <li>Thioridazine vs. clozapine and risperidone</li> </ul> | No new research was found. | One expert did not know of any additional studies, and believed the original report to be up to date. The other reviewer recommended examining FDA medical review reports. All reports except for lurasidone were published prior to the original CER. We identified only one trial comparing lurasidone to an FGA (vs. haloperidol) <sup>6</sup> with no reported mortality AEs.                      | Original conclusion is still valid and this portion of the original report does not need updating. |
| <p><b>Metabolic Syndrome</b></p> <p><b>SOE: Low – No differences found</b></p> <ul style="list-style-type: none"> <li>Haloperidol vs. olanzapine (2 studies) - 6 &amp; 12 week follow up</li> </ul> <p><b>SOE: Insufficient</b></p> <ul style="list-style-type: none"> <li>Haloperidol vs. clozapine</li> <li>Perphenazine vs. olanzapine, quetiapine, risperidone, and ziprasidone</li> </ul>   | No new research was found. | One expert did not know of any additional studies, and believed the original report to be up to date. The other reviewer recommended examining FDA medical review reports. All reports except for lurasidone were published prior to the original CER. We identified only one trial comparing lurasidone to an FGA (vs. haloperidol), <sup>6</sup> with no reported AEs related to metabolic syndrome. | Original conclusion is still valid and this portion of the original report does not need updating. |

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| <p><b>Diabetes Mellitus</b><br/> <b>SOE: Insufficient</b></p> <ul style="list-style-type: none"> <li>• Haloperidol vs. olanzapine</li> <li>• Perphenazine vs. olanzapine, quetiapine, risperidone, and ziprasidone</li> </ul>  | <p>No new research was found.</p> | <p>One expert did not know of any additional studies, and believed the original report to be up to date. The other reviewer recommended examining FDA medical review reports. All reports except for lurasidone were published prior to the original CER. We identified only one trial comparing lurasidone to an FGA (vs. haloperidol)<sup>6</sup> with no AEs related to diabetes reported.</p>   | <p>Original conclusion is still valid and this portion of the original report does not need updating.</p> |
| <p><b>Tardive Dyskinesia</b><br/> <b>SOE: Insufficient</b></p> <ul style="list-style-type: none"> <li>• Chlorpromazine vs. clozapine and ziprasidone</li> <li>• Haloperidol vs. clozapine, olanzapine, quetiapine, and ziprasidone</li> </ul>  | <p>No new research was found.</p> | <p>One expert did not know of any additional studies, and believed the original report to be up to date. The other reviewer recommended examining FDA medical review reports. All reports except for lurasidone were published prior to the original CER. We identified only one trial comparing lurasidone to an FGA (vs. haloperidol)<sup>6</sup> with no AEs related to tardive dyskinesia reported.</p>   | <p>Original conclusion is still valid and this portion of the original report does not need updating.</p> |
| <p><b>Cardiovascular</b><br/> <b>SOE: Insufficient</b></p> <ul style="list-style-type: none"> <li>• Chlorpromazine vs. clozapine, olanzapine, quetiapine, ziprasidone</li> <li>• Fluphenazine vs. quetiapine, risperidone</li> <li>• Haloperidol vs. aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone</li> <li>• Perphenazine vs. aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone</li> </ul>   | <p>No new research was found.</p> | <p>One expert identified a study that found that aripiprazole had less QTc prolongation than other antipsychotics to which it had been compared;<sup>8</sup> however, the meta-analysis included only SGAs and was published prior to the original CER. The other reviewer recommended examining FDA medical review reports. All reports except for lurasidone were published prior to the original CER. We identified only one trial comparing lurasidone to an FGA (vs. haloperidol)<sup>6</sup> with no difference in cardiovascular AEs reported.</p> | <p>Original conclusion is still valid and this portion of the original report does not need updating.</p> |
| <p><b>Key Question 4: For adults (age 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what is the comparative effectiveness of FGAs versus SGAs for the following other outcomes: Relapse and remission rates; medication adherence and persistent use; patient insight into illness; health-related quality of life; patient satisfaction; comorbidity: endpoints of victimization, homelessness, and substance abuse; patient reported outcomes; ability to obtain and retain employment and succeed in job duties; concomitant use of other medications, especially those</b></p> |                                   |   |   |

| <b>used to treat EPS; patient references.</b>   |                                   |  |   |
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| <p><b>Schizophrenia</b></p> <ul style="list-style-type: none"> <li>• Results for other outcomes were available for 19 head-to-head comparisons in studies of patients with schizophrenia or schizophrenia-related psychoses.</li> <li>• Few significant differences were found across the comparisons and outcomes examined.</li> <li>• For most significant findings, the SGA was preferred. The most commonly reported other outcome was response rate. A significant difference in response rates based on three studies was found favoring clozapine compared with chlorpromazine. Olanzapine was favored over haloperidol for remission (3 trials) and response rates (14 trials).</li> <li>• Significant differences were found favoring aripiprazole over haloperidol for caregiver satisfaction (1 trial) and patient satisfaction (1 trial).</li> <li>• Risperidone was favored over haloperidol for relapse rates (6 trials).</li> <li>• Olanzapine was favored over perphenazine for time to all cause medication discontinuation (1 trial).</li> <li>• Health-related quality of life was evaluated for the following comparisons, and no significant differences were found: haloperidol versus olanzapine, quetiapine, risperidone, and ziprasidone (1 trial each); olanzapine, quetiapine, risperidone, and ziprasidone (1 trial each).</li> </ul> | <p>No new research was found.</p> | <p>One expert identified a study that found that quetiapine has a shorter time to discontinuation than FGAs and other SGAs;<sup>9</sup> however, this study was published prior to the original CER. The other reviewer recommended examining FDA medical review reports. All reports except for lurasidone were published prior to the original CER. We identified only one trial comparing lurasidone to an FGA (vs. haloperidol)<sup>6</sup> with no AEs meeting criteria for KQ4 reported.</p> | <p>Original conclusion is still valid and this portion of the original report does not need updating.</p> |

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| <ul style="list-style-type: none"> <li>• There was a significant difference in HRQoL for perphenazine over aripiprazole (1 trial).</li> </ul> <p><b>Bipolar Disorder</b></p> <ul style="list-style-type: none"> <li>• Results for other outcomes were available for three head-to-head comparisons in studies of patients with bipolar disorder.</li> <li>• Significant differences were found for health-related quality of life in one trial comparing haloperidol versus olanzapine: haloperidol was favored for the mental summary score, and olanzapine was favored for the physical summary score. One study showed a significant difference favoring haloperidol compared with ziprasidone for response rates.</li> </ul> |  |  |  |
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**Key Question 5: For adults (age 18 to 64 years) with schizophrenia, schizophrenia-related psychoses, or bipolar disorder, what are the comparative effectiveness and risks of FGAs versus SGAs in subgroups defined by: disorder subtypes; sex; age group (18-35; 36-54; 55-64); race; comorbidities; drug dosage; follow-up period; treatment of a first episode versus treatment in the context of previous episodes; treatment resistance.**

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| <p><b>Schizophrenia</b></p> <ul style="list-style-type: none"> <li>• A total of 41 studies compared outcomes for predefined subgroups. Among the studies of patients with schizophrenia and schizophrenia-related psychoses, data were most often available for race and treatment resistance.</li> <li>• The race most often examined was Asian. No notable differences were observed for the subgroups compared to the overall findings.</li> </ul> <p><b>Bipolar Disorder</b></p> <ul style="list-style-type: none"> <li>• The only subgroup available for analysis in studies of patients with bipolar disorder was disorder subtype, specifically bipolar I and bipolar II.</li> <li>• The results were consistent with the overall findings. A significant difference favored haloperidol compared with ziprasidone for core illness symptoms (YMRS) in patients with bipolar I disorder.</li> </ul> | <p>No new research was found.</p> | <p>The two experts did not know of any additional studies, and either believed the original report to be up to date or did not know.</p> | <p>Original conclusion is still valid and this portion of the original report does not need updating.</p> |
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