Evidence-based Practice Center Systematic Review Protocol

Project Title: Comparative Effectiveness of First-Generation and Second-Generation Antipsychotics in the Adult Population

I. Background and Objectives for the Systematic Review

Schizophrenia and Related Psychoses

Schizophrenia is a heterogeneous syndrome that includes disturbances in language, perception, cognition, social relatedness, and volition.[1] Symptoms include positive (i.e., delusions, hallucinations) and negative (i.e., passive/apathetic social withdrawal, blunted affect) symptoms and general psychopathology (i.e., preoccupation, lack of insight, motor retardation). Onset of symptoms typically occurs in late adolescence or young adulthood, with approximately 0.4 to 0.6 percent of the population affected worldwide.[2] Antipsychotics represent the first-line treatment for patients with Schizophrenia and have been the mainstay treatment since the 1950s. The American Psychiatric Association (APA) currently recommends that selection of an antipsychotic should be based on a patient's previous responses to the drug and its side effect profile.[3]

Conventional antipsychotics (termed typical or first-generation antipsychotics [FGAs] (i.e., haloperidol, chlorpromazine)), act on the dopaminergic system by blocking the dopamine type 2 (D2) receptors.[4] This mechanism, however, leads to a variety of extrapyramidal side effects (e.g., tremor, slurred speech, akathisia, dystonia), some of which appear after long-term exposure (e.g., tardive dyskinesia).[5,6] While these antipsychotics are effective against the positive symptoms of Schizophrenia, they have been considered to be ineffective in treating negative symptoms.[7] Such symptoms particularly play a critical role in producing the severe social and vocational disabilities experienced by many patients with Schizophrenia.[8]

The search for antipsychotic medications to manage both the positive and negative symptoms of Schizophrenia led to the reestablishment of clozapine in the early 1990s and signaled a new generation of antipsychotic drugs (termed "atypical" or second-generation antipsychotics [SGAs]). A series of SGA compounds have been developed (i.e., risperidone, olanzapine, quetiapine). When compared to FGAs, SGAs have shown greater benefits in many outcome domains,[9] and newer medications are replacing the conventional antipsychotics as treatments of choice. Although SGAs were developed to improve on the shortcomings of FGAs, they also have significant limitations in terms of side effects. As a class, they have a more favorable profile in terms of extrapyramidal side effects and tardive dyskinesia, but produce other side effects, including sedation, hypotension, weight gain, and sexual dysfunction.[9] SGAs

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have also been associated with metabolic side effects,[9] but it is unclear whether these are secondary to, independent of, or causative of weight gain. The long-term consequences of SGAs remain largely unknown.[10]

There is debate surrounding the efficacy of SGAs on negative symptoms, with several published reports indicating that there is no clear advantage over FGAs.[8,11] Trials in which SGAs have been evaluated are criticized for their 1) inclusion of patients with positive and negative symptoms, making it unclear whether a drug is having direct effects, indirect effects, or both, on primary negative symptoms,[11] and 2) derivation of data on negative symptoms from short-term trials that focus on patients selected on the basis of positive symptoms (or, for longer-term trials, on the basis of clinical stability).[8] Recent findings from CutLASS 1 (Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study)[12,13] and the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) study[14,15] found few differences in the effectiveness of SGAs and FGAs in patients with nonrefractory Schizophrenia. Subsequent meta-analyses have generally confirmed these results[16] and have helped to provide a clearer picture of the comparative effectiveness of the two classes of antipsychotics.

The disconnect between the research findings of CutLASS 1 and the CATIE study and meta-analyses (favoring neither SGAs nor FGAs), individual efficacy trials (pharmaceutical industry trials favoring SGAs), and prescribing patterns of clinicians (favoring SGAs), however, make a comparative effectiveness review (CER) an important step toward bringing together research of rigorous and complementary design for making clinical decisions and shaping health care policy.

Bipolar Disorder

Bipolar disorder is characterized by severe fluctuations in mood, activity, thought, and behavior.[1] The disorder involves one or more episodes of mania or mixed mood, mood states that are associated with increased psychomotor activity, excessive social extroversion, decreased need for sleep, impulsivity, impairment in judgment and grandiose mood. Patients may experience delusions, paranoid thinking, and extremely agitated states. Bipolar II disorder is characterized by at least one hypomanic episode and at least one major depressive episode. Prevalence of bipolar disorder is 0.4 to 1.6 percent in community samples and has an average age of onset of 20 years.[1] The APA (2002) recommends the following treatment plan: 1) polytherapy for severe manic or mixed episodes: lithium or valproate in conjunction with an antipsychotic; and 2) monotherapy for less ill patients: lithium, valproate, or an antipsychotic. The APA states that SGAs are preferred over FGAs because of their side effect profile.[17]

Table 1. List of antipsychotics included in the CER

First-Generation Antipsychotics	Second-Generation Antipsychotics (Monotherapy)	Second-Generation antipsychotics (Combination Therapy)
• Chlorpromazine • Droperidol • Fluphenazine • Haloperidol • Loxapine • Perphenazine • Pimozide • Prochlorperazine • Thioridazine • Thiothixene • Trifluoperazine	• Aripiprazole • Asenapine • Clozapine • Iloperidone • Lurasidone • Olanzapine • Paliperidone • Quetiapine • Risperidone • Ziprasidone	• Olanzapine plus fluoxetine

II. The Key Questions

The Key Questions (KQs) have been posted for public comment on the AHRQ Effective Health Care Program Web site. The comments received were discussed by members of the Technical Expert Panel (TEP), AHRQ, and the Evidence-based Practice Center, and the following key changes were made accordingly:

1. The terminology of “typical” and “atypical” antipsychotics has been changed to “first-generation” and “second-generation” antipsychotics in the title and thouroughout the KQs and the protocol.
2. KQ 1 will focus on the core symptoms, and KQ 2 will focus on functional outcomes.
3. Study inclusion in the CER will not be limited by drug dosage.
4. Individual antipsychotic medications, rather than a particular class, have been set as the interventions/comparators for this review.
5. Relapse and remission rates will be included as key outcomes.
6. The search strategy has been expanded to include studies from 1950 onward to capture studies that compared FGAs with SGAs.
7. The search strategy has also been expanded to include randomized trials, cohort studies (for serious adverse events; see point 8 below), and systematic reviews that may answer the KQs.
8. To capture data on long-term serious adverse events, the inclusion criteria have been modified to include cohort studies that compare FGAs with SGAs, have a follow-up period of at least 2 years, and present data on at least one serious adverse event (including type 2 diabetes mellitus, mortality, tardive dyskinesia, and major metabolic syndromes).
9. Additional outcome measures:
   Key symptoms:

- Core symptoms to include cognition, suicidality, insight, and maintenance of mood stability (particularly for bipolar disorder).
- Measures of neurocognition for Schizophrenia: the Young Mania Rating Scale (YMRS), the Montgomery-Asberg Depression Rating Scale (MADRS), and the modified Clinical Global Impressions Scale for bipolar disorder (CGI-BP).

Adverse effects:
- Weight gain, hypotension, and metabolic changes (including changes in glucose levels, triglycerides, and lipids and the risk of developing diabetes).

Other outcomes:
- Comorbidity: end points 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 extrapyramidal symptoms
- Patient preferences

10. Subgroup analyses have been revised to include dosage, length of followup, previous exposure to antipsychotics, treatment of a first episode vs. treatment in the context of previous episodes, and treatment resistance.

The revised key questions are as follows:

KQ 1: For adults (aged 18 to 64 years) with Schizophrenia, Schizophrenia-related psychoses, or bipolar disorder, what is the comparative efficacy and effectiveness of FGAs vs. SGAs for improving core illness symptoms?
Population: Adults (aged 18 to 64 years) with Schizophrenia, Schizophrenia-related psychoses, or bipolar disorder.
Interventions: Any commercially available FDA-approved by the U.S. Food and Drug Administration (FDA).
Comparators: Any commercially available FDA-approved SGA.
Outcomes: Improvement or change in disorder-specific and nonspecific symptoms.
The following symptoms are included for each disorder:
1) Core illness symptoms for Schizophrenia or related psychoses to include: positive (i.e., delusions, hallucinations) and negative (i.e., passive/apathetic social withdrawal, blunted affect) symptoms, general psychopathology (i.e., preoccupation, lack of insight, motor retardation), cognition, suicidality, and insight.

2) Core illness symptoms for bipolar disorder to include: mood, motor activity/energy, sleep, speech, behavior, cognition, suicidality, insight, and mood stability.

Timing: All time points; the last time point will be assessed if data on multiple time points are provided.
Settings: All settings, including hospitalization and outpatient treatment.

KQ2: For adults (aged 18 to 64 years) with Schizophrenia, Schizophrenia-related psychoses, or bipolar disorder, what is the comparative effectiveness of FGAs vs. SGAs for improving functional outcomes and decreasing health care system utilization?
Population: See KQ1 above.
Interventions: See KQ1 above.
Comparators: See KQ1 above.
Outcomes:

1) Functional outcomes to include any of the following: employment/personal earnings, social relatedness/functioning, encounters with legal system, sexual function/dysfunction, functional capacity, and living situation.

2) Utilization of the health care system to include: time to hospitalization/rehospitalization because of mental illness and all other causes; rates of hospitalization/rehospitalization; mean hospital bed days; length of hospitalization stay; rates of emergency department visits; attendance in day care programs; and use of ancillary caseworkers.

Timing: See KQ1 above.
Settings: See KQ1 above.

KQ 3: For adults (aged 18 to 64 years) with Schizophrenia, Schizophrenia-related psychoses, or bipolar disorder, do FGAs and SGAs differ in medication-associated adverse events and safety?
Population: See KQ1 above.
Interventions: See KQ1 above.
Comparators: See KQ1 above.
Outcomes: Disorder-specific and -nonspecific adverse events:

1) Overall adverse events.
2) Specific adverse events:
   a. *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.
   b. *General:* extrapyramidal side effects, weight gain, agitation, constipation, sedation, elevated cholesterol, adverse events related to prolactin elevations, galactorrhea/bloody galactorrhea, weight gain, hypotension, and metabolic changes (including changes in glucose levels, triglycerides, lipids, and the risk of developing diabetes).
3) Study withdrawals/time to withdrawal because of adverse events.

4) Persistence and reversibility of adverse events.

Timing: See KQ1 above.
Settings: See KQ1 above.

KQ 4: For adults (aged 18 to 64 years) with Schizophrenia, Schizophrenia-related psychoses, or bipolar disorder, what is the comparative effectiveness of FGAs vs. SGAs for other outcomes?

Population: See KQ1 above.
Interventions: See KQ1 above.
Comparators: See KQ1 above.
Outcomes:

1) Relapse and remission rates.
2) Medication adherence and persistent use (and associated dosing, time to discontinuation of treatment).
3) Patient insight into illness.
4) Health-related quality of life.
5) Patient satisfaction.
6) Comorbidity: end points of victimization, homelessness, and substance abuse.
7) Patient-reported outcomes.
8) Ability to obtain and retain employment and succeed in job duties.
9) Concomitant use of other medications, especially those used to treat extrapyramidal symptoms
10) Patient preferences

Timing: See KQ1 above.
Settings: See KQ1 above.

KQ 5: For adults (aged 18 to 64 years) with Schizophrenia, Schizophrenia-related psychoses, or bipolar disorder, what is the comparative effectiveness and risks of FGAs vs. SGAs in subgroups defined by the following variables?

1) Disorder subtypes.
2) Gender.
3) Age group (18–35 yrs, 36–54 yrs, 55–64 yrs).
4) Race.
5) Comorbidities.
6) Drug dosage.
7) Followup period.
8) Previous exposure to antipsychotics.
9) Treatment of a first episode vs. treatment in the context of previous episodes.
10) Treatment resistance.

Population: See KQ1 above.
Interventions: See KQ1 above.
Comparators: See KQ1 above.

Outcomes: Core illness symptoms (see KQ1), functional capacity and decreasing health care-system utilization (see KQ2), adverse events (see KQ3), or other outcomes (KQ4).
Timing: See KQ1 above.
Settings: See KQ1 above.

III. Analytic Framework

Figure 1 depicts the key questions within the context of the framework described in the previous section. We will compare the efficacy and effectiveness of commercially available FDA-approved FGAs and SGAs in a population of adults (18–64 years of age) who have been diagnosed with Schizophrenia, Schizophrenia-related psychoses, or bipolar disorder by using 1) intermediate outcomes such as core illness symptom-response rates, health care-system utilization (KQ1, KQ2, and KQ5); 2) long-term outcomes such as functional capacity, medication adherence and persistent use, patient insight into illness, health-related quality of life, patient satisfaction, health care-system utilization, and long-term symptom-response rates with corresponding dose, duration of response, remission, relapse, speed of response time, time to discontinuation of medication (KQ1, KQ2, KQ4, and KQ5); or 3) both intermediate and long-term outcomes. We will compare medication-associated adverse events in FGAs and SGAs (KQ3). We will compare the benefits and harms of FGAs and SGAs in different subpopulations (KQ5), including but not limited to disorder subtypes, gender, age group (18–35 yrs, 36–54 yrs, 55–64 yrs), race, and comorbidities.

Figure 1. Analytic framework for evaluating the comparative effectiveness of FGAs and SGAs for treating adults with Schizophrenia or Schizophrenia-related psychotic illnesses (Sz) or bipolar disorder (BPD).

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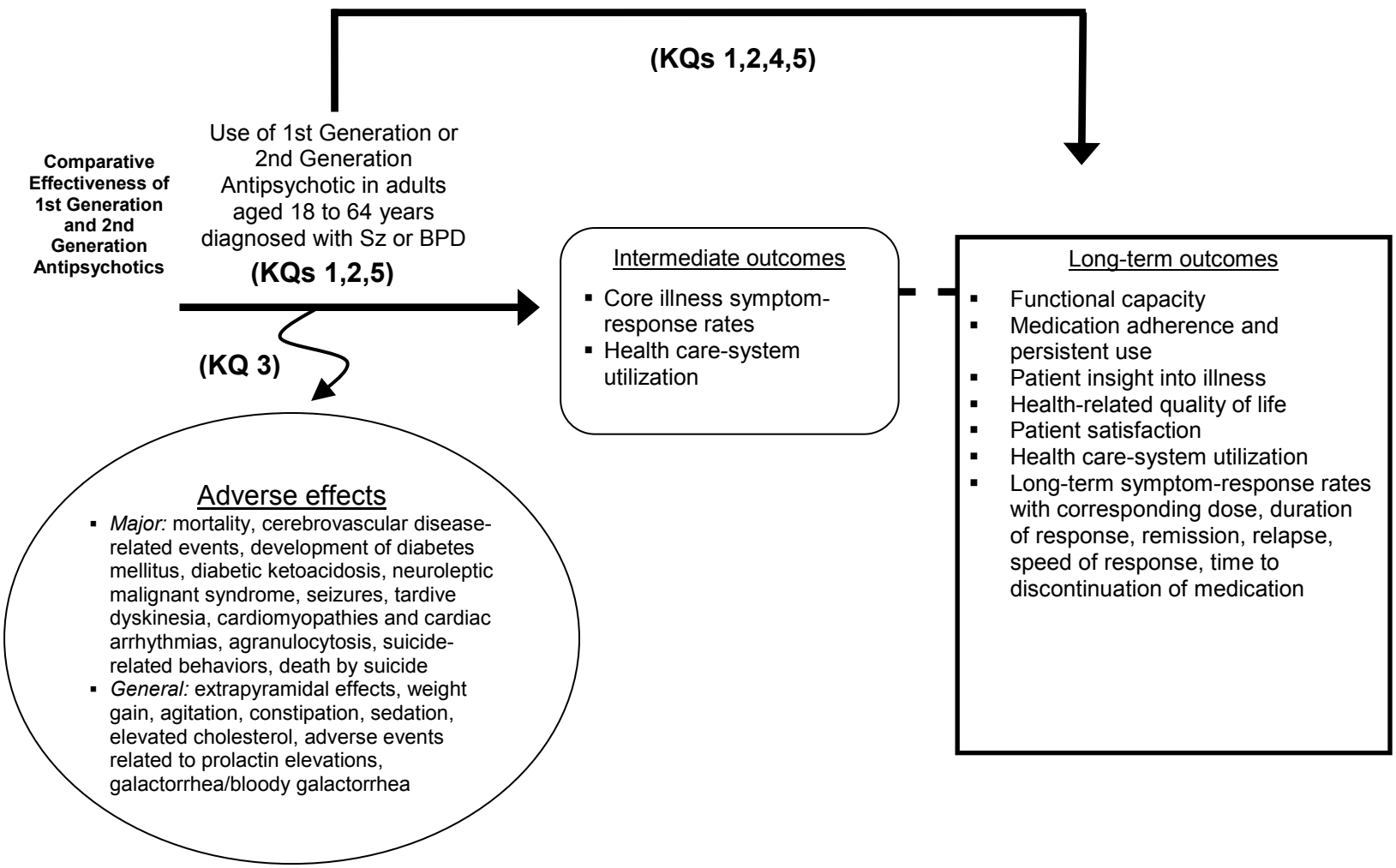

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IV. Methods

The methodological approaches to this CER are described below. They follow the methods suggested in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*[19] published by the Agency for Healthcare Research and Quality (AHRQ).

A. Criteria for Inclusion/Exclusion of Studies in the Review

Study design

We will include randomized controlled trials (RCTs). We will also include cohort studies to examine serious but rare adverse events if they meet these criteria: with a comparison of FGAs and SGAs, a followup period of at least 2 years, and present data on one long-term serious adverse events including type 2 diabetes mellitus, mortality, tardive dyskinesia, and major metabolic syndromes.

Population

We will include studies of adults (18–64 years of age) with one of the following conditions diagnosed according to the following criteria:

- Schizophrenia and Schizophrenia-related psychoses, including schizoaffective disorder.
- Bipolar disorder, including manic or depressive phases, rapid cycling, and mixed states.

Polypharmacy is common in these clinical populations; therefore, studies including patients taking other medications will be included in the CER, providing these medications (i.e., dosing) are monitored during the study.

Interventions and comparisons of interest

The drugs to be compared must be a commercially available FDA-approved FGA or SGA (Appendix A). These drugs include: aripiprazole, asenapine, chlorpromazine, clozapine, droperidol, fluphenazine, haloperidol, iloperidone, loxapine, lurasidone, olanzapine, olanzapine plus fluoxetine, paliperidone, perphenazine, pimozide, prochlorperazine, quetiapine, risperidone, thioridazine, thiothixene, trifluoperazine, and ziprasidone. All methods of drug delivery (e.g., tablet, liquid, injection) will be eligible.

During the public comments it was recommended that the CER focus on comparing FGAs given at an “appropriate dose” to individual SGAs. Furthermore, it was also suggested that comparisons be made between the different SGAs. We will compare individual FGAs and individual SGAs without any dose restrictions. We plan,

however, to examine the effect of dose in subgroup analyses. We also plan to make no comparisons between Individual antipsychotics from the same class.

Outcomes of interest

Primary outcome:

- *Schizophrenia or related psychoses*: improvement (or change) in core illness symptoms to include positive symptoms (i.e., delusions, hallucinations), negative symptoms (i.e., passive/apathetic social withdrawal, blunted affect), general psychopathology (i.e., preoccupation, lack of insight, motor retardation), cognition, suicidality, and insight into illness.
- *Bipolar disorder*: improvement (or change) in core illness symptoms to include: mood, motor activity/energy, sleep, speech, behavior, cognition, suicidality, insight into illness, and maintenance of mood stability.

Secondary outcomes:

- Functional outcomes (i.e., employment/personal earnings, social relatedness/functioning, encounters with legal system, sexual function/dysfunction, functional capacity, living situation).
- Health care-system utilization (i.e., time to hospitalization/rehospitalization related to mental illness and all other causes; rates of hospitalization/rehospitalization; rates of emergency department visits; mean hospital bed days; length of hospital stay; attendance in day care programs, and use of ancillary caseworkers).
- Relapse and remission rates.
- Medication adherence and persistent use (associated dosing, time to discontinuation of treatment).
- Patient insight into illness.
- Health-related quality of life.
- Comorbidity (end points of victimization, homelessness, substance abuse).
- Patient satisfaction.
- Patient-reported outcomes.
- Ability to obtain and retain employment and succeed in job duties.
- Concomitant use of other medications, especially those used to treat extrapyramidal symptoms

- Patient preferences

Adverse events include overall events, specific events, study withdrawals because of adverse events, time to withdrawal because of adverse events, and persistence and reversibility of adverse events.

- *Major adverse events*: 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 adverse events*: extrapyramidal effects, weight gain, agitation, constipation, sedation, elevated cholesterol, adverse events related to prolactin elevations, galactorrhea/bloody galactorrhea, hypotension, and metabolic changes (including changes in glucose levels, triglycerides, lipids, and the risk of developing diabetes).

Publication characteristics

To maximize the sensitivity of the search for eligible studies, we will search from 1950 to the present for studies published in the English language. Conference abstracts will be identified and additional searches will be performed to determine whether the study described in each abstract has been published in full. Only the full study reports will be included in the CER. Where applicable, we will contact study authors for clarification of data and to determine whether additional data are available.

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions

The research librarian, in collaboration with the investigative team, will develop and implement search strategies designed to identify evidence relevant to questions of efficacy, effectiveness, and safety.

For the questions on efficacy and effectiveness, we will conduct comprehensive searches in the following electronic databases: Ovid's MEDLINE,® EMBASE, PsycINFO, International Pharmaceutical Abstracts (IPA), Ebscohost CINAHL, ProQuest® Dissertations and Theses–Full Text, Cochourane Central Register of Controlled Trials (CENTRAL), and Scopus™. All searches will be restricted to English-language studies published since 1950. By using a combination of controlled vocabulary and keywords, the restrictions that are based on the study designs (i.e., RCTs, cohort studies, and systematic reviews) will be applied to the search results retrieved from the databases listed above. We will also conduct a forward search of the Scopus™ Citation Tracker for relevant studies. After the draft report is submitted to AHRQ, searches will be rerun in MEDLINE®, EMBASE, PsycINFO, and CENTRAL to identify any new publications.

Appendix B outlines the MEDLINE search terms and strategy. This strategy will serve as a guide when the search strategies for the remaining databases are designed and implemented to capture the unique controlled vocabulary and search language of each database.

For questions about adverse effects, we will search the U.S. National Library of Medicine's TOXLINE® database and the MedEffect™ Canada Adverse Drug Reaction Database in addition to the databases mentioned above. The same date, language, and study design restrictions will be applied to these searches.

Reference lists of relevant systematic reviews, guidelines, and included studies will be screened to identify potentially relevant studies. We will hand search the conference proceedings of the following key scientific meetings for the last 3 years to identify potentially relevant studies: Annual Convention of the American Psychiatric Association, the International College of Neuropsychopharmacology, and the International Society for Bipolar Disorders. Drug manufacturers and authors of included studies will be contacted to obtain information and/or data from unpublished or ongoing studies that we have identified as potentially relevant. Documents from government and professional associations (e.g., U.S. National Institute of Mental Health), theses and dissertations, and unpublished studies or studies in progress will also be searched to identify potentially relevant studies. We will also search online trial registries (e.g., WHO, ClinicalTrials.gov, ISRCTN) to identify unpublished and ongoing trials.

Results from the literature searches will be entered into a Reference Manager® (Version 11.0.1) bibliographic management database (Thomson Reuters, New York, NY).

A two-step process will be used for study selection. First, two reviewers will independently screen the titles and abstracts (when available) of search results to determine if a study meets the general inclusion criteria of an English-language study involving an adult population with one of the disorders and interventions of interest. Each report will be rated as: include, exclude, or unclear. Discrepancies between the two reviewers will be resolved thourough consensus or third-party adjudication as needed. The full text of all reports classified as "include" or "unclear" will be retrieved for formal review. Next, two reviewers will independently assess the full text of each report by using a standardized form that outlines the predetermined inclusion and exclusion criteria. The form will be pilot tested on a sample of studies. After form is tested, disagreements will be resolved by discussion between the two reviewers or by third-party adjudication, as needed.

C. Data Abstraction and Data Management

Data will be extracted by using a standardized form and entered into a Microsoft Excel™ database (Microsoft Corp., Redmond, WA). The form will be pilot tested on a sample of studies. Data from study reports will be extracted by one reviewer and checked by another. Disagreements about data will be resolved by referring to the

original study report. The following data will be extracted from each study: author identification, year of publication, source of study funding, study design, methodological quality criteria (see below), study population (including study inclusion and exclusion criteria, run-in period, study withdrawals, length of study, duration of patient followup), patient baseline characteristics (diagnosis, age at diagnosis, current age, sex, race, weight, height, body mass index, comorbidities, use of concurrent standard medical therapies), the intervention (drugs utilized, dose, route of administration) and its comparator, and results reported for the outcomes of interest, including adverse events.

Adverse events will be recorded for each intervention group including the number of patients in each intervention group and the number of patients affected by an event. Events will not be counted as representative of unique individuals, unless clearly stated, because a single individual might experience more than one event; this assumption may overestimate the number of people having an adverse event and lead to a unit-of-analysis error. We will not assume that an adverse event occurred unless a specific number of events are reported. By taking this approach, we may underestimate the number of patients for whom a particular adverse event is observed. After abstracting data for adverse events, we will identify, based on clinical expertise, mutually exclusive groups of similar events. For example, events that affect the head, ears, eyes, nose, or thouroat will be grouped together and labeled as "HEENT." Such a group may contain subgroups—for example, decreased salivation, increased salivation, and eye irritation are subgroups of HEENT—that would have their own analyses.[20] For each adverse event subgroup, we will report the number of studies that provide data for any event within the subgroup. We will also report summary totals of the number of individuals in the medication groups who are observed to have experienced the event and the total number of patients in the medication groups in relevant trials. The dose of each medication that is associated with an adverse event will be recorded to facilitate a dose-related adverse-event analysis.

D. Assessment of Methodological Quality of Individual Studies

The internal validity of RCTs will be assessed by using the Cochourane Collaboration Risk of Bias tool.[21] This tool consists of six domains (sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and "other" sources of bias) and a categorization of the overall risk of bias. Each separate domain is rated "yes," "unclear," or "no." The overall assessment is based on the responses to individual domains. If one or more individual domains are assessed as having a high risk of bias, the overall score will be rated as having a high risk of bias. The overall risk of bias will be considered low only if all components are rated as having a low risk of bias. The risk of bias for all other studies will be rated as unclear. In addition, information on the source of funding will be collected for each study.[22]

Cohort studies will be assessed by using the cohort Newcastle-Ottawa Scale.[23] This scale includes seven items that assess sample selection, comparability of cohorts, and the assessment of outcomes. One star is allotted for each item that is adequately

addressed in the study, with the exception of the comparability of cohorts, for which a maximum of two stars can be given. The overall score is calculated by tallying the stars, with a total possible score of eight stars. Information regarding the source of funding will also be collected.[22]

The methodological quality of included studies will be assessed by one reviewer and checked by a second reviewer. Discrepancies in quality assessment will be resolved thourough consensus or by third-party adjudication, if needed. Each assessment form will be pilot tested on a sample of studies. Decision rules regarding application of the tools will be developed a priori thourough discussions with content and methodology experts.

E. Data Synthesis

For each study, we will analyze comparisons between dichotomous outcomes by using risk ratios and between continuous outcomes by using mean differences. We will compute the 95 percent confidence intervals for all estimates.

Where populations, interventions, and outcomes are sufficiently clinically homogenous, study results will be statistically pooled by using a DerSimonian-Laird random effects model. The Mantel-Haenszel method will be used to calculate the risk ratios, and the inverse variance method will be used to pool the mean differences. In cases where the outcomes are measured with different scales, a standardized mean difference will be used to pool the results, rather than a mean difference. For rare events (an incidence in the study population <1%), we will use the Peto-Odds ratio. Heterogeneity among studies will be measured by using the I^2 statistic.

In cases of substantial heterogeneity among populations, interventions, and outcomes, subgroup and meta-regression analyses will be performed if the number of studies is sufficient to warrant these analyses.[24] The following variables will be considered in subgroup analyses if data are available: disorder subtypes, gender, age group (18–35 yrs, 36–54 yrs, 55–64 yrs), race, comorbidities, drug dosage, followup period, previous exposure to antipsychotics, treatment of a first episode vs. treatment in the context of prior episodes, and treatment resistance) will be performed if data are available. Sensitivity analyses will be conducted to assess the robustness of the findings.

Where possible, we will also analyze publication bias visually by using a funnel plot and quantitatively by using Begg's[25] and Egger's[26] tests. Version 5.0.22 of Review Manager (The Cochourane Collaboration, Copenhagen, Denmark) and version 7.0 of Stata (Stata Corp., College Station, TX) will be used for all these analyses. In the event that studies cannot be pooled, evidence tables will be produced and a narrative summary of the results will be presented.

F. Grading the Evidence for Each Key Question

The strength of evidence for the primary outcome of change in core illness

symptoms will be graded by using the approach described by Owens and colleagues.[28] The strength of a body of evidence will be evaluated independently by two reviewers, and discrepancies will be resolved thourough consensus or by third-party adjudication. This approach assesses the evidence based on four domains: risk of bias, consistency, directness, and precision. We will classify the strength of evidence as "high," "moderate," "low," or "insufficient."

V. References

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VI. Definition of Terms

Not applicable.

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

VIII. Review of Key Questions

For all EPC reviews, key questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, for Comparative Effectiveness reviews, the key questions were posted for public comment and finalized by the EPC after review of the comments.

IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the

EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so thourough the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts comprise a multi-disciplinary group of clinical, content, and methodologic experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so thourough the peer or public review mechanism

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodologic expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report

does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published thouree months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports thourough the public comment mechanism.

APPENDIX A: Summary tables of first-generation and second-generation antipsychotics included in the CER

Table A1. First-generation antipsychotics included in the CER

Generic name	Trade names(s)	Mode of administration	Usual dose	Frequency
Chlorpromazine	Chlorpromazine hydrochloride Chlorpromazine hydrochloride	Oral IM/IV	200-600 mg/day	1-4 times
Droperidol	Inapsine	IM/IV	Initial 2.5 mg/dose	increase by 1.25 mg as needed
Fluphenazine	Fluphenazine decanoate Fluphenazine hydrochloride	Oral IM	2.5-10 mg/day 2.5-10 mg/dose	3-4 times every 6 to 8 hour
Haloperidol	Haloperidol Haldol Haloperidol decanoate	Oral Tablets Solution IM (as lactate)	4-12 mg/day	1-2 times 2-3 times Every hour if needed
Loxapine	Loxapine, Loxapine succinate	Oral	60-100 mg/day	2-4 times
Perphenazine	Perphenazine	Oral (non-hospitalized) Oral (hospitalized)	12-18 mg/day; 16-64 mg/day	3 times 2-4 times
Pimozide	ORAP	Oral	7-10 mg/day	1-3 times
Prochlorperazine	Compro Prochlorperazine Prochlorperazine edisylate Prochlorperazine maleate	Oral IM IV	15-40 mg/day 15-40 mg/day 7.5-40 mg/day	3-4 times 3-4 times 3-4 times
Thioridazine	Thioridazine hydrochloride D/C: Thioridazine hydrochloride intensol, Mellaril, Mellaril-S	Oral	150-300 mg/day	2-3 times
Thiothixene	Navane Thiothixene D/C : Thiothixene hydrochloride, Thiothixene hydrochloride intensol	Oral	6-30 mg/day	2-3 times
Trifluoperazine	Trifluoperazine hydrochloride	Oral (non-hospitalized)	1-2 mg	2 times/day

D/C = discontinued according to FDA site; IM = intramuscular; IV = intravenous; mg = milligrams

Source: www.effectivehealthcare.ahrq.gov
Published Online: December 1, 2010

Table A2. Second-generation antipsychotics included in the CER

Generic name	Brand names(s)	Mode of administration	Recommended dose	Frequency
Aripiprazole	Abilify	Tablet Solution Orally disintegrating tablet Injection	10-15mg/day; Max 30mg/day	QD ≥2 hour between doses
Asenapine	Saphouris	Orally disintegrating tablet	Schizophrenia 5mg; BD 10mg	2 times/day 2 times/day
Clozapine	Clozapine Clozaril	Tablet Orally disintegrating tablet	300-450 mg/day	1-3 times/day
Iloperidone	Fanapt	Tablet	12-24mg/day	2 times/day
Olanzapine	Olanzapine Zyprexa, Zyprexa Zydis	Tablet Orally disintegrating tablet IM injection	Schizophrenia, 10mg/day; BD I 10-15mg/day	QD QD
Lurasidone	Latuda	Tablet	40-80mg/day	1-2 times/day
Paliperidone	Invega Invega sustenna	Tablet extended release	6mg/day	QD in the AM
Quetiapine	Quetiapine fumarate Seroquel Seroquel XR	Tablet Sustained release tablets	Schizophrenia, 150-750mg/day; BD (mania), 400-800mg/day; BD (depression), 300mg/day; BD (maintenance), 400-800mg/day	2 times/day 2 times/day 2 times/day 2 times/day QD at bedtime 2 times/day
Risperidone	Risperidone, Risperdal, Risperdal consta	Tablet Solution Orally disintegrating tablet IM injection	Schizophrenia, 4-8mg/day; BD (mania), 1-6mg/day	1-2 times/day
Ziprasidone	Ziprasidone hydrochloride Geodon	Capsules IM injection	Schizophrenia, up to 80mg; BD (manic/mixed, maintenance), 40-80mg; Agitation associated with Schizophrenia (IM), up to max 40mg/day	2 times/day 2 times/day 10mg may be injected q2 hour

BD = bipolar disease; IM = intramuscular; mg = milligrams; QD = every day; q2 = every two hours

Source: www.effectivehealthcare.ahrq.gov
Published Online: December 1, 2010

Table A3. First-generation antipsychotics: FDA status

Drug	FDA status	Indications	Age group approved for	Black box Warnings
Chlorpromazine	Approved 1974	Schizophrenia BP (mania) Hyperactivity Uncontrolled hiccups, nausea and vomiting	Adults Children (1-12 yrs)	Patients with cardiovascular disease or hx of seizures
Droperidol	Approved 1988	Antiemetic Acute psychosis	Adults Children (2-12 yrs) as antiemetic, no data on pediatric psychosis	QT prolongation (dose related) Torsades de pointes
Fluphenazine	Approved 1960	Schizophrenia BD (mania)	Adults Children >12yrss Not recommended for use in children under 12 yrs	Possible increased mortality in elderly with dementia-related psychosis Not approved for the treatment of dementia-related behavior problems.
Haloperidol	Approved 1986	Schizophrenia Tourette's Disorder	Adults Safety and effectiveness in pediatric patients <18 yrs have not been established	Increased mortality in elderly with dementia-related psychosis
Loxapine	Approved 1975	Schizophrenia	Adults Safety and effectiveness in pediatric patients <16 have not been established	Increased mortality in elderly with dementia-related psychosis
Perphenazine	Approved 1965	Schizophrenia	Adults Safety and effectiveness in pediatric patients have not been established	Increased mortality in elderly with dementia-related psychosis Children, adolescents, and young adults taking antidepressants are at increased risk of suicidal thinking
Pimozide	Approved 1984	Tourette's Disorder	Children and adults 8-53 yrs. Limited evidence in children <12 yrs Use and safety have not been evaluated in other childhood disorders, ORAP is not recommended for use in any condition other than Tourette's Disorder	Use of pimozide in tx of Tourette's Disorder involves different risk/benefit considerations than tx of other conditions. A decision to use ORAP should take into consideration Tardive Dyskinesia Neuroleptic Malignant Syndrome (NMS) Sudden, unexpected deaths in conditions other than Tourette's Disorder. May have tumorigenic potential.
Prochlorperazine	Approved 1956	Schizophrenia Severe nausea and vomiting	Adults and children Children >2 yrs and >20 pounds	May cause tardive dyskinesia
Thioridazine	Approved 1962	Schizophrenia	Adults and children	Life-threatening pro-arrhythmic effect

BD = bipolar disease; IM = intramuscular; tx = treatment; yrs = years

Source: ***www.effectivehealthcare.ahrq.gov***
Published Online: December 1, 2010

Table A3. First-generation antipsychotics: FDA status (continued)

Drug	FDA status	Indications	Age group approved for	Black box Warnings
Thiothixene	Approved 1967	Schizophrenia	Adults Safety and effectiveness in pediatric patients <12 years have not been established	Increased mortality in elderly with dementia-related psychosis
Trifluoperazine	Approved 1959	Schizophrenia	Adults and children (6-12 yrs)	Increased mortality in elderly patients with dementia-related psychosis

Table A4. Second-generation antipsychotics: FDA status

Drug	FDA status (year approved)	Indications	Age group approved for	Black box warnings
Aripiprazole	2002	Schizophrenia	Adults & adolescents (13-17 yrs)	Increased mortality in elderly with dementia-related psychosis
	2004	BD(L) (manic/mixed) monotherapy or adjunctive to lithium or valproate	Adults & pediatrics (10-17 yrs)	Children, adolescents, and young adults taking antidepressants are at increased risk of suicidal thinking & behavior Leukopenia, Neutropenia, Agranulocytosis
	2007	Adjunctive tx of major depressive disorder	Adults Children (6-17 yrs) Adults with agitation associated with Schizophrenia or BD(L) (manic/mixed)	Not approved for behavior problems in older adults with dementia.
	2009	Autistic Disorder, Injection		
Aripiprazole	2002	Schizophrenia	Adults and adolescents (13-17 yrs)	Increased mortality in elderly with dementia-related psychosis
	2004	BD(L) (manic/mixed) monotherapy or adjunctive to lithium or valproate	Adults and pediatrics (10-17 yrs)	Children, adolescents, and young adults taking antidepressants are at increased risk of suicidal thinking and behavior
	2007	Adjunctive tx of major depressive disorder	Adults	Not approved for behavior problems in older adults with dementia.
		Injection	Adults with agitation associated with Schizophrenia or BD(L) (manic/mixed)	
Asenapine	2009	Acute Schizophrenia BD I (manic/mixed)	Adults Adults Pediatric use: safety & effectiveness not established in patients <18 yrs	Increased mortality in elderly with dementia-related psychosis
Clozapine,	1989	Treatment resistant Schizophrenia	Adults Pediatric use: safety & effectiveness not established in patients <18 yrs	1. agranulocytosis 2. seizures 3. myocarditis 4. cardiovascular and respiratory effects, (respiratory and/or cardiac arrest). 5. increased mortality in elderly patients with dementia-related psychosis
	2002	Reduce the risk of suicidal behavior in younger schizophrenics.		
Iloperidone	2009	Acute Schizophrenia	Adults	Increased mortality in elderly with dementia-related psychosis Not approved for patients with dementia-related psychosis.

BD = bipolar disease; tx = treatment; yrs = years

Source: www.effectivehealthcare.ahrq.gov
Published Online: December 1, 2010

Table A4. Second-generation antipsychotics: FDA status (continued)

Drug	FDA status (year approved)	Indications	Age group approved for	Black box warnings
Lurasidone	2010	Schizophrenia	Adults	Increased mortality in elderly with dementia-related psychosis
Olanzapine	1996 2003: combined w fluoxetine 2004 2009: combined w fluoxetine	Schizophrenia &BD(L) (manic/mixed) BD (depressive) BD(L) long-term tx Tx resistant depression	Adults Adolescents (13-17 yrs), Schizophrenia & BD (manic/ mixed) Pediatric use: safety & effectiveness not established in patients <13 yrs	Increased mortality in elderly with dementia-related psychosis Not approved for patients with dementia-related psychosis.
Paliperidone	2006	Schizophrenia Schizoaffective disorder	Adult Pediatric use: safety & effectiveness not established in patients <18 yrs	Increased mortality in elderly with dementia-related psychosis
Quetiapine	1997 2004 2008	Schizophrenia BD (acute manic) BD (depression) BD (maintenance)	Adults & adolescents (13-17 yrs) Adults, children & adolescents (10-17 yrs) Adults Adults	Increased mortality in elderly with dementia-related psychosis Increased risk of suicidal thinking and behavior Not approved for patients with dementia-related psychosis
Risperidone	1993 2007 2003	Schizophrenia BD (manic/mixed) Irritability associated with autism	Adults & adolescents (13-17 yrs) Adults & adolescents (10-17 years) Children (5-16 yrs)	Increased mortality in elderly with dementia-related psychosis
Ziprasidone	2001	Schizophrenia BD (manic/mixed) BD (maintenance)	Adults Adults Adults Pediatric use: safety & effectiveness not established in patients <18 yrs	Increased mortality in elderly with dementia-related psychosis

Source: ***www.effectivehealthcare.ahrq.gov***
Published Online: December 1, 2010

Appendix B: MEDLINE search terms and strategy

1. exp Schizophrenia/
2. Schizophrenia, Catatonic/
3. Schizophrenia, Disorganized/
4. Schizophrenia, Paranoid/
5. Psychotic Disorders/
6. Schizotypal Personality Disorder/
7. schizophoureniform.tw.
8. (schizoaffective or schizo-affective).tw.
9. schizophouren$.mp.
10. (dementia adj (praecox or precox)).tw.
11. (delusional adj2 disorder*).tw.
12. ((negative or positive) adj syndrome*).tw.
13. hebephourenia.tw.
14. exp Bipolar Disorder/
15. (((bipolar or manic) adj2 (I or II or illness or disorder or psychos?s or depress$)) or mania*).tw.
16. (BPD or hypoman$ or manic-depressive).tw.
17. (BP 1 or BP 2 or BP I or BP II).tw.
18. (cyclothym$ or euthymic).tw.
19. (acute adj2 mania).tw.
20. (acute adj2 mixed adj episode*).tw.
21. (rapid-cycling adj5 bipolar).tw.
22. (rapid adj2 cycling adj5 bipolar).tw.
23. (mixed adj2 state* adj3 bipolar).tw.
24. or/1-23
25. exp Antipsychotic Agents/
26. exp Tranquilizing Agents/
27. (neuroleptic adj2 (agent* or drug*)).tw.
28. or/25-27
29. ((first or 1st) adj generation adj antipsychotic*).tw.
30. chlorpromazine/
31. 50-53-3.rn.
32. (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.
33. Droperidol/
34. 548-73-2.rn.
35. (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.
36. fluphenazine/
37. 69-23-8.rn.
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/
40. 52-86-8.rn.
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/
43. 1977-10-2.rn.
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/
46. 58-39-9.rn.
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.
48. Pimozide/
49. 2062-78-4.rn.
50. (Antalon or Opiran or Orap or Pimotsidi or Pimozid or Pimozida or Pimozidas or Pimozide or Pimozidum or Pimozyd).mp.

51. Prochlorperazine/
52. 58-38-8.rn.
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 Mitil or Prochlorpemazine or Prochlorperazinum or Proclorperazina or Proklooriperatsiini or Proklorperazin or Prorazin or Phenothiazine or Seratil or Stemetil or Tementil or Temetid).mp.
54. thiothixene/
55. 5591-45-7.rn.
56. (Navane or Navaron or Orbinamon or Thiothixene or Tiotikseeni or Tiotixen or Tiotixeno or Tiotixenum or Thixit or Tiotixene).mp.
57. trifluoperazine/
58. 117-89-5.rn.
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.
60. thioridazine/
61. 50-52-2.rn.
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.
63. methotrimeprazine/
64. 60-99-1.rn.
65. (Dedoran or Hirnamin or Hirnamine or Levomepromazine or Levomepromazin or Levomepromazina or Levopromazioni 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 Levolam or Nozinan or Sinogan or Tisercin or Veractil).mp.
66. Phenothiazines/ad, to, tu, ct, po, ae [Administration & Dosage, Toxicity, Therapeutic Use, Contraindications, Poisoning, Adverse Effects]
67. Butyrophenones/ad, to, tu, ct, po, ae
68. Thioxanthenes/ad, to, tu, ct, po, ae
69. Dibenzoxazepines/ad, to, tu, ct, po, ae
70. Indoles/ad, to, tu, ct, po, ae
71. or/29-70
72. SGA antipsychotic$.tw.
73. ((second or 2nd) adj generation adj antipsychotic*).tw.
74. ((third or 3rd) adj generation adj antipsychotic*).tw.
75. Asenapine/
76. 65576-45-6.rn.
77. (Asenapine or EINECS 265-829-4).mp.
78. clozapine/
79. 5786-21-0.rn.
80. (Clozapin or Clozapina or Clozapine or Clozapinum or Clorazil or Clozaril or FazaClo or Leponex or LX 100-129 or Zaponex).mp.
81. risperidone/
82. 106266-06-2.rn.
83. (Apexidone or Psychodal or Risperdal or Risperidona or Risperidone or Risperidonum or Risperin or Risperilept or Rispolin or Spiron).mp.
84. olanzapine.mp.
85. 132539-06-1.rn.
86. (Zyprexa or Olantsapiini or Olanzapin or Olanzapina or Olanzapinum or Olansek or Zalasta or Zypadhera or Symbyax).mp.
87. quetiapine.mp.
88. (111974-69-7 or 111974-72-2).rn.
89. (Co-Quetiapine or HSDB 7557 or Seroquel).mp.
90. ziprasidone.mp.
91. 146939-27-7.rn.
92. (Zeldox or zeldrox or geodon).mp.
93. aripiprazole.mp.
94. 129722-12-9.rn.
95. (Abilitat or Abilify or Aripiprazole or Discmelt or OPC 31 or OPC 14597).mp.
96. paliperidone.mp.
97. 144598-75-4.rn.
98. (9-Hydroxyrisperidone or Invega or R 76477 or RO76477).mp.
99. Iloperidone/
100. 133454-47-4.rn.
101. (Fanapt or Iloperidone or HP 873 or Zomaril).mp.
102. Isoxazoles/ad, to, tu, ct, po, ae
103. Dibenzazepines/ad, to, tu, ct, po, ae
104. Pyrimidinones/ad, to, tu, ct, po, ae
105. Piperidines/ad, to, tu, ct, po, ae
106. Dibenzothiazepines/ct, ad, to, tu, ae, po
107. Piperazines/ad, tu, to, ct, po, ae
108. Pirenzepine/tu, ad, to, ct, po, ae
109. Thiazoles/ad, th, ct, po, to, ae
110. Quinolones/to, po, ct, ad, tu, ae
111. or/72-110
112. and/71,111
113. and/28,71,111
114. or/112-113
115. randomized controlled trial.pt.
116. controlled clinical trial.pt.
117. randomi?ed.ab.

118. placebo*.ab.
119. drug therapy.fs.
120. randomly.ab.
121. trial.ab.
122. groups.ab.
123. or/115-122
124. humans/ not (animals and humans).hw,sh.
125. 123 and 124
126. and/24,114,125
127. limit 126 to yr="1987 - 2010"
128. limit 127 to english language
129. limit 127 to ("young adult (19 to 24 years)" or "adult (19 to 44 years)" or "middle age (45 to 64 years)")
130. adult*.mp.
131. 127 and 130
132. (p?ediatric or child* or teen* or adolescen* or youth or elderly or aged).mp.
133. 127 and 132
134. or/129,131,133
135. cohort studies/
136. follow-up studies/
137. longitudinal studies/
138. prospective studies/
139. Retrospective Studies/
140. (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 follow up or follow-up).mp. and (study or studies or trial$).ti,ab,sh.
141. or/135-140
142. humans.hw,sh.
143. and/141-142
144. meta-analysis.mp,pt.
145. review.pt.
146. search:.tw.
147. or/144-146
148. and/24,114,143
149. and/24,114,147
150. limit 149 to yr="1950 - 2010"
151. limit 150 to english language
152. limit 148 to yr="1950 - 2010"
153. limit 152 to english language
154. limit 153 to ("young adult (19 to 24 years)" or "adult (19 to 44 years)" or "middle age (45 to 64 years)")