Evidence-based Practice Center Systematic Review Protocol

Project Title: *Comparative Effectiveness of First and Second Generation Antipsychotics in the Pediatric and Young Adult Populations*

I. Background and Objectives for the Systematic Review

Antipsychotic medications are used to treat a number of psychiatric disorders, including schizophrenia, bipolar mania, dementia and psychotic depression. First generation antipsychotics were initially developed in the 1950s. Side effects vary among the various medications, but common side effects include dry mouth, sedation, extrapyramidal side effects (EPS; a cluster of symptoms consisting of akathisia, parkinsonism, and dystonias), and in severe cases, tardive dyskinesia or neuroleptic malignant syndrome. Second generation antipsychotics were first developed in the 1980s. They generally have lower risk of motor side effects, but are associated with significant weight gain, elevated lipids and prolactin levels, and have been associated with the development of type 2 diabetes.

Studies have shown that prescription patterns for psychotropics in children and youth have changed and use has increased over the last 20 years. This includes use of antipsychotic medications.[1-5] Use of these medications in the pediatric population is controversial mainly because of limited high quality and longitudinal data on which to base conclusive clinical practice recommendations, especially with regard to safety. In children and youth, antipsychotic medications have both on-label and off-label indications depending on the medication, country, and psychiatric condition. For example, on-label indications are available for treatment of childhood schizophrenia and bipolar disorder in the United States. Off-label prescriptions are used in younger children for behavioral symptoms (e.g., irritability and aggression) that are related to diagnosable conditions (e.g., pervasive developmental disorder). In some instances, however, off-label use may be for behaviors that are also part of the child's normal developmental trajectory and/or may reflect an adaptive response to an environmental stressor (e.g., parental divorce). In general, the choice of medication in children and youth is often driven by side effect profiles that may affect normative growth and development, medication adherence and persistence, as well as other important domains such as educational performance and health-related quality of life (HRQOL).[6] Therefore, close clinical monitoring is recommended.[7]

The objective of this comparative effectiveness review (CER) is to provide a comprehensive synthesis of the evidence examining the benefits and harms associated with first and second generation antipsychotics in the pediatric and young adult populations (24 years and younger). The CER is intended for a broad audience, including clinicians, policymakers and funding agencies, professional societies developing clinical practice guidelines, patients and their care providers, as well as researchers conducting studies on the use of antipsychotic medications in the pediatric and young adult populations.

For this CER, the Evidence-based Practice Center (EPC) was asked to study first and second generation antipsychotics (Table 1, Appendix A Tables A1 to A4) that are currently approved by the U.S. Food and Drug Administration (FDA). There is no consensus on the terminology to describe antipsychotic medications (e.g., first and second generation, typical and

atypical). For the purposes of this review, the terms "first generation" and "second generation" antipsychotics will be used.

We were asked to study the use of these drugs for the following conditions: 1) pervasive developmental disorders,[8] 2) disruptive behavior disorders and ADHD,[8] 3) pediatric bipolar disorder,[8] 4) schizophrenia and schizophrenia-related psychoses,[8] 5) obsessive compulsive disorder, 6) post traumatic stress disorder, 7) anorexia nervosa, 8) Tourette's syndrome and 9) behavioral issues, including aggression, agitation, anxiety, behavioral dyscontrol, irritability, mood lability, self-injurious behaviors and sleep disorders.

Table 1. List of antipsychotics included in the CER

First generation antipsychotics	Second generation antipsychotics
• Chlorpromazine	• Aripiprazole
• Flupenthixol	• Asenapine
• Fluphenazine	• Clozapine
• Haloperidol	• Iloperidone
• Loxapine	• Olanzapine
• Molindone	• Paliperidone
• Perphenazine	• Quetiapine
• Pimozide	• Risperidone
• Prochlorperazine	• Ziprasidone
• Thiothixene	
• Thioridazine	
• Trifluoperazine	

II. The Key Questions

The Key Questions (KQ) were posted for public comment on the Agency for Health Care Research and Quality (AHRQ) Effective Health Care Program website. Following review of the comments by members of the Technical Expert Panel, AHRQ and the EPC, the following changes were made to the original KQ:

- The terminology of "typical" and "atypical" antipsychotics has been changed to "first generation" and "second generation" antipsychotics in the topic title, and throughout the key questions and protocol.
- Wording has been changed to clarify that the CER will compare efficacy, effectiveness and safety across individual antipsychotics (not just at the 'class' level). In addition to head-to-head first versus second generation comparisons, the CER will include head-to-head comparisons of first versus first generation and second versus second generation medications.
- Patients with schizoaffective disorder and substance-induced psychoses have been included within the diagnostic group "schizophrenia and schizophrenia-related psychoses."
- Patients with attention deficit hyperactivity disorder (ADHD) have been added alongside the diagnostic group "disruptive behavior disorders."
- Obsessive compulsive disorder, post traumatic stress disorder, Tourette's syndrome and anorexia nervosa have been added to the list of disorders examined in this review.

- The list of behavior issues eligible for inclusion in the review has been expanded to include: anxiety, irritability, mood lability and sleep disorders.
- The following outcomes were added: patient or parent/caregiver preferences, work-related functional outcomes, patient insight into illness. Elevated transaminases was added to the list of general adverse events.
- The following subgroups were added to KQ4: monotherapy versus co-treatment; first episode psychosis vs. treatment in context of history of prior episodes (related to schizophrenia); duration of illness; naïve vs. history of previous antipsychotic use.

The KQ to be investigated in this CER are presented below.

Question 1: What is the comparative efficacy or effectiveness of first and second generation antipsychotics for treating disorder/illness specific and nonspecific symptoms in children, youth and young adults (≤ 24 years) for the following disorders or illnesses?

1) Pervasive developmental disorders (PDDs), including autistic disorder, Rett's disorder, childhood disintegrative disorder, Asperger's disorder, and pervasive developmental disorder not otherwise specified (NOS);
2) Attention deficit hyperactivity disorder (ADHD) and disruptive behavior disorders (DBDs), including conduct disorder, oppositional defiant disorder, and disruptive behavior disorder NOS;
3) Pediatric bipolar disorder, including manic or depressive phases, rapid cycling, mixed states;
4) Schizophrenia and schizophrenia-related psychoses, including schizoaffective disorder, drug-induced psychosis;
5) Obsessive compulsive disorder;
6) Post traumatic stress disorder;
7) Anorexia nervosa;
8) Tourette's syndrome;
9) Behavioral issues, including aggression, agitation, anxiety, behavioral dyscontrol, irritability, mood lability, self-injurious behaviors, and sleep disorders.

Population: Children, youth, and young adults (≤ 24 years) with PDD, ADHD, DBD, pediatric bipolar disorder, schizophrenia / schizophrenia-related psychosis, obsessive compulsive disorder, post traumatic stress disorder, anorexia nervosa, Tourette's syndrome or behavioral issues

Interventions: Any FDA-approved first or second generation antipsychotic

Comparators: Any other FDA-approved first or second antipsychotic, placebo, or another dose of the same antipsychotic

Outcomes: Disorder/illness specific and nonspecific symptoms

The following symptoms are included for each disorder or illness:

1) PDDs: qualitative impairment in social interactions, communication and restricted repetitive and stereotyped behaviors, interests, and activities;
2) ADHD and DBDs: negativistic, hostile and defiant behavior;
3) Bipolar disorder: mood disturbance, psychotic features;
4) Schizophrenia and related psychoses: positive and negative symptoms, disorganized behavior, impaired thought process, cognition and mood symptoms;

5) Obsessive compulisive disorder;
6) Post traumatic stress disorder;
7) Anorexia nervosa;
8) Tourette's syndrome;
9) Behavioral issues: aggression, agitation, anxiety, behavioral dyscontrol, irritability, mood lability, self-injurious behaviors, and sleep disorders.

Timing: All time points
Settings: All settings, including inpatient hospitalization and outpatient treatment

Question 2: Do first and second generation antipsychotics differ in medication-associated adverse events when used in children, youth, and young adults (≤ 24 years)? This includes:

1) Overall adverse events;
2) Specific adverse events;
3) Withdrawals/time to withdrawal due to adverse events;
4) Persistence and reversibility of adverse events.

Population: See KQ1 above
Interventions: See KQ1 above
Comparators: See KQ1 above
Outcomes: Medication-associated adverse events, withdrawal due to adverse events, persistence and reversibility of adverse events.

Major adverse events include:

- Mortality
- Cerebrovascular disease-related events
- Development of diabetes mellitus
- Diabetic ketoacidosis
- Neuroleptic malignant syndrome
- Seizures
- Tardive dyskinesia
- Cardiomyopathies
- Cardiac arrhythmias
- Agranulocytosis

General adverse events include:

- Extrapyramidal effects
- Weight gain (e.g., using Body Mass Index (BMI) growth charts)
- Agitation
- Constipation
- Sedation
- Elevated cholesterol
- Elevated transaminases
- Adverse events related to prolactin elevations
- Galactorrhea/bloody galactorrhea
- Exercise intolerance
- Precocious puberty

Timing: See KQ1 above
Settings: See KQ1 above

Question 3: Do first and second generation antipsychotics differ in other short- and long-term outcomes when used in children, youth, and young adults (≤24 years)? Short-term is defined as outcomes occurring within 6 months; long-term is defined as outcomes occurring post-6 months.

Population: See KQ1 above
Interventions: See KQ1 above
Comparators: See KQ1 above
Outcomes: Other short-term and long-term outcomes, including:

1) Response rates with corresponding dose, duration of response, remission, relapse, speed of response, time to discontinuation of medication;
2) Growth and maturation;
3) Cognitive and emotional development;
4) Suicide-related behaviors or death by suicide;
5) Medication adherence and persistence;
6) School performance/attendance;
7) Work-related functional capacity;
8) Patient insight into illness;
9) Patient or parent/care provider reported outcomes, including levels of physical activity/inactivity, diet (i.e., caloric intake, food preferences);
10) Health-related quality of life;
11) Legal/justice system interaction (i.e., arrests, detention);
12) Health care system utilization (e.g., protective services, social services);
13) 'Outcomes that matter' to children, youth and young adults, and their families. These *functional* outcomes may reflect a developmental perspective.

Timing: See KQ1 above
Settings: See KQ1 above

Question 4: Do the effectiveness and risks of first and second generation antipsychotics vary in differing sub-populations including:

1) Gender;
2) Age group (< 6 years, 6–12 years, 13–18 years, 19–24 years);
3) Race;
4) Co-morbidities, including substance abuse, ADHD;
5) Co-treatment versus monotherapy;
6) First episode psychosis vs. treatment in context of history of prior episodes (related to schizophrenia);
7) Duration of illness;
8) Treatment naïve versus history of previous antipsychotics use.

Population: Demographic and clinical subgroups of children, youth, and young adults (≤ 24 years) with PDD, DBD, pediatric bipolar disorder, obsessive compulsive disorder, post

traumatic stress disorder, anorexia nervosa, Tourette's syndrome, schizophrenia / schizophrenia-related psychosis or behavioral issues

Interventions: See KQ1 above

Comparators: See KQ1 above

Outcomes: Disorder specific and nonspecific symptoms (see KQ1); other short-term and long-term outcomes (see KQ3)

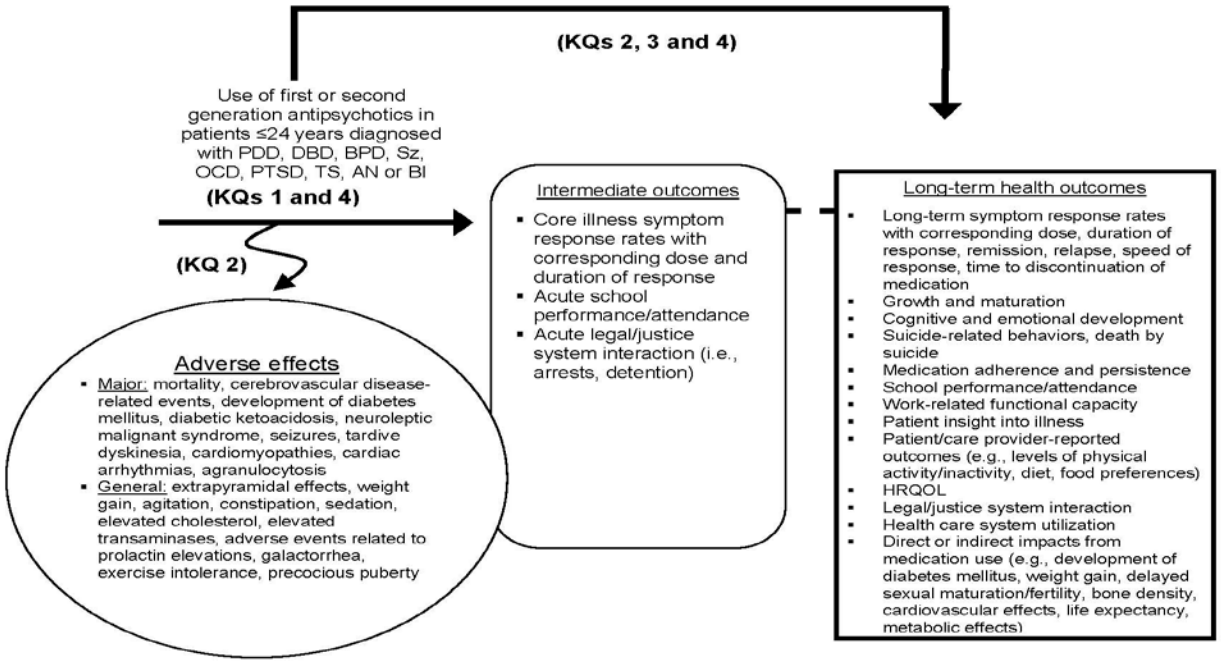
Timing: See KQ1 above

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 FDA-approved first generation and second generation antipsychotics in a population of children, youth and young adults (≤ 24 years) diagnosed with pervasive developmental disorder, disruptive behavioral disorder, bipolar disorder, schizophrenia and schizophrenia-related psychoses, obsessive compulsive disorder, post traumatic stress disorder, Tourette's syndrome, anorexia nervosa or behavioral issues using intermediate outcomes such as core illness symptom response rates with corresponding dose and duration response, school performance and/or attendance, and legal/justice system interaction (i.e., arrests, detention) (KQ1 and KQ4) and/or long-term outcomes such as long-term symptom response rates (with corresponding dose, duration of response, remission, relapse, speed of response time, time to discontinuation of medication), growth and maturation, cognitive and emotional development, suicide-related behaviors, medication adherence, health-related quality of life, school performance/attendance, work-related functional capacity and legal/justice system interaction (KQ2, KQ3 and KQ4). We will compare medication-associated adverse events in first and second generation antipsychotics (KQ2). We will compare the benefits and harms of first and second generation antipsychotics in different subpopulations (KQ4), including but not limited to age, gender, race, co-morbidity, co-treatment vs. monotherapy, and duration of illness.

Figure 1. Analytic framework for evaluating the comparative effectiveness of FDA-approved first generation and second generation antipsychotics in the pediatric and young adult population diagnosed with pervasive developmental disorder (PDD), disruptive behavior disorder (DBD), bipolar disorder (BPD), schizophrenia or other psychotic illnesses (Sz), obsessive compulsive disorder (OCD), post traumatic stress disorder (PTSD), Tourette's syndrome (TS), anorexia nervosa (AN) and behavioral issues (BI)



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IV. Methods

The methodological approaches to this CER are described below. They follow the methods suggested in the *Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews*, Version 1.0 published by AHRQ (available at http://effectivehealthcare.ahrq.gov/repFiles/2007_10DraftMethodsGuide.pdf).

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

Study design

For efficacy, we will include randomized controlled trials (RCT). For effectiveness and adverse events, we will include RCTs, nonrandomized controlled trials (NRCT), and cohort studies (retrospective or prospective).

Population

We will include studies that enroll children, youth and young adults (≤ 24 years) with one of the following conditions:

- PDD, including autistic disorder, Rett's disorder, childhood disintegrative disorder, Asperger's disorder, pervasive developmental disorder NOS (including atypical autism);
- ADHD and DBD, including conduct disorder, oppositional defiant disorder, disruptive behavior disorder NOS;
- Bipolar disorder, including manic or depressive phases, rapid cycling, mixed states;
- Schizophrenia and schizophrenia-related psychoses, including schizoaffective disorder and substance-induced psychoses;
- Obsessive compulsive disorder;
- Post traumatic stress disorder;
- Anorexia nervosa;
- Tourette's syndrome;
- Behavioral issues, including aggression, agitation, anxiety, behavioral dyscontrol, irritability, mood lability, self-injurious behaviors and sleep disorders.

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

Intervention drugs of interest

The intervention drug must be an FDA-approved first or second generation antipsychotic drug. These drugs include: aripiprazole, asenapine, clozapine, iloperidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone, chlorpromazine, flupenthixol, fluphenazine, haloperidol, loxapine, molindone, perphenazine, pimozide, prochlorperazine, thiothixene, thioridazine, trifluoperazine. All formulations of drug delivery (e.g., tablet, liquid, injectable) and doses are eligible.

Comparison drugs of interest

The comparison drug must be any other FDA-approved first or second generation antipsychotic drug, placebo, or a different dose of the same antipsychotic drug. All formulations of drug delivery (e.g., tablet, liquid, injectable) and doses are eligible.

Outcomes of interest

Primary outcome:

- Symptom response (e.g., behavioral issues, core features of the disorder/illness).

Secondary outcomes:

- Response rates with corresponding dose, duration of response, remission, relapse, speed of response, time to discontinuation of medication;
- Growth (using BMI growth charts) and maturation (Tanner stage);
- Cognitive and emotional development;
- Suicide-related behaviors or death by suicide;
- Medication adherence and persistence;
- School performance/attendance;
- Work-related functional capacity;
- Patient insight into illness;
- Patient or parent/care provider reported outcomes, including levels of physical activity/inactivity, diet (i.e., caloric intake, food preferences);
- Health-related quality of life;
- Legal/justice system interaction (i.e., arrests, detention);
- Health care system utilization (e.g., protective services, social services, hospitalization);
- 'Outcomes that matter' to children, youth and young adults, and their families. These *functional* outcomes may reflect a developmental perspective.

Adverse events include overall events, specific events, withdrawals due to adverse events, time to withdrawal due to 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;
- General adverse events: extrapyramidal effects, weight gain (e.g., using BMI growth charts), agitation, constipation, sedation, elevated cholesterol; adverse events related to prolactin elevations, galactorrhea/bloody galactorrhea, exercise intolerance, precocious puberty.

Publication characteristics

In order to coincide with the DSM-III-R diagnostic codes, only studies published after 1986 will be included. Given the substantial diagnostic changes that occurred in the 1987 revision, earlier research may not accurately reflect the conditions or patient symptom domains examined by research conducted following the publication of DSM-III-R.

Only studies published in the English language will be included. There are no restrictions on sample size. Conference abstracts will be included. Where applicable, we will contact study authors for clarification and additional data.

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, Cochrane Central Register of Controlled Trials (CENTRAL), and Scopus™. All searches will be restricted to English language studies published since 1987. Using a combination of controlled vocabulary and keywords, study design restrictions for RCTs, NRCTs, and cohort studies will be applied to the search results retrieved from the above listed databases. We will also conduct a forward search of the Scopus™ Citation Tracker for relevant studies. Following submission of the draft report to AHRQ, searches will be re-run in PubMed, EMBASE, PsycINFO, and CENTRAL to identify any new publications.

Appendix B outlines the MEDLINE search terms and strategy. This will serve as a guide when designing and implementing search strategies in the remaining databases in order to capture the unique controlled vocabulary and search language of each database.

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

Reference lists of relevant systematic reviews, guidelines, and included studies will be screened to identify potentially relevant studies. We will handsearch the conference proceedings of the following key scientific meetings for the last 3 years to identify potentially relevant studies: American Academy of Child and Adolescent Psychiatry, International College of Neuropsychopharmacology, and 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., National Institute of Mental Health), theses and dissertations, as well as unpublished studies or studies in progress will also be searched in order to identify potentially relevant studies. We will also search online trial registries (e.g., World Health Organization, ClinicalTrials.gov, ISRCTN) in order to identify unpublished as well as ongoing trials.

Results from the literature searches will be entered into a Thomson Reuters Reference Manager 11.0.1® bibliographic management database.

C. Study Selection

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 a pediatric or young adult population with one of the disorders and interventions of interest. Each report will be rated as: include, exclude, or unclear. 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 using a standard form that outlines the pre-determined inclusion and exclusion criteria. Disagreements will be resolved by discussion between the two reviewers or third party adjudication, as needed.

D. Data Abstraction and Data Management

Data will be extracted using a standardized form and entered into a Microsoft Excel™ database (Microsoft Corp., Redmond, WA). Data will be extracted by one reviewer and checked for accuracy and completeness by a second reviewer. Reviewers will resolve discrepancies by consensus or in consultation with a third party, as needed. The following data will be extracted from each study: author identification, year of publication, source of study funding, study design characteristics and 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 and age at diagnosis, age, sex, race, weight, height, body mass index, co-morbidities, use of concurrent standard medical therapies), details of the intervention and comparator (drugs utilized, dose, route of administration), and results reported for the outcomes of interest, including adverse events.

Adverse events will be recorded for each intervention group including the description of the adverse event, the number of patients in each group, and the number of patients affected. Each event will be counted as if it represents a unique individual. Because a single individual might experience more than one event, this assumption may overestimate the number of people having an adverse event. If a study mentions an adverse event in the discussion but does not report data on that adverse event, we will not include that study in the analysis. We will not assume 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 mutually exclusive groups of similar events, based on clinical expertise. For example, events that affect the head, ear, eye, nose, or throat will be grouped together as HEENT. A group may contain subgroups; for example, decreased salivation, increased salivation, and eye irritation are subgroups of HEENT, with their own analyses.[9] For each adverse event subgroup, we will report the number of studies that provide data for any event in 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-adverse event analysis.

E. Assessment of Methodological Quality of Individual Studies

The internal validity of RCTs and NRCTs will be assessed using the Cochrane Collaboration Risk of Bias tool.[10] 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." Blinding and incomplete outcome data will be assessed separately for subjective outcomes (e.g., quality of life or function scales) and objective clinical outcomes (e.g., weight gain, glucose tolerance test). 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 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 will be collected for each study on the source of funding.[11]

Cohort studies will be assessed using the cohort Newcastle-Ottawa Scale (NOS).[12] The NOS includes seven items assessing 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. In addition, information regarding the source of funding will be collected.[11]

Two reviewers will independently assess the methodological quality of included studies. Each assessment form will be pilot tested on a sample of studies. Decision rules regarding application of the tools will be developed a priori through discussions with content and methodology experts. Discrepancies in quality assessment will be resolved through consensus or third-party adjudication.

F. Data Synthesis

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

Where populations, interventions and outcomes are sufficiently clinically homogenous, results will be statistically pooled using a DerSimonian-Laird random effects model. This will be done using the Mantel-Haenszel method for RR and the inverse variance method for pooling mean differences. In cases where the outcomes are measured in different scales, a standardized mean difference (SMD) will be used to pool results, rather than a weighted mean difference (WMD). Heterogeneity among studies will be measured using the I^2 statistic. In cases of substantial heterogeneity, subgroup and meta-regression analyses will be performed if the number of studies is sufficient to warrant these analyses.[13] A priori subgroups have been identified in KQ4. Sensitivity analyses will be conducted to assess the robustness of the findings across study quality, parallel vs. crossover trial designs, and random effects vs. fixed effects analyses.

Where possible, we will also analyze publication bias both visually using the funnel plot and quantitatively using Begg's[14] and Egger's[15] tests. Review Manager version 5.0.22 (The Cochrane Collaboration, Copenhagen, Denmark) and Stata version 7.0 (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.

If in any disease/condition and outcome, we have comparative studies across several different interventions we will attempt to do a network meta-analysis in a Bayesian framework.[16] Non-informative prior distributions will be selected and sensitivity analyses will be performed to

determine the influence of the prior distribution on final results. Markov chain Monte Carlo simulation using WinBugs version 1.4 (Imperial College and MRC, London, UK) software will be used to perform all computations.

G. Grading the Evidence

The strength of evidence for the primary outcome for KQ1—symptom response for each disorder/illness—will be assessed using the EPC approach to grading the strength of a body of evidence.[17] 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

Not applicable.

VIII. Review of Key Questions

For Comparative Effectiveness reviews (CERs) the key questions were posted for public comment and finalized after review of the comments. For other systematic reviews, key questions submitted by partners are reviewed and refined as needed by the EPC and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed.

IX. Technical Expert Panel (TEP)

A TEP panel is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as healthy 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. The TEP provides information to the EPC to identify literature search strategies, review the draft report and recommend approaches to specific issues as requested by the EPC. The TEP does not do analysis of any kind nor contribute to the writing of the report.

X. Peer Review

Approximately five experts in the field will be asked to peer review the draft report and provide comments. The peer reviewer may represent stakeholder groups such as professional or advocacy organizations with knowledge of the topic. On some specific reports such as reports requested by the Office of Medical Applications of Research and National Institutes of Health there may be other rules that apply regarding participation in the peer review process. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. 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 three months after the publication of the Evidence report.

It is our policy not to release the names of the Peer reviewers or TEP panel members until the report is published so that they can maintain their objectivity during the review process.

Source: www.effectivehealthcare.ahrq.gov
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APPENDIX A: Summary tables of first 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 D/C : Intensol, Promapar, Sonazine, Thorazine	Oral IM/IV	Adult, 200-600 mg/day; Children ≥6mo, 0.5 to 1mg/kg/dose 300-800 mg/day	1-4 times q4-6 hr q4-6 hr
Fluphenazine	Fluphenazine decanoate Fluphenazine hydrochloride D/C: Fluphenazine, Permitil, Prolixin, Prolixin decanoate, Prolixin enanthate	Oral IM	2.5-10 mg/day 2.5-10 mg/dose	3-4 times Q6-8hr
Haloperidol	Haloperidol Haldol Haloperidol decanoate D/C: Haldol solutab, Haloperidol intensol, Haloperidol lactate	Oral Tablets Solution IM (as lactate)	Adult, 4-12 mg/day Children 3-12 yr, 0.5 to 0.15mg/kg/day Adult, maximum 20mg/day	1-2 times 2-3 times Every hr if needed
Loxapine	Loxapine, Loxapine succinate D/C : Loxitane, Loxitane C, Loxitane IM	Oral	Adult, 60-100 mg/day; Not recommended in children <16yr	2-4 times
Molindone	Moban	Oral	50-100 mg/day	3-4 times
Perphenazine	Perphenazine D/C : Trilafon	Oral (non-hospitalized) Oral (hospitalized)	12-18 mg/day; 16-64 mg/day	3 times 2-4 times
Pimozide	Orap	Oral	Adults, 7-10 mg/day; Children initiate at 0.05 mg/kg once at bedtime; increase every third day to a maximum of 0.2 mg/kg not to exceed 10 mg/day	1-3 times

D/C = discontinued according to FDA site

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Table A1. First generation antipsychotics included in the CER (continued)

Generic name	Trade names(s)	Mode of administration	Usual dose	Frequency
Prochlorperazine	Compro Prochlorperazine Prochlorperazine edisylate Prochlorperazine maleate D/C : Compazine,	Oral IM IV Rectal	15-40 mg/day 15-40 mg/day 7.5-40 mg/day 25-50 mg/day	3-4 times 3-4 times 3-4 times 1-2 times
Thiothixene	Navane Thiothixene D/C : Thiothixene hydrochloride, Thiothixene hydrochloride intensol	Oral	6-30 mg/day	2-3 times
Thioridazine	Thioridazine hydrochloride D/C: Thioridazine hydrochloride intensol, Mellaril, Mellaril-S	Oral	150-300 mg/day	2-3 times
Trifluoperazine	Trifluoperazine hydrochloride D/C: Stelazine	Oral (non-hospitalized) Oral (hospitalized)	Adult, 1-2 mg Adult, 15-21 mg/day Children (6-12 yrs), 1 mg	2 times/day 2 times/day 1-2 times/day

Source: www.effectivehealthcare.ahrq.gov
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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	Adult schizophrenia, 10-15mg/d; Adolescent schizophrenia, 10mg/d; Pediatric BD (mania), 10mg/d; Pediatric irritability with autistic disorder, 5-10 mg/d Max 30mg/d	QD ≥2 hr between doses
Asenapine	Saphris	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	Adult/Adolescent schizophrenia, 10mg/day; Adult BD I 10-15mg/day; Adolescent BD I 10mg/day	QD QD
Paliperidone	Invega Invega sustenna	Tablet extended release	6mg/day	QD in the AM
Quetiapine	Quetiapine fumarate Seroquel Seroquel XR	Tablet Sustained release tablets (Safety and effectiveness have not been established for pediatric use)	Adult schizophrenia, 150-750mg/day; Adolescent schizophrenia, 400-800mg/day; Adult BD (mania), 400-800mg/day; Child/adolescent BD (mania), 400-600mg/day; Adult BD (depression), 300mg/day; Adult BD (maintenance), 400-800mg/	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	Adult schizophrenia, 4-8mg/day; Adolescent schizophrenia, 3mg/day; Adult BD (mania), 1-6mg/day; Child/adolescent BD (mania), 2.5mg/day; Irritability childhood autism (≥ 5yrs), 0.5mg/day (<20kg); 1mg/day (≥ 20 kg)	1-2 times/day
Ziprasidone	Ziprasidone hydrochloride Geodon	Capsules IM injection	Adult 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 q 2 hr

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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 years)	Patients with cardiovascular disease or hx of seizures
Fluphenazine	Approved 1960	Schizophrenia BD (mania)	Adults Children >12yrs Not recommended for use in children under 12 years	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 years 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
Molindone	Approved 1974	Schizophrenia	Adults Use in pediatric patients <12 years is not recommended because safe and effective conditions for its usage 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 years. Limited evidence in children <12 years 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 years and > 20 pounds	May cause tardive dyskinesia

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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
Thioridazine	Approved 1962	Schizophrenia	Adults and children	Life-threatening pro-arrhythmic effect
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 yr)	Increased mortality in elderly with dementia-related psychosis
	2004	BD(L) (manic/mixed) monotherapy or adjunctive to lithium or valproate	Adults & pediatrics (10 -17 yr) Adults	Children, adolescents, and young adults taking antidepressants are at increased risk of suicidal thinking & behaviour Leukopenia, Neutropenia, Agranulocytosis
	2007	Adjunctive tx of major depressive disorder	Children (6-17 yr) 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 yr)	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 yr)	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 yr	Increased mortality in elderly with dementia-related psychosis
Clozapine,	1989 2002	Treatment resistant schizophrenia Reduce the risk of suicidal behavior in younger schizophrenics.	Adults Pediatric use: safety & effectiveness not established in patients <18 yr	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
Iloperidone	2009	Acute schizophrenia	Adults	Increased mortality in elderly with dementia-related psychosis Not approved for patients with dementia-related psychosis.

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

Drug	FDA status (year approved)	Indications	Age group approved for	Black box warnings
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 yr), schizophrenia & BD (manic/ mixed) Pediatric use: safety & effectiveness not established in patients <13 yr	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 yr	Increased mortality in elderly with dementia-related psychosis
Quetiapine	1997 2004 2008	Schizophrenia BD (acute manic) BD (depression) BD (maintenance)	Adults & adolescents (13-17 yr) Adults, children & adolescents (10-17 yr) 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 yr) Adults & adolescents (10-17 years) Children (5-16 yr)	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 yr	Increased mortality in elderly with dementia-related psychosis

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Appendix B: MEDLINE search terms and strategy

1. Child Development Disorders, Pervasive/
2. Asperger Syndrome/
3. Autistic Disorder/
4. Rett Syndrome/
5. Schizophrenia, Childhood/
6. Mental Retardation/
7. Movement Disorders/
8. "Attention Deficit and Disruptive Behavior Disorders"/
9. Conduct Disorder/
10. Childhood Disintegrative Disorder.tw.
11. "Pervasive Developmental Disorder Not Otherwise Specified".tw.
12. (atypical adj1 autism).tw.
13. Oppositional Defiant Disorder.tw.
14. "Disruptive Behavior Disorder Not Otherwise Specified".tw.
15. Schizophrenia/
16. Schizophrenia, Catatonic/
17. Schizophrenia, Disorganized/
18. Schizophrenia, Paranoid/
19. Psychotic Disorders/
20. first episode schizophrenia.tw.
21. (prodrom$ and schizophren$).tw.
22. Schizotypal Personality Disorder/
23. Bipolar Disorder/
24. "Depressive Disorder, Major"/ and (refractory or chronic or resistant).ti,ab.
25. Depression/ and (refractory or chronic or resistant).ti,ab.
26. Depressive Disorder/
27. Obsessive-Compulsive Disorder/
28. OCD.tw.
29. exp anorexia nervosa/
30. ((anorexia adj nervosa*) or anorexia*).tw.
31. exp stress disorders, post-traumatic/
32. ((chronic or acute or delayed onset) and (post-traumatic adj stress adj disorder*)).tw.
33. ((posttraumatic or post-traumatic or post traumatic) adj (neuroses or disorder)).tw.
34. ptsd.tw.
35. exp tourette syndrome/
36. ($tourette* adj (syndrome or disorder or disease)).tw.
37. (tic adj disorder).tw.
38. (multiple adj motor adj vocal adj tic adj disorder).tw.
39. or/1-38
40. Antipsychotic Agents/
41. Tranquilizing Agents/
42. chlorpromazine/
43. fluphenazine/
44. haloperidol/
45. loxapine/
46. molindone/
47. perphenazine/
48. thiothixene/
49. trifluoperazine/
50. thioridazine/
51. methotrimeprazine/
52. Phenothiazines/ad, to, tu, ct, po, ae [Administration & Dosage, Toxicity, Therapeutic Use, Contraindications, Poisoning, Adverse
53. Butyrophenones/ad, to, tu, ct, po, ae
54. Thioxanthenes/ad, to, tu, ct, po, ae
55. Dibenzoxazepines/ad, to, tu, ct, po, ae
56. Indoles/ad, to, tu, ct, po, ae
57. or/40-56
58. atypical antipsychotic$.tw.
59. clozapine/
60. risperidone/
61. olanzapine.tw.
62. quetiapine.tw.
63. ziprasidone.tw.
64. aripiprazole.tw.
65. paliperidone.tw.
66. Isoxazoles/ad, to, tu, ct, po, ae
67. Dibenzazepines/ad, to, tu, ct, po, ae
68. Pyrimidinones/ad, to, tu, ct, po, ae
69. Piperidines/ad, to, tu, ct, po, ae
70. Dibenzothiazepines/ct, ad, to, tu, ae, po
71. Piperazines/ad, tu, to, ct, po, ae
72. Pirenzepine/tu, ad, to, ct, po, ae
73. Thiazoles/ad, th, ct, po, to, ae
74. Quinolones/to, po, ct, ad, tu, ae
75. or/40-41,58-74
76. or/57,75
77. and/39,76
78. randomized controlled trial.pt.
79. controlled clinical trial.pt.
80. randomi?ed.ab.
81. placebo.ab.
82. drug therapy.fs.
83. randomly.ab.
84. trial.ab.
85. groups.ab.
86. or/78-85
87. (editorial or letter or comment).pt. or case reports/
88. (animals not (humans and animals)).sh,hw.
89. 86 not 87
90. 89 not 88
91. cohort studies/
92. follow-up studies/
93. longitudinal studies/
94. prospective studies/
95. Retrospective Studies/
96. Case-Control Studies/
97. (cohort$ or longitudinal or retrospective or prospective or follow-up or case-control).tw.
98. or/91-97
99. 98 not 87
100. 99 not 88
101. exp infant/
102. exp child/
103. exp adolescent/
104. exp pediatrics/
105. ($child$ or adolescen$ or p*ediatric$).tw.
106. or/101-105
107. and/77,90,106
108. and/77,100,106

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Effects]
110. 77 and 100
111. 109 or 110
112. limit 111 to "all child (0 to 18 years)"
113. 107 or 108
114. 112 or 113
115. limit 114 to english language
116. limit 115 to yr="1987 -Current"
117. limit 111 to "young adult (19 to 24 years)"
118. limit 117 to english language
119. limit 118 to yr="1987 -Current"
109. 77 and 90
120. 119 not 116
121. exp Young Adult/
122. (young adj adult*).tw.
123. ((college or university) adj2 (age or student*)).tw.
124. students/
125. or/121-124
126. and/77,90,125
127. and/77,100,125
128. or/126-127
129. limit 128 to (english language and yr="1987 -Current")
130. 129 not 116
131. 120 or 130