

Drug Class Review

Second-Generation Antipsychotic Drugs[†]

Final Update 5 Report

Appendixes and Evidence Tables

October 2016

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Appendix A. Glossary

This glossary defines terms as they are used in reports produced by the Drug Effectiveness Review Project. Some definitions may vary slightly from other published definitions.

Absolute risk: The probability or chance that a person will have a medical event. Absolute risk is expressed as a percentage. It is the ratio of the number of people who have a medical event divided by all of the people who could have the event because of their medical condition.

Add-on therapy: An additional treatment used in conjunction with the primary or initial treatment.

Adherence: Following the course of treatment proscribed by a study protocol.

Adverse drug reaction: An adverse effect specifically associated with a drug.

Adverse event: A harmful or undesirable outcome that occurs during or after the use of a drug or intervention but is not necessarily caused by it.

Adverse effect: An adverse event for which the causal relation between the intervention and the event is at least a reasonable possibility.

Active-control trial: A trial comparing a drug in a particular class or group with a drug outside of that class or group.

Allocation concealment: The process by which the person determining randomization is blinded to a study participant's group allocation.

Applicability: see *External Validity*

Before-after study: A type nonrandomized study where data are collected before and after patients receive an intervention. Before-after studies can have a single arm or can include a control group.

Bias: A systematic error or deviation in results or inferences from the truth. Several types of bias can appear in published trials, including selection bias, performance bias, detection bias, and reporting bias.

Bioequivalence: Drug products that contain the same compound in the same amount that meet current official standards, that, when administered to the same person in the same dosage regimen result in equivalent concentrations of drug in blood and tissue.

Black box warning: A type of warning that appears on the package insert for prescription drugs that may cause serious adverse effects. It is so named for the black border that usually surrounds the text of the warning. A black box warning means that medical studies indicate that the drug carries a significant risk of serious or even life-threatening adverse effects. The US Food and Drug Administration (FDA) can require a pharmaceutical company to place a black box warning on the labeling of a prescription drug, or in literature describing it. It is the strongest warning that the FDA requires.

Blinding: A way of making sure that the people involved in a research study — participants, clinicians, or researchers — do not know which participants are assigned to each study group. Blinding usually is used in research studies that compare two or more types of treatment for an illness. Blinding is used to make sure that knowing the type of treatment does not affect a participant's response to the treatment, a health care provider's behavior, or assessment of the treatment effects.

Case series: A study reporting observations on a series of patients receiving the same intervention with no control group.

Case study: A study reporting observations on a single patient.

Case-control study: A study that compares people with a specific disease or outcome of interest (cases) to people from the same population without that disease or outcome (controls).

Clinical diversity: Differences between studies in key characteristics of the participants, interventions or outcome measures.

Clinically significant: A result that is large enough to affect a patient's disease state in a manner that is noticeable to the patient and/or a caregiver.

Cohort study: An observational study in which a defined group of people (the cohort) is followed over time and compared with a group of people who were exposed or not exposed to a particular intervention or other factor of interest. A prospective cohort study assembles participants and follows them into the future. A retrospective cohort study identifies subjects from past records and follows them from the time of those records to the present.

Combination Therapy: The use of two or more therapies and especially drugs to treat a disease or condition.

Confidence interval: The range of values calculated from the data such that there is a level of confidence, or certainty, that it contains the true value. The 95% confidence interval is generally used in Drug Effectiveness Review Project reports. If the report were hypothetically repeated on a collection of 100 random samples of studies, the resulting 95% confidence intervals would include the true population value 95% of the time.

Confounder: A factor that is associated with both an intervention and an outcome of interest.

Controlled clinical trial: A clinical trial that includes a control group but no or inadequate methods of randomization.

Control group: In a research study, the group of people who do not receive the treatment being tested. The control group might receive a placebo, a different treatment for the disease, or no treatment at all.

Convenience sample: A group of individuals being studied because they are conveniently accessible in some way. Convenience samples may or may not be representative of a population that would normally be receiving an intervention.

Crossover trial: A type of clinical trial comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another.

Direct analysis: The practice of using data from head-to-head trials to draw conclusions about the comparative effectiveness of drugs within a class or group. Results of direct analysis are the preferred source of data in Drug Effectiveness Review Project reports.

Dosage form: The physical form of a dose of medication, such as a capsule, injection, or liquid. The route of administration is dependent on the dosage form of a given drug. Various dosage forms may exist for the same compound, since different medical conditions may warrant different routes of administration.

Dose-response relationship: The relationship between the quantity of treatment given and its effect on outcome. In meta-analysis, dose-response relationships can be investigated using meta-regression.

Double-blind: The process of preventing those involved in a trial from knowing to which comparison group a particular participant belongs. While double-blind is a frequently used term

in trials, its meaning can vary to include blinding of patients, caregivers, investigators, or other study staff.

Double-dummy: The use of two placebos in a trial that match the active interventions when they vary in appearance or method of administrations (for example, when an oral agent is compared with an injectable agent).

Effectiveness: The extent to which a specific intervention *used under ordinary circumstances* does what it is intended to do.

Effectiveness outcomes: Outcomes that are generally important to patients and caregivers, such as quality of life, responder rates, number and length of hospitalizations, and ability to work. Data on effectiveness outcomes usually comes from longer-term studies of a “real-world” population.

Effect size/estimate of effect: The amount of change in a condition or symptom because of a treatment (compared to not receiving the treatment). It is commonly expressed as a risk ratio (relative risk), odds ratio, or difference in risk.

Efficacy: The extent to which an intervention produces a beneficial result *under ideal conditions* in a selected and controlled population.

Equivalence level: The amount which an outcome from two treatments can differ but still be considered equivalent, as in an equivalence trial, or the amount which an outcome from treatment A can be worse than that of treatment B but still be considered noninferior, as in a noninferiority trial.

Equivalence trial: A trial designed to determine whether the response to two or more treatments differs by an amount that is clinically unimportant. This lack of clinical importance is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence level of clinically acceptable differences.

Exclusion criteria: The criteria, or standards, set out before a study or review. Exclusion criteria are used to determine whether a person should participate in a research study or whether an individual study should be excluded in a systematic review. Exclusion criteria may include age, previous treatments, and other medical conditions. Criteria help identify suitable participants.

External validity: The extent to which results provide a correct basis for generalizations to other circumstances. For instance, a meta-analysis of trials of elderly patients may not be generalizable to children. (Also called generalizability or applicability.)

Fixed-effect model: A model that calculates a pooled estimate using the assumption that all observed variation between studies is due to by chance. Studies are assumed to be measuring the same overall effect. An alternative model is the random-effects model.

Fixed-dose combination product: A formulation of two or more active ingredients combined in a single dosage form available in certain fixed doses.

Forest plot: A graphical representation of the individual results of each study included in a meta-analysis and the combined result of the meta-analysis. The plot allows viewers to see the heterogeneity among the results of the studies. The results of individual studies are shown as squares centered on each study’s point estimate. A horizontal line runs through each square to show each study’s confidence interval—usually, but not always, a 95% confidence interval. The overall estimate from the meta-analysis and its confidence interval are represented as a diamond. The center of the diamond is at the pooled point estimate, and its horizontal tips show the confidence interval.

Funnel plot: A graphical display of some measure of study precision plotted against effect size that can be used to investigate whether there is a link between study size and treatment effect.

Generalizability: See *External Validity*.

Half-life: The time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%.

Harms: See *Adverse Event*

Hazard ratio: The increased risk with which one group is likely to experience an outcome of interest. It is similar to a risk ratio. For example, if the hazard ratio for death for a treatment is 0.5, then treated patients are likely to die at half the rate of untreated patients.

Head-to-head trial: A trial that directly compares one drug in a particular class or group with another in the same class or group.

Health outcome: The result of a particular health care practice or intervention, including the ability to function and feelings of well-being. For individuals with chronic conditions – where cure is not always possible – results include health-related quality of life as well as mortality.

Heterogeneity: The variation in, or diversity of, participants, interventions, and measurement of outcomes across a set of studies.

I²: A measure of statistical heterogeneity of the estimates of effect from studies. Values range from 0% to 100%. Large values of I² suggest heterogeneity. I² is the proportion of total variability across studies that is due to heterogeneity and not chance. It is calculated as $(Q - (n - 1)) / Q$, where n is the number of studies.

Incidence: The number of new occurrences of something in a population over a particular period of time, e.g. the number of cases of a disease in a country over one year.

Indication: A term describing a valid reason to use a certain test, medication, procedure, or surgery. In the United States, indications for medications are strictly regulated by the Food and Drug Administration, which includes them in the package insert under the phrase "Indications and Usage".

Indirect analysis: The practice of using data from trials comparing one drug in a particular class or group with another drug outside of that class or group or with placebo and attempting to draw conclusions about the comparative effectiveness of drugs within a class or group based on that data. For example, direct comparisons between drugs A and B and between drugs B and C can be used to make an indirect comparison between drugs A and C.

Intent to treat: The use of data from a randomized controlled trial in which data from all randomized patients are accounted for in the final results. Trials often incorrectly report results as being based on intent to treat despite the fact that some patients are excluded from the analysis.

Internal validity: The extent to which the design and conduct of a study are likely to have prevented bias. Generally, the higher the internal validity, the better the quality of the study publication.

Inter-rater reliability: The degree of stability exhibited when a measurement is repeated under identical conditions by different raters.

Intermediate outcome: An outcome not of direct practical importance but believed to reflect outcomes that are important. For example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and myocardial infarction (heart attack).

Logistic regression: A form of regression analysis that models an individual's odds of disease or some other outcome as a function of a risk factor or intervention.

Masking: See *Blinding*

Mean difference: A method used to combine measures on continuous scales (such as weight) where the mean, standard deviation, and sample size are known for each group.

Meta-analysis: The use of statistical techniques in a systematic review to integrate the results of included studies. Although the terms are sometimes used interchangeably, meta-analysis is not synonymous with systematic review. However, systematic reviews often include meta-analyses.

Meta-regression: A technique used to explore the relationship between study characteristics (for example, baseline risk, concealment of allocation, timing of the intervention) and study results (the magnitude of effect observed in each study) in a systematic review.

Mixed treatment comparison meta-analysis: A meta-analytic technique that simultaneously compares multiple treatments (typical 3 or more) using both direct and indirect evidence. The multiple treatments form a network of treatment comparisons. Also called multiple treatment comparisons, network analysis, or umbrella reviews.

Monotherapy: the use of a single drug to treat a particular disorder or disease.

Multivariate analysis: Measuring the impact of more than one variable at a time while analyzing a set of data.

N-of-1 trial: A randomized trial in an individual to determine the optimum treatment for that individual.

Noninferiority trial: A trial designed to determine whether the effect of a new treatment is not worse than a standard treatment by more than a prespecified amount. A one-sided version of an equivalence trial.

Nonrandomized study: Any study estimating the effectiveness (harm or benefit) of an intervention that does not use randomization to allocate patients to comparison groups. There are many types of nonrandomized studies, including cohort studies, case-control studies, and before-after studies.

Null hypothesis: The statistical hypothesis that one variable (for example, treatment to which a participant was allocated) has no association with another variable or set of variables.

Number needed to harm: The number of people who would need to be treated over a specific period of time before one bad outcome of the treatment will occur. The number needed to harm (NNH) for a treatment can be known only if clinical trials of the treatment have been performed.

Number needed to treat: An estimate of how many persons need to receive a treatment before one person would experience a beneficial outcome.

Observational study: A type of nonrandomized study in which the investigators do not seek to intervene, instead simply observing the course of events.

Odds ratio: The ratio of the odds of an event in one group to the odds of an event in another group. An odds ratio of 1.0 indicates no difference between comparison groups. For undesirable outcomes an odds ratio that is <1.0 indicates that the intervention was effective in reducing the risk of that outcome.

Off-label use: When a drug or device is prescribed outside its specific FDA-approved indication, to treat a condition or disease for which it is not specifically licensed.

Outcome: The result of care and treatment and/ or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the

effectiveness of care/treatment/rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.

Outcome measure: Is the way in which an outcome is evaluated---the device (scale) used for measuring. With this definition YMRS is an outcome measure, and a patient's outcome after treatment might be a 12-point improvement on that scale.

One-tailed test (one-sided test): A hypothesis test in which the values that reject the null hypothesis are located entirely in one tail of the probability distribution. For example, testing whether one treatment is better than another (rather than testing whether one treatment is either better or worse than another).

Open-label trial: A clinical trial in which the investigator and participant are aware which intervention is being used for which participant (that is, not blinded). Random allocation may or may not be used in open-label trials.

Per protocol: The subset of participants from a randomized controlled trial who complied with the protocol sufficiently to ensure that their data would be likely to exhibit the effect of treatment. Per protocol analyses are sometimes misidentified in published trials as intent-to-treat analyses.

Pharmacokinetics: the characteristic interactions of a drug and the body in terms of its absorption, distribution, metabolism, and excretion.

Placebo: An inactive substance commonly called a "sugar pill." In a clinical trial, a placebo is designed to look like the drug being tested and is used as a control. It does not contain anything that could harm a person. It is not necessarily true that a placebo has no effect on the person taking it.

Placebo-controlled trial: A study in which the effect of a drug is compared with the effect of a placebo (an inactive substance designed to resemble the drug). In placebo-controlled clinical trials, participants receive either the drug being studied or a placebo. The results of the drug and placebo groups are then compared to see if the drug is more effective in treating the condition than the placebo is.

Point estimate: The results (e.g. mean, weighted difference, odds ratio, relative risk or risk difference) obtained in a sample (a study or a meta-analysis) which are used as the best estimate of what is true for the relevant population from which the sample is taken. A confidence interval is a measure of the uncertainty (due to the play of chance) associated with that estimate.

Pooling: The practice of combining data from several studies to draw conclusions about treatment effects.

Power: The probability that a trial will detect statistically significant differences among intervention effects. Studies with small sample sizes can frequently be underpowered to detect difference.

Precision: The likelihood of random errors in the results of a study, meta-analysis, or measurement. The greater the precision, the less the random error. Confidence intervals around the estimate of effect are one way of expressing precision, with a narrower confidence interval meaning more precision.

Prospective study: A study in which participants are identified according to current risk status or exposure and followed forward through time to observe outcome.

Prevalence: How often or how frequently a disease or condition occurs in a group of people. Prevalence is calculated by dividing the number of people who have the disease or condition by the total number of people in the group.

Probability: The likelihood (or chance) that an event will occur. In a clinical research study, it is the number of times a condition or event occurs in a study group divided by the number of people being studied.

Publication bias: A bias caused by only a subset of the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (for example, only outcomes or subgroups for which a statistically significant difference was found).

P value: The probability (ranging from zero to one) that the results observed in a study could have occurred by chance if the null hypothesis was true. A *P* value of ≤ 0.05 is often used as a threshold to indicate statistical significance.

Q-statistic: A measure of statistical heterogeneity of the estimates of effect from studies. Large values of *Q* suggest heterogeneity. It is calculated as the weighted sum of the squared difference of each estimate from the mean estimate.

Random-effects model: A statistical model in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis. When there is heterogeneity among the results of the included studies beyond chance, random-effects models will give wider confidence intervals than fixed-effect models.

Randomization: The process by which study participants are allocated to treatment groups in a trial. Adequate (that is, unbiased) methods of randomization include computer generated schedules and random-numbers tables.

Randomized controlled trial: A trial in which two or more interventions are compared through random allocation of participants.

Regression analysis: A statistical modeling technique used to estimate or predict the influence of one or more independent variables on a dependent variable, for example, the effect of age, sex, or confounding disease on the effectiveness of an intervention.

Relative risk: The ratio of risks in two groups; same as a risk ratio.

Retrospective study: A study in which the outcomes have occurred prior to study entry.

Risk: A way of expressing the chance that something will happen. It is a measure of the association between exposure to something and what happens (the outcome). Risk is the same as probability, but it usually is used to describe the probability of an adverse event. It is the rate of events (such as breast cancer) in the total population of people who could have the event (such as women of a certain age).

Risk difference: The difference in size of risk between two groups.

Risk Factor: A characteristic of a person that affects that person's chance of having a disease. A risk factor may be an inherent trait, such as gender or genetic make-up, or a factor under the person's control, such as using tobacco. A risk factor does not usually cause the disease. It changes a person's chance (or risk) of getting the disease.

Risk ratio: The ratio of risks in two groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of 1 indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is < 1 indicates that the intervention was effective in reducing the risk of that outcome.

Run-in period: Run in period: A period before randomization when participants are monitored but receive no treatment (or they sometimes all receive one of the study treatments, possibly in a blind fashion). The data from this stage of a trial are only occasionally of value but can serve a valuable role in screening out ineligible or non-compliant participants, in ensuring that participants are in a stable condition, and in providing baseline observations. A run-in period is sometimes called a washout period if treatments that participants were using before entering the trial are discontinued.

Safety: Substantive evidence of an absence of harm. This term (or the term “safe”) should not be used when evidence on harms is simply absent or is insufficient.

Sample size: The number of people included in a study. In research reports, sample size is usually expressed as "n." In general, studies with larger sample sizes have a broader range of participants. This increases the chance that the study's findings apply to the general population. Larger sample sizes also increase the chance that rare events (such as adverse effects of drugs) will be detected.

Sensitivity analysis: An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

Side effect: Any unintended effect of an intervention. Side effects are most commonly associated with pharmaceutical products, in which case they are related to the pharmacological properties of the drug at doses normally used for therapeutic purposes in humans.

Standard deviation (SD): A measure of the spread or dispersion of a set of observations, calculated as the average difference from the mean value in the sample.

Standard error (SE): A measure of the variation in the sample statistic over all possible samples of the same size. The standard error decreases as the sample size increases.

Standard treatment: The treatment or procedure that is most commonly used to treat a disease or condition. In clinical trials, new or experimental treatments sometimes are compared to standard treatments to measure whether the new treatment is better.

Statistically significant: A result that is unlikely to have happened by chance.

Study: A research process in which information is recorded for a group of people. The information is known as data. The data are used to answer questions about a health care problem.

Study population: The group of people participating in a clinical research study. The study population often includes people with a particular problem or disease. It may also include people who have no known diseases.

Subgroup analysis: An analysis in which an intervention is evaluated in a defined subset of the participants in a trial, such as all females or adults older than 65 years.

Superiority trial: A trial designed to test whether one intervention is superior to another.

Surrogate outcome: Outcome measures that are not of direct practical importance but are believed to reflect outcomes that are important; for example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and heart attacks. Surrogate endpoints are often physiological or biochemical markers that can be relatively quickly and easily measured, and that are taken as being predictive of important clinical outcomes. They are often used when observation of clinical outcomes requires long follow-up.

Survival analysis: Analysis of data that correspond to the time from a well-defined time origin until the occurrence of some particular event or end-point; same as time-to-event analysis.

Systematic review: A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research and to collect and analyze data from the studies that are included in the review.

Tolerability: For therapeutic drugs, it refers a drug's lack of "nuisance side effects," side effects that are thought to have no long-term effect but that are unpleasant enough to the patient that adherence to the medication regimen is affected.

The extent to which a drug's adverse effects impact the patient's ability or willingness to continue taking the drug as prescribed. These adverse effects are often referred to as nuisance side effects, because they are generally considered to not have long-term effects but can seriously impact compliance and adherence to a medication regimen.

Treatment regimen: The magnitude of effect of a treatment versus no treatment or placebo; similar to "effect size". Can be calculated in terms of relative risk (or risk ratio), odds ratio, or risk difference.

Two-tailed test (two-sided test): A hypothesis test in which the values that reject the null hypothesis are located in both tails of the probability distribution. For example, testing whether one treatment is different than another (rather than testing whether one treatment is either better than another).

Type I error: A conclusion that there is evidence that a treatment works, when it actually does not work (false-positive).

Type II error: A conclusion that there is no evidence that a treatment works, when it actually does work (false-negative).

Validity: The degree to which a result (of a measurement or study) is likely to be true and free of bias (systematic errors).

Variable: A measurable attribute that varies over time or between individuals. Variables can be

- *Discrete:* taking values from a finite set of possible values (e.g. race or ethnicity)
- *Ordinal:* taking values from a finite set of possible values where the values indicate rank (e.g. 5-point Likert scale)
- *Continuous:* taking values on a continuum (e.g. hemoglobin A1C values).

Washout period: [In a cross-over trial] The stage after the first treatment is withdrawn, but before the second treatment is started. The washout period aims to allow time for any active effects of the first treatment to wear off before the new one gets started.

Appendix B. Scales used to assess efficacy and adverse events

The following narrative briefly describes each of the most commonly used assessment scales and summarizes methods of scoring and validation. The subsequent table lists abbreviations for all assessment scales noted in this review. The references cited here are listed at the end of this appendix.

Population-Specific Scales

Autism

The Aberrant Behavior Checklist (ABC)¹ irritability subscale is rated by the parent or primary caretaker. The 15-item scale includes questions about aggression, self-injury, tantrums, agitation, and unstable mood on a scale of 0 to 45, with higher scores indicating greater severity.

The Children's Psychiatric Rating Scale (CPRS)² is a 63-item scale developed by the Psychopharmacology Branch of the National Institute of Mental Health to rate childhood psychopathology. Each item is rated from 1 (not present) to 7 (extremely severe). Four factors have been derived from the items: Autism Factor (social withdrawal, rhythmic motions/stereotype, abnormal object relations, unspontaneous relation to examiner, underproductive speech), Anger/Uncooperativeness Factor (angry affect, labile affect, negative and uncooperative), Hyperactivity Factor (fidgetiness, hyperactivity, hypoactivity), and Speech Deviance Factor (speech deviance, low voice).

Bipolar I Disorder

The Young Mania Rating Scale (YMRS) is an 11-item, clinician-administered interview scale designed to quantify the severity of mania. Clinicians select from 5 grades of severity specific to each item when making YMRS ratings. YMRS total scores range from 0 to 60. Clinical trials of individuals with Bipolar I Disorder generally required scores equal to or greater than 20 for enrollment and specified scores equal to or below 12 as representing symptomatic remission. One validity study reported high correlations between the YMRS and the Petterson Scale ($r=0.89$, $P<0.001$), the Beigel Scale ($r=0.71$, $P<0.001$), and an unspecified, 8-point global rating scale ($r=0.88$, $P<0.001$).³

Disruptive Behavior Disorders

The Nisonger Child Behavior Rating Form⁴ was developed for children with developmental disabilities. The Parent version has two positive/social subscales (Compliant/Calm and Adaptive/Social) comprising 10 items. It has 66 Problem Behavior items that score onto 6 subscales: Conduct Problem, Insecure/Anxious, Hyperactive, Self-Injury/Stereotypic, Self-Isolated/Ritualistic, and Overly Sensitive.

The Rating of Aggression against People and/or Property (RAAP)⁵ is a global rating scale of aggression that is completed by a clinician. It is scored from 1 (no aggression reported) to 5 (intolerable behavior).

Schizophrenia

The Positive and Negative Syndrome Scale (PANSS) is a 30-item instrument designed to assess schizophrenia symptoms. Each item is rated using a 7-point severity scale (1=absent, 2=minimal, 3=mild, 4=moderate, 5=moderate-severe, 6=severe, 7=extreme). The PANSS is administered by

qualified clinicians using combinations of unstructured, semistructured, and structured interview strategies. The PANSS is composed of three subscales, a 7-item Positive Scale, a 7-item Negative Scale and a 16-item General Psychopathology Scale. The PANSS Total Score ranges from 30 to 210. The PANSS also provides a method of assessing relationships of positive and negative syndromes to one another and to general psychopathology. High correlations between the PANSS Positive Syndrome Scale and the Scale for the Assessment of Positive Symptoms (SAPS) ($r=0.77$, $P<0.0001$), the Negative Syndrome Scale and the Scale for the Assessment of Negative Symptoms (SANS) ($r=0.77$, $P<0.0001$), and the General Psychopathology Syndrome scale and the Clinical Global Impressions Scale (CGI) ($r=0.52$, $P<0.0001$) supports the scale's criterion-related validity.⁶

Scales for General Use

Extrapyramidal Side Effect Scales

The Barnes Akathisia Scale (BAS) is a tool used for diagnosis of drug-induced akathisia.⁷ The BAS consists of items that assess the objective presence and frequency of akathisia, the level of an individual's subjective awareness and distress, and global severity. The objective rating is made using a 4-point scale (0=normal limb movement, 1=restlessness for less than half the time observed, 2=restlessness for at least half of the time observed, 3=constant restlessness). The BAS subjective component consists of two items, both rated using 4-point scales. One is Awareness of Restlessness (0=absent, 1=non-specific sense, 2=complaints of inner restlessness, 3=strong desire to move most of the time) and the other is Distress Related to Restlessness (0=none, 1=mild, 2=moderate, 3=severe). The BAS Global Clinical Assessment of Akathisia is rated using a 6-point scale (0=absent, 1=questionable, 2=mild, 3=moderate, 4=marked, 5=severe).

The Simpson Angus Scale (SAS) is composed of 10 items and used to assess pseudoparkinsonism. Grade of severity of each item is rated using a 5-point scale. SAS scores can range from 0 to 40. Signs assessed include gait, arm-dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head dropping, glabella tap, tremor, and salivation. In more than 1 randomized controlled trial of bipolar I disorder,⁸ treatment-emergent parkinsonism was defined as a SAS score of greater than 3 at any time following a score of 3 or less.

The Abnormal Involuntary Movement Scale (AIMS) is composed of 12 items and used to assess dyskinesia. Items related to severity of orofacial, extremity, and trunk movements, global judgment about incapacitation, and patient awareness are rated using a 5-point scale (0=none to 4=severe). Two items related to dental status are scored using "yes" or "no" responses. Overall AIMS scores range from 0 to 42. Randomized controlled trials of second generation antipsychotics in bipolar I disorder populations defined treatment-emergent dyskinesia as, "a score of 3 or more on any of the first 7 AIMS items, or a score of 2 or more on any two of the first 7 AIMS items."^{8,9}

The Extrapyramidal Symptom Rating Scale (ESRS) was designed to assess frequency and severity of parkinsonism, dyskinesia, akathisia, and dystonia.¹⁰ The ESRS involves a physical exam and 12 questionnaire items that assess abnormalities both subjectively and objectively. Most of the items focus on features of parkinsonism.

Depression Scales

The 17 items of the Hamilton Depression Rating Scale (HAM-D) are designed to measure symptoms of depression. Each item is rated using a 5-point scale (0=absent, 1=mild,

2=moderate, 3=severe, 4=incapacitating). Scores ranging from 10 to 13 suggest mild depression; 14-17, mild to moderate; and >17, moderate to severe.¹¹ A 21-item version of the Hamilton Depression Rating Scale (HAMD-21) is also available. The HAMD-21 includes the following additional items: “diurnal variation”, “depersonalization and derealization”, “paranoid symptoms”, and “obsessional and compulsive symptoms”. It is the HAMD-21 that is most commonly used in randomized controlled trials of second generation antipsychotics. One randomized controlled trial of bipolar I disorder identified a HAMD-21 score of at least 20 as indicating moderate to severe depression.¹²

The Montgomery-Asberg Depression Rating Scale (MADRS) is another instrument extensively used in psychopharmacological research to assess severity of depressive symptoms.¹³ The MADRS has 10 items, each rated using a 7-point severity scale. Scores range from 0 to 60. MADRS, HAM-D, and CGI appear to be highly correlated ($r > 0.85$, $P < 0.0001$), with the best cut off for *severe* depression being 31 on MADRS (sensitivity 93.5%, specificity 83.3%).¹³ One study of patients with bipolar I depression limited enrollment by requiring a score of at least 20 on the MADRS.¹⁴

Other Scales

The Brief Psychiatric Rating Scale (BPRS) is a 16-item scale designed to assess treatment change in psychiatric patients.¹⁵ The severity of each item is rated using a 7-point scale (1=not present, 2=very mild, 3=mild, 4=moderate, 5=moderately severe, 6=severe, 7=extremely severe). BPRS ratings are made using a combination of observations of and verbal report from patients. BPRS scores range from 16 to 112. This review includes numerous randomized controlled trials that assessed efficacy of second generation antipsychotics in schizophrenia or bipolar I disorder populations using the BPRS, generally as a secondary endpoint.

The Clinical Global Impression Scale (CGI) consists of 3 items (Severity of Illness, Global Improvement, and Efficacy Index) designed to assess treatment response. A 7-point scale is used to rate Severity of Illness (1=normal to 7=extremely ill) and Global Improvement (1=very much improved to 7=very much worse). Efficacy Index is rated on a 4-point scale (from “none” to “outweighs therapeutic effect”). The Clinical Global Impressions Scale for use in bipolar illness (CGI-BP) is a modification of the original CGI and designed specifically for rating severity of manic and depressive episodes and the degree of change from the immediately preceding phase and from the worst phase of illness.¹⁶

Scales used to assess outcomes

Scale	Abbreviation	Scale	Abbreviation
Aberrant Behavior Checklist	ABC	Montgomery-Asberg Depression Rating Scale	MADRS
Abnormal Involuntary Movement Scale	AIMS	Multnomah Community Ability Scale	MCAS
Adverse effects checklist		Munich Quality of Life Dimensions List	
Association for Methodology and Documentation in Psychiatry		North American Adult Reading Test - Revised	NAART-R
Barnes Akathisia Scale	BAS	Negative Symptom Assessment	NSA
Bech Rafaelsen Melancholia Scale	BRMS	Neuropsychiatric Inventory	NPI

Scale	Abbreviation	Scale	Abbreviation
Behavioral Pathology in Alzheimer's Disease Rating Scale	BEHAVE-AD	Nisonger Child Behavior Rating Form	
Benton Visual Retention Test	BVRT	Nurses Observation Scale for In-Patient Evaluation	NOSIE
Brief Psychiatric Rating Scale	BPRS	Occupational Functioning Assessment Scale	
Calgary Depression Scale	CDS	Overall Safety Rating	
California Verbal Learning Test	CVLT	Paced Auditory Serial Addition Task	PASAT
Children's Psychiatric Rating Scale	CPRS	Patient Global Impression	PGI
Chemical Use, Abuse, and Dependence Scale	CUAD	Phillips Scale	
Client Satisfaction Questionnaire-8	CSQ-8	Positive and Negative Syndrome Scale for Schizophrenia	PANSS
Clinical Global Impression Scale	CGI	Psychotic Anxiety Scale	
Clinical Global Impressions-Improvement	CGI-I	Psychotic Depression Scale	
Clinicians Global Impressions of Change	CGI-C	Quality of Life Scales	QLS
Clinicians Global Impressions-Severity of Illness Scale	CGI-S	Rating of Aggression Against People and/or Property	RAAP
Coding Symbols for a Thesaurus for Adverse Reaction Terms	COSTART	Repeatable Battery for the Assessment of Neuropsychological Status	RBANS
Cohen-Mansfield Agitation Inventory	CMAI	Role Functioning Scale	RFS
Consonant Trigram		Scale for the Assessment of Negative Symptoms	SANS
Continuous Performance Test	CPT	Scale for the Assessment of Positive Symptoms	SAPS
Controlled Word Association Test of Verbal Fluency		Schneiderian Symptom Rating Scale	
Covi-Anxiety Scale		Simpson Angus Rating Scale for Extrapyramidal Side Effects	SAS, SARS
Delayed Recall Test		Simpson-Angus Neurologic Rating Scale	
Diagnostic Interview Schedule III-R	DIS-III-R	Slow-wave sleep	SWS
Digit Span Distractibility Test		Social Adjustment Scale	SAS-SM
Digit Symbol Substitution Test		Social Functioning Scale	SFS
Disability Assessment Schedule	DAS	Social and Occupational Functioning Assessment	SOFA
Drug Attitude Inventory	DAI-30	Social Verbal Learning Test	SVLT
Drug-Induced Extrapyramidal Symptoms Scale	DIEPS	Stroop Color-Word Test	
Dyskinesia Identification System Condensed User Scale	DISCUS	Subjective response to treatment scale	
EuroQuol-Visual Analogue Scale		Subjective Well-Being Under Neuroleptics Scale	

Scale	Abbreviation	Scale	Abbreviation
Extrapyramidal Symptom Rating Scale	ESRS	Trail Making Test	TMT
Final Global Improvement Rating	FGIR	Tremor, akathisia	
Global Assessment of Functioning	GAF	UKU Side Effect Rating Scale	
Global Assessment Scale	GAS	Verbal Fluency Categories	
Hamilton Rating Scale for Depression	HAM-D	Verbal Fluency Letters	
Heinrichs-Carpenter Quality of Life Scale		Verbal List Learning Immediate Test	
Last Observation Carried Forward	LOCF	Wechsler Adult Intelligence Scales - Maze Test	WAIS
Level of Functioning Scale		Wisconsin Card Sort Test	WCST
Maryland Assessment of Social Competence		World Health Organization – Quality of Life [Brief]	WHO-QOL (BREF)
Medical Outcomes Study Short Form 36-Item Health Survey		Young Mania Rating Scale	YMRS
Mini Mental State Examination	MMSE		

Appendix B References

1. Aman MG, Singh NN, Stewart AW, Field CJ. The aberrant behavior checklist: a behavior rating scale for the assessment of treatment effects. *American Journal of Mental Deficiency*. 1985;89(5):485-491.
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Appendix C. Abbreviations

Abbreviations	Definition
ADHD	Attention-deficit/hyperactivity disorder
ADI-R	Autism Diagnostic Interview-Revised
AE(s)	Adverse event(s)
AIMS	Abnormal Involuntary Movement Scale
BARS	Barnes Akathisia Rating Scale
bid	Twice daily
BP	Blood pressure
BPRS	Brief Psychiatric Rating Scale
CCMD-3	Chinese Classification of Mental Disorders, 3rd edition
CDRS-R	Children's Depression Rating Scale-Revised scale
CDSS	Calgary Depression Scale for Schizophrenia
CGI	Clinical Global Impression scale
CI	Confidence Interval
CIDI	Composite International Diagnostic Interview
C-SSRS	Columbia Suicide Severity Rating Scale
CY-BOCS	Children's Yale-Brown Obsessive Compulsive Scale
d	Day(s)
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (4th edition)
ED	Emergency Department
ER (or XR)	Extended-release
HDL	High-density lipoprotein
HR	Hazard ratio
ICD-10	International Classification of Diseases (revision 10)
IQR	Interquartile range
IRR	Incidence rate ratio
ITT	Intention-to-treat
LAI	Long-acting injection
LOCF	Last observation carried forward
LS	Least-squares (mean)
m	Month(s)
mg	Milligram
M-RLRS	Modified Real Life Rating Scale for Autism
NCEP ATP-III	National Cholesterol Education Program Adult Treatment Panel III
NIMH	National Institute of Mental Health
NR	Not reported
OR	Odds ratio
PANSS	Positive and Negative Syndrome Scale
PedsQL	Pediatric Quality of Life Inventory

RR	Relative risk
SANS	Scale for the Assessment of Negative Symptoms
SAPS	Scale for the Assessment of Positive Symptoms
SAS	Simpson–Angus Scale
SD	Standard deviation
SE	Standard error
SMD	Standardized mean difference
SWN-K	Subjective Well-Being Under Neuroleptics Scale short form
TEAE	Treatment-emergent adverse event
US	United States
w	Week(s)
WAE	Withdrawals due to adverse events
y	Year(s)
YMRS	Young Mania Rating Scale

Appendix D. Literature search strategies for Update 5

* *Searches were updated in July 2016*

Database: Ovid MEDLINE(R) <1946 to February Week 2 2016>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <February 17, 2016>

Search Strategy:

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- 1 aripiprazole.mp. (2871)
 - 2 abilify.mp. (44)
 - 3 asenapine.mp. (267)
 - 4 saphris.mp. (16)
 - 5 clozapine.mp. (10563)
 - 6 clozaril.mp. (79)
 - 7 fazaclo.mp. (2)
 - 8 versacloz.mp. (0)
 - 9 iloperidone.mp. (155)
 - 10 fanapt.mp. (5)
 - 11 lurasidone.mp. (211)
 - 12 latuda.mp. (8)
 - 13 olanzapine.mp. (7469)
 - 14 zyprexa.mp. (62)
 - 15 paliperidone.mp. (788)
 - 16 invega.mp. (14)
 - 17 quetiapine.mp. (3915)
 - 18 seroquel.mp. (145)
 - 19 risperidone.mp. (8231)
 - 20 risperdal.mp. (67)
 - 21 ziprasidone.mp. (1706)
 - 22 geodon.mp. (17)
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 - 25 Psychotic Disorders/ (38725)
 - 26 psychotic disorders.mp. (40994)
 - 27 Schizophreniform Disorder\$.mp. (511)
 - 28 Delusional Disorder\$.mp. (744)
 - 29 Schizoaffective disorder\$.mp. (3679)
 - 30 Bipolar Disorder.mp. or exp Bipolar Disorder/ (39277)
 - 31 bipolar\$.mp. (63730)
 - 32 exp AUTISM/ or autism.mp. or autistic\$.mp. (31455)
 - 33 Rett's Disorder.mp. or exp Rett Syndrome/ (2011)
 - 34 rett\$.mp. (5867)
 - 35 childhood disintegrative disorder.mp. (68)
 - 36 Asperger's disorder.mp. or exp Asperger Syndrome/ (1699)
 - 37 pervasive developmental disorder.mp. (1073)
 - 38 Conduct Disorder.mp. or exp Conduct Disorder/ (4675)
 - 39 Oppositional Defiant Disorder.mp. (1390)

- 40 Disruptive Behavior Disorder.mp. (211)
 41 exp Child Development Disorders, Pervasive/ (23652)
 42 "Attention Deficit and Disruptive Behavior Disorders"/ or Conduct Disorder/ (4494)
 43 exp Depressive Disorder, Major/ (21530)
 44 major depress\$.mp. (34677)
 45 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or
 41 or 42 or 43 or 44 (274948)
 46 23 and 45 (15721)
 47 limit 46 to (english language and humans) (12076)
 48 (201305\$ or 201306\$ or 201307\$ or 201308\$ or 201309\$ or 20131\$ or 2014\$ or 2015\$ or
 2016\$.ed. (2756996)
 49 47 and 48 (1649)
 50 limit 49 to (case reports or clinical conference or comment or congresses or editorial or in vitro or
 letter) (453)
 51 49 not 50 (1196)

Database: Ovid MEDLINE(R) <1946 to February Week 2 2016>, Ovid MEDLINE(R) In-Process & Other
 Non-Indexed Citations <February 17, 2016>

Search Strategy:

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 3 rexulti.mp. (3)
 4 cariprazine.mp. (52)
 5 vraylar.mp. (0)
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 13 Schizoaffective disorder\$.mp. (3679)
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 15 bipolar\$.mp. (63730)
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 17 Rett's Disorder.mp. or exp Rett Syndrome/ (2011)
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 23 Oppositional Defiant Disorder.mp. (1390)
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 27 exp Depressive Disorder, Major/ (21530)

- 28 major depress\$.mp. (34677)
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- 30 7 and 29 (61)
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- 32 limit 31 to (case reports or clinical conference or comment or congresses or editorial or in vitro or letter) (3)
- 33 31 not 32 (24)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <January 2016>
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 - 6 clozaril.mp. (11)
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 - 8 versacloz.mp. (0)
 - 9 iloperidone.mp. (36)
 - 10 fanapt.mp. (0)
 - 11 lurasidone.mp. (136)
 - 12 latuda.mp. (0)
 - 13 olanzapine.mp. (2156)
 - 14 zyprexa.mp. (7)
 - 15 paliperidone.mp. (227)
 - 16 invega.mp. (3)
 - 17 quetiapine.mp. (999)
 - 18 seroquel.mp. (94)
 - 19 risperidone.mp. (2151)
 - 20 risperdal.mp. (22)
 - 21 ziprasidone.mp. (493)
 - 22 geodon.mp. (3)
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 - 26 psychotic disorders.mp. (1572)
 - 27 Schizophreniform Disorder\$.mp. (134)
 - 28 Delusional Disorder\$.mp. (42)
 - 29 Schizoaffective disorder\$.mp. (755)
 - 30 Bipolar Disorder.mp. or exp Bipolar Disorder/ (2698)
 - 31 bipolar\$.mp. (4363)
 - 32 exp AUTISM/ or autism.mp. or autistic\$.mp. (1152)
 - 33 Rett's Disorder.mp. or exp Rett Syndrome/ (18)
 - 34 rett\$.mp. (70)

- 35 childhood disintegrative disorder.mp. (1)
- 36 Asperger's disorder.mp. or exp Asperger Syndrome/ (48)
- 37 pervasive developmental disorder.mp. (51)
- 38 Conduct Disorder.mp. or exp Conduct Disorder/ (370)
- 39 Oppositional Defiant Disorder.mp. (164)
- 40 Disruptive Behavior Disorder.mp. (27)
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- 42 "Attention Deficit and Disruptive Behavior Disorders"/ or Conduct Disorder/ (330)
- 43 exp Depressive Disorder, Major/ (2533)
- 44 major depress\$.mp. (6908)
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- 46 23 and 45 (4222)
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Database: EBM Reviews - Cochrane Central Register of Controlled Trials <January 2016>

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 - 12 Delusional Disorder\$.mp. (42)
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 - 23 Oppositional Defiant Disorder.mp. (164)
 - 24 Disruptive Behavior Disorder.mp. (27)
 - 25 exp Child Development Disorders, Pervasive/ (644)
 - 26 "Attention Deficit and Disruptive Behavior Disorders"/ or Conduct Disorder/ (330)
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 - 28 major depress\$.mp. (6908)

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Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to February 12, 2016>
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 - 11 lurasidone.mp. (10)
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- 47 limit 46 to (full systematic reviews and last 4 years) (60)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to February 12, 2016>
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 - 11 Schizophreniform Disorder\$.mp. (103)
 - 12 Delusional Disorder\$.mp. (96)
 - 13 Schizoaffective disorder\$.mp. (221)
 - 14 Bipolar Disorder.mp. or exp Bipolar Disorder/ (174)
 - 15 bipolar\$.mp. (298)
 - 16 exp AUTISM/ or autism.mp. or autistic\$.mp. (91)
 - 17 Rett's Disorder.mp. or exp Rett Syndrome/ (4)
 - 18 rett\$.mp. (66)
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 - 20 Asperger's disorder.mp. or exp Asperger Syndrome/ (10)
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 - 22 Conduct Disorder.mp. or exp Conduct Disorder/ (50)
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 - 27 [exp Depressive Disorder, Major/] (0)
 - 28 major depress\$.mp. (285)
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 - 30 7 and 29 (3)
 - 31 limit 30 to full systematic reviews (3)

Database: PsycINFO <1806 to February Week 1 2016>

Search Strategy:

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 - 3 asenapine.mp. (156)
 - 4 saphris.mp. (7)
 - 5 clozapine.mp. (6852)
 - 6 clozaril.mp. (52)
 - 7 fazaclo.mp. (1)
 - 8 versacloz.mp. (0)
 - 9 iloperidone.mp. (82)
 - 10 fanapt.mp. (5)
 - 11 lurasidone.mp. (121)
 - 12 latuda.mp. (4)
 - 13 olanzapine.mp. (5518)
 - 14 zyprexa.mp. (35)
 - 15 paliperidone.mp. (384)
 - 16 invega.mp. (10)
 - 17 quetiapine.mp. (3048)
 - 18 seroquel.mp. (90)
 - 19 risperidone.mp. (6152)
 - 20 risperdal.mp. (54)
 - 21 ziprasidone.mp. (1195)
 - 22 geodon.mp. (15)
 - 23 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 (17050)
 - 24 exp SCHIZOPHRENIA/ or schizophren\$.mp. (112725)
 - 25 Psychotic Disorders/ (0)
 - 26 psychotic disorders.mp. (5456)
 - 27 Schizophreniform Disorder\$.mp. (734)
 - 28 Delusional Disorder\$.mp. (971)
 - 29 Schizoaffective disorder\$.mp. (5215)
 - 30 Bipolar Disorder.mp. or exp Bipolar Disorder/ (26667)
 - 31 bipolar\$.mp. (34450)
 - 32 exp AUTISM/ or autism.mp. or autistic\$.mp. (38174)
 - 33 Rett's Disorder.mp. or exp Rett Syndrome/ (726)
 - 34 rett\$.mp. (1216)
 - 35 childhood disintegrative disorder.mp. (115)
 - 36 Asperger's disorder.mp. or exp Asperger Syndrome/ (656)
 - 37 pervasive developmental disorder.mp. (1602)
 - 38 Conduct Disorder.mp. or exp Conduct Disorder/ (6678)
 - 39 Oppositional Defiant Disorder.mp. (2595)
 - 40 Disruptive Behavior Disorder.mp. (467)
 - 41 exp Child Development Disorders, Pervasive/ (0)
 - 42 "Attention Deficit and Disruptive Behavior Disorders"/ or Conduct Disorder/ (3750)
 - 43 exp Depressive Disorder, Major/ (0)

- 44 major depress\$.mp. (107603)
 45 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or
 41 or 42 or 43 or 44 (278247)
 46 23 and 45 (11707)
 47 limit 46 to (human and english language) (9911)
 48 limit 47 to yr="2013 -Current" (1555)

Database: PsycINFO <1806 to February Week 1 2016>

Search Strategy:

-
- 1 aristada.mp. (0)
 - 2 brexpiprazole.mp. (13)
 - 3 rexulti.mp. (0)
 - 4 cariprazine.mp. (23)
 - 5 vraylar.mp. (0)
 - 6 invega trinza.mp. (0)
 - 7 1 or 2 or 3 or 4 or 5 or 6 (35)
 - 8 exp SCHIZOPHRENIA/ or schizophren\$.mp. (112725)
 - 9 Psychotic Disorders/ (0)
 - 10 psychotic disorders.mp. (5456)
 - 11 Schizophreniform Disorder\$.mp. (734)
 - 12 Delusional Disorder\$.mp. (971)
 - 13 Schizoaffective disorder\$.mp. (5215)
 - 14 Bipolar Disorder.mp. or exp Bipolar Disorder/ (26667)
 - 15 bipolar\$.mp. (34450)
 - 16 exp AUTISM/ or autism.mp. or autistic\$.mp. (38174)
 - 17 Rett's Disorder.mp. or exp Rett Syndrome/ (726)
 - 18 rett\$.mp. (1216)
 - 19 childhood disintegrative disorder.mp. (115)
 - 20 Asperger's disorder.mp. or exp Asperger Syndrome/ (656)
 - 21 pervasive developmental disorder.mp. (1602)
 - 22 Conduct Disorder.mp. or exp Conduct Disorder/ (6678)
 - 23 Oppositional Defiant Disorder.mp. (2595)
 - 24 Disruptive Behavior Disorder.mp. (467)
 - 25 exp Child Development Disorders, Pervasive/ (0)
 - 26 "Attention Deficit and Disruptive Behavior Disorders"/ or Conduct Disorder/ (3750)
 - 27 exp Depressive Disorder, Major/ (0)
 - 28 major depress\$.mp. (107603)
 - 29 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
 or 26 or 27 or 28 (278247)
 - 30 7 and 29 (30)
 - 31 limit 30 to (human and english language) (17)

Appendix E. Excluded studies for Update 5

The following full-text publications were considered for inclusion but failed to meet the criteria for this report.

Exclusion codes: 1=Foreign language, 2=Outcome not included, 3=Intervention not included, 4=Population not included, 5=Publication type not included, 6=Study design not included, 7=Study not obtainable, 8=Outdated or ineligible systematic review

Excluded Reference	Exclusion Code
1. D1050301: A 6-week, randomized, parallel, double-blind, placebo-controlled, fixed-dose, multicenter study to evaluate the efficacy and safety of lurasidone in adolescent subjects with schizophrenia. NCT01911429.	6
2. D1050296: A randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of lurasidone as adjunctive therapy with lithium or valproate for the prevention of recurrence in patients with bipolar I depression. NCT01358357.	6
3. Acosta FJ, China E, Hernandez JL, et al. Influence of antipsychotic treatment type and regimen on the functionality of patients with schizophrenia. <i>Nord J Psychiatry</i> . 2014;68(3):180-188.	6
4. Alamo C, Lopez-Munoz F. Efficacy of extended release quetiapine in affective symptoms. <i>Rev</i> . 2012;5 Suppl 1:3-19.	1
5. Albayrak Y, Beyazyuz M, Ozturk N, Binbay Z, Kuloglu M. Comparison of serum prolactin levels between risperidone and paliperidone extended-release in female patients with schizophrenia. <i>European psychiatry</i> . 2013;28(6).	5
6. Alphas L, Benson C, Bossie C, Mao L, Starr HL. A pragmatic analysis comparing once-monthly paliperidone palmitate versus daily oral antipsychotic treatment in patients with schizophrenia. <i>Neuropsychopharmacology</i> . 2014;39(7).	6
7. Alphas L, Benson C, Cheshire-Kinney K, et al. Real-world outcomes of paliperidone palmitate compared to daily oral antipsychotic therapy in schizophrenia: a randomized, open-label, review board-blinded 15-month study. <i>J. Clin. Psychiatry</i> . 2015;76(5):554-561.	6
8. Alphas L, Bossie C, Mao L, Lee E, Starr HL. Treatment effect with paliperidone palmitate compared to oral antipsychotics in patients with early and more chronic schizophrenia. <i>Schizophr. Bull</i> . 2015;41(28).	5
9. Alphas L, Mao L, Lynn Starr H, Benson C. A pragmatic analysis comparing once-monthly paliperidone palmitate versus daily oral antipsychotic treatment in patients with schizophrenia. <i>Schizophr Res</i> . 2016;170(2-3):259-264.	6
10. Alphas L, Mao L, Rodriguez SC, Hulihan J, Starr HL. Design and rationale of the Paliperidone Palmitate Research in Demonstrating Effectiveness (PRIDE) study: a novel comparative trial of once-monthly paliperidone palmitate versus daily oral antipsychotic treatment for delaying time to treatment failure in persons with schizophrenia. <i>J. Clin. Psychiatry</i> . 2014;75(12):1388-1393.	6
11. Alphas L, Starr H, Mao L. Once-monthly paliperidone palmitate compared with oral conventional or oral atypical antipsychotic treatment in patients with schizophrenia. Poster presented at the 28th European College of Neuropsychopharmacology (ECNP), August 29-September 1, 2015, Amsterdam, The Netherlands. Study Identifier: NCT01157351. 2015.	6
12. Alphas L, Turkoz I, Fu DJ. Design of the schizophrenia disease recovery evaluation and modification (DREaM) study. <i>Biol. Psychiatry</i> . 77(9 SUPPL. 1):202S.	5

Excluded Reference	Exclusion Code
13. Amri I, Millier A, Toumi M. Minimum Clinically Important Difference in the Global Assessment Functioning in Patients with Schizophrenia. Value Health. 2014;17(7):A765-766.	3
14. Anderson JP, Joshi K, Icten Z. Treatment patterns among schizophrenia patients receiving paliperidone palmitate or atypical oral antipsychotics in community behavioral health organizations. Poster presented at the 28th Annual US Psychiatric and Mental Health Congress, September 10-13, 2015, San Diego, California. Study Identifier: PALM-OUT-110. 2015.	6
15. Arango C, Giraldez M, Merchan-Naranjo J, et al. Second-generation antipsychotic use in children and adolescents: a six-month prospective cohort study in drug-naive patients. J. Am. Acad. Child Adolesc. Psychiatry. 2014;53(11):1179-1190,1190.e1171-1174.	6
16. Asmal L, Flegar SJ, Wang J, Rummel-Kluge C, Komossa K, Leucht S. Quetiapine versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev. 2013;11:CD006625.	8
17. Awad G, Ng-Mak D, Rajagopalan K, Hsu J, Pikalov A, Loebel A. Long-term health-related quality of life improvements among patients treated with lurasidone: Results from the open-label extension of a switch trial in schizophrenia. BMC Psychiatry Vol 16 Dec 2016, ArtID 176. 2016;16.	6
18. Ayesa-Arriola R, Rodriguez-Sanchez JM, Perez-Iglesias R, et al. Long-term (3-year) neurocognitive effectiveness of antipsychotic medications in first-episode non-affective psychosis: a randomized comparison of haloperidol, olanzapine, and risperidone. Psychopharmacology (Berl). 2013;227(4):615-625.	6
19. Baker R, Okame T, Perry P, Matsushima Y, Weiller E. Switching from inadequate adjunctive treatments: Open-label study of brexpiprazole effects on depressive symptoms, cognitive and physical functioning. Eur Neuropsychopharmacol. 2015;25(29).	5
20. Baker RA, Eramo A, Tsai LF, Peters-Strickland T, Sanchez R. The effects of aripiprazole once-monthly on the PANSS Marder factors in the treatment of patients with schizophrenia. Eur. Neuropsychopharmacol. 2014;24(18).	5
21. Baker RA, Okame T, Perry P. Switching from inadequate adjunctive treatment options to brexpiprazole adjunctive to antidepressant: an open-label study on the effects on depressive symptoms and cognitive and physical functioning. Abstract presented at: the New Clinical Drug Evaluation Unit/American Society of Clinical Psychopharmacology Annual Meeting; June 22-25, 2015; Miami, FL. ClinicalTrials.gov Identifier: NCT02012218. 2015.	6
22. Bauer M, Dell'osso L, Kasper S, et al. Extended-release quetiapine fumarate (quetiapine XR) monotherapy and quetiapine XR or lithium as add-on to antidepressants in patients with treatment-resistant major depressive disorder. J. Affect. Disord. 2013;151(1):209-219.	6
23. Bianchini O, Porcelli S, Nespeca C, et al. Effects of antipsychotic drugs on insight in schizophrenia. Psychiatry Res. 2014;218(1-2):20-24.	2
24. Bloechliger M, Ruegg S, Jick SS, Meier CR, Bodmer M. Antipsychotic drug use and the risk of seizures: Follow-up study with a nested case-control analysis. CNS Drugs. 2015;29(7):591-603.	4
25. Bobo WV, Cooper WO, Stein CM, et al. Antipsychotics and the risk of type 2 diabetes mellitus in children and youth. JAMA Psychiatry. 2013;70(10):1067-1075.	6
26. Borlido C, Remington G, Graff-Guerrero A, et al. Switching From 2 antipsychotics to 1 Antipsychotic in schizophrenia: A randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2016;77(1):e14-e20.	6
27. Brown R, Taylor MJ, Geddes J. Aripiprazole alone or in combination for acute mania. Cochrane Database Syst Rev. 2013;12:CD005000.	6

Excluded Reference	Exclusion Code
28. Brunner E, Falk DM, Jones M, Dey DK, Shatapathy CC. Olanzapine in pregnancy and breastfeeding: a review of data from global safety surveillance. <i>BMC Pharmacol Toxicol.</i> 2013;14:38.	6
29. Brunner E, Tohen M, Osuntokun O, Landry J, Thase ME. Efficacy and safety of olanzapine/fluoxetine combination vs fluoxetine monotherapy following successful combination therapy of treatment-resistant major depressive disorder. <i>Neuropsychopharmacology.</i> 2014;39(11):2549-2559.	6
30. Buckley PF, Schooler NR, Goff D, et al. PROACTIVE (Preventing Relapse Oral Antipsychotics Compared to Injectables Evaluating Efficacy): Relapse, symptoms, and medication profiles over 30 months of study. <i>Schizophr. Bull.</i> 2013;39(21).	5
31. Buckley PF, Schooler NR, Goff DC, et al. Second and third relapses in a relapse prevention trial of long-acting injectable versus oral antipsychotics: A comparative analysis of successive relapses over 30 months. <i>Schizophr. Bull.</i> 2015;41(28).	5
32. Buoli M, Serati M, Altamura AC. Is the combination of a mood stabilizer plus an antipsychotic more effective than mono-therapies in long-term treatment of bipolar disorder? A systematic review. <i>J. Affect. Disord.</i> 2014;152-154:12-18.	8
33. Cai S, Lu H, Bai Z, Wu R, Zhao J. Paliperidone extended-release tablets in Chinese patients with schizophrenia: Meta-analysis of randomized controlled trials. <i>Neuropsychiatric Disease and Treatment Vol 11 Jul 2015, ArtID 1817-1834.</i> 2015;11.	8
34. Calabrese J, Rajagopalan K, Ng-Mak D, et al. Effect of lurasidone on meaningful change in health-related quality of life in patients with bipolar depression. <i>Int. Clin. Psychopharmacol.</i> 2016;31(3):147-154.	6
35. Ceskova E, Prikryl R, Libiger J. Gender differences in the pharmacotherapy of schizophrenia. <i>International journal of neuropsychopharmacology.</i> 2014;17(66).	5
36. Chang JS, Ha TH, Jung HY, Ha K. Differential changes in metabolic profile of bipolar patients following switching to aripiprazole. <i>International journal of neuropsychopharmacology.</i> 2014;17(53).	5
37. Citrome L, Kalsekar I, Baker RA, Hebden T. A review of real-world data on the effects of aripiprazole on weight and metabolic outcomes in adults. <i>Curr. Med. Res. Opin.</i> 2014;30(8):1629-1641.	6
38. Citrome L, Ota A, Nagamizu K, Perry P, Weiller E, Baker R. The effect of brexpiprazole (OPC-34712) versus aripiprazole in adult patients with acute schizophrenia: An exploratory study. <i>Biol. Psychiatry.</i> 77(9 SUPPL. 1):203S.	5
39. Clayton AH, Baker RA, Sheehan JJ, et al. Comparison of adjunctive use of aripiprazole with bupropion or selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors: analysis of patients beginning adjunctive treatment in a 52-week, open-label study. <i>BMC Res Notes.</i> 2014;7:459.	6
40. Connolly JG, Toomey TJ, Schneeweiss MC. Metabolic monitoring for youths initiating use of second-generation antipsychotics, 2003-2011. <i>Psychiatr Serv.</i> 2015;66(6):604-609.	2
41. Coppola D, Russo LJ, Kwarta RF, Jr., Varughese R, Schmider J. Evaluating the postmarketing experience of risperidone use during pregnancy: pregnancy and neonatal outcomes. <i>Drug Saf.</i> 2007;30(3):247-264.	6
42. Correll C, Cucchiario J, Silva R, Hsu J, Pikalov A, Loebel A. Long-term safety and effectiveness of lurasidone in schizophrenia: a 22-month, open-label extension study [published online ahead of print April 6, 2016]. <i>CNS Spectr.</i> 2016.	6
43. Correll CU, Cucchiario J, Silva R. Long-term safety and effectiveness of lurasidone in schizophrenia: a 22-month, open-label extension study. <i>CNS Spectrums.</i> 2016; in press. 2016.	6

Excluded Reference	Exclusion Code
44. Correll CU, Skuban A, Ouyang J. Long-term safety of brexpiprazole (OPC-34712) in schizophrenia: results from two 52-week, open-label studies. Poster presented at: the 15th International Congress on Schizophrenia Research; March 28-April 1, 2015b; Colorado Springs, Colorado. ClinicalTrials.gov Identifier: Study 1: NCT01649557 (1-6 mg); Study 2: NCT01397786 (1-4 mg). 2015.	6
45. Cutler AJ, Durgam S, Lu K, et al. Trajectory of cariprazine treatment effects across schizophrenia symptoms: Post hoc analysis of a randomized, double-blind, placebo and active-controlled trial. Schizophr. Bull. 2015;41(28).	5
46. Davis LL, Ota A, Perry P. Adjunctive brexpiprazole (OPC-34712) in patients with major depressive disorder and anxiety symptoms: an exploratory study. Poster presented at: the Society of Biological Psychiatry 70th Annual Scientific Meeting; May 14-16, 2015; Toronto, Canada. ClinicalTrials.gov Identifier: NCT02013531. 2015.	6
47. Debelle M, Faradzs-zade S, Szatmari B, et al. Cariprazine in negative symptoms of schizophrenia: Post hoc analyses of a fixed-dose, placebo and active-controlled trial. Eur Neuropsychopharmacol. 2014;24(18).	5
48. Debelle M, Faradzs-zade S, Szatmari B, et al. Cariprazine in negative symptoms of schizophrenia: Post-Hoc analyses of a fixed-dose phase III, randomized double-blind placebo and active-controlled trial. European psychiatry. 2015;30(242).	5
49. Duffy R, Ouyang J, Skuban A, Eramo A, Kane JM. Analysis of efficacy and metabolic tolerability profile from two phase 3 studies of brexpiprazole in patients with acute schizophrenia. Schizophr. Bull. 2015;41(28).	5
50. Duhig MJ, Saha S, Scott JG. Efficacy of risperidone in children with disruptive behavioural disorders. J. Paediatr. Child Health. 2013;49(1):19-26.	8
51. Durgam S, Cutler AJ, Lu K, et al. Cariprazine in acute exacerbation of schizophrenia: a fixed-dose, phase 3, randomized, double-blind, placebo- and active-controlled trial. J Clin Psychiatry. 2015;76(12):e1574-1582.	6
52. Durgam S, Earley W, Guo H, et al. Efficacy and safety of adjunctive cariprazine in inadequate responders to antidepressants: A randomized, double-blind, placebo-controlled study in adult patients with major depressive disorder. J Clin Psychiatry. 2016;77(3):371-378.	6
53. Durgam S, Earley W, Lipschitz A, et al. An 8-Week Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Cariprazine in Patients With Bipolar I Depression. Am J Psychiatry. 2016;173(3):271-281.	6
54. Durgam S, Laszlovszky I, Nagy K, Lu K, Volk S, Litman R. Categorical improvements in severity of mania and schizophrenia symptoms: Pooled analyses of cariprazine phase II/III trials. International journal of neuropsychopharmacology. 2014;17(54).	5
55. Durgam S, Litman RE, Papadakis K, Li D, Nemeth G, Laszlovszky I. Cariprazine in the treatment of schizophrenia: A proof-of-concept trial. Int Clin Psychopharmacol. 2016;31(2):61-68.	6
56. Emsley R, Chiliza B, Asmal L, Mashile M, Fusar-Poli P. Long-acting injectable antipsychotics in early psychosis: a literature review. Early Interv Psychiatry. 2013;7(3):247-254.	8
57. Ennis ZN, Damkier P. Pregnancy exposure to olanzapine, quetiapine, risperidone, aripiprazole and risk of congenital malformations. A systematic review. Basic Clin Pharmacol Toxicol. 2015;116(4):315-320.	8

Excluded Reference	Exclusion Code
58. Eramo A, Skuban A, Ouyang J. Incidence, onset, duration and severity of akathisia of brexpiprazole (OPC-34712) in acute schizophrenia: a pooled analysis of two pivotal studies. Abstract presented at: the New Clinical Drug Evaluation Unit/American Society of Clinical Psychopharmacology Annual Meeting; June 22-25, 2015; Miami, FL. ClinicalTrials.gov Identifier: Study 3/Study 231: NCT01396421; Study 4/Study 230: NCT01393613. 2015.	6
59. Eriksson H, Weiller E, Weiss C. Efficacy and safety of brexpiprazole (OPC-34712) as adjunctive treatment in major depressive disorder: pooled analysis of two pivotal studies. Poster presented at: the American Psychiatric Association 168th Annual Meeting; May 16-20, 2015; Toronto, Canada. ClinicalTrials.gov Identifier: Study 1/Study 228: NCT01360645 (2 mg); Study 2/Study 227: NCT01360632 (1 mg and 3 mg). 2015.	6
60. Ernst Nielsen R, Odur F, Ostergaard T, Munk-Jorgensen P, Nielsen J. Comparison of the effects of Sertindole and Olanzapine on Cognition (SEROLA): A double-blind randomized 12-week study of patients diagnosed with schizophrenia. Therapeutic Advances in Psychopharmacology. 2014;4(1):4-14.	4
61. Falissard B, Sapin C, Loze J-Y, Landsberg W, Hansen K. Defining the minimal clinically important difference (MCID) of the Heinrichs-carpenter quality of life scale (QLS). Int J Methods Psychiatr Res. 2016;25(2):101-111.	3
62. Farmer CA, Brown NV, Gadow KD, et al. Comorbid symptomatology moderates response to risperidone, stimulant, and parent training in children with severe aggression, disruptive behavior disorder, and attention-deficit/hyperactivity disorder. J. Child Adolesc. Psychopharmacol. 2015;25(3):213-224.	6
63. Farooq S, Singh SP. Fixed dose-combination products in psychiatry: Systematic review and meta-analysis. J. Psychopharmacol. (Oxf). 2015;29(5):556-564.	6
64. Fava M, Durgam S, Mergel V, Earley W, Nemeth G, Laszlovszky I. Efficacy and safety of cariprazine as adjunctive therapy in major depressive disorder: A double-blind, placebo-controlled study. Neuropsychopharmacology. 2014;39(7).	5
65. Fava M, Weiller E, Zhang P, Weiss C. The effect of adjunctive brexpiprazole (OPC-34712) on depressive symptoms in patients with irritability: results from post-hoc analyses. Poster presented at: the New Clinical Drug Evaluation Unit/American Society of Clinical Psychopharmacology Annual Meeting; June 22-25, 2015; Miami, FL. ClinicalTrials.gov Identifier: Study 1/Study 228: NCT01360645 (2 mg); Study 2/Study 227: NCT01360632 (1 mg and 3 mg). 2015.	6
66. Fervaha G, Foussias G, Agid O, Remington G. Motivational and neurocognitive deficits are central to the prediction of longitudinal functional outcome in schizophrenia. Acta Psychiatr. Scand. 2014;130(4):290-299.	6
67. Findling RL, Cavus I, Pappadopulos E, et al. Ziprasidone in adolescents with schizophrenia: results from a placebo-controlled efficacy and long-term open-extension study. J. Child Adolesc. Psychopharmacol. 2013;23(8):531-544.	6
68. Findling RL, Landbloom RP, Mackle M, et al. Safety and Efficacy from an 8 Week Double-Blind Trial and a 26 Week Open-Label Extension of Asenapine in Adolescents with Schizophrenia. J. Child Adolesc. Psychopharmacol. 2015;25(5):384-396.	6
69. Findling RL, Pathak S, Earley WR, Liu S, DelBello M. Safety, tolerability, and efficacy of quetiapine in youth with schizophrenia or bipolar I disorder: a 26-week, open-label, continuation study. J. Child Adolesc. Psychopharmacol. 2013;23(7):490-501.	6
70. Fleischhacker WW, Sanchez R, Jin N, et al. Personal and social performance in schizophrenia: Double-blind, non-inferiority study of once-monthly vs oral aripiprazole. Eur. Neuropsychopharmacol. 2013;23(5).	5

Excluded Reference	Exclusion Code
71. Fleischhacker WW, Sanchez R, Lan-Feng T, et al. Safety and effectiveness of aripiprazole oncemonthly for the treatment of schizophrenia: A pooled analysis of two double-blind, randomized, controlled trials (246 and 247). <i>Neuropsychopharmacology</i> . 2013;38(8).	5
72. Fleischhacker WW, Sanchez R, Perry PP, et al. Aripiprazole once-monthly for the treatment of schizophrenia: A double-blind, randomized, noninferiority study versus oral aripiprazole. <i>CNS spectrums</i> . 2013;18(6):376.	5
73. Gao K, Yuan C, Wu R, et al. Important clinical features of atypical antipsychotics in acute bipolar depression that inform routine clinical care: a review of pivotal studies with number needed to treat. <i>Neurosci Bull</i> . 2015;31(5):572-588.	8
74. Geddes JR, Briess D. Bipolar disorder. <i>Clin Evid (Online)</i> . 2007.	8
75. Gentile S. Adverse effects associated with second-generation antipsychotic long-acting injection treatment: a comprehensive systematic review. <i>Pharmacotherapy: The Journal of Human Pharmacology & Drug Therapy</i> . 2013;33(10):1087-1106.	8
76. Gentile S. A safety evaluation of aripiprazole for treating schizophrenia during pregnancy and puerperium. <i>Expert Opin Drug Saf</i> . 2014;13(12):1733-1742.	5
77. Gerhard T, Huybrechts K, Olfson M, et al. Comparative mortality risks of antipsychotic medications in community-dwelling older adults. <i>Br. J. Psychiatry</i> . 2014;205(1):44-51.	4
78. Girardi P, Serafini G. Enhancing stability in bipolar disorder. <i>Journal of Psychopathology / Giornale di Psicopatologia</i> . 2013;19(2):172-184.	3
79. Goldstein DJ, Corbin LA, Fung MC. Olanzapine-exposed pregnancies and lactation: early experience. <i>J. Clin. Psychopharmacol</i> . 2000;20(4):399-403.	6
80. Gopal S, Hough D, Karcher K, et al. Risk of cardiovascular morbidity with risperidone or paliperidone treatment: analysis of 64 randomized, double-blind trials. <i>J. Clin. Psychopharmacol</i> . 2013;33(2):157-161.	6
81. Gopal S, Xu H, Bossie C, et al. Incidence of tardive dyskinesia: a comparison of long-acting injectable and oral paliperidone clinical trial databases. <i>Int. J. Clin. Pract</i> . 2014;68(12):1514-1522.	6
82. Grunder G, Heinze M, Cordes J, Ruther E, Timm J. The "neuroleptic strategy study" (NeSSy)-first vs. Second generation antipsychotics for the treatment of schizophrenia. <i>Neuropsychopharmacology</i> . 2014;39(7).	5
83. Guelfucci F, Watt M, Vimont A, Roiz J, Cadi-Soussi N. Comparative efficacy and metabolic side effects of lurasidone for the management of acute schizophrenia: A systematic literature review and mixed treatment comparison with first and second generation antipsychotics. <i>Value Health</i> . 2013;16(7):A542-A543.	5
84. Habermann F, Fritzsche J, Fuhlbruck F, et al. Atypical antipsychotic drugs and pregnancy outcome: a prospective, cohort study. <i>J. Clin. Psychopharmacol</i> . 2013;33(4):453-462.	6
85. Han X, Yuan YB, Yu X, et al. The Chinese First-Episode Schizophrenia Trial: background and study design. <i>East Asian arch</i> . 2014;24(4):169-173.	6
86. Harvey P, Siu CO, Cucchiario J, Pikalov A, Loebel A. Impact of improved insight in schizophrenia: A double-blind lurasidone and quetiapine XR study. <i>Eur. Neuropsychopharmacol</i> . 2013;23(5).	5
87. Harvey PD, Siu CO, Hsu J, Cucchiario J, Maruff P, Loebel A. Effect of lurasidone on neurocognitive performance in patients with schizophrenia: a short-term placebo- and active-controlled study followed by a 6-month double-blind extension. <i>Eur. Neuropsychopharmacol</i> . 2013;23(11):1373-1382.	4

Excluded Reference	Exclusion Code
88. Hassan M. Comparison of treatment adherence among new-start patients on lurasidone vs other atypical antipsychotics: Results from a multi-state Medicaid population among adults with schizophrenia. Poster presented at U.S. Psychiatric and Mental Health Congress, September 30 - October 3, 2013; Las Vegas, NV. 2013.	5
89. Hassan M. Inpatient admissions among schizophrenia patients before and after initiating lurasidone in a multi-state Medicaid population. Poster presented at U.S. Psychiatric and Mental Health Congress, September 30 - October 3, 2013; Las Vegas, NV. 2013.	6
90. Hassan M. Changes in cardiometabolic parameters and metabolic syndrome status in patients with schizophrenia switching from other antipsychotics to lurasidone. Poster presented at American Psychiatric Association, May 18 - 22, 2013; San Francisco, CA. 2013.	6
91. Hassan M. Treatment adherence among patients initiated on lurasidone vs other atypical antipsychotics: Results from a multi-state Medicaid population among adults with bipolar disorder. Poster presented at U.S. Psychiatric and Mental Health Congress, September 30 - October 3, 2013; Las Vegas, NV. 2013.	5
92. Hassan M. Six-month evaluation of changes in inpatient admissions among patients with bipolar disorder who switched to lurasidone in a commercial health plan population. Poster presented at Academy of Managed Care Pharmacy, April 2 - 4, 2014; Tampa, FL. 2014.	6
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Appendix F. Strength of evidence for Update 5

Table 1: Asenapine compared to olanzapine for treatment of bipolar disorder in adults

Domains pertaining to strength of evidence					Magnitude of effect	Strength of evidence
Number of studies; Number of subjects	Risk of bias (design/quality)	Consistency	Directness	Precision	Summary effect size (95% CI)	High, moderate, low, insufficient
Response ($\geq 50\%$ improvement from baseline in YMRS)						
1; 504	Moderate	Unknown	Direct	Precise	No difference in response (90% vs. 92%; RR 0.98, 95% CI 0.92 to 1.04).	Low
Quality of life						
1; 504	Moderate	Unknown	Direct	Imprecise	No difference in mean SF-12 scores.	Insufficient
Extrapyramidal symptoms						
1; 504	Moderate	Unknown	Direct	Imprecise	No difference between groups (15% vs. 13%; RR 1.14, 95% CI 0.70 to 1.84)	Insufficient
Withdrawal due to adverse events						
1; 504	Moderate	Unknown	Direct	Imprecise	No difference between groups (13% vs. 10%; RR 1.38, 95% CI 0.80 to 2.38)	Insufficient

Table 2: Olanzapine compared to risperidone for treatment of bipolar disorder in adults

Domains pertaining to strength of evidence					Magnitude of effect	Strength of evidence
Number of studies; Number of subjects	Risk of bias (design/quality)	Consistency	Directness	Precision	Summary effect size (95% CI)	High, moderate, low, insufficient
Response ($\geq 50\%$ improvement from baseline in YMRS)						
1; 329	Moderate	Unknown	Direct	Precise	No difference in response (62% vs. 60%; RR 1.03, 95% CI 0.87 to 1.23)	Low
Quality of life						
1; 329	Moderate	Unknown	Indirect	Imprecise	No difference in mean SF-12 scores.	Insufficient
Withdrawal due to adverse events						
1; 329	Moderate	Unknown	Indirect	Imprecise	No difference (5% vs. 9%; RR 0.64, 95% CI 0.28 to 1.43)	Insufficient

Table 3: Paliperidone compared to olanzapine for treatment of bipolar disorder in adults

Domains pertaining to strength of evidence					Magnitude of effect	Strength of evidence
Number of studies; Number of subjects	Risk of bias (design/ quality)	Consistency	Directness	Precision	Summary effect size (95% CI)	High, moderate, low, insufficient
Response ($\geq 50\%$ improvement from baseline in YMRS)						
1; 235	Moderate	Unknown	Direct	Imprecise	No difference in response (numbers NR).	Insufficient
Extrapyramidal symptoms						
1; 235	Moderate	Unknown	Indirect	Precise	Greater with paliperidone than olanzapine (34% vs. 16%; RR 2.18, 95% CI 1.47 to 3.22)	Low
Withdrawal due to adverse events						
1; 235	Moderate	Unknown	Indirect	Imprecise	No difference (3% vs. 8%; RR 0.39, 95% CI 0.13 to 1.19)	Insufficient

Table 4: Paliperidone compared to quetiapine for treatment of bipolar disorder in adults

Domains pertaining to strength of evidence					Magnitude of effect	Strength of evidence
Number of studies; Number of subjects	Risk of bias (design/ quality)	Consistency	Directness	Precision	Summary effect size (95% CI)	High, moderate, low, insufficient
Response ($\geq 50\%$ improvement from baseline in YMRS)						
1; 493	Moderate	Unknown	Direct	Imprecise	No difference (65% vs. 58%; RR 1.12, 95% CI 0.95 to 1.31).	Insufficient
Withdrawal due to adverse events						
1; 493	Moderate	Unknown	Indirect	Imprecise	No difference (5% vs. 6%; RR 0.85, 95% CI 0.36 to 2.00).	Insufficient

Table 5: Olanzapine compared to risperidone for treatment of bipolar disorder in children

Domains pertaining to strength of evidence					Magnitude of effect	Strength of evidence
Number of studies; Number of subjects	Risk of bias (design/ quality)	Consistency	Directness	Precision	Summary effect size (95% CI)	High, moderate, low, insufficient
Response ($\geq 30\%$ improvement from baseline in YMRS)						
1; 31	Moderate	Unknown	Direct	Imprecise	No difference in response (53% vs. 69%; RR 0.78, 95% CI 0.44 to	Insufficient

Domains pertaining to strength of evidence					Magnitude of effect	Strength of evidence
					1.38)	
Weight change						
1; 31	Moderate	Unknown	Direct	Imprecise	No difference in weight gain between groups (3.2 vs. 2.2 kg, p=0.2)	Insufficient
Withdrawal due to adverse events						
1; 31	Moderate	Unknown	Direct	Imprecise	Greater discontinuation in olanzapine group 40% vs. 6%; RR 5.65, 95% CI 0.76 to 41.89), mostly due to lack of efficacy.	Insufficient

Table 6: Aripiprazole compared with risperidone in autism spectrum disorder

Domains pertaining to strength of evidence					Magnitude of effect	Strength of evidence
Number of studies; Number of subjects	Risk of bias (design/ quality)	Consistency	Directness	Precision	Summary effect size (95% CI)	High, moderate, low, insufficient
Outcome 1. ABC-Irritability, Agitation, Crying						
1; 59	Moderate	Unknown	Direct	Imprecise	-2.6 (p=0.5)	Insufficient
Outcome 2. ABC-Lethargy/Social Withdrawal						
1; 59	Moderate	Unknown	Direct	Imprecise	-1.0 (p=0.5)	Insufficient
Outcome 3. ABC-Stereotypic Behavior						
1; 59	Moderate	Unknown	Direct	Imprecise	0.4 (p=0.6)	Insufficient
Outcome 4. ABC-Hyperactivity/Noncompliance						
1; 59	Moderate	Unknown	Direct	Imprecise	0.9 (p=0.06)	Insufficient
Outcome 5. ABC-Inappropriate Speech						
1; 59	Moderate	Unknown	Direct	Imprecise	-0.5 (p=0.3)	Insufficient
Outcome 6. CGI-Improvement						
1; 59	Moderate	Unknown	Direct	Imprecise	No difference (p=0.3)	Insufficient
Outcome 7. Weight Change						
1; 59	Moderate	Unknown	Direct	Imprecise	No difference (p=0.5)	Insufficient
Outcome 8. Withdrawal due to Adverse Events						
1; 59	Moderate	Unknown	Direct	Imprecise	1/27 vs. 1/29 RR 1.07 (0.07, 16)	Insufficient
Outcome 9. Dyskinesia						
1; 59	Moderate	Unknown	Direct	Imprecise	1/27 vs. 2/29 RR 0.54 (0.05, 5.59)	Insufficient

Evidence Table 1. Data abstraction of randomized controlled trials in patients with schizophrenia

Author, Year Country Trial name (Quality rating)	Population	Interventions Duration	Age Gender Ethnicity	Other population characteristics	N
Citrome, 2016 ¹ U.S. (Fair)	Adult patients (18 to 65 y) with DSM-IV-TR diagnosis of schizophrenia confirmed by the MINI International Neuropsychiatric Interview.	Brexpiprazole 3 mg/d (N=64) vs. Aripiprazole 15 mg/d (N=33) Duration: 6 w	Age, y: 42.2 Gender, % Female: 29.2% Ethnicity, %: White: 23.1% African-American: 73.9% Asian: 0.8% Other: 2.3%	PANSS total score baseline, mean: 93.7 Duration of current episode: 3.1 w	97
Di Fiorino 2014 ² Italy (Fair)	Adults (aged 18 to 65 y) with a documented DSM-IV diagnosis of diagnosis of schizophrenia or schizoaffective disorder.	Quetiapine extended-release 400 to 800 mg/day (n=109) vs. Risperidone 4 to 6 mg/day (n=107) Duration: 12 w	Age, y: 42.3 Gender, % female: 43.3 Ethnicity, %: White: 100	PANSS severity of illness score: 101.4 Schizoaffective, %: 47.7	216

Evidence Table 1. Data abstraction of randomized controlled trials in patients with schizophrenia

Author, Year Country Trial name (Quality rating)	Efficacy/effectiveness outcomes	Harms
Citrome, 2016 ¹ U.S. (Fair)	Brexipiprazole vs. Aripiprazole Change in baseline PANSS total score, LS mean at 6 w: -22.9; P<0.0001 vs. -19.4; P<0.0001 Response rate at 6 w, % (n/N)*: 60.9% (39/64), (95% CI 47.9 to 72.9) vs. 48.5% (16/33), (95% CI 30.8 to 66.5)	Brexipiprazole vs. Aripiprazole Overall AEs, % (n/N): 57.8% (37/64) vs. 63.6% (21/33) Withdrawal due to AEs, % (n/N): 4.7% (3/64) vs. 3.0% (1/33) All-cause mortality: 0 vs. 0 Clinically relevant weight gain (≥7% increase from baseline) at 6 w, % (n/N): 35% (14/40) vs. 19% (4/21) Extrapyramidal AEs, % (n/N): 14.1% (9/64) vs. 30.3% (10/33). Simpson Angus, Abnormal Involuntary Movement, and BARS global clinical assessment scales used but no differences were found between them.
Di Fiorino 2014 ² Italy (Fair)	Quetiapine extended-release 400 to 800 mg/day vs. Risperidone 4 to 6 mg/day PANSS total score, LSM (SD): -30.0 (22.9) vs. -21.1 (23.8) Treatment difference: -8.9, P=0.0002	Quetiapine extended-release 400 to 800 mg/day vs. Risperidone 4 to 6 mg/day Overall AE, n/N (%): 40/107 (37.4) vs. 36/103 (35.0) Withdrawals due to AE, n/N (%): 10/107 (9.4) vs. 7/103 (6.8)

Evidence Table 1. Data abstraction of randomized controlled trials in patients with schizophrenia

Author, Year Country Trial name (Quality rating)	Funding/Comments
Citrome, 2016 ¹ U.S. (Fair)	Funding: Otsuka Pharmaceutical Commercialization and Development Inc.; H. Lundbeck A/S *Reduction of 30% or more from baseline in PANSS total score, or CGI-I score of 1 or 2.
Di Fiorino 2014 ² Italy (Fair)	AstraZeneca Italy *Included disorientation, psychotic disorder, delusion, and extrapyramidal syndrome vs. fainting, acute psychosis, acute respiratory failure, social stay hospitalization, and cardiocirculatory arrest

Evidence Table 1. Data abstraction of randomized controlled trials in patients with schizophrenia

Author, Year Country Trial name (Quality rating)	Population	Interventions Duration	Age Gender Ethnicity	Other population characteristics	N
Durgam, 2014 ³ U.S., Eurasia (Fair)	Adults ages 18 to 60 years with schizophrenia (first episode excluded).	Cariprazine 1.5 mg/day (n=145) vs. Cariprazine 3.0 mg/day (n=146) vs. Cariprazine 4.5 mg/day (n=147) vs. Risperidone 4.0 mg/day (n=140) (Placebo arm also included.) Duration: 6 w	Age, mean y: 36.5 Gender, % female: 31.0 Ethnicity, %: White: 50.0 African American: 24.0% Asian: 25.0 Other: 0.7 (Placebo arm excluded.)	Duration of illness: 11.5 y Duration of current illness/psychosis: less than 2 weeks to be eligible Hospitalization data (current): NR Severity of illness: 97.3 (PANSS) Schizoaffective: 0% (excluded) Substance use: 0% (excluded) Antipsychotic drug naïve: first episode of psychosis excluded	578 (active treatment arms)

Evidence Table 1. Data abstraction of randomized controlled trials in patients with schizophrenia

Author, Year Country Trial name (Quality rating)	Efficacy/effectiveness outcomes	Harms
Durgam, 2014 ³ U.S., Eurasia (Fair)	<p>Cariprazine 1.5 mg/day vs. Cariprazine 3.0 mg/day vs. Cariprazine 4.5 mg/day vs. Risperidone 4.0 mg/day</p> <p>PANSS responders (≥30% improvement from baseline): % (n/N) 31.4 (44/140) vs. 35.7 (50/140) vs. 35.9 (52/145) vs. 43.5 (60/138) (No P-values comparing active treatments reported.)</p>	<p>Cariprazine 1.5 mg/day vs. Cariprazine 3.0 mg/day vs. Cariprazine 4.5 mg/day vs. Risperidone 4.0 mg/day</p> <p>Treatment-emergent adverse events: % (n/N) 68.3 (99/145) vs. 71.2 (104/146) vs. 73.5 (108/147) vs. 67.9 (95/140)</p> <p>WAE: % (n/N) 9.7 (14/145) vs. 5.5 (8/146) vs. 8.2 (12/147) vs. 9.3 (13/140)</p> <p>Extrapyramidal disorder (treatment-emergent): 9.0 (13/145) vs. 8.9 (13/146) vs. 11.6 (17/142) vs. 12.9 (18/140)</p>

Evidence Table 1. Data abstraction of randomized controlled trials in patients with schizophrenia

Author, Year Country Trial name (Quality rating)	Funding/Comments
Durgam, 2014 ³ U.S., Eurasia (Fair)	Forest Research Institute and Gedeon Richter Plc.

Evidence Table 1. Data abstraction of randomized controlled trials in patients with schizophrenia

Author, Year Country Trial name (Quality rating)	Population	Interventions Duration	Age Gender Ethnicity	Other population characteristics	N
Fleischhacker, 2014 ⁴ International ASPIRE EU, NCT00706654 (Fair)	Adults 18 to 60 y, DSM-IV-TR schizophrenia for ≥3 y and a history of symptom exacerbation when not receiving antipsychotic treatment.	Aripiprazole once-monthly 400 mg (n = 265) vs. Oral aripiprazole 10 to 30 mg/day (n = 266) vs. Aripiprazole once-monthly 50 mg (n = 131) Duration: 38 w	Age, mean y: 41.0 Gender, % female: 38.7 Ethnicity, %: White: 58.5 Black or African American: 23.1 Asian: 10.4 Other: 8.0	PANSS total score, mean: 56.9 CGI-Severity score, mean: 3.07 CGI-Improvement score, mean: 3.2	662

Evidence Table 1. Data abstraction of randomized controlled trials in patients with schizophrenia

Author, Year Country Trial name (Quality rating)	Efficacy/effectiveness outcomes	Harms
Fleischhacker, 2014 ⁴ International ASPIRE EU, NCT00706654 (Fair)	Aripiprazole once-monthly 400 mg vs. Oral aripiprazole (10 to 30 mg/day) vs. Aripiprazole once-monthly 50 mg Estimated relapse rate, %: 7.12 vs. 7.76 vs. 21.80 Treatment difference: -0.6 (95% CI -5.26 to 3.99) Discontinued, n (%): 69 (26) vs. 83 (33.1) vs. 70 (53.4) Observed impending relapse (ITT sample): 22/265 (8.30) vs. 21/266 (7.89) vs. 29/131 (22.14); HR (vs. aripiprazole once-monthly 50 mg) 3.158 (95% CI 1.81 to 5.50) vs. 3.131 (95% CI 1.78 to 5.49) Responders (ITT sample), %: 237/264 (89.8) vs. 235/263 (89.4) vs. 97/129 (75.2) Remitters (ITT sample), %: 105/215 (48.8) vs. 107/201 (53.2) vs. 43/72 (59.7) PANSS Total Score (efficacy sample, LOCF): Change from baseline at w 38, least square mean (SE): -1.66 (0.72) vs. 0.58 (0.71) vs. 3.08 (1.01) CGI Severity (efficacy sample, LOCF): Change from baseline at w 38, least square mean (SE): -0.13 (0.05) vs. 0.05 (0.05) vs. 0.23 (0.07) CGI Improvement (efficacy sample, LOCF): At week 38, mean (SD): 3.27 (1.16) vs. 3.66 (1.16) vs. 4.02 (1.32) Safety sample, observed cases: SAS total score, change from baseline at week 38, LS mean (SE): -0.16 (0.09) vs. -0.22 (0.09) vs. -0.21 (0.16) AIMS movement rating score, change from baseline at week 38, LS mean (SE): -0.00 (0.07) vs. -0.11 (0.07) vs. -0.01 (0.12) BARS global score, change from baseline at week 38, LS mean (SE): 0.06 (0.03) vs. -0.05 (0.03) vs. -0.06 (0.06)	Aripiprazole once-monthly 400 mg vs. Oral aripiprazole (10 to 30 mg/day) vs. Aripiprazole once-monthly 50 mg Discontinued due to AE, n (%): 8 (3.0) vs. 7 (2.6) vs. 7 (5.3) Weight increased, n (%): 24 (9.1) vs. 35 (13.2) vs. 7 (5.3) Suicidality, safety sample, observed cases: CGI-SS, change from baseline at week 38, LS mean (SE): -0.01 (0.10) vs. 0.00 (0.00) vs. -0.02 (0.13) C-SSRS, change from baseline at week 38, LS mean (SE): -0.1 (1.0) vs. 0.1 (1.3) vs. 0.0 (0.0)

Evidence Table 1. Data abstraction of randomized controlled trials in patients with schizophrenia

Author, Year Country Trial name (Quality rating)	Funding/Comments
Fleischhacker, 2014 ⁴ International ASPIRE EU, NCT00706654 (Fair)	Otsuka Pharmaceutical Commercialization, Inc.

Evidence Table 1. Data abstraction of randomized controlled trials in patients with schizophrenia

Author, Year Country Trial name (Quality rating)	Population	Interventions Duration	Age Gender Ethnicity	Other population characteristics	N
Ishigooka, 2015 ⁵ Asia (Fair)	Asian adults (18 years and older) diagnosed with schizophrenia according to DSM-IV-TR criteria.	Aripiprazole 300 to 400 mg once-monthly injection (n=228)* vs. Aripiprazole 6 to 24 mg/day orally (n=227) Duration: 52 weeks (double-blind phase)	Age, y: 39.2 Gender, % female: 39.2 Ethnicity, % Asian: 100	Duration of illness (time since first episode), months (mean): 151.6 PANSS severity of illness: 53.9	455

Evidence Table 1. Data abstraction of randomized controlled trials in patients with schizophrenia

Author, Year Country Trial name (Quality rating)	Efficacy/effectiveness outcomes	Harms
Ishigooka, 2015 ⁵ Asia (Fair)	<p>Aripiprazole 300 to 400 mg monthly vs. Aripiprazole 6 to 24 mg/day</p> <p>Non-exacerbation of psychotic symptoms/non-relapse rate at week 26 (Kaplan-Meier)**: 95.0 vs. 94.7 Difference 0.3 (95% CI -3.9 to 4.5)</p> <p>Time to exacerbation of psychotic symptoms/relapse (Kaplan-Meier): HR 0.94 (95% CI 0.46 to 1.92)</p> <p>Proportion of patients achieving remission** exacerbation of psychotic symptoms/relapse, % (n/N): 6.6% (15/228) vs. 6.6% (15/227)</p> <p>Stabilization of psychotic symptoms/relapse, % (n/N): 92.5% (211/228) vs. 92.5% (210/227)</p> <p>Remission, % (n/N): 69.4% (129/228) vs. 71.1% (123/227)</p> <p>Quality of life, mean change from baseline in MOS 36-item SF-36 at week 52 Mental component: 0.82 vs. 0.38 Difference 0.44 (95% CI -1.24 to 2.12) ANCOVA Physical component: 0.23 vs. -0.27 Difference 0.50 (95% CI -1.11 to 2.11) ANCOVA</p> <p>All-cause discontinuation: 25.9% vs. 33.5% Time to all-cause discontinuation: HR 0.74 (95% CI 0.52 to 1.03)</p>	<p>Aripiprazole 300 to 400 mg monthly vs. Aripiprazole 6 to 24 mg/day</p> <p>Overall AE: % (n/N): 77.2% (176/228) vs. 79.3% (180/227) Withdrawal due to AE: % (n/N): 7.5% (17/228) vs. 11.5% (25/227) Extrapyramidal AE: % (n/N): 16.2% (40/228) vs. 14.1% (32/227) Tardive dyskinesia: % (n/N): 0 vs. 0.4% (1/227) Akathisia: % (n/N): 6.6% (12/228) vs. 6.2% (14/227)</p>

Evidence Table 1. Data abstraction of randomized controlled trials in patients with schizophrenia

Author, Year Country Trial name (Quality rating)	Funding/Comments
Ishigooka, 2015 ⁵ Asia (Fair)	Otsuka Pharmaceutical Co., Ltd. *Injection arm patients received 6 or 12 mg/day of oral aripiprazole for 2 weeks after start of randomized period **Exacerbation/relapse based on CCG-I and PANSS scores, hospitalization, violent behavior resulting in injury

Evidence Table 1. Data abstraction of randomized controlled trials in patients with schizophrenia

Author, Year Country Trial name (Quality rating)	Population	Interventions Duration	Age Gender Ethnicity	Other population characteristics	N
Koshikawa, 2016 ⁶ Japan (Fair) Companion: Takekita, 2016 ⁷	≥20 y old, DSM-IV-TR diagnosis of schizophrenia or schizoaffective disorder (nonacute phase of the disease), PANSS total score ≤120, received risperidone long-acting for ≥2 mo.	Risperidone long-acting injection, adjustable dose (upper limit of 50 mg) every 2 w (N=16) vs. Paliperidone palmitate adjustable dose (upper limit of 150 mg) every 4 w (N=14) Duration: 6 mo.	Age, y: 45.0 Gender, % female: 38.0 Ethnicity: Japanese (% NR)	Duration of illness, y*: 13.8 PANSS total score, mean: 80.6 Schizoaffective disorder, %: 5.0	30
Li, 2014 ⁸ China (Fair)	Adults (18 to 65 y) with a DSM-IV diagnosis of schizophrenia.	Aripiprazole 10 to 30 mg/day orally (n=139) vs. Risperidone 2 to 6 mg/day orally (n=140) Duration: 6 w	Age, y: 32.4 Gender, % female: 67.0 Ethnicity, %: Han Chinese 100	Duration of illness: 7.3 y PANSS severity of illness: 87.1 Schizoaffective, %: 0 Substance use, %: 0	279
Liu, 2014 ⁹ China (Fair)	Female patients (age 18 to 44 y) with first-episode schizophrenia diagnosis based on Chinese Classification of Mental Disorders-3rd edition.	Risperidone 3.4 mg/day (mean) orally (n=40) vs. Quetiapine 420 mg/day (mean) (n=40) Duration: 12 m	Age, y: 29.0 Gender, % Female: 100 Ethnicity, % Asian: 100 (Chinese)	Duration of illness, mean months: 4.5 PANSS severity of illness: 80.4	80

Evidence Table 1. Data abstraction of randomized controlled trials in patients with schizophrenia

Author, Year Country Trial name (Quality rating)	Efficacy/effectiveness outcomes	Harms
Koshikawa, 2016 ⁶ Japan (Fair) Companion: Takekita, 2016 ⁷	Risperidone long-acting injection vs. Paliperidone palmitate Koshikawa, 2016: Social Functioning Scale total score, mean change from baseline (SD): -1.64 (17.56) vs. 14.60 (18.75), P=0.038 No difference in PANSS total score between treatment groups at 6 mo. Takekita, 2016: PANSS total score, mean change from baseline to 6 mo. (SD): -5.09 (8.18) vs. -1.70 (5.08), P=0.349	Risperidone long-acting injection vs. Paliperidone palmitate Koshikawa, 2016: Overall AEs, n: 0 vs. 2 Takekita, 2016: DIEPSS** total score, mean change from baseline (SD): -0.09 (0.30) vs. 0.30 (1.06), P=0.220
Li, 2014 ⁸ China (Fair)	Aripiprazole 10 to 30 mg/day vs. Risperidone 2 to 6 mg/day PANSS responders ($\geq 30\%$ decrease in total score from baseline), n/N (%): 99/139 (71.0) vs. 107/140 (76.0); P=0.323	Aripiprazole 10 to 30 mg/day vs. Risperidone 2 to 6 mg/day Overall AE, n/N (%): 105/139 (76.0) vs. 116/140 (83.0) Withdrawal due to AE, n/N (%): 0 vs. 1/140 (<1.0) Clinically relevant weight increase ($\geq 7\%$ in body weight), n/N (%): 4/139 (3.0) vs. 17/140 (12.0) Extrapyramidal symptoms, n/N (%): 35/139 (25.0) vs. 34/140 (24.0) Akathisia, n/N (%): 32/139 (23.0) vs. 31/140 (22.0) Cardiovascular system, n/N (%): 11/139 (8.0) vs. 9/140 (6.0)
Liu, 2014 ⁹ China (Fair)	Risperidone 3.4 mg/day vs. Quetiapine 420 mg/day PANSS total score, change at 12 w: -37.2 vs. -40.9	Risperidone 3.4 mg/day vs. Quetiapine 420 mg/day Dropout rate of 20% over one-year treatment period.

Evidence Table 1. Data abstraction of randomized controlled trials in patients with schizophrenia

Author, Year Country Trial name (Quality rating)	Funding/Comments
Koshikawa, 2016 ⁶ Japan (Fair) Companion: Takekita, 2016 ⁷	Funding: NR *Duration of illness calculated based on average age at onset and average age at study enrollment. **Drug-induced extrapyramidal symptoms scale.
Li, 2014 ⁸ China (Fair)	Jiangsu Nhwa Pharmaceutical Co., Ltd and the National Key Project (2012ZX09303- 003), and the Shanghai municipal incubation grant for talented researcher of health care (XBR2011049)
Liu, 2014 ⁹ China (Fair)	Huzhou Ministry of Technology

Evidence Table 1. Data abstraction of randomized controlled trials in patients with schizophrenia

Author, Year Country Trial name (Quality rating)	Population	Interventions Duration	Age Gender Ethnicity	Other population characteristics	N
Naber, 2013 ¹⁰ International RECOVER NCT00600756 (Fair)	Adults 18 to 65 y, a DSM-IV-TR diagnosis of schizophrenia, schizoaffective disorder or schizophreniform disorder, and a certain level of reduced subjective well-being.	Quetiapine XR (400 to 800 mg) (n=395) vs. Risperidone (2 to 6 mg) (n=403) once daily Duration: 12 m	Age, mean y: 39.65 Gender, % female: 41.8 Ethnicity, %: NR	Concurrent substance abuse: Alcohol use, %: 12.1 Cannabis use, %: 1.9 DSM-IV schizophrenia subtype diagnosis, %: Schizoaffective disorder of bipolar type: 8.3 Schizoaffective disorder of depressive type: 7.8 Median duration of present episode, m: 2.5 Mean years since first known schizophrenia diagnosis: 11.35 Hospitalizations due to schizophrenia in the previous 6 months, % patients: 16.1 SWN-K total score, mean: 64.35	798

Evidence Table 1. Data abstraction of randomized controlled trials in patients with schizophrenia

Author, Year Country Trial name (Quality rating)	Efficacy/effectiveness outcomes	Harms
Naber, 2013 ¹⁰ International RECOVER NCT00600756 (Fair)	Quetiapine XR (400 to 800 mg) vs. Risperidone (2 to 6 mg) Discontinued at month 12, n (%): 183 (46.3) vs. 176 (43.7) CGI-SCH overall severity: Month 12 mean, change from baseline to m 12, mean (SD): 2.3 vs. 2.5; -1.5 (1.07) vs. -1.3 (1.15) CGI change score improved n (%): 176/379 (83.4) vs. 178/392 (78.4) Treatment effect for improved: 1.46 (95% CI 0.87 to 2.43) CDSS Total score: Month 12 mean, change from baseline to m 12, mean (SD): 1.7 vs. 2.6; -5.3 (5.10) vs. -3.8 (4.6) Treatment difference: -1.0 (95% CI -1.6 to -0.4)	Quetiapine XR (400 to 800 mg) vs. Risperidone (2 to 6 mg) Discontinued due to AE at month 12, n (%): 53 (13.4) vs. 44 (10.9) n/N (%); number of events TEAE: 238/391 (60.9); 791 vs. 258/402 (64.2); 834 TEAE leading to discontinuation: 57/391 (14.6); 72 vs. 48/402 (11.9); 80 Serious TEAE: 45/391 (11.5); 49 vs. 26/402 (6.5); 31 Serious TEAE leading to death: 0 (0) vs. 1/402 (0.2); 1 Weight increased: 18/391 (4.6); 18 vs. 25/402 (6.2); 25

Evidence Table 1. Data abstraction of randomized controlled trials in patients with schizophrenia

Author, Year Country Trial name (Quality rating)	Funding/Comments
Naber, 2013 ¹⁰ International RECOVER NCT00600756 (Fair)	AstraZeneca.

Evidence Table 1. Data abstraction of randomized controlled trials in patients with schizophrenia

Author, Year Country Trial name (Quality rating)	Population	Interventions Duration	Age Gender Ethnicity	Other population characteristics	N
Naber, 2015 ¹¹ International QUALIFY (Fair) Companion: Potkin, 2015 ¹²	Adults (18 to 60 y) with DSM-IV- TR–defined schizophrenia.	Aripiprazole 300 to 400 mg monthly injection (n=148) vs. Paliperidone 50 to 150 mg (EU/Canada) or Paliperidone palmitate 78 to 234 mg (US) monthly injection (n=147) Duration: 28 weeks	Age, y: 41.9 Gender, % female: 40.2 Ethnicity, %: White: 69.7 Black/African American: 27.0 Asian: 1.5 Other: 1.1 Unknown: 0.7	CGI-S severity of illness score: 4.0	295

Evidence Table 1. Data abstraction of randomized controlled trials in patients with schizophrenia

Author, Year Country Trial name (Quality rating)	Efficacy/effectiveness outcomes	Harms
Naber, 2015 ¹¹ International QUALIFY (Fair) Companion: Potkin, 2015 ¹²	Aripiprazole 300 to 400 mg monthly vs. Paliperidone 50-150 mg/Paliperidone palmitate 78 to 234 mg monthly Naber, 2015: Heinrichs-Carpenter Quality-of-Life total score (QLS), LSM change from baseline at week 28: 7.47 (n=136) vs. 2.80 (n=132) LSM difference 4.67 (95% CI 0.32 to 9.02) Potkin, 2015: QLS total score, difference in change from baseline to 28 w: 4.67 (95% CI 0.32 to 9.02) QLS total score, LS mean changes (SE): 7.47 (1.53) vs. 2.80 (1.62) CGI-S LS mean (SE) change from baseline to 28 w: -0.75 (0.07) vs. -0.46 (0.07) LS mean difference: -0.28 (95% CI -0.48 to -0.09) Patient-rated Tool scale, LSM treatment difference: -0.70 (95% CI: -1.51 to 0.12) Clinician-rated WoRQ total scores, LSM treatment difference: -1.16 (95% CI: -1.96 to -0.37) 'No' to 'Yes' in readiness to work at 28 w, %: 26.4 vs. 12.2	Aripiprazole 300 to 400 mg monthly vs. Paliperidone 50-150 mg/Paliperidone palmitate 78 to 234 mg monthly Naber, 2015: Overall AE: % (n/N): 62/119 (52.1%) vs. 72/109 (66.1%)* Overall withdrawal due to AE: % (n/N): 11.1% (16/148) vs. 19.7% (27/147) AE related extrapyramidal symptoms: % (n/N) Akathisia: 2.5% (2/119) vs. 1.8% (2/109)* Dystonia: 0.8% (1/119) vs. 0%* Extrapyramidal disorder: 0% vs. 0%* Muscle rigidity: 0.8% (1/119) vs. 0 Muscle spasms: 0 vs. 0.9% (1/109) Tremor: 1.7% (2/119) vs. 1.8% (2/109) Potkin, 2015: Discontinuation due to AE, n/N (%): 16/144 (11.1) vs. 27/137 (19.7) Weight increased, n/N (%): 0 (0.0) vs. 2/137 (1.5) ASEX total score mean (SD) change from baseline to 28 w: -1.9 (6.3) vs. -0.8 (6.1) Decrease in sexual dysfunction at 28 w, %: 30 vs. 4

Evidence Table 1. Data abstraction of randomized controlled trials in patients with schizophrenia

Author, Year Country Trial name (Quality rating)	Funding/Comments
Naber, 2015 ¹¹ International QUALIFY (Fair) Companion: Potkin, 2015 ¹²	H. Lundbeck A/S and Otsuka Pharmaceutical Development & Commercialization, Inc *Treatment continuation period (main period of interest with respect to safety evaluation (n=119 vs. n=109)

Evidence Table 1. Data abstraction of randomized controlled trials in patients with schizophrenia

Author, Year Country Trial name (Quality rating)	Population	Interventions Duration	Age Gender Ethnicity	Other population characteristics	N
Parabiaghi, 2016 ¹³ Italy (Fair) Companion to Parabiaghi, 2011 ¹⁴ and Parabiaghi, 2015 ¹⁵	>18 y old, DSM-IV diagnosis of schizophrenia based on the Mini-International Neuropsychiatric Interview.	Aripiprazole 19.7 mg/d* (N=100) vs. Olanzapine 13.7 mg/d* (N=103) Duration: 1 y (Haloperidol arm not abstracted)	Age, y: 42.7 Gender, % female: 42.0 Ethnicity: Italian (% NR)	Duration of illness, y from first psychiatric contact (%): 0-2 y: 12.0 3+ y: 72.0 Hospitalization, % in-patient: 20.0 Current substance abuse or dependence, %: 5.0 Antipsychotic drug-naïve, %: 6.0	300
Robinson, 2015 ¹⁶ U.S. and Canada (Fair)	Adults and adolescent (15 to 40 y) with DSM-IV-defined diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder or psychotic disorder not otherwise specified.	Aripiprazole 5 to 30 mg/day orally (n=106) vs. Risperidone 1 to 6 mg/day orally (n=103) Duration: 12 w	Age, y: 22.1 Gender, % female: 29 Ethnicity, %: Caucasian: 24.0 African-American: 37.0 Hispanic: 10.0 Other/mixed: 9.0	Duration of current illness/psychosis, w: 125.5* BPRS-A severity of illness: 45.1 Schizoaffective, %: 3 Substance use, %: 0 Antipsychotic drug naïve: lifetime antipsychotic drug medication treatment 2 w or less	209

Evidence Table 1. Data abstraction of randomized controlled trials in patients with schizophrenia

Author, Year Country Trial name (Quality rating)	Efficacy/effectiveness outcomes	Harms
Parabiaghi, 2016 ¹³ Italy (Fair) Companion to Parabiaghi, 2011 ¹⁴ and Parabiaghi, 2015 ¹⁵	NR	Aripiprazole vs. Olanzapine Metabolic syndrome at 1 y in ITT population, n/N (%): 37/100 (37.0) vs. 48/103 (46.6); OR 1.50 (95% CI 0.8 to 2.6) Withdrawals due to AEs, n (%): 6 (12.6) vs. 6 (18.8); OR 0.98 (95% CI 0.3 to 3.19)
Robinson, 2015 ¹⁶ U.S. and Canada (Fair)	Aripiprazole 5-30 mg/day vs. Risperidone 1-6 mg/day Cumulative response rate at w 12 ^{**} : 62.8% (95% CI 50.8 to 74.8) vs. 56.8% (95% CI 43.9 to 69.9) Mean time to response, w: 8.0 (95% CI 7.9 to 8.1) vs. 8.2 (95% CI 7.3 to 9.2) Discontinuation of controlled treatment before 12 weeks (n, due to safety concerns): 0 vs. 3 (1 metabolic syndrome, 1 tardive dyskinesia, 1 hematologic abnormalities)	Aripiprazole 5-30 mg/day vs. Risperidone 1-6 mg/day Sexual dysfunction, % (n/N): 7.8% (8/102) vs. 12.5% (12/96)

Evidence Table 1. Data abstraction of randomized controlled trials in patients with schizophrenia

Author, Year Country Trial name (Quality rating)	Funding/Comments
Parabiagli, 2016 ¹³ Italy (Fair) Companion to Parabiagli, 2011 ¹⁴ and Parabiagli, 2015 ¹⁵	Funding: IRCCS-Istituto di Ricerche Farmacologiche 'Mario Negri' and Bristol- Myers Squibb *Mean dose of treatment.
Robinson, 2015 ¹⁶ U.S. and Canada (Fair)	National Institutes of Health and NARSAD Young Investigator Grant to J.A.G. from the Brain & Behavior Research Foundation *Report states: "duration of psychotic symptoms before study week (weeks)" **Response criteria based on BPRS-A and CGI scores

Evidence Table 1. Data abstraction of randomized controlled trials in patients with schizophrenia

Author, Year Country Trial name (Quality rating)	Population	Interventions Duration	Age Gender Ethnicity	Other population characteristics	N
Savitz, 2015 ¹⁷ International (Fair)	Adolescents (aged 12 to 17 y) diagnosed with schizophrenia (DSM-IV criteria) for ≥1 y before screening.	Paliperidone extended release 3 to 9mg/day orally (n=113) vs. Aripiprazole 2 to 15mg/day orally (n=115) Duration: 26 w (8 w double-blind treatment phase + 18 w maintenance phase)	Age, y: 15.3 Gender, % female: 34.0 Ethnicity, %: White: 76.0 Asian: 17.0 Black/African American: 6.0 Other: <1.0 Multiple: <1.0	Duration of illness, y: 2.9 Hospitalized, %: 61.0 Duration of most recent hospitalization before double blind (mean d): 60.9 PANSS severity of illness: 90.8 Schizoaffective, %: 0 Substance use, %: 0 Antipsychotic drug naïve: 11.0% (89.0% reported prior use)	228
Savitz, 2016 ¹⁸ International (Good)	Adult patients age 18 to 70 y with a DSM-IV diagnosis of schizophrenia.	Paliperidone palmitate 3-month injection (N=504) vs. Paliperidone palmitate 1-month injection (N=512) Duration: 48 w	Age, y: 38.7 Gender, % Female: 47% Ethnicity, %: White: 58% African American: 6% American Indian: 35% Other: 1%	Prior hospitalizations, %: None: 41.0 Once: 37.0 Twice: 16.0 Three times: 3.0 Four or more: 2.0 PANSS Total Score at baseline: 85.0 (ITT); 57.8 (double blind) Previous antipsychotic use, %: 76.0 (new-generation antipsychotics)	1,016

Evidence Table 1. Data abstraction of randomized controlled trials in patients with schizophrenia

Author, Year Country Trial name (Quality rating)	Efficacy/effectiveness outcomes	Harms
Savitz, 2015 ¹⁷ International (Fair)	<p>Paliperidone extended release 3 to 9 mg/day vs. Aripiprazole 2 to 15 mg/day</p> <p>Maintenance of clinical stability at both day 56 and 182, %*: 52.0% vs. 60.0%</p> <p>Patients achieving remission at both days 56 and 182, n/N (%)**: 44/112 (39.3%) vs. 48/114 (42.1%)</p>	<p>Paliperidone extended release 3 to 9 mg/day vs. Aripiprazole 2 to 15 mg/day</p> <p>Overall AE, n/N (%): 87/113 (77.0) vs. 76/114 (66.7)</p> <p>Withdrawal due to AE, n/N (%): 5/113 (4) vs. 0</p> <p>Non-completed suicide attempts, n/N (%): 2/112 (1.8) vs. 0</p> <p>Weight gain ≥7%, n/N (%): 29/113 (26.0) vs. 21/114 (18.0)</p>
Savitz, 2016 ¹⁸ International (Good)	<p>Paliperidone palmitate 3-month injection vs. Paliperidone palmitate 1-month injection</p> <p>Relapse free patients, % (n/N)*: 8.0% (37/504) vs. 9.0% (45/512)</p> <p>Clinical response (≥20% reduction in PANSS total score), % (n/N): 50.1% (241/481) vs. 47.3% (237/501)</p> <p>≥30%: 36.4% (175/481) vs. 36.1% (181/501)</p> <p>≥40%: 26.4% (127/481) vs. 27.1% (136/501)</p> <p>Symptomatic remission (meeting Andreasen remission criteria 6 months before end of study), %: 58.0% vs. 59.0%</p> <p>Psychiatric hospitalizations, % (n/N): 3.0% (16/504) vs. 4.0% (22/512)</p>	<p>Paliperidone palmitate 3-month injection vs. Paliperidone palmitate 1-month injection</p> <p>Overall AEs, % (n/N): 68.0% (342/504) vs. 66.0% (340/512)</p> <p>Withdrawals due to AEs, % (n/N): 3.0% (15/504) vs. 3.0% (13/512)</p> <p>All-cause mortality, n: 1 vs. 3</p> <p>Diabetes mellitus/hyperglycemia, % (n/N): 2.6% (13/504) vs. 4.9% (25/512)</p> <p>Extrapyramidal AEs, % (n/N): 8.0% (42/504) vs. 7.0% (38/512)</p> <p>Weight change of ≥7%, % (n/N): 27.0% (136/504) vs. 30.0% (150/512)</p> <p>Tardive dyskinesia, n: 1 vs. 1</p>

Evidence Table 1. Data abstraction of randomized controlled trials in patients with schizophrenia

Author, Year Country Trial name (Quality rating)	Funding/Comments
Savitz, 2015 ¹⁷ International (Fair)	Janssen Research and Development, LLC *Defined as $\geq 20\%$ improvement in PANSS total score and CGI-S scores, no hospitalizations, no emergence of clinically significant suicidal or homicidal ideation **Based on PANSS scores
Savitz, 2016 ¹⁸ International (Good)	Funding: Otsuka, Janssen, Cilag, and Lundbeck *Relapse as ≥ 1 of following: 1) hospitalization for schizophrenia symptoms; 2) 25% increase in PANSS total score for patients scoring >40 or a 10-point increase for patients scoring ≤ 40 ; 3) increase PANSS items; 4) clinically significant self-injury or violent behavior resulting in suicide, injury, or damage; 5) suicidal/homicidal ideation

Evidence Table 1. Data abstraction of randomized controlled trials in patients with schizophrenia

Author, Year Country Trial name (Quality rating)	Population	Interventions Duration	Age Gender Ethnicity	Other population characteristics	N
Shoja Shafti, 2015 ¹⁹ Iran (Fair)	Female inpatients diagnosed as having schizophrenia, according to the DSM-V.	Aripiprazole 5 to 25 mg/day orally (n=25) vs. Quetiapine 25 to 600 mg/day (n=25) Duration: 12 w	Age, y: 36.8 Gender, % female: 100 Ethnicity: NR	Duration of illness, y: 6.4 Hospitalization, %: 100 CGI-S severity of illness: 3.74 Schizoaffective, %: 0	50
Subotnik, 2015 ²⁰ United States (Fair)	Adults (18 to 45 y) with DSM-IV diagnosis of schizophrenia, schizoaffective disorder, mainly depressed type, or schizophreniform disorder, with an onset of psychosis within the last 2 y.	Risperidone modal dosage 25 mg/2 w (12.5 to 37.5 mg) long acting injectable (n=43) vs. Risperidone modal dosage 2 mg/day (1.0 to 7.5mg) oral (n=43) Both arms subsequently randomized in cognitive remediation or healthy-behaviors training. Duration: 12 m	Age, y: 21.5 Gender, % female: 22.0 Ethnicity, %: White: 49.0 Asian: 11.0 Native American: 5.0 African American: 28.0 Pacific Islander: 1.0 Mixed: 6.0	Duration of illness, m: 7.4 (time since psychosis onset) Severity of illness (BPRS): Thought disturbance factor at randomization: 2.1 Withdrawal-retardation factor at randomization: 1.9 Schizophrenia, %: 55.0 Schizophreniform disorder, %: 33.0 Schizoaffective, %: 12.0 Substance use, %: 0	86

Evidence Table 1. Data abstraction of randomized controlled trials in patients with schizophrenia

Author, Year Country Trial name (Quality rating)	Efficacy/effectiveness outcomes	Harms
Shoja Shafti, 2015 ¹⁹ Iran (Fair)	NR	Aripiprazole 5 to 25 mg/day vs. Quetiapine 25 to 600 mg Withdrawal due to AE, n/N (%): 0 vs. 0
Subotnik, 2015 ²⁰ United States (Fair)	Risperidone 25 mg/2 w long acting vs. Risperidone 2 mg/day Psychotic exacerbation/relapse, n/N (%)*: 2/40 (5.0) vs. 14/43 (33.0); P<0.001 Hospitalizations due to mental illness, n/N (%): 2/40 (5.0) vs. 8/43 (18.6); P=0.05 Early discontinuation due to inadequate treatment response, n/N (%): 1/40 (2.5) vs. 7/42 (17.0), P=0.01 Risk of exacerbation and/or relapse over time was significantly lower for long-acting injectable risperidone than for oral risperidone: P<0.004 Mean time to relapse, d: 298.5 vs. 218.6 Medication adherence was better for long-acting risperidone vs. oral risperidone: P<0.001 Medication adherence was associated with prevention of exacerbation and/or relapse (P=0.003) and control of breakthrough psychotic symptoms (P=0.04).	Risperidone 25 mg/2 w long acting vs. Risperidone 2 mg/day WAE, n/N (%): 4/40 (10.0) vs. 9/43 (21.0)

Evidence Table 1. Data abstraction of randomized controlled trials in patients with schizophrenia

Author, Year Country Trial name (Quality rating)	Funding/Comments
Shoja Shafti, 2015 ¹⁹ Iran (Fair)	Research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors
Subotnik, 2015 ²⁰ United States (Fair)	NIH and Janssen Scientific Affairs, LLC *Based on BPRS scale

Evidence Table 1. Data abstraction of randomized controlled trials in patients with schizophrenia

Author, Year Country Trial name (Quality rating)	Population	Interventions Duration	Age Gender Ethnicity	Other population characteristics	N
Tybura, 2014 ²¹ Poland (Fair)	Caucasian patients of Polish descent suffering from paranoid schizophrenia. Diagnosis based on Polish version of the CIDI and the ICD-10 criteria.	Ziprasidone 120 to 160mg/day orally (n=59) vs. Olanzapine 10 to 20 mg/day orally (n=72) vs. Perazine 300 to 600mg/day orally (n=60) Duration: 12 w	Age, y: 35.8 Gender, % female: 55.1 Ethnicity, %: Caucasian: 100 (Polish descent)	Duration of illness: 9.9 y* PANSS severity of illness: 99.8 Schizoaffective, %: 0 Antipsychotic drug naïve, %: 0	191
Wani, 2015 ²² India (Fair)	Adult patients with schizophrenia who had achieved clinical stability with olanzapine and who were assessed as having metabolic syndrome using modified NCEP ATP-III criteria. Schizophrenia diagnoses were made using the DSM IV.	Olanzapine 10 to 20 mg/day orally (n=31) vs. Aripiprazole 5 to 20mg/day orally (n=31)* Duration: 24 w	Age, y: 29.8 Gender, % female: 37.1 Ethnicity: Asian (Indian)	Duration of illness: 4.75 y PANSS severity of illness: 68.9 Antipsychotic drug naïve, %: 0	62

Evidence Table 1. Data abstraction of randomized controlled trials in patients with schizophrenia

Author, Year Country Trial name (Quality rating)	Efficacy/effectiveness outcomes	Harms
Tybura, 2014 ²¹ Poland (Fair)	Ziprasidone 120 to 160mg/day vs. Olanzapine 10 to 20 mg/day vs. Perazine 300 to 600mg/day All-cause discontinuation at week 12, n/N (%)**: 41/60 (68.0) vs. 52/72 (76.0) vs. 40/59 (68.0)	NR
Wani, 2015 ²² India (Fair)	Olanzapine 10 to 20 mg/day vs. Aripiprazole 5 to 20mg/day All-cause hospitalization, n/N %: 2/26 (7.7) vs. 2/21 (9.5)	Olanzapine 10 to 20 mg/day vs. Aripiprazole 5 to 20mg/day Patients meeting modified NCEP ATP-III criteria for the presence of metabolic syndrome, n/N (%)**: 26/26 (100) vs. 15/31 (42.8); P<0.001

Evidence Table 1. Data abstraction of randomized controlled trials in patients with schizophrenia

Author, Year Country Trial name (Quality rating)	Funding/Comments
Tybura, 2014 ²¹ Poland (Fair)	Pfizer Independent Research Grant *Based mean age upon entering trial and mean age of first psychotic episode **Based on retention rate
Wani, 2015 ²² India (Fair)	Funding NR *With accompanying reduction of continuing olanzapine (reduction from 25% to 100% after 3 weeks **Based on modified NCEP ATP-III criteria for the Asian population (waist circumference, triglycerides, HDL, Systolic BP, fasting glucose)

Evidence Table 2. Quality assessment of randomized controlled trials in patients with schizophrenia

Author, Year Study Name	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors blinded?	Clinician blinded?	Patient blinded?	Intention to treat?	Acceptable level of overall attrition (≤20%)?
Citrome, 2016 ¹	Unclear	Yes, interactive response system	Yes, though comorbidity NR	No (raters aware)	No: open-label	No	Yes (none excluded)	No (37%)
Crespo-Facorro, 2013 ²³	Unclear	Unclear	No: differences in duration of illness, sex, and substance use	Unclear	No	No	No	Yes
Detke, 2014 ²⁴	Unclear	Unclear	Yes: age, sex, age at onset, length of current episode, and baseline severity all similar	Unclear	No: open-label	No	Yes	No; 52.5%
Di Fiorino, 2014 ²	Yes	Yes	Unclear	No	No	No	Yes	Yes (25%)
Durgam, 2014 ³	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Yes	No: excluding placebo arm, 193/578 = 33% discontinued
Fleischhacker, 2014 ⁴ ASPIRE EU	Unclear	Unclear	Yes	Unclear; dosing adjustments allowed - no explanation given for how conducted to maintain blinding.	Unclear; dosing adjustments allowed - no explanation given for how conducted to maintain blinding.	Yes	Yes	No: 157/531 = 30%
Hu, 2013 ²⁵	Yes: computer- generated randomization list	Unclear	Unclear: reported only for the 70% of participants completing the study	No: open-label	No: open-label	No: open- label	No: 24/80 (30%) excluded	Yes: 30%

Evidence Table 2. Quality assessment of randomized controlled trials in patients with schizophrenia

Author, Year Study Name	Acceptable level of differential attrition (<10%)?	Overall quality
Citrome, 2016 ¹	Yes (38% vs. 36%)	Fair
Crespo-Facorro, 2013 ²³	No (11% to 32%)	Poor
Detke, 2014 ²⁴	Yes	Poor
Di Fiorino, 2014 ²	Yes: 17% vs. 25%	Fair
Durgam, 2014 ³	Yes: excluding placebo, range 27.9 to 37.9%	Fair
Fleischhacker, 2014 ⁴ ASPIRE EU	Yes: 26% vs. 33%	Fair
Hu, 2013 ²⁵	No: 17.5% vs. 42.5%	Poor

Evidence Table 2. Quality assessment of randomized controlled trials in patients with schizophrenia

Author, Year Study Name	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors blinded?	Clinician blinded?	Patient blinded?	Intention to treat?	Acceptable level of overall attrition (≤20%)?
Ishigooka, 2015 ⁵ ALPHA	Yes	Yes	Unclear: gender, age, baseline severity similar, but duration of illness 163 vs. 140 months	Unclear; dosing adjustments allowed - no explanation given for how conducted to maintain blinding.	Unclear; dosing adjustments allowed - no explanation given for how conducted to maintain blinding.	Yes	Yes	No: 135/455 = 30%
Koshikawa, 2016 ⁶	Yes: computer- generated	Unclear	Unclear: reported only for the 70% of participants completing the study	No: open-label	No: open-label	No: open- label	No: 9/30 (30%) excluded	Yes: 30%
Li, 2014 ⁸	Unclear: only described as randomized	Unclear: "Assigned sequentially in ascending order"	Yes	Yes: double- dummy	Yes: double-dummy	Yes: double dummy	Yes: none excluded	Yes: 41/279 = 15%
Liu, 2014 ⁹	Yes	Unclear	Unclear: age and baseline PANSS similar but duration of illness 4.5 vs. 5.5 months	No	No	No	Yes	Yes
Maat, 2014 ²⁶	Unclear: only described as randomized	Unclear	Yes	No: open-label	No: open-label	No: open- label	No: 36/80 = 45% excluded	No: 40% discontinued
Naber, 2013 ¹⁰ RECOVER	Unclear	Yes: IVRS	Mostly yes	No	No	No	Yes with LOCF	No; 45%
Naber, 2015 ²⁷ QUALIFY	Yes: stratified randomization	Unclear	Unclear: age, age at onset, and gender similar, but baseline severity not reported for all patients randomized (9% excluded)	Yes for QLS and IAQ but not for other assessments	No	No	No	No: 112/295 = 38%

Evidence Table 2. Quality assessment of randomized controlled trials in patients with schizophrenia

Author, Year Study Name	Acceptable level of differential attrition (<10%)?	Overall quality
Ishigooka, 2015 ⁵ ALPHA	Yes: 26% to 33%	Fair
Koshikawa, 2016 ⁶	Yes: 29% vs. 31%	Fair
Li, 2014 ⁸	Yes: 17% vs. 12%	Fair
Liu, 2014 ⁹	Yes	Fair
Maat, 2014 ²⁶	No: 47.4% vs. 33.3%	Poor
Naber, 2013 ¹⁰ RECOVER	Yes	Fair
Naber, 2015 ²⁷ QUALIFY	No: 32% vs. 44%	Fair

Evidence Table 2. Quality assessment of randomized controlled trials in patients with schizophrenia

Author, Year Study Name	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors blinded?	Clinician blinded?	Patient blinded?	Intention to treat?	Acceptable level of overall attrition (≤20%)?
Parabiaghi, 2016 ¹³ GiSAS	Yes: computer- generated, stratified, block	Yes: central with IVRS	Yes, mostly similar though some baseline data incomplete	Yes: outcome assessment and data analysis blinded	No: open-label	No: open- label	Yes: none excluded, both LOCF and multiple imputation used	No: 86/200 = 43%
Park, 2013 ²⁸	Yes: stratified randomization	Unclear	Unclear: PANSS 67.5 vs. 82.0 (small sample, N=20)	No: open-label	No: open-label	No: open- label	Unclear: follow- up and N's analyzed NR	Unclear: follow-up NR
Robinson, 2015 ¹⁶	Yes: stratified randomization	Unclear	Some differences: duration of psychiatric and psychotic symptoms were 7.3 and 6.6 months longer in aripiprazole group.	Yes	Yes	Yes	Yes: 11/209 (5.3%) not analyzed	No: 93/209 = 44%
Sanz-Fuentenebro, 2013 ²⁹	No (alternating assignment)	No	Some differences: 60% vs 80% male and duration of active psychosis 7.5 months vs. 12.3 months.	Unclear	No	No	Yes with LOCF	No (53.3%)
Savitz, 2015 ¹⁷	Yes	Unclear	Unclear: age, gender, and baseline PANSS similar, but duration of illness 2.04 vs 2.84 years, duration of recent hospitalization 55.2 vs 66.8 days	Unclear	Unclear	Unclear	Yes	Yes
Savitz, 2016 ¹⁸	Yes (computer- generated)	Yes (IWRS)	Yes, though comorbidity NR	Unclear	Yes (double dummy)	Yes (double dummy)	Yes (2.1% excluded from MITT set in double-blind phase)	Yes (17%)
Shoja Shafti, 2015 ¹⁹	Unclear: only described as randomized	Unclear	Yes	Yes	Yes	Yes	Unclear: follow- up and N's analyzed NR	Unclear: overall withdrawals NR

Evidence Table 2. Quality assessment of randomized controlled trials in patients with schizophrenia

Author, Year Study Name	Acceptable level of differential attrition (<10%)?	Overall quality
Parabiaghi, 2016 ¹³ GiSAS	No: 53% vs. 33%	Fair
Park, 2013 ²⁸	Unclear	Poor
Robinson, 2015 ¹⁶	Yes (8%)	Fair
Sanz-Fuentenebro, 2013 ²⁹	No (20% vs. 47%)	Poor
Savitz, 2015 ¹⁷	Yes	Fair
Savitz, 2016 ¹⁸	Yes (16% vs. 18%)	Good
Shoja Shafti, 2015 ¹⁹	Unclear	Fair

Evidence Table 2. Quality assessment of randomized controlled trials in patients with schizophrenia

Author, Year Study Name	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors blinded?	Clinician blinded?	Patient blinded?	Intention to treat?	Acceptable level of overall attrition (≤20%)?
Subotnik, 2015 ²⁰	Unclear	Unclear	Unclear: age, sex, % schizoaffective and baseline symptoms similar but time since onset 7.9 vs. 6.9 months	No	No	No	Yes	31%
Tybura, 2013 ³⁰	Unclear	Unclear	Unclear: age and baseline PANSS similar, but no other baseline characteristics reported.	No: open-label	No: open-label	No: open-label	Yes: Tables show N's at baseline and 3 months as the same	Yes: Tables show N's at baseline and 3 months as the same
Tybura, 2014 ²¹	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes: 36/131 = 27% discontinued (SGAs only)
Wani, 2015 ²²	Unclear: only described as randomized	Unclear	Yes	No: open-label	No: open-label	No: open-label	Unclear: states that LOCF but gives N's analyzed at 24 weeks as those continuing treatment (Fig 1; excludes 24%)	Yes: 15/62 = 24%
Zhang, 2014 ³¹	Yes	Unclear	Some differences: PANSS baseline 89.1 vs 88.8 vs 93.7 (max difference 4.3 points)	Yes: PANSS "conducted by two senior psychiatrists... blind to the treatment status of the patients"	No (blinding not mentioned)	No (blinding not mentioned)	No; missing 8,5%	Yes

Evidence Table 2. Quality assessment of randomized controlled trials in patients with schizophrenia

Author, Year Study Name	Acceptable level of differential attrition (<10%)?	Overall quality
Subotnik, 2015 ²⁰	No; 25% vs 37%	Fair
Tybura, 2013 ³⁰	Yes: Tables show N's at baseline and 3 months as the same	Poor
Tybura, 2014 ²¹	Yes: 32% vs. 24%	Fair
Wani, 2015 ²²	No: 16% vs. 32%	Fair
Zhang, 2014 ³¹	Yes	Poor

Evidence Table 3. Data abstraction of observational studies in patients with schizophrenia

Author, Year Country (Quality rating)	Study Design	Interventions	Time frame Data source	N	Population characteristics
Bitter, 2013 ³² Hungary (Fair)	Parallel-group, register-based observational follow-up study	Aripiprazole (n=601) vs. Clozapine (n=790) vs. Olanzapine (n=1633) vs. Quetiapine (n=1587) vs. Risperidone (n=2480) vs. Ziprasidone (n=461) vs. Depot formulation risperidone (RLAI) (n=1095)	Time frame: 7/1/2007 to 6/30/2008 Data Source: national central register	9,567	Mean age, y: 47.1 Gender, % female: 60.2 Hospitalizations 6 m prior baseline, %: 38.7

Evidence Table 3. Data abstraction of observational studies in patients with schizophrenia

Author, Year Country (Quality rating)	Efficacy/effectiveness outcomes	Harms
Bitter, 2013 ³² Hungary (Fair)	<p>Aripiprazole vs. clozapine vs. olanzapine vs. quetiapine vs. risperidone vs. ziprasidone vs. RLAI</p> <p>Overall discontinuation, n (%): 431 (71.7) vs. 573 (72.5) vs. 1,118 (68.5) vs. 1,209 (76.2) vs. 2,111 (85.1) vs. 348 (75.5) vs. 667 (60.9)</p> <p>Time to discontinuation, median d: 102 (95% CI 81 to 126) vs. 76 (95% CI 54 to 92) vs. 136 (95% CI 121 to 153) vs. 89 (95% CI 81 to 100) vs. 55 (95% CI 41 to 63) vs. 93 (95% CI 82 to 119) vs. 215 (95% CI 181 to 242)</p> <p>All-cause discontinuations by treatment, Adjusted Hazard Ratios (95% CI):</p> <p>Aripiprazole vs. Clozapine: 1.01 (0.86 to 1.18)</p> <p>Aripiprazole vs. Olanzapine: 0.84 (0.75 to 0.94)</p> <p>Aripiprazole vs. Quetiapine: 1.08 (0.96 to 1.21)</p> <p>Aripiprazole vs. Risperidone: 1.26 (1.12 to 1.43)</p> <p>Aripiprazole vs. RLAI: 0.71 (0.62 to 0.82)</p> <p>Aripiprazole vs. Ziprasidone: 1.13 (0.98 to 1.31)</p> <p>Clozapine vs. Aripiprazole: 0.99 (0.84 to 1.17)</p> <p>Clozapine vs. Olanzapine: 0.86 (0.75 to 0.98)</p> <p>Clozapine vs. Quetiapine: 0.98 (0.86 to 1.12)</p> <p>Clozapine vs. Risperidone: 1.19 (1.04 to 1.36)</p> <p>Clozapine vs. RLAI: 0.73 (0.63 to 0.85)</p> <p>Clozapine vs. Ziprasidone: 1.08 (0.90 to 1.30)</p> <p>Olanzapine vs. Aripiprazole: 1.19 (1.06 to 1.34)</p> <p>Olanzapine vs. Clozapine: 1.17 (1.02 to 1.33)</p> <p>Olanzapine vs. Quetiapine: 1.29 (1.18 to 1.40)</p> <p>Olanzapine vs. Risperidone: 1.55 (1.42 to 1.68)</p> <p>Olanzapine vs. RLAI: 0.86 (0.77 to 0.96)</p> <p>Olanzapine vs. Ziprasidone: 1.35 (1.18 to 1.53)</p> <p>Quetiapine vs. Aripiprazole: 0.93 (0.83 to 1.04)</p>	<p>Aripiprazole vs. clozapine vs. olanzapine vs. quetiapine vs. risperidone vs. ziprasidone vs. RLAI</p> <p>Death, n (%): 14 (2.3) vs. 20 (2.5) vs. 49 (3) vs. 80 (5) vs. 133 (5.4) vs. 12 (2.6) vs. 37 (1.1)</p>

Evidence Table 3. Data abstraction of observational studies in patients with schizophrenia

Author, Year Country (Quality rating)	Funding/Comments
Bitter, 2013 ³² Hungary (Fair)	Janssen-Cilag Hungary Ltd, Budapest, Hungary.

Evidence Table 3. Data abstraction of observational studies in patients with schizophrenia

Author, Year Country (Quality rating)	Study Design	Interventions	Time frame Data source	N	Population characteristics
Bitter, 2013 ³² Hungary (Fair) cont.					
Jiang, 2015 ³³ U.S. (Fair)	Retrospective cohort	Paliperidone (n=264) vs. Lurasidone (n=182) vs. Aripiprazole (n=2,583) vs. Quetiapine (n=4,741) vs. Risperidone (n=5,351) vs. Olanzapine (n=2,482)	Time frame: 01/2007–06/2013 Data Source: Humana medical and pharmacy claims	15,603	Mean age, y: 53.7 Gender, % female: 52.2 Ethnicity, %: White: 54.9 Hospitalizations, %: 4.08

Evidence Table 3. Data abstraction of observational studies in patients with schizophrenia

Author, Year Country (Quality rating)	Efficacy/effectiveness outcomes	Harms
Bitter, 2013 ³² Hungary (Fair) cont.	<p>Aripiprazole vs. clozapine vs. olanzapine vs. quetiapine vs. risperidone vs. ziprasidone vs. RLAI</p> <p>All-cause discontinuations by treatment, Adjusted Hazard Ratios (95% CI), continued:</p> <p>Quetiapine vs. Clozapine: 1.02 (0.89 to 1.16) Quetiapine vs. Olanzapine: 0.78 (0.72 to 0.85) Quetiapine vs. Risperidone: 1.16 (1.07 to 1.26) Quetiapine vs. RLAI: 0.63 (0.57 to 0.71) Quetiapine vs. Ziprasidone: 1.04 (0.92 to 1.18) Risperidone vs. Aripiprazole: 0.79 (0.70 to 0.89) Risperidone vs. Clozapine: 0.84 (0.74 to 0.96) Risperidone vs. Olanzapine: 0.65 (0.59 to 0.70) Risperidone vs. Quetiapine: 0.86 (0.79 to 0.93) Risperidone vs. RLAI: 0.53 (0.48 to 0.60) Risperidone vs. Ziprasidone: 0.83 (0.73 to 0.95) RLAI vs. Aripiprazole: 1.40 (1.21 to 1.62) RLAI vs. Clozapine: 1.37 (1.17 to 1.60) RLAI vs. Olanzapine: 1.16 (1.04 to 1.30) RLAI vs. Quetiapine: 1.58 (1.41 to 1.77) RLAI vs. Risperidone: 1.88 (1.67 to 2.10) RLAI vs. Ziprasidone: 1.58 (1.34 to 1.86) Ziprasidone vs. Aripiprazole: 0.89 (0.77 to 1.03) Ziprasidone vs. Clozapine: 0.93 (0.77 to 1.11) Ziprasidone vs. Olanzapine: 0.74 (0.65 to 0.84) Ziprasidone vs. Quetiapine: 0.96 (0.85 to 1.09) Ziprasidone vs. Risperidone: 1.20 (1.05 to 1.37) Ziprasidone vs. RLAI: 0.63 (0.54 to 0.75)</p>	
Jiang, 2015 ³³ U.S. (Fair)	<p>Paliperidone vs. Lurasidone vs. Aripiprazole vs. Quetiapine vs. Risperidone vs. Olanzapine</p> <p>Hospitalization, mean number of events (SD): 3.93 (9.38) vs. 0.74 (2.56) vs. 4.48 (9.70) vs. 5.62 (10.86) vs. 4.26 (10.04) vs. 4.43 (10.37) ED attendance, mean number of events (SD): 1.54 (3.39) vs. 0.37 (1.44) vs. 1.89 (4.52) vs. 2.60 (5.12) vs. 1.78 (3.76) vs. 1.55 (3.31) Episode duration, d: 159.3 (141.7) vs. 149.8 (139.4) vs. 220.4 (147.9) vs. 240.7 (144.7) vs. 246.2 (142.3) vs. 244.6 (143.3)</p>	NR

Evidence Table 3. Data abstraction of observational studies in patients with schizophrenia

Author, Year Country (Quality rating)	Funding/Comments
Bitter, 2013 ³² Hungary (Fair) cont.	
Jiang, 2015 ³³ U.S. (Fair)	None.

Evidence Table 3. Data abstraction of observational studies in patients with schizophrenia

Author, Year Country (Quality rating)	Study Design	Interventions	Time frame Data source	N	Population characteristics
Joshi, 2016a ³⁴ U.S. (Fair) Companions: Joshi, 2015 ³⁵ Joshi, 2016b ³⁶	Retrospective cohort study	Risperidone LAI (n = 822) vs. Paliperidone Palmitate (n = 519) Duration: 12 m follow-up	Time frame: 1 July 2007 and 31 December 2012 Data Source: the Truven MarketScan Commercial, Medicare Supplemental, and Medicaid Multi-State insurance databases	1341	≥18 years and schizophrenia or schizoaffective disorder diagnosis Age, mean y: 39 % Female: 42.6 % with comorbidity substance abuse: 43.2

Evidence Table 3. Data abstraction of observational studies in patients with schizophrenia

Author, Year Country (Quality rating)	Efficacy/effectiveness outcomes	Harms
Joshi, 2016a ³⁴ U.S. (Fair) Companions: Joshi, 2015 ³⁵ Joshi, 2016b ³⁶	<u>Joshi, 2016a:</u> Risperidone LAI vs. Paliperidone Palmitate Overall discontinuation %: 53.3 vs. 36.5; P<0.001 Inpatient Hospitalization, aOR (95% CI): 0.72 (0.55 to 0.95) Inpatient Hospitalization, aIRR (95% CI): 0.88 (0.77 to 1.00) ED visit, aOR (95% CI): 0.91 (0.69 to 1.20) ED visit, aIRR (95% CI): 0.67 (0.61 to 0.73) Length of inpatient stay, aIRR (95% CI): 0.86 (0.82 to 0.90) <u>Joshi, 2015:</u> Paliperidone Palmitate vs. Risperidone Hospitalized, %: 35.3 vs. 43.7; OR 0.72 (95% CI 0.55 to 0.95) Patients with physician office visits, %: 88.4 vs. 83.8; OR 1.48 (95% CI 1.01 to 2.20) Inpatient length of stay: RR -0.86; P<0.0001 ER visits: RR 0.67; P<0.0001 Physician office visits: RR 1.55; P<0.0001 <u>Joshi, 2016b:</u> Paliperidone Palmitate vs. Risperidone Likelihood of hospitalization, adjusted OR: 0.72 (95% CI 0.55 to 0.95) Likelihood of doctor visit, adjusted OR 1.48 (95% CI 1.01 to 2.18) Inpatient length of stay, adjusted IRR 0.86 (95% CI 0.82 to 0.90) ER visits, adjusted IRR: 0.67 (95% CI: 0.61 to 0.73) Doctor visits, adjusted IRR: 1.54 (95% CI 1.50 to 1.59)	NR

Evidence Table 3. Data abstraction of observational studies in patients with schizophrenia

Author, Year Country (Quality rating)	Funding/Comments
Joshi, 2016a ³⁴ U.S. (Fair) Companions: Joshi, 2015 ³⁵ Joshi, 2016b ³⁶	Janssen Scientific Affairs LLC

Evidence Table 3. Data abstraction of observational studies in patients with schizophrenia

Author, Year Country (Quality rating)	Study Design	Interventions	Time frame Data source	N	Population characteristics
Kiviniemi, 2013 ³⁷ Finland (Good)	Register-based, 5-year follow- up study	Risperidone (n=1,038) vs. Clozapine (n=42) vs. Olanzapine (n=501) vs. Quetiapine (n=112)	Time frame: 01/1998- 12/2003 Data Source: the National Hospital Discharge Register (FHDR), the National Causes-of-Death Register, and registers of disability pensions from the Social Insurance Institution (SII) and from the Finnish Centre for Pensions (FCP)	6,987	Mean age, y: 33.8 Gender, % female: 42.2
Rybakowski, 2014 ³⁸ Europe EUFEST	Post-hoc analysis of EUFEST trial	Olanzapine vs. Quetiapine vs. Ziprasidone	Time frame: main study published in 2008 Data source: EUFEST trial	498	Age, y: 26.0 Gender, % female 59.8 Schizoaffective, %: 7.0

Evidence Table 3. Data abstraction of observational studies in patients with schizophrenia

Author, Year Country (Quality rating)	Efficacy/effectiveness outcomes	Harms
Kiviniemi, 2013 ³⁷ Finland (Good)	NR	<p>Risperidone vs. Clozapine vs. Olanzapine vs. Quetiapine</p> <p>Users of medication deceased, n (%): 68 (38.6) vs. 21 (16.3) vs. 73 (40.3) vs. 26 (19.4); Likelihood for death (all-cause mortality), adjusted OR: 1.0 (95% CI 0.75 to 1.43) vs. 0.35 (95% CI 0.21 to 0.58) vs. 0.73 (95% CI 0.54 to 1.00) vs. 0.46 (95% CI 0.30 to 0.72) Patients who died due to suicide, n (%): 22 (40.7) vs. 9 (22.0) vs. 29 (47.5) vs. 11 (25.6) Likelihood for suicide, adjusted OR: 1.10 (95% CI 0.63 to 1.90) vs. 0.29 (95% CI 0.14 to 0.63) vs. 0.82 (95% CI 0.49 to 1.36) vs. 0.52 (95% CI 0.26 to 1.05) Patients died due to cardiovascular disease: 12 (30.8) vs. 2 (6.9) vs. 16 (37.2) vs. 7 (20.6) Likelihood for cardiovascular death, adjusted OR: 0.82 (95% CI 0.41 to 1.66) vs. 0.23 (95% CI 0.05 to 1.02) vs. 0.89 (95% CI 0.46 to 1.72) vs. 0.72 (95% CI 0.30 to 1.73)</p>
Rybakowski, 2014 ³⁸ Europe EUFEST	NR	<p>Olanzapine vs. Quetiapine vs. Ziprasidone</p> <p>Parkinsonism, % Visit 1 (baseline): 5.8 vs. 7.8 vs. 18.5 Visit 9 (12 months): 0 vs. 2.4 vs. 6.5</p> <p>Akathisia, %: Visit 1 (baseline): 7.7 vs. 9.8 vs. 9.9 Visit 9 (12 months): 0 vs. 7.3 vs. 6.5</p>

Evidence Table 3. Data abstraction of observational studies in patients with schizophrenia

Author, Year Country (Quality rating)	Funding/Comments
Kiviniemi, 2013 ³⁷ Finland (Good)	None.
Rybakowski, 2014 ³⁸ Europe EUFEST	Funding: AstraZeneca, Pfizer and Sanofi-Aventis

Evidence Table 4. Quality assessment of observational studies in patients with schizophrenia

Author, Year Study Name	Non-biased selection?	High overall loss to follow-up or differential loss to follow up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Bitter, 2013 ³²	Yes	No	Yes for discontinuation of treatment; unclear for others	Unclear; exact methods not described	Unclear	Yes	Yes	Fair
Chan, 2015 ³⁹	Unclear	No	Unclear: clinical outcomes listed but not defined	No	Unclear: data sources not described	No	Yes	Poor
Jiang, 2015 ³³	Yes	No	Yes	Yes	Unclear	Yes	Yes	Fair
Joshi, 2016 ³⁴	Unclear: exclusions NR, though same methods used to select both drug groups	NA: retrospective cohort, 12 months' follow-up required	Yes for discontinuation of treatment; unclear for others	No	Unclear: validation and blinding NR	Yes: propensity score matching	Yes (12 months)	Fair
Kiviniemi, 2013 ³⁷	Yes	No	Yes	Yes	Yes	Yes	Yes	Good

Evidence Table 5. Data abstraction of systematic reviews in patients with schizophrenia

Author, Year (Quality rating)	Aims	Time period covered	Patient N Study N	Characteristics of identified articles: study designs
Harvey, 2016 ⁴⁰ (Good)	To explore the relative efficacy of antipsychotics used in the treatment of early-onset schizophrenia (EOS).	Searches through January 2015.	Patient N = 1,714 Study N = 11	10 RCTs, 1 controlled trial (not randomized)
Harvey, 2016 ⁴⁰ (Good) cont.				

Evidence Table 5. Data abstraction of systematic reviews in patients with schizophrenia

Author, Year (Quality rating)	Characteristics of identified articles: populations	Characteristics of identified articles: interventions
Harvey, 2016 ⁴⁰ (Good)	≤ 18 years old with schizophrenia, schizoaffective disorder or schizophreniform disorder	Aripiprazole vs Olanzapine vs. Paliperidone vs. Quetiapine vs. Risperidone vs. Ziprasidone Also included, not abstracted: haloperidol, molindone and placebo Duration: 6 - 12 weeks.
Harvey, 2016 ⁴⁰ (Good) cont.		

Evidence Table 5. Data abstraction of systematic reviews in patients with schizophrenia

Author, Year (Quality rating)	Efficacy/effectiveness outcomes
Harvey, 2016 ⁴⁰ (Good)	Total PANSS, Mean difference (95% credible interval): Ziprasidone vs. Risperidone vs. Quetiapine vs. Paliperidone vs. Olanzapine vs. Aripiprazole: 9.03 (-1.46 to 19.08) vs. 5.57 (-6.63 to 17.48) vs. 2.82 (-9.87 to 15.85) vs. 10.37 (-1.21 to 21.43) vs. 3.81 (-8.23 to 15.70) Risperidone vs. Quetiapine vs. Paliperidone vs. Olanzapine vs. Aripiprazole: -3.39 (-12.77 to 6.30) vs. -6.05 (-16.75 to 5.69) vs. 1.36 (-5.86 to 8.74) vs. -5.21 (-15.42 to 5.63) Quetiapine vs. Paliperidone vs. Olanzapine vs. Aripiprazole: -2.67 (-15.27 to NR) vs. 4.8 (-6.38 to 15.70) vs. -1.82 (-13.91 to NR) Paliperidone vs. Olanzapine vs. Aripiprazole: 7.48 (-5.03 to 19.49) vs. 0.9 (-11.72 to NR) Olanzapine vs. Aripiprazole: -6.64 (-17.75 to 5.13)
Harvey, 2016 ⁴⁰ (Good) cont.	All-cause discontinuation, Odds Ratio (95% credible interval): Ziprasidone vs. Risperidone vs. Quetiapine vs. Olanzapine: 1.21 (0.47 to 3.59) vs. 1.36 (0.41 to 4.50) vs. 1.16 (0.35 to 3.68) Risperidone vs. Quetiapine vs. Olanzapine: 1.12 (0.36 to 3.08) vs. 0.96 (0.34 to 2.33) Quetiapine vs. Olanzapine: 0.85 (0.24 to 2.85)

Evidence Table 5. Data abstraction of systematic reviews in patients with schizophrenia

Author, Year (Quality rating)	Harms outcomes	Funding/Comments
Harvey, 2016 ⁴⁰ (Good)	Weight change, Mean difference (95% credible interval): Ziprasidone vs. Risperidone vs. Quetiapine vs. Paliperidone vs. Olanzapine vs. Aripiprazole: -1.57 (-3.85 to 0.61) vs. -2.5 (-5.18 to 0.21) vs. -0.99 (-3.67 to 1.58) vs. -4.06 (-6.31 to -1.73) vs. -0.98 (-3.54 to 1.72) Risperidone vs. Quetiapine vs. Paliperidone vs. Olanzapine vs. Aripiprazole: -0.93 (-3.14 to 1.39) vs. 0.6 (-1.55 to 2.77) vs. -2.47 (-3.80 to -1.12) vs. 0.59 (-1.62 to 2.96) Quetiapine vs. Paliperidone vs. Olanzapine vs. Aripiprazole: 1.52 (-1.09 to 4.12) vs. -1.56 (- 3.99 to 0.90) vs. 1.53 (-1.17 to 4.32) Paliperidone vs. Olanzapine vs. Aripiprazole: -3.07 (-5.34 to -0.79) vs. 0 (-2.63 to 2.64) Olanzapine vs. Aripiprazole: 3.08 (0.71 to 5.45)	No funding
Harvey, 2016 ⁴⁰ (Good) cont.		

Evidence Table 5. Data abstraction of systematic reviews in patients with schizophrenia

Author, Year (Quality rating)	Aims	Time period covered	Patient N Study N	Characteristics of identified articles: study designs
Kishi, 2015 ⁴¹ (Good)	To clarify the pharmacological profile of aripiprazole in the treatment of schizophrenia. Comparisons of aripiprazole with other pooled antipsychotics in the Japanese population.	To January 5, 2014	Patient N=684 Study N=5	Randomized active-controlled trials. Open-label and crossover studies included to increase sample size for meta-analysis.
Leucht, 2013 ⁴² (Good)	Integrate the available evidence - create hierarchies of the comparative efficacy, risk of all-cause discontinuation, and major side-effects of antipsychotic drugs	Searches through September 1, 2012	Patient N=43,049 Study N=212	RCTs of 6-week duration (4 to 12 weeks, 6 weeks given preference)

Evidence Table 5. Data abstraction of systematic reviews in patients with schizophrenia

Author, Year (Quality rating)	Characteristics of identified articles: populations	Characteristics of identified articles: interventions
Kishi, 2015 ⁴¹ (Good)	Schizophrenia in Japanese-only cohorts.	Aripiprazole versus other antipsychotics (e.g. haloperidol, mosapramine, olanzapine, quetiapine, perospirone, and risperidone).
Leucht, 2013 ⁴² (Good)	Schizophrenia or related disorders (schizoaffective, schizophreniform, or delusional disorder [as defined by any diagnostic criteria])	Clozapine vs. olanzapine vs. risperidone vs. paliperidone vs. quetiapine vs. aripiprazole vs. ziprasidone vs. asenapine vs. lurasidone vs. iloperidone (Also included the following, not of interest: amisulpride, zotepine, haloperidol, sertindole, chlorpromazine, placebo)

Evidence Table 5. Data abstraction of systematic reviews in patients with schizophrenia

Author, Year (Quality rating)	Efficacy/effectiveness outcomes
Kishi, 2015 ⁴¹ (Good)	<p>Aripiprazole vs. pooled antipsychotics</p> <p>Difference in PANSS total score (response): SMD 0.10 (95% CI -0.10 to 0.31)</p>
Leucht, 2013 ⁴² (Good)	<p>All cause discontinuation, OR (95% CrI):</p> <p>Clozapine vs. Olanzapine, Risperidone, Paliperidone, Quetiapine, Aripiprazole, Ziprasidone, Asenapine, Lurasidone, Iloperidone: 1.00 (0.68 to 1.43) vs. 0.87 (0.59 to 1.22) vs. 0.97 (0.63 to 1.42) vs. 0.76 (0.50 to 1.10) vs. 0.76 (0.51 to 1.09) vs. 0.65 (0.43 to 0.95) vs. 0.68 (0.43 to 1.01) vs. 0.61 (0.39 to 0.90) vs. 0.67 (0.45 to 0.99)</p> <p>Olanzapine vs. Risperidone, Paliperidone, Quetiapine, Aripiprazole, Ziprasidone, Asenapine, Lurasidone, Iloperidone: 0.87 (0.76 to 1.01) vs. 0.97 (0.78 to 1.20) vs. 0.76 (0.63 to 0.91) vs. 0.76 (0.64 to 0.90) vs. 0.65 (0.53 to 0.79) vs. 0.68 (0.53 to 0.86) vs. 0.61 (0.47 to 0.77) vs. 0.68 (0.54 to 0.84)</p> <p>Risperidone vs. Paliperidone, Quetiapine, Aripiprazole, Ziprasidone, Asenapine, Lurasidone, Iloperidone: 1.12 (0.88 to 1.40) vs. 0.87 (0.73 to 1.04) vs. 0.88 (0.72 to 1.06) vs. 0.75 (0.61 to 0.91) vs. 0.78 (0.60 to 1.01) vs. 0.70 (0.53 to 0.89) vs. 0.78 (0.62 to 0.96)</p> <p>Paliperidone vs. Quetiapine, Aripiprazole, Ziprasidone, Asenapine, Lurasidone, Iloperidone: 0.79 (0.61 to 1.01) vs. 0.79 (0.61 to 1.02) vs. 0.68 (0.52 to 0.88) vs. 0.71 (0.52 to 0.95) vs. 0.63 (0.47 to 0.85) vs. 0.70 (0.53 to 0.93)</p> <p>Quetiapine vs. Aripiprazole, Ziprasidone, Asenapine, Lurasidone, Iloperidone: 1.01 (0.80 to 1.25) vs. 0.86 (0.68 to 1.07) vs. 0.90 (0.68 to 1.19) vs. 0.81 (0.61 to 1.03) vs. 0.89 (0.70 to 1.13)</p> <p>Aripiprazole vs. Ziprasidone, Asenapine, Lurasidone, Iloperidone: 0.86 (0.68 to 1.07) vs. 0.90 (0.68 to 1.18) vs. 0.80 (0.6 to 1.05) vs. 0.89 (0.69 to 1.14)</p> <p>Ziprasidone vs. Asenapine, Lurasidone, Iloperidone: 1.06 (0.78 to 1.41) vs. 0.94 (0.70 to 1.24) vs. 1.05 (0.81 to 1.33)</p> <p>Asenapine vs. Lurasidone, Iloperidone: 0.91 (0.64 to 1.22) vs. 1.01 (0.73 to 1.36)</p> <p>Lurasidone vs. Iloperidone: 1.12 (0.83 to 1.50)</p>

Evidence Table 5. Data abstraction of systematic reviews in patients with schizophrenia

Author, Year (Quality rating)	Harms outcomes	Funding/Comments
Kishi, 2015 ⁴¹ (Good)	Aripiprazole vs. pooled antipsychotics Discontinuations due to AEs: OR 1.03 (95% CI 0.65 to 1.65) At least 1 AE: OR 0.21 (95% CI 0.06 to 0.76) At least 1 extrapyramidal symptom: OR 0.46 (95% CI 0.27 to 0.79) Dyskinesia: OR 0.21 (95% CI 0.08 to 0.56)	No funding sources received for this study.
Leucht, 2013 ⁴² (Good)	Extrapyramidal side-effects (OR 95% CrI): Ziprasidone vs. Lurasidone, Aripiprazole, Asenapine, Paliperidone, Risperidone, Quetiapine, Iloperidone, Clozapine, Olanzapine: 1.59 (0.85 to 2.71) vs. 0.78 (0.41 to 1.34) vs. 1.07 (0.49 to 2.04) vs. 1.17 (0.64 to 1.98) vs. 1.35 (0.85 to 2.03) vs. 0.65 (0.37 to 1.06) vs. 1.00 (0.35 to 2.29) vs. 0.20 (0.07 to 0.43) vs. 0.64 (0.41 to 0.96) Lurasidone vs. Aripiprazole, Asenapine, Paliperidone, Risperidone, Quetiapine, Iloperidone, Clozapine, Olanzapine: 0.51 (0.26 to 0.91) vs. 0.71 (0.31 to 1.40) vs. 0.77 (0.41 to 1.34) vs. 0.89 (0.52 to 1.43) vs. 0.43 (0.24 to 0.71) vs. 0.68 (0.21 to 1.67) vs. 0.13 (0.04 to 0.29) vs. 0.42 (0.25 to 0.68) Aripiprazole vs. Asenapine, Paliperidone, Risperidone, Quetiapine, Iloperidone, Clozapine, Olanzapine: 1.46 (0.64 to 2.90) vs. 1.59 (0.82 to 2.82) vs. 1.83 (1.08 to 2.94) vs. 0.89 (0.48 to 1.51) vs. 1.39 (0.43 to 3.47) vs. 0.26 (0.09 to 0.59) vs. 0.88 (0.50 to 1.42) Asenapine vs. Paliperidone, Risperidone, Quetiapine, Iloperidone, Clozapine, Olanzapine: 1.20 (0.54 to 2.34) vs. 1.38 (0.69 to 2.47) vs. 0.67 (0.31 to 1.26) vs. 1.05 (0.29 to 2.74) vs. 0.20 (0.06 to 0.47) vs. 0.66 (0.33 to 1.17) Paliperidone vs. Risperidone, Quetiapine, Iloperidone, Clozapine, Olanzapine: 1.21 (0.71 to 1.91) vs. 0.58 (0.32 to 0.97) vs. 0.91 (0.28 to 2.24) vs. 0.17 (0.06 to 0.39) vs. 0.57 (0.35 to 0.89) Risperidone vs. Quetiapine, Iloperidone, Clozapine, Olanzapine: 0.49 (0.32 to 0.73) vs. 0.77 (0.26 to 1.80) vs. 0.15 (0.06 to 0.30) vs. 0.48 (0.34 to 0.66) Quetiapine vs. Iloperidone, Clozapine, Olanzapine: 1.62 (0.52 to 3.91) vs. 0.31 (0.11 to 0.66) vs. 1.02 (0.64 to 1.53) Iloperidone vs. Clozapine, Olanzapine: 0.24 (0.05 to 0.68) vs. 0.79 (0.26 to 1.85) Clozapine vs. Olanzapine: 3.94 (1.56 to 8.68)	NR

Evidence Table 5. Data abstraction of systematic reviews in patients with schizophrenia

Author, Year (Quality rating)	Aims	Time period covered	Patient N Study N	Characteristics of identified articles: study designs
Leucht, 2013 ⁴² (Good) cont.				

Evidence Table 5. Data abstraction of systematic reviews in patients with schizophrenia

Author, Year (Quality rating)	Characteristics of identified articles: populations	Characteristics of identified articles: interventions
Leucht, 2013 ⁴² (Good) cont.		

Evidence Table 5. Data abstraction of systematic reviews in patients with schizophrenia

Author, Year (Quality rating)	Efficacy/effectiveness outcomes
Leucht, 2013 ⁴² (Good) cont.	Weight gain, standard mean differences (95% CrI): Ziprasidone vs. Lurasidone, Aripiprazole, Asenapine, Paliperidone, Risperidone, Quetiapine, Iloperidone, Clozapine, Olanzapine: 0.00 (-1.16 to 0.16) vs. -0.07 (-0.21 to 0.08) vs. -0.13 (-0.32 to 0.06) vs. -0.28 (-0.43 to -0.13) vs. -0.32 (-0.45 to -0.19) vs. -0.33 (-0.48 to -0.19) vs. -0.52 (-0.67 to -0.36) vs. -0.55 (-0.91 to -0.20) vs. -0.64 (-0.76 to -0.52) Lurasidone vs. Aripiprazole, Asenapine, Paliperidone, Risperidone, Quetiapine, Iloperidone, Clozapine, Olanzapine: -0.07 (-0.23 to 0.10) vs. -0.13 (-0.32 to 0.05) vs. -0.28 (-0.43 to -0.12) vs. -0.32 (-0.46 to -0.19) vs. -0.33 (-0.48 to -0.19) vs. -0.52 (-0.69 to -0.35) vs. -0.55 (-0.90 to -0.19) vs. -0.64 (-0.77 to -0.51) Aripiprazole vs. Asenapine, Paliperidone, Risperidone, Quetiapine, Iloperidone, Clozapine, Olanzapine: -0.06 (-0.25 to 0.12) vs. -0.21 (-0.37 to -0.06) vs. -0.25 (-0.38 to -0.12) vs. -0.26 (-0.41 to -0.12) vs. -0.45 (-0.61 to -0.28) vs. -0.49 (-0.83 to -0.13) vs. -0.57 (-0.70 to -0.45) Asenapine vs. Paliperidone, Risperidone, Quetiapine, Iloperidone, Clozapine, Olanzapine: -0.15 (-0.34 to 0.04) vs. -0.19 (-0.36 to -0.02) vs. -0.20 (-0.38 to -0.03) vs. -0.39 (-0.58 to -0.19) vs. -0.42 (-0.79 to -0.06) vs. -0.51 (-0.67 to -0.35) Paliperidone vs. Risperidone, Quetiapine, Iloperidone, Clozapine, Olanzapine: -0.04 (-0.17 to 0.09) vs. -0.05 (-0.19 to 0.08) vs. -0.24 (-0.40 to -0.08) vs. -0.27 (-0.63 to 0.08) vs. -0.36 (-0.48 to -0.24) Risperidone vs. Quetiapine, Iloperidone, Clozapine, Olanzapine: -0.01 (-0.12 to 0.10) vs. -0.20 (-0.33 to -0.06) vs. -0.23 (-0.57 to 0.12) vs. -0.32 (-0.41 to -0.24) Quetiapine vs. Iloperidone, Clozapine, Olanzapine: -0.19 (-0.33 to -0.03) vs. -0.22 (-0.55 to 0.12) vs. -0.31 (-0.41 to -0.20) Iloperidone vs. Clozapine, Olanzapine: -0.04 (-0.39 to 0.32) vs. -0.12 (-0.26 to 0.01) Clozapine vs. Olanzapine: -0.09 (-0.43 to 0.24)

Evidence Table 5. Data abstraction of systematic reviews in patients with schizophrenia

Author, Year (Quality rating)	Harms outcomes	Funding/Comments
Leucht, 2013 ⁴² (Good) cont.		

Evidence Table 5. Data abstraction of systematic reviews in patients with schizophrenia

Author, Year (Quality rating)	Aims	Time period covered	Patient N Study N	Characteristics of identified articles: study designs
Samara, 2016 ⁴³ (Good)	To integrate all the randomized evidence from the available antipsychotics used for treatment-resistant schizophrenia by performing a network meta-analysis.	Searches through June 30, 2014.	Patient N = 5,172 Study N = 40 (90 articles)	Published and unpublished blinded RCTs.

Evidence Table 5. Data abstraction of systematic reviews in patients with schizophrenia

Author, Year (Quality rating)	Characteristics of identified articles: populations	Characteristics of identified articles: interventions
<p>Samara, 2016⁴³ (Good)</p>	<p>Treatment-resistant schizophrenia</p> <p>Age, mean: 38.3 % Female: 28.5 (studies with sex indicated, patient n = 4813) Mean duration of illness: 16.2 y Mean # of previous hospitalizations: 6.9</p> <p>Median trial duration: 11 weeks.</p>	<p>Clozapine vs. olanzapine vs. risperidone vs. aripiprazole vs. ziprasidone vs. quetiapine vs. haloperidol vs. fluphenazine</p> <p>Also included, not abstracted: chlorpromazine, sertindole, and thiothixene hydrochloride</p>

Evidence Table 5. Data abstraction of systematic reviews in patients with schizophrenia

Author, Year (Quality rating)	Efficacy/effectiveness outcomes
<p>Samara, 2016⁴³ (Good)</p>	<p>Mean score reduction in overall symptoms of schizophrenia, PANSS, SMDs (95% CI): Olanzapine vs. Ziprasidone vs. Clozapine vs. Risperidone vs. Quetiapine vs. Haloperidol vs. Fluphenazine: -0.04 (-0.34 to 0.24) vs. -0.07 (-0.21 to 0.08) vs. -0.14 (-0.33 to 0.08) vs. -0.29 (-0.56 to -0.02) vs. -0.29 (-0.44 to -0.13) vs. -0.38 (-0.85 to 0.03) Ziprasidone vs. Clozapine vs. Risperidone vs. Quetiapine vs. Haloperidol vs. Fluphenazine: -0.02 (-0.29 to 0.26) vs. -0.10 (-0.41 to 0.23) vs. -0.24 (-0.54 to 0.05) vs. -0.25 (-0.53 to 0.05) vs. -0.35 (-0.88 to 0.17) Clozapine vs. Risperidone vs. Quetiapine vs. Haloperidol vs. Fluphenazine: -0.08 (-0.25 to 0.10) vs. -0.22 (-0.47 to 0.02) vs. -0.22 (-0.38 to -0.07) vs. -0.33 (-0.79 to 0.12) Risperidone vs. Quetiapine vs. Haloperidol vs. Fluphenazine: -0.14 (-0.43 to 0.13) vs. -0.15 (-0.36 to 0.02) vs. -0.25 (-0.71 to 0.21) Quetiapine vs. Haloperidol vs. Fluphenazine: 0.00 (-0.22 to 0.24) vs. -0.18 (-0.59 to 0.25) Haloperidol vs. Fluphenazine: -0.09 (-0.54 to 0.32)</p>

Evidence Table 5. Data abstraction of systematic reviews in patients with schizophrenia

Author, Year (Quality rating)	Harms outcomes	Funding/Comments
<p>Samara, 2016⁴³ (Good)</p>	<p>Weight gain, SMD (95% CI): Haloperidol vs. fluphenazine vs. Ziprasidone vs. quetiapine vs. risperidone vs. clozapine vs. olanzapine: -0.04 (-1.04 to 0.98) vs. -0.05 (-1.04 to 0.97) vs. -0.16 (-0.79 to 0.46) vs. -0.31 (-0.86 to 0.24) vs. -0.78 (-1.25 to -0.28) vs. -0.99 (-1.47 to -0.51) Fluphenazine vs. Ziprasidone vs. quetiapine vs. risperidone vs. clozapine vs. olanzapine: -0.02 (-1.31 to 1.31) vs. -0.13 (-1.14 to 0.88) vs. -0.28 (-1.18 to 0.62) vs. -0.74 (-1.70 to 0.23) vs. -0.95 (-1.93 to 0.02) Ziprasidone vs. quetiapine vs. risperidone vs. clozapine vs. olanzapine: -0.11 (-1.23 to 0.97) vs. -0.26 (-1.25 to 0.70) vs. -0.73 (-1.62 to 0.15) vs. -0.94 (-1.90 to -0.01) Quetiapine vs. risperidone vs. clozapine vs. olanzapine: -0.15 (-0.81 to 0.52) vs. -0.62 (-1.26 to 0.05) vs. -0.83 (-1.46 to -0.19) Risperidone vs. clozapine vs. olanzapine: -0.47 (-0.87 to -0.04) vs. -0.68 (-1.14 to -0.22) Clozapine vs. olanzapine: -0.21 (-0.57 to 0.12)</p>	<p>German Federal Ministry of Education and Research.</p>

Evidence Table 5. Data abstraction of systematic reviews in patients with schizophrenia

Author, Year (Quality rating)	Aims	Time period covered	Patient N Study N	Characteristics of identified articles: study designs
Samara, 2016 ⁴³ (Good) cont.				

Evidence Table 5. Data abstraction of systematic reviews in patients with schizophrenia

Author, Year (Quality rating)	Characteristics of identified articles: populations	Characteristics of identified articles: interventions
Samara, 2016 ⁴³ (Good) cont.		

Evidence Table 5. Data abstraction of systematic reviews in patients with schizophrenia

Author, Year (Quality rating)	Efficacy/effectiveness outcomes
<p>Samara, 2016⁴³ (Good) cont.</p>	<p>Response Rates, reduction in positive symptoms, OR (95% CI): Risperidone vs. Clozapine vs. Ziprasidone vs. Olanzapine vs. Quetiapine vs Fluphenazine vs. Haloperidol : 1.01 (0.61 to 1.83) vs. 1.21 (0.45 to 2.89) vs. 1.18 (0.56 to 2.28) vs. 1.16 (0.57 to 3.54) vs. 2.81 (0.40 to 10.11) vs. 2.27 (1.11 to 4.73) Clozapine vs. Ziprasidone vs. Olanzapine vs. Quetiapine vs. Fluphenazine vs. Haloperidol: 1.11 (0.50 to 2.39) vs. 1.08 (0.67 to 1.70) vs. 1.13 (0.61 to 3.03) vs. 2.63 (0.39 to 9.27) vs. 2.09 (1.26 to 3.82) Ziprasidone vs. Olanzapine vs. Quetiapine vs. Fluphenazine vs. Haloperidol: 0.93 (0.41 to 2.33) vs. 1.09 (0.53 to 3.07) vs. 1.27 (0.34 to 10.07) vs. 1.80 (0.87 to 4.76) Olanzapine vs. Quetiapine vs. Fluphenazine vs. Haloperidol: 1.07 (0.55 to 2.98) vs. 2.54 (0.36 to 9.10) vs. 2.00 (1.16 to 3.76) Quetiapine vs. Fluphenazine vs. Haloperidol: 2.16 (0.30 to 7.73) vs. 1.75 (0.81 to 3.21) Fluphenazine vs. Haloperidol: 0.77 (0.22 to 5.28)</p> <p>All-cause discontinuation, OR (95% CI): Olanzapine vs. clozapine vs. ziprasidone vs. risperidone vs. quetiapine vs. vs. haloperidol vs. fluphenazine : 0.89 (0.54 to 1.31) vs. 0.92 (0.32 to 2.07) vs. 0.79 (0.41 to 1.31) vs. 0.70 (0.31 to 1.38) vs. 0.56 (0.33 to 0.87) vs. 0.24 (0.03 to 0.87) Clozapine vs. ziprasidone vs. risperidone vs. quetiapine vs. haloperidol vs. fluphenazine: 1.06 (0.40 to 2.40) vs. 0.90 (0.55 to 1.41) vs. 0.70 (0.37 to 1.66) vs. 0.61 (0.41 to 1.04) vs. 0.27 (0.03 to 1.05) Ziprasidone vs. risperidone vs. quetiapine vs. haloperidol vs. fluphenazine: 0.81 (0.33 to 2.41) vs. 0.70 (0.30 to 2.10) vs. 0.58 (0.25 to 1.71) vs. 0.12 (0.03 to 1.17) Risperidone vs. quetiapine vs. haloperidol vs. fluphenazine: 0.79 (0.40 to 1.98) vs. 0.68 (0.41 to 1.34) vs. 0.31 (0.04 to 1.16) Quetiapine vs. haloperidol vs. fluphenazine: 0.78 (0.39 to 1.70) vs. 0.36 (0.04 to 1.30) Haloperidol vs. fluphenazine: 0.44 (0.05 to 1.67)</p>

Evidence Table 5. Data abstraction of systematic reviews in patients with schizophrenia

Author, Year (Quality rating)	Harms outcomes	Funding/Comments
Samara, 2016 ⁴³ (Good) cont.	Extrapyramidal side-effects, OR (95% CI): Clozapine vs. ziprasidone vs. olanzapine vs. quetiapine vs. risperidone vs. fluphenazine vs. haloperidol: 0.92 (0.16 to 2.69) vs. 0.55 (0.08 to 1.85) vs. 0.38 (0.03 to 1.48) vs. 0.15 (0.04 to 0.39) vs. 0.20 (0.01 to 1.23) vs. 0.07 (0.01 to 0.31) Ziprasidone vs. olanzapine vs. quetiapine vs. risperidone vs. fluphenazine vs. haloperidol: 1.02 (0.07 to 5.18) vs. 0.18 (0.03 to 3.52) vs. 0.12 (0.03 to 1.08) vs. 0.04 (0.01 to 2.22) vs. 0.03 (0.01 to 0.68) Olanzapine vs. quetiapine vs. risperidone vs. fluphenazine vs. haloperidol: 0.46 (0.13 to 3.09) vs. 0.24 (0.08 to 1.22) vs. 0.11 (0.02 to 2.99) vs. 0.06 (0.01 to 0.75) Quetiapine vs. risperidone vs. fluphenazine vs. haloperidol: 0.40 (0.13 to 2.22) vs. 0.66 (0.06 to 3.22) vs. 0.23 (0.03 to 0.77) Risperidone vs. fluphenazine vs. haloperidol: 1.35 (0.09 to 0.68) vs. 0.50 (0.06 to 2.03) Fluphenazine vs. haloperidol: 0.91 (0.05 to 4.43)	

Evidence Table 5. Data abstraction of systematic reviews in patients with schizophrenia

Author, Year (Quality rating)	Aims	Time period covered	Patient N Study N	Characteristics of identified articles: study designs
Zhang, 2016 ⁴⁴ (Fair)	Summarize the efficacy, effectiveness, and safety of paliperidone in the treatment of schizophrenia in the Chinese population.	Searches from January 1, 2008, to May 22, 2015.	Patient N = NR Study N = 63 (122 publications)	RCTs n = 38, open-label, single-arm n = 17, observational n = 4, pharmacokinetic study n = 3 + 1 ER vs. PP study Paliperidone ER (study n = 53) PP (study n = 9) ER vs. PP (study n = 1)

Evidence Table 5. Data abstraction of systematic reviews in patients with schizophrenia

Author, Year (Quality rating)	Characteristics of identified articles: populations	Characteristics of identified articles: interventions
Zhang, 2016 ⁴⁴ (Fair)	Schizophrenia and residents of People's Republic of China, Taiwan, or Hong Kong.	Paliperidone oral extended- release (ER) vs. Paliperidone palmitate (PP) long-acting injection Duration: 1 - 12 months.

Evidence Table 5. Data abstraction of systematic reviews in patients with schizophrenia

Author, Year (Quality rating)	Efficacy/effectiveness outcomes
Zhang, 2016 ⁴⁴ (Fair)	Paliperidone ER vs. Paliperidone palmitate Median change in PANSS total score (overall): RCTs: -38.60 Single-arm: -34.48 Study n PANSS total score at the end point was >40%: RCTs: 21/33

Evidence Table 5. Data abstraction of systematic reviews in patients with schizophrenia

Author, Year (Quality rating)	Harms outcomes	Funding/Comments
Zhang, 2016 ⁴⁴ (Fair)	NR	National Key Technology R&D Program

Evidence Table 6. Quality assessment of systematic reviews in patients with schizophrenia

Author, Year	Report clear review question, state inclusion and exclusion criteria of primary studies?	Substantial effort to find relevant research?	Adequate assessment of validity of included studies?	Sufficient detail of individual studies presented?	Primary studies summarized appropriately?	Overall Rating
Harvey, 2016 ⁴⁰	Yes	Yes	Yes (CASP checklist with citation)	Yes	Yes (NMA, assessment of heterogeneity)	Good
Kishi, 2015 ⁴¹	Yes	Yes	Unclear: Cochrane risk of bias tool used, but review and consensus process NR for QA	Yes	Yes	Good
Leucht, 2013 ⁴²	Yes	Yes	Yes	Yes in appendix	Yes	Good
Samara, 2016 ⁴³	Yes	Yes	Yes (Cochrane RoB)	Yes (eTable 1)	Yes (NMA, assessment of heterogeneity)	Good
Zhang, 2016 ⁴⁴	Yes, though number of reviewers NR	Yes	Unclear: method NR though quality issues mentioned in Discussion	Yes	Yes (narrative)	Fair

Evidence Table 7. Data abstraction of companion publications of previously included studies in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity
Gaebel, 2010 ⁴⁵ Multi-Center Companions: Rouillon, 2013 ⁴⁶ Smeraldi, 2013 ⁴⁷	Symptomatically stable adults, >18 y, DSM-IV criteria for schizophrenia or schizoaffective disorder. Considered symptomatically stable when using stable dose >4 wks (including monotherapy with oral risperidone <6mg daily, olanzapine <20 mg daily, or a conventional neuroleptic <10 mg haloperidol or its equivalent) and were living in the same residence for >30 ds.	RLAI = 50 mg. Max dose. Quetiapine = 750 mg. Max dose. Duration: 2 y	NR	Mean Age = 42 Male = 58% Female = 42% Ethnicity: NR

Evidence Table 7. Data abstraction of companion publications of previously included studies in patients with schizophrenia

Author, year Study design	Other population characteristics	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed
Gaebel, 2010 ⁴⁵ Multi-Center Companions: Rouillon, 2013 ⁴⁶ Smeraldi, 2013 ⁴⁷	Schizophrenia = 82% Schizoaffective disorder = 18%	808/808/710	395/19/666

Evidence Table 7. Data abstraction of companion publications of previously included studies in patients with schizophrenia

Author, year Study design	Results
Gaebel, 2010 ⁴⁵ Multi-Center Companions: Rouillon, 2013 ⁴⁶ Smeraldi, 2013 ⁴⁷	RLAI vs Quetiapine Gaebel, 2010: Relapse: 16.5% vs, 31.3% Symptom response: PANSS Total Scores at endpoint: mean (N): 63.4 (326) vs. 72.1 (325) Rouillon, 2013: SF-12 Between group differences at 6 m: P=0.03 Between group differences at 18 m: P=0.01 Between group differences at endpoint: P=0.09 SQLS-R4 Within-treatment changes from baseline: P<0.0001 (for total, psychosocial, and vitality for both drugs at each assessment and endpoint). Smeraldi, 2013: Full remission (including both severity and duration criteria), n/N (%): 167/327 (51.1) vs. 128/326 (39.3); P=0.003 Among patients achieving full remission, remission maintained at the end of the trial, n/N (%): 144/167 (86.2) vs. 102/128 (79.7)

Evidence Table 7. Data abstraction of companion publications of previously included studies in patients with schizophrenia

Author, year Study design	Adverse effects reported
Gaebel, 2010 ⁴⁵ Multi-Center Companions: Rouillon, 2013⁴⁶ Smeraldi, 2013⁴⁷	Overall adverse events: Treatment-emergent potentially prolactin-related AEs: 5% vs. 2% Hyperprolactinemia: 13.1% vs. 1.5% Somnolence: 2% vs. 11% Weight gain: 7% vs. 6%, mean end point increases 1.25±6.61 vs. 0±6.55 kg

Evidence Table 7. Data abstraction of companion publications of previously included studies in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Gaebel, 2010 ⁴⁵ Multi-Center Companions: Rouillon, 2013⁴⁶ Smeraldi, 2013⁴⁷	Extrapyramidal AEs: 10% vs. 6%

Evidence Table 7. Data abstraction of companion publications of previously included studies in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Gaebel, 2010 ⁴⁵ Multi-Center Companions: Rouillon, 2013⁴⁶ Smeraldi, 2013⁴⁷	Withdrawals due to adverse events: 4.6%	Bold = new data for Update 5.

Evidence Table 7. Data abstraction of companion publications of previously included studies in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity
Lieberman, 2005 ⁴⁸ (CATIE Study) Row 1 of 4 Companion: Arnold, 2013 ⁴⁹	Patients age 18-65, DSM-IV criteria for schizophrenia, be appropriate candidates for oral therapy (patients assessment in conjunction with clinician), have adequate decisional capacity to decide to participate.	olanzapine 7.5mg quetiapine 200mg risperidone 1.5mg perphenazine 8mg ziprasidone 40mg The dose of medications was flexible, ranging from one to four capsules daily, and was based on the study doctor's judgment	Concomitant medications were permitted throughout the trial, except for additional antipsychotic agents.	Mean age: 40.6 y 26% Female Ethnicity: white 60%; black 35%; Hispanic 12%; 5% other

Evidence Table 7. Data abstraction of companion publications of previously included studies in patients with schizophrenia

Author, year Study design	Other population characteristics	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed
Lieberman, 2005 ⁴⁸ (CATIE Study) Row 1 of 4 Companion: Arnold, 2013⁴⁹	depression 28% alcohol dependence or alcohol abuse 25% drug dependence or drug abuse 29% obsessive-compulsive disorder 5% other anxiety disorder 14%	NR/NR/1493	NR/NR/1460

Evidence Table 7. Data abstraction of companion publications of previously included studies in patients with schizophrenia

Author, year Study design	Results
Lieberman, 2005 ⁴⁸ (CATIE Study) Row 1 of 4 Companion: Arnold, 2013⁴⁹	<p>The time to the discontinuation of treatment for any cause: HR (95%CI)</p> <ul style="list-style-type: none"> olanzapine vs quetiapine: 0.63(0.52-0.76) olanzapine vs risperidone: 0.75(0.62-0.90) olanzapine vs perphenazine: 0.78(0.63-0.96), NS after adjustment olanzapine vs ziprasidone: 0.76(0.60-0.97), NS after adjustment quetiapine vs risperidone: 1.19(0.99-1.42) quetiapine vs perphenazine: 1.14(0.93-1.39) quetiapine vs ziprasidone: 1.01(0.81-1.27) risperidone vs perphenazine: 1.00(0.82-1.23) risperidone vs ziprasidone: 0.89(0.71-1.14) perphenazine vs ziprasidone: 0.90(0.70-1.16) <p>The time to the discontinuation of treatment for lack of efficacy: HR (95%CI)</p> <ul style="list-style-type: none"> olanzapine vs quetiapine: 0.41(0.29-0.57) olanzapine vs risperidone: 0.45(0.32-0.64) olanzapine vs perphenazine: 0.47(0.31-0.70) olanzapine vs ziprasidone: 0.59(0.37-0.93), NS after adjustment quetiapine vs risperidone: 0.49(NR) quetiapine vs perphenazine: 0.47(NR) quetiapine vs ziprasidone: 0.69(NR) risperidone vs perphenazine: 0.59(NR) risperidone vs ziprasidone: 0.93(NR) perphenazine vs ziprasidone: 0.44(NR) <p>The time to the discontinuation of treatment owing to intolerability: HR (95%CI)</p> <ul style="list-style-type: none"> olanzapine vs quetiapine: 0.84(NR) olanzapine vs risperidone: 0.62(0.41-0.95) olanzapine vs perphenazine: 0.49(NR) olanzapine vs ziprasidone: 0.28(NR) quetiapine vs risperidone: 0.65(0.42-1.00) quetiapine vs perphenazine: 0.97(NR) quetiapine vs ziprasidone: 0.87(NR) risperidone vs perphenazine: 0.60(0.36-0.98) risperidone vs ziprasidone: 0.79(0.46-1.37) perphenazine vs ziprasidone: 0.19(NR)

Evidence Table 7. Data abstraction of companion publications of previously included studies in patients with schizophrenia

Author, year Study design	Adverse effects reported
Lieberman, 2005 ⁴⁸ (CATIE Study) Row 1 of 4 Companion: Arnold, 2013 ⁴⁹	olanzapine vs quetiapine vs risperidone vs perphenazine vs ziprasidone, p value Hospitalization for exacerbation of schizophrenia, no(%): 33(11%) vs 68(20%) vs 51(15%) vs 41(16%) vs 33(18%), p<0.001 Hospitalization risk ratio: 0.29 vs 0.66 vs 0.45 vs 0.51 vs 0.57 Any serious AEs, no(%): 32(10%) vs 32(9%) vs 33(10%) vs 29(11%) vs 19(10%), p=0.47 Any moderate or severe spontaneously reported AE, no(%): 122(36%) vs 113(34%) vs 123(36%) vs 79(30%) vs 65(35%), p=0.10 Insomnia: 55(16%) vs 62(18%) vs 83(24%) vs 66(25%) vs 56(30%), p,0.001 Hypersomnia: 104(31%) vs 103(31%) vs 96(28%) vs 74(28%) vs 45(24%), p=0.18 Urinary hesitancy, dry mouth, constipation: 79(24%) vs 105(31%) vs 84(25%) vs 57(22%) vs 37(20%), p,0.001 Decreased sex drive, arousal, ability to reach orgasm: 91(27%) vs 69(20%) vs 91(27%) vs 64(25%) vs 35(19%), p=0.59 Gynecomastia, galactorrhea: 7(2%) vs 6(2%) vs 14(4%) vs 4(2%) vs 6(3%), p=0.15 Menstrual irregularities: 11(12%) vs 5(6%) vs 16(18%) vs 7(11%) vs 8(14%), p=0.17 Incontinence, nocturia: 18(5%) vs 15(4%) vs 25(7%) vs 6(2%) vs 10(5%), p=0.04 Orthostatic faintness: 31(9%) vs 38(11%) vs 37(11%) vs 29(11%) vs 24(13%), p=0.08 Discontinuation of treatment owing to intolerability, no(%) -discontinuation: 62(18%) vs 49(15%) vs 34(10%) vs 40(15%) vs 28(15%), p=0.04 -weight gain or metabolic effects: 31(9%) vs 12(4%) vs 6(2%) vs 3(1%) vs 6(3%), p<0.001 -extrapyramidal effects: 8(2%) vs 10(3%) vs 11(3%) vs 22(8%) vs 7(4%), p=0.002 -sedation: 7(2%) vs 9(3%) vs 3(1%) vs 7(3%) vs 0(0%), p=0.10 -other effects: 16(5%) vs 18(5%) vs 14(4%) vs 8(3%) vs 15(8%), p=0.16

Evidence Table 7. Data abstraction of companion publications of previously included studies in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Lieberman, 2005 ⁴⁸ (CATIE Study) Row 1 of 4 Companion: Arnold, 2013⁴⁹	Olanzapine vs quetiapine vs risperidone vs perphenazine vs ziprasidone, P value Simpson-Angus Extrapyramidal Signs Scale mean score ≥ 1 : 23(8%) vs 12(4%) vs 23(8%) vs 15(6%) vs 6(4%), p=0.47

Evidence Table 7. Data abstraction of companion publications of previously included studies in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Lieberman, 2005 ⁴⁸ (CATIE Study) Row 1 of 4 Companion: Arnold, 2013⁴⁹	Olanzapine vs quetiapine vs risperidone vs perphenazine vs ziprasidone, <i>P</i> value Total WD, no(%): 210(64%) vs 269(82%) vs 245(74%) vs 192(75%) vs 145(79%) discontinuation due to intolerability: 62(18%) vs 49(15%) vs 34(10%) vs 40(15%) vs 28(15%), <i>P</i> =0.04	Bold = new data for Update 5.

Evidence Table 7. Data abstraction of companion publications of previously included studies in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity
Lieberman, 2005 ⁴⁸ (CATIE Study) Row 2 of 4 (for results and AEs) Companion: Arnold, 2013 ⁴⁹				

Evidence Table 7. Data abstraction of companion publications of previously included studies in patients with schizophrenia

Author, year Study design	Other population characteristics	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed
Lieberman, 2005 ⁴⁸ (CATIE Study) Row 2 of 4 (for results and AEs) Companion: Arnold, 2013 ⁴⁹			

Evidence Table 7. Data abstraction of companion publications of previously included studies in patients with schizophrenia

Author, year Study design	Results
<p>Lieberman, 2005⁴⁸ (CATIE Study) Row 2 of 4 (for results and AEs)</p> <p>Companion: Arnold, 2013⁴⁹</p>	<p>Duration of successful treatment: HR (95%CI) olanzapine vs quetiapine: 0.53(0.43-0.67) olanzapine vs risperidone: 0.69(0.55-0.87) olanzapine vs perphenazine: 0.73(0.57-0.93) olanzapine vs ziprasidone: 0.75(0.58-0.94) quetiapine vs risperidone: 1.30(1.04-4.63) quetiapine vs perphenazine: 1.28(1.00-1.64) quetiapine vs ziprasidone: 1.06(0.85-1.33) risperidone vs perphenazine: 0.72(NR) risperidone vs ziprasidone: 0.74(NR) perphenazine vs ziprasidone: 0.25(NR)</p> <p>Patients' decision to discontinue treatment: HR (95%CI) olanzapine vs quetiapine: 0.56(0.42-0.75) olanzapine vs risperidone: 0.67(0.50-0.90) olanzapine vs perphenazine: 0.70(0.50-0.98) olanzapine vs ziprasidone: 0.63(0.43-0.93) quetiapine vs risperidone: 0.21(NR) quetiapine vs perphenazine: 0.46(NR) quetiapine vs ziprasidone: 0.63(NR) risperidone vs perphenazine: 0.95(NR) risperidone vs ziprasidone: 0.21(NR) perphenazine vs ziprasidone: 0.27(NR)</p> <p>*p=0.004 for the interaction between treatment and time</p> <p>From Meyer 2008 Change in metabolic syndrome: Olanzapine vs Risperidone vs Quetiapine vs Ziprasidone Metabolic Syndrome prevalence at 3 mos 43.9% vs 30.6% vs 37.1% vs 29.9% Olanzapine vs Ziprasidone p=0.001 Olanzapine vs quetiapine vs Risperidone vs Ziprasidone 3 mos changes from baseline in non fasting triglyceride(mg/dl) Adjusted LSM±SE: 23.4±22.8 vs 54.7±23.5 vs -18.4 ±24.0 vs 0.0 ±32.7, p=0.0009 % of patients reporting paid employment at 18 mos: 17% vs 25% vs 23% vs 31%, (Data interpreted from Graph) p=NS Decline in rates of violence at 6 mos: 33.9% vs 14.1% vs 25.0%, 24.3%</p>

Evidence Table 7. Data abstraction of companion publications of previously included studies in patients with schizophrenia

Author, year Study design	Adverse effects reported
Lieberman, 2005 ⁴⁸ (CATIE Study) Row 2 of 4 (for results and AEs) Companion: Arnold, 2013 ⁴⁹	Weight gain >7%: 92(30%) vs 49(16%) vs 42(14%) vs 29(12%) vs 12(7%), p<0.001 Weight change, lb, mean(SE): 9.4(0.9) vs 1.1(0.9) vs 0.8(0.9) vs -2.0(1.1) vs -1.6(1.1), p<0.001 Weight change, lb/mo, mean(SE): 2(0.3)vs 0.5(0.2) vs 0.4(0.3) vs -0.2(0.2) vs -0.3(0.3), p<0.001 AIMS global severity score >= 2: 32(14%) vs 30(13%) vs 38(16%) vs 41(17%) vs 18(14%), p=0.23 Barnes Akathisia Rating Scale global score >= 3: 15(5%) vs 16(5%) vs 20(7%) vs 16(7%) vs 14(9%), p=0.24 Simpson-Angus Extrapyramidal Signs Scale mean score >= 1: 23(8%) vs 12(4%) vs 23(8%) vs 15(6%) vs 6(4%), p=0.47 Laboratory values, change from baseline, mean(SE) after adjustment, p value -blood glucose, mg/dl: 13.7(2.5) vs 7.5(2.5) vs 6.6(2.5) vs 5.4(2.8), p=0.59 -glycosylated hemoglobin, %: 0.40(0.07) vs 0.04(0.08) vs 0.07(0.08) vs 0.09(0.09) vs 0.11(0.09), p=0.01 -cholesterol, mg/dl: 9.4(2.4) vs 6.6(2.4) vs -1.3(2.4) vs 1.5(2.7) vs -8.2(3.2), p<0.001 -triglycerides, mg/dl: 40.5(8.9) vs 21.2(9.2) vs -2.4(9.1) vs 9.2(10.1) vs -16.5(12.2), p<0.001 -prolactin, ng/dl: -8.1(1.4) vs -10.6(1.4) vs 13.8(1.4) vs -1.2(1.6) vs -5.6(1.9), p<0.001 Prolonged corrected QT interval, no(%): 0(0%) vs 6(3%) vs 7(3%) vs 2(1%) vs 2(1%), p=0.03

Evidence Table 7. Data abstraction of companion publications of previously included studies in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Lieberman, 2005 ⁴⁸ (CATIE Study) Row 2 of 4 (for results and AEs) Companion: Arnold, 2013 ⁴⁹	

Evidence Table 7. Data abstraction of companion publications of previously included studies in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Lieberman, 2005 ⁴⁸ (CATIE Study) Row 2 of 4 (for results and AEs) Companion: Arnold, 2013⁴⁹		Bold = new data for Update 5.

Evidence Table 7. Data abstraction of companion publications of previously included studies in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity
Lieberman, 2005 ⁴⁸ (CATIE Study) Row 3 of 4 (for results only) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C. Meyer 2008 "change in metabolic.. Meyer 2008 "Impact of antipsychotic treatment Resnick 2008 Swanson 2008 Swartz 2008 Miller 2008 Levine 2011 Companion: Arnold, 2013⁴⁹				

Evidence Table 7. Data abstraction of companion publications of previously included studies in patients with schizophrenia

Author, year Study design	Other population characteristics	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed
Lieberman, 2005 ⁴⁸ (CATIE Study) Row 3 of 4 (for results only) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C. Meyer 2008 "change in metabolic.. Meyer 2008 "Impact of antipsychotic treatment Resnick 2008 Swanson 2008 Swartz 2008 Miller 2008 Levine 2011 Companion: Arnold, 2013⁴⁹	Meyer 2008 "Change in metabolic.. Olanzapine verus Risperidone vs Quetiapine vs Ziprasidone n=164 vs 147 vs 143 vs 77 Proportion of patients with metabolic syndrome at baseline: 34.8% vs 30.6% vs 37.8% vs 37.7%		

Evidence Table 7. Data abstraction of companion publications of previously included studies in patients with schizophrenia

Author, year Study design	Results
Lieberman, 2005 ⁴⁸ (CATIE Study) Row 3 of 4 (for results only) Funding: NIH grant, Foundation of Hope of Raleigh, N.C. Meyer 2008 "change in metabolic.. Meyer 2008 "Impact of antipsychotic treatment Resnick 2008 Swanson 2008 Swartz 2008 Miller 2008 Levine 2011	Difference in incidence or severity of TEAE between Olanzapine vs Quetiapine vs Risperidone vs Ziprasidone=NS based on rating scales for Parkinsonism, Akathisia, Dystonia or tardive Dyskinesia use of antiparkinsonism medications greater with risperidone and lower with quetiapine (P=0.029), and lower rates of discontinuation due to Parkinsonism symptoms were found with quetiapine and ziprasidone (P< 0.05; rates NR). Remission rates over 18 months irrespective of switching medications: Dropouts (%) vs. Completers (%) vs. Total (%) No symptom remission: 60.0 vs. 40.0 vs. 55.53 Any symptomatic remission: 32.7 vs. 67.3 vs. 44.47 At least 3 months: 19.9 vs. 80.1 vs. 21.03 At least 6 months: 13.0 vs. 87.0 vs. 11.68 Prevalence of attaining and maintaining remission rates for at least 6 months, while taking the first randomized antipsychotic medication (phase 1): Olanzapine: 12.4% Quetiapine: 8.2% Perphenazine: 6.8% Ziprasidone: 6.5% Risperidone: 6.3% Pairwise comparisons from ANCOVA adjusted for multiple comparisons: Olanzapine-tx patients had significantly or nearly significantly higher rates of any period of sx remission than quetiapine (p=0.02; adj. p=0.06), ziprasidone (p<0.01; adj. p<0.01), risperidone (p<0.01; adj. p<0.01), and perphenazine (p=0.01; adj. p=0.05).
Companion: Arnold, 2013⁴⁹	Rates of any sx remission period were higher for perphenazine (p=0.03; adj. p=0.09) and quetiapine (p=0.02; adj. p=0.06) than ziprasidone. Rates of attaining and maintaining 3 months of remission were higher for the olanzapine group than the perphenazine (p=0.04; adj. p=0.17), quetiapine (p=0.09; adj. p=0.34), risperidone (p=0.01; adj. p=0.04) and ziprasidone groups (p=0.04; adj. p=0.23), but differences were not significant after controlling for multiple comparisons.

Evidence Table 7. Data abstraction of companion publications of previously included studies in patients with schizophrenia

Author, year Study design	Adverse effects reported
Lieberman, 2005 ⁴⁸ (CATIE Study) Row 3 of 4 (for results only) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C. Meyer 2008 "change in metabolic.. Meyer 2008 "Impact of antipsychotic treatment Resnick 2008 Swanson 2008 Swartz 2008 Miller 2008 Levine 2011	Rates of discontinuation and time to all-cause discontinuation median time in mos (illicit drug non users) Olanzapine: 56%, 13.02 mo Quetiapine:81%, 5.02 mo Risperidone: 69%, 5.57 mo Discontinuation rate significantly lower and time to all cause discontinuation significantly longer for olanzapine compared to quetiapine and risperidone Ziprasidone: 77%, 4.34 mo Odds of discontinuation olanzapine vs quetiapine (HR=0.52, CI 0.40 to 0.67, p<0.001) olanzapine vs risperidone (HR=0.70 , CI 0.53 to 0.92, p=0.01) olanzapine vs ziprasidone (HR=0.78, CI 0.56 to 1.08, p=0.13) Quetiapine to risperidone: (HR=1.35; CI 1.05 to 1.73, p=0.021) Rates of medication compliance=NSD between groups. Rates of discontinuation and time to all-cause discontinuation median time in mos (illicit drug users) Olanzapine: 74%, 6.75 mo Quetiapine:82%, 4.36 mo Risperidone: 79%, 4.61 mo Ziprasidone: 82%, 3.29 mo, discontinuation rates between olanzapine and other drugs NSly different. olanzapine vs quetiapine: HR=0.90, CI 0.67 to 1.20, p=0.47 olanzapine vs risperidone: HR=0.93, CI 0.70 to 1.24 olanzapine vs ziprasidone :HR=0.75, CI0.53 to 1.07, p=0.11
Companion: Arnold, 2013⁴⁹	

Evidence Table 7. Data abstraction of companion publications of previously included studies in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Lieberman, 2005 ⁴⁸ (CATIE Study) Row 3 of 4 (for results only) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C. Meyer 2008 "change in metabolic.. Meyer 2008 "Impact of antipsychotic treatment Resnick 2008 Swanson 2008 Swartz 2008 Miller 2008 Levine 2011 Companion: Arnold, 2013⁴⁹	

Evidence Table 7. Data abstraction of companion publications of previously included studies in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
Lieberman, 2005 ⁴⁸ (CATIE Study) Row 3 of 4 (for results only) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C. Meyer 2008 "change in metabolic.. Meyer 2008 "Impact of antipsychotic treatment Resnick 2008 Swanson 2008 Swartz 2008 Miller 2008 Levine 2011 Companion: Arnold, 2013⁴⁹		Bold = new data for Update 5.

Evidence Table 7. Data abstraction of companion publications of previously included studies in patients with schizophrenia

Author, year Study design	Eligibility criteria	Interventions (drug, dose, duration)	Allowed other medications	Age Gender Ethnicity
Lieberman, 2005 ⁴⁸ (CATIE Study) Row 4 of 4 (for results only) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C. Meyer 2008 "change in metabolic.. Meyer 2008 "Impact of antipsychotic treatment Resnick 2008 Swanson 2008 Swartz 2008 Miller 2008 Levine 2011 Companion: Arnold, 2013⁴⁹				

Evidence Table 7. Data abstraction of companion publications of previously included studies in patients with schizophrenia

Author, year Study design	Other population characteristics	Number screened/ eligible/ enrolled	Withdrawn/ Lost to follow-up/ Analyzed
Lieberman, 2005 ⁴⁸ (CATIE Study) Row 4 of 4 (for results only) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C. Meyer 2008 "change in metabolic.. Meyer 2008 "Impact of antipsychotic treatment Resnick 2008 Swanson 2008 Swartz 2008 Miller 2008 Levine 2011 Companion: Arnold, 2013⁴⁹			

Evidence Table 7. Data abstraction of companion publications of previously included studies in patients with schizophrenia

Author, year Study design	Results
Lieberman, 2005 ⁴⁸ (CATIE Study) Row 4 of 4 (for results only) Funding: NIH grant, Foundation of Hope of Raleigh, N.C. Meyer 2008 "change in metabolic.. Meyer 2008 "Impact of antipsychotic treatment Resnick 2008 Swanson 2008 Swartz 2008 Miller 2008 Levine 2011	<p>Rates of attaining and maintaining 6 months of remission were higher for the olanzapine group than the perphenazine (p=0.03; adj. p=0.12) and risperidone (p=0.02; adj. p=0.01) groups but differences were not significant after controlling for multiple comparisons.</p> <p>Sensitivity analysis 1: The olanzapine group who did not receive off-label doses (n=79) was significantly (adj. and unadj. p<0.05) more likely to attain any period of sx remission gradients than the four other medication groups studied. Any period of remission was more likely for perphenazine than ziprasidone (p=0.03; adj. p=0.09), and quetiapine than both risperidone (p=0.07; adj. p=0.14) and ziprasidone (p=0.01; adj. p=0.03) groups. Significant differences were not observed between medication groups over 3- or 6-month remission periods.</p> <p>Sensitivity analysis 2: The olanzapine group (n=132) was significantly (unadj. and adj. p<0.05) more likely to attain any period of sx remission gradients than the four other antipsychotic medication groups studied. Any period of sx remission was more likely for groups treated with perphenazine than ziprasidone (p=0.03; adj. p=0.09), quetiapine than risperidone (p=0.07; adj. p =0.14) and ziprasidone (p=0.02; adj. p=0.06). The olanzapine group was significantly (unadj. and adj. p<0.05) more likely to attain 3 months of sx remission than the other four medication groups studied.</p> <p>Olanzapine was associated with a higher 6-month remission rate than quetiapine (p=0.03; adj. p=0.12), risperidone (p=0.01; adj. p=0.06), ziprasidone (p=0.01; adj. p=0.10) and perphenazine (p=0.01; adj. p=0.04).</p> <p>Sensitivity analysis 3: patients randomized after the inclusion of ziprasidone (n=612) Significantly higher rates of any sx remission period for olanzapine than risperidone (p<0.01; adj. p=0.01) and ziprasidone (p<0.01; adj. p=0.01).</p>
Companion: Arnold, 2013⁴⁹	<p>Sx remission over any period was higher for the quetiapine than ziprasidone group (p=0.03; adj. p=0.13). Remission over 3 months was higher for the olanzapine than risperidone (p<0.01; adj. p=0.02), quetiapine (p=0.08; adj. p=0.33) and ziprasidone (p=0.03; adj. p=0.15) groups.</p> <p>Arnold, 2013: Kaplan-Meier estimates of proportion discontinuing antipsychotic medication for lack of efficacy, n (%): Non-Hispanic whites: 159 (28) vs. 168 (45) vs. 173 (46) African Americans: 118 (14) vs. 112 (51) vs. 119 (31) Hispanics: 42 (9) vs. 48 (45) vs. 38 (35)</p>

Evidence Table 7. Data abstraction of companion publications of previously included studies in patients with schizophrenia

Author, year Study design	Adverse effects reported
Lieberman, 2005 ⁴⁸ (CATIE Study) Row 4 of 4 (for results only) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C. Meyer 2008 "change in metabolic.. Meyer 2008 "Impact of antipsychotic treatment Resnick 2008 Swanson 2008 Swartz 2008 Miller 2008 Levine 2011 Companion: Arnold, 2013⁴⁹	

Evidence Table 7. Data abstraction of companion publications of previously included studies in patients with schizophrenia

Author, year Study design	Extrapyramidal symptoms
Lieberman, 2005 ⁴⁸ (CATIE Study) Row 4 of 4 (for results only) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C. Meyer 2008 "change in metabolic.. Meyer 2008 "Impact of antipsychotic treatment Resnick 2008 Swanson 2008 Swartz 2008 Miller 2008 Levine 2011 Companion: Arnold, 2013⁴⁹	

Evidence Table 7. Data abstraction of companion publications of previously included studies in patients with schizophrenia

Author, year Study design	Total withdrawals; withdrawals due to adverse events	Comments
<p>Lieberman, 2005⁴⁸ (CATIE Study) Row 4 of 4 (for results only) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C. Meyer 2008 "change in metabolic.. Meyer 2008 "Impact of antipsychotic treatment Resnick 2008 Swanson 2008 Swartz 2008 Miller 2008 Levine 2011</p> <p>Companion: Arnold, 2013⁴⁹</p>		<p>Bold = new data for Update 5.</p> <p>*Accelerated failure time analysis comparisons for all randomly assigned participants. Total N=977: 500 non- Hispanic whites, 349 African Americans, and 128 Hispanics. Medication $\chi^2=24.1$, $df=2$, $p \leq .001$; race-ethnicity $\chi^2=6.6$, $df=2$, $p=.037$; medication X ethnicity interaction, $\chi^2=6.9$, $df=4$, $p=.142$</p>

Evidence Table 8. Data abstraction of randomized controlled trials in patients with bipolar disorder

Author, Year Country Trial name (Quality rating)	Population	Interventions Duration	Age Gender Ethnicity	Other population characteristics	N
Findling, 2014 ⁵⁰ International NCT00811473 (Fair)	Adolescents aged 10 to 17 y with bipolar I or II disorder and a YMRS score ≤16.	Quetiapine XR 150 to 300 mg/day (n=93) vs. Placebo (n=100) Duration: 8 w	Age, y: 14.0 Gender, % female: 50.0 Ethnicity, %: White: 65.0 Black: 18.0 Other: 8.0 Asian: 5.0 American Indian 3.0	NR	193

Evidence Table 8. Data abstraction of randomized controlled trials in patients with bipolar disorder

Author, Year Country Trial name (Quality rating)	Efficacy/effectiveness outcomes	Harms
Findling, 2014 ⁵⁰ International NCT00811473 (Fair)	Quetiapine XR 150 to 300 mg/day vs. Placebo CDRS-R response rate (≥50% reduction in total score from baseline), n/N (%): 58/92 (63.0) vs. 55/100 (55.0); OR 1.20 (95% CI NR); RR 1.15 (95% CI 0.90 to 1.45) CDRS-R remission rate (score ≤28 at week 8), n/N (%): 42/92 (46.0) vs. 34/100 (34.0); OR 1.60 (95% CI NR); RR 1.34 (95% CI 0.94 to 1.91)	Quetiapine XR 150 to 300 mg/day vs. Placebo Treatment-emergent adverse events, n/N (%): 68/92 (73.9) vs. 66/100 (66.0); RR 1.12 (95% CI 0.93 to 1.35) Withdrawal due to adverse events, n/N (%): 3/92 (3.3) vs. 12/100 (12.0); RR 0.27 (95% CI 0.08 to 0.93)

Evidence Table 8. Data abstraction of randomized controlled trials in patients with bipolar disorder

Author, Year Country Trial name (Quality rating)	Funding/Comments
Findling, 2014 ⁵⁰ International NCT00811473 (Fair)	AstraZeneca

Evidence Table 8. Data abstraction of randomized controlled trials in patients with bipolar disorder

Author, Year Country Trial name (Quality rating)	Population	Interventions Duration	Age Gender Ethnicity	Other population characteristics	N
Findling, 2015 ⁵¹ NCT01244815 (Fair)	Adolescents aged 10-17 y with bipolar I disorder with current manic or mixed episodes, with or without psychotic features, with a YMRS score ≥ 20 and CGI-BP score ≥ 4 .	Asenapine 2.5 mg bid (n=104) vs. Asenapine 5 mg bid (n=99) vs. Asenapine 10 mg bid (n=99) vs. Placebo (n=101) Duration: 3 w	Age, y: 13.8 Gender, % female: 53.0 Ethnicity, %: White: 68.0 Black: 24.0 Mixed race: 6.0 Asian: 1.0	Concomitant stimulant use, %: 23.8 Antipsychotic use (discontinued before baseline), %: 44.8	403

Evidence Table 8. Data abstraction of randomized controlled trials in patients with bipolar disorder

Author, Year Country Trial name (Quality rating)	Efficacy/effectiveness outcomes	Harms
Findling, 2015 ⁵¹ NCT01244815 (Fair)	Asenapine 2.5 mg bid vs. Asenapine 5 mg bid vs. Asenapine 10 mg bid vs. Placebo YMRS responders (≥50% improvement from baseline), n/N (%): 42/101 (42.0) vs. 53/98 (54.0) vs. 51/98 (52.0) vs. 27/98 (28.0) Asenapine 2.5 mg bid vs. Placebo, n/N (%): OR 1.9 (95% CI 1.0 to 3.4) Asenapine 5 mg bid vs. Placebo, n/N (%): OR 3.2 (95% CI 1.7 to 5.8) Asenapine 10 mg bid vs. Placebo, n/N (%): OR 2.9 (95% CI 1.6 to 5.3)	Asenapine 2.5 mg bid vs. Asenapine 5 mg bid vs. Asenapine 10 mg bid vs. Placebo Overall adverse events (treatment emergent), n/N (%): 78/104 (75.0) vs. 72/99 (73.0) vs. 85/99 (86.0) vs. 56/101 (55.0) Asenapine 2.5 mg bid vs. Placebo, n/N (%): RR 1.35 (95% CI 1.10 to 1.66) Asenapine 5 mg bid vs. Placebo, n/N (%): RR 1.31 (95% CI 1.06 to 1.62) Asenapine 10 mg bid vs. Placebo, n/N (%): RR 1.55 (95% CI 1.28 to 1.88) Withdrawal due to adverse events, n/N (%): 7/104 (6.7) vs. 5/99 (5.1) vs. 5/99 (5.1) vs. 4/101 (4.0) Asenapine 2.5 mg bid vs. Placebo, n/N (%): RR 1.70 (95% CI 0.51 to 5.63) Asenapine 5 mg bid vs. Placebo, n/N (%): RR 1.28 (95% CI 0.35 to 4.61) Asenapine 10 mg bid vs. Placebo, n/N (%): RR 1.28 (95% CI 0.35 to 4.61) Extrapyramidal symptoms, n/N (%): 4/104 (3.8) vs. 4/99 (4.0) vs. 5/99 (5.1) vs. 2/101 (2.0) Weight gain >7%, n/N (%): 11/92 (12.0) vs. 8/90 (8.9) vs. 7/87 (8.0) vs. 1/89 (1.1) Asenapine 2.5 mg bid vs. Asenapine 10 mg bid, n/N (%): RR 10.64 (95% CI 1.40 to 80.73) Asenapine 5 mg bid vs. Placebo, n/N (%): RR 8.00 (95% CI 1.02 to 62.64) Asenapine 10 mg bid vs. Placebo, n/N (%): RR 7.16 (95% CI 0.90 to 57.00)

Evidence Table 8. Data abstraction of randomized controlled trials in patients with bipolar disorder

Author, Year Country Trial name (Quality rating)	Funding/Comments
Findling, 2015 ⁵¹ NCT01244815 (Fair)	Merck

Evidence Table 8. Data abstraction of randomized controlled trials in patients with bipolar disorder

Author, Year Country Trial name (Quality rating)	Population	Interventions Duration	Age Gender Ethnicity	Other population characteristics	N
Kowatch, 2015 ⁵² (Fair)	Outpatients aged 3 to <8 y, with bipolar I disorder and a YMRS score ≥ 20 .	Risperidone, mean dose 0.5 mg/day (n=18) vs. Placebo (n=7) (Valproic acid group not abstracted) Duration: 6 w	Age, y: 5.3 Gender, % female sex: 36.0 Ethnicity, %: White: 64.0 Black: 12.0 Hispanic: 12.0 Other: 8.0 Asian: 4.0	Comorbid ADHD, %: 26.0	25

Evidence Table 8. Data abstraction of randomized controlled trials in patients with bipolar disorder

Author, Year Country Trial name (Quality rating)	Efficacy/effectiveness outcomes	Harms
Kowatch, 2015 ⁵² (Fair)	Risperidone, mean dose 0.5 mg/day vs. Placebo YMRS responders ($\geq 50\%$ improvement from baseline): HR 6.97 (95% CI 1.9 to 25.9) [product-limit survival estimate, no proportions reported]	Risperidone, mean dose 0.5 mg/day vs. Placebo Withdrawal due to adverse events, n/N (%): 2/18 (11.0) vs. 0/7 (0); RR 2.11 (95% CI 0.11 to 39.11)

Evidence Table 8. Data abstraction of randomized controlled trials in patients with bipolar disorder

Author, Year Country Trial name (Quality rating)	Funding/Comments
Kowatch, 2015 ⁵² (Fair)	NIMH

Evidence Table 9. Quality assessment of randomized controlled trials in patients with bipolar disorder

Author, Year Study Name	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors blinded?	Clinician blinded?	Patient blinded?	Intention to treat?
Findling, 2013 ⁵³ NCT00265330 (OLE) and NCT00257166 (RCT)	Unclear	Unclear	Yes	Unclear, described as double-blind	Unclear, described as double-blind	Unclear, described as double- blind	No
Findling, 2014 ⁵⁰ NCT00811473	Unclear	Unclear	Yes	Unclear, described as double-blind	Unclear, described as double-blind	Unclear, described as double- blind	Yes
Findling, 2015 ⁵¹ NCT01244815	Yes	Yes	No	Yes	Yes	Yes	Yes
Kowatch, 2015 ⁵²	Unclear	Unclear	No	Unclear	Yes	Yes	Yes
Masi, 2015 ⁵⁴	Unclear	Unclear	Yes	Unclear	No	No	No
Rezayat, 2014 ⁵⁵	Yes	Unclear	No	Unclear	Yes	Yes	No

Evidence Table 9. Quality assessment of randomized controlled trials in patients with bipolar disorder

Author, Year Study Name	Acceptable level of overall attrition ($\leq 20\%$)?	Acceptable level of differential attrition ($< 10\%$)?	Overall quality
Findling, 2013 ⁵³ NCT00265330 (OLE) and NCT00257166 (RCT)	No	Yes	Poor
Findling, 2014 ⁵⁰ NCT00811473	Yes	Yes	Fair
Findling, 2015 ⁵¹ NCT01244815	Yes	Yes	Fair
Kowatch, 2015 ⁵²	Yes	Yes	Fair
Masi, 2015 ⁵⁴	Yes	No	Poor
Rezayat, 2014 ⁵⁵	Yes	Yes	Poor

Evidence Table 10. Data abstraction of observational studies in patients with bipolar disorder

Author, Year Country (Quality rating)	Study Design	Interventions	Time frame Data source	N	Population characteristics
Koek, 2012 ⁵⁶ United States (Good)	Retrospective chart review	Risperidone (n=30) vs. Risperidone + mood stabilizer (n=70) vs. Olanzapine (n=20) vs. Olanzapine + mood stabilizer (n=62) vs. Quetiapine (n=19) vs. Quetiapine + mood stabilizer (n=34) (First-generation antipsychotic groups not abstracted)	Time frame: 1994 to December 31, 2002 Data source: Veterans Administration Greater Los Angeles Healthcare System Computerized Patient Record System	235	Patients with chart diagnosis of bipolar I or II, schizoaffective disorder bipolar type, or bipolar NOS Mean age, y: 47.0 Gender, % female: 12.0

Evidence Table 10. Data abstraction of observational studies in patients with bipolar disorder

Author, Year Country (Quality rating)	Efficacy/effectiveness outcomes	Harms	Funding/Comments
Koek, 2012 ⁵⁶ United States (Good)	Risperidone vs. Olanzapine vs. Quetiapine (monotherapy) Hospitalization for suicidal ideation or intent, n/N (%): 1/30 (3.3) vs. 1/20 (5.0) vs. 2/19 (10.5) Attempted suicide, n/N (%): 1/30 (3.3) vs. 1/20 (5.0) vs. 0 (0) Risperidone + mood stabilizer vs. Olanzapine + mood stabilizer vs. Quetiapine + mood stabilizer (combination therapy with mood stabilizer) Hospitalization for suicidal ideation or intent, n/N (%): 13/70 (18.6) vs. 4/62 (6.5) vs. 2/34 (5.9) Attempted suicide, n/N (%): 1/70 (1.4) vs. 0 (0) vs. 0 (0)	NR	Abbott Laboratories

Evidence Table 11. Quality assessment of observational studies in patients with bipolar disorder

Author, Year	Non-biased selection?	High overall loss to follow-up or differential loss to follow up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Koek, 2012 ⁵⁶	Yes	No	Yes	Yes	Yes	Yes	Yes	Good

Evidence Table 12. Data abstraction of randomized controlled trials in patients with autism spectrum disorder

Author, Year Country Trial name (Quality rating)	Population	Interventions Duration	Age Gender Ethnicity	Other population characteristics	N
Ghanizadeh, 2014 ⁵⁷ Iran IRCT201110233930 N15 (Fair)	Children and adolescents 4–18 y with autism spectrum disorder (DSM-IV and ADI-R diagnosis).	Risperidone titrated to 2–3 mg/d, mean dose 5.5 mg/d (n=29) vs. Aripiprazole titrated to 10–15 mg/d, mean dose 1.12 mg/d (n=30) twice daily Duration: 2 m	Age, mean y: 9.6 Gender, % female: 18.6 Ethnicity, %: NR	CGI Severity, %: Severely ill: 50.0 Among most extremely ill: 50.0	59
Loebel, 2016 ⁵⁸ United States NCT01911442 (Fair)	Children and adolescents 6–17 y with autistic disorder and serious behavioral problems (DSM-IV and ADI-R diagnosis).	Lurasidone 20 mg/day (n=50) vs. Lurasidone 60 mg/day (n=49) vs. Placebo (n=51) once-daily Duration: 6 w	Age, mean y: 10.7 Gender, % female: 18.0 Ethnicity, %: White: 77 Black: 16 Other: 7	ABC irritability/agitation: 28 CGI-S: 4.9	150

Evidence Table 12. Data abstraction of randomized controlled trials in patients with autism spectrum disorder

Author, Year Country Trial name (Quality rating)	Efficacy/effectiveness outcomes	Harms
Ghanizadeh, 2014 ⁵⁷ Iran IRCT201110233930 N15 (Fair)	Risperidone 2-3 mg/d vs. Aripiprazole 10-15 mg/d Overall discontinuation, n/N (%): 3/29 (10.3) vs. 3/30 (10.0) CGI scores at endpoint, n/N (%): "Much improved": 5/29 (17.2) vs. 9/30 (30.0) "Minimally improved": 12/29 (41.4) vs. 7/30 (23.3) "No change": 8/29 (27.6) vs. 5/30 (16.7) "Minimally worse": 2/29 (6.9) vs. 3/30 (10.0)	Risperidone 2-3 mg/d vs. Aripiprazole 10-15 mg/d Seizure, n (%): 1 (3.3) vs. 0
Loebel, 2016 ⁵⁸ United States NCT01911442 (Fair)	Lurasidone 20 mg/d vs. Lurasidone 60 mg/d vs. Placebo CGI Severity score, LS mean change (SE): -1.1 (0.2) vs. -1.0 (0.2) vs. -0.7 (0.2) Treatment difference: Lurasidone 20 mg/d vs. Placebo: -0.3 (95% CI -0.8 to 0.2) Lurasidone 60 mg/d vs. Placebo: -0.3 (95% CI -0.8 to 0.2) CGI Improvement score, LS mean at 6 w (SE): 2.8 (0.2) vs. 3.1 (0.2) vs. 3.4 (0.2) Treatment difference: Lurasidone 20 mg/d vs. Placebo: -0.6 (95% CI -1.1 to 0) Lurasidone 60 mg/d vs. Placebo: -0.3 (95% CI -0.8 to 0.2) CY-BOCS Compulsions, LS mean change (SE): -1.0 (0.5) vs. -1.0 (0.4) vs. -1.2 (0.5) Treatment difference: Lurasidone 20 mg/d vs. Placebo: 0.2 (95% CI -1.2 to 1.5) Lurasidone 60 mg/d vs. Placebo: 0.2 (95% CI -1.1 to 1.5) All-cause discontinuation, n/N (%): 6/49 (12.2) vs. 4/51 (7.8) vs. 12/50 (24.0) CGI-Improvement "very much improved" at LOCF-endpoint, %: 12.5 vs. 5.9 vs. 8.2 CGI-Improvement "much improved" at LOCF-endpoint, %: 27.9 vs. 22.4	Lurasidone 20 mg/d vs. Lurasidone 60 mg/d vs. Placebo Discontinuation rates due to AE, n/N (%): 2/49 (4.1) vs. 2/51 (3.9) vs. 4/50 (8.0) Any AE, n/N (%): 35/49 (71.4) vs. 38/51 (74.5) vs. 28/49 (57.1) Weight increased, n/N (%): 1/49 (2.0) vs. 4/51 (7.8) vs. 1/49 (2.0)

Evidence Table 12. Data abstraction of randomized controlled trials in patients with autism spectrum disorder

Author, Year Country Trial name (Quality rating)	Funding/Comments
Ghanizadeh, 2014 ⁵⁷ Iran IRCT201110233930 N15 (Fair)	Funding: Shiraz University of Medical Sciences
Loebel, 2016 ⁵⁸ United States NCT01911442 (Fair)	Funding: Sunovion Pharmaceuticals Inc.

Evidence Table 13. Quality assessment of randomized controlled trials in patients with autism spectrum disorder

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors blinded?	Clinician blinded?	Patient blinded?	Intention to treat?
Findling, 2014 ⁵⁹	Yes	Yes	No	Unclear	Yes	Yes	Yes
Ghanizadeh, 2014 ⁵⁷	Unclear	Unclear	Yes	Yes	No	No; some blinded, but not all	Yes
Loebel, 2016 ⁵⁸	Yes	Yes	No	Unclear	Unclear; described as double blind	Yes; matching placebo	Yes

Evidence Table 13. Quality assessment of randomized controlled trials in patients with autism spectrum disorder

Author, Year	Acceptable level of overall attrition ($\leq 20\%$)?	Acceptable level of differential attrition ($< 10\%$)?	Overall quality
Findling, 2014 ⁵⁹	No	Yes	Poor
Ghanizadeh, 2014 ⁵⁷	Yes	Yes	Fair
Loebel, 2016 ⁵⁸	Yes	No	Fair

Evidence Table 14. Data abstraction of observational studies in patients with autism spectrum disorder

Author, Year Country (Quality rating)	Study Design	Interventions	Time frame Data source	N	Population characteristics
Aman, 2015 ⁶⁰ United States (Fair)	Naturalistic study	Risperidone vs. Placebo	Time frame: Assessment 21.4 months after entry into parent trial Data source: RUPP 2002	84	Age, mean y: 8.8 Gender, % female: 20.2 Ethnicity, %: White (not of Hispanic origin): 67.9 Black (not of Hispanic Origin): 11.9 Asian/Pacific Islander: 7.1 Hispanic: 6.0 Other: 7.1
Wink, 2014 ⁶¹ United States (Fair)	Longitudinal	Risperidone vs. Aripiprazole	Time frame: 17/2004- 04/2012 Data source: RedCap medication management database	142	Age, mean y: 9.1 Gender, % female: 18.0 Ethnicity, %: Caucasian: 77.0 African American: 8.0 Hispanic: 1.0 Other Race/Ethnicity: 1.0

Evidence Table 14. Data abstraction of observational studies in patients with autism spectrum disorder

Author, Year Country (Quality rating)	Efficacy/effectiveness outcomes	Harms
Aman, 2015 ⁶⁰ United States (Fair)	Risperidone vs. Placebo CY-BOCS* total score at follow up, mean (SD): 11.67 (4.48) vs. 13.08 (4.60) Vineland Adaptive Behavior Scales, mean at follow up (SD): Daily Living Skills: 40.56 (20.30) vs. 38.54 (21.60) Social Skills: 50.63 (15.10) vs. 44.21 (18.07) CGI Severity, mean at follow up (SD): 4.40 (0.89) vs. 4.65 (1.09) M-RLRS**, mean at follow up (SD): Sensory Motor: 4.67 (3.06) vs. 4.20 (3.42) Social Relationships: 1.02 (4.23) vs. 2.40 (3.16) Affectual Responses: 3.49 (1.88) vs. 4.04 (1.88) Sensory Responses: 11.02 (7.10) vs. 14.80 (7.08) Language: -0.15 (3.99) vs. 1.96 (4.30)	Risperidone vs. Placebo Seizure, n: 2 (3.7) vs. 0 Weight gain, n: 3 (5.5) vs. NR
Wink, 2014 ⁶¹ United States (Fair)	Risperidone vs. Aripiprazole Final CGI-I score, mean (SD): 3.2 (1.2) vs. 2.9 (1.2) BMI change per year of treatment, mean (SD): 2.36 (3.80) vs. 2.05 (5.02) BMI Z-score change per year of treatment, mean (SD): 0.53 (1.21) vs. 0.56 (2.21)	NR

Evidence Table 14. Data abstraction of observational studies in patients with autism spectrum disorder

Author, Year Country (Quality rating)	Funding/Comments
Aman, 2015 ⁶⁰ United States (Fair)	Funding: Mental Health (NIMH), National Institutes of Health (NIH), and NIH/National Center for Research Resources (NIH/NCRR) *Children's Yale-Brown Obsessive Compulsive Scale (assessing symptoms and severity). **Modified Real Life Rating Scale for Autism.
Wink, 2014 ⁶¹ United States (Fair)	NR

Evidence Table 15. Quality assessment of observational studies in patients with autism spectrum disorder

Author, Year	Non-biased selection?	High overall loss to follow-up or differential loss to follow up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Aman, 2015 ⁶⁰	No; only risperidone responders randomized	No	Yes	Yes	Yes	Yes	Yes	Fair
Wink, 2014 ⁶¹	Unclear	No	Yes	Yes	Yes	Yes	Yes	Fair

Evidence Table 16. Data abstraction of systematic reviews in patients with autism spectrum disorder

Author, Year (Quality rating)	Aims	Time period covered	Patient N Study N	Characteristics of identified articles: study designs	Characteristics of identified articles: populations
Hirsch, 2016 ⁶²	To assess the safety and efficacy of aripiprazole as medication treatment for individuals with autism spectrum disorders (ASD).	Searches 1990 through October 2015.	Patient N = 316 Study N = 3	RCTs	ASD

Evidence Table 16. Data abstraction of systematic reviews in patients with autism spectrum disorder

Author, Year (Quality rating)	Characteristics of identified articles: interventions	Efficacy/effectiveness outcomes
Hirsch, 2016 ⁶²	Aripiprazole vs. placebo Duration: 8 - 26 weeks.	Aripiprazole vs. placebo: ABC Irritability subscale mean score changes, n, mean difference (95% CI): 210 vs. 98, -6.17 (-9.07 to -3.26) ABC Hyperactivity subscale mean score changes, n, mean difference (95% CI): 210 vs. 98, -7.93 (-10.98 to -4.88) ABC Stereotypy subscale mean score changes, n, mean difference (95% CI): 210 vs. 98, -2.66 (-3.55 to -1.77) ABC Inappropriate Speech subscale mean score changes, n, mean difference (95% CI): 210 vs. 98, -1.43 (-2.60 to -0.27) ABC Lethargy/Withdrawal subscale mean score changes, n, mean difference (95% CI): 210 vs. 98, -1.19 (-2.77 to 0.40) CGI Severity subscale mean score changes, n, mean difference (95% CI): 210 vs. 98, -0.57 (-0.96 to -0.18) CGI Improvement subscale mean score changes, n, mean difference (95% CI): 210 vs. 98, -1.33 (-1.75 to -0.92) CY-BOCS mean scores changes, n, mean difference (95% CI): 210 vs. 98, -1.93 (-3.86 to 0.00)

Evidence Table 16. Data abstraction of systematic reviews in patients with autism spectrum disorder

Author, Year (Quality rating)	Harms outcomes	Funding/Comments
Hirsch, 2016 ⁶²	Aripiprazole vs. placebo: Any extrapyramidal symptom event (side effect), n, Risk Ratio (95% CI): 212 vs. 101, 1.89 (0.98 to 3.66) Clinically relevant weight gain, n, Risk Ratio (95% CI): 210 vs. 98, 3.78 (1.78 to 8.02) Weight gain, n, mean difference (95% CI): 210 vs. 98, 1.13 (0.71 to 1.54) BMI change from baseline, n, mean difference (95% CI): 215 vs. 98, 0.44 (-0.27 to 1.16)	University of Calgary, Department of Clinical Neurosciences, Canada.

Evidence Table 17. Data abstraction of pooled analyses in patients with autism spectrum disorder

Author, Year Country Trial Name	Population	Interventions Duration	Age Gender Ethnicity	Other population characteristics	N
Mankoski, 2013 ⁶³ NCT00332241 and NCT00337571	Ages 6 to 17 y with autistic disorder (DSM-IV-TR and ADI-R).	Aripiprazole flexibly dosed 2 to 15 mg/d (Owen, 2009) or fixed-dose (Marcus, 2009) vs. placebo (data from both studies pooled then stratified by prior antipsychotic exposure) Antipsychotic naïve (AN) (n=256) vs. Prior antipsychotic exposure (PAE) (n = 57) Duration: 8 w	Age, y, range: 9.4 to 10.0 Gender, % female, range: 3.5 to 12.7 Ethnicity: NR	Antipsychotic drug-naïve, %: 81.8 ABC-I scores: 28.4 to 31.0 CGI-S scores: AN: 4.8 to 4.9 PAE: 5.2 to 5.3	316

Evidence Table 17. Data abstraction of pooled analyses in patients with autism spectrum disorder

Author, Year Country Trial Name	Efficacy/effectiveness outcomes	Harms	Funding/Comments
Mankoski, 2013 ⁶³ NCT00332241 and NCT00337571	NR	AN (Aripiprazole vs. placebo) vs. PAE (Aripiprazole vs. placebo) Discontinuation due to AE: 10.8 vs. 7.5 vs. 8.3 vs. 4.8 Extrapyramidal disorder: 12/176 (6.8) vs. 0 vs. 1/36 (2.8) vs. 0 Clinically significant weight gain (≥7% increase from baseline): AN: RR 4.6 (95% CI 1.8 to 12.1) PAE, n/N (%): 3/32 (9.2) vs. 0	Funding: Bristol-Myers Squibb

Evidence Table 18. Data abstraction of companion publications of previously included studies in patients with autism spectrum disorder

Author, year Country Trial name (Quality score)	N	Duration	Study design setting	Population	Eligibility criteria
McCracken, 2002 ⁶⁴ United States RUPP Trial (Fair) Companions: Arnold, 2003 ⁶⁵ Aman, 2005 ⁶⁶ Arnold, 2010 ⁶⁷ Levine, 2016⁶⁸	101	8 weeks	Double-blind, multicenter.	Autism	Ages 5 to 17 years, weight at least 15 kg, mental age of at least 18 months; meeting criteria for autistic disorder described in DSM-IV, with tantrums, aggression, self-injurious behavior, or a combination of these.

Evidence Table 18. Data abstraction of companion publications of previously included studies in patients with autism spectrum disorder

Author, year Country Trial name (Quality score)	Exclusions	Interventions	Allowed other medications/interventions
McCracken, 2002 ⁶⁴ United States RUPP Trial (Fair) Companions: Arnold, 2003 ⁶⁵ Aman, 2005 ⁶⁶ Arnold, 2010 ⁶⁷ Levine, 2016 ⁶⁸	Serious medical disorders and other psychiatric disorders requiring medication; receiving a psychotropic drug that was deemed effective for the treatment of aggression, tantrums, or self-injurious behavior.	Children 20 to 45 kg: risperidone 0.5 mg, increased to 1 mg on day 4. Dose gradually increased in 0.5 mg increments to a maximum of 2.5 mg per day by day 29 Children over 45 kg: slightly accelerated dose schedule used, maximum dose of 3.5 mg. Children less than 20 kg: initial dose 0.25 mg. Scheduled dose increases could be delayed because of adverse effects or because of marked improvement at a lower dose. Dose reductions to manage side effects were allowed at any time, but there were no dose increases after day 29.	Treatment with an anticonvulsant agent for seizure control was allowed if the dose had been unchanged for at least 4 weeks and if there had been no seizures for at least 6 months.

Evidence Table 18. Data abstraction of companion publications of previously included studies in patients with autism spectrum disorder

Author, year Country Trial name (Quality score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/enrolled	Number withdrawn/ lost to follow-up/ analyzed
McCracken, 2002 ⁶⁴ United States RUPP Trial (Fair) Companions: Arnold, 2003 ⁶⁵ Aman, 2005 ⁶⁶ Arnold, 2010 ⁶⁷ Levine, 2016⁶⁸	Mean age 8.8 (SD 2.7), range 5-17 81% male 66% white, 11% black, 7% Hispanic, 8% Asian, 8% other ethnicity	Mental development (risperidone vs placebo) Average or above-average IQ: 7% vs 4% Borderline IQ: 17% vs 9% Mild or moderate retardation: 43% vs 51% Severe retardation: 33% vs 36% (NS)	270 screened/158 eligible/101 enrolled	18 withdrawn/3 lost to followup/101 analyzed/

Evidence Table 18. Data abstraction of companion publications of previously included studies in patients with autism spectrum disorder

Author, year Country Trial name (Quality score)	Results	Overall withdrawals/ Withdrawals due to adverse events
McCracken, 2002 ⁶⁴ United States RUPP Trial (Fair) Companions: Arnold, 2003 ⁶⁵ Aman, 2005 ⁶⁶ Arnold, 2010 ⁶⁷ Levine, 2016⁶⁸	Change in mean Irritability score from baseline to 8 weeks risperidone: -14.9 (56.9% decrease) placebo: -3.6 (14.1% decrease) (p<0.001) Positive response (at least 25% improvement on Irritability subscale and rating of much improved or improved on CGI-I) risperidone: 34/49 (69%) placebo: 6/52 (12%) (p<0.001) Moderator analysis: Mean decrease in ABC irritability subscale score from baseline at 8 weeks [reported as mean, (SD)] Placebo vs risperidone sex: interaction: $\chi^2=2.21$, p=0.14, Pool variance=78.61 male: 5.17 (7.43) vs 15.25 (10.34), female: 0.83 (8.98) vs 18.33 (7.48) Age: interaction: $\chi^2=0.16$, p=0.69, pooled variance=79.75 >8.15 years: 2.87 (8.10) vs 14.61 (10.81), <8.15 years: 6.05 (7.34) vs 16.70 (9.24) Education: interaction $\chi^2=1.61$, p=0.20, pooled variance: 77.18 university degree: 3.70 (7.00) vs 13.00 (7.87), <university degree 4.86 (8.66) vs 18.61 (10.87) Ethnicity: interaction $\chi^2=0.01$, p=0.91, pooled variance=81.56 non-Caucasian: 4.67 (10.53) vs 15.50 (8.82), Caucasian: 4.11 (6.10) vs 16.03 (10.39) Income: interaction $\chi^2=0.09$, p=0.91, pooled variance: 81.56 High: 5.20 (5.01) vs 15 (10.43), low: 4.48 (8.87) vs 16.32 (8.98) Levine, 2016: Association of initial disease severity with irritability and lethargy in ABC. Symptom improvement in moderate to severe autism correlated with initial disease severity with risperidone. No interaction between treatment and initial disease severity with other subscales of ABC or CGI.	3/49 (6%) risperidone 18/52 (35%) placebo (p=0.001)/ No withdrawals due to AEs

Evidence Table 18. Data abstraction of companion publications of previously included studies in patients with autism spectrum disorder

Author, year Country Trial name (Quality score)	Adverse events	Comments
McCracken, 2002 ⁶⁴ United States RUPP Trial (Fair) Companions: Arnold, 2003 ⁶⁵ Aman, 2005 ⁶⁶ Arnold, 2010 ⁶⁷ Levine, 2016⁶⁸	Mean weight gain at 8 weeks: risperidone: 2.7 kg (SD 2.9) placebo: 0.8 kg (SD 2.2) (p<0.001) No extrapyramidal symptoms in either group. No serious adverse events in risperidone group. Parents reported 5 neurological side effects, of these, tremor was significantly more common in the risperidone group (p=0.06) 60 different adverse events recorded, 29 of which occurred in 5% or more of patients. Adverse events with a significantly different incidence (risperidone vs placebo) Increased appetite (mild): 49% vs 25% (p=0.03) Increased appetite (moderate): 24% vs 4% (p=0.01) Fatigue: 59% vs 27% (p=0.003) Drowsiness: 49% vs 12% (p<0.001) Drooling: 27% vs 6% (p=0.02) Dizziness: 16% vs 4% (p=0.05)	Bold = new data for Update 5

Evidence Table 19. Data abstraction of observational studies in patients with mixed diagnoses

Author, Year Country Study Name (Quality rating)	Study Design	Interventions	Time frame Data source	N	Population characteristics
Jiang, 2014 ⁶⁹ United States (Fair)	Retrospective cohort	Ziprasidone (n=4,665) vs. Olanzapine (n=4,913)	Time frame: January 2007 to December 2010 Data source: Lifelink Health Plan Claims database	9,097	Age, y: 43.6 Gender, % female: 62.5 Duration of current illness, d: 77.6 Hospitalizations (n in baseline period): 7.1 Schizoaffective, %: 8.4
Lipscombe, 2014 ⁷⁰ Canada (Fair)	Retrospective cohort	Risperidone (reference group) vs. Olanzapine (also arms for "Other atypical antipsychotics"* and "All typical antipsychotics"**)	Time frame: April 1998 to March 2010 Data source: health data from 7 provinces and UK Clinical Practice Research Datalink	725,489 (patients)	Age: 18-65 y: 44.7% ≥66 y: 55.3% Gender, % female: 18-65 y: 52.5 ≥66 y: 60.6

Evidence Table 19. Data abstraction of observational studies in patients with mixed diagnoses

Author, Year Country Study Name (Quality rating)	Efficacy/effectiveness outcomes	Harms	Funding/Comments
Jiang, 2014 ⁶⁹ United States (Fair)	Ziprasidone vs. Olanzapine Hospitalization* Number of ED attendances, total effect (Poisson regression): -0.076 (95% CI -0.114 to -0.039) Number of hospitalizations, total effect (Poisson regression): -1.117 (95% CI -1.127 to -1.017)	NR	Funding: None *Adjusted effects of ziprasidone compared with olanzapine (ED attendances n=6,687; hospitalizations n=3,998)
Lipscombe, 2014 ⁷⁰ Canada (Fair)	NR	Risperidone vs. Olanzapine Hyperglycemic emergency, n/N (%)*** Age 18-65y: 76,212/324,512 (23.5) vs. 47,699/324,512 (14.7) Age ≥66 y: 158,019/400,977 (39.4) vs. 52,351/400,977 (13.1)	Funding: Canadian Institutes of Health Research *In 18-65 y, 98.7% quetiapine; ≥66 y, 99.6% quetiapine **E.g. haloperidol, phenothiazines ***Hyperglycemic emergency defined as first hospital admission in the 365 days following drug initiation (cohort entry) that was associated with a pre-admission diagnosis of hyperglycemia, DKA, or hyperglycemic hyperosmolar state (HHS) using the ICD-9 and ICD-10 diagnosis codes.

Evidence Table 19. Data abstraction of observational studies in patients with mixed diagnoses

Author, Year Country Study Name (Quality rating)	Study Design	Interventions	Time frame Data source	N	Population characteristics
Pasternak, 2014 ⁷¹ Denmark (Good)	Retrospective cohort	Olanzapine (n=15,744) vs. Quetiapine (n=18,717) vs. Risperidone (n=14,134)	Time frame: January 1, 2007 to December 31, 2011 Data source: Central Person Register of Denmark	48,625	Age, y: 38.9 Gender, % female: 50.3 Psychiatric hospitalizations/ED visits in previous year, %: 10.0 Alcohol or drug abuse, %: 12.3

Evidence Table 19. Data abstraction of observational studies in patients with mixed diagnoses

Author, Year Country Study Name (Quality rating)	Efficacy/effectiveness outcomes	Harms	Funding/Comments
Pasternak, 2014 ⁷¹ Denmark (Good)	NR	<p>Olanzapine vs. Quetiapine vs. Risperidone</p> <p>All-cause mortality, n events, rate per 1000 person-years, adjusted HR (95% CI)*: 99, 17.5, HR 1.09 (95% CI 0.79 to 1.49) vs. 60, 8.6, HR 0.75 (95% CI 0.53 to 1.07) vs. 62, 12.4, HR 1 (reference)</p> <p>Cardiovascular mortality, n events, rate per 1000 person-years, adjusted HR (95% CI)*: 9, 1.6, HR 0.99 (95% CI 0.37 to 2.67) vs. 6, 0.9, HR 0.76 (95% CI 0.25 to 2.28) vs. 7, 1.4, HR 1 (reference)</p> <p>Ischemic stroke, n events, rate per 1000 person-years, adjusted HR (95% CI)*: 9, 1.6, HR 1.40 (95% CI 0.47 to 4.19 vs. 7, 1.0, HR 1.12 (95% CI 0.35 to 3.57) vs. 5, 1.0, HR 1 (reference)</p> <p>Acute coronary syndrome, n events, rate per 1000 person-years, adjusted HR (95% CI)*: 12, 2.1, HR 0.67 (95% CI, 0.31 to 1.44) vs. 10, 1.4, HR 0.62 (95% CI 0.27 to 1.41) vs. 14, 2.8, HR 1 (reference)</p>	<p>Funding: Danish Health and Medicines Authority</p> <p>*Adjusted for disease risk score.</p>

Evidence Table 20. Quality assessment of observational studies in patients with mixed diagnoses

Author, Year	Non-biased selection?	High overall loss to follow-up or differential loss to follow up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Jiang, 2014 ⁶⁹	Yes	No	Yes	Yes for persistence, unclear for hospitalizations/ED visits	Yes for persistence, unclear for hospitalizations/ED visits	Yes	Yes	Fair
Lipscombe, 2014 ⁷⁰	Yes	No	Yes	Yes	Unclear	Yes	Yes	Fair
Pasternak, 2014 ⁷¹	Yes	No	Yes	Yes	Yes	Yes	Yes	Good

Evidence Table 21. Data abstraction of systematic reviews in patients with any diagnosis taking antipsychotic treatment

Author, Year (Quality rating)	Aims	Time period covered	Patient N Study N	Characteristics of identified articles: study designs	Characteristics of identified articles: populations
Galling, 2016 ⁷²	To assess type 2 diabetes mellitus risk associated with antipsychotic treatment in youth.	Searches through May 4, 2015.	Patient N = 1,826,029 Study N = 13 (14 cohorts)	Retrospective database investigations, N = 11 (patient N = 1,825,343) Prospective naturalistic cohort investigations, N = 2 (patient n = 565) Pooled data, 1 publication of 6 prospective studies (patient N = 121) Studies with psychiatric controls: N = 7 Studies with healthy controls: N = 8 (Two studies did not have a control group)	Patients 0 to 24 y old exposed to antipsychotics for at least 3 m without type 2 diabetes mellitus. Age, mean: 13.9 Gender, % female: 44.0 Diagnosis, antipsychotic exposed and psychiatric controls: Disruptive behavior or ADHD, %: 49.4 (exposed and controls) Depression, %: 26.8 Mood disorder, %: 28.5 (exposed and controls) Bipolar depression, %: 16.2 (Data for healthy controls not abstracted)

Evidence Table 21. Data abstraction of systematic reviews in patients with any diagnosis taking antipsychotic treatment

Author, Year (Quality rating)	Characteristics of identified articles: interventions	Efficacy/effectiveness outcomes
Galling, 2016 ⁷²	Antipsychotics, including first- and second-generation.	NR

Evidence Table 21. Data abstraction of systematic reviews in patients with any diagnosis taking antipsychotic treatment

Author, Year (Quality rating)	Harms outcomes	Funding/Comments
Galling, 2016 ⁷²	<p>Antipsychotic exposed vs. Psychiatric controls</p> <p>Type 2 diabetes mellitus risk, unadjusted, cumulative event rate (95% CI) per 1,000 patients: 5.72 (95% CI 3.45 to 9.48) vs. 2.61 (95% CI 0.80 to 8.52)</p> <p>Risk of type 2 diabetes mellitus, OR (95% CI): 2.09 (95% CI 1.50 to 2.90)</p> <p>Type 2 diabetes mellitus, incidence rate (95% CI) per 1,000 patient-years: 3.09 (95% CI 2.35 to 3.82) vs. 1.74 (95% CI 1.10 to 2.38)</p> <p>Risk of type 2 diabetes mellitus, IRR (95% CI): 1.79 (95% CI 1.31 to 2.44)</p>	<p>Zucker Hillside Hospital, through the National Institute of Mental Health Advanced Center for Intervention and Services Research for the Study of Schizophrenia and AHRQ grants.</p>

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