

Atypical Antipsychotics

Key Questions and Inclusion Criteria

Update # 3

Key Questions

1. For adults and adolescents with schizophrenia and other psychotic disorders, do the atypical antipsychotic drugs differ in benefits (efficacy, effectiveness) or harms?
 - a. For adults and adolescents experiencing a first episode of schizophrenia, do the atypical antipsychotic drugs differ in benefits (efficacy, effectiveness) or harms?
2. For adults and youths with bipolar disorder, do the atypical antipsychotic drugs differ in benefits (efficacy, effectiveness) or harms?
3. For adults with major depressive disorder, do the atypical antipsychotic drugs differ in benefits (efficacy, effectiveness) or harms?
4. For adults and adolescents with schizophrenia (including first-episode) and other psychotic disorders, adults and youths with bipolar disorder, or adults with major depressive disorder, what is the comparative evidence that differences in adherence or persistence among the atypical antipsychotic drugs correlate with a difference in clinical outcomes?
5. For youths with pervasive developmental disorders, do the atypical antipsychotic drugs differ in benefits (efficacy, effectiveness) or harms?
6. For youths with disruptive behavior disorders, do the atypical antipsychotic drugs differ in benefits (efficacy, effectiveness) or harms?
7. For older adults with Behavioral and Psychological Symptoms of Dementia (BPSD), do the atypical antipsychotic drugs differ in benefits (efficacy, effectiveness) or harms?
8. Are there subgroups of patients based on demographics (age, racial groups, gender), socioeconomic status, other medications, or co-morbidities for which one atypical antipsychotic drug is more effective or associated with fewer harms?

Inclusion Criteria

Populations

- Adults (age 18 years or older) and adolescents (age 13 to 17 years) with a DSM III-R or DSM-IV diagnosis of schizophrenia, including other psychotic disorders such as schizophreniform-, delusional- and schizoaffective disorders, and including:
 - First episode schizophrenia
 - Patients refractory to treatment

- Adults (age 18 years or older) and youths (under age 18 years) with bipolar disorder (manic or depressive phases, rapid cycling, mixed states)
- Adults with major depressive disorder
- Older Adults (≥ 65 years of age) with Behavioral and Psychological Symptoms of Dementia (BPSD)
- Youths (under age 18) with a DSM-III-R or DSM-IV diagnosis for a pervasive developmental disorder, including:
 - Autistic Disorder
 - Rett's Disorder
 - Childhood Disintegrative Disorder
 - Asperger's Disorder
 - Pervasive Developmental Disorder Not Otherwise Specified, (including Atypical Autism)
- Youths (under age 18) with a DSM-III-R or DSM-IV diagnosis of a disruptive behavior disorder, including:
 - Conduct Disorder
 - Oppositional Defiant Disorder
 - Disruptive Behavior Disorder Not Otherwise Specified

Interventions

Generic Name	Trade Name	Forms
Aripiprazole*	Abilify®	Oral tablet Oral solution Orally disintegrating tablet Injectable
Asenapine	Saphris®	Sublingual tablets
Clozapine [§]	Clozaril® Fazaclo ODT®*	Oral tablet Orally disintegrating tablet
Iloperidone	Fanapt®	Oral tablet
Olanzapine	Zyprexa® Zyprexa Zydis®	Oral tablet Injectable [†] Orally disintegrating tablet
Quetiapine	Seroquel® Seroquel XR®	Oral tablet Oral extended release tablet
Paliperidone*	Invega®	Oral extended release tablet
Paliperidone palmitate	Invega Sustenna®	Extended release injectable suspension
Risperidone [§]	Risperdal® Risperdal M-Tab® Risperdal Consta®	Oral tablet Orally disintegrating tablet Oral solution Injectable
Ziprasidone*	Geodon®	Oral capsule Oral solution Injectable

*Not available in Canada.

[†] Trade name for Zyprexa Injectable is Zyprexa Intramuscular in Canada.

[§]Generic products are available in Canada.

Effectiveness outcomes

Population	Outcomes
Schizophrenia and other psychotic disorders	<ul style="list-style-type: none"> • Mortality • Quality of Life • Functional capacity (e.g., employment, encounters with legal system, etc.) • Hospitalization (due to mental illness and all-cause), emergency department visits, etc. • Symptom response (e.g., global state, mental state, positive symptoms, negative symptoms), response rates, duration of response, remission, relapse, speed of response, time to discontinuation of medication, etc.
First-episode schizophrenia	<ul style="list-style-type: none"> • Mortality • Quality of Life • Functional capacity (e.g., employment, encounters with legal system, etc.) • Hospitalization (due to mental illness and all-cause), emergency department visits, etc. • Symptom response (e.g., global state, mental state, positive symptoms, negative symptoms), response rates, duration of response, remission, relapse, speed of response, time to discontinuation of medication, etc.
Bipolar Disorder	<ul style="list-style-type: none"> • Mortality • Quality of Life • Functional capacity (e.g., employment, encounters with legal system, etc.) • Hospitalization (due to mental illness and all-cause), emergency department visits, etc. • Symptom response (e.g., global or specific): response rates, duration of response, remission, relapse, speed of response, time to discontinuation of medication, etc.
Major depressive disorder	<ul style="list-style-type: none"> • Mortality • Quality of Life • Functional capacity (e.g., employment, encounters with legal system, etc.) • Hospitalization (due to mental illness and all-cause), emergency department visits, etc. • Symptom response (e.g., global or specific): response rates, duration of response, remission, relapse, speed of response, time to discontinuation of medication, etc.
Behavioral and Psychological Symptoms of Dementia (BPSD)	<ul style="list-style-type: none"> • Mortality • Quality of Life • Functional capacity (e.g., quality of life, activities of daily living, etc.) • Hospitalization (due to mental illness and all-cause), emergency department visits, etc. • Caregiver burden • Symptom response (e.g., global state, aggression, agitation, psychosis, etc.) response rates, duration of response, remission, relapse, speed of response, time to discontinuation of medication, etc.
Pervasive Developmental Disorders	<ul style="list-style-type: none"> • Functional capacity (e.g., activities of daily living, etc.) • Quality of Life • Hospitalization, emergency department visits, etc. • Symptom response (e.g., global state, irritability, aggressiveness, self-injurious behavior, etc.) response rates, duration of response, remission, relapse, speed of response, time to discontinuation of medication, etc. • Caregiver burden

Population	Outcomes
Disruptive behavior disorders	<ul style="list-style-type: none">• Functional capacity (e.g., social, academic, occupational, quality of life, etc.)• Disciplinary consequences (e.g., detention, suspension, encounters with legal system)• Hospitalization, emergency department visits, etc.• Symptom response (e.g., global state, irritability, noncompliance, aggressive conduct, property damage or theft), response rates, duration of response, remission, relapse, speed of response, time to discontinuation of medication, etc.• Caregiver burden

In addition, for all of the above patient populations:

- Adherence; the ability to take medication as prescribed, also known as compliance
- Persistence; ability to continue taking medication over time

Harms

- Overall adverse events
- Withdrawals due to adverse events, time to withdrawal due to adverse events
- Specific adverse events
 - ◇ Major: those that are life-threatening, result in long-term morbidity, or require medical intervention to treat (e.g. Mortality, cerebrovascular disease-related events, development of diabetes mellitus, diabetic ketoacidosis, weight gain, neuroleptic malignant syndrome, seizures, tardive dyskinesia, cardiomyopathies and cardiac arrhythmias, agranulocytosis)
 - ◇ General: extrapyramidal effects, weight gain, agitation, constipation, sedation, elevated cholesterol, adverse events related to prolactin elevations, and others

Study designs

- Effectiveness: Randomized, controlled, effectiveness trials^{1,2}, good quality systematic reviews, comparative observational studies (cohort studies including database studies, and case-control studies).
- Efficacy and general adverse events: Head to head randomized controlled trials, good quality systematic reviews. If no direct head to head evidence exists, placebo-controlled trials will be considered. If no placebo-controlled trial evidence exists, trials comparing an atypical antipsychotic drug to a typical antipsychotic drug will be considered.
- Major Adverse Events: For life-threatening adverse events or those that are important and occur only with longer-term treatment, head to head randomized controlled trials, good quality systematic reviews and meta-analyses, and comparative observational studies (cohort studies including database studies, and case-control studies) will be included. Before-after studies or single-arm extension studies will only be included if follow up is longer than 2 years.
- Adherence and Persistence: Randomized controlled trials, comparative observational studies (cohort studies including database studies examining the relationship between improved adherence or persistence and improved outcomes).

1. Gartlehner G, Hansen RA, Nissman D, Lohr KN, Carey TS. A simple and valid tool distinguished efficacy from effectiveness studies. *Journal of Clinical Epidemiology*. 2006;59(10):1040-1048.
2. Gartlehner G, Hansen RA, Nissman D, Lohr KN, Carey TS. *Criteria for distinguishing effectiveness from efficacy trials in systematic reviews*. Rockville, MD: Evidence-based Practice Center: RTI-University of North Carolina April 2006. Publication No. 06-0046.