Acute Antipsychotic Treatments Compared

Most available antipsychotics are similarly effective for acute treatment of early-onset schizophrenia, according to a network meta-analysis. However, adverse-effect profiles differ considerably. Based on the risk-benefit profiles, aripiprazole and quetiapine can be recommended as first-line therapy.

Background: Previously, standard pairwise meta-analyses suggested equivalent but minimal efficacy of different agents in early-onset schizophrenia; the network meta-analysis is a way to maximize the sparse information from existing clinical trials.

Methods: The analysis was based on all available trials (excluding trials from China due to validity concerns) of an antipsychotic compared with a placebo control or an active comparator in patients aged \( \leq 19 \) years. Patients fulfilled DSM-5 or ICD-10 criteria for schizophrenia spectrum disorders, excluding affective psychoses. Studies in patients with refractory disease were excluded. Pharmaceutical companies were asked to provide unpublished data. The analysis compared the major efficacy outcomes of mean change from baseline on total and positive symptoms on the Positive and Negative Syndrome Scale (PANSS) or the Brief Psychiatric Rating Scale, and a number of negative outcomes including body weight, extrapyramidal symptoms, and treatment discontinuation.

Results: The network meta-analysis included 12 studies with a total of 2158 patients. There were 8 placebo-controlled trials and 4 with 2 or 3 active comparators. Patients had an average age of 15 years (range, 8–19 years), and 61% were male. Treatment arms included aripiprazole, asenapine, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone, and molindone. Patients received treatment for 6–12 weeks. The studies’ risk of bias was generally low.

Most agents had comparable effects on PANSS total, positive, and negative symptoms. The exception was ziprasidone, which showed inferiority on PANSS total symptoms compared with molindone, olanzapine, paliperidone, quetiapine, and risperidone. Ziprasidone was also less effective in terms of PANSS negative symptoms than molindone, olanzapine, and
risperidone and less effective on Clinical Global Impression (CGI) Improvement scores than olanzapine and risperidone. Effects on CGI-Severity scores did not differ among treatments. All antipsychotics except ziprasidone and asenapine were superior to placebo for the PANSS total symptom change.

Among antipsychotic-related harms, olanzapine, quetiapine, and risperidone produced more clinically significant weight gain compared with placebo in significantly larger proportions of patients. All of the agents except asenapine, olanzapine, and quetiapine produced more extrapyramidal effects than placebo. All drugs except asenapine, quetiapine, and ziprasidone produced more akathisia than placebo. Increases in prolactin were greater than placebo for risperidone, paliperidone, and olanzapine; similar to placebo for molindone and quetiapine; and lower than placebo for aripiprazole. Discontinuation of treatment for any reason or for adverse events did not differ from placebo for any antipsychotic.

**Discussion:** Of the 8 antipsychotics, 6 appear to be unsuited for first-line treatment in this patient population. Aripiprazole and quetiapine had the most favorable balance of efficacy and tolerability, although even these agents had significant adverse effects.

**Study Rating**—18 (100%): This study met all criteria for a systematic review/meta-analysis.

**Common Drug Trade Names:**
- aripiprazole—A bilify
- asenapine—Saphris
- molindone—M oban
- olanzapine—Zyprexa
- paliperidone—Invega
- quetiapine—Seroquel
- risperidone—Risperdal
- ziprasidone—Geodon

*See Reference Guide.

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**Time Perception in ADHD**

In a clinical study, unmedicated boys with ADHD demonstrated significant deficits in time perception and processing speed, compared with boys with other psychiatric disorders.

**Methods:** Study participants were 103 boys, aged 7–16 years, referred for diagnostic assessment to an outpatient clinic of a psychiatric hospital. All were suspected of having ADHD on the basis of parent- or teacher-reported symptoms. Only those who eventually received a psychiatric diagnosis (excluding autism, low IQ, psychosis, PTSD, and some others) were included in the analysis: 50 with ADHD and 53 with other disorders, predominantly anxiety, adjustment, conduct, or learning disorders. During their clinical evaluation for ADHD, all patients completed the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV). In addition, they were asked retrospectively to estimate the amount of time it took them to complete the Matrix Reasoning subtest of the WISC-IV.

**Results:** Both groups completed the Matrix Reasoning subtest of the WISC-IV in an average of 5.5 minutes. WISC-IV processing-speed scores were significantly lower for the boys with ADHD (p<0.001). The groups did not differ in WISC-IV full-scale IQ, verbal comprehension, perceptual reasoning, or working memory scores.

Time estimation in boys with ADHD had greater systematic error—i.e., they gave significantly higher time estimates than those with other disorders, overestimating the time by an average of 40%, compared with 3% in controls (p<0.001). Accuracy scores, reflecting deviation from the true value in either a positive or negative direction, were nearly twice as high for boys with ADHD as controls (p=0.003). In boys with ADHD, but not those with other disorders, processing speed was negatively correlated with both systematic error and accuracy. Results of
all analyses were similar in subgroups of boys with either the combined or predominantly inattentive ADHD subtype.

**Discussion:** Deficits in temporal processing are believed to be 1 of several primary causes of ADHD symptoms. Persons with ADHD are believed to have a faster internal pacemaker-accumulator clock. Time estimation for tasks can be measured retrospectively, as in this study, or prospectively, by informing subjects beforehand that they will be asked to estimate time. Both appear to be altered in ADHD. The 2 tasks have different mechanisms—prospective timing takes attention away from the task at hand, while retrospective timing may be based on alterations in pacemaker speed or reference memory. The present study differs from previous research in testing retrospective time estimation for a relatively long task duration of about 5 minutes and by including a control group with disorders that may emulate true ADHD. The present results suggest that assessing retrospective time estimation may be useful in the differential diagnosis of ADHD.

Walg M, Hapfelmeyer G, El-Wahsch D, Prior H: The faster internal clock in ADHD is related to lower processing speed: WISC-IV profile analyses and time estimation tasks facilitate the distinction between real ADHD and pseudo-ADHD. European Child and Adolescent Psychiatry 2017; doi 10.1007/s00787–017–0971–5. From the Zentrum fur seelische Gesundheit des Kindes und Jugendalters, Remscheid, Germany; and other institutions. **Source of funding not stated.** The authors declared no competing interests.

### Neuropsychiatric Risks of Adolescent Cannabis Use

Current clinical research indicates that exposure to cannabis in adolescence is associated with poor cognitive and psychiatric outcomes in adulthood, according to a review. It is difficult to know the extent to which cannabis is a cause of these outcomes, since it coexists with an "entire landscape" of other influences. Studies in animals can directly measure the effect of cannabis on the adolescent brain, but the preclinical and clinical research do not always point to the same conclusions.

The expansion of recreational marijuana will likely lead to increased access by adolescents, who now use cannabis more than cigarettes. Adolescents also have legal access to a constant stream of new, synthetic cannabinoids whose introduction outpaces legal regulation and that can have very different effects from cannabis. The data thus far suggest that cannabis is a markedly less harmful recreational drug than alcohol or tobacco when used in adults, but decades of research suggest early-onset cannabis use is associated with negative life outcomes.

Ethical concerns limit research in young subjects to observational rather than experimental designs, which makes it difficult to explore the direction of causation. Genetic studies suggest cannabis use and psychiatric disorders, such as depression and schizophrenia, may share a common liability.

Adolescent-onset cannabis use is associated with cognitive deficits, such as impaired attention, memory, and visual processing, and decreased full-scale and verbal IQ. These cognitive sequelae may be limited to persons who began using cannabis before age 15 or 16 years; they do not appear to affect late-onset adolescent users, and it is not clear whether they improve if cannabis use is discontinued. Despite methodological limitations, research suggests early-onset or frequent marijuana use is also associated with mood and anxiety disorders. Alternative explanations for the association include shared vulnerability and self-medication of emerging emotional symptoms. Evidence of an association with suicidal behavior or ideation is inconsistent. There is a well-documented higher prevalence of early-onset cannabis use in persons with psychosis, and adults with a psychotic disorder and early-onset cannabis use have more frequent relapses, poorer treatment adherence, and increased hospitalization. Early cannabis use is associated with later nicotine dependence and substance use disorders, but again the role of common behavioral and genetic liability is unclear.
Animal models of cannabis exposure can help clarify its effects on the adolescent brain. These experiments suggest adolescent animals are uniquely vulnerable to long-term consequences of cannabis exposure, similar to outcomes seen in humans, including altered later-life cognition, affect, psychosis-related behavior, and sensitivity to other drugs of abuse. Animal research on psychosis and drug cross-sensitization is the most consistent with human research. Animal models may have identified molecular changes that underlie persistent emotional deficits in adults who were exposed to cannabis as adolescents. A major pitfall of animal research to date is its reliance on synthetic cannabinoids, which have different pharmacologic properties to natural cannabis. Results also vary depending on strain and dosage, the gender of the animals, and the behavioral tests used.

Despite the need for additional research, it can be concluded that clinicians should view adolescents who use cannabis as an at-risk group for cognitive difficulties and psychiatric morbidity, including suicidality. Earlier onset and heavier use indicate higher risk.


### Biomarker for Transition to Psychosis

Low levels of erythrocyte glutathione were predictive of transition to psychosis in a small sample of high-risk adolescents and young adults. Glutathione is a major antioxidant present in the brain and cerebrospinal fluid that can be measured in blood or erythrocytes using a commercially available assay.

**Background:** Glutathione is the most important antioxidant defense of the brain. Low levels of glutathione in the brain have been observed in patients with schizophrenia and in those with first-episode psychosis, but they have not previously been assessed as a possible biomarker for transition in high-risk individuals. It is not clear whether peripheral glutathione levels accurately reflect status in the central nervous system. Low blood levels have been associated with the loss of cortical grey matter in patients with first-episode psychosis, and dysregulation of the antioxidant defense system in the brain is associated with dysregulation of glutamatergic and dopaminergic systems.

**Methods:** This analysis was conducted as part of a larger clinical trial of omega-3 fatty acids in patients, aged 13–25 years, judged to be at high risk of psychosis based on attenuated positive symptoms, transient psychosis, or genetic risk with a recent decrease in functioning. Patients received study treatment for 12 weeks and were assessed 12 months and 7 years post-randomization. The baseline assessment included measurement of erythrocyte glutathione using a commercial assay, with results expressed as µmol/L lysate. The present analysis was limited to 36 patients in the placebo group who had glutathione measured at baseline.

**Results:** Of the 36 participants, 11 had transitioned to psychosis at 12 months and another 4 at the 7-year follow-up. Mean baseline glutathione levels were significantly lower in the group that transitioned at 7 years than in those who did not transition (p<0.001). The comparison at 12 months was not statistically significant.

Using a cutoff value for low glutathione of 41.8 µmol/L, transition at 7 years was predicted with a sensitivity* of 0.9 and a specificity* of 0.7. The positive predictive value was 83%—i.e., 10 of 12 participants with erythrocyte glutathione below the cutoff transitioned to psychosis. The negative predictive value was 79%—i.e., of 24 persons with levels above the cutoff, 19 did not transition. There was no correlation between glutathione and baseline scores on the Positive and Negative Syndrome Scale, Montgomery-Asberg Depression Rating Scale, or Global Assessment of Function.
**Discussion:** Based on the findings in the present sample, low glutathione may be a better predictor of long-term than short-term outcome. More research is needed to identify an ideal cutoff or a normal range.

Lavoie S, Berger M, Schlogelhofer M, Schafer M, et al: Erythrocyte glutathione levels as long-term predictor of transition to psychosis. Translational Psychiatry 2017; doi 10.1038/tp.2017.30. From Orygen, the National Centre of Excellence in Youth Mental Health, Parkville, Australia; and other institutions. Funded by the Stanley Medical Research Institute; and other sources. The authors declared no competing interests.

*See Reference Guide.

**Neurocognitive Effects of Early Antibiotic Exposure**

Antibiotic exposure during infancy was associated with adverse cognitive, behavioral, and emotional outcomes throughout childhood, according to a population-based longitudinal study.

**Background:** Data from animal models indicate that absent gut microbiota in early life is associated with increased anxiety- and depression-like behavior and increased stress reactivity, in addition to negative metabolic outcomes. Emerging clinical literature has focused mainly on the benefits of probiotic treatment during early life—e.g., it may reduce risk of ADHD.

**Methods:** An analysis was conducted using data from a longitudinal study of the outcome of low birth weight. The population consisted of low-birth-weight infants and normal-weight controls, all born in New Zealand between late 1995 and late 1997. All pregnancies were singleton and full-term. Data were collected at birth, 12 months, and 3.5, 7, and 11 years. Mothers were asked to report antibiotic use during each period. Assessments included the Strengths and Difficulties Questionnaire, Conners Rating Scale-Revised, Center for Epidemiologic Studies Depression Scale for children, age-appropriate IQ tests, and a standardized test of reading ability.

**Results:** Of 871 mother-child pairs enrolled in the study, between 493 and 550 were seen at each of the 3 childhood assessment points. A total of 27% of mothers received antibiotics during pregnancy, 70% of children received an antibiotic during their first year, and 92% received antibiotics between 1 and 3.5 years of age.

Antibiotic use in infancy was associated with poorer outcomes throughout childhood, including lower IQ scores at all ages; poorer reading ability at age 7 years; higher behavioral difficulty ratings at 3.5 and 7 years; higher parent ratings for oppositional behavior; and more depressive and ADHD symptoms at age 11 years. After adjusting for other factors that could influence outcomes, exposed children still had significantly higher parent-rated total behavioral difficulty scores at age 3.5 and 11 years (p=0.028 and p=0.013, respectively). Antibiotic use also showed a multivariate association with conduct problems at age 11 years (p<0.0001) and higher self-rated peer difficulties and lower self-rated prosocial behavior at age 11 years (p=0.05 and p=0.044, respectively). Eleven-year-old exposed children also had higher parent-rated and teacher-rated ADHD symptoms and higher self-rated depression symptoms.

Effect sizes* for most outcomes were small; however, those for parent- and teacher-rated ADHD and oppositional subscales of the Conners Rating Scale ADHD in 11 year olds were much larger, ranging from 1.4 to 2.8. Maternal antibiotic use during pregnancy was not associated with any adverse neurocognitive outcomes; nor was antibiotic exposure between ages 1 and 3.5.

**Discussion:** In the present study, the widespread use of antibiotics suggests they were being prescribed for minor conditions; therefore the adverse effects cannot be explained by serious underlying infections.


*See Reference Guide.
Melatonin and Antipsychotic-Related Weight Gain

In a placebo-controlled trial of adolescents with bipolar disorder, coadministering melatonin modestly attenuated weight associated with olanzapine (Zyprexa) and lithium treatment.¹

**Background:** Melatonin regulates circadian rhythms and may have beneficial effects on sleep and mood, which in turn may influence food intake, metabolism, and weight. Melatonin has beneficial effects on body composition in animal models, including rats given olanzapine, and it has possible cardiovascular and metabolic health benefits in human adults. A single study of melatonin in adults with schizophrenia found that it limited olanzapine-related weight gain.²

**Methods:** Study subjects were 48 patients, aged 11–17 years, with a new diagnosis of DSM-IV-TR bipolar I disorder. Participants had baseline weight in the normal range, with a body mass index (BMI) between 18 and 25, and did not have an eating disorder. All patients received 5–10 mg/day olanzapine and lithium based on therapeutic blood levels. They were also randomly assigned to receive 3 mg/day melatonin or placebo. Weight and height were measured again after 6 and 12 weeks of treatment.

**Results:** Patients had an average age of 14.5 years and a mean baseline BMI of about 20. Five patients in the placebo group and 3 in the melatonin group stopped their psychotropic medication during the study because of weight gain, and 2 in the melatonin group were lost to follow-up, leaving 19 in each group. Among these patients, the mean increase in BMI was 2.45 in the melatonin group, compared with 3.25 in the placebo group (p=0.061). Patients gained a mean of 13 lbs with melatonin, compared with 18 lbs with placebo (p=0.065). Adjusting the analysis to account for baseline weight did not affect the results.

**Discussion:** Weight gain is among the most troublesome adverse effects of psychotropic treatment. Although the between-group difference in weight gain was not statistically significant in this study, the sample size was small and the 5-lb difference in weight gain with melatonin over 3 months may be clinically relevant.

**Study Rating*—17 (100%):** This study met all criteria for a randomized controlled trial.

¹Mostafavi S-A, Solhi M, Mohammadi M-R, Akhondzadeh S: Melatonin for reducing weight gain following administration of atypical antipsychotic olanzapine for adolescents with bipolar disorder: a randomized, double-blind, placebo-controlled trial. *Journal of Child and Adolescent Psychopharmacology* 2017; doi 10.1089/cap.2016.0046. From Tehran University of Medical Sciences, Iran. **Funded by the university. The authors declared no competing interests.**


*See Reference Guide.

**Reference Guide**

**Effect Size:** The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance, and large effect sizes do not ensure treatment efficacy.

**Sensitivity and Specificity:** Statistical measures of the performance of binary classification tests. Sensitivity measures the proportion of actual positives that are correctly identified (i.e., the percentage of sick people who are correctly identified as having the condition). Specificity measures the proportion of negatives that are correctly identified (i.e., the percentage of healthy people who are correctly identified as not having the condition). A perfect predictor would have 100% sensitivity and specificity.

**Study Rating:** A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists are posted at www.alertpubs.com.

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