

NATIONAL QUALITY FORUM—Evidence (subcriterion 1a)

Measure Number (if previously endorsed): [Click here to enter NQF number](#)

Measure Title: [Antipsychotic Use in Children Under 5 Years Old](#)

IF the measure is a component in a composite performance measure, provide the title of the Composite Measure here: [N/A](#)

Date of Submission: [1/16/2014](#)

Instructions

- For composite performance measures:
 - A separate evidence form is required for each component measure unless several components were studied together.
 - If a component measure is submitted as an individual performance measure, attach the evidence form to the individual measure submission.
- Respond to all questions as instructed with answers immediately following the question. All information needed to demonstrate meeting the evidence subcriterion (1a) must be in this form. An appendix of supplemental materials may be submitted, but there is no guarantee it will be reviewed.
- If you are unable to check a box, please highlight or shade the box for your response.
- Maximum of 10 pages (includes questions/instructions; minimum font size 11 pt; do not change margins). **Contact NQF staff if more pages are needed.**
- Contact NQF staff regarding questions. Check for resources at [Submitting Standards webpage](#).

Note: The information provided in this form is intended to aid the Steering Committee and other stakeholders in understanding to what degree the evidence for this measure meets NQF's evaluation criteria.

1a. Evidence to Support the Measure Focus

The measure focus is evidence-based, demonstrated as follows:

- **Health outcome:**³ a rationale supports the relationship of the health outcome to processes or structures of care. Applies to patient-reported outcomes (PRO), including health-related quality of life/functional status, symptom/symptom burden, experience with care, health-related behavior.
- **Intermediate clinical outcome:** a systematic assessment and grading of the quantity, quality, and consistency of the body of evidence⁴ that the measured intermediate clinical outcome leads to a desired health outcome.
- **Process:**⁵ a systematic assessment and grading of the quantity, quality, and consistency of the body of evidence⁴ that the measured process leads to a desired health outcome.
- **Structure:** a systematic assessment and grading of the quantity, quality, and consistency of the body of evidence⁴ that the measured structure leads to a desired health outcome.
- **Efficiency:**⁶ evidence not required for the resource use component.

Notes

3. Generally, rare event outcomes do not provide adequate information for improvement or discrimination; however, serious reportable events that are compared to zero are appropriate outcomes for public reporting and quality improvement.
4. The preferred systems for grading the evidence are the U.S. Preventive Services Task Force (USPSTF) [grading definitions and methods](#), or Grading of Recommendations, Assessment, Development and Evaluation ([GRADE guidelines](#)).
5. Clinical care processes typically include multiple steps: assess → identify problem/potential problem → choose/plan intervention (with patient input) → provide intervention → evaluate impact on health status. If the measure focus is one step in such a multistep process, the step with the strongest evidence for the link to the desired outcome should be selected as the focus of measurement. Note: A measure focused only on collecting PROM data is not a PRO-PM.
6. Measures of efficiency combine the concepts of resource use and quality (see NQF's [Measurement Framework: Evaluating Efficiency Across Episodes of Care](#); [AQA Principles of Efficiency Measures](#)).

1a.1. This is a measure of: (should be consistent with type of measure entered in De.1)

Outcome

- Health outcome: Click here to name the health outcome
- Patient-reported outcome (PRO): Click here to name the PRO
PROs include HRQoL/functional status, symptom/symptom burden, experience with care, health-related behaviors
- Intermediate clinical outcome (e.g., lab value): Click here to name the intermediate outcome

X Process:

- Structure: Click here to name the structure
- Other: Click here to name what is being measured

HEALTH OUTCOME/PRO PERFORMANCE MEASURE *If not a health outcome or PRO, skip to 1a.3*

1a.2. Briefly state or diagram the path between the health outcome (or PRO) and the healthcare structures, processes, interventions, or services that influence it.

1a.2.1. State the rationale supporting the relationship between the health outcome (or PRO) to at least one healthcare structure, process, intervention, or service (i.e., influence on outcome/PRO).

Note: For health outcome/PRO performance measures, no further information is required; however, you may provide evidence for any of the structures, processes, interventions, or service identified above.

INTERMEDIATE OUTCOME, PROCESS, OR STRUCTURE PERFORMANCE MEASURE

1a.3. Briefly state or diagram the path between structure, process, intermediate outcome, and health outcomes. *Include all the steps between the measure focus and the health outcome.*

It has been shown that the measured process, antipsychotic medications dispensed in children under 5, leads to undesired health outcomes. If these medications were not prescribed for these children, they would avoid the related increased risk of the short- and long-term adverse effects as further described. In general, adverse effects from receipt of antipsychotic medication by adults and children include an increased risk of metabolic syndrome, hyperprolactemia, thyroid dysfunction, diabetes, depression, agranulocytosis, and extrapyramidal syndromes; though, many of these adverse effects have been shown to occur at a higher rate or to a greater degree in children than in the adult population. More specifically, studies have demonstrated that children who receive antipsychotic medications have a greater risk of diabetes, metabolic, and cardiovascular issues, and adverse effects such as increases in weight, BMI, total cholesterol, triglycerides, QTc interval, heart rate, and liver function abnormalities. These adverse effects have been demonstrated not only in immediate complications but also in long term complications and ill effects on health.

1a.3.1. What is the source of the systematic review of the body of evidence that supports the performance measure?

- Clinical Practice Guideline recommendation – **complete sections 1a.4, and 1a.7**
- US Preventive Services Task Force Recommendation – **complete sections 1a.5 and 1a.7**
- Other systematic review and grading of the body of evidence (e.g., Cochrane Collaboration, AHRQ Evidence Practice Center) – **complete sections 1a.6 and 1a.7**

X Other – **complete section 1a.8**

There is a substantial amount of evidence that supports this performance measure, and its source has been classified as “other”, as indicated above. With respect to the availability of clinical practice guidelines, in general, over time the lack of widespread studies, evidence and indications for use of antipsychotic medications in pediatric patients has limited the availability of relevant clinical practice guidelines, and even more so for the pediatric population under age 5. It is only within the past 15-20

years that these medications have been used increasingly in pediatric patients. The AMA has recently urged the National Institute of Mental Health to assist in developing guidelines for use of antipsychotics in pediatric patients. With respect to systematic reviews, while there are several available, they have been included in the “other” evidence section of this form, because they focus on a broader pediatric population rather than specifically on patients under the age of 5, which is the target of this measure.

Report of the Council on Science and Public Health: Use of Atypical Antipsychotics in Pediatric Patients. American Medical Association. Available from: <http://www.ama-assn.org/resources/doc/csaph/i12-csaph1-atypical.pdf>

Please complete the sections indicated above for the source of evidence. You may skip the sections that do not apply.

1a.4. CLINICAL PRACTICE GUIDELINE RECOMMENDATION

1a.4.1. Guideline citation (including date) and URL for guideline (if available online):

1a.4.2. Identify guideline recommendation number and/or page number and quote verbatim, the specific guideline recommendation.

1a.4.3. Grade assigned to the quoted recommendation with definition of the grade:

1a.4.4. Provide all other grades and associated definitions for recommendations in the grading system. (Note: If separate grades for the strength of the evidence, report them in section 1a.7.)

1a.4.5. Citation and URL for methodology for grading recommendations (if different from 1a.4.1):

1a.4.6. If guideline is evidence-based (rather than expert opinion), are the details of the quantity, quality, and consistency of the body of evidence available (e.g., evidence tables)?

Yes → **complete section [1a.7](#)**

No → **report on another systematic review of the evidence in sections [1a.6](#) and [1a.7](#); if another review does not exist, provide what is known from the guideline review of evidence in [1a.7](#)**

1a.5. UNITED STATES PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

1a.5.1. Recommendation citation (including date) and URL for recommendation (if available online):

1a.5.2. Identify recommendation number and/or page number and quote verbatim, the specific recommendation.

1a.5.3. Grade assigned to the quoted recommendation with definition of the grade:

1a.5.4. Provide all other grades and associated definitions for recommendations in the grading system. (Note: the grading system for the evidence should be reported in section 1a.7.)

1a.5.5. Citation and URL for methodology for grading recommendations (if different from 1a.5.1):

Complete section [1a.7](#)

1a.6. OTHER SYSTEMATIC REVIEW OF THE BODY OF EVIDENCE

1a.6.1. Citation (including date) and URL (if available online):

1a.6.2. Citation and URL for methodology for evidence review and grading (if different from 1a.6.1):

Complete section [1a.7](#)

1a.7. FINDINGS FROM SYSTEMATIC REVIEW OF BODY OF THE EVIDENCE SUPPORTING THE MEASURE

If more than one systematic review of the evidence is identified above, you may choose to summarize the one (or more) for which the best information is available to provide a summary of the quantity, quality, and consistency of the body of evidence. Be sure to identify which review is the basis of the responses in this section and if more than one, provide a separate response for each review.

1a.7.1. What was the specific structure, treatment, intervention, service, or intermediate outcome addressed in the evidence review?

1a.7.2. Grade assigned for the quality of the quoted evidence with definition of the grade:

1a.7.3. Provide all other grades and associated definitions for strength of the evidence in the grading system.

1a.7.4. What is the time period covered by the body of evidence? (*provide the date range, e.g., 1990-2010*). Date range: [Click here to enter date range](#)

QUANTITY AND QUALITY OF BODY OF EVIDENCE

1a.7.5. How many and what type of study designs are included in the body of evidence? (*e.g., 3 randomized controlled trials and 1 observational study*)

1a.7.6. What is the overall quality of evidence across studies in the body of evidence? (*discuss the certainty or confidence in the estimates of effect particularly in relation to study factors such as design flaws, imprecision due to small numbers, indirectness of studies to the measure focus or target population*)

ESTIMATES OF BENEFIT AND CONSISTENCY ACROSS STUDIES IN BODY OF EVIDENCE

1a.7.7. What are the estimates of benefit—magnitude and direction of effect on outcome(s) across studies in the body of evidence? (*e.g., ranges of percentages or odds ratios for improvement/decline across studies, results of meta-analysis, and statistical significance*)

1a.7.8. What harms were studied and how do they affect the net benefit (benefits over harms)?

UPDATE TO THE SYSTEMATIC REVIEW(S) OF THE BODY OF EVIDENCE

1a.7.9. If new studies have been conducted since the systematic review of the body of evidence, provide for each new study: 1) citation, 2) description, 3) results, 4) impact on conclusions of systematic review.

1a.8 OTHER SOURCE OF EVIDENCE

If source of evidence is NOT from a clinical practice guideline, USPSTF, or systematic review, please describe the evidence on which you are basing the performance measure.

The evidence on which this performance measure is based is from peer-reviewed literature, systematic reviews (which may contain a broader age range) and from FDA prescribing and indication guidance.

1a.8.1 What process was used to identify the evidence?

The evidence was identified by: (1) reviewing package inserts and FDA prescribing guidelines for each of the antipsychotic medications; (2) reviewing the Cochrane database; and (3) completing a PubMed search using key words [Antipsychotic medications] OR [Antipsychotics AND [Children] OR [Pediatrics].

1a.8.2. Provide the citation and summary for each piece of evidence.

The evidence presented in this section is organized by source and then content theme where relevant.

1) Package inserts and FDA prescribing guidelines for each of the antipsychotic medications.

Of the long list of antipsychotic medications available, only two – chlorpromazine and haloperidol – have indications for use in patients less than 5 years of age; however, these indications were granted in 1954 and 1986, respectively. The increased numbers of studies, meta-analysis, and systematic reviews that have been completed since that time have demonstrated that these medications have the same adverse effects as other antipsychotics, which would caution against and do not include indications for their use.

Abidi S, Bhaskara SM. From chlorpromazine to clozapine – antipsychotic adverse effects and the clinician's dilemma. *Can J Psychiatry.* 2003 Dec;48(11):749-55.

Seida JC, Schouten JR, Boylan K, et al. Antipsychotics for children and young adults: a comparative effectiveness review. *Pediatrics.* 2012 Mar 1; 129(3): e771 -e784. Available from: <http://pediatrics.aappublications.org/content/129/3/e771.full.pdf+html>

2) Evidence from systematic evidence reviews, meta-analyses and literature summary studies.

Ben Amor L. Antipsychotics in pediatric and adolescent patients: a review of comparative safety data. *J Affect Disord.* 2012;138 Suppl:S22-30.

- A comparative review of antipsychotic medications in terms of safety and adverse effects. Significant adverse effects were demonstrated, particularly with use of olanzapine and risperidone including weight gain, metabolic complications, increase in prolactin levels, and increased incidence of EPS as compared to quetiapine, ziprasidone, and aripiprazole.

Correll CU. Weight gain and metabolic effects of mood stabilizers and antipsychotics in pediatric bipolar disorder: a systematic review and pooled analysis of short-term trials. *J Am Acad Child Adolesc Psychiatry.* 2007 Jun;46(6):687-700. Available from:

<http://www.sciencedirect.com/science/article/pii/S0890856709621481>

- This systematic review examined the weight and metabolic adverse effects of antipsychotics in pediatric bipolar disorder. 75% of the studies demonstrated a significant increase in weight. Additionally, in trials lasting less than 12 weeks, antipsychotic monotherapy had an average increase in weight of 3.4 ± 1.3 kg and antipsychotic and mood stabilizer combination therapy had an increase in weight of 5.5 ± 1.8 kg.

Pringsheim T, Panagiotopoulos C, Davidson J, et al. Evidence-based recommendations for monitoring safety of second generation antipsychotics in children and youth. *J Can Acad Child Adolesc Psychiatry.* 2011 Aug;20(3):218-33. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3143700/>

- In this systematic review of controlled clinical trials in children taking second-generation antipsychotics, the study authors examined metabolic and neurologic side effects. In a meta-analysis of risperidone clinical trials, the following changes as compared to placebo were noted: a weight gain of 1.72 kg and prolactin elevation of 20.7 ng/dL. Neurologic side effects were common in risperidone, aripiprazole, and olanzapine. Olanzapine—followed by clozapine then quetiapine—was noted to have the highest risk of weight gain.

Seida JC, Schouten JR, Boylan K, et al. Antipsychotics for children and young adults: a comparative effectiveness review. *Pediatrics.* 2012 Mar 1; 129(3): e771 -e784. Available from:

<http://pediatrics.aappublications.org/content/129/3/e771.full.pdf+html>

- In this literature review of over 80 studies, the adverse effects of various antipsychotics were examined and compared. Olanzapine was demonstrated to have significant weight gain compared to quetiapine (5.5kg more with olanzapine), risperidone (2.5 kg more with olanzapine), and aripiprazole and greater dyslipidemia as compared to risperidone. Haloperidol demonstrated significantly greater EPS than olanzapine and risperidone. Overall, second-generation antipsychotics caused more adverse effects than placebo.

Vitiello B, Correll C, van Zwieten-Boot B, et al. Antipsychotics in children and adolescents: increasing use, evidence for efficacy and safety concerns. *Eur Neuropsychopharmacol.* 2009 Sep;19(9):629-35. Available from: <http://www.ecnp.eu/~media/Files/ecnp/communication/talk-of-the-month/Celso%20Arango/110303%20paper%20Arango%20Antipsychotics%20in%20children%20and%20adolescents%20increasing%20use%20evidence.pdf>

- In this summary publication, an expert panel reviewed and made recommendations on the medical literature surrounding the efficacy and safety of antipsychotics. The expert panel found that there is a greater risk of adverse effects (EPS, metabolic and endocrine abnormalities) in pediatric patients as compared to adults. For example, children gain more weight and at a faster pace than adults. These factors increase the risk of negative long-term health outcomes including hypertension, hyperlipidemia, and diabetes, which are increased risk factors for cardiovascular diseases and reduced life expectancy and quality of life. Additionally, it is difficult to determine the benefit/risk ratio in the pediatric population utilizing antipsychotics.

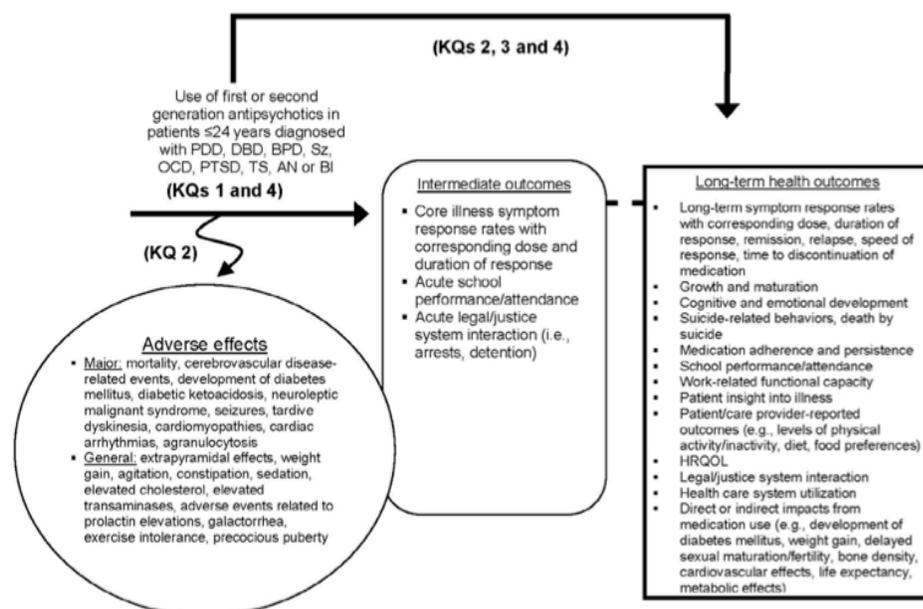
Talib HJ, Alderman EM. Gynecologic and reproductive health concerns of adolescents using selected psychotropic medications. *J Pediatr Adolesc Gynecol.* 2013 Feb;26(1):7-15. doi: 10.1016/j.jpag.2012.05.011. Epub 2012 Aug 25. Available from: [http://linkinghub.elsevier.com/retrieve/pii/S1083-3188\(12\)00094-0](http://linkinghub.elsevier.com/retrieve/pii/S1083-3188(12)00094-0)

- This review article examined the potential gynecologic and reproductive adverse effects that may occur due to antipsychotic usage based on systematic review of literature. Hyperprolactemia has been noted in a wide range of antipsychotic medication including risperidone, paliperidone, haloperidol, olanzapine, ziprasidone, etc. Hyperprolactemia can cause severe adverse effects including menstrual disorders, acne, hirsutism, galactorrhea, gynecomastia, decreased bone mineral density, and hypogonadism. In the review of 29 studies, 4.8% of the aggregated study group demonstrated symptomatic side effects.

Pringsheim T, Lam D, Ching H, Patten S. Metabolic and neurological complications of second-generation antipsychotic use in children: a systematic review and meta-analysis of randomized controlled trials. *Drug Safety* 2011; 34(8): 651-668. Available from: <http://link.springer.com/content/pdf/10.2165/11592020-000000000-00000.pdf#page-1>

- This meta-analysis included double blind, randomized controlled trials of second-generation antipsychotics (specifically risperidone, olanzapine, quetiapine, aripiprazole, clozapine, ziprasidone, paliperidone) in the pediatric population. The study primarily looked at the specific metabolic and neurologic adverse effects. The meta-analysis found mean weight gain between 0.85 kg to 3.47 kg in pediatric patients receiving olanzapine, risperidone, quetiapine, and aripiprazole. Increases in prolactin levels were demonstrated with risperidone and olanzapine treatment. Abnormal cholesterol and triglyceride values were found with olanzapine and clozapine. There also were increased risks of extrapyramidal symptoms associated with risperidone, aripiprazole, and olanzapine. The number of antipsychotic recommendations for patients with ADHD has tripled from 2005 to 2009 even though none of these medications has an indication for primary ADHD.

AHRQ, Comparative Effectiveness of First and Second Generation Antipsychotics in the Pediatric and Young Adult Populations, June 2010. Available from: <http://effectivehealthcare.ahrq.gov/ehc/products/147/453/Peds%20Antipsychotics%20Protocol%20Final.pdf>



3a) With regard to evidence from individual studies, two general themes were found. The first is that an increased risk of metabolic and cardiovascular adverse effects has been noted with the usage of antipsychotic medications in the pediatric populations.

Blair J, Scahill L, State M, Martin A. Electrocardiographic changes in children and adolescents treated with ziprasidone: a prospective study. *J Am Acad Child Adolesc Psychiatry*. 2005 Jan;44(1):73-9. Available from: [http://www.jaacap.com/article/S0890-8567\(09\)61344-7/abstract](http://www.jaacap.com/article/S0890-8567(09)61344-7/abstract)

- The safety of low-dose ziprasidone was tested in 20 pediatric patients. The study utilized electrocardiograms to test for heart rate, PR, QTc, and QRS intervals. A statistically significant change was found in heart rate, PR, and QTc intervals with the mean increase of 28±25 milliseconds.

Chavez B, Chavez-Brown M, Sopko MA Jr, Rey JA. Atypical antipsychotics in children with pervasive developmental disorders. *Paediatr Drugs*. 2007;9(4):249-66. Available from: <http://link.springer.com/article/10.2165%2F00148581-200709040-00006>

- This study looked at the use of atypical antipsychotics in treating pervasive development disorders and the results of previously conducted studies. Olanzapine and quetiapine demonstrated a high incidence of weight gain with minimal clinical benefit in treating these symptoms in patients. Additionally, it was noted that all antipsychotics carry the risk of metabolic syndrome.

Correll CU, Manu P, Olshanskiy V, Napolitano B, et al. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA*. 2009 Oct 28;302(16):1765-73. doi: 10.1001/jama.2009.1549. Available from: <http://jama.jamanetwork.com/article.aspx?articleid=184782>

- In this cohort study, patients ages 4 to 19 were treated with aripiprazole, olanzapine, quetiapine, or risperidone for a median of 10.5 weeks. In regards to adverse effects, weight gain increased with olanzapine by 8.6 kg, risperidone by 5.3 kg, and with aripiprazole by 4.4 kg. Statistically significant increases in total cholesterol (mean increase 9.1-15.6 mg/dL), triglyceride (mean increase 24.3-37.0 mg/dL), and non-HDL (mean increase 9.9-16.8 mg/dL) were found with olanzapine and quetiapine. Risperidone also demonstrated a statistically significant increase in triglycerides (9.7 mg/dL). *The study authors concluded: "Cardiometabolic adverse effects, such as age-inappropriate weight gain, obesity, hypertension, and lipid and glucose abnormalities, are particularly problematic during development because they predict adult obesity, the metabolic syndrome, cardiovascular morbidity, and malignancy."*

Correll, C.U., Carlson, H.E., 2006. Endocrine and metabolic adverse effects of psychotropic medications in children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 2006 Jul;45(7):771-91. Available from: <http://www.sciencedirect.com/science/article/pii/S0890856709615240>

- This study reiterated how there is limited safety data around antipsychotic medications but endocrine and metabolic adverse effects have been noted as areas of concern in pediatric patients. These include thyroid dysfunction with lithium, polycystic ovarian syndrome with valproate, and mild growth retardation in some patients (possibly due to decreased height or expected weight gain) in a variety of antipsychotics. It was noted that children appear to be at a higher risk of hyperprolactemia, weight gain, and metabolic abnormalities as compared to adults.

Gerbino-Rosen G, Roofeh D, Tompkins DA, et al. Hematological adverse events in clozapine-treated children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 2005 Oct;44(10):1024-31. Available from: [www.jaacap.com/article/S0890-8567\(09\)61764-0/abstract](http://www.jaacap.com/article/S0890-8567(09)61764-0/abstract)

- This study looked at the rate of hematologic adverse events (HAE) in hospitalized children treated with clozapine. The study specifically looked at development of agranulocytosis and neutropenia

over a median observation period of 8 months. Neutropenia occurred in 13% of patients while agranulocytosis only occurred in 0.6% of patients. The cumulative probability of having an initial HAE in one year of clozapine treatment was 16.1%.

Harrison-Woolrych M, Garcia-Quiroga J, Ashton J, Herbison P. Safety and usage of atypical antipsychotic medicines in children: a nationwide prospective cohort study. *Drug Saf.* 2007;30(7):569-79. Available from: <http://link.springer.com/article/10.2165%2F00002018-200730070-00002>

- Children between the ages of 2 and 15 who were prescribed atypical antipsychotics between April and July 2003 were followed in this prospective observational cohort study. Risperidone was the most commonly utilized drug-94% of patients. Within the 420-patient study, 31% of children reported an adverse event, which frequently included weight gain, severe dental caries, and somnolence although diabetes and depression were also noted as adverse events.

Kryzhanovskaya L, Schulz SC, McDougle C, et al. Olanzapine versus placebo in adolescents with schizophrenia: a 6-week, randomized, double-blind, placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry.* 2009 Jan;48(1):60-70. doi: 10.1097/CHI.0b013e3181900404. Available from: http://www.laboratoriosilesia.com/upfiles/sibi/p_007_olanzapine.pdf

- The study examined the use of olanzapine in the treatment of adolescent patients ages 13-17 years with schizophrenia for up to 6 weeks as compared to placebo. Olanzapine demonstrated statistically significant changes in adverse events as compared to placebo in terms of weight gain (4.3 kg versus 0.1 kg) and percentage of patients gaining greater than 7% of body weight during treatment (45.7% versus 14.7%). Prolactin and triglyceride baseline-to-endpoint levels were higher in the treatment group versus placebo. During the study, significant increases were noted in olanzapine-treated patients including weight, triglycerides, prolactin, liver function tests, and uric acid.

Laita P, Cifuentes A, Doll A, et al. Antipsychotic-related abnormal involuntary movements and metabolic and endocrine side effects in children and adolescents. *J Child Adolesc Psychopharmacol.* 2007 Aug;17(4):487-502. Available from: <http://online.liebertpub.com/doi/abs/10.1089/cap.2006.0039?journalCode=cap>

- In this cross-sectional study, two patient groups were examined: 60 children who had taken antipsychotics for less than 1 month and 66 children who had taken antipsychotics for greater than 12 months. Mild dyskinesic movements were seen in 21.7% of the short treatment duration patients and 37.9% in the longer treatment duration patients. Hyperprolactemia was also high being 78.6% in the short-term group and 48.5% in the long-term group. The longer treatment duration patients had statistically significantly higher BMI, cholesterol levels, and LDL.

Sikich L, Hamer RM, Bashford RA, et al. A pilot study of risperidone, olanzapine, and haloperidol in psychotic youth: a double-blind, randomized, 8-week trial. *Neuropsychopharmacology.* 2004 Jan;29(1):133-45.

- Pediatric patients—ages 8-19—were treated with risperidone, olanzapine, or haloperidol for one or more positive psychotic symptoms. Greater than 50% of patients had mild to moderate Parkinsonian symptoms with a large number of these patients requiring low-dose anticholinergics to control the symptoms (53-67% depending on drug). Increases in BMI were also noted during the trial period (mean of 5.7-7.4 weeks, depending on drug). The increases were statistically significant: risperidone: 1.4 (+1.2) kg/m²; olanzapine: 2.3 (+1.2) kg/m²; and haloperidol: 1.1 (+1.2) kg/m². Risperidone was also noted to cause increase in AST from 21.9 U/L to 28.1 U/L and increase in ALT from 20.9 U/L to 32.8 U/L. Olanzapine patients were also noted to have a trend in the random blood glucose level of an increase from 87.2 mg/dl to 97.2 mg/dl. High rates of side effects occurred in the pediatric population as compared to the adult population during clinical trials: sedation (92%), nervousness (58%), headache (56%), dry mouth (56%), blurry vision (56%), musculoskeletal pain (56%), nausea (54%), and light headedness (42%).

Sikich L, Frazier JA, McClellan J, et al. Double-blind comparison of first- and second-generation antipsychotics in early-onset schizophrenia and schizo-affective disorder: findings from the treatment of early-onset schizophrenia spectrum disorders (TEOSS) study. *Am J Psychiatry*. 2008 Nov;165(11):1420-31. doi: 10.1176/appi.ajp.2008.08050756. Epub 2008 Sep 15. Available from: <http://ajp.psychiatryonline.org/article.aspx?articleID=100316>

- This double-blind study enrolled pediatric patients ages eight to nineteen years with early-onset schizophrenia and schizoaffective disorder to treatment with olanzapine, risperidone, or molindone. Adverse effects were frequently noted in the pediatric patients with olanzapine and risperidone being associated with significant weight gain. Olanzapine had the highest weight gain risk (increase in 6.1 kg and BMI increase of 2.2kg/m²) and increased appetite and also demonstrated significant increases in insulin, liver transaminase, low density lipoprotein, QT-intervals (11.2 msec increase) and fasting cholesterol. Sedation, irritability, and anxiety were commonly observed.

Woods SW, Martin A, Spector SG, et al. Effects of development on olanzapine-associated adverse events. *J Am Acad Child Adolesc Psychiatry*. 2002 Dec;41(12):1439-46. Available from: <http://www.jaacap.com/article/S0890-8567%2809%2960738-3/fulltext>

- In this analysis of post-marketing surveillance database for olanzapine, the rates of adverse effects in pediatrics ages zero to nineteen years were compared to rates in adults. The rate of EPS was similar in adolescents as in adults, but still occurred. In patients less than 9 years of age, certain adverse effects were reported at a higher rate as compared to adults: sedation, weight gain, liver function abnormalities and tardive dyskinesia.

3b) The second set of themes found in individual studies is that an increase in antipsychotic usage in pediatric patients has been noted and disparities have been found in the rate of usage between Medicaid patients and privately insured patients along with increased prevalence rates in foster children.

Dosreis S, Yoon Y, Rubin DM, Riddle MA, Noll E, Rothbard A. Antipsychotic treatment among youth in foster care. *Pediatrics*. 2011 Dec;128(6):e1459-66. doi: 10.1542/peds.2010-2970. Epub 2011 Nov 21. Available from: <http://pediatrics.aappublications.org/content/128/6/e1459.full.pdf>

- The study looked at children younger than 20 years of age enrolled in a Medicaid program on antipsychotic treatment. Expanding on previously obtained results that demonstrated a higher prevalence of antipsychotic use in foster children, this study examined the average duration of antipsychotic use. The average antipsychotic use in Temporary Assistance for Needy Families (TANF) was 135+101 days while it was 222+110 days in foster care.

Lagnado L. U.S. Probes Use of Antipsychotic Drugs on Children: Federal health officials are reviewing antipsychotic drug use on children in the Medicaid system. *Wall Street Journal*. 2013 Aug 11 [accessed 2013 Aug 11]. Available from:

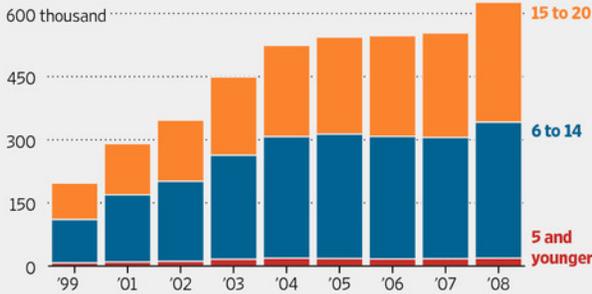
<http://online.wsj.com/news/articles/SB10001424127887323477604578654130865747470>

- The inspector general's office at the Department of Health and Human Services announced a probe into the pediatric antipsychotic usage in the Medicaid population. In addition to the probe, HHS agencies are requiring officials in every state to examine and tighten the oversight of antipsychotic medication in Medicaid pediatric patients. The WSJ cited a Mathematica analysis that found a three-fold increase in Medicaid prescriptions from 1999 to 2008 for antipsychotic medications in patients under 20 years of age. CMS chief medical officer reported that the government wants to reduce the "unnecessarily high utilization of antipsychotics." WSJ cited Medicaid representatives who reported that in 2008, 19,045 children under the age of 5 were prescribed antipsychotics through Medicaid, up from 7,759 in 1999.

Powerful Medicine

Children in the Medicaid system are more likely than privately insured ones to receive antipsychotic drugs, the largest drug class funded by the program.

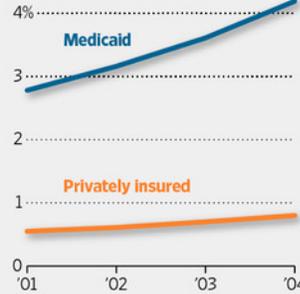
Number of children in the Medicaid system on antipsychotic drugs*



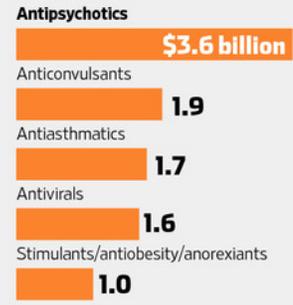
*No data available for 2000 †Ages 6 to 17

Sources: Mathematica Policy Research for the Centers for Medicare & Medicaid Services (age groups, drug groups); Stephen Crystal, Rutgers University, and Health Services Research Journal (coverage) The Wall Street Journal

Percentage of children' on antipsychotics, by type of coverage



Top five drug groups paid for by Medicaid, 2008



Pringsheim T, Lam D, Patten SB. The pharmacoepidemiology of antipsychotic medications for Canadian children and adolescents: 2005-2009. *J Child Adolesc Psychopharmacol*. 2011 Dec;21(6):537-43. doi: 10.1089/cap.2010.0145. Epub 2011 Dec 2. Available from: <http://online.liebertpub.com/doi/abs/10.1089/cap.2010.0145>

- This study looked at the prevalence of antipsychotic use in children—ages one to eighteen years—in Canada. The study demonstrated a high increase in usage, especially in light of the lack of pediatric approval. Antipsychotics drug recommendations had an increase of 114% from 2005 to 2009 while psychostimulants and SSRIs increased 36% and 44%.

Zito JM, Burcu M, Ibe A, Safer DJ, Magder LS. Antipsychotic use by medicaid-insured youths: impact of eligibility and psychiatric diagnosis across a decade. *Psychiatr Serv*. 2013 Mar 1;64(3):223-9. doi: 10.1176/appi.ps.201200081. Available from:

<http://ps.psychiatryonline.org/article.aspx?articleid=1486122>

- This article is a cross-sectional study examining the increased antipsychotic medication usage in youth in various Medicaid-eligible categories. In examining computerized administrative claims data, the prevalence of antipsychotic use in pediatric patients increased from 1.2% in 1997 to 3.2% in 2006. The greatest increase of odds of antipsychotic usage was in youths enrolled in SCHIP (AOR=5.9), foster children (AOR=4.1), Temporary Assistance for Needy Families (AOR=3.6), and supplemental security income (AOR=2.8). Additionally, the proportion of antipsychotic usage increase was significantly higher in African Americans and Hispanics as compared to Caucasians.