

Are antipsychotics overprescribed for children?

Dramatic increase since atypicals were introduced

Five times more children and adolescents were prescribed antipsychotics in 2002 than in 1993, according to a recent study by Olfson et al (*Box, page 46*).¹ A *New York Times* article about the 10-year trend² asked whether psychiatrists are overprescribing antipsychotics to children and adolescents.

To explore that question, CURRENT PSYCHIATRY Associate Editor Philip G. Janicak, MD, interviewed Robert A. Kowatch, MD, a clinician and researcher in child and adolescent mood disorders and psychopharmacology at Cincinnati Children's Hospital Medical Center.

Dr. Janicak: Why do you think there was a five-fold increase in antipsychotic prescriptions for children and adolescents? What does this statistic mean?

Dr. Kowatch: The reason antipsychotics are used so much to treat childhood psychiatric disorders is because they work.

The Olfson et al study showed that 9% of mental health visits and 18% of visits to psychiatrists by youths from 2000 to 2002 included antipsychotic treatment. When an antipsychotic was prescribed, 92% of prescriptions were for second-generation antipsychotics (SGAs).

These "atypicals"—introduced in the early



Dr. Kowatch is professor of psychiatry and pediatrics, department of psychiatry, University of Cincinnati, and director, pediatric mood disorders center, Cincinnati Children's Hospital Medical Center.

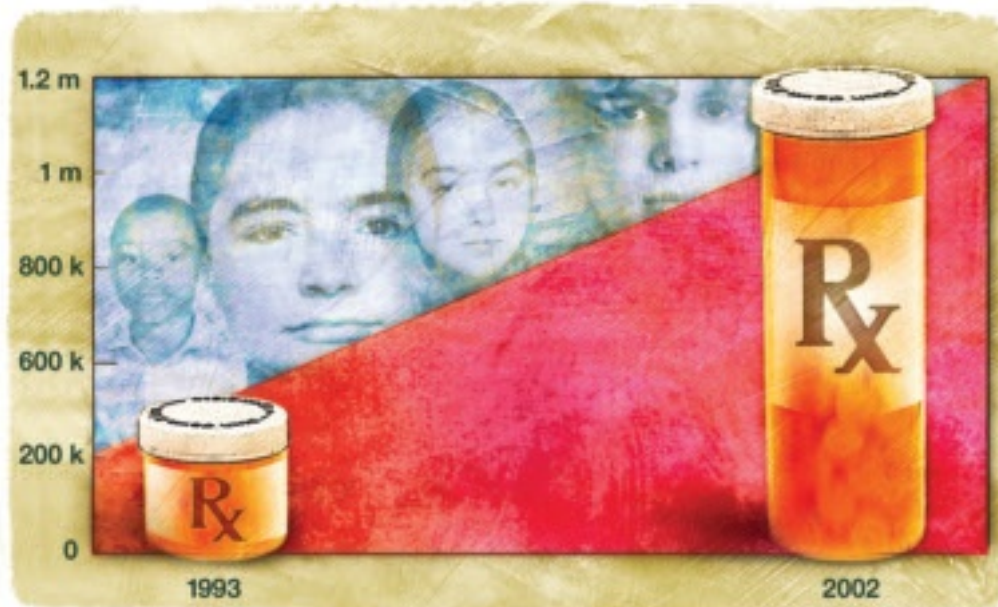


Dr. Janicak is professor of psychiatry, Rush University Medical Center, Chicago. His interests include psychopharmacology, mood disorders, and psychotic disorders in adults and older adolescents.

1990s—are used in child and adolescent psychiatry for just about everything except attention deficit/hyperactivity disorder. They're used to treat psychosis, schizophrenia, bipolar disorder, conduct disorder, and posttraumatic stress disorder (PTSD), and adjunctively for anxiety and treatment-resistant depression.

Dr. Janicak: The *Times* article quoted Dr. John March, professor of child and adolescent psychiatry at Duke University, as saying the use of antipsychotics "amounts to a huge experiment with the lives of American kids." Do you agree?

Office visits by youth that included antipsychotic treatment, 1993 to 2002*



* Antipsychotic therapy was included in an estimated 201,000 office visits by U.S. youth in 1993 and in 1,224,000 visits in 2002.
Source: Reference 1

Dr. Kowatch: I think that's an overstatement. We have good, long-term safety data on SGAs in children with autism and behavior problems related to mental retardation. Evidence is emerging on their use in other disorders, including three controlled trials in bipolar disorder and a controlled trial using clozapine in early-onset schizophrenia.

Obviously, we could use more long-term data, but clinicians use SGAs because doing so makes their patients better. I don't think that's an experiment; it's the nature and practice of medicine.

Dr. Janicak: So, despite the shortage of long-term clinical studies, you don't have a problem with prescribing antipsychotics for children?

Dr. Kowatch: You have to weigh the risks with the benefits. What choice do we have in clinical practice? By the time these kids get to a psychiatrist's office, they are very dysfunctional at home and in

school. Many times families come in desperate; their children are out of control, and they've tried everything except medication.

Dr. Janicak: Do you think decreased availability of psychiatric hospital beds helps explain antipsychotics' dramatic rise in pediatrics over 10 years? Or is it because SGAs became more available during that time?

Dr. Kowatch: Both. As more kids are treated as outpatients, they need more medications. But kids in hospitals are probably getting the same drugs. So, I think probably 80% of the reason is that these drugs are effective and work quickly.

Dr. Janicak: What about concerns of antipsychotic side effects in children?

Dr. Kowatch: SGAs clearly cause fewer side effects than first-generation antipsychotics (FGA) such as haloperidol, chlorpromazine, or thiothixene. We

'When these kids get to a psychiatrist, they are out of control and their families are desperate'



Antipsychotics overprescribed?

Box

Growth in pediatric antipsychotic use since atypicals were introduced

- Estimated number of office visits by youth that included antipsychotic treatment increased more than five-fold, from 201,000 in 1993 to 1,224,000 in 2002
- Boys were 2.5 times as likely as girls to receive antipsychotics
- White non-Hispanic youth were 3.5 times more likely to receive antipsychotics compared with youth in other racial and ethnic groups
- From 2000 to 2002, 92% of antipsychotic prescriptions were for second-generation agents
- Diagnoses for which antipsychotics were prescribed included disruptive behavior disorders (38% of visits), mood disorders (32% of visits), pervasive developmental disorders or mental retardation (17% of visits), and psychotic disorders (14% of visits)

Source: Reference 1

saw more extrapyramidal symptoms (EPS) with FGAs. Our concern with SGAs is the risk of metabolic and cardiac effects; we also are concerned about tardive dyskinesia and prolactin increases.

METABOLIC CHANGES

Dr. Janicak: Diabetes is almost an epidemic in this country. Do SGAs increase the risk of diabetes in young patients?

Dr. Kowatch: Yes. In our center, we see metabolic syndrome in about one-third of the children we have on SGAs. Their appetite definitely increases; they aren't satiated, and they eat more. Weight gain leads to type 2 diabetes and hyperlipidemia. We see some weight gain with aripiprazole,

clozapine, quetiapine, and olanzapine. We don't see as much weight gain with ziprasidone, but it's harder to dose because children sometimes need more than the recommended 160 mg/d.

Dr. Janicak: How do you monitor children's metabolic response to SGAs? Do you use body mass index (BMI) measures, lipid levels, glucose levels?

Dr. Kowatch: We look for serum triglycerides >110 mg/dL or fasting glucose >110 mg/dL. We'll intervene with:

- a weight increase >5% of baseline
- or an increase in the BMI z-score >0.5 standard deviations.

In children, BMI values calculated by the adult formula (weight in kilograms/[height in meters]²) vary too much during development to be useful. Therefore, you must use sex- and age-adjusted BMI percentiles and z scores for children (see *Related resources*).

It's best to intervene early with lifestyle changes, such as reducing intake of soft drinks and carbohydrates and increasing exercise. If that doesn't work, we refer patients to an endocrinologist for possible treatment with metformin.

Dr. Janicak: How effective are lifestyle changes versus metformin?

Dr. Kowatch: About one-half of children taking antipsychotics lose weight with lifestyle changes. They definitely lose weight with metformin, but I'm not comfortable monitoring its use by myself.

Dr. Janicak: What are the risks with metformin?

Dr. Kowatch: Patients can develop lactic acidosis. It's not a medication you prescribe casually.

Dr. Janicak: Does prophylactic metformin prevent diabetes?

Dr. Kowatch: That's a big question. We don't know.

OTHER SIDE EFFECTS

Dr. Janicak: Have any of your patients developed life-threatening cardiac rhythm disturbances while taking SGAs?

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Dr. Kowatch: No, because if we see a trend toward a prolonged QTc interval we tend to switch patients to a different atypical agent.

Dr. Janicak: Which antipsychotics are most likely to cause cardiac side effects?

Dr. Kowatch: We used to use thioridazine but backed off because of QTc prolongation. We sometimes see QTc prolongation with ziprasidone. Say a patient starts out with a normal QTc of about 40 msec, and when you increase ziprasidone to 120 mg/d the interval goes up to 48 msec. Then you decide whether to risk increasing the dosage.

Dr. Janicak: How often do you obtain ECGs?

Dr. Kowatch: With ziprasidone we get a baseline ECG and repeat when we increase the dosage above 100 or 120 mg/d.

Dr. Janicak: How do you monitor prolactin?

Dr. Kowatch: Prolactin increases with olanzapine, ziprasidone, or risperidone, but there are no clear monitoring guidelines. Boys can develop gynecomastia while taking risperidone. In pubertal girls, experts recommend a baseline prolactin level, and repeating every 6 months.

Psychiatrists need better guidelines for monitoring prolactin, cardiac side effects, and metabolic

syndrome in children and adolescents taking SGAs.

Dr. Janicak: It seems FGAs have been relegated to a distant secondary role. Is that because of neuro-motor side effects and tardive dyskinesia?

Dr. Kowatch: Primarily. We used to use haloperidol in kids, but you get EPS and cognitive dulling. Children have trouble learning when they're sedated. So pediatric use of FGAs declined for a combination of reasons, including parkinsonian symptoms, EPS, sedation, and weight gain.

Dr. Janicak: When would you use an FGA instead of an SGA?

Dr. Kowatch: If a child is psychotic and not responding to atypicals.

'We're using atypical antipsychotics as first-line treatment for mania in children and adolescents'

BIPOLAR DISORDER

Dr. Janicak: There is controversy—even among child and adolescent psychiatrists—about how to distinguish

bipolar from psychotic disorders, and whether bipolar disorder exists before puberty.

Dr. Kowatch: Yes, the debate continues. Many psychiatrists do agree that mania in kids doesn't look the same as it does in adults.

Children and younger adolescents do not have clear episodes of mania. Diagnosing a child or adolescent with bipolar disorder is more difficult because of developmental differences in symptom expression, frequent comorbid disorders, and lack of biologic tests to confirm this disorder.³

DSM-IV-TR criteria for mania/hypomania were developed for adults. None take into account developmental differences in bipolar disorder between adults and youths.

Dr. Janicak: If a child or young adolescent develops bipolar disorder, would you start with an SGA? Or would you start with a classic mood stabilizer such as lithium or divalproex sodium?

Dr. Kowatch: If the patient has psychotic symptoms, it's pretty clear that SGAs are an effective first-line treatment. For mood symptoms, we have

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- ▶ **Avoid psychotropic weight gain**
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Related resources

- ▶ Kowatch RA, Fristad MA, Birmaher B, et al. Treatment guidelines for children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 2005;44(3):213-35.
- ▶ Janicak PG, Davis JM, Preskorn SH, et al. Psychopharmacotherapy in early life. In: *Principles and practice of psychopharmacotherapy*, 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2006:553-61.
- ▶ Centers for Disease Control and Prevention. Sex- and age-adjusted BMI percentiles and z scores for children. www.cdc.gov/growthcharts.

DRUG BRAND NAMES

Aripiprazole • Abilify
 Chlorpromazine • Thorazine
 Haloperidol • Haldol
 Quetiapine • Seroquel
 Metformin • Glucophage

Olanzapine • Zyprexa
 Risperidone • Risperdal
 Thiothixene • Navane
 Ziprasidone • Geodon

DISCLOSURES

Dr. Janicak receives grant/research support from AstraZeneca Pharmaceuticals, Bristol-Myers Squibb Co., Janssen Pharmaceutica, Solvay Pharmaceuticals, and Neuronetics; is a consultant to Janssen Pharmaceutica; and is a speaker for Abbott Laboratories, AstraZeneca Pharmaceuticals, Bristol-Myers Squibb Co., Janssen Pharmaceutica, and Pfizer.

Dr. Kowatch receives grant/research support from Bristol-Myers Squibb, Stanley Research Foundation, National Institute of Mental Health, and National Institute on Chemical Dependency; is a consultant to Eli Lilly & Company, GlaxoSmithKline, Janssen Pharmaceutica, Otsuka America Pharmaceutical, Cephalon, and Abbott Laboratories; and is a speaker for AstraZeneca and Abbott Laboratories.

better data with lithium and not as much with valproate. The practical reality is that SGAs work faster, and usually you don't have to draw blood as often as with traditional mood stabilizers.

Dr. Janicak: Would you consider an SGA in pediatric patients without psychosis but with strong evidence for bipolar disorder?

Dr. Kowatch: Yes. We're using SGAs first-line for mania in children and adolescents.

Dr. Janicak: What about psychotic depression in this age group?

Dr. Kowatch: We start with a selective serotonin reuptake inhibitor (SSRI) if we don't suspect bipolar disorder and there's no family history of bipolarity. If the patient doesn't respond to the SSRI, then we often augment with quetiapine, which has a relatively low risk of EPS or weight gain. We don't see much sedation at dosages above 300 or 400 mg/d, and it is very safe.

LONG-TERM EFFECTS

Dr. Janicak: I sense that you think psychiatrists are underusing—not overusing—SGAs in children and adolescents.

Dr. Kowatch: That's correct. In June 2004, the National Health Policy Forum reported 21% of 9- to 17-year-olds have a diagnosable mental disorder. If one-half of them might respond to an SGA, then we're probably under-prescribing.

Dr. Janicak: So you believe the benefit of using antipsychotics outweighs the risk?

Dr. Kowatch: With the caveat that we don't have a lot of long-term data and must monitor carefully. Overall, the short-term benefit is clear. The long term is less clear because we don't know the effects of physiologic changes such as elevated prolactin.

Dr. Janicak: Do we need more clinical experience or better long-term trials?

Dr. Kowatch: I think the latter. We need trials that look at the effects of prolactin elevation on growth, development, and the hormonal system.

Dr. Janicak: In what kind of a timeframe?

Dr. Kowatch: Quite honestly, 5 or 10 years. If you put a 9-year-old girl with bipolar disorder on risperidone and she responds, the question is what's she going to be like when she's 20 or 30?

Dr. Janicak: So you're thinking of something like the Framingham study, where patients are followed for decades to see what happens.

Dr. Kowatch: Correct. In the meantime, people need to recognize that we don't live in an ideal world. Doctors are trying to help their patients, and that's why SGAs are used so much in children and adolescents.

References

1. Olsson M, Blanco C, Liu L, et al. National trends in the outpatient treatment of children and adolescents with antipsychotic drugs. *Arch Gen Psychiatry* 2006;63:679-85.
2. Carey B. Use on antipsychotics by the young rose fivefold. *New York Times* June 6, 2006;Health section. Available at: <http://www.nytimes.com> (search NYT since 1981, "antipsychotics" and "Carey").
3. Kowatch RA, Youngstrom EA, Danielyan A, Findling RL. Review and meta-analysis of the phenomenology and clinical characteristics of mania in children and adolescents. *Bipolar Disord* 2005;7(6):483-96.