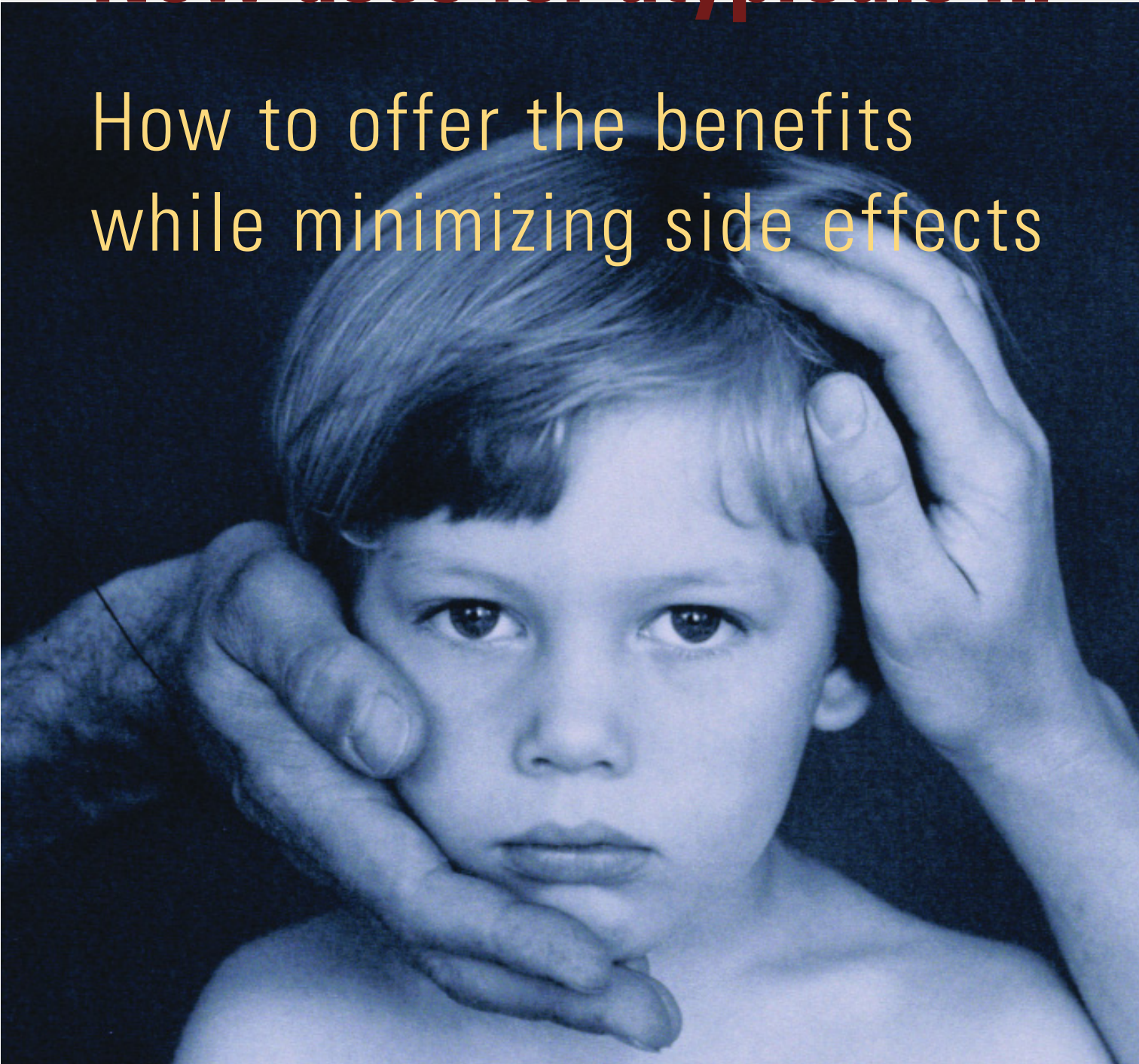


New uses for atypicals in

How to offer the benefits
while minimizing side effects



pediatric patients

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Using antipsychotics in children can improve intractable symptoms, but the drugs' long-term health effects are unknown. These authors scour the literature to help you safely treat young patients with schizophrenia, bipolar disorder, and psychotic depression.

Prescribing of atypical antipsychotics for children and adolescents is increasing, despite a lack of randomized controlled clinical trials. Like many psychiatrists, you may be treating pediatric patients with these medications for a variety of indications beyond psychosis.

Three factors are driving the use of atypical antipsychotics for broader indications:

- substantial evidence that these newer agents are safer and more effective than typical antipsychotics¹
- inadequate response of childhood and adolescent psychiatric disorders to their primary treatments
- evidence that atypical antipsychotics have potential thymoleptic, antiaggressive, and anxiolytic properties.

These attributes already have expanded atypical antipsychotic use in adult patients. In fact, atypicals are being used more extensively in adults for affective and nonpsychotic conditions than for schizophrenia.²

In preparing the following two-part article for *Current Psychiatry*, we scoured the available literature—Medline, abstracts from scientific meetings, and American Academy of Child and Adolescent Psychiatry (AACAP) practice parameters—to examine the evolving role of atypical antipsychotics in children and adolescents. In part 1 of this article, we discuss using atypicals in childhood/adolescent-onset schizophrenia, bipolar disorder, and psychotic depression. In

continued



Box 1

RECOMMENDED WORK-UP BEFORE PRESCRIBING ANTIPSYCHOTICS

Before prescribing antipsychotic medications for children and adolescents, always conduct a comprehensive history and complete physical examination.

History. Include information about:

- seizures, head trauma, and cardiac or endocrine problems (often elicited with questions about fatigue, temperature intolerance, or weight concerns)
- perinatal history (apnea, Apgar scores, days in hospital)
- family history (e.g., significant medical problems).

Physical exam. Obtain baseline blood pressure, pulse, body weight and habitus, and laboratory tests—complete blood count, comprehensive metabolic profile with liver function tests, and cholesterol/triglyceride levels.

Educate the parent and child about possible side effects, whether they are likely to be transient or persistent, and ways to minimize them (e.g., bedtime dosing to prevent daytime sedation, dietary recommendations to lessen potential weight gain).

Monitor lab values and weight throughout treatment (compared with normal growth curves). Use words the child understands when asking about side effects (e.g., “Have you had leakage from your breasts?”). Continually weigh the benefits versus the risks of antipsychotics, and discuss this balance with the parent and child.

part 2 (page 54), we look at evidence for using atypicals in children with autism and developmental disorders, Tourette’s and other tic disorders, disruptive behavior disorders, anorexia nervosa, anxiety disorders, and stuttering.

Shift in pharmacotherapy of schizophrenia.

One-quarter of patients with schizophrenia develop the disorder before age 15, and subtle psychotic manifestations are often observed in early childhood.³ In general, schizophrenia’s presenting symptoms are comparable in adults and children, but the childhood/adolescent-onset form is more severe.^{4,5}

During the past 5 years, pharmacotherapy of adult schizophrenia has shifted dramatically away from typical antipsychotics. Atypical agents have shown greater efficacy and tolerability, especially with respect to extrapyramidal symptoms (EPS) and tardive dyskinesia (TD).¹

In a recent survey, most general and specialist psychiatrists (86%) said they prefer using atypical antipsychotics as first-line treatment for new-onset schizophrenia and as maintenance therapy. They also reported using atypicals to treat patients with dementia (80%), personality disorders (69%), developmental delay/mental retardation (65%), and autism (40%).⁶

Translating adult findings to children. Most evidence of atypical antipsychotics’ efficacy and tolerability is derived from adult studies, which likely will continue to influence clinical practice more than the limited number of child and adolescent studies. In 1998, a thorough review of atypical antipsychotic use in child and adolescent psychiatry found only five blinded placebo-controlled clinical trials, 24 open-label trials, and 33 case series.⁷ A follow-up review in 1999 again found mainly case reports and case series, with a handful of controlled studies.⁸

Available atypical antipsychotics include clozapine, risperidone, olanzapine, quetiapine, and ziprasidone. An investigational agent—aripiprazole—is likely to be available soon for clinical use.

Issues in pediatric use of atypicals

When prescribing atypical antipsychotics, it is important to balance the benefit of treatment

with the risk of exposing children to possible adverse effects. Side effects associated with atypicals include weight gain, secondary metabolic disturbances such as hyperglycemia, hyperprolactinemia, and cardiac conduction abnormalities. These side effects are health concerns for all patients but particularly for children and adolescents, who may require years of exposure to antipsychotics.

Weight gain. Younger patients may be particularly susceptible to weight gain with the use of the atypicals. In a state hospital adult population, Buckley et al found a strong inverse relationship between patient age and weight gain associated with atypical antipsychotic use.⁹ Key issues for pediatric populations are:

- Will children have difficulties losing weight over time?
- Will they stop their medications over time?
- Will they stop their medications because of this effect?

- Will they be further stigmatized at school because of obesity?
- Are they at increased risk to develop diabetes mellitus?
- What are the long-term consequences of antipsychotic-induced obesity and metabolic disturbances for this patient population?

Hyperprolactinemia in children and adolescents may lead to breast enlargement and galactorrhea, which are particularly distressing in this age group. Sustained elevation of prolactin may affect the regulation of other hormones, result-

ing in low estrogen and testosterone levels. The long-term impact of these changes on adolescent growth and development is unknown. Antipsychotic-induced hyperprolactinemia also may be associated with reduced bone density.¹⁰

Abnormal cardiac conduction. Thioridazine recently received a “black box” label warning from the FDA because of sudden deaths and a prolonged QTc interval seen on electrocardiogram (ECG) readings. Several other antipsychotics also show ECG evidence of QTc prolongation.¹¹ However, the clinical significance of this finding is unclear.

Box 2

HOW ANTIPSYCHOTICS ARE METABOLIZED IN CHILDREN AND ADOLESCENTS

Younger patients respond differently than do adults to antipsychotic medications because of developmental differences in pharmacokinetics: absorption, distribution, metabolism, and excretion.

Absorption. Stomach contents tend to be less acidic in younger persons than in adults, potentially slowing absorption of weakly acidic drugs. In theory, the absorption of antidepressants and psychostimulants is more likely to be altered than that of antipsychotics. Children may also have fewer and less diverse intestinal microflora, which may explain why phenothiazines (absorbed or metabolized in the intestinal wall) must be given at higher-than-adult oral dosages for clinical effect.¹²

Children may absorb certain psychotropic medications (e.g., imipramine) more rapidly than adults. This contributes to greater fluctuations in blood levels and possible cardiac toxicity—often a function of peak plasma concentrations.

Distribution. Drug distribution patterns in infants, children, and adolescents—especially those going through puberty—are not homogenous.¹³ Fat stores and the relative proportion of total body water to extracellular water affect distribution and change with development.

The proportion of fat to body weight is highest in the first year of life, declines steadily during childhood, increases prior to puberty, then declines thereafter. Thus, although individuals have variable degrees of fat stores, children in general have a lower proportion of body fat than adults and therefore a smaller volume of

distribution. This becomes significant when prescribing antipsychotics, which are lipid-soluble.

If one considers only a drug’s distribution, one would expect to find a higher plasma concentration in a child if a child and an adult were given the same weight-adjusted dose of a lipophilic drug. Children, however, exhibit a lower plasma concentration of lipophilic drugs than do adults because of differences in metabolism.¹³

Metabolism. Children’s increased metabolic rate is directly related to age-related changes in hepatic enzymes. In general, metabolic pathways for many drugs function at a low level during the perinatal period, mature by 6 months, peak between ages 1 and 5, and decline gradually to adult values by about age 15. Liver mass is also greater in children than in adults. Therefore, higher ratios of milligrams of drug to kilograms of body weight may be needed in children to achieve steady-state plasma levels comparable to those seen in adults.

Excretion. Infant and adult renal functioning are approximately the same. With the exception of lithium, developmental changes in renal function do not contribute substantially to age-related differences in psychotropic drug excretion.¹³

Summary. When compared with adults, children require a higher milligram-to-kilogram dosage of antipsychotics to achieve the same plasma concentration but clinically require a lower milligram-to-kilogram dosage—starting dosages usually less than one-half of an adult dose—to avoid unwanted side effects.



Table

SUGGESTED DOSAGES OF ATYPICAL ANTIPSYCHOTICS

Drug	FDA-approved dosages for psychosis in adults	For psychosis in children and adolescents	For bipolar disorder in children and adolescents
Clozapine	Initial: 25 mg bid; increase gradually to 300 to 800 mg/d in divided doses	Not recommended for children under age 16 Initial: 12.5 to 25 mg bid; increase gradually to 300 to 450 mg/d (divided) Increased risk of seizures; potential for agranulocytosis	Limited research
Olanzapine	Psychosis. Initial: 5 to 10 mg qd or 5 mg bid; increase to 20 mg qd or 10 mg bid Bipolar disorder. Similar initial; lower maintenance (10 to 20 mg qd or 10 mg bid can often be obtained)	Clinical benefit in children age ≤ 10 at 2.5 to 10 mg/d; For age >10 , 5 to 20 mg qd or 10 mg bid may be used Sedation and weight gain are common side effects	Clinically beneficial at dosages comparable to those used in psychosis Maintenance dosage may be lower than that required in a primary psychotic disorder
Quetiapine	Initial: 25 mg bid; increase to 300 to 800 mg/d divided in two to three doses	Initial: 12.5 mg bid (<50 kg) to 25 mg bid (>50 kg) Maintenance: 50 mg bid (<50 kg) to 100 mg bid (>50 kg) Few controlled trials in children <10 yrs	Limited research
Risperidone	Initial: 2 mg/d; may be increased to 4 to 6 mg/d in divided doses	Clinical trials indicate benefit at 0.25 to 0.5 mg qd or bid May be increased as needed to 0.5 to 1.5 mg/d in single or divided doses	Clinically beneficial at dosages comparable to those used in psychosis
Ziprasidone	Initial: 20 to 40 mg bid; may be increased to 40 to 80 mg bid	Preliminary studies suggest benefit at 10 to 20 mg bid, increasing to 20 to 60 mg bid Not recommended as first-line therapy in this population	Limited research

* The FDA has not approved a specific indication for these agents for use in children and adolescents. In adult patients, atypical antipsychotics have been approved for psychosis, and olanzapine is FDA-approved for psychosis and mood disorders.

Special care is required to decrease the risks associated with using antipsychotics in children and adolescents and to increase compliance with medication recommendations (*Box 1*).

Pharmacokinetics in children and adolescents

Administering medications to children and adolescents requires special precautions. Younger patients respond differently than adults to psychotropic medications because of differences in pharmacokinetics—how the body handles a drug—and pharmacodynamics—the drug’s effect on the body.

During a child’s growth and development, physiologic changes in absorption, distribution, metabolism, and excretion may affect drug delivery to target tissue (*Box 2*).^{12,13} Maturation of brain regions and neurotransmitter systems also may alter a medication’s effect at different ages.

Antipsychotic dosage recommendations and therapeutic ranges for children and adolescents have been published but are extrapolated from adult studies because studies in children are lacking. There is danger, however, in using body weight and proportionately reducing an adult dosage to obtain a pediatric dosage. The plasma concentration may ultimately be subtherapeutic or toxic.¹⁴

The liver metabolizes most antipsychotics. The higher rate of hepatic metabolism in children would suggest that on a milligram-to-kilogram basis a child or adolescent would need a higher dose. Children, however, require smaller weight-adjusted doses of antipsychotics than do adults to achieve the same therapeutic effect.¹⁵ Children have a greater density of dopamine D-1 and D-2 receptors than do adults, suggesting a greater sensitivity to the beneficial and adverse effects of antipsychotics. To date, dopamine receptor occupancy in children/adolescents with schizophrenia has not been studied with positron emission tomography.

Summary. Compared with adults, children require a reduced milligram-to-kilogram dosage of antipsychotics to achieve the same therapeutic effect and avoid unwanted side effects. Children younger than age 10 or weighing less than 50 kg typically should start with the lowest starting dose, given once or twice a day (*Table*). The dose should be slowly increased based on the presence of side effects and remission of symptoms.

Maximum daily dosages for children weighing less than 50 kg should rarely exceed one-half of an adult antipsychotic

Box 3

CASE REPORT: ANTIPSYCHOTIC DOSING FOR A TEEN WITH PARANOIA

An adolescent boy, age 13 and weighing 47 kg, presents with the chief complaint of paranoia, which is impairing his academic functioning. On examination, his interaction is guarded, and he exhibits severe emotional withdrawal and a paucity of thought content. His family history is significant for a maternal uncle with early-onset schizophrenia, which is chronic but under reasonable control with olanzapine, 10 mg bid.

The boy’s treatment is started with olanzapine, 2.5 mg once daily. After 2 weeks, the dosage is increased to 2.5 mg in the morning and 5 mg at bedtime, with good symptom resolution.

dosage, particularly when used for symptoms of disorders other than primary psychosis. However, dosages closer to those used in adults may be necessary when treating primary psychosis in early-onset schizophrenia, especially in an adolescent (*Box 3*).

Childhood/adolescent-onset schizophrenia

Typical antipsychotics appear to have limited efficacy in childhood/adolescent-onset schizophrenia, based on a small number of available case series and relatively short open-label trials.¹⁶ In a single-arm, placebo-controlled trial, haloperidol was effective in 16 children ages 5 to 12, but its use was associated with substantial EPS. A similar intolerance was demonstrated in a comparative trial of thioridazine and thiothixene.

Less is known about the incidence of tardive dyskinesia, but there is no reason to believe that the rate is lower in children and adolescents than in adults with schizophrenia (estimated at 5% per year for the first 5 years of treatment).

Clozapine. Information is emerging on the efficacy and tolerability of atypical antipsychotics in childhood/adolescent-onset schizophrenia.¹⁶ Clozapine has been studied more than other atypicals, in part because of the severity of early-onset schizophrenia and because clozapine has been used in clinical practice longer than the other agents in that class.

Early case reports and small open-labeled trials confirmed that clozapine was effective for children and adoles-



cents with schizophrenia who had failed prior antipsychotic treatments.¹⁷⁻¹⁹ A randomized, double-blind, controlled trial from the childhood schizophrenia division of the National Institute of Mental Health provided the most reliable information.¹⁷ In that 6-week treatment study, 21 severely ill adolescents (mean age 14) received clozapine, mean dosage 176 mg/d, or haloperidol, mean dosage 16 mg/d. Response to clozapine was greater for both positive and negative symptoms, and the difference was clinically and statistically significant. In addition, 62% of clozapine-treated patients were rated very much improved on the Clinical Global Impression (CGI) scale.

In the same trial, clozapine treatment was complicated by higher rates of adverse effects than are typically observed in adult studies:

- Sedation was reported in 90% of patients.
- 2 of 10 patients had a seizure during clozapine therapy.
- A 2% rate of agranulocytosis was disconcerting, given the lower adult rate (0.38%) and the brevity of the trial. As older age is a known risk factor for clozapine-induced agranulocytosis, it may be that children and the elderly are more susceptible to this side effect.

Risperidone. Most of the information on risperidone therapy in childhood/adolescent-onset schizophrenia is derived from small case series,⁷ which confirm its efficacy for both positive and negative symptoms. Recently, low-dose risperidone (less than 1.5 mg/d) was shown to be effective in young patients with schizophrenia's prodrome.²⁰ In general, risperidone dosages of 1 to 2 mg/d are appropriate for patients with childhood/adolescent-onset schizophrenia. Children have been observed to be particularly sensitive to the drug's EPS and prolactin-elevating effects.

Olanzapine has been effective in this patient population at dosages up to 10 mg/d.^{7,16,21} In a pilot study, Kumra et al administered olanzapine to 23 children with schizophrenia who had not previously responded to neuroleptic treatment. After 8 weeks, the children improved on the Brief Psychiatric Rating Scale, the Scale for the Assessment of Negative Symptoms, and the Scale for the Assessment of Positive Symptoms.²¹

Risperidone at 1 to 2 mg/d is generally appropriate for patients with pediatric-onset schizophrenia

Similarities and differences in olanzapine's side effects in adults and children/adolescents with schizophrenia were seen in a recent study. Children had more weight gain, sedation, and dystonia, whereas adults had significantly more cardiac arrhythmias.²²

Quetiapine. McConville and colleagues examined the efficacy and tolerability of quetiapine in 10 adolescents with chronic psychosis (7 with schizoaffective disorder and 3 with bipolar disorder). In this 3-week study, quetiapine was well-tolerated; in several patients, dosages exceeded 750 mg/d.

Psychotic symptoms were reduced, and there was global improvement in functioning.²³

Other antipsychotics. There are no published data on the use of ziprasidone or aripiprazole in childhood/adolescent-onset schizophrenia.

Comparative data are very limited. One retrospective analysis compared the tolerability of risperidone, olanzapine, and quetiapine in 116 adolescent patients.²⁴ Over 3 months, 75 patients received risperidone (mean 2.6

mg/d), 16 received olanzapine (mean 13.3 mg/d), and 25 were treated with quetiapine (mean 210.3 mg/d). Weight gain was the most common side effect; patients gained an average 8.6 lb with risperidone, 7.2 lb with quetiapine, and 14.1 lb with olanzapine. EPS were treated in seven (10%) patients taking risperidone, four (25%) taking olanzapine, and no patients taking quetiapine.

Bipolar disorder

As in the adult population, there has been substantial use of antipsychotics in children and adolescents with bipolar illness. Bipolar I disorder affects an estimated 0.6% of adolescents and is even being diagnosed in prepubertal patients.

Lithium, valproate, carbamazepine, and adjunctive treatment with benzodiazapines traditionally have been used to treat bipolar I disorders. Although practice guidelines recommend lithium and divalproex sodium as first-line treatments for bipolar illness, these recommendations are generally based on a preference for first-line agents that have potential use in maintenance treatment. The benefit of medications in bipolar disorder, however, is two-fold:

- Initial pharmacotherapy is usually instituted to target manic or mixed symptoms, and continued treatment is necessary to avoid relapse. The new antipsychotics—particularly risperidone, olanzapine, and quetiapine—are

beneficial to treat agitated mania and disrupted sleep that may impair function and/or mandate inpatient stabilization. The highly sedative properties offer an acute benefit in restoring disrupted sleep.

- Psychotic symptoms seen in mania may need to be targeted independent of the mood symptoms and would thus suggest the use of an antipsychotic. In early-onset bipolar disorder, antipsychotics are used primarily as adjuncts to mood stabilizers.

Evidence. The 1997 AACAP practice parameters on treating bipolar disorders included limited information on the use of antipsychotics. No studies had examined the efficacy of neuroleptics (i.e., haloperidol) in children and adolescents, and only one case study had been published on the benefit on a newer antipsychotic agent.²⁵ Since then, case reports and open studies have contributed to our understanding of the role the newer antipsychotics may play in treating this disorder:

- In the 1994 case report, an adolescent with bipolar disorder showed benefit when treated with clozapine.²⁶
- In a retrospective chart review, 28 children ages 4 to 17 with bipolar disorder (25 mixed and 3 hypomanic) were treated with adjunctive risperidone for 6 months. Most (82%) showed significant improvement in mania and aggression on a mean dosage of 1.7 +/- 1.3 mg/d. Attention-deficit/hyperactivity disorder symptoms improved in 8% of the patients.²⁷
- Affective symptoms (predominantly suggestive of bipolar disorder), aggression, and violent behavior in 11 children and adolescents ages 5 to 16 showed therapeutic response to an open trial of adjunctive low-dose (0.75 to 2.5 mg/d) risperidone.²⁸

Olanzapine. Recent interest in olanzapine's thymoleptic properties has contributed to its clinical use in bipolar disorder, specifically in psychotic mania. Olanzapine has also been studied as long-term maintenance therapy in bipolar disorder. In a 47-week study, adult patients receiving olanzapine improved significantly more than those receiving valproate (47% vs. 34% by the Young Mania Rating Scale) after 3 weeks. Both medications were effective throughout the long-term, randomized, double-blind study.²⁹

Two case series and one open trial have examined olanzapine as primary or adjunctive treatment for children and adolescents with bipolar disorder. In the open study, Frazier

and colleagues gave olanzapine, 2.5 to 20 mg/d, to 23 children ages 5 to 14.³⁰ After 8 weeks, the response rate was 61% (defined as 30% or greater improvement on the Young Mania Rating Scale). Weight gain was the predominant side effect (mean increase 5 kg).

Chang and colleagues demonstrated "marked improvement" in CGI scores when using olanzapine as adjunctive therapy for three youths with bipolar disorder.³¹ Similar findings were reported when treating seven youths with acute mania.³² Olanzapine's broad affinity for dopaminergic and serotonergic receptors may explain

these positive outcomes.

Other atypicals. No studies have been published on the use of quetiapine, ziprasidone, or aripiprazole in childhood mood disorders.

Psychotic depression

Psychosis can complicate depression in adults and adolescents. In a small study of adolescents with psychotic depression, Gellar et al demonstrated conventional neuroleptics' benefit in combination with antidepressants.³³ We have no data, however, on use of atypicals in childhood depression, and published accounts of depression in bipolar patients treated with atypicals are of some concern.

In one study,³⁴ four of six patients with bipolar disorder developed dysphoric mood within 3 months of starting risperidone. Two met the criteria for major depression and required antidepressant therapy. This finding was somewhat surprising, given risperidone's antidepressant benefit in some adults, most likely due to its 5-HT₂ antagonistic effect. Frazier and colleagues similarly noted that one patient discontinued treatment during an open-label trial examining the benefit of olanzapine in juvenile bipolar disorder.³⁰

These findings in the adolescent bipolar population should not be ignored when you consider treating a primary depressive disorder with psychosis. Antipsychotics certainly can be useful for treating psychotic depression, especially acutely for stabilization and preventing harm to self. Atypical antipsychotics have consistently been proven to have less adverse side effects than typical antipsychotics and thus would be preferred in children and adolescents. Research is needed to examine possible worsening of dysphoria.

In bipolar mania, the sedative properties of atypicals offer an acute benefit in restoring disrupted sleep


continued



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Related resources

- ▶ Hermann RC, Yang D, Ettner SL, et al. Prescription of antipsychotic drugs by office-based physicians in the United States, 1989-1997. *Psychiatric Services* 2002;53:425-30.
- ▶ Stigler KA, Potenza MN, McDougle CJ. Tolerability profile of atypical antipsychotics in children and adolescents (review). *Paediatric Drugs* 2001;3(12):927-94
- ▶ American Academy of Child and Adolescent Psychiatry <http://www.aacap.org>

DRUG BRAND NAMES

Clozapine • Clozaril	Risperidone • Risperdal
Olanzapine • Zyprexa	Ziprasidone • Geodon
Quetiapine • Seroquel	Aripiprazole (investigational)

DISCLOSURE

Dr. Londino reports that she serves as a consultant to Eli Lilly and Co.

Ms. Wiggins reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

Dr. Buckley reports that he receives grant support from and serves as a consultant and speaker for AstraZeneca Pharmaceuticals, Eli Lilly and Co., Janssen Pharmaceutica, and Novartis Pharmaceuticals Corp.

Prescribing of atypical antipsychotics for pediatric patients is increasing. To avoid unwanted side effects, children generally require less than one-half the initial adult dosage. Because the long-term effects of antipsychotics are unknown, their use in children requires careful consideration of the possible risks and benefits.

BottomLine