Current PSYCHIATRY

Clinical trials support new algorithm for treating pediatric bipolar mania

4 atypical antipsychotics are proposed as first-line therapy, based on current evidence

Five recent randomized controlled trials (RCTs) have demonstrated the efficacy of atypical antipsychotics for treating bipolar disorder in children and adolescents, but 4 of these 5 trials remain unpublished. The lag time between the completion of these trials and publication of their results—typically 4 to 5 years[1]—leaves psychiatrists without important evidence to explain to families and critics[2] why they might recommend using these powerful medications in children with mental illness.

This article previews the preliminary results of these 5 RCTs of atypical antipsychotics, offers a treatment algorithm supported by this evidence, and discusses how to manage potentially serious risks when using antipsychotics to treat children and adolescents with bipolar disorder (BPD).

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Where do atypical antipsychotics fit in?

Details of the 5 industry-sponsored RCTs of atypical antipsychotics in children and adolescents with bipolar I manic or mixed episodes are summarized in ***Table 1 (page 24)***.[3-7] Only the olanzapine study[4] has been published; data from the other 4 trials were presented at medical meetings in 2007 and 2008.

Change in Young Mania Rating Scale (YMRS) score was the primary outcome measure in these 5 trials, and each compound was more effective than placebo. The trials demonstrated statistically significant and clinically relevant differences between each antipsychotic and placebo. The number needed to treat (NNT)—how

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many patients need to be treated for 1 to benefit in a controlled clinical trial—ranged from 2 to 4. For comparison, the NNT for statins in the prevention of coronary events is 12 to 22,[8] and the NNT in an analysis of trials of selective serotonin reuptake inhibitors for pediatric major depressive disorder was 9.[9] Thus, an NNT of ≤4 represents a clinically significant effect.

Risperidone is FDA-approved for short-term treatment of acute bipolar I manic or mixed episodes in patients age 10 to 17. Aripiprazole is approved for acute and maintenance treatment of bipolar I manic or mixed episodes (with or without psychosis) as monotherapy or with lithium or valproate in patients age 10 to 17. In June, an FDA advisory committee recommended pediatric bipolar indications for olanzapine, quetiapine, and ziprasidone.

'Mood stabilizers' such as lithium, valproate, and carbamazepine have been used for years to treat bipolar mania in adults, adolescents, and children, despite limited supporting evidence. Preliminary results of a National Institute of Mental Health-funded double-blind RCT provide insights on their efficacy.[10]

The 153 outpatients age 7 to 17 in a bipolar I manic or mixed episode were randomly assigned to lithium, divalproex, or placebo for 8 weeks. Response rates—based on a Clinical Global Impressions-Improvement score of 1 or 2 (very much or much improved)—were divalproex, 54%; lithium, 42%; and placebo, 29%. Lithium showed a trend toward efficacy but did not clearly separate from placebo on the primary outcome measures. Effect sizes for lithium and divalproex were moderate.[10]

Only 1 study has compared a mood stabilizer with an atypical antipsychotic for treating mania in adolescents. In a double-blind trial, DelBello et al[11] randomly assigned 50 patients age 12 to 18 with a bipolar I manic or mixed episode to quetiapine, 400 to 600 mg/d, or divalproex, serum level 80 to 120 µg/mL, for 28 days. Manic symptoms resolved more rapidly, and remission rates measured by the YMRS were higher with quetiapine than with divalproex. Both medications were well tolerated.

Combination therapy. BPD as it presents in children and adolescents is often difficult to treat because of the disorder's various phases (manic, depressed, mixed), frequent psychotic symptoms, and high rate of comorbidity. Pediatric BPD patients

Pediatric mania

Clinical Point

A mood stabilizer plus an atypical antipsychotic may be more effective than a mood stabilizer alone for treating adolescent mania

Table 1

RCTs of atypical antipsychotics in patients age 10 to 17 with bipolar I disorder*

Antipsychotic and source	Bipolar I episode (# of subjects)	Trial duration (days)	Dosage (mg/d)	Response rate or YMRS score change	NNT	Mean weight gain (kg)
Risperidone Pandina et al[3] AACAP 2007	Manic, mixed (169)	21	0.5 to 2.5 3 to 6	59% 63%	3.3 3.5	1.9 1.4
Olanzapine Tohen et al[4]	Manic, mixed (161)	21	10.4 ± 4.5	49%	4.1	3.7 ± 2.2
Quetiapine DelBello et al[5] AACAP 2007	Manic (284)	21	400 600	64% 58%	4.4 4.2	1.7 1.7
Aripiprazole Wagner et al[6] ACNP 2007	Manic, mixed (296)	28	10 30	45% 64%	4.1 2.4	0.9 0.54
Ziprasidone DelBello et al[7] APA 2008	Manic, mixed (238)	28	80 to 160	–13.83 with ziprasidone, –8.61 with placebo	3.7	None

*Each trial included a 6-month open extension phase; results are pending
AACAP: American Academy of Child and Adolescent Psychiatry; ACNP: American College of Neuropsychopharmacology; APA: American Psychiatric Association; NNT: number needed to treat; RCT: randomized controlled trial; YMRS: Young Mania Rating Scale

frequently require several psychotropics, including mood stabilizers and atypical antipsychotics.

In a double-blind, placebo-controlled study, 30 adolescents in a bipolar I manic or mixed episode initially received divalproex, 20 mg/kg/d, then were randomly assigned to 6 weeks of adjunctive quetiapine, titrated to 450 mg/d in 7 days (n=15), or placebo (n=15). Those receiving divalproex plus quetiapine showed a statistically significant greater reduction in manic symptoms (P = .03) and a higher response rate (87% vs 53%, P = .05), compared with those receiving divalproex and placebo. This suggests that a mood stabilizer plus an atypical antipsychotic is more effective than a mood stabilizer alone for adolescent mania. Quetiapine was well tolerated.[12]

Treatment. The American Psychiatric Association's outdated 2002 practice guideline for acute bipolar I manic or mixed episodes in adults recommends lithium, valproate, and/or an antipsychotic.[13] The more recent Texas Medication Algorithm Project (TMAP) guidelines recommend monotherapy with lithium, valproate, aripiprazole, quetiapine, risperidone, or ziprasidone for adults with euphoric or irritable manic or hypomanic symptoms.[14]

Based on the TMAP algorithm, recent clinical trial evidence, and our experience in treating pediatric BPD, we offer an approach for treating mania/hypomania in patients age 10 to 17 ***(see Proposed Algorithm, page 30)***. For dosing and precautions when using atypical antipsychotics in children and adolescents with BPD, see ***Table 2 (page 29)***.[15-17]

Comorbid psychiatric illnesses (such as anxiety disorders) are prevalent in adolescents with BPD. Evidence in adults and adolescents suggests that some atypical antipsychotics may provide additional benefit for these conditions as well. Thus, consider comorbid conditions and symptoms when choosing antimanic agents.

Attention-deficit/hyperactivity disorder (ADHD) is a common comorbidity in children with BPD, and stimulant medications are most often prescribed to treat inattentiveness and hyperactivity. Caution is imperative when treating bipolar youth with stimulants, which can exacerbate manic symptoms. Treat the patient's mania before adding or reintroducing stimulant medication. Research and clinical experience sug-

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Table 2

Recommended antipsychotic use in pediatric bipolar disorder

Drug	Starting dosage (mg)	Target dosage (mg/d)	Precautions
Aripiprazole	2.5 to 5 at bedtime	10 to 30	Monitor for CYP 3A4 and 2D6 interactions, weight, BMI, cholesterol, lipids, and glucose
Olanzapine	2.5 bid	10 to 20	Monitor for CYP 2D6 interactions, weight, BMI, cholesterol, lipids, glucose, and prolactin levels
Quetiapine	50 bid	400 to 1,200	Monitor for weight, BMI, cholesterol, lipids, and glucose
Risperidone	0.25 bid	1 to 2.5	Monitor for EPS, hyperprolactinemia (and associated sexual side effects, including galactorrhea), weight, BMI, cholesterol, lipids, glucose, and prolactin levels
Ziprasidone	20 bid	80 to 160	Check baseline ECG and as dose increases or with reason for high level of concern; monitor prolactin levels

BMI: body mass index; CYP: cytochrome P450; ECG: electrocardiography; EPS: extrapyramidal symptoms
Source: References 15-17

gest that if you first stabilize these patients on a mood stabilizer or atypical antipsychotic, adding a stimulant can be very helpful in treating comorbid ADHD symptoms. Start with low stimulant doses, and increase slowly.

Managing adverse effects

Although clinically effective, atypical antipsychotics may cause serious side effects that must be recognized and managed. These include extrapyramidal symptoms (EPS), tardive dyskinesia (TD), weight gain and obesity, hyperlipidemia, increased prolactin levels, and QTc changes. Counsel patients and families about the risks and benefits of antipsychotics when you consider them for children and adolescents with BPD (***Table 3, page 31***).

EPS. Drug-induced parkinsonism and akathisia are the most common EPS in children and adolescents with BPD treated with atypical antipsychotics.[18]

Correll et al[19] reported a 10% rate of EPS in patients treated with aripiprazole. Treatment-emergent EPS also was observed in the RCT of risperidone.[20] EPS-related adverse events were associated with higher doses of risperidone, although none of the akathisia/EPS measures were thought to be "clinically significant."

EPS frequency was relatively low and similar to placebo in the 3-week quetiapine trial,[21] and no changes in movement disorder scale scores were observed during the olanzapine or ziprasidone RCTs.[4,7]

Recommendations. If your pediatric patient develops EPS, first try an antipsychotic dose reduction. Because anticholinergics can contribute to antipsychotic-induced weight gain, reserve them until after a dosage reduction has been unsuccessful.

Benztropine (0.25 to 0.5 mg given 2 to 3 times daily, not to exceed 3 mg/d) or diphenhydramine (25 to 50 mg given 3 to 4 times daily; maximum dosage 5 mg/kg/d) can be effective in treating EPS. Avoid anticholinergics in children with narrow-angle glaucoma or age <3.

Akathisia may be managed with propranolol (20 to 120 mg/d in divided doses). Multiple doses (typically 3 times daily) are needed to prevent interdose withdrawal symptoms. Use this beta blocker with caution in children with asthma because of the possibility of bronchospasm.

TD. Short-term trials and a meta-analysis of atypical antipsychotic trials (>11 months' duration, subject age <18) suggest a low annual risk for TD (0.4%).[22] Large, prospective, long-term trials of atypical antipsychotics are necessary to more accurately define the risk of TD in the pediatric population, how-

Clinical Point

If EPS develop, first try reducing the antipsychotic dose; an anticholinergic might be next, unless contraindicated

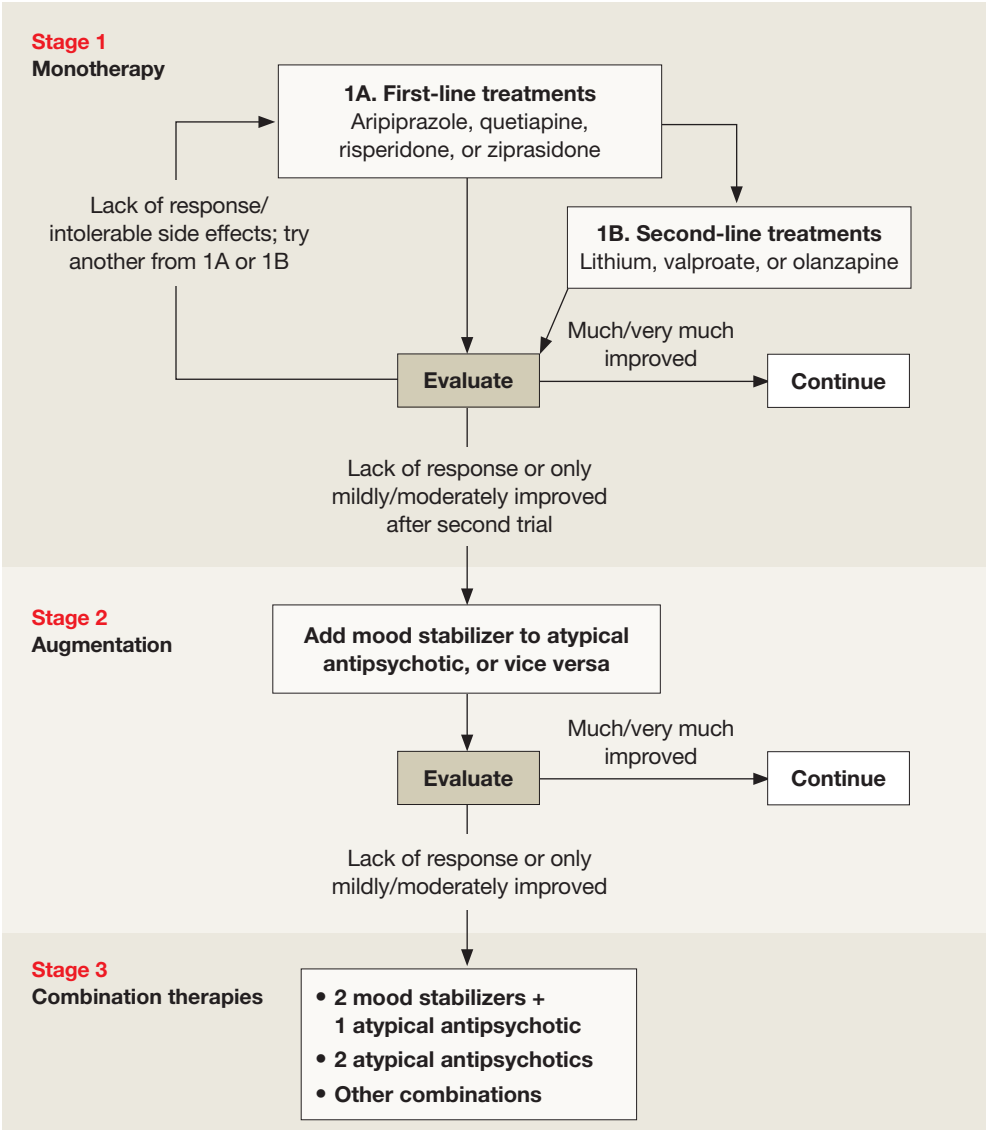
Pediatric mania

Clinical Point

Propranolol may manage akathisia, but use this agent with caution in children with asthma because of the risk of bronchospasm

Proposed Algorithm

Treating a bipolar mixed/manic episode in patients age 10 to 17



Stage 1. Consider patient's experience with antipsychotics, body weight, and family history when choosing first-line monotherapy (1A). Quetiapine poses low risk for extrapyramidal symptoms and tardive dyskinesia. Aripiprazole and ziprasidone pose relatively low risk of weight gain. Risperidone is potent at low doses but increases prolactin levels (long-term effect unknown).

Second-line choices (1B) are mood stabilizers lithium and valproate (because of lower potency than atypical antipsychotics), and olanzapine (which—although potent—causes substantial weight gain). In case of lack of response or intolerable side effects with initial agent, select an alternate from 1A or 1B. If this is not effective, move to Stage 2.

Stage 2. Consider augmentation for patients who show partial response to monotherapy (in your clinical judgment "mild to moderately improved" but not "much or very much improved").

Stage 3. Combination therapy could include 2 mood stabilizers (such as lithium and valproate) plus an atypical antipsychotic; 2 atypical antipsychotics; or other combinations based on patient's past responses. No research has shown these combinations to be efficacious in bipolar children and adolescents, but we find they sometimes help those with treatment-resistant symptoms.

Duration. Maintain psychotropics 12 to 18 months. When patient is euthymic, slowly taper 1 medication across several months. If symptoms recur, reintroduce the mood-stabilizing agent(s).

Source: Adapted and reprinted with permission from Kowatch RA, Fristad MA, Findling R, et al. Clinical manual for the management of bipolar disorder in children and adolescents. Arlington, VA: American Psychiatric Publishing, Inc.; 2008

ever. Retrospective analyses of adolescents treated with antipsychotics suggest 3 TD risk factors:

- early age of antipsychotic use
- medication nonadherence
- concomitant use of antiparkinsonian agents.[23]

Kumra et al[24] identified lower premorbid functioning and greater positive symptoms at baseline as factors associated with "withdrawal dyskinesia/tardive dyskinesia" in children and adolescents with early-onset psychotic-spectrum disorders treated with typical or atypical antipsychotics.

Recommendations. To minimize TD risk, use the lowest effective antipsychotic dose, monitor for abnormal involuntary movements with standardized assessments (such as the Abnormal Involuntary Movement Scale), review risks and benefits with parents and patients, and regularly evaluate the indication and need for antipsychotic therapy. It is reasonable to attempt to lower the antipsychotic dose after the patient has attained remission and been stable for 1 year.

Neuroleptic malignant syndrome (NMS). This complication of dopamine-blocking medications:

- is among the most serious adverse effects of antipsychotic treatment
- continues to be associated with a mortality rate of 10%.[25]

Recommendation. At least 1 recent review of pediatric NMS cases suggests that essential features (hyperthermia and severe muscular rigidity) are retained in children.[26] Nonetheless, monitor for variant presentations; hyperthermia or muscle rigidity may be absent or develop slowly over several days in patients treated with atypical antipsychotics.[27]

Weight gain and glucose metabolism. A major adverse effect of most atypical antipsychotics is increased appetite, weight gain, and possible obesity.[28] In children, "obesity" refers to a body mass index (BMI) >95th percentile for age and sex; "overweight" refers to BMI between the 85th and 95th percentile. Mean weight gain in the 5 atypical antipsychotic pediatric bipolar trials ranged from 0 to 8 lbs across 3 to 4 weeks of treatment (*Figure, page 32*).[3-7]

Table 3

Talking to families about using antipsychotics in children with bipolar disorder

Effectiveness. Large, placebo-controlled studies have shown that atypical antipsychotics can significantly reduce manic symptoms in children and adolescents with bipolar disorder
Safety data. Additional 6-month safety data indicate that atypical antipsychotics continue to be effective in children and adolescents, without dramatic changes in side effects
Precautions. Antipsychotics are powerful medications and must be used carefully in pediatric patients
Potential side effects. All antipsychotics have serious potential side effects that must be recognized, monitored, and managed
Potential benefits from using atypical antipsychotics include mood stabilization, treatment of psychotic symptoms, and lower risk of extrapyramidal symptoms compared with typical antipsychotics
Risk vs benefit. On balance, the potential benefit of these agents outweighs the potential risk for children and adolescents with bipolar disorder

Recommendations. Emphasize diet and exercise, with restriction of high-carbohydrate food, "fast foods," and soft drinks. Another option is a trial of metformin, which decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

Klein et al[29] studied 39 patients age 10 to 17 with mood and psychotic disorders whose weight increased by >10% during <1 year of olanzapine, risperidone, or quetiapine therapy. In this 16-week, double-blind, placebo-controlled trial, weight was stabilized in subjects receiving metformin, whereas those receiving placebo continued to gain weight (0.31 kg [0.68 lb]/week).

The usual starting metformin dose is 500 mg bid with meals. Increase in increments of 500 mg weekly, up to a maximum

Clinical Point

Watch for variants of neuroleptic malignant syndrome; hyperthermia or muscle rigidity may be absent or develop over several days

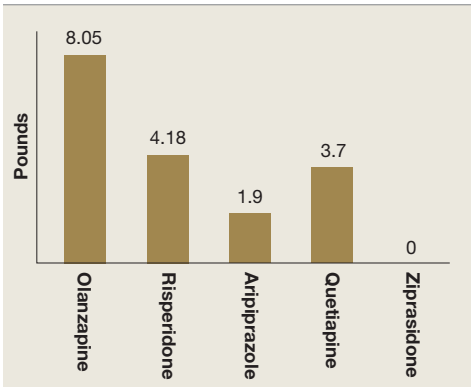
Pediatric mania

Clinical Point

For weight control, emphasize diet and exercise; another option is a trial of metformin, starting with 500 mg twice daily with meals

Figure

Mean weight gain with atypical antipsychotics in pediatric bipolar trials



Weight gain in children and adolescents with bipolar disorder varied among atypical antipsychotics used in 5 recent randomized controlled trials. Treatment duration was 3 weeks with olanzapine, risperidone, and quetiapine and 4 weeks with aripiprazole and ziprasidone. Dosages were olanzapine, 10.4 ± 4.5 mg/d; risperidone, 0.5 to 2.5 mg/d or 3 to 6 mg/d; aripiprazole, 10 or 30 mg/d; quetiapine, 400 or 600 mg/d; and ziprasidone, 80 to 160 mg/d.

Source: References 3-7

of 2,000 mg/d in divided doses. Potential side effects include diarrhea, nausea/vomiting, flatulence, and headache.

Hyperlipidemia. Patients who gain weight with atypical antipsychotics also may develop hyperlipidemia. Fasting serum triglycerides >150 mg/dL (1.70 mmol/L) in obese children are considered to be elevated and an early sign of metabolic syndrome.[30] Fasting total cholesterol >200 mg/dL (5.18 mmol/L) or low-density lipoprotein cholesterol >130 mg/dL (3.38 mmol/L) is consistent with hyperlipidemia.

Recommendation. Monitor and treat hyperlipidemia, which increases the risk of atherosclerosis as obese children grow older.[31]

Prolactin. Elevated prolactin concentrations may have deleterious effects in the developing child or adolescent, including gynecomastia, oligomenorrhea, and amenorrhea.[17] Long-term effects on growth and sexual maturation have not been fully evaluated.

The relative tendency of atypical antipsychotics to cause hyperprolactinemia is roughly: risperidone/paliperidone > olanzapine > ziprasidone > quetiapine > clozapine > aripiprazole.[18] In the risperidone RCT, mean changes in baseline prolactin levels were 41 ng/mL for boys and 59 ng/mL in girls.[3] Results of the olanzapine RCT suggest a high incidence of hyperprolactinemia (26% of girls, 63% of boys).[4] Decreases in serum prolactin were observed in bipolar children and adolescents treated with aripiprazole for 30 weeks.[19]

Recommendations. For any pediatric patient treated with an atypical antipsychotic that increases prolactin levels:

- Obtain a baseline prolactin level.
- Repeat after 6 months of treatment or with the emergence of elevated prolactin symptoms, such as gynecomastia in boys. Ask about increases in breast size, galactorrhea, changes in menstruation, sexual functioning, and pubertal development.

Switch patients who develop any of these side effects to another atypical agent that does not increase serum prolactin.[32]

QTc interval prolongation. All atypical antipsychotics can cause QTc prolongation. Several cases of significant QTc prolongation have been reported in children and adolescents treated with ziprasidone.[33,34] In the RCT of ziprasidone, QTc prolongation was not clinically significant in most of the patients in which it was reported, and it did not lead to adverse events.[34] Mean QTc change was 8.1 msec at study termination.[7]

Patients enrolled in clinical trails are screened very carefully, however, and those with preexisting medical abnormalities typically are excluded. Thus, these findings may have limited usefulness for "real-world" patients.

Recommendations. Until additional information is known about the cardiac effects of atypical antipsychotics in children and adolescents:

- Perform a careful history, review of symptoms, and physical exam looking for any history of palpitations, shortness of breath, or syncope.
- Query specifically about any family history of sudden cardiac death.
- Perform a baseline resting ECG for pa-

tients starting ziprasidone or clozapine, or for other atypicals if indicated by history, review of systems, physical exam, etc.

- For patients treated with ziprasidone or clozapine, repeat ECG as the dose increases or if the patient has cardiac symptoms (unexplained shortness of breath, palpitations, skipped beats, etc.).

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Related Resources

- Child and Adolescent Bipolar Foundation. www.bpkids.org.
- University of Illinois at Chicago Pediatric Mood Disorders Clinic. www.psych.uic.edu/pmdc.
- Ryan Licht Sang Bipolar Foundation. www.ryanlichtsang bipolarfoundation.org.

Drug Brand Names

Aripiprazole • Abilify
Benztropine • Cogentin
Carbamazepine • Carbatrol
Clozapine • Clozaril
Diphenhydramine • Benadryl
Divalproex sodium • Depakote
Lithium • Lithobid, others
Metformin • Glucophage
Olanzapine • Zyprexa
Paliperidone • Invega
Propranolol • Inderal
Quetiapine • Seroquel
Risperidone • Risperdal
Valproate • Depacon
Ziprasidone • Geodon

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Clinical Point

If a patient develops elevated prolactin symptoms, switch to a different atypical antipsychotic that does not increase serum prolactin

Bottom Line

Studies of 5 atypical antipsychotics' efficacy and tolerability support their use for treating acute mania in children and adolescents. Four of these agents can be justified as first-line treatments, before lithium or divalproex. At the same time, antipsychotics' potentially serious side effects—extrapyramidal symptoms, tardive dyskinesia, weight gain, hyperlipidemia, hyperprolactinemia, and QTc changes—must be recognized, monitored, and managed.

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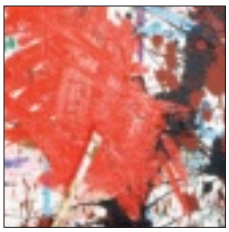

Pediatric mania

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