

Assistant Editor's Note: *Psychopharmacology Perspectives* will bridge clinical and research expertise in pediatric psychopharmacology, with the goal of providing clinicians with practical clinical insights and up-to-date assessments of the evidence base. Authors will be invited to submit in-depth discussions of various topics in pediatric psychopharmacology, including experience-based practical guidance and the scientific rationale for treatment recommendations. Please feel free to contact me at ckratoch@unmc.edu if you have comments on this feature's revised format, or recommendations for future psychopharmacology topics of interest.

Antipsychotic Use in Children and Adolescents: Minimizing Adverse Effects to Maximize Outcomes

CHRISTOPH U. CORRELL, M.D.

In children and adolescents, antipsychotics are being used in large and increasing quantities for a wide range of disorders and psychopathology, including psychotic, mood, and disruptive behavior disorders.¹ Moreover, antipsychotics are also being used in children and adolescents to treat irritability associated with autism, tic disorders, obsessive-compulsive disorder, posttraumatic stress disorder and aggression²⁻⁴; however, the widespread use exceeds the database regarding efficacy as well as safety and tolerability in this population. At the time of this writing, only three antipsychotics—haloperidol, thiorida-

zine, and risperidone—have been approved for use in children and adolescents by the U.S. Food and Drug Administration, with most randomized controlled data being available for risperidone. To appropriately use this potent class of medications, clinicians need to actively weigh the potential risks and benefits of individual agents. The present article aims to succinctly review available data on antipsychotic-related adverse effects in children and adolescents and provide a practical guide for the evaluation and management of antipsychotic-related adverse effects in this vulnerable population.

Psychopharmacology Perspectives aims to discuss practical approaches to everyday issues in pediatric pharmacotherapy. The discussions may address aspects of clinical care related to psychopharmacology for which we do not have adequate applicable controlled trials. Given the need to address symptoms in youths with often complex, severe, and comorbid disorders, recommendations are likely to be off-label from the perspective of the U.S. Food and Drug Administration. We fully appreciate that for virtually all disorders, medication is only one aspect of comprehensive care. This column focuses primarily on psychopharmacological management. Although it is important that clinicians address psychosocial issues in the evaluation and treatment of their patients, such discussion is beyond the specific scope of this feature. These are not meant to be practice guidelines, but rather examples of the thought process that may go into pharmacotherapy decision making.

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Dr. Correll is with The Zucker Hillside Hospital, North Shore-Long Island Jewish Health System, and the Albert Einstein College of Medicine.

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Correspondence to Dr. Christoph U. Correll, The Zucker Hillside Hospital, Psychiatry Research, Glen Oaks, NY 11004; e-mail: ccorrell@lij.edu.

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RECEPTOR PHARMACOLOGY PREDICTS CLINICAL EFFECTS

Antipsychotic agents differ in their effects on brain neuroreceptor systems (Table 1). Although still limited, current knowledge links therapeutic and adverse effects of antipsychotics to their different effects on dopaminergic, noradrenergic, serotonergic, histaminergic, and cholinergic receptors, among others (Table 2). Recently, the presence of withdrawal or rebound phenomena has also been recognized (Table 2), which can result from a too-rapid transition from antipsychotics with substantial anticholinergic or antihistaminergic effects (e.g., clozapine, olanzapine, quetiapine) to agents with minimal cholinergic or histaminergic blockade (e.g., aripiprazole, ziprasidone). In addition to pharmacodynamic differences, therapeutic and adverse effects can vary substantially depending on differences in antipsychotic absorption, half-life, dose, and interindividual susceptibility that is usually unknown until a specific medication

TABLE 1
 Receptor Binding Profiles and Half-Life of Second-Generation Antipsychotics and Haloperidol, Molindone, and Perphenazine

Receptor	Aripiprazole	Olanzapine	Paliperidone	Risperidone	Quetiapine	Ziprasidone	Clozapine	Haloperidol	Molindone	Perphenazine
Pharmacodynamic receptor binding profile: receptor binding affinity expressed as equilibrium constant (K _i) ^a										
D ₂	0.66 ^{b,c}	20	2.8	3.77	770	2.6	210	2.6	120	1.4 ^c
5-HT _{1A}	5.5 ^{b,c}	610	480	190	300	1.9 ^{b,c}	160	1,800	3,797 ^c	421
5-HT _{2A}	8.7 ^c	1.5	1.2	0.15	31	0.12	2.59	61	5,000	5 ^c
5-HT _{2c}	22 ^c	4.1	48	32	3,500	0.9	4.8	4,700	>10,000 ^c	132 ^c
α ₁	26 ^c	44	10	2.7	8.1	2.6	6.8	17	2,500	10
H ₁	30 ^c	0.08	3.4	5.2	19	4.6	3.1	260	123,456	8
M ₁	6,780 ^c	2.5 ^c	>10,000 ^c	>10,000 ^c	120 ^c	300 ^c	1.4 ^c	>10,000 ^c	384,000	1,500
M ₂	3,510 ^c	622 ^c	>10,000 ^c	>10,000 ^c	630 ^c	>3,000 ^c	204 ^c	>10,000 ^c	N/A	N/A
M ₃	4,680 ^c	126 ^c	>10,000 ^c	>10,000 ^c	1,320 ^c	>1,300 ^c	109 ^c	>10,000 ^c	>10,000 ^c	1,848 ^c
M ₄	1,520 ^c	350 ^c	>10,000 ^c	>10,000 ^c	660 ^c	>1,600 ^c	27 ^c	>10,000 ^c	N/A	N/A
Pharmacokinetic profile: half-life										
t _{1/2} , h	72	30	20	3	7	7	16	20	1.5–3	8–12

Note: Based exclusively on data from human brain receptors.^{49–56}

^a Data represented as the equilibrium constant (K_i) (nM), i.e., nanomolar amount of the antipsychotic needed to block 50% of the receptors in vitro. Therefore, a lower number denotes stronger receptor affinity and binding.

^b Partial agonism.

^c Data from cloned human brain receptors.

TABLE 2
Adverse and Therapeutic Effects of Antipsychotic Receptor Occupancy and Withdrawal

Receptor	Occupancy	Rebound/Withdrawal
Histamine H ₁	Anxiolytic, sedation, weight gain, anti-EPs/akathisia	Agitation, insomnia, anxiety, EPs
α ₁ -Adrenergic	Postural hypotension, dizziness, syncope	Tachycardia, hypertension
Muscarinic M ₁ (central)	Memory, cognition, anti-EPs/akathisia	Agitation, confusion, anxiety, insomnia
Muscarinic M ₂₋₄ (peripheral)	Dry mouth, constipation, urinary retention	Diarrhea, diaphoresis
Dopamine D ₂	Antipsychotic, antimanic, antiaggressive, EPs/akathisia, tardive dyskinesia, prolactin increase, sexual or reproductive system dysfunction	Psychosis, mania, agitation, akathisia, withdrawal dyskinesia
Serotonin 5-HT _{1A} (partial agonism)	Anxiolytic, antidepressant, anti-EPs/akathisia (?)	EPs/akathisia
Serotonin 5-HT _{2A}	Anti-EPs/akathisia	EPs/akathisia
Serotonin 5-HT _{2c}	Increased appetite/weight (?)	Decreased appetite (?)

Note: EPs = extrapyramidal symptoms.

trial is undertaken. For example, dopamine rebound/withdrawal syndromes (Table 2) can occur during a switch when the first antipsychotic drug achieved a comparatively high dopamine blockade and is then switched too abruptly to an antipsychotic that achieves a considerably lower dopamine blockade. This can occur when the second antipsychotic is dosed much lower during the initial titration process, has a longer relative half-life, thus taking longer to reach the equivalent blood level (e.g., aripiprazole), or because the absorption is dependent on food and the antipsychotic is taken without food (e.g., ziprasidone). To avoid rebound/withdrawal phenomena under these circumstances, the initial antipsychotic should not be discontinued abruptly, and cross-titration or (even better) overlapping switch strategies should be used.⁵

Table 3 summarizes the time course, dose/titration dependency, and general side effect propensities across the seven second-generation antipsychotics (SGAs) available in the United States and haloperidol as examples of a high-potency, first-generation antipsychotics (FGAs), as well as perphenazine and molindone as examples of mid-potency FGAs that were used in recent large-scale, randomized trials in adults and adolescents, respectively. Because, unfortunately, antipsychotic therapeutic and adverse effect data in children and adolescents are still sparse, much of the safety information in Table 3 is extrapolated from adult data. However, as children and adolescents receiving antipsychotics are also experiencing enormous physical and psychological maturation, it is not surprising that therapeutic and adverse effects can differ between pediatric and adult populations.

NEUROMOTOR ADVERSE EFFECTS

Extrapyramidal Side Effects

In general, children and adolescents are more likely to experience extrapyramidal side effects (EPs; i.e., parkinsonian side effects and dystonia) associated with FGAs and SGAs than adults.⁶ To date, only one double-blind, randomized pediatric study directly compared EPS rates with an FGA (i.e., haloperidol; mean dose 5.0 mg/day) and SGAs (i.e., risperidone, mean dose 4.0 mg/day, and olanzapine, mean dose 12.3 mg/day).⁷ Results of substantial EPs not only with haloperidol (67%) but also with olanzapine (56%) and risperidone (53%) suggest that children and adolescents are at risk for EPs, even when treated with SGAs, at least at doses required to control psychosis. Although overall EPS rates were not significantly different in this study ($n = 40$), the severity was greater with haloperidol, indicating that reporting global incidence rates are insufficient to guide clinical treatment. In several short-term, double-blind, placebo-controlled trials, risperidone was associated with EPS rates between 8% and 26%.⁸⁻¹¹ In four open-label extension trials lasting 11 to 36 months, EPS rates ranged from 8.6% to 26.0% (mean 15.7%).¹² Although in these trials, rating scale-measured EPS severity generally did not increase, EPS rates could be underestimated because they are based on spontaneous reports of mostly prepubertal individuals with autism spectrum disorder treated with relatively modest mean risperidone doses (1–2 mg/day). As in adults, clozapine^{13,14} and quetiapine¹⁵ appear to be associated with relatively low EPS rates in pediatric patients, whereas more data are needed for ziprasidone and aripiprazole. In one recently presented double-blind, placebo-controlled

TABLE 3
Comparative Overview of Side Effect Profiles of Second-Generation Antipsychotic Medications in Children and Adolescents

Adverse Effect	Time Course	Dose/ Titration		Aripiprazole	Clozapine	Olanzapine	Paliperidone	Quetiapine	Risperidone	Ziprasidone	Haloperidol	Molindone	Perphenazine
		Dependent	Independent										
Anticholinergic	Early	++	0	0	+++	++	0	0/+	0	0	0	0/+	0/+
Acute parkinsonism	Early	+++	+	+	0	+	++	0	++	+	+++	++	++
Akathisia	Early/intermediate	+++	++	++	+	+	+	+	+	+	+++	++	++
Cerebrovascular events	?	0?	?	?	?	?	?	?	?	?	?	?	?
Diabetes	Late	0?	0/+ ^a	+++	+++	+++	+ ^a	++	+	0/+ ^a	0/+ ^a	0/+ ^a	+
↑ Lipids	Early?	0?	0/+ ^a	++	++	++	+ ^a	+	+	0/+ ^a	0/+ ^a	0/+ ^a	+
Neutropenia	Most likely within first 6 mo	++	0/+	++	++	0/+	0/+	0/+	0/+	0/+	0/+	0/+	0/+
Orthostasis	Early	+++	0/+	+++	+++	++	+	+ ^b	+	0	0	+	+
↑ Prolactin/sexual dysfunction	Early, may improve	+++	0	0	0	+/++	+++	0	+++	+	++	++	++
↓ Prolactin	Early	++	++	0	0	0	0	0	0	0	0	0	0
↑ QTc interval	?	++	0/+ ^c	+	+	0/+ ^c	+	+ ^c	+ ^c	++	0/+ ^c	+	+ ^c
Sedation	Early, may improve	+++	0/+	+++	+++	++	+	+ ^b	+	0/+	0/+	+	+
Seizures	During titration	+++	0/+	++ ^a	++	0/+	0/+	0/+	0/+	0/+	0/+	0/+	0/+
Tardive dyskinesia	Late	++	0/+ ^a	0	0	0/+ ^d	0/+ ^a	0/+ ^d	0/+	0/+ ^b	++	+/++	+/++
Withdrawal dyskinesia	Early during (fast) switch	+++	++	0	0	0/+	+	0/+	+	+	++	+/++	+/++
Weight gain	First 3–6 mo	0?	+	+++	+++	+++	+/++	++	++	+	+	0/+	++

Note: A large part of the data are extrapolated from adult populations. Therefore, information contained in the table may change as more data from large pediatric populations become available. ↑ = increased; ↓ = decreased; 0 = none; 0/+ = minimal; + = mild; ++ = moderate; +++ = severe.

^a Insufficient long-term data to fully determine risk.

^b Less at higher doses.

^c Relevance for the development of torsade de pointes not established.

^d Less than 1%/year in adults that were often pretreated with first-generation antipsychotics.

study of aripiprazole in adolescents with schizophrenia, EPSs occurred in 18% of patients.¹⁶ Of note, due to complementary actions of dopamine and serotonin regarding EPSs, concurrent treatment with serotonin reuptake inhibitors may trigger or aggravate EPSs. Treatment options are listed in Table 4.

Akathisia. In children and adolescents, less is known regarding the risk for akathisia, which has been substantial with FGAs across age groups. In general, it can be difficult to properly diagnose akathisia because the presentation overlaps with psychomotor agitation due to psychosis, mania, and anxiety. In children and

TABLE 4

Suggested Monitoring and Management Strategies in Children and Adolescents Treated With Antipsychotic Agents

Assessment	Baseline	Routine Follow-up ^a	Selected Interventions for Relevant Abnormality
Personal and family medical history ^b	✓	Annually	—
Lifestyle behaviors ^c	✓	Each visit	Healthy lifestyle instruction or intervention program
Sedation/somnolence	✓	Each visit	Wait, if tolerance develops, adjust dose; switch to lower risk drug; modafinil coadministration
Sexual/reproductive dysfunction	✓	During titration, then every 3 mo	Reduce dose; switch to lower risk drug; for performance; add bupropion, sildenafil, etc.
Parkinsonism, akathisia	✓	During titration, at 3 mo and annually (SAS or ESRS)	Slow down titration, reduce dose; switch to lower risk drug; anticholinergic, beta-blocker, benzodiazepine, etc.
Tardive dyskinesia	✓	At 3 mo and annually (AIMS)	Reduce dose; increase dose (masking); if possible, replace with nonantipsychotic; switch to clozapine; add vitamin E
Height, weight, BMI percentile, BMI <i>z</i> score	✓	Each visit	Switch to lower risk drug; healthy lifestyle intervention; weight loss agents (metformin, orlistat, amantadine, topiramate, bupropion, etc.)
Blood pressure and pulse	✓	At 3 mo and annually	Switch to lower risk drug; healthy lifestyle intervention; weight loss agents (metformin, orlistat, amantadine, topiramate, etc.); antihypertensive
Electrolytes, full blood count, renal and liver function	✓	Annually (more frequent blood counts if taking clozapine)	Switch to lower risk drug, address specific abnormality as needed
Fasting blood glucose and lipids	✓	At 3 mo, then every 6 mo	Switch to lower risk drug; healthy lifestyle intervention; weight loss agents (metformin, orlistat, amantadine, topiramate, etc.); lipid lowering or antihyperglycemic agent
Liver function tests	✓	At 3 mo and annually	Reassess need for medication; consider switch
Prolactin	Only if symptomatic ^d	Only if symptomatic ^d	If asymptomatic, may wait if values normalize with time; reduce dose; switch to lower risk drug if symptomatic; obtain MRI of the sella turcica or bone density scan, or coadminister a full (e.g., bromocriptine, amantadine, cabergoline) or partial (e.g., aripiprazole) dopamine agonist only after symptomatic hyperprolactinemia continues despite switch to a low-risk antipsychotic
EKG	If taking ziprasidone or clozapine	If taking ziprasidone: during titration and at maximum dose	Reassess need for medication; consider switch

Note: AIMS = Abnormal Involuntary Movement Scale⁵⁷; ESRS = Extrapyrimal Symptom Rating Scale⁵⁸; SAS = Simpson Angus Rating Scale.⁵⁹

^a More frequent assessments of abnormalities occur if patient is at high risk for specific adverse events by personal or family history.

^b Including components of the metabolic syndrome (obesity, arterial hypertension, diabetes, dyslipidemia), medical history of coronary heart disease or coronary heart disease equivalent disorders (i.e., diabetes mellitus, peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease); history of premature coronary heart disease in first-degree relatives (males younger than 55 years and females younger than 65 years), and past efficacy and adverse effect experiences in patients and/or family members.

^c Lifestyle behaviors: diet, exercise, smoking, substance use, sleep hygiene.

^d In case of abnormal sexual symptoms or signs, fasting blood draw in the morning and approximately 12 hours after the last antipsychotic dose.

adolescents, akathisia may present as difficulty falling asleep and can be mistaken for attention-deficit/hyperactivity disorder. In one study,⁷ olanzapine was associated with akathisia in 12.5% of pediatric patients. Aripiprazole, the only available antipsychotic with partial dopamine D₂ agonism, has been associated with akathisia in adults. In one retrospective chart review of 30 children and adolescents (mean age 13.3 years, range 5–19), akathisia was recorded in as many as 23% of patients taking aripiprazole.¹⁷ However, the mean starting dose of 9 ± 4 mg in this sample was relatively high and almost identical to the mean final dose of 10 ± 3 mg. Furthermore, it is unclear whether abrupt switches could also have increased the akathisia rate via withdrawal/rebound phenomena (Table 2). In a large randomized placebo-controlled study of more than 300 patients, aripiprazole dosed at 10 or 30 mg/day was associated with akathisia in <10% of adolescents with schizophrenia, but patients were titrated from a starting dose of 2 mg/day, reaching the maximum dose at day 5 or 13, respectively.¹⁶ This suggests that slower titration of a partial agonist may reduce the rate of akathisia in some patients. As for parkinsonian adverse effects, concurrent use of serotonin reuptake inhibitors can also trigger or aggravate akathisia. Treatment options are listed in Table 4.

Withdrawal Dyskinesia. During treatment with FGAs, children and adolescents seem to be at risk for developing withdrawal dyskinesias, yet, different from adults, these are frequently reversible.¹⁸ Rates of withdrawal dyskinesia appear to be lower with SGAs compared with FGAs,¹⁹ although a switch from an antipsychotic with strong D₂ affinity (e.g., risperidone, aripiprazole) to one with less potent affinity (e.g., quetiapine) may predispose to withdrawal dyskinesia. In one study,²⁰ 2 of 13 children (15.4%) developed mild, reversible withdrawal dyskinesia after 7 months of risperidone treatment. In another, more recent study, however, 0 of 38 patients developed withdrawal dyskinesia after risperidone (mean dose 2 mg/day) was discontinued after 4 months of treatment.²¹ The risk for withdrawal dyskinesia can be reduced with slow cross-titration and overlapping cross-titration.⁵

Tardive Dyskinesia (TD). A recent meta-analysis of 10 studies lasting at least 11 months reported on TD rates in 783 pediatric patients ages 4 to 18 (weighted mean 9.8) years old.¹² Most patients were prepubertal (79.2%), male (81.7%), and white (78.4%). Across these studies, only three cases of TD were reported, resulting in an annualized incidence rate of 0.4%.

Although this pediatric rate is approximately half the risk found in another meta-analysis of 1,964 nonelderly adults,²² firm conclusions are precluded by the facts that none of the pediatric studies were designed specifically to detect TD, antipsychotic doses were low, and lifetime exposure was relatively short.

Neuroleptic Malignant Syndrome.

Neuroleptic malignant syndrome (NMS) is a rare but potentially fatal medical emergency that can result from antipsychotic treatment. The clinical picture consists of severe (“lead pipe”) rigidity, tachycardia, fever, arterial hyper- or hypotension, elevated creatinine phosphokinase, and elevated white cell count. It has been suggested that SGAs may be associated less with NMS than FGAs and that SGAs are associated with a more benign course of NMS,²³ but this is unclear. In children and adolescents, several cases of NMS have been reported, even with SGAs. Thus, clinicians should be vigilant and rule out NMS in antipsychotic-treated children and adolescents presenting with fever, tachycardia, and rigidity.

WEIGHT GAIN AND METABOLIC ADVERSE EFFECTS

Although pediatric data are largely missing and the effects of illness versus treatment history are unclear, children and adolescents with psychiatric disorders seem to be at increased risk for being overweight/obese.²⁴ Age-inappropriate weight gain is of particular concern in children and adolescents due to its association with glucose and lipid abnormalities and cardiovascular morbidity/mortality.²⁵ Reasons for weight gain are likely complex, including psychiatric illness, unhealthy lifestyle, and the treatment used. A recent review of pediatric data suggested that the weight gain potential of SGAs follows roughly the same ranking order as found in adults (Table 3), but that the magnitude is greater.²⁶ Exceptions may be a greater relative weight gain propensity of risperidone,²⁷ and a greater likelihood of aripiprazole and ziprasidone to not be weight neutral in subgroups of pediatric patients.²⁶ Of note, combined SGA treatment with a stimulant does not seem to substantially attenuate SGA-induced weight gain,²⁸ whereas combined treatment with a mood stabilizer or combination treatment seems associated with more weight gain than monotherapy with mood stabilizers and may lead to greater weight gain than treatment with just one SGA.²⁹

Although in adults the link between antipsychotic treatment and adverse metabolic consequences, such as dyslipidemia, hyperglycemia, diabetes, and the metabolic syndrome, has been established,²⁵ the few published pediatric studies^{7,30,31} have produced conflicting results. However, interpretation of these data is limited by the small sample size, varying treatment histories, and inclusion of random glucose assessments. Case reports of new-onset diabetes in antipsychotic-treated children and adolescents²⁶ and the established link between weight gain and metabolic abnormalities suggest that children and adolescents are at least as liable to develop metabolic abnormalities as adults, which is suggested also by an ongoing prospective pediatric safety study.²⁶

PROLACTIN-RELATED SIDE EFFECTS

As recently summarized,²⁶ FGAs and SGAs can elevate prolactin levels, but other reasons for hyperprolactinemia need to be ruled out, including hyperthyroidism, renal failure, pregnancy, or oral contraception. Hyperprolactinemia can result in sexual side effects, such as amenorrhea and oligomenorrhea, erectile dysfunction, decreased libido, and hirsutism, and breast symptoms, such as enlargement, engorgement, pain, and galactorrhea, although prolactin levels are not closely correlated with these symptoms. Available data also suggest that hyperprolactinemia is dose dependent, seems to normalize over time, and resolves after antipsychotic discontinuation. Similar to adults, albeit at higher levels during adolescence, the relative potency of antipsychotic drugs in inducing hyperprolactinemia is roughly as follows: risperidone/paliperidone > haloperidol > olanzapine > ziprasidone > quetiapine > clozapine > aripiprazole. Aripiprazole may lower prolactin below baseline values, with low endpoint levels being most likely in boys and prepubertal individuals who have low baseline values. Whether hyperprolactinemia at the levels found in response to antipsychotics alters bone density, sexual maturation, or the risk for breast cancer or benign prolactinomas during periods of critical maturation is unclear, partly because data are largely based on prepubertal boys treated with risperidone, lacking enough peripubertal patients followed for sufficient periods of time.²⁶

Due to the lack of evidence for the physiological risks of asymptomatic, subclinical prolactin elevations, current guidelines do not suggest routine prolactin monitoring, unless sexual adverse effects are present. Sexual functioning needs to be actively inquired about, but screening is less

sensitive in prepubertal individuals and those not sexually active. Because prolactin levels vary during the day and can be elevated by food, exercise, stress, and medications, blood should be obtained after fasting in the morning and before medications are taken. In asymptomatic patients with elevated prolactin (usually <100 ng/mL), one may wait to see whether values normalize over time. In overtly symptomatic patients, dose reduction or a switch to a lower risk agent is indicated. Magnetic resonance imaging of the sella turcica to rule out prolactinomas or bone density scans, using dual x-ray absorptiometry, or coadministration of a full (e.g., bromocriptine, amantadine, cabergoline) or partial (e.g., aripiprazole) dopamine agonist are recommended only after symptomatic hyperprolactinemia continues despite a switch to a low-risk antipsychotic.

CARDIAC SIDE EFFECTS

Dizziness/Orthostasis

Antipsychotics with more pronounced α_1 blockade (e.g., clozapine, quetiapine) are most likely to lead to usually transient dizziness. This effect is enhanced in patients receiving antihypertensive medications used for hyperactivity (α_2 agonists) or for akathisia or tremor (beta-blockers). Slowing the titration and waiting for the adrenergic system to adjust are usually sufficient to deal with this adverse effect. Due to beginning blockade of the α_2 autoreceptors at doses at or around 300 mg/day, quetiapine may actually lead to less dizziness and orthostasis at higher than at lower doses.

QTc Prolongation

Antipsychotics can differentially prolong the heart rate-corrected QT interval of the electrocardiogram, which may lead to torsade de pointes, a potentially fatal arrhythmia.³² In adults, QTc prolongation is usually minimal compared with placebo, except for thioridazine and droperidol.³³ Among SGAs, QTc prolongation to >430 milliseconds has been described in 3 of 20 pediatric patients treated prospectively with ziprasidone (mean QTc prolongation of 28 ± 26 milliseconds), without relationship to ziprasidone dose.³² However, in an earlier albeit smaller study, no significant increase was found,³⁴ and the clinical relevance of this degree of QTc prolongation is unclear. In adults, SGAs, especially those with marked anticholinergic activity, have been noted to affect heart rate variability,³⁵ but the clinical significance of this for pediatric patients is unclear.

Myocarditis

Among the SGAs, only clozapine has been associated with a relevant risk for myocarditis, which is most prominent early on in treatment, but even in children and adolescents, the incidence seems relatively low.³⁶

MISCELLANEOUS ADVERSE EFFECTS

Sedation/Somnolence

Sedation/somnolence are frequent and often impairing side effects of antipsychotics that usually are dose

TABLE 5

Clinically Relevant Thresholds for Body Weight and Metabolic Parameters in Adults and in Children and Adolescents

Variables	Adults	Children and Adolescents
Body weight		
Underweight	BMI <18.5 ^a	BMI <5th percentile for sex and age^b
Normal weight	BMI 18.5–<25 ^a	BMI 5th– <85th percentile for sex and age^b
Overweight (adults)/at risk for overweight (children and adolescents)	BMI 25–<30 ^a	BMI 85th– <95th percentile for sex and age^b
Obese (adults)/overweight (children and adolescents)	BMI >30 ^a	BMI >95th percentile for sex and age^b
Blood lipids		
Total cholesterol	≥200 mg/dL	≥170 mg/dL
Low-density lipoprotein cholesterol	Dependent on CHD risk	≥130 mg/dL
If 0–1 CHD risk factors	>160 mg/dL	No thresholds available
If >2 CHD risk factors or 10-yr CHD risk ^c of 10%–20%	>130 mg/dL	No thresholds available
If CHD or CHD equivalents, ^d or 10-year CHD risk ^d of >20%	>100 mg/dL	No thresholds available
If diabetic patients	>70 mg/dL	No thresholds available
HDL cholesterol	<40 mg/dL in males; <50 mg/dL in females	<40 mg/dL in males and females
Triglycerides	≥150 mg/dL	≥110 mg/dL
Blood glucose and insulin		
Fasting hyperglycemia	100–125 mg/dL	100–125 mg/dL
2-h postglucose load hyperglycemia	140–199 mg/dL	140–199 mg/dL
Fasting diabetes (needs to be repeated)	≥126 mg/dL	≥126 mg/dL
2-h postglucose load diabetes	≥200 mg/dL	≥200 mg/dL
Fasting hyperinsulinemia	?	>20 μmol/L
Insulin resistance		
Homeostasis model assessment ^e	?	≥4.4
Triglycerides: HDL cholesterol ratio	>3.5	? >3.5
Metabolic syndrome	≥3 of 5 criteria required	≥3 of 5 criteria required
Abdominal obesity criterion	Waist circumference >40 inches (102 cm) in males; >35 inches (88 cm) in females	Waist circumference > 90th percentile or BMI > 95th percentile for sex and age^f
Fasting triglycerides criterion	≥150 mg/dL	≥110 mg/dL
Fasting HDL cholesterol criterion	<40 mg/dL in males; <50 mg/dL in females	<40 mg/dL in males and females
Blood pressure criterion	≥130/85 mmHg	≥90th percentile for sex and age^g
Fasting glucose criterion	≥110 mg/dL	≥110 mg/dL

Note: Based on criteria from references 43, 44, 60, and 61. Thresholds that are shown in bold are specific for children and adolescents.

BMI = body mass index; CHD = coronary heart disease; HDL = high-density lipoprotein.

^a BMI (unadjusted: weight [kg]/height [m]²; or weight [lb] × 733/height [inches]).

^b Sex and age adjusted BMI expressed in percentile (population norm: 50th BMI percentile) or BMI z scores (population norm: 0 BMI z score): Growth charts: www.cdc.gov/growthcharts/ or Web-based calculators: <http://www.kidnutrition.org/bodycomp/bmiz2.html> or <http://www.gcr.uci.edu/utilities/bmi2.cfm>. Stable age-, sex-, and growth-adjusted weight is indicated by the absence of any change in BMI percentile and BMI z score over time.

^c A 10-year CHD risk calculation based on Framingham Point Scoring System.⁶¹

^d CHD equivalents: peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease.

^e Homeostasis model assessment = fasting insulin (μmol/L) × glucose (mmol/L)/22.5; glucose mmol/L = glucose m/dL/17.979797.

^f Sex- and age-adjusted waist circumference percentile tables.⁶²

^g Sex- and age-adjusted blood pressure percentile tables.⁶³

dependent, although tolerance may develop over time in many patients. Similar to orthostasis, an exception to the dose-dependent nature of sedation may be quetiapine, which seems to be less sedating at doses ≥ 300 mg/day where α_2 blockade sets in. Although limited by the mixture of studies with different populations, doses, and methodologies, a recent comparison of adult U.S. Food and Drug Administration labeling trials with pediatric data suggested a similar rank order for the propensity to lead to sedation, but overall increased rates in children and adolescents compared with adults.⁶ In the reviewed pediatric studies, sedation rates ranged from 0% to 33% for aripiprazole, 42% to 69% for ziprasidone, 25% to 80% for quetiapine, 29% to 89% for risperidone, and 44% to 94% for olanzapine and 46% to 90% with clozapine. In randomized controlled and open-label extension studies with risperidone, somnolence was spontaneously reported in 12% to 61% of patients taking risperidone and 10% to 13% taking placebo.^{9,28,37–39} In studies following patients who had tolerated and benefited from acute treatment, somnolence rates dropped as low as 6% and 1.7%.³⁷ Of note, patients with autism spectrum disorders cotreated with psychostimulants had lower rates of somnolence than those treated with risperidone monotherapy (37% versus 51%).²⁸

Liver Toxicity

Increased liver enzymes have been reported with antipsychotics in several pediatric studies.^{7,40} Although the extent and significance of liver toxicity are unclear, the combination of divalproex with antipsychotics, particularly olanzapine, may increase the risk for abnormal liver function and, possibly, pancreatitis or steatohepatitis (fatty infiltration of the liver).⁴¹

Neutropenia and Agranulocytosis

With the exception of clozapine, the decrease in white blood cell counts is generally not clinically significant with antipsychotics. In a chart review of 172 clozapine-treated pediatric patients,⁴² the cumulative 1-year probability of an initial adverse hematologic event was 16.1% (neutropenia: $n = 23$, 13%; agranulocytosis: $n = 1$, 0.6%). However, 11 (48%) of the 24 children and adolescents with newly emerging neutropenia were successfully rechallenged, and only 8 patients (5%) discontinued clozapine because of agranulocytosis ($n = 1$) or neutropenia ($n = 7$). In general, specific monitoring is not required for other antipsychotics, except in patients with low baseline white blood cell counts.

ASSESSMENT AND MONITORING

Adverse effect assessment and monitoring in pediatric patients must be proactive. Suggested baseline and follow-up assessments and intervals, as well as management strategies for adverse effects, are detailed in Table 4. Before adding another medication to counter side effects of the antipsychotic, which may have additional adverse effects and lead to drug–drug interactions, prescribers should reevaluate the need for the antipsychotic and consider dose reduction or a switch to a lower risk medication. It is important to note that in growing individuals, the assessment of a number of physical and laboratory measures needed to gauge the level of adverse effects requires taking into consideration developmental norms that incorporate age- and sex-specific thresholds as listed in Tables 5 and 6.

Although it can be difficult to obtain fasting blood values, every attempt should be made to accommodate the patient's schedule to facilitate the sample collection (e.g., 8-hour daytime fast, using a laboratory close to home/with convenient hours) because particularly glucose, triglyceride, and low-density lipoprotein cholesterol levels are strongly affected by nonfasting status.

TABLE 6

Proposed Criteria for the Definition of Significant Weight Gain/Changes in Body Composition in Children and Adolescents

Duration of Treatment	Threshold for Significant Change in Body Composition
First 3 mo	>5% of weight increase compared to baseline
Any duration	≥ 0.5 increase in BMI z score
Any duration	Crossing into the at-risk weight category (i.e., >85–94.9 BMI percentile) <i>plus</i> presence of one other obesity-related complication, such as hypertension (i.e., >90th percentile), dyslipidemia (i.e., fasting cholesterol >200 mg/dL, LDL cholesterol >130 mg/dL, HDL cholesterol <40 mg/dL, or triglycerides >150 mg/dL), hyperglycemia (i.e., fasting glucose >100 mg/dL), insulin resistance (i.e., fasting insulin >20 μ mol/L), orthopedic disorders, sleep disorders, or gallbladder disease
Any duration	Crossing into obesity (i.e., >95th BMI percentile) or abdominal obesity (i.e., >90th waist circumference percentile)

Note: Modified from Correll and Carlson.²⁶ BMI = body mass index; LDL = low-density lipoprotein; HDL = high-density lipoprotein.

Only if fasting assessments cannot be obtained, then a 2-hour postprandial blood draw after a large meal can be used as the last resort to potentially identify patients with hyperglycemia (Table 6). To assess the effect of weight gain or antipsychotic treatment on the risk for diabetes, fasting glucose is a highly insensitive marker. Before hyperglycemia develops, the body compensates by increasing insulin levels. If the insulin level required to keep the blood glucose normal is $>20 \mu\text{U/L}$ (i.e., hyperinsulinemia)⁴³ or the product of fasting glucose and insulin (i.e., homeostasis model assessment: fasting insulin ($\mu\text{mol/L}$) \times glucose (mmol/L)/22.5; glucose $\text{mmol/L} = \text{glucose m/dL}/17.979797$) is >4.19 in adolescents,⁴⁴ insulin resistance is present. Although the homeostasis model assessment is the most sensitive noninvasive marker of insulin resistance, insulin levels are not widely obtained. A relatively crude but simple proxy measure for insulin resistance, used in adults and not validated in children and adolescents, is the ratio of (≥ 8 -hour) fasting triglycerides/fasting high-density lipoprotein cholesterol. The triglyceride:high-density lipoprotein cholesterol ratio should be <3.5 and can be used for tracking of development/worsening of insulin resistance.²⁶ Hemoglobin A_{1C} is not suggested as a screening test because it is insensitive and should only be used as a long-term monitoring tool in patients with diabetes.⁴⁵

TABLE 7

A 12-Step Healthy Lifestyle Program

Do's	Don'ts
Replace sugar-containing drinks with water	Skip breakfast
Eat 4–5 small meals/day, with no more than 1 meal in the evening or at night	Consume fast food $>1/\text{wk}$
Serve small meal portions	Consume saturated or processed fat-free food (containing high amounts of fast-degradable sugars)
Eat slowly, drink water, take seconds only after delay	Watch TV, play computer games $>2 \text{ h/day}$
Eat food with a low glycemic index (<55)	
Consume >25 – 30 g of soluble fiber per day	
Snack only when hungry and only fruit or vegetables	
Perform moderate physical activity for >30 – 60 min/day	

Modified from Correll and Carlson.²⁶

MANAGEMENT

Education about adverse effects and healthy lifestyle behaviors should be part of any psychiatric medication prescribing process. Table 7 lists one proposed 12-step program designed to promote healthy behaviors. Because simultaneously initiating all of the following steps is often unrealistic, the first contact should be used to start by identifying the degree to which patients deviate from the suggested behaviors. Next, one or two of the unhealthiest behaviors that can be addressed most easily should be targeted first, followed by others, once initial goals have been achieved.

In addition to healthy lifestyle instructions, minimizing concerning adverse effects can be achieved most effectively by choosing a lower risk antipsychotic, ideally at the beginning of treatment. Should adverse effects occur, a switch to a lower risk agent, if available, should be considered. Furthermore, the importance of a healthy lifestyle program should be reinforced. Finally, for clinically relevant abnormalities, targeted treatments (Table 4) and/or referrals to specialists for comanagement should be initiated.

SUMMARY

Although more data are needed, children and adolescents seem generally more susceptible to develop sedation, acute EPSs, withdrawal dyskinesia, hyperprolactinemia, and age-inappropriate weight gain with related metabolic abnormalities. Clinicians and researchers should use age-appropriate side effect measures that also take severity and time course of the adverse effects into account to help evaluate and manage more comprehensively antipsychotic risks and benefits in a given individual. Although antipsychotic safety and tolerability data in children and adolescents are limited and most extensive for risperidone, this is likely to change. Several large-scale, randomized, placebo-controlled data sets have either been completed^{11,16,46–52} or are under way for all nonclozapine SGAs. In addition, a federally funded trial, the Treatment of Early Onset Psychosis Study,⁴⁸ was recently completed that compared olanzapine, risperidone, and molindone. To counter randomization bias and provide safety and tolerability data in generalizable patient populations and settings, large-scale observational studies will also be helpful. Collectively, safety and efficacy data should inform a carefully weighed antipsychotic selection that takes

general probabilities and patient/family preferences into account. Finally, because adverse effects are generally more easily predicted than therapeutic efficacy and because differences in efficacy between antipsychotics are generally smaller than those for adverse effects, initial treatment selection should be guided largely by varying adverse effect profiles across agents.

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