Monitoring Psychiatric Medications in Children

Robert J. Hilt, MD, FAAP

Psychiatric medications can be prescribed effectively and safely in primary care when families receive adequate informed consent; when they learn the key side effects to watch for; and when an appropriate monitoring plan is followed. Toward that end, a brief and practical guide to the safe use of these medications can be valuable.

This article presents a general overview of three major classes of psychiatric medications: (attention-deficit/hyperactivity disorder [ADHD] medications; selective serotonin reuptake inhibitors [SSRIs]; and antipsychotics) and the informed consent and monitoring steps one should generally follow while prescribing them. Although both common and potentially serious medication side effects are highlighted, not every possible medication side effect is intended to be addressed in this review.

STIMULANT MEDICATIONS

During the past 50 years, stimulants have been extensively researched in children, leading us to have a robust knowledge base about both their benefits and side effects. There are two main stimulant families from which many different brands and formulations have been created: the methylphenidate and the amphetamine/dextroamphetamine families.

These two types of stimulants have very similar pharmacologic profiles in that they both increase intrasynaptic dopamine and norepinephrine in the prefrontal cortex primarily through reuptake inhibition. Amphetamines differ pharmacologically from methylphe-
nidade in a few ways, such as causing greater neuronal promotion of the release of dopamine, and being more likely to increase the amount of serotonin in the intraneuronal space.¹

Individual patients respond to or tolerate one stimulant family differently over another, but unfortunately, there is no current method to predict these variable responses in advance. The response rate for using either family of stimulant is around 65% to 75%, and if both stimulant families are tried sequentially, the overall stimulant response rate rises to about 85%.²

Potency of the families differs in a predictable manner such that 5 mg of amphetamine/dextroamphetamine is roughly bioequivalent to 10 mg methylphenidate.¹

All stimulants have the following common side effects: decreased appetite; nausea; weight loss; insomnia; headaches; stomachaches; dry mouth; and dizziness. The methylphenidate family has slightly less association with weight loss over time than dextroamphetamine, but this is still a very common side effect for both stimulant families.³

Stimulants can further cause new psychological symptoms such as irritability, dysphoria, cognitive dulling, obsessiveness, and anxiety in some children.¹,⁴

Rarely, stimulants can lead to hallucinations (typically visual or tactile), mania, or, in the case of methylphenidate, can suppress blood counts with prolonged use.³ Overdosage of a stimulant can produce dysrhythmia or a seizure.⁵ Side effects are reversible upon discontinuation.

Growth retardation from using stimulants has been a recent area of controversy. There is some evidence to suggest that long-term use of stimulants can decrease final adult height from the child’s predicted adult height by up to 1 inch; this may be something to discuss in the informed-consent process.⁶

However, other longitudinal studies have failed to find this association, making this appear to be less of a general class effect than a signal of some individual variation in growth response to stimulants.² A decrease from projected normal weight gain is very common but tends to resolve over time; often this is managed successfully by simply increasing caloric content of meals. Tracking both height and weight on a growth curve carefully over time is the best means to identify any significant growth changes that would require intervention.⁷

**Other ADHD Medications**

Atomoxetine is a nonstimulant medication that binds to the norepinephrine transporter, increasing norepinephrine and dopamine in the prefrontal cortex. It has been shown to be an effective treatment for ADHD, with clinical effects that develop gradually over several weeks during use.

Similar to stimulants, atomoxetine can cause mood swings, irritability, nausea, decreased appetite, insomnia, decreases in height and weight, and increases in

**Stimulants can cause irritability, dysphoria, cognitive dulling, obsessiveness, and anxiety in some children.**

Children with ADHD as part of their disorder have a higher than average risk for developing a substance abuse problem, a risk that appears to be mitigated by successful pharmacologic treatment of ADHD.² Therefore, one should inform parents that it is the ADHD itself that places their child at risk for substance abuse problems as an adolescent, and that reducing ADHD symptoms such as impulsivity may lower that risk.

The cardiovascular impact of using any stimulant is to increase slightly, on average, pulse and blood pressure.² This is considered clinically insignificant for healthy children, particularly when routine blood pressure and pulse measurements after initiating a stimulant are normal.

However, if a child has a pre-existing cardiac condition such as cardiac hypertrophy or long QT syndrome and there happens to be an individually moderate to large increase in pulse and blood pressure from a stimulant, then this change can be clinically significant.

It is recommended to take a careful cardiac history, to do further cardiac evaluations when indicated by history prior to use of a stimulant, and to do routine blood pressure and pulse monitoring after stimulant initiation.⁴,⁹ Despite some recent controversy, routine echocardiograms (ECGs) for healthy children with no familial cardiac risks are not recommended.⁹

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day dosing, and 24-hour treatment ben-
trasts such as low abuse potential, once
quires the same medical monitoring that
pulse and blood pressure; it therefore re-
quires the same medical monitoring that
is recommended for stimulants.3,5

Atomoxetine has several desirable
traits such as low abuse potential, once
daily dosing, and 24-hour treatment ben-
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include an overall more modest clinical
effect than that of stimulants, and some
further potential side effects, including
dry mouth, vomiting, liver toxicity, and
a risk of suicidal ideation (it carries the
same suicidality black box warning that
exists for selective serotonin reuptake
inhibitor [SSRI] medications).2,5,7

Central acting alpha-2 agonists (cloni-
dine and guanfacine) are anti-hyperten-
sive medications that have been used
off-label for ADHD for years, but there
have been recent FDA approvals of new
modified-duration formulations of these
medications for ADHD. In both cases,
these new formulations differ from their
immediate-release counterparts by having
sustained-release delivery system, and a
significantly lower clinical effect size on
ADHD than seen with stimulants. Other
common side effects include dizziness,
dry mouth, headache, nausea, constipa-
tion, abdominal pain, irritability, and hy-
potension.10 After prolonged use, there
is a potential for rebound hypertension
with abrupt discontinuation.2

With all ADHD medications, monitor-
ing for clinical benefits can occur by serial-
lly inquiring about target symptoms at each
appointment and comparing responses. If
treatment response is unclear, repeat ad-
mistration of an ADHD specific rating
scale, such as the Vanderbilt ADHD Rating
Scale, helps to quantify treatment response.

### SSRIs

SSRI medications have been shown to
have clinical benefits for adolescent de-
pression and for childhood anxiety disor-
ders (like obsessive-compulsive disorder
[OCD] and generalized anxiety disorder
[GAD]). SSRIs that have had at least
one randomized controlled trial show-
ing clinical benefits in children include
fluoxetine, sertraline, fluvoxamine, cita-
lopram, and escitalopram.10,11

Clinical guidelines that describe the
appropriate use of SSRIs in children rec-
ommend that they be used with ongoing
counseling such as cognitive-behavior
therapy (CBT) for both depressive and
anxiety disorders.12,13 Treatment with a
SSRI medication alone is generally a less
preferred option, both with regard to less
overall clinical effectiveness and less sup-
port for treatment monitoring.12,13

Particularly for the depressive disor-
ders in which suicidality may be a con-
cern, it is helpful to have another pro-
fessional such as a therapist seeing the
child on a frequent basis to monitor for
and address any suicidality that may ap-
ppear in the course of care.

Although the SSRIs have similar side
effect profiles overall, individual patients
can vary greatly in their response to or
side effects from a specific SSRI, which

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**TABLE 1.**

**Selected Stimulant Side Effects**5,10*

<table>
<thead>
<tr>
<th>Common (&gt;10%)</th>
<th>Less Common</th>
<th>Notable Rare Reactions (≤2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Decreased appetite</td>
<td>• Irritability</td>
<td>• Hallucinations</td>
</tr>
<tr>
<td>• Nausea</td>
<td>• Dysphoria</td>
<td>• Mania</td>
</tr>
<tr>
<td>• Weight loss</td>
<td>• Cognitive dulling</td>
<td>• Seizure</td>
</tr>
<tr>
<td>• Insomnia</td>
<td>• Obsessiveness</td>
<td>• Loss of adult height potential</td>
</tr>
<tr>
<td>• Headaches</td>
<td>• Anxiety</td>
<td>• Blood count suppression (MPH)</td>
</tr>
<tr>
<td>• Stomachaches</td>
<td>• Tics</td>
<td></td>
</tr>
<tr>
<td>• Dry mouth</td>
<td>• Dizziness</td>
<td></td>
</tr>
<tr>
<td></td>
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</tr>
</tbody>
</table>

*Summarized from individual medications in class.

MPH=methylphenidate.

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**TABLE 2.**

**Monitoring Stimulant Medications**4,5,10*

<table>
<thead>
<tr>
<th>Monitoring Recommendation</th>
<th>Frequency Suggestion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height and weight</td>
<td>At baseline and each follow-up, at least every 6 months.</td>
</tr>
<tr>
<td>Blood pressure and pulse</td>
<td>At baseline and at least once on a given dose of medication.</td>
</tr>
<tr>
<td>Cardiac history</td>
<td>At baseline to determine if any risks from adrenergic stimulation.</td>
</tr>
<tr>
<td>Refill monitoring</td>
<td>Track date of each refill to identify signs of drug diversion.</td>
</tr>
<tr>
<td>CBC with diff</td>
<td>For methylphenidate only, at least once after 6 months.</td>
</tr>
<tr>
<td>Determine if treatment response</td>
<td>Repeat ADHD specific rating scale(s) until remission is achieved. Increase at 2- to 4-week intervals if insufficient benefit.</td>
</tr>
</tbody>
</table>

*Summarized from individual medications in class.

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can occasionally be predicted based on the prior medication experience of a first-degree relative. Since it is difficult to predict which SSRI will be most effective and best tolerated by an individual child, at least two different SSRI trials are useful before abandoning the overall treatment strategy.

Clinical response should be reassessed at 4-week intervals since the time to observed clinical response is between 1 to 2 months at a given dosage. Given this delay in benefit, patients with severe symptoms may benefit from having their SSRI dosages escalated more rapidly (such as after only 2 weeks if no early side effects appear) to reduce the chance that a child will have a long duration of inadequately treated severe symptoms.

The most common SSRI side effects include changes in alertness (insomnia or sedation); appetite (increase or decrease); gastrointestinal symptoms (nausea, constipation, dry mouth); restlessness; diarrhea; headaches; and sexual dysfunction. “Behavioral activation” of impulsivity, agitation, irritability, silliness, and general hypomanic appearance commonly occurs in children at a rate of around 5%, and is reversible with discontinuation. Although a child who develops hypomanic symptoms in response to a SSRI could be at risk for having a bipolar disorder, most children who experience this side effect do not.

A rare risk is the induction of excessive serotonin levels, also known as serotonin syndrome (ie, agitation, ataxia, diarrhea, hyperreflexia, mental status changes, tremor, and hyperthermia). Serotonin syndrome is usually only an issue at very high SSRI doses or when the SSRI has been combined with other proserotonergic medications. There is also a rare risk of increased bleeding that is presumed due to SSRIs’ altering platelet serotonin function, which could be an issue if the child has surgery while taking the medication.

**SSRIs and Suicidality**

SSRIs have received a lot of attention since the issuance of a black box warning regarding suicidal ideation in 2004. That FDA warning was based on a review of 24 short-term randomized controlled trials with SSRIs in children for any indication, which found there was a two-fold increased risk of suicidal thoughts or behaviors while taking a SSRI versus taking a placebo. Since that time, subsequent research looking specifically at this issue has found different results.

At the case series level, such as looking at autopsies of youth suicide completions, there is no clear sign that SSRI use leads to completed suicides. At the population level, repeated analyses of Western societies show that more use of SSRIs is associated with reduced completed youth suicides.

**TABLE 3.**

Selected SSRI Side Effects

<table>
<thead>
<tr>
<th>Common (&gt;10%)</th>
<th>Less Common</th>
<th>Notable Rare Reactions (≤2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Insomnia</td>
<td>• Agitation</td>
<td>• New suicidality</td>
</tr>
<tr>
<td>• Sedation</td>
<td>• Restlessness</td>
<td>• Serotonin syndrome</td>
</tr>
<tr>
<td>• Appetite change (up and/or down)</td>
<td>• Impulsivity</td>
<td>• Easy bleeding</td>
</tr>
<tr>
<td>• Nausea</td>
<td>• Irritability</td>
<td>• Hypornatremia</td>
</tr>
<tr>
<td>• Dry mouth</td>
<td>• Silliness</td>
<td>• Mania</td>
</tr>
<tr>
<td>• Headache</td>
<td>• Constipation</td>
<td>• Prolonged QT interval</td>
</tr>
<tr>
<td>• Sexual dysfunction</td>
<td>• Dizziness</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 4.**

Suggested SSRI Monitoring

<table>
<thead>
<tr>
<th>Monitoring Recommendation</th>
<th>Frequency Suggestion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measure height and weight</td>
<td>At baseline and each follow-up, at least every 6 months.</td>
</tr>
<tr>
<td>Inquire about bleeding/bruising</td>
<td>At least once after initiation of medication.</td>
</tr>
<tr>
<td>Inquire about activation symptoms</td>
<td>Screen for new irritability or agitation around week 2 and weeks 4 to 6.</td>
</tr>
<tr>
<td>Inquire about new suicidal thoughts</td>
<td>Screen for suicidality around week 2, weeks 4 to 6, and other visits.</td>
</tr>
<tr>
<td>Determine treatment response</td>
<td>Repeat disorder specific rating scale(s) until remission is achieved. Increase at 4- to 6-week intervals if insufficient benefit.</td>
</tr>
</tbody>
</table>

*Summarized trends of the individual medications in class. Source: Hilt RJ. Reprinted with permission.

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more likely they will additionally report something similar to having experienced suicidal thoughts.

Another possibility is that clinical improvement from an SSRI may be leading to more willingness to discuss having suicidal thoughts. A third possible reason is that, although, on average, these medications seem to be reducing actual suicides, select individuals who may be experiencing the common “behavioral activation” side effect from an SSRI do in fact experience new suicidal thoughts or behaviors as part of a general dysphoria side effect.13 Whatever the explanation, it is prudent to inform all families before initiating use of an SSRI that their child may experience irritability, agitation, or suicidal thinking after starting treatment in the office or over the phone (a call possibly made by a mid-level provider), then see the child again around 4 weeks after starting the medication when a decision about next steps in dosage can be made. Appropriate ongoing monitoring of SSRI use in children includes following the child’s weight, and inquiring about any emergence of suicidal thoughts, new onset of easy bruising or bleeding, new irritability, sleep problems, or high-energy manic symptoms.4,13 Monitoring for clinical benefits can be done by serially inquiring about target symptoms and asking about subjective improvements seen by both parents and child. It may be more helpful to quantify symptom response through repeated office administration of a disorder specific rating scale such as the PHQ-9 for adolescent depression or the SCARED for anxiety, which can function like a vital sign to monitor treatment response.

### ANTIPSYCHOTICS

Antipsychotics increasingly are prescribed to children for a variety of indications, including treatment of severe aggression from autism, bipolar mania,

<table>
<thead>
<tr>
<th>TABLE 5. Selected Atypical Antipsychotic Side Effects$^{4,10*}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common (&gt;10%)</strong></td>
</tr>
<tr>
<td>• Weight gain</td>
</tr>
<tr>
<td>• Muscle rigidity</td>
</tr>
<tr>
<td>• Parkinsonism</td>
</tr>
<tr>
<td>• Constipation</td>
</tr>
<tr>
<td>• Dry mouth</td>
</tr>
<tr>
<td>• Dizziness</td>
</tr>
<tr>
<td>• Somnolence/fatigue</td>
</tr>
<tr>
<td><strong>Less Common</strong></td>
</tr>
<tr>
<td>• Tremors</td>
</tr>
<tr>
<td>• Nausea or abdominal pain</td>
</tr>
<tr>
<td>• Akathisia (restlessness)</td>
</tr>
<tr>
<td>• Headache</td>
</tr>
<tr>
<td>• Agitation</td>
</tr>
<tr>
<td>• Orthostasis</td>
</tr>
<tr>
<td>• Elevated glucose</td>
</tr>
<tr>
<td>• Elevated cholesterol triglycerides</td>
</tr>
<tr>
<td><strong>Notable Rare Reactions (≤2%)</strong></td>
</tr>
<tr>
<td>• Tardive dyskinesia</td>
</tr>
<tr>
<td>• Neuroleptic malignant syndrome</td>
</tr>
<tr>
<td>• Lowered blood cell counts</td>
</tr>
<tr>
<td>• Elevated liver enzymes</td>
</tr>
<tr>
<td>• Prolonged QT interval</td>
</tr>
<tr>
<td>• Tachycardia</td>
</tr>
</tbody>
</table>

$^{*}$Summarized from the individual medications in class.

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<table>
<thead>
<tr>
<th>TABLE 6. Monitoring Atypical Antipsychotic Medications$^{4,5,10*}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monitoring Recommendation</strong></td>
</tr>
<tr>
<td><strong>Frequency Suggestion</strong></td>
</tr>
<tr>
<td>Height and weight</td>
</tr>
<tr>
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and psychotic disorders. Antipsychotics are divided into two classes: the “first generation” or “typical” antipsychotics, and the “second generation” or “atypical” antipsychotics. With the exception of clozapine, which has somewhat superior efficacy (but is not recommended or covered further in this review due to having greater treatment risks), the two groups arguably have the same overall clinical efficacy.

Atypical antipsychotics are distinguished by having a lower risk of causing extrapyramidal side effects (acute muscle rigidity, tremors, and Parkinsonism) and tardive dyskinesia (TD). Of all antipsychotic prescriptions currently written for children, 98% are for atypical antipsychotics, largely due to these reduced neurologic side effects. All antipsychotics exhibit some degree of type 2 dopamine receptor blockade in the brain, which is generally thought to be the mechanism responsible for their antipsychotic properties.

Antipsychotics vary from “low” to “high” potency depending on the strength of their D2 receptor blockade, and thus the number of milligrams required to produce an antipsychotic effect. In general, the lower potency agents such as chlorpromazine and quetiapine tend to have biologic effects on many other brain receptors, such as anticholinergic and antihistamine properties that can lead to sedation.

Higher-potency agents such as haloperidol and risperidone have biological activity that is generally more restricted to the dopamine transmitter, and thus a group tend to be less sedating. However, this is only a generalization, since some children receiving risperidone can experience excessive sedation, and some children receiving quetiapine can experience very little sedation.

TD is a serious clinical risk of the use of antipsychotics. This is a movement disorder in which choreiform and/or athetotic movements occur repetitively in skeletal muscles at rest, can involve any voluntary muscle group (but most often peri-oral/lingual), and is potentially irreversible since there is no accepted treatment besides stopping the antipsychotic; and fewer than 50% of cases spontaneously resolve within 1 year of onset. TD is more likely to occur after use of antipsychotics at high dosage and/or for long duration. Although reliable figures are lacking, it has been estimated that with the first-generation antipsychotics, TD occurs in about 5% of patients per each year of use, increasing to a maximum lifetime risk of around 50%. With atypical antipsychotics, this is less common, with estimates of around 0.5% to 1% per year of use.

Children receiving any antipsychotic should be re-evaluated periodically for a new-onset movement disorder. The administration of the Abnormal Involuntary Movement Scale (AIMS) exam can be used to quickly detect the onset of tardive movements.

A more common side effect of atypical antipsychotics is the “metabolic syndrome,” which can include excessive appetite, abdominal obesity, hyperglycemia, hypercholesterolemia, and hyperlipidemia. The metabolic syndrome exists without the use of atypical antipsychotics, but with these agents, patients have a roughly twofold increase of this problem.

An analysis of atypical antipsychotics in children showed that for children previously naïve to this class of medications, weight gain is both common and significant for each of the atypical agents (ie, average gain of 9.5 to 18.5 pounds over 11 weeks). Ziprasidone and aripiprazole are relatively weight neutral for adults compared with other atypicals; however, this does not appear to be true for medication-naïve children. Weight-gain potential should be assumed to be similar for all the atypicals in children, with the exception of olanzapine, which has reported weight gain consistently higher than the rest. The cumulative risk of weight gain, the metabolic syndrome, and TD from atypical antipsychotic use should cause frequent reassessment of need to continue using an antipsychotic. Parents and providers should make yearly attempts to decrease or even discontinue the agent if clinical circumstances allow.

Regular monitoring of weight, fasting blood sugar, lipids, and cholesterol is required for safe usage. It is also prudent to consider checking a CBC with differential to screen for the rare occurrence of antipsychotic-induced bone marrow suppression at least once after about 1 to 2 months of treatment.

Besides weight gain, other common side effects include: extrapyramidal effects (rigidity, tremors, and Parkinsonism); nausea; abdominal pain; dry mouth; physical restlessness (akathisia); dizziness; headache; somnolence/sedation; insomnia; anxiety; and orthostasis. Families should be notified specifically about the possibility of acute dystonia, a sustained involuntary muscular contraction, that can occur early in the course of treatment.
If this happens, acute treatment includes the immediate administration of an anticholinergic medication such as diphenhydramine. As a precaution, asking families to keep a supply during treatment initiation seems prudent.

A very rare but serious side effect is the neuroleptic malignant syndrome. This is essentially an adverse reaction to an antipsychotic that occurs early in the course of therapy and is characterized by high fever (ie, 104° to 106°F); muscle stiffness; autonomic instability; altered mental status; and elevated serum creatine phosphokinase (CPK). Untreated, this is a potentially fatal complication.

Treatment involves immediate discontinuation of the antipsychotic, hydration, fever control, anticholinergic drugs, and symptomatic support. Families starting use of an antipsychotic should be warned to contact a physician immediately if their child develops a new high grade fever or “flu-like symptoms” within the first month of treatment.

CONCLUSION

Children can be helped greatly by the appropriate use of psychiatric medications, but doing so requires awareness of both common and certain rare, but clinically significant, side effects of these medicines. By informing patients and parents about the key side effects, and by using a specific follow-up plan for monitoring SSRIs, antipsychotics and ADHD medications, practitioners can use these medications safely and effectively.

REFERENCES


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