Diagnosis of ADHD

- Refer to and follow the DSM-IV diagnostic criteria as part of the evaluation and diagnosis of ADHD in children and adolescents (see Page 2).

- The publicly available Vanderbilt ADHD Rating Scales are recommended as part of the evaluation and diagnosis of ADHD in children and adolescents. According to the Vanderbilt scoring instructions, the following can be screened: Inattention, Hyperactivity/Impulsivity, Combined subtype, Oppositional defiant and conduct disorders, anxiety or depressive symptoms.

- The following behavior rating scales are options to be used in addition to the initial evaluation:
  - Conners’ Rating Scales: (CPRS-R, CTRS-R, CASS)
  - Achenbach Scales: (CBCL, TRF, YSR)
  - ADHD Rating Scale-IV: (ADHD RS-IV)
  - Swan, Nolan, and Pelham Questionnaire: (SNAP)

Achenbach and Vanderbilt behavioral rating scales can be used to assess some comorbid disorders.

This recommendation is limited to the behavioral rating scales. Evaluation to determine a diagnosis of ADHD, while following the DSM-IV criteria, includes other components that were not addressed in this evidence-based guideline, such as physical, school and behavioral history (including history of substance abuse); parent and student interviews; and any additional material needed for an appropriate diagnosis.

- Evaluation for the presence of comorbid psychiatric disorders and conditions is recommended for children and adolescents with ADHD. Common conditions include:
  - Disruptive Behavior Disorders
    (Oppositional Defiant Disorder, Conduct Disorder)
  - Learning Disorders
  - Anxiety Disorders
  - Mood Disorders (Depression, Bipolar Disorder)
  - Tic Disorder

- The Vanderbilt Rating Scales are recommended for assessing symptoms associated with some common comorbid conditions.

Drug Therapy for ADHD (see Tables 1–2)

- A shared medical-decision making approach is recommended. Parents/guardians, and the child or adolescent diagnosed with ADHD, should be informed of the potential benefits and harms of treatment with stimulants, and encouraged to make a personal decision about treatment, in collaboration with a physician.

- Stimulant medication is recommended as first-line treatment for children and adolescents diagnosed with ADHD (with or without comorbid conditions).

- If medication is chosen, initiate a course of one of the following first-line stimulant medications:

<table>
<thead>
<tr>
<th>First-Line Stimulants</th>
<th>Methylphenidate preparations</th>
<th>Amphetamine preparations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate</td>
<td>Amphetamine mixed salts</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dextroamphetamine</td>
<td></td>
</tr>
</tbody>
</table>

There is insufficient evidence to determine which of the above first-line stimulant medications is most effective for treatment. Given the lack of evidence on a clearly superior stimulant medication, when choosing a first-line treatment, decisions should be based on clinician and parent preferences, side effects, pharmacokinetics (rapidity of onset, duration of action), cost, and formulary availability (see Tables 1 and 2). If two or more first-line stimulant formulations are contraindicated, not tolerated, or ineffective; the second-line non-stimulant treatments atomoxetine or guanfacine are an option.

Warnings on hepatotoxicity and suicidality from atomoxetine exist. All ADHD drugs also have cardiovascular risk warnings. Instruct patients and caregivers to recognize signs and symptoms of liver dysfunction, cardiovascular risks, and suicidality. Liver function tests can be considered for patients prescribed atomoxetine.

- There is insufficient evidence to recommend for or against the following drug treatments for routine use in children and adolescents diagnosed with ADHD:
  - Bupropion
  - Venlafaxine
  - Imipramine
  - Nortriptyline
  - Clonidine

- The balance of the benefits and harms is too close to justify a general recommendation for routine use of desipramine in children and adolescents diagnosed with ADHD.
ADHD Evaluation and Diagnosis Algorithm

Children and Adolescents with suspected ADHD

Refer to and follow the DSM-IV diagnostic criteria to evaluate:

- Onset and duration of core symptoms of ADHD (e.g., inattention, hyperactivity, and impulsivity).
- Behavior in several settings (e.g., school, work, home).
- Impairment in social, academic, or occupational functioning.

The publicly available Vanderbilt ADHD Rating Scales are recommended as part of the evaluation and diagnosis of ADHD.

Use at least one of the following behavioral rating scales:

- Vanderbilt ADHD Rating Scales: (VADRS, VADTRS) (preferred):
- Conners' Rating Scales: CPRS-R, CTERS-R, CASS
- ADHD Rating Scale-IV: (ADHD RS-IV)†
- Swan, Nolan, and Pelham Questionaire: SNAP†
- Achenbach Scales: CBCL, TRF, YSR

(broadband scale, an option to use in addition to one of the ADHD rating scales).

Evaluate for comorbid psychiatric disorders and other conditions. The most common disorders coexisting with ADHD include:

- Disruptive Behavior Disorders (Oppositional Defiant Disorder, Conduct Disorder)
- Learning Disorders
- Anxiety Disorders
- Mood Disorders (Depression, Bipolar Disorder)
- Tic Disorder

The Vanderbilt Rating Scales are recommended for assessing symptoms associated with some common comorbid conditions.‡

Begin Treatment and Coordinate Management of Care.
See Medication Management Algorithm.

Does ADHD appear to be the primary diagnosis?

NO

NO

Any significant additional comorbidities identified?

YES

YES

Coordinate with subspecialty(s) for further evaluation and as indicated.
See Medication Management Algorithm.

* DSM-IV-based.
† The recommendation is limited to the behavioral rating scales. Evaluation to determine a diagnosis of ADHD, while following the DSM-IV criteria, includes other components that were not addressed in the evidence-based guideline (i.e., physical, school and behavioral history (including history of substance abuse), parent and student interviews, and any additional material needed for an appropriate diagnosis).
‡ This recommendation is limited to global rating scales that are appropriate for use in the primary care setting. Additional evaluations, diagnostic testing, and examinations may be necessary for diagnosis. The Vanderbilt Rating Scales do not assess learning and tic disorders, because learning disorders require evaluation through academic testing in an educational setting, and tic disorders can be addressed through clinical presentation.
Non-Drug Interventions for ADHD

- The following clinic-based non-drug interventions are options for children or adolescents diagnosed with ADHD, with or without comorbidities, for whom drug treatment is contraindicated, not tolerated, or a decision has been made not to initiate drug therapy:
  - Behavioral Therapy/Cognitive Behavioral Training
  - Family Therapy
  - Parent Training
  - Social Skills Training

- Additional educational services offered outside of Kaiser Permanente, such as through the school system, are recommended for children or adolescents diagnosed with ADHD.

Combined Drug and Non-Drug Therapy

- For children and adolescents who are responding adequately to medication management, adding a clinic-based, non-drug intervention to drug treatment is not routinely recommended for treating the core symptoms of ADHD (inattention, impulsivity, and hyperactivity).

- For children and adolescents with mild symptoms associated with common comorbid conditions, adding a clinic-based, non-drug intervention to drug intervention is an option to be considered on a case-by-case basis.

Combined Drug Therapy

- Drug therapy consisting of two or more drugs in different classes is not routinely recommended for treating the core symptoms of ADHD in children and adolescents.

- Combining medications within the same class is an option to augment a morning dose and provide all-day coverage.

Treatment Strategy for ADHD With Common Comorbid Conditions

- The GDT recommends clinic-based behavioral interventions or other drug therapy regimens. If no improvement is seen, this may be due to lack of response to treatment or to an accompanying comorbidity. At that point consider pursuing a) a second-line treatment, or b) a referral to a sub-specialist. If no improvement is seen after second-line treatment, a referral should be made to a sub-specialist.

- Referral or consultation with a specialist, including child psychiatry, behavioral health, a behavioral pediatrician, or ADHD champion, is an option for children or adolescents with common comorbid conditions such as oppositional defiant disorder, conduct disorder, anxiety disorders, mood disorders, and tic disorder.

Diagnostic Criteria for Attention-Deficit/Hyperactivity Disorder (DSM-IV-TR, 2000)

A. Either (1) or (2):

1. Six (or more) of the following symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

   a. Often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
   b. Often has difficulty sustaining attention in tasks or play activities
   c. Often does not seem to listen when spoken to directly
   d. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
   e. Often has difficulty organizing tasks and activities
   f. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
   g. Often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)
   h. Often easily distracted by extraneous stimuli
   i. Is often forgetful in daily activities

2. Six (or more) of the following symptoms of hyperactivity-impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

   a. Often fidgets with hands or feet or squirms in seat
   b. Often leaves seat in classroom or in other situations in which remaining seated is expected
   c. Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
   d. Often has difficulty playing or engaging in leisure activities quietly
   e. Is often “on the go” or often acts as if “driven by a motor”
   f. Often talks excessively

Impulsivity

   a. Often blurts out answers before questions have been completed
   b. Often has difficulty waiting turn
   c. Often interrupts or intrudes on others (e.g., butts into conversations or games)

B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.

C. Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home).

D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.

E. The symptoms do not occur exclusively during the course of a pervasive developmental disorder, schizophrenia, or other psychotic disorder and are not better accounted for by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, or a personality disorder).

Copyright © 2000 American Psychiatric Association.
All rights reserved.
Monitoring Drug Therapy for ADHD

- One in-person office visit with a practitioner with prescriptive authority is recommended for children and adolescents during the 30-day initiation phase of drug treatment for ADHD.

- A minimum of 2 follow-up visits within 9 months after the 30-day initiation phase visit are recommended for children and adolescents continuing drug treatment for ADHD. One of the visits may be a telephone visit with a practitioner.

The above recommendations are consistent with HEDIS 2009 standards and apply to children aged 6-12.

Newly prescribed medication applies to any patient with no medication history for ADHD in the past 4 months (no drug for ADHD dispensed within the last 120 days).

- More frequent follow-up visits may be conducted on a case-by-case basis.

At all follow-up visits, assess patient for adverse effects, adherence to treatment, and response to treatment. Monitor for changes in core symptoms of ADHD (hyperactivity, impulsivity, and inattention), educational function, psychosocial function, and potential side effects, such as headaches, abdominal pain, and changes in height, weight, blood pressure, pulse, or eating and sleeping patterns. (Note: Not specifically required for HEDIS.)

ADHD Medication Management Algorithm

A shared medical-decision-making approach is recommended: Parents/guardians, and the child or adolescent diagnosed with ADHD, should be informed of the potential benefits and harms of the treatment with stimulants, and encouraged to make a personal decision, in collaboration with a physician, about treatment.

If two or more first-line stimulant formulations are contraindicated, not tolerated, or ineffective; the non-stimulant treatments atomoxetine or guanfacine are an option. Drug therapy of two or more drugs in different classes is not routinely recommended; however, combining medications within the same class is an option to augment a morning dose and provide all-day coverage.

Stimulant medication is recommended as first-line treatment. Given the lack of evidence on a clearly superior stimulant medication, when choosing a first-line treatment, decisions should be based on clinician and parent preferences, side effects, pharmacokinetics (rapidity of onset, duration of action), cost, and formulary availability.

Consider increasing the dose if there is no immediate response to the medication started. If increasing the dose produces side effects or has no response, consider trying a second first-line medication.

Successful first-line medication trial(s)?

Maintain and continue care

Referral or consultation with a specialist, including child psychiatry, behavioral health, a behavioral pediatrician, or ADHD champion, is an option for children or adolescents with common comorbid conditions such as oppositional defiant disorder, conduct disorder, anxiety disorders, mood disorders, and tic disorder.

Any significant additional comorbidities identified?

NO

YES

NO
Overview of the Evidence on the Efficacy of the First-Line Stimulant Formulations

There is good evidence that methylphenidate and fair evidence that dexmethylphenidate, dextroamphetamine, mixed-amphetamine salts, lisdexamfetamine dimesylate, and modafinil are efficacious in reducing core symptoms of ADHD and, in some cases, other measures of educational and psychosocial function. The evidence on methylphenidate includes a well-designed meta-analysis on several available trials. The evidence on dexmethylphenidate, dextroamphetamine, mixed-amphetamine salts, lisdexamfetamine dimesylate, and modafinil includes a more limited number of trials. Although there is fair evidence that adverse events do occur in children with all of these drugs, with the exception of modafinil, the benefits were determined to outweigh the risk of harm for routine use.

Table 1: Medications Used in the Treatment of ADHD

<table>
<thead>
<tr>
<th>Drug (reference brand)</th>
<th>Est. Duration of Effect &amp; PEAK (hours)</th>
<th>Strength (mg)</th>
<th>Doses Per Day</th>
<th>Usual Dose (labeled maximum dose)</th>
<th>Comments</th>
<th>Relative Cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FIRST-LINE STIMULANTS USED IN THE TREATMENT OF ADHD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SHORT-ACTING</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphetamine mixed salts (Adderall)</td>
<td>5 – 8 3</td>
<td>5, 7.5, 10, 12.5, 15, 20, 30</td>
<td>1 – 2</td>
<td>• Initial dose 2.5–5 mg qAM or BID.</td>
<td>• Available generically.</td>
<td>$</td>
</tr>
<tr>
<td>Dextroamphetamine (Dexedrine; DextroStat)</td>
<td>6 – 10 1 – 3</td>
<td>5, 10</td>
<td>2 – 3</td>
<td>• Initial dose 2.5–5 mg qAM–BID.</td>
<td>• Available generically.</td>
<td>$</td>
</tr>
<tr>
<td>Methylphenidate (Ritalin; Methylin)</td>
<td>3 – 5 1 – 3</td>
<td>5, 10, 20</td>
<td>2 – 3</td>
<td>• Initial dose 5 mg BID.</td>
<td>• Available generically.</td>
<td>$</td>
</tr>
<tr>
<td>Dexmethylphenidate (Focalin)</td>
<td>6 – 8 1.5 – 3</td>
<td>2.5, 5, 10</td>
<td>2</td>
<td>• Initial dose 2.5 mg BID.</td>
<td>• Dose is ½ that of methylphenidate.</td>
<td>$$$</td>
</tr>
<tr>
<td><strong>INTERMEDIATE-ACTING</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylphenidate sustained-release (Ritalin SR, Methylin ER, Metadate ER)</td>
<td>3 – 8 3.5</td>
<td>10, 20</td>
<td>1 – 2</td>
<td>• Initial dose 10 mg qAM.</td>
<td>• Available generically.</td>
<td>$</td>
</tr>
<tr>
<td>Dextroamphetamine biphasic release (Dexedrine Spansule)</td>
<td>6 – 10 8</td>
<td>5, 10, 15</td>
<td>1 – 2</td>
<td>• 5–40 mg qAM (40 mg).</td>
<td>• Available generically.</td>
<td>$$$</td>
</tr>
<tr>
<td>Methylphenidate extended-release capsule (Metadate CD®) (biphasic release: 30% IR, 70% SR)</td>
<td>8–9 1st PEAK: 1.5 2nd PEAK: 4.5</td>
<td>10, 20, 30, 40, 50, 60</td>
<td>1</td>
<td>• Initial dose 10 mg qAM.</td>
<td>• Capsule may be opened and contents sprinkled on applesauce.</td>
<td>$$$$</td>
</tr>
<tr>
<td>Methylphenidate extended-release capsule (Ritalin LA®) (bimodal release: 50% IR, 50% SR)</td>
<td>8–10 1st PEAK: 2 2nd PEAK: 6.5</td>
<td>10, 20, 30, 40</td>
<td>1</td>
<td>• Initial dose 10 mg qAM.</td>
<td>• Capsule may be opened and contents sprinkled on applesauce.</td>
<td>$$$$</td>
</tr>
<tr>
<td>Dexmethylphenidate extended-release capsule (Focalin XR)</td>
<td>8–12 1st PEAK: 1.5 2nd PEAK: 6.5</td>
<td>5, 10, 15, 20</td>
<td>1</td>
<td>• Children ≥ 6: Initial 5 mg qAM, dosage may be increased in increments of 5 mg at weekly intervals to a maximum of 20 mg qAM.</td>
<td>• Capsule may be opened and contents sprinkled on applesauce.</td>
<td>$$$$</td>
</tr>
</tbody>
</table>

* Cost Legend
- $ ≤ $25/month
- $26 - $50/month
- $51 - 100/month
- $101 - 150/month

Acquisition cost based on the following comparative daily doses:
- Dextroamphetamine 20 mg
- Methylphenidate 40 mg
- Amphetamine mixed salts 20 mg

© 2009 Kaiser Permanente Medical Care Program
For use within Kaiser Permanente only.
<table>
<thead>
<tr>
<th>Drug (reference brand)</th>
<th>Est. Duration of Effect &amp; PEAK (hours)</th>
<th>Strength (mg)</th>
<th>Doses per Day</th>
<th>Usual Dose (labeled maximum dose)</th>
<th>Comments</th>
<th>Relative Cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FIRST-LINE STIMULANTS USED IN THE TREATMENT OF ADHD continued</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LONG-ACTING</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Amphetamine mixed salts extended-release capsule (Adderall XR) (biphasic release: 50% IR, 50% SR) | 10–12 7 | 5, 10, 15, 20, 25, 30 | 1 | • Children 6–12: Initial 5 mg qAM; dosage may be increased in increments of 5–10 mg at weekly intervals to a maximum of 30 mg qAM.  
• Adolescents 13–17: Initial 10 mg qAM; dosage may be increased in increments of 5–10 mg at weekly intervals to a maximum of 40 mg qAM.  
• Conversion from IR amphetamine mixed salts: Patients taking divided doses (BID) may be switched to Adderall XR at the same total daily dose taken once daily in the morning. | | $$$ |
| Methylphenidate extended-release tablet (Concerta®) (biphasic release: 22% IR, 78% SR) | 12 (up to 24) 1st PEAK: 1 2nd PEAK: 6.8 | 18, 27, 36, 54 | 1 | • Children 6–12: Initial 18 mg qAM; dosage may be increased at weekly intervals to a maximum of 54 mg qAM.  
• Adolescents 13–17: Initial 18 mg qAM; dosage may be increased at weekly intervals to a maximum of 72 mg qAM not to exceed 2 mg/kg/day.  
• Conversion from IR methylphenidate:  
  • 5 mg BID-TID = 18 mg qAM  
  • 10 mg BID-TID = 36 mg qAM  
  • 15 mg BID-TID = 54 mg qAM | | $$$$ |
| Methylphenidate transdermal patch (Daytrana) NON-FORMULARY | 12 7.5 – 10 | 10 mg/9 h 15 mg/9 h 20 mg/9 h 30 mg/9 h | 1 | • Should be applied to alternating hip area 2 hours before effect is needed and should be removed 9 hours after application.  
• Initial dose 10 mg/9 h; dose should be titrated to effect, if response is not maximized, at weekly intervals.  
• Use may lead to contact sensitization.  
• Patients should be advised to avoid exposing application site to direct external heat sources; increases drug release > 2-fold from the patch.  
• A noticeable effect may not occur until about 2 hours after application, which may be problematic when getting children ready for school in the morning. | | $$$$ |
| Lisdexamfetamine capsule (Vyvanse) NON-FORMULARY | 10–12 3.5 | 20, 30, 40, 50, 60, 70 | 1 | • Children 6–12: Initial 30 mg qAM; dosage may be increased in increments of 20 mg at weekly intervals to a maximum of 70 mg qAM.  
• Capsule may be opened and entire contents dissolved in water to form a solution. | | $$ |

* Cost Legend

| Acquisition cost based on the following comparative daily doses: |
| Dextroamphetamine 20 mg | Methylphenidate 40 mg | Lisdexamfetamine 20 mg |
| $ ≤ $25/month | $5 = $26 - $50/month | $55 = $51 - 100/month |

(continued on next page)
<table>
<thead>
<tr>
<th>Drug (reference brand)</th>
<th>Est. Duration of Effect &amp; PEAK (hours)</th>
<th>Strength (mg)</th>
<th>Doses per Day</th>
<th>Usual Dose (labeled maximum dose)</th>
<th>Comments</th>
<th>Relative Cost *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SECOND-LINE AGENTS USED IN THE TREATMENT OF ADHD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atomoxetine (Strattera) NON-FORMULARY</td>
<td>24</td>
<td>10, 18, 25, 40, 60, 80, 100</td>
<td>1–2</td>
<td>• &lt; 70 kg: Initial 0.5 mg/kg/day; increase after a minimum of 3 days to target dose of about 1.2 mg/kg/day given either as a single daily dose in morning or as evenly divided doses in morning and late afternoon/early evening (1.4 mg/kg/day or 100 mg/day, whichever is less). • &gt; 70 kg: Initial 20-40 mg/day; increase after a minimum of 3 days as tolerated and as needed to target dose of ~ 80 mg/day given either as a single daily dose in morning or as evenly divided doses in morning and late afternoon/early evening (100 mg/day).</td>
<td>• Norepinephrine-reuptake inhibitor. • Not a controlled substance. • Second-line drug for patients in whom stimulants are poorly tolerated, ineffective, or contraindicated. • Do not open capsule. • Dose should be reduced in hepatic insufficiency and may need to be reduced in CYP2D6 poor metabolizers. • Slower titration may reduce uncomfortable side effects.</td>
<td>1 cap per day: $$$$ Giving 2 caps per day (e.g., 40 mg BID) effectively doubles the cost of therapy compared to 1 cap/day (e.g., 80 mg once daily).</td>
</tr>
<tr>
<td>Guanfacine (Intuniv) NON-FORMULARY</td>
<td>8–12</td>
<td>1, 2, 3, 4</td>
<td>1</td>
<td>• Begin at dose of 1 mg once daily in the morning and adjust in increments of no more than 1 mg/week. • Maintain the dose within the range of 1.4 mg/day, depending on clinical response and tolerability. • Consider dosing on a mg/kg basis. Improvements observed at starting doses of 0.05-0.08 mg/kg once daily. Doses up to 0.12 mg/kg once daily may provide additional benefit.</td>
<td>• A selective alpha2A-adrenergic receptor agonist. • Not a controlled substance. • Mechanism of action in ADHD is not known. • Extended-release tablet; tablets should not be crushed, chewed, or broken before swallowing because this will increase the rate of guanfacine release. • Do not administer with high-fat meals, because of increased exposure.</td>
<td>$$$$</td>
</tr>
</tbody>
</table>

### Table 2: Adverse Events Associated with Medication Used in the Treatment of ADHD

<table>
<thead>
<tr>
<th>MINOR (Expected, tolerable)</th>
<th>MAJOR (May require dose reduction, prohibits higher dose)</th>
<th>PROHIBITIVE (Requires dose reduction or discontinuation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Mild anorexia (or weight loss)</td>
<td>• Moderate anorexia (or weight loss)</td>
<td>• Severe anorexia (or weight loss)</td>
</tr>
<tr>
<td>• Mild insomnia (&gt;1 hr)</td>
<td>• Moderate insomnia (&gt; 1 – 1.5 hr)</td>
<td>• Severe insomnia (&gt; 1.5 hr)</td>
</tr>
<tr>
<td>• Mild headaches</td>
<td>• Moderate headaches</td>
<td>• Severe, unrelenting headaches</td>
</tr>
<tr>
<td>• Fleeting negligible tics, causing no impairment</td>
<td>• Fleeting new tics</td>
<td>• New, marked, severe tics</td>
</tr>
<tr>
<td>• Mild GI cramps</td>
<td>• Moderate GI cramps</td>
<td>• GI cramps, intolerable</td>
</tr>
<tr>
<td>• Mild picking at skin, nail-biting</td>
<td>• Moderate picking at skin, nail-biting</td>
<td>• Severe picking at skin, nail-biting</td>
</tr>
<tr>
<td>• Mild anxiety</td>
<td>• Moderate anxiety</td>
<td>• Severe anxiety</td>
</tr>
<tr>
<td>• Mild irritability</td>
<td>• Moderate irritability</td>
<td>• Severe irritability, leading to aggression</td>
</tr>
<tr>
<td>• Mild depression</td>
<td>• Depression, not pre-existing</td>
<td>• Depression, not pre-existing</td>
</tr>
<tr>
<td>• Dull, tired, listless</td>
<td>• Questionable hallucinations</td>
<td>• Hallucinations</td>
</tr>
<tr>
<td></td>
<td>• “Zombie” part of the day</td>
<td>• “Zombie” all day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Psychosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Signs of liver toxicity:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pruritus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Jaundice</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Dark urine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Right upper-sided abdominal weakness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Unexplained “flu-like” symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Suicidal thoughts or behavior:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Agitation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Irritability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Clinical worsening</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Changes in behavior</td>
</tr>
</tbody>
</table>