# ADHD Agents (Adult)

## Prior Authorization Criteria

<table>
<thead>
<tr>
<th>Brand</th>
<th>Generic</th>
<th>Dosage Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adderall®</td>
<td>amphetamine/dextroamphetamine</td>
<td>oral tablet[a]</td>
</tr>
<tr>
<td>Adderall XR®</td>
<td>amphetamine/dextroamphetamine</td>
<td>extended-release oral capsule</td>
</tr>
<tr>
<td>Concerta®</td>
<td>methylphenidate</td>
<td>extended-release tablet</td>
</tr>
<tr>
<td>Daytrana®</td>
<td>methylphenidate</td>
<td>transdermal system</td>
</tr>
<tr>
<td>Desoxyn®</td>
<td>methamphetamine</td>
<td>oral tablet</td>
</tr>
<tr>
<td>DextroStat®</td>
<td>dextroamphetamine</td>
<td>oral tablet[a]</td>
</tr>
<tr>
<td>Dexedrine®</td>
<td>dextroamphetamine</td>
<td>extended-release capsule[a]</td>
</tr>
<tr>
<td>Focalin®</td>
<td>dextmethylphenidate</td>
<td>oral tablet[a]</td>
</tr>
<tr>
<td>Focalin® XR</td>
<td>dextmethylphenidate</td>
<td>extended-release capsule</td>
</tr>
<tr>
<td>Intuniv®</td>
<td>guanfacine</td>
<td>extended-release tablet</td>
</tr>
<tr>
<td>Methylin® c</td>
<td>methylphenidate</td>
<td>chewable tablet, oral tablet, [a] oral solution[a]</td>
</tr>
<tr>
<td>Metadate® CD</td>
<td>methylphenidate</td>
<td>extended-release capsule</td>
</tr>
<tr>
<td>Metadate® ER</td>
<td>methylphenidate</td>
<td>extended-release capsule[a]</td>
</tr>
<tr>
<td>Procentra®</td>
<td>dextroamphetamine</td>
<td>oral solution[b]</td>
</tr>
<tr>
<td>Ritalin®</td>
<td>methylphenidate</td>
<td>oral tablet[a]</td>
</tr>
<tr>
<td>Ritalin LA®</td>
<td>methylphenidate</td>
<td>extended-release tablet</td>
</tr>
<tr>
<td>Ritalin SR®</td>
<td>methylphenidate</td>
<td>extended-release tablet[a]</td>
</tr>
<tr>
<td>Strattera®</td>
<td>atomoxetine</td>
<td>oral capsule</td>
</tr>
<tr>
<td>Vyvanse®</td>
<td>lisdexamfetamine</td>
<td>oral capsule</td>
</tr>
</tbody>
</table>

[a] generic available  
[b] generic Liquadd oral solution 5mg/5mL may be available until 10/1/2010 (obsolete date)  
[c] Methylin chewable tablets and Methylin oral solution are considered brand agents and will edit as a target drug. Methylin oral tablet and Methylin ER edit as generic agents and are accepted as generic prerequisites
FDA APPROVED INDICATIONS

The following information is taken from individual drug prescribing information and is provided here as background information only. Not all FDA-approved indications may be considered medically necessary. All criteria are found in the section “Prior Authorization (PA) Criteria for Approval.”

<table>
<thead>
<tr>
<th>Agent</th>
<th>FDA Labeled Indication (age restrictions-years)</th>
<th>Narcolepsy</th>
<th>ADHD</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>amphetamine/dextroamphetamine</td>
<td>✓ (Adderall)</td>
<td>✓ (Adderall ≥ 3)</td>
<td>Adderall XR &gt; 6</td>
<td></td>
</tr>
<tr>
<td>(Adderall, Adderall XR*)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dexamfetamine</td>
<td>✓ ≥ 6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Focalin, Focalin XR*)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dextroamphetamine (Dexedrine, DextroStat, Liquadd)</td>
<td>✓ (≥ 6)</td>
<td>✓ (≥ 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lisdexamfetamine (Vyvanse*)</td>
<td>✓ (≥ 6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methamphetamine (Desoxyn)</td>
<td>✓ (≥ 6)</td>
<td></td>
<td></td>
<td>exogenous obesity (≥ 12)</td>
</tr>
<tr>
<td>Methylphenidate (Ritalin*, Ritalin SR*, Ritalin LA, Metadate ER, Metadate CD, Methylin, Concerta*, Daytrana)</td>
<td>✓ (Ritalin, Ritalin SR, Methylin)</td>
<td>✓ (≥ 6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atomoxetine (Strattera*)</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guanfacine ER (Intuniv)</td>
<td>✓ (≥ 6)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADHD=attention deficit hyperactivity disorder

*R Products with prescribing information indicating approval for use in adult ADHD

RATIONALE FOR PRIOR AUTHORIZATION

The intent of the prior authorization (PA) criteria for the attention deficit hyperactivity disorder (ADHD) agents, or stimulants, is to appropriately select patients according to product labeling and/or clinical guidelines and/or clinical studies and to direct use to more cost-effective generic agents as appropriate. The PA edit will not be applied to generic stimulant agents but will target brand stimulant or ADHD agents. The edit is applied to adults and not children and adolescents because use of stimulants in patients under eighteen years of age is predominantly for treatment of Attention Deficit Disorder (ADD) and ADHD. The age limit of eighteen years or older is used in the PA criteria because clinical trials define child and adolescent ages as through 17 years of age and adults as 18 years of age and above. These criteria use the term ADHD to encompass both ADHD and ADD.

ADHD - Guidelines, Reviews

Treatment guidelines authored by the American Academy of Child and Adolescent Psychiatry (AACAP) for assessment and treatment of children and adolescents with ADHD (2007) consider stimulants as first-line treatments for ADHD. Evidence suggests that the two stimulant types, methylphenidate or amphetamine, are equally efficacious in the treatment of ADHD and either would be appropriate choices for initiation of therapy. Comparisons of efficacy of atomoxetine versus the stimulants have shown a greater treatment effect of the stimulants (atomoxetine 0.62 compared with 0.91 and 0.95 for immediate-release and long-acting stimulants, respectively). Atomoxetine may be considered for initial therapy in patients with an active substance abuse problem, comorbid anxiety, or tics, and is also preferred if the patient has severe side effects to stimulants (e.g., mood lability, tics).

An Institute for Clinical Systems Improvement (ICSI) 2007 guideline recommends use of any agent approved for the treatment of ADHD as initial pharmacologic treatment. Agents include dextroamphetamine, methylphenidate, mixed salts amphetamine, and atomoxetine. Response to one stimulant does not indicate response to others. Studies indicate a 70% to 80% response rate to each stimulant independent of one another: therefore, a patient that does not respond to one stimulant may be able to be treated successfully with a second or third stimulant agent. The ICSI guideline on ADHD, like the AACAP guideline, recommends the use of atomoxetine as a first-line agent when stimulants may not be an option for patients with comorbid anxiety, sleep disorder, substance abuse, tics, or if initially preferred by patient or physician.
The National Institute for Health and Clinical Excellence (NICE) 2008 clinical guideline recommendations for the management of ADHD in children, young adults, and adults indicate drug treatment as first-line therapy for adults with moderate to severe ADHD and methylphenidate as the first option.22 If methylphenidate is ineffective or contraindicated, atomoxetine or dexamphetamine are alternatives.22 If there is a concern for drug misuse or diversion, atomoxetine may be considered as the first-line agent.22

An Oregon Health & Science University drug class review (2007) on pharmacologic treatments for ADHD developed by the Evidence-based Practice Center compared the benefits and harms of different pharmacologic treatments for ADHD.23 There were no conclusions made concerning the effectiveness of the different pharmacotherapies for ADHD. However, the reviewers state that evidence for comparative efficacy and adverse events for these agents is limited by small sample sizes, very short durations, and lack of studies measuring functional or long-term outcomes. The methods used to measure symptom control vary significantly among studies. Existing head-to-head trials were not considered of good quality by the reviewers and the small numbers of patients in these trials limits the ability to show a difference between drugs, if one exists.23

The decision regarding the initial pharmacologic treatment of ADHD is based on several factors including the different adverse effects of the agents, issues regarding compliance, potential drug diversion and/or misuse, the presence of comorbid conditions, and the preference of the patient.20 For instance, treatment with an extended-release agent may be preferred over multiple daily dosing or if drug diversion is a consideration. Atomoxetine may be considered as a first choice agent for individuals with an active substance abuse problem, comorbid anxiety, or tics.20 Atomoxetine may be preferred if the patient experiences severe side effects or contraindications to stimulants.21 Contraindications may include, but are not limited to glaucoma, advanced arteriosclerosis, symptomatic cardiovascular disease, hypertension, hyperthyroidism, anxiety, agitation, Tourettes, motor tics, or history of drug abuse.1-17

Extended-release formulations are available for many of the agents decreasing some of the difficulties associated with multiple daily dosing such as compliance, the social stigma and inconvenience of taking medications in a school setting, and the potential of drug diversion.20-22 Generic versions of amphetamines and methylphenidate are marketed in immediate-release and extended-release formulations. Atomoxetine is not yet available as a generic but may be approved for use as a first-line agent for the treatment of ADHD through the manual prior authorization (PA) process.

Narcolepsy, Hypersomnias, Obesity
Many of the stimulant agents for ADHD have FDA-approved labeling for the treatment of narcolepsy. A consensus statement in “Practice Parameters for the Treatment of Narcolepsy and other Hypersomnias of Central Origin” (2007) authored by the American Academy of Sleep Medicine, recommends the following agents for the treatment of sleepiness associated with narcolepsy; modafinil, sodium oxybate, amphetamine, methamphetamine, dextroamphetamine, methylphenidate, and selegiline.24,25 Tricyclic antidepressants and fluoxetine are effective treatments for cataplexy, sleep paralysis, and hypnagogic hallucinations. For other hypersomnias of central origin, modafinil, amphetamine, methamphetamine, dexamphetamine, and methylphenidate are reasonable options for therapy.24,25 With the exception of modafinil, which is not included as a target drug in this program, stimulant agents are available as generics and brand agents prescribed for the treatment of narcolepsy will be subject to the same PA requirements as for an ADHD diagnosis. Because the Sleep Medicine practice parameter recommends the ADHD agents, in general, for treatment of narcolepsy, the PA criteria will not differentiate the stimulants by diagnosis for the treatment of ADHD and narcolepsy. There are no generic agents in this program approved for the treatment of obesity. Desoxyn may be approved through the manual PA process when prescribed for this indication.

Off-Label Uses
The American Hospital Formulary Service (AHFS) Drug Information compendia does not recommend any off-label uses for stimulant agents or Strattera.26 However, the Clinical Pharmacology database, indicates that methylphenidate is occasionally used off-label for treatment of post-stroke depression or other depressive disorders refractory to other treatments.21 Adderall was once labeled and marketed for the treatment of obesity under the brand name Obitrol® (prior to 1994) but this indication is not included in the Adderall label.27 The PA criteria will not approve the stimulants, Strattera or Intuniv for off-label use unless the prescriber is able to provide evidence or documentation in support of use for the intended diagnosis.
Alpha-Agonists (guanfacine, clonidine)

Medications that have less extensive evidence supporting their use [off-label] in ADHD are considered for patients who do not respond or cannot tolerate first line medications, including: bupropion, alpha 2A-agonists (e.g., clonidine and guanfacine), and tricyclic antidepressants.\(^\text{20,28,29}\) Data suggests that effect sizes on ADHD symptoms for nonstimulants (e.g., alpha-agonists, atomoxetine, antidepressants) are less than those for stimulants. A meta-analysis of greater than 50 studies found the mean effect sizes for nonstimulants, immediate-release stimulants, and long-acting stimulants to be 0.62, 0.91, and 0.95, respectively.\(^\text{37}\)

There is a lack of data on safety and efficacy of guanfacine ER in adults with ADHD; studies have included children and adolescents.

The efficacy of guanfacine ER was studied for the treatment of ADHD in two placebo-controlled clinical trials (8 and 9 weeks in duration) in children and adolescents ages 6-17 who met DSM-IV criteria for ADHD. In both studies, the primary outcome was the change from baseline to endpoint in mean ADHD Rating Scale (ADHD-RS-IV) scores. The mean reductions in ADHD-RS-IV scores at endpoint were statistically significantly greater for guanfacine ER compared to placebo in each study.\(^\text{30,35,36}\)

Guanfacine has been used [off-label] in patients with ADHD and comorbid tics. Tics and ADHD symptoms commonly occur together. Data suggests that half of children with Tourette’s syndrome may experience comorbid ADHD symptoms, and about 20% of children with ADHD may develop a chronic tic disorder. Although stimulants (methylphenidate, dextroamphetamine/amphetamine) are considered the first-line treatment for children with ADHD, their use in children with comorbid tics remains controversial.\(^\text{31}\)

A meta-analysis (2009) included double-blind, randomized, placebo controlled trials examining the efficacy of medications in treatment of ADHD in children with comorbid tics (9 studies; N=477). Medications included dextroamphetamine, methylphenidate, alpha-2 agonists (clonidine and guanfacine), desipramine, and atomoxetine. Results of the analysis suggested that methylphenidate, alpha-2 agonists (e.g., clonidine, guanfacine), desipramine, and atomoxetine demonstrated efficacy in improving ADHD symptoms in children with comorbid tics. Alpha-2 agonists and atomoxetine also improved comorbid tic symptoms. None of the four medications appeared to worsen tic severity. Some data suggests that high doses of dextroamphetamine may worsen tics.\(^\text{31}\)

An open-label study in patients with suboptimal control of ADHD symptoms on methylphenidate or amphetamine alone, added guanfacine ER to their stimulant therapy for 9 weeks. Results of the study suggested coadministration of guanfacine with either methylphenidate or amphetamine did not produce unique adverse effects apart from what has been observed during monotherapy with psychostimulant or guanfacine ER pharmacotherapy. However, higher guanfacine ER doses were associated with greater mean decreases in blood pressure and pulse rate, although this relationship was not seen in the guanfacine ER + amphetamine group at the highest dose of guanfacine ER analyzed. Results suggested there were improvements from baseline (psychostimulant only) to end point in ADHD-RS-IV total score in both combination subgroups.\(^\text{32}\)

American Academy of Child Adolescent Psychiatry- Practice Parameters (2007): Bupropion, tricyclic antidepressants and alpha-agonists may have effect sizes considerably less than those of the approved agents and comparable with the effectiveness of behavior therapy. Although not as extensively studied as other agents, they have shown effectiveness in small controlled trials or open trials.\(^\text{20}\)

Alpha-agonists (clonidine and guanfacine) have been widely prescribed for patients with ADHD, for the disorder itself, for comorbid aggression, or to combat side effects of tics or insomnia. Extensive controlled trials of these agents are lacking. One small double blind trial\(^\text{33}\) showed superiority of guanfacine over placebo in treatment of children with ADHD and comorbid tics. A gradual titration is required and clinical consensus suggests alpha agonists are more successful in treating hyperactive/impulsive symptoms than inattention symptoms, although this remains to be proven by clinical trials. In recent years, clinical consensus has led to the use of clonidine as adjunctive therapy to treat tics or stimulant induced insomnia rather than as primary treatment for ADHD. If alpha agonists are deemed ineffective after an adequate trial, the medication should be tapered gradually over 1 to 2 weeks to avoid a sudden increase in blood pressure.
Side effects of alpha agonists include sedation, dizziness, and possible hypotension. In the previous decade there was controversy over the use of alpha-agonists, particularly clonidine in children. There were 20 case reports of children suffering significant changes in heart rate and blood pressure, particularly after clonidine dose adjustment. Four cases of death were reported in children taking a combination of methylphenidate and clonidine, but there were many atypical aspects to these cases. There were doubts of any causative relationship between stimulant/agonist combination and the patients’ deaths. There were no further reports of severe cardiovascular adverse events associated with clonidine use in ADHD patients. Nevertheless, physicians must be cautious. The patient’s blood pressure and pulse should be assessed periodically and abrupt discontinuations of the alpha-agonist are to be avoided. The patient and family should report any cardiac symptoms (e.g., dizziness, fainting, or unexplained change in heart rate).

A systematic review on treatment of ADHD suggests that guanfacine has a longer half-life than clonidine and appears to cause fewer problems with sedation, changes in blood pressure, and pulse vs clonidine.\textsuperscript{34}

**ELECTRONIC EDIT**
The PA criteria for adult ADHD is applied to patients aged eighteen years of age and older.

**PRIOR AUTHORIZATION CRITERIA FOR APPROVAL**

**Brand ADHD Agents**

Initial and Renewal Evaluation

1. Is the patient eighteen years of age or older?
   If yes, continue to 2. If no, refer to ADHD agents (Pediatric) Step Therapy Criteria.

2. Is the requested agent a generic stimulant for treatment of ADHD or narcolepsy?
   If yes, review does not apply. Claim will adjudicate. If no, continue to 3.

3. Has the patient been diagnosed with adult ADHD or narcolepsy?
   If yes, continue to 4. If no, continue to 7.

4. Has the patient tried and failed at least one of generic stimulant agent (amphetamine, dextroamphetamine, mixed amphetamine salts, methylphenidate, dexmethylphenidate) approved for treating ADHD or narcolepsy?
   If yes, approve indefinitely. If no, continue to 5.

5. Does the patient have an allergy, contraindication or intolerance to generic agents?
   If yes, approve indefinitely. If no, continue to 6.

6. Has the patient been prescribed Strattera or Intuniv due to comorbid conditions, concerns about controlled substance use, or after a trial and failure of a stimulant?
   If yes, approve indefinitely. If no, continue to 7.

7. Is the brand requested Desoxyn prescribed for the treatment of obesity?
   If yes, approve for 12 months. If no, continue to 8.

8. Has the physician submitted and the pharmacist reviewed evidence in support of the use of the prescribed ADHD agent for the intended diagnosis?
   If yes, pharmacist must review and may approve for 12 months. If no, deny.

**SUMMARY**
The prior authorization criteria for the ADHD agents applies to patients who are 18 years of age or older and encourages the use of brand ADHD agents for FDA labeled indications. The PA process allows approval of brand agents through the manual PA process when patients are not able to take a generic due to allergy, contraindication, or intolerance. Strattera or Intuniv may be approved if use of a controlled substance or adverse effects of stimulants are a concern or Desoxyn may be approved if prescribed for treatment of
obesity. Brand agents will be reviewed for off-label use if the prescriber submits evidence in support of use for the intended diagnosis.

REFERENCES


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**Document History**

Original Prime Standard for Strattera PA approved by External UM Committee 05/2007

Original Prime Standard for ADHD (Adult) PA criteria approved by External UM Committee 05/2008

Client Specific Initial Review, Prime Standard Criteria approved by HCSC Corporate Clinical Committee 08/2008

Annual review Prime Standard criteria approved by P&T UM Committee 05/2009

Document revised to include Procentra as target and Liquadd as generic after MSC change 5/2009

Client Specific Annual Review with changes, Prime Standard Criteria approved by HCSC Corporate Clinical Committee 09/2009

Mid-year Review Prime Standard criteria (addition of Intuniv, Focalin XR 30mg) approved by P&T UM Committee 02/2010

Client Specific Mid-year Revision Prime Standard criteria (addition of Intuniv, Focalin XR 30 mg) added per administrative actions policy 03/2010

Administrative Addition (generic methylphenidate solution) 10/2010