

## HERC Coverage Guidance – Treatment of Attention Deficit Hyperactivity Disorder Disposition of Public Comments

### General Comments

Stakeholder	#	Comment	Disposition
<i>Pediatrician</i> Salem, OR	1	This on the whole appears to be well thought out incorporation of the latest information on ADHD treatment for children. Three areas of clarification I would request:  1. Clarity around the age. Guideline is written to say older than 6. I interpret this as 7 years or older. The latest ADHD guideline separates recommendations prior to 6th birthday or after 6th birthday. Simple clarification could be "6 years and older" when age is referenced.	Guidance changed to reflect this wording.
	2	2. You quote evidence on better tolerability of methylphenidate and mixed amphetamine salts. This is well known and clinicians in my office often do start with methylphenidate products. My concern is mixed amphetamine salts are not listed in concluding paragraph as recommend treatment for children. They are FDA approved and equally effective. Many patients tolerate them better so the availability of the option needs to be clear. My concern is medical directors would interpret the concluding paragraph to imply that only methylphenidate was recommended pharmacologic treatment.	The summary paragraph only lists MPH and atomoxetine because those are the only two agents that the evidence source determined to have a low strength of evidence for long-term (>12 mo) effectiveness. The evidence source states "many researchers and clinicians assume all psychostimulants are effective and safe for extended periods of time. The documentation for this assertion is not yet robust."  The only medication for which there is evidence of poorer tolerability was guanfacine. There were no comparative long-term studies of MAS to another stimulant included in the review.
	3	3. I agree that behavior support should be first line for children prior to 6 years old. Unfortunately this service is lacking in most communities and even when available is difficult to access. A statement stating something to the effect of "if behavior therapy is unavailable for a patient or is ineffective in reaching patient and family goals, then medications should be considered." would be helpful.	According to comment #6 and #7, OPEC provides parenting education throughout much of the state.
<i>Health Plan Medical Director</i> Coos Bay, OR	4	Thanks for an excellent review. When you reviewed the evidence, did you find any evidence for doses of stimulants above the package insert recommended doses? We frequently see requests for escalating doses, yet some of my resources say there is little evidence for improvement over, for example, 30mg of Adderall XR. If there is good evidence to support escalating doses (or not escalation doses), that would be useful new clinical information for us to take to our physicians. Thanks again for your work.	For the most part, dosages were not specified in the evidence source. When they were, the highest noted dose for MPH was 54mg, for MAS was 30 mg, for atomoxetine was 2.0 mg/kg/day, for guanfacine was 4 mg/day. Table of included medications and FDA approved doses added to the guidance.

## HERC Coverage Guidance – Treatment of Attention Deficit Hyperactivity Disorder Disposition of Public Comments

Stakeholder	#	Comment	Disposition
<p><i>Physician</i> Bend, Oregon</p>	5	<p>The HERC coverage guidelines are fairly complete regarding stimulant treatment of ADHD. The guidelines do not discuss comorbid conditions and the complexity they add to treatment. Additionally, the need for school communication to obtain information on diagnosis and assess treatment is not mentioned. Frequency of follow up is also important, especially regarding monitoring and record keeping to modify treatment as needed.</p> <p>We could tie up treatment recommendations including parent training and comorbidity and expand the resources available to an interested clinician by including the American Academy of Pediatrics 2011 revised guidelines:  <a href="http://pediatrics.aappublications.org/content/early/2011/10/14/peds.2011-2654.full.pdf">http://pediatrics.aappublications.org/content/early/2011/10/14/peds.2011-2654.full.pdf</a> and the 2007 American Academy of Child and Adolescent Psychiatry recommendations:  <a href="http://www.aacap.org/galleries/PracticeParameters/JAACAP_ADHD_2007.pdf">http://www.aacap.org/galleries/PracticeParameters/JAACAP_ADHD_2007.pdf</a></p> <p>In their present form, the HERC ADHD treatment guidelines add too little to clinicians' knowledge to be helpful.</p>	<p>The guidance document is a derivative product that is based on the AHRQ systematic review of the evidence. It is not intended to serve as a practice guideline, but as a recommendation for coverage. Thank you for providing these references. They do not conflict with the coverage guidance statements.</p>
<p><i>Outreach Coordinator</i> Corvallis, OR</p>	6	<p>It is heartening to see the potential of parenting education included in the coverage for families who have young children diagnosed with ADHD in the HERC draft coverage document. Research has shown that effective early parenting contributes to later development of cognitive and social skills, positive peer relationships, and prevention of delinquency, risky behaviors, and school failure. Research also indicates that differences in parenting practices account for up to 50 percent of the gaps in school readiness. Effective parenting education programs have been linked with decreased rates of child abuse and neglect, better physical, cognitive and emotional development in children, increased parental knowledge of child development and parenting skills, improved parent-child communication, reduced youth substance abuse, and more effective parental monitoring and discipline. Of the parenting education programs suggested in the HERC document, The Incredible Years is the most widely used in Oregon. The program would be easily accessible to parents throughout the state, including rural areas.</p>	<p>Thank you for your comment.</p>
	7	<p>There are many organizations and agencies throughout the state that offer parenting education. There is not an umbrella agency in Oregon with the responsibility of overseeing the broad implementation of parenting education in the state. Therefore, it is difficult to generalize about the quality of implementation by all organizations. Oregon State University has been working for several years to evaluate and provide technical assistance to grantees funded by private foundations to provide parenting education programs in their local communities. The newest initiative is the Oregon Parenting Education Collaborative (OPEC). OPEC is a partnership between four of Oregon's largest foundations (The Oregon Community Foundation, The Ford Family Foundation, the Meyer Memorial Trust and The Collins Foundation) and Oregon State University (OSU). In addition to funding, OPEC supports grantees through evaluation, technical assistance, and professional development led by OSU. This is a multi-year grant program to support the delivery of evidence-based parenting education programs, increase access for parents to quality programs and to</p>	<p>Thank you for providing this information.</p>

## HERC Coverage Guidance – Treatment of Attention Deficit Hyperactivity Disorder Disposition of Public Comments

Stakeholder	#	Comment	Disposition
		provide leadership in coordinating existing programs within their regions. OPEC has created eleven parenting education “Hubs” that reach 19 of 36 Oregon counties. (The vision is that by 2020, the initiative would be statewide.) Grantees are held to a high degree of accountability in their delivery of evidence-based programs. All facilitators must be trained by a professional trainer representing the curricula and implemented in the recommended manner. In addition, all OPEC Hubs are extensively evaluated. Outcomes are available for individual parents, as well as for the system. For information about the OPEC initiative, visit <a href="http://www.oregoncf.org/receive/grants/grant-opportunities/ready-to-learn/parent-ed-collaborative">http://www.oregoncf.org/receive/grants/grant-opportunities/ready-to-learn/parent-ed-collaborative</a> . This webpage also has links to the OPEC First Year Report, A Snapshot of Parenting Education in Oregon, and What We Know about Parenting Education.	
	8	I believe that there is great potential for community-based organizations to meet the needs of parenting education as proposed by HERC. Many of them are prepared to fill the need immediately. If you would like more information about the evaluation we have been conducting or about OPEC, please let me know.	Thank you for your comment.
Lilly Indianapolis, IN	9	HERC has requested public comment on its draft coverage guidance on the treatment of ADHD. On page 6 of the guidance, overall summary states: <sup>1</sup> “There is evidence to support the long-term effectiveness of both methylphenidate and atomoxetine for improving ADHD symptoms, as well as methylphenidate combined with psychosocial interventions, in children age six and over.” <sup>1</sup> However, the guidance does not recommend atomoxetine. <sup>1</sup> Lilly is submitting the following evidence as supplementary support for the recommendation of atomoxetine as another first-line treatment option for ADHD.	The guidance recommends “psychostimulant medication.” While it is understood that atomoxetine is not a true stimulant, some resources refer to it as a psychostimulant. Wording changed to “pharmacotherapy,” limited to medications with FDA approval to treat ADHD.
	10	“For a decade, Oregon has led the nation in methamphetamine-treatment admissions per 100,000 people; treatment admissions for methamphetamine are second only to those for alcohol...Although many people believe those addicted to methamphetamine do not recover, their rate of recovery is about the same as that for people addicted to cocaine, heroin and other stimulants.” <sup>2</sup> Atomoxetine has not shown a pattern of response that suggests stimulant or euphoric properties. <sup>3-4,13</sup> Furthermore, clinical study data in over 2000 children, adolescents, and adults with ADHD and over 1200 adults with depression showed only isolated incidents of drug diversion or inappropriate self-administration associated with atomoxetine. <sup>13</sup>	Thank you for this information.
	11	The review did not take into account evidence-based guidelines, which HERC considers as high-medium quality evidence. <sup>5</sup> Atomoxetine use has been discussed in various guidelines. AACAP (2007) <sup>6</sup> treatment guidelines suggest “an initial treatment plan that includes atomoxetine, amphetamine or methylphenidate preparations.” <sup>6</sup> The guidelines state atomoxetine “may be considered as the first medication for ADHD in persons with an active substance abuse problem, comorbid anxiety, or tics.” <sup>6</sup> Atomoxetine is preferred in patients who experience severe side effects to stimulants, such as mood lability or tics. <sup>6</sup> CADDRA (2011) <sup>7</sup> lists atomoxetine as a first-line agent for ADHD. <sup>7</sup> The guidelines state that atomoxetine may be particularly useful to ADHD patients with tic spectrum disorders or comorbid anxiety, and resistance and/or side effects	Thank you for providing these references. AACAP guideline states, “Direct comparisons of the efficacy of atomoxetine with that of MPH and amphetamine have shown a greater treatment effect of the stimulants.” CADDRA is the Canadian ADHD Resource Alliance. EbGS does not base their

## HERC Coverage Guidance – Treatment of Attention Deficit Hyperactivity Disorder Disposition of Public Comments

Stakeholder	#	Comment	Disposition
		to stimulant medications, including problems with worsening of sleep. <sup>7</sup> NICE (2008) <sup>8</sup> recommends that healthcare professionals should consider methylphenidate or atomoxetine when tics, Tourette’s syndrome, anxiety disorder, stimulant misuse, or risk of stimulant diversion are present. <sup>8</sup> Among FDA-approved non-stimulant agents, AAP (2011) <sup>9</sup> ranks the level of evidence for the treatment of elementary school-aged children (6-11 years of age) in the order of atomoxetine, followed by extended-release guanfacine, and extended-release clonidine. <sup>9</sup>	decisions on the decisions of other guideline groups. Preferred treatment algorithms may be decided by other entities.
	12	Furthermore, the review only considered evidence up to May 2010. Since May 2010, additional evidence has been published supporting comparable efficacy for atomoxetine vs. methylphenidate in children/adolescents with ADHD (Please see attached publications for details). <sup>10-12</sup>	Preferred treatment algorithms may be decided by other entities. Hanwella: meta-analysis of 9 RCTs of atomoxetine vs. MPH, longest trial was 12 weeks. Found no difference in efficacy, response rate or acceptability (measured by all-cause discontinuation). On subgroup analysis, MPH OROS was more efficacious than atomoxetine, although immediate release MPH was not. Hazell: meta-analysis of 7 RCTs of atomoxetine vs. MPH, longest trial was 10 weeks. Found similar response rates. van Wyk: meta-analysis 7 RCTs of atomoxetine vs. MPH, longest trial was 10 weeks. Found similar response to treatment, overall, and in patients with ODD. Response based on subtype (hyperactive, inattentive) also showed no difference.
	13	In closing, atomoxetine’s value summary is: <ul style="list-style-type: none"> <li>• Atomoxetine offers continuous efficacy and has been proven effective in both hyperactive/impulsive and inattentive symptoms of ADHD.</li> <li>• Atomoxetine provides long-term control of ADHD symptoms with proven maintenance treatment in children/adolescents.</li> <li>• Atomoxetine is not a scheduled substance.<sup>13</sup></li> <li>• Atomoxetine does not worsen anxiety or tics in patients with ADHD and co-existing Tourette’s disorder or anxiety disorders.<sup>13-15</sup></li> </ul>	EbGS does not dispute the efficacy and safety of atomoxetine and other FDA approved medications for ADHD.

## HERC Coverage Guidance – Treatment of Attention Deficit Hyperactivity Disorder Disposition of Public Comments

Stakeholder	#	Comment	Disposition
		Proven safety and tolerability profile in children, adolescents, and adults.	
	14	<p><b><u>Safety and Tolerability</u></b>  <b>Please see full prescribing information for complete safety information.</b></p> <ul style="list-style-type: none"> <li>• Strattera (atomoxetine) contains a black box warning about an increased risk for suicidal ideation in children and adolescents with ADHD; therefore, anyone considering the use of Strattera in a child or adolescent must balance this risk with the clinical need. All pediatric patients who are started on therapy should be monitored closely for suicidality (suicidal thinking and behavior), clinical worsening, or unusual changes in behavior, especially during the initial few months of drug therapy or at times of dose changes, either increases or decreases.<sup>13</sup> Families and caregivers should be advised of the need for close observation and communication with the prescriber.<sup>13</sup> Strattera is approved for ADHD in pediatric and adult patients.<sup>13</sup> Strattera is not approved for major depressive disorder.<sup>13</sup> Pooled analyses of short-term (6 to 18 weeks) placebo-controlled trials of Strattera in children and adolescents (a total of 12 trials involving over 2200 patients, including 11 trials in ADHD and 1 trial in enuresis) have revealed a greater risk of suicidal ideation early during treatment in those receiving Strattera compared to placebo.<sup>13</sup> The average risk of suicidal ideation in patients receiving Strattera was 0.4% (5/1357 patients), compared to none in placebo-treated patients (851 patients).<sup>13</sup> No suicides occurred in these trials. A similar analysis in adult patients treated with Strattera for either ADHD or major depressive disorder (MDD) did not reveal an increased risk of suicidal ideation or behavior associated with the use of Strattera.<sup>13</sup></li> <li>• Strattera is contraindicated in patients known to be hypersensitive to Strattera or other constituents of the product, and in patients with narrow angle glaucoma, pheochromocytoma or a history of pheochromocytoma, or severe cardiovascular disorders.<sup>13</sup></li> <li>• Strattera should not be taken with a Monoamine Oxidase Inhibitor (MAOI) or within 14 days after discontinuing an MAOI or other drugs that affect brain monoamine concentrations.<sup>13</sup></li> <li>• Strattera can cause severe liver injury and should be discontinued and not restarted in patients with jaundice or laboratory evidence of liver injury.<sup>13</sup></li> <li>• Strattera should not be used in patients with severe cardiovascular disorders whose condition would be expected to deteriorate if they experience increases in blood pressure or heart rate that could be clinically important (e.g., 15 to 20 mm Hg in blood pressure or 20 beats per minute in heart rate).<sup>13</sup> Strattera should be used with caution in patients whose underlying medical conditions could be worsened by increases in blood pressure or heart rate such as certain patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease.<sup>13</sup> Pulse and blood pressure should be measured at baseline, following Strattera dose increases, and periodically while on therapy to detect possible clinically important increases.<sup>13</sup></li> </ul>	Thank you for this information.

## HERC Coverage Guidance – Treatment of Attention Deficit Hyperactivity Disorder Disposition of Public Comments

Stakeholder	#	Comment	Disposition
		<ul style="list-style-type: none"> <li>• Strattera at usual doses can cause treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania.<sup>13</sup> Discontinuation of treatment with Strattera should be considered if such symptoms occur.<sup>13</sup></li> <li>• Other potentially serious side effects include slowing of growth, priapism, and difficulty urinating.<sup>13</sup></li> </ul>	

DRAFT