STEP THERAPY POLICY

POLICY: Attention Deficit Hyperactivity Disorder Non-Stimulant Medications Step Therapy Policy

DATE REVIEWED: 05/06/2020

DRUGS AFFECTED:

- Strattera® (atomoxetine capsules – Eli Lilly and Company, generics)
- Intuniv® (guanfacine extended-release tablets – Shire Pharmaceuticals)
- Kapvay® (clonidine hydrochloride extended-release tablets – Shionogi Pharma)

OVERVIEW

Attention deficit hyperactivity disorder (ADHD) is a neurobehavioral disorder that typically begins in childhood and often persists into adulthood.[1] ADHD is characterized by developmentally inappropriate levels of inattention and hyperactivity resulting in functional impairment in academic, family, and social settings. ADHD is the most commonly diagnosed neurobehavioral disorder of childhood.

Numerous stimulants are approved for the treatment of ADHD in adolescents, as well as adults.[2-4] Additionally, atomoxetine capsules (Strattera®, generics) is indicated for the treatment of ADHD in children ≥ 6 years of age, adolescents, and adults.[5] Limited data are available with atomoxetine in children < 6 years of age.[6] Two alpha agonists are currently approved for the treatment of ADHD: guanfacine extended-release tablets (Intuniv®, generics) and clonidine extended-release tablets (Kapvay®, generics). Both of these agents are approved for use in children and adolescents aged 6 years to 17 years.[7,8] No controlled studies have studied guanfacine extended-release tablets or clonidine extended-release tablets in children < 6 years of age or adults. The effectiveness of guanfacine extended-release tablets and clonidine extended-release tablets for longer-term use (more than 9 weeks and 5 weeks, respectively) has not been systematically evaluated in controlled trials. However, long-term efficacy of guanfacine extended-release tablets was assessed in two 24-month open-label extension studies.[9,10]

Treatment

The American Academy of Pediatrics (AAP) clinical practice guideline for the diagnosis, evaluation, and treatment of ADHD in children and adolescents (2019) indicate that stimulants have the most evidence for efficacy and safety in the treatment of ADHD, and remain the first choice of medication treatment.[1] For preschool-aged children (4 years to 5 years of age), the primary care clinician should prescribe behavior therapy as the first line of treatment (strong recommendation). The clinician may prescribe methylphenidate if the behavior interventions do not provide significant improvement and there is moderate-to-severe continuing disturbance in the child's function. In areas where evidence-based behavioral treatments are not available, the clinician needs to weigh the risks of starting medication at an early age against the harm of delaying diagnosis and treatment (strong recommendation). For elementary school–aged children (6 years to 11 years of age), the primary care clinician should prescribe FDA–approved medications for ADHD (strong recommendation) and/or behavior therapy as treatment for ADHD, preferably both (strong recommendation). The evidence is particularly strong for stimulant medications and sufficient but less strong for atomoxetine, extended-release guanfacine, and extended-release clonidine (in that order) (strong recommendation). For adolescents (12 years to 18 years of age), the primary care clinician should prescribe FDA–approved medications for ADHD with the assent of the adolescent (strong recommendation) and may prescribe behavior therapy as treatment for ADHD (recommendation), preferably both. The dose of medication should be titrated to achieve maximum benefit with minimum adverse events (AEs).

Comparative Efficacy

Guanfacine extended-release tablets or clonidine extended-release tablets have not been compared with any of the stimulants in head-to-head studies, and they have not been compared with each other or with atomoxetine.

Several published studies[11-17] compare atomoxetine with a stimulant. More well-designed studies are needed that directly compare atomoxetine with methylphenidate and amphetamine-type products. A review article (published in 2006) evaluated five of the head-to-head comparison studies between atomoxetine and stimulants.[12] Overall, there was no difference between atomoxetine and methylphenidate immediate-release in efficacy as measured by ADHD rating scale total score; methylphenidate osmotic oral release system (OROS) showed significantly greater improvement at Weeks 1 and 2 compared with atomoxetine and more patients treated with methylphenidate OROS were considered responders; and both atomoxetine and mixed amphetamine salts (MAS) extended-release (XR) showed significant improvements at endpoint; however, Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) scores were significantly better with MAS XR.

A meta-analysis of 133 double-blind, randomized, controlled trials (published in 2018) found that all included drugs (amphetamines, methylphenidate, atomoxetine, bupropion, clonidine, guanfacine, and modafinil) were superior to placebo for clinicians' ratings of ADHD core symptoms in children and adolescents.[18] When evaluating teachers' ratings, only methylphenidate and modafinil were more efficacious than placebo. In clinicians' ratings of adults, amphetamines, methylphenidate, bupropion, and atomoxetine, but not modafinil, demonstrated improvements over placebo. With respect to tolerability, amphetamines were inferior to placebo in children, adolescents, and adults; guanfacine was inferior to placebo in children and adolescents only; and atomoxetine, methylphenidate, and modafinil were less well tolerated than placebo in adults only. In head-to-head comparisons, differences in efficacy (based on clinicians' ratings) were found that favored amphetamines over modafinil, atomoxetine, and methylphenidate in children, adolescents, and adults. Taking into account both efficacy and safety, evidence from this meta-analysis supports the use of methylphenidate in children and adolescents and amphetamines in adults, as preferred first-line medications for treatment of ADHD.

POLICY STATEMENT

A step therapy program has been developed to encourage use of a Step 1 product prior to a Step 2 product. If the step therapy rule is not met for a Step 2 agent at the point of service, coverage will be determined by the step therapy criteria below. All approvals are provided for 1 year in duration. Note: Generic guanfacine extended-release tablets and generic clonidine extended-release tablets are not included in either Step 1 or Step 2 of this program.

Automation: This program looks back for one Step 1 medication in the previous 130 days. If criteria for use of one stimulant medication within the last 130 days (automated) are not met at the point of service, coverage will be determined by the step therapy criteria below.

Step 1: generic atomoxetine capsules, stimulant medications (amphetamine and methylphenidate/dexmethylphenidate products)

Amphetamines (Note: This is not an all inclusive list.)

- Amphetamine sulfate tablets (Evekeo™)
- Amphetamine extended-release orally disintegrating tablets (Adzenys XR-ODT™)
- Amphetamine extended-release oral suspension (Dyanavel™ XR, Adzenys ER™)

- Mixed amphetamine salts [dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine sulfate, amphetamine aspartate] immediate-release tablets (Adderall®, generics)/ extended-release capsules (Adderall XR®, generics)
- Dextroamphetamine immediate release tablets (Dexedrine®, Zenzedi®, generics)/sustained-release capsules (Dexedrine® Spansules®, generics)
- Dextroamphetamine sulfate oral solution (ProCentra®, generics)
- Methamphetamine tablets (Desoxyn®, generics)
- Lisdexamfetamine capsules (Vyvanse®)

Methylphenidate/dexmethylphenidate (**Note: This is not an all inclusive list.**)

- methylphenidate extended-release tablets or capsules (Adhansia XR™, Aptensio XR™, Concerta®, Metadate® CD, Metadate® ER, Ritalin® LA, Ritalin-SR®, generics)
- methylphenidate immediate release tablets, oral solution, and chewable tablets (Ritalin®, Methylin®, Methylin® Chewable, generics)
- dexmethylphenidate immediate-release tablets (Focalin®, generics)
- dexmethylphenidate extended-release capsules (Focalin XR®, generics)
- methylphenidate transdermal system (Daytrana®)
- methylphenidate extended-release oral suspension (Quillivant™ XR, QuilliChew ER™)

Step 2: Strattera (brand), Intuniv (brand), Kapvay (brand)

CRITERIA

Exceptions for a Step 2 agent can be made for patients with one of the following conditions/situations:

1. If the patient has tried a Step 1 agent, then authorization for a Step 2 agent may be given.

2. No other exceptions are recommended.

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