Alpha-Agonist Use in Pediatric Members
A Retrospective Drug Utilization Review

The American Academy of Pediatrics (AAP) published updated guidelines for the treatment of Attention-Deficit Hyperactivity Disorder (ADHD) in 2011.

Included in the treatment guidelines are two central alpha$_{2A}$-adrenergic receptor agonists: extended-release guanfacine (Intuniv), and extended-release clonidine (Kapvay). These agents are FDA-approved for monotherapy or adjunctive therapy in elementary school-aged children and adolescents.[1]

Dosage guideline:

Extended-release clonidine (Kapvay)

- **DOSAGE:** Initial dosage of 0.1 mg at bedtime, adjusted in increments of 0.1 mg/day at weekly intervals until the desired response is achieved.
- **FREQUENCY:** Twice a day, with either equal or a higher split dosage given at bedtime.
- **NOTE:** Other clonidine products (e.g., Catapres) should not be substituted on a mg-per-mg basis.[2]

Extended-release guanfacine (Intuniv)

- **DOSAGE:** Initial dosage of 1 mg once daily in the morning or evening and adjusted at no more than 1 mg/week.
- **FREQUENCY:** Daily; not to exceed 4 mg (age 6-12) or 7 mg (ages 13-17) daily.
- **NOTE:** Immediate-release products should not be substituted on a mg-per-mg basis.[3]

Drug Utilization Review Findings:

Duplication of alpha-agonists

In a retrospective drug utilization review (DUR) of UnitedHealthcare Community Plan pediatric prescription interventions in 2017, it was found that approximately one-third of the interventions involved an alpha-agonist.

Over 1,700 of the interventions were a therapeutic duplication of alpha-agonists, predominantly involving the concomitant use of clonidine with guanfacine or immediate-release guanfacine with extended-release guanfacine.

- Clonidine and guanfacine are anti-hypertensive medications, and concomitant use may potentially result in additive pharmacodynamic effects, leading to hypotension and syncope.[4]
- The package insert for Kapvay specifically states to avoid concomitant use with other products containing clonidine (e.g., Catapres).[2]
- Per the prescribing information for Intuniv: if switching from immediate-release guanfacine (Tenex), discontinue that treatment and titrate with Intuniv as directed.[3] Though Intuniv and Tenex have the same active pharmaceutical ingredient, there is less evidence to support the use of immediate-release guanfacine for the treatment of ADHD due to the decreased effectiveness from the rapid absorption and clearance of the drug.[5]

Alpha-agonist interactions

Drug-drug interactions were also analyzed in this retrospective DUR. UnitedHealthcare Community Plan intervened on over 1,200 interactions between an alpha-agonist and mirtazapine, and almost 900 interactions between an alpha-agonist and a tricyclic antidepressant.

- There is a major interaction between mirtazapine and clonidine due to the opposing actions the drugs have on central alpha$_{2A}$-adrenergic receptors, which leads to the antagonism of the antihypertensive effects of clonidine.[6]
- Tricyclic antidepressants have many uses, including the off-label use for ADHD. Both clonidine and guanfacine have a major interaction with tricyclic antidepressants. When used concurrently, tricyclic antidepressants block the anti-hypertensive effects of alpha-agonists. There is also additive CNS depression including sedation and somnolence observed in concomitant use of these medications.[4]
- While the above interactions are focused primarily on the anti-hypertensive effects of alpha-agonists, the effect of the combination when used in patients being treated for ADHD is unclear and concurrent use of these medications should be avoided whenever possible.

Goal of the Drug Utilization Review Team

The UnitedHealthcare Community Plan retrospective drug utilization review program is administered to promote the safe and efficacious use of medications. These interventions do not take into consideration patient-specific variables. The intent of this review is to bring attention to potential medication-related issues that have been found during an analysis of the retrospective DUR data regarding alpha-agonists. Alpha-agonists have an important role in therapy and UnitedHealthcare Community Plan is committed to continuing to provide the best possible care for our members.

Working to build healthier communities.

UnitedHealthcare® Community Plan

[1]American Academy of Pediatrics, Subcommittee on Attention-Deficit Hyperactivity Disorder, Steering Committee on Quality Improvement and Management. ADHD: Clinical Practice Guideline for Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. *Pediatrics.* 2011;128:1007-1022.
[2]Kapvay [package insert]. Atlanta, GA. Shionogi Pharma, Inc.; 2010.
[3]Intuniv [package insert]. Wayne, PA. Shire US Inc.; 2013.
[4]Martin P Cruz. Guanfacine extended-release tablets (Intuniv), a nonstimulant selective alpha$_{2A}$-adrenergic receptor agonist for attention-deficit/hyperactivity disorder. P T. 2010 Aug; 35(8):448-451. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2935643/.
[5]Vanja Sikirica, Jipan Xie, Tony Lizhang He, et al. Immediate-release versus extended-release guanfacine for treatment of attention-deficit/hyperactivity disorder. *Am J Pharm Benefits.* 2013;5(4):e85-e94. [6]Clonidine. Clinical Pharmacology [Internet]. Tampa, FL: Elsevier. 2018

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