Alpha-2 Agonists for Attention-Deficit/Hyperactivity Disorder in Youth: A Systematic Review and Meta-Analysis of Monotherapy and Add-On Trials to Stimulant Therapy

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Objective: To meta-analyze the efficacy and safety of α-2 agonists in pediatric attention-deficit/hyperactivity disorder (ADHD). **Method:** We searched MEDLINE, EMBASE, Cochrane Library, CINAHL, and PsycINFO until May 2013 for randomized trials comparing α-2 agonists with placebo in ADHD youth. Primary outcome was reduction in overall ADHD symptoms. Secondary outcomes included hyperactivity/impulsivity, inattentiveness, oppositional defiant disorder symptoms (ODD symptoms), all-cause discontinuation, specific-cause discontinuation, and adverse effects. Standardized mean differences (SMD), relative risk (RR), and number-needed-to-treat/number-needed-to-harm (NNT/NNH) were calculated. Data were analyzed separately in monotherapy and as add-on to psychostimulants. **Results:** Altogether, 12 studies (N = 2,276) were included. Across 9 studies (n = 1,550), α-2 agonist monotherapy significantly reduced overall ADHD symptoms (SMD = −0.59, $p < .00001$), hyperactivity/impulsivity (SMD = −0.56, $p < .00001$), inattention (SMD = −0.57, $p < .00001$), and ODD symptoms (SMD = −0.44, $p = .0004$). Similarly, α-2 agonist add-on treatment (3 studies, n = 726) significantly reduced overall ADHD symptoms (SMD = −0.36, $p < .0001$), hyperactivity/impulsivity (SMD = −0.33, $p < .0001$), and inattention (SMD = −0.34, $p < .0001$), but effect sizes were lower than in monotherapy trials ($p = .03$–0.04). As monotherapy, α-2 agonists had lower all-cause (RR = 0.70, $p = .01$, NNT = 10) and inefficacy-related (RR = 0.39, $p < .0001$) discontinuations than did placebo; however, intolerability-related discontinuation was similar, despite significantly more common fatigue (NNH = 10), sedation (NNH = 17), and somnolence (NNH = 4) and significantly greater hypotensive (clonidine-IR), bradycardic (clonidine-IR), and QTc prolonging (guanfacine-XR) effects. Added to stimulants, α-2 agonists had all-cause and specific-cause discontinuations that were comparable to those of placebo, but somnolence (NNH = 10) was more common, and hypotensive and bradycardic effects (clonidine-XR and guanfacine-XR) were greater than with placebo. **Conclusions:** α-2 Agonist monotherapy and, possibly to a lesser extent, co-treatment, are significantly superior to placebo for overall, hyperactivity, and inattentive ADHD symptoms. Efficacy advantages need to be balanced against fatigue, somnolence/sedation, hypotension, bradycardia, and possibly QTc prolongation. J. Am. Acad. Child Adolesc. Psychiatry, 2014;53(2):153–173. **Key Words:** α-2 agonists, attention-deficit/hyperactivity disorder (ADHD), clonidine, guanfacine, oppositionality

Attention-deficit/hyperactivity disorder (ADHD) is a common childhood neurodevelopmental disorder characterized by persistent patterns of inattention, hyperactivity, and/or impulsivity that can seriously impair childhood emotional, educational, and social development.[1] In addition, ADHD can continue into adulthood.[2]

According to the U.S. National Survey of Children's Health, the percentage of children aged 4 to 17 years with a parent-reported ADHD diagnosis increased from 7.8% to 9.5% from 2003

This article is discussed in and editorial by Dr. Michael H. Bloch on page 135.

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to 2007, and 66.3% of children and adolescents with current ADHD are medicated for the disorder.[3] Stimulants and nonstimulant medications are used to treat ADHD. Meta-analyses in youth[4] and in adults[5] demonstrated superiority of stimulants over non-stimulants in the short-term, and stimulants are also recommended as mainstay treatment by the American Academy of Pediatrics.[6] Nevertheless, inadequate symptom reduction and side effects limit their use in 25% to 30% of patients.[7,8] Adverse effects of stimulants include weight loss/age-inappropriate deceleration of body weight and height increase,[9] irritability, insomnia, and tic development or worsening.[10,11] Although stimulant-related cardiovascular toxicity has been largely dispelled,[12-14] concern regarding their potential abuse has emerged. In a systematic review,[15] 5% to 9% of grade- and high-school–aged students and 5% to 35% of college-aged individuals reported nonprescribed stimulant use in the year before the study, and 16% to 29% of students with stimulant prescriptions reported diversion of their stimulants.

In this context, α-2 adrenergic agonists are considered as an alternative or adjunctive treatment to stimulants for patients with ADHD.[16] Among α-2 agonists, clonidine binds to α-2A, 2B, and 2C receptors in the prefrontal cortex (PFC), whereas guanfacine binds specifically to α-2A receptors.[17] The PFC is thought to be critical in regulating behavior, attention, and affect, via modulation of pyramidal neurons that interconnect with dendritic spines.[18,19] Although the pathophysiology of ADHD remains unclear, blockade of PFC α-2A receptors of monkeys resulted in impaired regulation of attention and behavior, with poor impulse control and hyperactivity.[20,21] Furthermore, 1 genetic study suggested the involvement of α-2C receptors in the etiology of ADHD.[22]

Clonidine and guanfacine, the immediate-release (IR) formulations of α-2 receptor agonists, which are Food and Drug Administration (FDA) approved antihypertensive medications, have been used off-label for many years for ADHD. Their efficacy for ADHD symptoms was initially demonstrated in several small trials,[23-25] supported subsequently by randomized controlled trials (RCTs).[26,27] Extended-release (XR) formulations of guanfacine and clonidine were FDA approved for pediatric ADHD in 2009 and 2010, respectively, based on several larger-scale RCTs,[28,29] increasing their use in clinical practice.

Because no formal meta-analysis has pooled the available data on α-2 agonists for pediatric ADHD, we aimed to systematically review and to meta-analyze the efficacy and tolerability of α-2 agonists compared with placebo in the treatment of pediatric ADHD. In addition to summarizing the available evidence base, we aimed to further inform clinical care by providing benchmarks that can be used to compare the effects of α-2 agonists with those reported for psychostimulants and atomoxetine.

METHOD

Eligibility Criteria and Search Strategy

Eligibility for the study was based on the following inclusion criteria: double-blind or single-blind, randomized controlled trials (RCTs) comparing clonidine or guanfacine either in IR or XR formulation with placebo; patients diagnosed with ADHD and younger than 18 years old; and, at a minimum, change or endpoint values in the means ± standard deviations of the α-2 agonist and placebo from a rating scale based assessment of ADHD symptoms, or categorical assessments of all-cause or specific-cause discontinuations, study-defined treatment response or adverse events frequencies are either published or obtainable from the authors.

To identify relevant studies, we searched MEDLINE, the Cochrane Library databases, CINAHL, EMBASE, and PsycINFO citations from database inception until May 2013, using the following key words: (clonidine OR guanfacine OR alpha 2 agonist*) AND (attention deficit OR attention-deficit OR "attention-deficit disorder with hyperactivity" OR ADHD OR "ADD" OR "inattentive" OR "hyperactiv*" OR "hyperkinetic" OR impulsiv*) AND (random* OR placebo). In addition, we contacted pharmaceutical companies that produce α-2 agonists, and searched the FDA Web site to investigate further citations. Two authors (T.H. and C.C.) scrutinized the identified studies regarding fulfillment of inclusion and exclusion criteria. The reference lists of included articles and review articles in this area were hand searched for citations of further relevant published and unpublished research.

Outcomes

A change from baseline in total ADHD symptoms scores (or, alternatively, the mean endpoint value) was used as the primary outcome measure. Total ADHD symptoms had to be based on a rating scale, including ADHD Rating Scale–IV (ADHD-RS-IV), Conners' Parent Rating Scale (CPRS), Conners' Teacher Rating Scale (CTRS), and Conners' Abbreviated Symptom Questionnaire for Teachers (ASQ-Teacher). Whenever 2 or more scales were used in the same study, the