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Alpha-2 Adrenergic Receptors and Attention—Deficit/ Hyperactivity Disorder

L. Cinnamon Bidwell, M.A.[1,2], **Rachel E. Dew, M.D., MHSc**[1], and **Scott H. Kollins, Ph.D.**[1]
[1]Department of Psychiatry, Duke University Medical Center

[2]Department of Psychology and Neuroscience, University of Colorado at Boulder

Abstract

Pharmacological management of attention-deficit hyperactivity disorder (ADHD) has expanded beyond stimulant medications to include alpha 2 adrenergic agonists. These agents exert their actions through presynaptic stimulation and likely involve facilitation of both dopamine and noradrenaline neurotransmission, which are both thought to play critical roles in the pathophysiology of ADHD. Further, frontostratial dysfunction giving rise to neuropsychological weaknesses has been well-established in patients with ADHD and may explain how alpha 2 agents exert their beneficial effects. In the following review, we consider relevant neurobiological underpinnings of ADHD with respect to why alpha 2 agents may be effective in treating this condition. We also review new formulations of alpha 2 agonists, emerging data on their use in ADHD, and implications for clinical practice. Integrating knowledge of pathphysiological mechanisms and mechanisms of drug action may inform our medication choices and facilitate treatment of ADHD and related disorders.

Keywords

guanfacine; clonidine; prefrontal; noradrenaline; ADHD

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) affects 8.7% of children [1] and 4.4% of adults [2] in the United States. This disorder conveys chronic impairment affecting individuals, families, and society at large, through lost work days[3], treatment costs [4], academic failure [5] and other complications. Pharmacological management of ADHD is the most widely used approach to treatment, and psychostimulant medications, such as methylphenidate and amphetamine-based products are the most commonly used and studied class of agents. Despite a vast literature documenting the efficacy and relative safety of this class of drugs, the psychostimulants are not recommended or sufficient for a proportion of patients. Due to side effects that range in severity from insomnia or loss of appetite to significant growth suppression, some clinicians and parents may be reluctant to use stimulant medication [6*]. Stimulant medications are also abused, diverted, and misused, particularly among adolescents and young adults, raising additional concern about their

Corresponding Author: Scott H. Kollins, Ph.D., Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Box 3431, Durham, NC 27710, Telephone: (919) 416-2098, Fax: (919) 286-7081, kolli001@duke.edu.
Addresses of co-authors:
L. Cinnamon Bidwell, M.A., Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Box 3431, Durham, NC 27710, Telephone: (919) 416-2091, Fax: (919) 286-7081, cinnamon.bidwell@duke.edu
Rachel E. Dew, M.D., Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Box 3431, Durham, NC 27710, Telephone: (919) 416-2429, Fax: (919) 286-7081, rachel.dew@duke.edu

widespread use [7]. Finally, some patients may not respond adequately to stimulants, requiring alternative or adjunctive medications [8]. Given the chronic, debilitating, and prevalent nature of ADHD, and the limitations of front-line psychostimulant treatment, continuous development and evaluation of alternative treatments for this group is imperative.

One alternative class of medications used over the last 25 years in treatment of ADHD is the alpha 2 adrenergic agonists – particularly clonidine and guanfacine. These drugs activate pre-synaptic autoreceptors that dampen adrenergic tone [8]. This property accounts for their usefulness in severe hypertension, opiate withdrawal, and pain syndromes. The precise mechanism of action for treating ADHD is not clear, but is likely to involve facilitation of both dopamine and noradrenaline neurotransmission, which are both thought to play critical roles in the pathophysiology of ADHD [9*]. Further, frontostratial dysfunction giving rise to neuropsychological weaknesses has been well-established in patients with ADHD and may explain how alpha 2 agents exert their beneficial effects [9*].

In the current review we consider relevant neurobiological underpinnings of ADHD with respect to why alpha 2 agents may be helpful in this condition. We then review new formulations of alpha 2 agonists, emerging data on their use in ADHD, and implications for clinical practice.

Neurobiology of Alpha-2 system and Relevance to ADHD

Neurobiology of adrenergic system

Basic properties of Alpha 2 Adrenoceptors—The noradrenergic system uses norepinephrine (NE) as its main chemical messenger and serves multiple brain functions, including arousal, attention, mood, learning, memory and stress response [10]. Noradrenergic neurons are localized in brainstem nuclei such as the locus ceruleus(LC), and noradrenergic axons project diffusely to almost every part of the brain [11]. NE's effects are mediated by three families of adrenergic receptors: α1, α2 and β [12]. In this review we focus on the α2 receptors, which are presynaptic and inhibitory, and consist of three subtypes: A, B and C. The three receptor subtypes are encoded by distinct intron-less genes, located in humans on chromosomes 10, 2, and 4 respectively [13]. The A subtype is the predominant subtype in the brain and is concentrated in the prefrontal cortex (PFC), but also found in the locus ceruleus, amygdala, hippocampus, and septum [14]. The B subtype is expressed primarily in the thalamus [15]. The C subtype is widely distributed in the striatum, hippocampus, and PFC [15], but has little cell surface localization [16]. Therefore, the A subtype is likely to mediate most of the central effects of alpha 2 agonists that are relevant to the pathophysiology and treatment of ADHD [13].

Alpha 2 system and Prefrontal Cortex—Noradrenaline-containing neurons of the locus LC, arising from the brainstem, form one of the ascending modulatory systems innervating the forebrain [17]. When LC neurons fire, NE is released into the PFC and works presynaptically to decrease cell firing and NE release. NE, as with dopamine, exhibits an inverted U influence on PFC cognitive functions. Moderate levels of alpha 2A receptor stimulation improve PFC regulation of attention, behavior and emotion by strengthening network connections between neurons with shared inputs [18]. However, too little or too much stimulation impairs PFC function [18].

The alpha 2 agonists clonidine and guanfacine mimic NE actions in the PFC through the stimulation of alpha 2A receptors on PFC neurons [19]. Clonidine has high affinity for all three subtypes of alpha 2 receptors (A, B, and C), as well as for imidazole I1 receptors [20, 21], which mediate many of the hypotensive effects of clonidine in the brainstem [22]. The

sedative effects are probably mediated via all three subtypes, including potent actions at presynatic receptions and actions in the thalamus [18]. Guanfacine acts more preferentially at postsynaptic NE alpha 2A receptors strengthening PFC network connectivity [18].

Alpha 2 system and ADHD—The PFC uses representational knowledge (i.e., working memory) to guide overt responses (movement) as well as covert responses (attention), allowing inhibition of inappropriate behaviors and attenuation to irrelevant stimuli [23]. Deficits in PFC function lead to poor impulse control, distractibility, hyperactivity, forgetfulness, and poor organization and planning [24]. There is general agreement that ADHD involves weakened PFC function and medications that treat ADHD ameliorate PFC deficits [25]. Although initial causal theories focused on dopaminergic dysfunction in frontal-striatal circuits, more recent work demonstrates that noradrenergic dysfunction underlies many of the cognitive and behavioral manifestations of ADHD. The work of Arnsten and colleagues has been instrumental in exploring the role of noradrenergic PFC circuitry in ADHD[9*]. For example, blockade of α2- receptors in monkey PFC with yohimbine induces a profile similar to that of ADHD: inducing locomotor hyperactivity and impulsivity, and impairing working memory [26]. Electrophysiological studies from this group have demonstrated that guanfacine enhances delay-related firing of PFC neurons, which is important for overcoming distraction and behavioral inhibition [18]. Further substantiating NE's influence on prefrontal network activity, guanfacine improved sustained attention and reduced hyperactivity in a rat model of ADHD in a dose dependent manner [27]. Below we review the current animal and human studies examining the role of the alpha 2 adrenergic system in prefrontal cognitive functions important in ADHD.

Alpha 2 agonists and cognitive function

Animal studies—Electrophysiological studies have demonstrated that the LC noradrenergic system plays an important role in arousal, vigilance, and responses to novel, salient stimuli [e.g. 28]. Studies in rodents have investigated the effects of noradrenaline lesions and administration of α2-adrenoceptor agonists on performance on a test of sustained attention and vigilance [e.g. 29]. A noradrenaline lesion in rats reduced accuracy of responding under distracting conditions, suggesting that lesion impairs information processing occurring in situations where there is a high load on attention processing resources [30]. In the same task, administration of an α2-adrenoceptor agonist, dexmedetomidine, increased omissions and decreased responding during the intertrial interval, indicative of decreased vigilance [31]. Further, low tonic levels of cortical noradrenaline are associated with increased response variability in rats [32]

The α2-adrenoceptor agonists, guanfacine and clonidine, have been shown to improve attention and working memory in rats and monkeys [19, 27, 33]. In monkeys, guanfacine improved working memory and attentional functions in a dose-dependent manner; facilitatory effects were more prominent in elderly monkeys with presumed noradrenaline deficiency [34, 35]. Working memory improvement was accompanied by reduced distractibility [36] and enhanced regional cerebral blood flow in the dorsolateral prefrontal cortex [37]. Blockade of alpha 2A-adrenoceptors in monkey PFC with yohimbine profoundly impaired spatial working memory [38] and eroded delay-related firing of PFC neurons [39]. Other research suggests that the alpha 2A-receptor subtype likely underlies guanfacine's beneficial effects on PFC function [40], as α2 agonists lose efficacy in mice with a functional knockout of the alpha 2a-adrenoreceptor subtype, but remain effective in alpha 2C-adrenoreceptor knockout mice [41, 42]. Further, the cognitive and hypotensive effects of guanfacine were reversed by idazoxan, an α2A-adrenergic antagonist [43, 44].

Human studies—There is evidence for a role for the α2-system in the modulation of attentional functions in humans: 1) In a sustained attention task clonidine impairs performance and broadens the focus of attention [45]; 2) the α2-adrenoceptor antagonist, atipamezole, improves focused attention and impairs behavioral and electrophysiological measures of divided attention [46]; and 3) another α2-adrenoceptor antagonist, idazoxan, can reverse the impairment resulting from clonidine on a focused attention task [47].

Jakala et al. [48–50] examined the effects of clonidine and guanfacine during visual memory, spatial working memory, and planning tasks in human and demonstrated that guanfacine and clonidine both improved visual memory performance, but did not affect performance when there was a delay. However, only guanfacine improved planning and working memory performance in a dose dependent fashion, and clonidine disrupted performance on these tasks. Further, only clonidine disrupted performance in an attentional task with distracters. The lower α2A- vs. α2C-adrenoceptor selectivity ratio of clonidine and the affinity for α1-adrenoceptors of clonidine may have been responsible for the different action of these drugs on attention, planning, and working memory. Indeed, α2C adrenoceptors are also found in the LC [51] and clonidine may more effectively modulate activity of these receptors than guanfacine. Therefore, it is possible that clonidine may be more effective than guanfacine in inhibiting LC firing and therefore impair function of the ascending noradrenergic fibers in the modulation of attention.

A recent fMRI study tested the role that postsynaptic α2A adrenoceptors play in the activation of dorsolateral prefrontal cortex (DLPFC) evoked by warning cues using a placebo-controlled challenge with guanfacine and found that guanfacine selectively increased the cue-evoked activation of the left DLPFC and right anterior cerebellum. These results provide supporting evidence that guanfacine selectively potentiates activation to preparatory cues in DLPFC and anterior cerebellar regions as part of a broader thalamofrontal-striatal network specialized for response preparation [52].

Other studies in healthy volunteers found no effects of alpha 2 agents on attention. One study examine the effects of guanfacine on performance and task-related brain activation as measured by fMRI during a task of visuospatial attention with variably cued choice reactions and found no changes in cognitive function [53]. Similarly, clonidine had no effect on cognitive performance in a planning task [54] and Muller et al [55] found no effects on tests of memory, planning, motor inhibition, and executive attention after guanfacine administration.

In this way, stimulation of postsynaptic α2-receptors has been shown in some studies to strengthen PFC functions in healthy humans. However these findings have not been entirely consistent across human studies and further research is needed. In addition, research comparing the classes of α2 receptors is needed to draw strong conclusions regarding potential differences among the receptors' functions.

Studies in clinical populations—Alpha 2 agents have been used to improve attention in various disorders, including schizophrenia, epilepsy, and ADHD [56–58]. Only one study has directly examined the effects of alpha 2 agents on cognitive performance in individuals with ADHD [57]. In this placebo-controlled clinical trial, children who were comorbid for DSM-IV ADHD Combined Type and a tic disorder were treated with guanfacine, which not only improved total ADHD symptoms and tic severity, but also improved their performance on measures of sustained attention and response inhibition on a Continuous Performance Task. However, additional research supports the notion that noradrenergic dysfunction may underlie many of the cognitive deficits of ADHD. In a study of children who met criteria for any DSM-IV ADHD subtype, sustained attention, response inhibition, and reaction time

variability were each correlated with noradrenergic, and not dopaminergic, metabolite measures [59]. In addition, studies have shown that selective norepinephrine transporter blockers improve cognitive deficits in ADHD. For example, in children with ADHD, deficient stop signal reaction time (SSRT) was improved by desipramine, a noradrenaline re-uptake inhibitor [60]. Similarly, Chamberlain et al. [61] showed that atomoxetine, a selective noradrenaline reupkate inhibitor, improves response inhibition and working memory deficits in adults with ADHD.

Genetic underpinnings

The α2A-receptor gene (*ADRA2A*) and the dopamine β-hydroxylase (the enzyme needed for the synthesis of NE) gene (*DBH*) have both been associated with ADHD, although these associations are not entirely consistent across studies [62]. However, results of a recent meta-analysis showed significant heterogeneity in associations between ADHD and both *ADRA2A* and *DBH* genes, indicating that there may be important variables (e.g. ADHD subtype, gender, cognitive or environmental risk factors) moderating the relationship between noradrenergic genetic variants and ADHD. Studies have begun to examine the association with genotype to putative cognitive endophentypes of ADHD. The *ADRA2A* gene has been associated with working memory and arousal on executive function tasks in individuals with ADHD [63]. Similarly, variation in the *DBH* gene has been related to deficits in executive function and the ability to sustain attention [64, 65]. These studies suggest that weaker NE production may impair the PFC circuits mediating the regulation of attention and behavior.

Clinical Use of Alpha 2 Agonists in ADHD

Alpha 2 agonists have held a place among standard ADHD treatments for over twenty-five years, primarily useful as adjunctive or alternative agents to stimulant drugs. Providers have tended to consider this class in patients with pre-existing tic disorders, with tics emerging during stimulant therapy, or those who for other reasons are unable to tolerate psychostimulants. Until recently, however, use of alpha 2 agents represented “off-label” therapy in that no drug in this class had received FDA approval for treatment of ADHD. This has changed with the 2009 FDA approval of Intuniv® (guanfacine XR) for treatment of ADHD in children and adolescents. In addition, a long-acting form of clonidine, a frequently used alpha 2 agonist, is being developed for use in ADHD.

Older Alpha 2 Agents

The first alpha 2 agonist widely used in ADHD was clonidine hydrocloride, an imidizoline derivative originally developed, and still used as, an anti-hypertensive agent [66]. Through down-regulation of norepinephrine release from the locus ceruleus, the drug has been found helpful in management of ADHD symptoms, as well as other neuropsychiatric symptoms such as motor and vocal tics, aggression, opiate withdrawal, and insomnia. A 1999 meta-analysis including 11 clinical trials of clonidine in ADHD found it beneficial with a moderate effect size of 0.58, confirming the clinical usefulness of the drug but also its inferiority to stimulant medication in providing symptomatic relief [67]. Drawbacks to treatment include multiple daily dosing, and the occurrence of sedation, irritability, low blood pressure, and rebound hypertension.

Guanfacine hydrocloride was developed in the late 1970s as another centrally-acting antihypertensive; it is a phenylacetylguanidine derivative and more selective for alpha 2 adrenoceptors than is clonidine. Other advantages of guanfacine include a longer half-life enabling less frequent dosing, as well as evidence of less sedative and hypotensive side effects [68]. Its use in ADHD is supported by two small double-blind randomized trials and

several open label studies. In one randomized controlled trial in children and adolescents, guanfacine showed superiority to placebo in reducing teacher-rated, but not parent-rated, ADHD symptoms [69]. A double-blind crossover study in 17 adults with ADHD found superiority to placebo and did not find a difference in efficacy of guanfacine versus dexamphetamine [70].

New Alpha 2 Agents for ADHD

Guanfacine Extended Release—Although evidence for efficacy of immediate-release guanfacine in ADHD is sparse, an extended-release form of this drug has been more extensively studied. This drug, marketed as Intuniv®, has recently received FDA approval for treatment of children and adolescents aged 6–17 with ADHD. Guanfacine extended release (GXR) offers the advantage of once-daily dosing. Phase I studies indicated linear pharmacokinetic properties, and failed to demonstrate either rebound hypertension following abrupt discontinuation or significant adverse cardiovascular effects [71–73]. In three double-blind placebo controlled trials, involving a combined 884 child and adolescent subjects, guanfacine XR showed superiority to placebo in reducing symptoms measured by the ADHD Rating Scale—IV, the Clinical Global Impression--Improvement scale, and other measures of ADHD symptomatology [6*, 74*, 75]. These three trials evaluated doses of 1–4 mg, dosed daily. Somnolence, headaches, and fatigue were common side effects seen in the active drug groups. In none of the three studies were clinically meaningful changes in vital signs or serious treatment-emergent adverse events observed.

In addition to short-term efficacy, research has confirmed long-term benefits of GXR in ADHD. A two-year open-label follow-up study of GXR in children and adolescents, with or without co-administration of stimulants, demonstrated continued efficacy and similar side effect profile seen in short term RCTs. However, over 75% of the subjects dropped out prior to the end of the study [76]. A second two-year open study following an RCT found monotherapy with GXR to be efficacious and well-tolerated, again in the context of >75% drop-out. The most common side effects were somnolence and headache. Slight changes in pulse, blood pressure, and QT interval were clinically insignificant. Syncope occurred in two subjects [77].

Clonidine Modified Release—Currently being considered for FDA approval to treat ADHD is a modified release (MR) from of clonidine, to be marketed as Clonicel® by Addrenex Pharmaceuticals. At this time, two Phase III randomized, double blind, placebo-controlled studies have been completed evaluating efficacy clonidine in children and adolescents with ADHD. One of these assessed clonidine MR as monotherapy, while another studied it as an add-on agent in subjects on a stable but non-optimal stimulant drug regimen. In both trials, clonidine MR significantly reduced ADHD symptoms from baseline and was well-tolerated. A long-term open-label study is currently underway to investigate the efficacy and safety of this agent over one year; interim safety data showed that chronic dosing was well tolerated [78, 79].

Conclusions and Summary

Relevance for clinical management of ADHD

Clonidine and guanfacine have been shown to be effective for the treatment of hyperactivity, impulsiveness, and inattention across several studies. After nearly three decades of experience with clonidine, its advantages and disadvanges are well known. While support remains sparse for immediate release guanfacine as an efficacious treatment for ADHD, substantial evidence demonstrates the efficacy of extended release guanfacine in the treatment of children with ADHD. In 2009, Intuniv® (guanfacine XR) was the first among

alpha 2 agents to be FDA approved for use for treatment of ADHD in children and adolescents. In addition, a long-acting form of clonidine, a frequently used alpha 2 agonist, is in the process of being developed for use in ADHD.

These developments will facilitate treatment of the substantial minority of ADHD patients who cannot be managed with stimulants. Such patient groups may include those with tic disorders, congenital heart defects, genetically mediated heightened risk for sudden cardiac death, adults with unstable hypertension or coronary artery disease, or children at risk for significant growth suppression.

Relevance for helping better understand pathophysiology of disorder

Although substantial evidence suggests ADHD is associated with low levels of striatal dopamine [80], ADHD is not a unitary disorder. The behavioral and cognitive manifestations of ADHD are not easily explained by the reduced dopamine hypothesis alone. The role of NE in the pathophysiology of ADHD is supported by many converging lines of research. Animal and human studies support the role of NE in many of cognitive deficits found in ADHD, i.e. working memory, vigilance, response variability, and planning. In addition, there is substantial support in animals that many of these deficits are ameliorated by alpha 2 agonists used to treat ADHD. However, studies in humans are more mixed with regard to the effects of alpha 2 agonists on cognitive function. Further evidence from genetic studies suggests that variation in genes that responsible for NE production can disrupt the PFC circuits mediating the regulation of attention and behavior. It is likely that a combination of both dopaminergic and noradrenergic disruptions are critical in explaining the heterogeneous cognitive deficits and behavioral symptoms of ADHD.

Future directions

With a broader armamentarium of medication options from which to choose, clinicians may be able to more precisely match patients with favorable treatments. Such precision would save health care costs by reducing the need for multiple drug trials and unwarranted polypharmacy. Future work involving the alpha 2 agonists should seek to decipher which symptoms and/or patient types are most responsive to these agents. Data indicate that increasing NE levels in the PFC is effective in the treatment of ADHD. Further, NE disruptions are important in the prefrontal deficits associated with ADHD. A better understanding of the neurobiological circuitry underlying attention and impulse control and their relationship to genetic and environmental insults will improve our ability to match treatments with individual needs of patients.

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