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Abstract: Background: Attention-deficit/hyperactivity disorder (ADHD) is a widespread diagnosis that affects many children and adolescents’ ability to function and succeed in academics, socially, or other situations. Non-stimulant medications have become widely utilized in this population, especially in stimulant-resistant individuals, whether due to poor efficacy or intolerance of side effects. However, these, too, harbor their own side effect profiles, including cardiovascular and sleep or energy level disturbances.

Objectives: We review the literature in discussion of the presentation and management of these adverse events for non-stimulant medications for ADHD, with a particular focus on atomoxetine and alpha agonists guanfacine and clonidine.

Conclusion: Non-stimulants are for the most part well tolerated but monitoring for cardiac and sleep difficulty is warranted.

Keywords: Mental health, children and adolescents, psychopharmacology, ADHD, attention deficit disorder, atomoxetine, alpha agonists.

1. INTRODUCTION

The management of attention-deficit/hyperactivity disorder (ADHD) focuses on regulating functionally impairing symptoms of excessive inattention, hyperactivity and impulsivity to allow people to function well. This disorder affects about 5% of children and adolescents globally, impacting academics, family, and social activities [1]. There are many efficacious and well-tolerated options for the management of ADHD, stimulants are primarily used due to a larger effect size [2]. Non-stimulant drugs are widely practiced when symptoms are poorly controlled, when patients have contraindication or experience intolerable side effects of stimulants, or history of drug abuse. Among the most common and well-tolerated non-stimulants utilized to treat child and adolescent ADHD are atomoxetine and the alpha-adrenergic receptor agonists clonidine and guanfacine.

Atomoxetine acts similarly to stimulants, by increasing synaptic cleft noradrenaline and dopamine availability. Thus, it may lead to similar side effect profiles to amphetamines including raising heart rate and blood pressure, which should then be monitored. Alpha 2-adrenergic agonists, particularly clonidine and guanfacine have been used for the treatment of ADHD for over three decades [3]. Both are available in immediate-release and extended release forms, with varying side effects.

Guanfacine especially as an add-on therapy has been linked to improvements in prefrontal cortical cognitive function and working memory, with significant improvements in children’s symptoms as
measured by ADHD Rating Scale version IV (ADHD-RS-IV) scale compared to baseline, Clinical Global Impression-Improvement (CGI-I) scale, and the Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P; learning and school, and family domains) when compared to placebo [4]. However, these too require blood pressure monitoring but for hypertensive effects. Both atomoxetine and alpha 2 agonists mentioned above have also been associated with sleep disturbance. Here, we review the most significant side effects of non-stimulant drugs for ADHD and their management.

2. ADVERSE EFFECTS

2.1. Cardiac Effects

2.1.1. Clinical Aspects

Similar to stimulants such as amphetamines, atomoxetine has been reported to result in a similar increase in systolic and diastolic blood pressures and heart rate, which is a theoretical risk factor for cardiovascular morbidity and mortality in adults [5].

Due to its mechanism of action, guanfacine has been shown to lower heart rate and vascular resistance, and therefore blood pressure [6, 7]. Immediate release guanfacine has been shown to lead to decreased heart rate which self-resolved with sustained therapy, and tolerably decreased systolic and diastolic blood pressures [8] Compared to clonidine, it results in a lesser degree of hypotension and sedation [9].

An array of common medications can lead to orthostatic hypotension, including alpha agonists/anti-hypertensives such as clonidine that are also used to treat ADHD [10]. Orthostatic hypotension results when autonomic compensatory mechanisms are insufficient or impaired [10]. Symptoms include dizziness, lightheadedness, or unsteadiness upon standing.

2.1.2. Management

Due to atomoxetine’s effect of sympathomimetic increases in systolic and diastolic blood pressure and heart rate, these vital signs should be closely monitored in those prescribed this drug [5]. Thus, it is contraindicated for those with cardiovascular diseases that could be exacerbated by elevated heart rate or blood pressure [11, 12]. Post-approval, clonidine was also reported to worsen cardiac conduction abnormalities including sinus node dysfunction and AV block [13, 14].

Nonpharmacologic therapy for orthostatic hypotension typically starts with discontinuing the offending medication, or administering it at bedtime instead of during the day [15]. A different medication in the same class with a lower risk of hypotension may be trialed in lieu of the offending agent. For example, guanfacine has a lower degree of hypotension reported compared to clonidine [9]. Dietary modifications have also been shown to be beneficial in raising blood pressure including limiting carbohydrate-rich meals, avoiding alcohol, ensuring adequate hydration of about 2 to 2.5 L fluid daily and cautiously increasing salt intake to 6 to 10 g sodium chloride [16].

Inability to tolerate the sympathomimetic effects of atomoxetine may warrant a trial of an alpha 2 agonist such as guanfacine, which typically has the opposite effect on blood pressure and heart rate compared to atomoxetine [17]. Some experts suggest that using a combination of guanfacine intermediate release and dexmethylphenidate extended release can attenuate the cardiovascular side effects of monotherapy with either one [8].

2.2. Sleep Disturbance, Fatigue and Others

2.2.1. Clinical Aspects

Multiple studies have reported that guanfacine tends to be well-tolerated in children [8, 18, 19]. In a phase III randomized controlled trial of children taking guanfacine extended release form for ADHD, about 70% of subjects reported mild to moderate but tolerable side effects. The most commonly reported adverse effects are somnolence/sedation, headache and fatigue [8, 19, 20]. Adverse effects rarely lead to discontinuation of guanfacine monotherapy, with somnolence/sedation and fatigue being the most likely reason if seen [19, 21]. Rugino (2014) reported preliminary evidence that guanfacine extended release is associated with decreased sleep time and daytime somnolence [22]. Immediate-release alpha2-adrenergic receptor agonists, clonidine and guanfacine, require frequent dosing, with subsequently reported side effects of dry mouth and sedation [23, 24].
Atomoxetine typically has a mild side effect profile. In a randomized double-blind phase IIIb study, it was reported that generally atomoxetine was well-tolerated with mostly mild to moderate adverse effects [25]. The most common side effects include headache, nausea, somnolence, decreased appetite and fatigue with 10-16% of study participants reporting each. Less than 10% experienced weight loss, insomnia/sedation, vomiting, nasopharyngitis, dry mouth, abdominal pain, irritability, diarrhea or constipation [25]. Reversibility of the growth deficit was reported in the longer term, although the study could not account for the effect of puberty or constitutional growth delay on the increased growth velocity [26]. The FDA safety also warns of risk of hallucinations reported by those using clonidine and guanfacine; however, this is infrequent and management is usually discontinuation of the drug.

2.2.2. Management

Similar to the management of most adverse events, discontinuing the offending medication may help to restore sleep patterns and pre-medication states. Proper sleep evaluation - sleep diary or polysomnography - is important to diagnose pre-existing sleep difficulties. If central or obstructive sleep disorder breathing is ruled out, consider a trial of melatonin. Since sleep interference can be due to rebound effects, dosing atomoxetine at night is recommended [27-30]. The majority of the reported side effects may be managed supportively; this includes increased fluid intake for dry mouth, headache due to dehydration (as well as vomiting and diarrhea) or over-the-counter analgesics for headache and abdominal pain.

In order to minimize the dry mouth and sedative effects of clonidine and guanfacine, some clinicians prefer the extended-release forms of these drugs; both of these are approved for both monotherapy and adjunctive with stimulants in children and adolescents in the United States [31].

Alternatively, one may use a trial of a medication of the same class with less sleep disturbance reported. For example, ADHD monotherapy with extended release form of guanfacine tends to be less sedating than extended-release clonidine [32].

CONCLUSION

Non-stimulant medications for ADHD include atomoxetine and alpha agonists. Adverse effects include cardiovascular, sleep disturbance, and fatigue. Principles of management are considered. Helping patients understand potential side effects and their management will improve overall benefit and acceptance of patients as well as families for these medications.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

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REFERENCES


