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Non-Stimulant Treatment for Attention Deficit Hyperactivity Disorder

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD), as defined in *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV), is a disorder of childhood onset and is characterized by symptoms of inattentiveness and hyperactivity-impulsivity. Based on the type of symptoms that predominate, ADHD, if further sub-classified, is a combined type in which both inattention and hyperactivity-impulsivity symptoms are present, a predominantly inattentive subtype, and a predominantly hyperactive-impulsive subtype. There is also a separate category of ADHD not otherwise specified (NOS) for individuals with atypical features.

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EPIDEMIOLOGY

It is estimated that ADHD affects up to five percent of school-age children. Approximately 2 to 2.5 percent of all school-aged children in North America receive pharmacological intervention for hyperactivity.[1]

However, its effect on society in terms of financial cost,

health/school/social service utilization, and the stress to families is enormous.

ETIOLOGY

The precise etiology of ADHD is unknown. Family, genetic, twin, and adoption studies strongly suggest a genetic etiology. Dysregulation of dopamine and norepinephrine neurotransmitters are thought to be responsible for the clinical manifestations of ADHD.

TREATMENT

Ideally, a biopsychosocial approach should be used in the treatment of ADHD to obtain and maintain successful treatment. However, the discussion of all the treatment approaches is beyond the scope of this article. Here we discuss mainly the role of non-stimulants in the treatment of ADHD.

Stimulants. Stimulants are the first class of compounds reported as effective in the treatment of hyperactivity and disruptive behaviors in ADHD.[2] Clinical experience and the studies done so far suggest that up to 70 percent of the patients respond to a stimulant[3] and if two stimulants are used consecutively, the response rate could be as high as 80 to 90 percent.[4]

Despite the proven safety and efficacy of stimulants since 1937, alternative medications have been explored for several reasons:

1. Response—Approximately 30 percent of the patients do not respond adequately to stimulants.[5]
2. Side effects—The most common side effects associated with stimulants are appetite suppression and sleep disturbances. Less common but equally troublesome side effects include headaches, abdominal discomfort, increased lethargy, and fatigue. The cardiovascular side effects include increased heart rate and blood pressure, which may be of significance in patients with cardiovascular problems. Occasionally stimulant-induced psychosis can also occur. Another stimulant, magnesium pemoline, has been associated with a hypersensitivity reaction involving the liver. Therefore, baseline and repeat liver function studies are recommended with the administration of this compound. The US Food and Drug Administration (FDA) now mandates liver function monitoring every two weeks when pemoline is used.
3. Tics—It has long been suspected that stimulants are associated with the development of tics.[6] However, recent studies have questioned this assumption.[7] A recent study found no difference in the incidence of tics between placebo and methylphenidate.[8] But more information is needed, and long-term data might be helpful to come to a definitive conclusion.
4. Controlled substance—All stimulants are controlled substances and are associated with all the Drug Enforcement Agency (DEA) restrictions in terms of special prescriptions and not allowing telephone refills. This can cause hardship on the physicians, the patients, and the patients' families.
5. Abuse potential—Although none of the studies have shown that stimulants are abused when prescribed and monitored carefully, the potential for abuse still remains.
6. Concerns about the long-term administration of stimulants, especially regarding growth suppression—Although there are conflicting reports, several studies showed that ultimate height appears to be unaffected if treatment is discontinued in adolescence.

Non-stimulants. The non-stimulants used in the treatment for ADHD can be classified into the following:

1. Tricyclic antidepressants
2. Non-tricyclic antidepressants
3. Specific norepinephrine re-uptake inhibitors
4. Alpha-2 noradrenergic agonists
5. Non-schedule stimulants
6. Others.

CLASSIFICATION OF NON-STIMULANTS USED FOR ADHD

1. **Tricyclic antidepressants**
2. **Non-tricyclic antidepressants**
3. **Specific norepinephrine re-uptake inhibitors**
4. **Alpha-2 noradrenergic agonists**
5. **Non-schedule stimulants**
6. **Others**

Tricyclic antidepressants (TCA). To date, tricyclic antidepressants have the most evidence for the treatment of ADHD in the non-stimulant category. Out of 33 studies (21 controlled, 12 open) evaluating in children and adolescents (n=1139), and adults (n=78), 91 percent reported improvement in ADHD symptoms.[9] Of all the TCAs, imipramine and desipramine are the most studied.[10]

Desipramine was shown to be superior to placebo in a double-blind, placebo controlled trial. The effect size was found to be similar to stimulants. In this randomized, placebo-controlled, parallel-design, six-week clinical trial, desipramine was found to be effective in 62 children with ADHD, most of whom had failed to respond to a stimulant. Clinically and statistically significant results were found for desipramine (average daily dosage 5mg/kg) over placebo. In addition, desipramine-treated patients showed a significant reduction in depressive symptoms compared with patients who received placebo.[11] Desipramine was also found to be effective in the treatment of ADHD symptoms in adults. In a similar trial with 41 adults who had ADHD, desipramine was statistically and clinically more effective than placebo. Sixty-eight percent of the desipramine-treated patients responded compared with none of

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the placebo-treated patients (P<0.0001). In this study, the average daily dosage was 150mg, and the average serum levels were 113ng/mL. It is to be noted that although the full desipramine dose was achieved at Week 2, the clinical response improved further over the following four weeks, indicating a latency of response. Response was independent of dose and the serum desipramine levels, sex, or psychiatric comorbidity with anxiety or depressive disorders.[12]

Despite all the evidence, desipramine has fallen out of favor because of the concerns raised by the sudden and unexplained deaths of four children who were treated with desipramine.[13] Although a causal link between these deaths and desipramine was never established, clinicians by and large use imipramine and nortriptyline as second line agents. Imipramine has been extensively studied in the treatment of ADHD.[14] Imipramine is typically started at a divided dose of 1mg/kg/day, with titration to doses of 2.0 to 2.5mg/kg/day over a 1 to 2 week period. If the response is inadequate or no response is noted, the dose is increased at a rate of 1mg/Kg/day/week, for up to a maximum of 5mg/kg/day. At doses greater than 2mg/kg/day, serum levels should be obtained to ensure they are below 200ng/mL. Once stable, blood levels and an EKG should be repeated annually or whenever a dose adjustment is made.[15] Nortriptyline was studied in a prospective, placebo-controlled discontinuation trial. The subjects were 35 school-age children and the dose of nortriptyline was increased up to 2mg/kg/day. In that study, 80 percent of the subjects responded by Week 6 in the open phase. During the discontinuation phase, subjects randomized to placebo relapsed, while those receiving nortriptyline maintained the efficacy.[16] Another TCA, protriptyline, was tried in a treatment-refractory ADHD patients but the response was not significant.[17]

TCAs should be started at a low dose and titrated carefully. Prior to starting any TCA, an electrocardiogram (EKG) should be obtained. During treatment heart rate should be monitored and periodic EKGs are also recommended. If necessary, serum levels of TCAs should also be obtained. Medication interactions should also be considered, especially those that inhibit cytochrome P450 2D enzymes. These drugs can elevate TCA levels to dangerous levels.[15] Despite these limitations, TCAs are still used as second-line agents and are found to be effective in a subgroup of patients who do not respond to stimulants. Also, they are useful in patients who have experienced exacerbations of tics with stimulants.

Non-tricyclic antidepressants. Bupropion is a dopamine and norepinephrine re-uptake inhibitor. It has been shown to be effective for ADHD in children and adults. In a multisite, double-blind, placebo-controlled, parallel-group study, bupropion was found to be superior to placebo in the treatment of ADHD in children.[18] In another study, bupropion, in a dose of up to 400mg/day, was found to be superior to placebo in adults. The response peaked in Weeks 5 and 6 of the study.[19] A recent study used bupropion SR in an open trial in 35 adult patients who had comorbid bipolar disorder. The subjects received up to 400mg/day of bupropion (mean: 362mg/day) and were assessed for both bipolar and ADHD symptoms at the end of six weeks. Significant reduction in both ADHD and symptoms and Young Mania Rating Scale were noted.[20] However, it is to be noted that there is a huge overlap in symptoms of ADHD and mania. Bupropion is associated with a risk of drug-induced seizures (0.4%). However, this is seen mainly with high doses, a history of seizures, and eating disorders.

Venlafaxine is a serotonin and norepinephrine reuptake inhibitor. It has been used in treatment of ADHD with varying success. Several open studies found venlafaxine to be effective in decreasing the ADHD symptoms, but most of these studies also reported high dropout rates due to side effects. The most important side effect was an increase in hyperactivity.[21]

Few studies suggest that monamine oxidase inhibitors (MAOIs) may be effective in ADHD. However, the potential for hypertensive crisis associated with the irreversible MAOIs, drug interactions, and the dietary restrictions have limited their use.

Atomoxetine is one of the newer additions to the armamentarium of non-stimulants used in the treatment of ADHD. It is a spe-

cific norepinephrine reuptake inhibitor. This drug has been extensively studied and has been approved by the FDA for the treatment of ADHD. To date there are four randomized, double-blind, placebo-controlled trials (two in children and two in children and adolescents).[10] In one of these studies, children and adolescents were randomized to different doses of atomoxetine (0.5, 1.2 and 1.8mg/Kg/day) in two divided doses or placebo for a period of eight weeks. Atomoxetine showed a graded dose response and the best response was noted at a dose of 1.2 or 1.8mg/kg/day. This study also used The Child Health Questionnaire to assess the well being of the child and the family. Atomoxetine in this study showed a dose-dependent improvement in the social and family functioning.[22] Two studies compared atomoxetine with methylphenidate. The results suggest that atomoxetine might be comparable in terms of clinical effect, but more data is needed to establish this.[23,24] Atomoxetine also has an excellent safety profile. It is usually well tolerated and the common side effects reported are mild appetite suppression and sleepiness. Mild increases in heart rate and diastolic blood pressure were also noted, but they did not cause any symptoms and did not worsen at one-year follow up.[25] Atomoxetine may be particularly useful in patients with ADHD who have a comorbid substance abuse disorder or tic disorder.

Alpha-2 adrenergic agonists. Clonidine and guanfacine are the two drugs that have been used from this class to treat ADHD. Although clonidine is widely used in the treatment ADHD in children there is limited evidence for its safety and efficacy.[26] Some argue that the efficacy of clonidine is secondary to non-specific sedative effect leading to decreased agitation rather than having any effect on cognition.[15] A double-blind, placebo-controlled trial published by National Institute of Neurological Disorders and Stroke is worth mentioning. It compared the efficacy of methylphenidate, clonidine, methylphenidate in combination of clonidine and placebo in a 16-week trial. The combination was found to be superior to both medications on their own, and methylphenidate also reduced the tics. However, the increased benefits because of clonidine in the combination group came at the expense of more side effects, particularly sedation. It is important to note that there are four sudden deaths reported in patients taking a combination of methylphenidate and clonidine.[26]

Guanfacine, another alpha-2 adrenergic receptor agonist, has very little data. There are only three small open studies and one small double-blind, placebo-controlled trial. Guanfacine was found to be effective in the treatment of ADHD symptoms. However, further evidence is required to prove its efficacy and safety.

All alpha-agonists are associated with certain unknown effects on blood pressure. Alpha-agonists should be tapered off gradually and despite this, elevated levels of blood pressure were noted in adult volunteers for up to two weeks.[15]

Non-schedule stimulant. Modafinil is a non-schedule stimulant approved by the FDA for the treatment of narcolepsy and sleep problems associated with shift work. The exact mechanism of its action is not known. However, it is believed to be a histaminergic agonist in hypothalamus and stabilizes the orexins, leading the activation of hypothalamus. A small open trial found modafinil to be effective in the treatment of ADHD symptoms.[27] Another randomized, double blind, placebo-controlled crossover study of modafinil and dextroamphetamine found both drugs to be equally efficacious and superior to placebo.[28] However, further studies are required to definitely confirm their efficacy.

Others. Beta-blockers (propranolol, nadolol, and pindolol) have been studied and all of these were found to be effective mainly in decreasing the angry outbursts, aggression, and behavioral problems.[10] No definitive effects were noted on the cognitive symptoms.

Buspirone, an anxiolytic, is a 5-HT1A receptor agonist and is used to treat anxiety disorders. An open study of 12 children with ADHD reported that buspirone at a dose of 0.5 mg/kg/day improved both ADHD symptoms and psychosocial

Although stimulants still remain the primary treatment, there is a growing trend in using non-stimulants, especially if the stimulants do not adequately treat the symptoms, are not tolerated, or are in the presence of contraindications for the use of stimulants.

function. However, these findings were not replicated in further studies.

Typical antipsychotics have been tried and found to have some efficacy,[5] but the long-term side effects limit their use in ADHD.

Literature review suggests that carbamazepine, an anti-epileptic, may be useful in ADHD.[29]

CONCLUSIONS

Today, the clinicians have a wide variety of non-stimulants for the treatment of ADHD. A large amount of research and data support the use of non-stimulants in ADHD. Although stimulants still remain the primary treatment, there is a growing trend in using non-stimulants, especially if the stimulants do not adequately treat the symptoms, are not tolerated, or are in the presence of contraindications for the use of stimulants.

Extensive ongoing research in this fascinating field is aimed not only at understanding the neurobiology of ADHD, but also at developing newer and more efficacious drugs. Hopefully, this will result in a variety of new drugs that are safe and effective.

DRUG KEY

Atomoxetine—Strattera®
Eli Lilly
Bupropion—Wellbutrin®
GlaxoSmith Kline
Buspirone—Buspar®
Bristol-Myers Squibb Co.
Clonidine—Catapres®
Boehringer Ingelheim
Desipramine—Norpramin®
Aventis
Dextroamphetamine—Adderall®
Shire Pharmaceutical
Imipramine —Tofranil®
Ciba Geigy
Methylphenidate—Ritalin®
Novartis Phaarmaceutical
Modafinil—Provigil®
Cephalon
Nortriptyline—Aventyl®
Eli Lilly
Protriptyline—Vivactil®
Merck & Co.
Venlafaxine—Effexor®
Wyeth Pharmaceutical

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