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This October is the month of "Moving Forward with ADHD", according to ADHD Awareness Month Coalition https://www.adhdawarenessmonth.org[1] In this edition of *AU Informed* we will be discussing this disease state in preparation for October as it is ADHD Awareness Month.

Key Inforbits

- What is ADHD?
- Pathophysiology & Etiology
- The 3 Types of ADHD
- Treatments: Stimulants vs Non-stimulants
- Other Medications Used in ADHD
- Recent News

What is ADHD?

ADHD is attention deficit/hyperactivity disorder. It is characterized by impairment in ability to self-regulate arousal and inhibit behavior according to socially acquired rules of conduct.[2]

Background[2-4]

ADHD is a well-known and heavily researched psychiatric condition. It is commonly diagnosed in childhood, though it is also prevalent in adulthood. Within the last 10 years, diagnosis of ADHD has increased significantly. According to a meta-analysis, published in JAMA, looking at trends in prevalence of ADHD in 5,282,877 patients of different ethnic/racial groups, ADHD diagnosis has increased among adults since 2007.[3] Investigators suspect this increase is related to an increased awareness of this disorder.

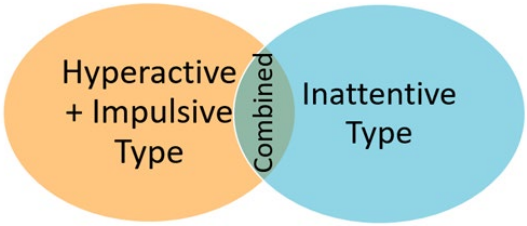
About 5-10% of children and 2.5-5% of adults have ADHD. Patients most likely to be affected by this condition are male Caucasian or African American children. Understanding the affected population is important, but what causes this condition? The exact pathogenesis is not fully understood, however the most commonly accepted hypothesis is a decrease in certain neurotransmitters in the brain. This deficiency can be attributed to 1 of 2 factors-genetics and environment. Genetics play a major role in ADHD. "ADHD is 74% genetic in origin."[2] This was confirmed by incidence of the condition in first-degree relatives as well as studies in twins. Decreased brain volume, delay in cortical maturation, and dysregulation of normal processes in the brain are all attributable to genetics. Secondarily, there are many environmental factors that may contribute to the etiology of ADHD. These include young mothers, premature birth, and prenatal exposure to smoke from the mother. Anatomy and metabolism also may play a role.

Table 1: The 3 Types of ADHD[5]

Hyperactive and Impulsive Type	Inattentive Type
-Fidgeting with hands and feet, being unable to sit still -Leaving their seat unexpectedly, for example, during class or meetings -Often feeling restless -Unable to take part in leisure activities quietly -Perceived as restless, hard to keep up with, or "always on the go" -Tendency to talk excessively -Blurting out answers before a question or sentence is complete -Difficulty waiting their turn -Interrupting or intruding on what other people are doing	-Losing or misplacing important items -Often distracted by unrelated thoughts -Often forgetting to complete daily activities -Short attention span and difficulty remaining focused -Poor listening skills and inability to pay attention when spoken to directly -Unable to finish tasks or follow instructions -Avoiding work that requires sustained attention and mental focus -Unable to pay close attention to details, resulting in careless mistakes -Difficulty organizing tasks, time, or workspace

ADHD Types

Combined Type: Patients may exhibit symptoms that don't exclusively fall under the category of hyperactive/impulsive behavior or inattentive behavior. In that case, they may be diagnosed with combined type ADHD.



Treatment [2]

ADHD is thought to be caused by low levels of neurotransmitters such as dopamine and/or norepinephrine. Dopamine plays a role in reward, risk, and impulse, while norepinephrine plays a role in attention and arousal. Therefore, in order to treat ADHD, one approach is to increase these neurotransmitters in the brain. This can be done by using stimulants, which are the first-line therapy, or by using nonstimulants.

Stimulants[2,6]

These medications work primarily by increasing dopamine and norepinephrine. Common side effects are reduced appetite, headache, and insomnia. More rare/severe side effects of this class are psychosis, severe anxiety, sudden death in patients with a history of cardiac abnormalities, and stunted growth.

Table 2: Stimulant Medications[6]

Type	Generic	Brand	Mechanism of Action	Adverse Reactions
Short Acting, IR	Dexmethylphenidate hydrochloride*	Focalin	Blocks norepinephrine and dopamine reuptake	Headache, insomnia, decreased appetite, anxiety, jitteriness, abdominal pain
Short Acting, IR	Methylphenidate hydrochloride*‡	Methylin Chewable, Methylin Oral Solution, Ritalin	Blocks norepinephrine and dopamine reuptake	Dizziness, headache, insomnia, dry mouth, decrease appetite, nausea
Short Acting IR	Dextroamphetamine mixed salts and amphetamine†‡	Adderall	Promote release of dopamine and norepinephrine and block the reuptake of catecholamines	Decreased appetite, abdominal pain, headache, insomnia, anorexia
Short Acting, IR	Methamphetamine hydrochloride‡	Desoxyn	Increases release of dopamine. Inhibits reuptake of catecholamines.	Increased blood pressure, palpitations, tachycardia, GI distress, dizziness, dry mouth, trouble sleeping, weight loss
Short Acting, IR	Amphetamine sulfate†‡	Evekeo, Evekeo ODT	Increases release of dopamine. Inhibits reuptake of catecholamines.	Dizziness, dry mouth, headache, GI distress, insomnia, weight loss, feeling nervous
Short Acting, IR	Dextroamphetamine Sulfate‡	Zenzedi	Increases release of dopamine. Inhibits	Decreased appetite, headache, trouble sleeping, upset stomach, nervousness

			reuptake of catecholamines.	
Long Acting, XR/ER	Methylphenidate HCl ER[*‡]	Concerta, Quillichew XR, Jornay PM	Blocks norepinephrine and dopamine reuptake	Dizziness, headache, insomnia, dry mouth, decrease appetite, nausea
Long Acting XR/ER	Serdexmethylphenidate and dexmethylphenidate[*‡]	Azstarys	Blocks norepinephrine and dopamine reuptake	Dizziness, headache, insomnia, dry mouth, decrease appetite, nausea, weight loss
Long Acting XR/ER	Methylphenidate[*‡]	Cotempla XR ODT, Daytrana (patch)	Blocks norepinephrine and dopamine reuptake	Decreased appetite, nausea, headache, insomnia, irritability, dermatitis with Daytrana
Long Acting XR/ER	Dexmethylphenidate hydrochloride[*‡]	Focalin XR	Blocks norepinephrine and dopamine reuptake	Headache, insomnia, decreased appetite, anxiety, jitteriness, abdominal pain
Long Acting XR/ER	Dextroamphetamine mixed salts and amphetamine[†‡]	Adderall XR	Increases release of dopamine. Inhibits reuptake of catecholamines.	Abdominal pain, insomnia, headache, decreased appetite, systolic hypertension
Long Acting XR/ER	Amphetamine[†‡]	Dyanavel XR, Adzenys XR ODT	Increases release of dopamine. Inhibits reuptake of catecholamines.	Abdominal pain, decreased appetite, insomnia
Long Acting XR/ER	Mixed salts of a single entity amphetamine[†‡]	Mydayis	Increases release of dopamine. Inhibits reuptake of catecholamines.	Insomnia, decreased appetite at a young age
Long Acting XR/ER	Lisdexamfetamine dimesylate[*‡]	Vyvanse, Vyvanse Chewable	Increases release of dopamine. Inhibits reuptake of catecholamines.	Insomnia, decreased appetite, abdominal pain, xerostomia

Black Box Warnings: [*]Dependence [†]Cardiovascular events [‡]Abuse potential

Non Stimulants [2,6]

These medications work primarily by norepinephrine reuptake inhibition and alpha-2 agonism. These are not as effective as stimulants, however they provide good alternatives when first-line therapies cannot be used. Benefits of using non-stimulants include lack of abuse potential and decreased side effects. Side effects vary based on class and MOA.

Table 3: Non-Stimulant Medications[6]

Generic	Brand	Mechanism of Action	Adverse Reactions
Atomoxetine HCl*	Strattera	Selective norepinephrine reuptake inhibitor	Upset stomach, decreased appetite, fatigue, sedation, dizziness, cardiac adverse events
Viloxazine*	Qelbree	Selective norepinephrine reuptake inhibitor	Somnolence, decreased appetite, fatigue, nausea, vomiting, insomnia, irritability
Clonidine HCl †	Kapvay	Alpha 2 Adrenergic agonist	Sedating, dizziness, headache, abdominal pain
Guanfacine HCl	Intuniv	Alpha 2 Adrenergic agonist	Constipation, xerostomia, dizziness, drowsiness, fatigue
Bupropion*	Wellbutrin	Dopamine/Norepinephrine-Reuptake Inhibitor	Tachycardia, weight loss, constipation, nausea, agitation, dizziness, insomnia, blurred vision

*Black Box Warnings: *Suicidal ideation †Epidural Use*

Other medications [7-9]

While current recommended therapies, especially stimulants, are effective for ADHD, side effects and abuse plague these medications. It is important that ongoing research is being conducted on other options for the treatment of this disorder. With the increase in diagnoses, it is important to remember that not all patients will respond the same to all medications. Having multiple treatment options allows for individualization of therapy. Medications that may be helpful in the future for ADHD are listed below.

SNRIs - Strattera (atomoxetine) is an SNRI approved for treatment of ADHD, though there is not a universal recommendation for the entire class. Studies have been conducted in the past to determine if any other SNRIs would be effective. One SNRI in particular that has been researched is duloxetine. Two studies were conducted looking at the effects of duloxetine on ADHD. The first recruited 17 adolescents while the second consisted of 30 adults. The dose used was 60 mg/day and the studies each lasted 6 weeks. Both studies had similar results-ADHD symptoms were improved with duloxetine, but adverse events were intolerable, leading to dropout. Current data on alternative SNRIs, specifically duloxetine, is not conclusive and should be investigated further, ideally in larger controlled trials that escalate dose slowly to minimize the impact of adverse events on therapy retention.

NMDA receptor antagonists - Another class of medications with potential efficacy for ADHD are the NMDA receptor antagonists. Amantadine and memantine are noncompetitive antagonists of NMDA receptors, which increase dopamine release and inhibit dopamine reuptake. Currently, they are used for dementia treatment. Amantadine was studied in a double-blind randomized controlled trial in 40 children, in which it was

dosed at 100-150 mg compared to methylphenidate 20-30 mg. Surprisingly, there was no difference in efficacy while side effects such as decreased appetite and restlessness were increased in the methylphenidate group. This trial shows promising results, although larger trials need to be conducted in order to confirm efficacy and safety. The other NMDA receptor antagonist mentioned earlier-memantine-has also been a medication of interest for the treatment of ADHD. It has been tested in several trials involving adults and children with sample sizes ranging from 12-40. Results from these trials showed that memantine was effective in reducing ADHD symptoms and had similar efficacy to methylphenidate. However, these same trials also had high dropout rates and tolerability issues in the memantine groups. Overall, amantadine seems to show the most promise within this class of medications. Memantine may also be useful in the future. Larger trials looking at efficacy and safety of these drugs for the use of ADHD would be interesting and beneficial.

TCAs - Tricyclic antidepressants have not been approved by the FDA for ADHD treatment but have been used off-label. This class has been a consistent topic of research for ADHD with over 33 trials looking at over 1000 patients of all ages. Of these trials, 91% show efficacy for treatment of ADHD. Side effects of this class include excessive sweating, dry mouth, constipation, blurred vision, hypertension or orthostatic hypotension, and prolonged QT interval. Authors have expressed different opinions about the effectiveness of TCAs as treatment for ADHD. While some point out that they are effective in decreasing hyperactivity, others note that they do not seem to help inattentive symptoms. When used as off-label treatment, desipramine is not the preferred second-line agent due to safety concerns in children; nortriptyline and imipramine are typically used.

Other stimulants - Modafinil and armodafinil are characterized as central nervous system stimulants and work by increasing the amount of dopamine in the brain. However, they differ from amphetamines as they have lower affinity for dopamine receptors. Despite this difference, these medications are often used off-label for the treatment of ADHD. There is not sufficient research regarding these medications and their use in ADHD treatment. One meta-analysis published in 2018 compared several different approved and off-label ADHD medications to each other and placebo in order to assess efficacy and tolerability. Over 18,000 adults and children were included in the efficacy assessment, while 16,000 were included in the tolerability arm. Conclusions of this study were that modafinil is less effective and less tolerated than placebo.

In order to make any conclusions about alternative medications for the treatment of ADHD, further, more in-depth studies are required. The most promising medication seems to be amantadine, while others are hindered by their side effect profile.

Recent News

Medication Shortages [10,11] Drug shortages are a problem that pharmacies across the nation are facing. From antibiotics to weight loss medications, patient care is being hindered by supply shortage. ADHD medication is not exempt from these problems. There has been a shortage of these medications since 2022. This is likely due to the increase in ADHD diagnosis and prescriptions, especially within the last 10 years. According to the FDA's website, current shortages include:

- Methylphenidate IR, ER, film-coated
- Amphetamine Aspartate Monohydrate, Amphetamine Sulfate, Dextroamphetamine Saccharate, Dextroamphetamine Sulfate tablets

- Vyvanse 60 + 70 mg tablets

These medications are all stimulants-which are our first-line therapy for ADHD. However, these are not our only options. With school having started within the last two months, ADHD diagnosis and medication prescribing is at its peak. With limited stimulant options, we may see an increase in non-stimulant medications. As mentioned previously non-stimulant medications have a different mechanism of action, but still counteract hyperactivity/inattention.

Vyvanse Generic is Now Available [12]

Vyvanse is one of the most prescribed stimulants used in the treatment of ADHD. It is also one of the more expensive ones, with the average cost being $300-$400 for a 30 day supply without insurance. This high cost is due to Takeda Pharmaceuticals, having an (previous) active patent that prevents competitor products. However, once the patent expires, other drug companies can manufacture their own generics typically at a much cheaper cost. Takeda's patent for Vyvanse expired in February of this year, and the FDA approved multiple generics in August. This should help combat increased costs of ADHD medications. It will also help to address the ongoing stimulant medication shortage, as there will be increased supply of lisdexamfetamine dimesylate, though it may take several months for production to catch up.

Summary

ADHD is a common psychiatric condition more commonly affecting male children. There are several factors that contribute to development of ADHD, but the most likely are environmental and genetics. First-line treatment are stimulants which have common side effects of appetite suppression, headache, and insomnia. Unfortunately, these medications are currently in shortage, therefore, we may see an uptick in the prescription of nonstimulants. Examples of this treatment group are atomoxetine and guanfacine. One stimulant in particular, Vyvanse, has recently become available as a generic and may be able to help alleviate this medication shortage. Other less well known medications may potentially have a role in treatment including memantine, duloxetine, and modafinil. October is ADHD Awareness Month, therefore, it is important that we educate our communities, ask questions, and share experiences with the condition.

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The last "dose" …

I have not failed. I have just found 10,000 ways that won't work
-Thomas Edison [American inventor, 1847 – 1931]