Attention Deficit Hyperactivity Disorder

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Attention-deficit Hyperactivity Disorder is one of the most common childhood mental health disorders, affecting about 5.6% of the population worldwide.

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1. Attention Deficit Hyperactivity Disorder Overview

ADHD exhibits a complex etiology integrating genetic and environmental factors for studied cases [1][2][3][4]. Further updates in the research literature have advanced our understanding of the disorder [5]. Existing family and twin studies support genetics as an important factor in the onset of ADHD [6]. Specifically, twin studies have concluded that the heritability of ADHD is estimated to be 60–90% [6][7][8][9]. However, when evaluated based on isolated genes and risk variants, ADHD demonstrates a poor correlation to any specific gene [10][11].

ADHD typically has had an onset at a young age. In 2013, the DSM V updated the age limit for the onset of qualifying symptoms for ADHD from age 6 to age 12 to prevent the misdiagnosis of normal inattention symptoms in the pediatric population [12]. For diagnosis, adolescents (17 years or older) can display less hyperactive or inattentive symptoms (at least five). Increasingly, it has become accepted that ADHD can exhibit a late manifestation or maintain symptoms throughout adulthood [13][14][15][16]. As a baseline for diagnosis, ADHD must also be present in at least two settings where symptoms present in various environments like the home and school.

1.1. Pathophysiology

ADHD presents a variety of cognitive and functional deficits which originate from abnormalities in the brain [17]. The two most common theories surrounding the mechanisms of ADHD involve a top-down and bottom-up model. Top-down models emphasize cognitive control and executive functioning. Specifically, abnormal executive function manifesting as impaired response inhibition has been used to explain the cognitive symptoms of ADHD [18][19][20][21]. In contrast, bottom-up models emphasize motivational, incentive, or reward responses.

The use of brain imaging has helped researchers elucidate the mechanisms behind ADHD [22][23]. Specifically, structural imaging studies using MRI have determined abnormal symptoms arising from a smaller size of the cerebrum, cerebellum, anterior cingulate cortex, and dorsolateral prefrontal cortex. Imaging studies also support theories about brain developmental patterns, as studies evaluating cortical thickness reported a delay in growth among ADHD patients [24][25]. An imaging study using MRI found widespread changes in the maturation of white matter fiber bundles and gray matter density in the brain which lead to structural shape changes in the middle and superior temporal gyrus, and fronto-basal portions of both frontal lobes [26]. On the circuitry level, dysfunctions in the super longitudinal fasciculus and cortico-limbic areas are found in those with ADHD [26]. These morphological findings predicted an ADHD diagnosis correctly in up to 83% of the cases in this imaging study [26]. Furthermore, imaging for ADHD has also supported top-down and bottom-up theories by visualizing the structural environment of the brain [27].

1.2. Epidemiology

Previous studies have estimated that ADHD affects approximately 2–7% of the global population [28][29][30][31]. Subsequently, the prevalence of ADHD in adults (between 19 and 45 years) has been estimated at 2.5% [32] where 40–60% exhibit partial remission of symptoms [33]. The most comprehensive meta-analysis, which was conducted by Polanczyk and colleagues, estimated a prevalence of 5.29% based upon 153 evaluated studies [29]. Variability in prevalence values reflected differences in diagnostic criteria, information sources, and functional impairment requirements [28][33][34]. Additionally, point prevalence did not change from 1985 to 2012 or between geographical regions across the globe [29][34].

2. Treatment

Pharmacologic treatments for ADHD can be divided into non-stimulants and stimulants. Stimulants, including amphetamine and methylphenidate-based medications, are considered first-line in treating ADHD in children and adults [35]. These stimulants boost arousal in the prefrontal cortex by increasing norepinephrine and dopamine concentrations in the brain [36]. Increasing synaptic dopamine and catecholamine are main mechanisms of action of both methylphenidate and amphetamine. However, there are specific differences that affect how they alter concentrations [35]. The stimulant methylphenidate exerts its effects by inhibiting the dopamine transporters (DAT) and norepinephrine transporters (NET). It increases dopaminergic neurotransmission by inhibiting presynaptic DAT and, as a result, reuptake at the synapse [35][36].

Studies have demonstrated that methylphenidate directly interacts with adrenergic receptors to stimulate excitability in the cortex via activation of a2 adrenergic receptors [35]. Methylphenidate also exerts agonistic activity at the 5-HT1a receptor [35]. This results in the elevation of extracellular dopamine and norepinephrine levels, and as a result, increased binding to their respective receptors [35].

Another stimulant used in treating ADHD is an amphetamine salt, whose primary mechanism of action is to increase catecholamine release [35]. It acts as a competitive inhibitor of DAT and as a pseudo-substrate at norepinephrine binding sites. It acts to increase dopamine release by inhibiting the VMAT-2, or vesicular monoamine transporter 2, and it also inhibits monoamine oxidase activity to decrease the cytosolic breakdown monoamines [36]. Both methylphenidate and amphetamine increase dopamine release, which increases responsiveness to external stimuli [35][36]. These stimulants have *d* and *l* isomers, with the *d* isomer being more potent than its *l* counterpart. Specifically, the *d* isomer is more potent at the norepinephrine transporter and dopamine transporter binding sites b [36].

Non-stimulant medication treatment includes atomoxetine and bupropion. Although the mechanism is not completely clear, atomoxetine is thought to selectivity inhibit norepinephrine uptake and preferentially binds to areas of known high distribution of noradrenergic neurons [37]. Bupropion is an anti-depressant that has a variety of uses, including depression, anxiety, ADHD, and smoking cessation. Its mechanism of action likely involves the reuptake inhibition of the catecholamines, dopamine, and noradrenaline [38]. This mechanism is like the one for psychostimulants, but bupropion is not a controlled substance. Clonidine is another choice, which is an alpha 2 adrenergic receptor agonist. Clonidine is good for impulsivity and hyperactivity but not useful for symptoms of inattention [39]. Guanfacine is a direct alpha 2α subtype agonist within the central nervous system leading to reduced peripheral sympathetic outflow and strengthening of regulation of both attention and behavior within the prefrontal cortex through modulation at norepinephrine receptors [39]. Its actions are found in the locus coeruleus and can result in improved attention [39]. Clonidine and Guanfacine are considered second or third-line treatments after the use of stimulants has failed [40].

3. Attention Deficit Hyperactivity Disorder and Bipolar Disorder

There is an overlap in terms of symptoms when looking at ADHD and BD. These two disorders often co-occur, and they are associated with worse outcomes [41]. There is evidence that children with ADHD have a higher risk of being diagnosed with BD later in life [42]. There have been attempts to develop neuropsychological testing that can better identify those with both disorders. However, research has shown that these tests have limited power to differentiate between BD adults with and without childhood ADHD [41].

Symptoms of both ADHD and BD can have overlap which will be further explored in the next section. Mania is associated with bipolar disorder and is highlighted with increased energy and disorganized thinking with the inability to plan which can be seen in the increased goal-related activity. These are things that are also seen in ADHD. Other mood disorders such as depression and anxiety can have decreased concentration, which can also be seen in ADHD. So, at times, it can be hard to separate what diagnosis is correct because of the overlapping symptoms.

Treatment is a question that has been looked at in the research as the overlapping symptoms that cause issues and distress to the patient may be worsened by traditional ADHD treatment of stimulants. There is concern that the use of stimulants may worsen mania and psychosis and further debilitate the patient [42]. A study performed by Galanter et al. suggests that youth treated with stimulants did not have an increase in mania or psychotic symptoms [43]. Furthermore, children in the first month of treatment who had ADHD symptoms and manic symptoms had a more robust response to stimulant treatment. However, the studies in adults are less promising. In a review of three cases, the use of stimulants increased psychosis in patients [44]. The authors concluded that patients need to be monitored for adverse responses to treatment. In the next section, the review will look at the clinical studies regarding the overlap of ADHD and BD.

Genome Wide Association Studies

There have been studies that have looked at genetic loci as conferring genetic risk for both bipolar disorder and ADHD. Demonitis et al. performed a genome-wide association study (GWAS) on 20,183 individuals with ADHD and 35,191 controls [45]. The study found around 2932 genes that showed significant association with ADHD [45]. They found that there was also a genetic correlation with both schizophrenia and bipolar disorder, however, this was not significant.

Another GWAS was performed by Mullins et al. looked at genes that could be associated with the increased risk of developing BD [46]. They performed a GWAS of 41,917 BD cases and 371,549 controls of European ancestry. Their study found 64 associated genomic loci in their study population. These risk alleles were genes in the synaptic signaling pathways and brain-expressed genes, which had high specificity of expression in neurons of the prefrontal cortex and hippocampus [46]. These are also areas that are implicated to be dysfunctional in ADHD; however, the authors made no connections to ADHD in their study so only references can be drawn.

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