Attention Deficit Hyperactive Disorder: Pathophysiology, Pharmacological, and Nutrition Treatments.

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Abstract

Attention deficit hyperactive disorder (ADHD) is one of the most common neurological disorders among children with approximately 5.4 million children diagnosed in the United States. Inattention and hyperactivity are two major symptoms associated with ADHD interfering with the ability to function well at school or work. The etiology of ADHD is very complex involving genetics, brain structure and function, and neurotransmitters. Stimulant medication is the most common method for treating ADHD, though nutritional therapies are becoming more popular due to the side effects of stimulant medication. Holistic approaches to ADHD treatment have shown promise as an effective treatment for the disorder.
Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurocognitive disorders among children with eight to twelve percent of children being diagnosed with the disorder (Verlaet, Noriega, Hermans, & Savelkoul, 2014). Approximately 5.4 million children in the United States between the ages of 4-17 have been diagnosed with ADHD (Johnson et al., 2011). For as many as 60% of those diagnosed with ADHD as a child the symptoms persist into adulthood representing 4-5% of the adult population (Dela Pena & Cheong, 2013; Rucklidge, Johnstone, Gorman, Boggis, & Frampton, 2013). The main symptoms of ADHD are hyperactivity, impulsivity, and inattention (Verlaet et al., 2014). Those who have ADHD tend to achieve lower levels of both education and employment accompanied by higher levels of unemployment (Mueller & Tomblin, 2012). ADHD is the subject of much research because of its prevalence and the difficulties associated with the disorder.

The pathophysiology of ADHD has been studied a great deal, though the etiology of the disorder are not fully understood. Neurological abnormalities lead to a decrease in neurotransmitters crossing synapse in the brain of those with ADHD (Kar, 2013). The cause of these abnormalities has been linked to structural changes in the brain, genetics, and environmental factors all of which contribute the symptoms associated with ADHD (Bush, Valera, & Seidman, 2005; Choudhry et al., 2012). It is difficult to determine the cause of the disorder because of the complex interactions between the factors influencing ADHD.

Almost half of the children in the United States who have been diagnosed ADHD are being treated with medication (Johnson et al., 2011). Stimulant medication is the most common treatment for ADHD, with methylphenidate being the most frequently prescribed (Dela Pena, Kim, Han, Kim, & Cheong, 2013). Stimulant medications have been shown to be an effective ADHD treatment, though the occurrence of side effects is driving the search for alternative
treatments (Karpouzis & Bonello, 2012; Ryan, Katsiyannis, & Hughes, 2011). Nutritional therapies are a one of the most common alternatives to traditional medication with as many as 12% of children diagnosed with ADHD using alternative treatments (Karpouzis & Bonello, 2012).

Ever increasing data indicates possible treatments for this complex disorder. However, more research needs to be conducted to understand the physical and chemical interactions and make recommendations for treatment.

Pathophysiology

It has long been suspected that dopamine and norepinephrine play a critical role in the pathophysiology of ADHD. This idea was first suggested in 1937 by Charles Bradley in a study where Bradley observed 30 children that exhibited the symptoms now known to be associated with ADHD. Bradley gave these children a mixture of amphetamine called Benzedrine for a week. There were improvements seen in 15 of the subjects in school and in the way they interacted with other children (Kar, 2013). This initial study lead to other studies examining the effects of dopamine and norepinephrine on ADHD, and the etiology of the problems with these neurotransmitters.

The problems with the dopamine and norepinephrine pathways most likely involve the prefrontal cortex and subcortical regions of the brain (Mueller & Tomblin, 2012). Prefrontal regions of the brain assist executive function. Thought processing in these areas is inhibited by ADHD (Valera, Faraone, Murray, & Seidman, 2007.)

Studies have shown dopamine levels are affected by a combination of factors associated with ADHA. First, an increase in the amount of dopamine transporter leads to an increased reuptake of dopamine. This increased reuptake reduced the amount of dopamine in the synapse
(Kar, 2013). However, the studies showing the increase in dopamine transporters were conducted with children that had been treated with psychostimulant medications. Subjects tested that were drug-naïve were found to have lower dopamine transporter levels, suggesting the increased dopamine transporter may have been caused by the stimulant exposure (Fasar-Poli, Rubia, Rossi, Sartori, & Balotn, 2012). Second, dopamine receptor activity and dopamine transporters are reduced in the midbrain and striatal regions. Both areas are associated with attention and motivation (Kar, 2013). Third, reduced dopamine synthesis has been shown in the prefrontal cortex of ADHD subjects resulting in reduced amount of dopamine it the synapse (Kar, 2013). The association of lower dopamine levels with ADHD is supported by these findings.

Many researchers have used structural imaging techniques in an attempt to discover the cause of dopamine deficiencies. In these studies normal brains and brains of people with ADHD are compared looking for structural differences. The most common imaging techniques used in studying ADHD are single photon emission computed tomography (SPECT), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI). The frontal, parietal, occipital, and temporal lobes, as well as, the caudate, cerebellum, and regions of the corpus callosum have all been shown to be smaller in children with ADHD (Valera et al., 2007). Children with ADHD have been shown to have 3-5% smaller cerebrum, with the right hemisphere having a larger disparity than the left (Seidman, Valera, & Makris, 2005).

The anterior cingulate cortex has been studied in great depth. This area is of interest because it is thought to play a major role in cognitive processing, target detection, response selection and inhibition, error detection, performance monitoring, and motivation, ADHD subjects struggle with all these challenges (Bush et al., 2005). Using fMRI and the Counting
Stroop test, Bush et al. (1999) showed the anterior cingulate did not activate in children with ADHD the way it did in a control group of normal children. In this same study, Bush et al. (1999) did see that different areas of the brain activated. Indicating that children with ADHD may process information differently than children without ADHD.

The prefrontal cortex is associated with organization, planning, working memory, attention, and motor movement. The knowledge that patients with prefrontal cortex damage show impairment in some tasks associated with it contributed to the interest in the prefrontal cortex activity in ADHD (Tsujimoto et al., 2013). The dorsolateral prefrontal cortex and orbital frontal areas of the prefrontal cortex are thought to be involved with ADHD (Seidman et al. 2005). Structural imaging studies have shown the prefrontal cortex to have reduced volumes in ADHD leading to the prefrontal cortex being an area of interest (Bush et al., 2005). Verbal working memory tasks have shown reduced activation in the right prefrontal region in adults with ADHD (Valera et al., 2007). Tsujimoto et al. (2013) using functional near-infrared spectroscopy, showed hyperactivity in the prefrontal cortex in children with ADHD when performing working memory tasks with distractors. Also using near-infrared spectroscopy Negoro et al. (2009) found that the prefrontal cortex of ADHD children were not as active as normal children when performing Stroop color-word tasks. Supporting the idea the prefrontal cortex is an area involved in ADHD.

Basal ganglia or striatum which includes the caudate and the putamen is also associated with executive functions. Therefore it is an area of interest in ADHD. Dopamine transporter abnormalities have been found in the striatum adding to the suspicion the striatum is involved with ADHD (Bush et al., 2005). Dopamine transporter binding in the basal ganglia has been shown to be significantly higher in drug-naïve children with ADHD supporting the idea that
dopamine abnormalities are a key cause of ADHD (Cheon et al., 2003). Boys with ADHD have been shown to have smaller volume and different shaped basal ganglia than boys without ADHD (Qiu et al., 2009). Qiu et al., (2009) used large deformation diffeomorphic metric mapping to get more detailed structural images showing compressions and expansions of the basal ganglia of boys with ADHD. The areas of the basal ganglia showing shape differences are associated with many different frontal-subcortical circuits indicating ADHD has a multifractal pathophysiology (Qiu et al., 2009). However, Qiu et al., (2009) did not find these same basal ganglia differences in girls with ADHD.

The cerebellum is strongly linked with the prefrontal cortex and the basal ganglia indicating a strong possible relationship with these areas and ADHD (Ivanov, Murrough, Bansal, Hao, & Peterson, 2014). Attention shifting, visual-spatial processing, working memory, and emotion have all been linked to the cerebellum (Ivanov et al., 2014). Reduced activation in the left cerebellum as well as in the contralateral right prefrontal cortex during working memory tasks in children with ADHD support the idea the cerebellum plays a role in the disorder (Valera et al., 2007). Using diffusion tensor imaging Ashtari et al., (2005) found that children with ADHD had reduced white matter tracts in the left middle cerebellar peduncle, and left cerebellum. They also found the larger the deficit in white matter, the larger the severity of inattention scores on the Conner’s Attention Deficit Scale. Reduced cerebellar volumes have been consistently shown to negatively correlate with attention problems (Seidman et al., 2005). Using magnetic resonance imaging, it has been shown that children with ADHD have smaller volumes in the left anterior cerebellar hemisphere and right cerebellar crus when compared to normal children (Ivanov et al., 2014). They also found increased symptoms of hyperactivity and inattention have been associated with smaller cerebellar volumes. Magnet-resonance-
spectroscopy has shown there are neurochemical alterations in the cerebellum of adults with ADHD that may interfere with dopaminergic neurotransmission (Perlov et al., 2010).

Seidman et al. (2005) found differences in the size of the posterior portion of the corpus callosum in children with ADHD. Differences were found in the splenium that links the parietal, temporal, and occipital cortexes (Hutchinson, Mathias, & Banich, 2008). More severe attention problems have been connected with smaller spleniums and overall corpus callosum volumes (Kayl, Moore, Slopis, Jackson, & Leeds, 2000). Sustained attention and divided attention are functions of the parietal region suggesting that smaller splenium volumes in children with ADHD may lead to difficulties with inattention (Hutchinson et al., 2008). The memory problems associated with ADHD may also be caused by inattention issues.

Single photon computed emission tomography has shown decreased activity in the prefrontal cortex orbits, prefrontal cortex poles, posterior frontal regions, cerebella, right parietal, and right occipital lobes in older ADHD patients (Amen, Hanks, & Prunella, 2008). Amen et al. (2008) looked at 21 regions of interest and found differences in 16 of these regions with significant differences in the areas previously listed. Amen et al. (2008) findings support the role executive dysfunction is a part of the cognitive and behavioral manifestations of ADHD. A study using functional magnetic resonance imaging found decreased activation in the parietal cortex, including posterior cingulate, bilateral occipital, pons, cerebellum, and the temporal lobe (Silk, Vance, Rinehart, Bradshaw, & Cunnington, 2008). Silk et al. (2008) results indicate there may be a wide spread effect inhibiting the visuo-spatial information processing of children with ADHD. Both studies support the idea that multiple areas of the brain are contributing to the manifestations of ADHD.
Attention deficit hyperactivity disorder is familial and inheritable indicating ADHD may have a strong genetic factor. Approximately 30%-35% of children with a first degree relative with ADHD will also have the disorder, making these children six to eight times more likely to have the ADHD (Faraone & Biederman, 2000). Even nonaffected siblings of children with ADHD have shown impairments when compared with controls who have no family history of the disorder, indicating either a genetic factor, an environmental factor, or both are involved (Albrecht et al., 2014). When looking at the possible genetic component of ADHD, it is important to note that no single gene has been shown to have significant associations with ADHD (Bralten et al., 2013). This suggests the combination of many small multiple genes effects may be the cause of ADHD (Martin, Hamshere, Stergiakouli, O’Donovan, & Thapar, 2014). This combination effect makes it very difficult to determine which genes may cause ADHD. Martin et al, (2014) suggest the traits that contribute to ADHD are common among the general population. However, those with a clinical diagnosis of ADHD tend to display these traits in a more extreme way.

Much of the genetic research has been focused on the DAT1 gene that helps to regulate the neurotransmitter dopamine by signaling for reuptake at the synapse near the presynaptic terminal (Azeredo et al., 2014). While examining the 5’ end of the DAT1 Azeredo et al. (2014) found a strong correlation between the rs2652511 C-allele and ADHD. The rs2652511 C-allele is a possible contributor to the increase of the neurotransmitter DAT in children with ADHD (Azeredo et al., 2014). During a study of two different genes, one on the 3’ end of DAT1 known as DAT1, SLC6A3 and the dopamine D4 receptor gene DRD4 7R, Albrecht et al. (2014) found that polymorphisms on these genes may lead to a combination effect on those with ADHD. DAT1, SLC6A3 may lead to an increase in the reuptake of dopamine at the presynaptic terminal.
DRD4 7R may cause the D4 receptor to have decreased affinity for dopamine (Albrecht et al., 2014).

Latrophilin3 (LPHN3) is another gene that has been shown to have a significant association with ADHD (Arcos-Burgos et al., 2010). Arcos-Burgos et al., (2012) were able to take the association of LPHN3 and ADHD across three generation of families. In addition, a significant association of single nucleotide polymorphism of the LPHN3 gene was found in children with ADHD whose mothers had smoked while they were pregnant (Choudhry et al., 2012). This association shows a link between both environment and genetics when looking at ADHD. The expression of LPHN3 has been affiliated with the areas of the brain that have been shown to be implicated with ADHD. It may be possible to more effectively treat the disorder by targeting the effects of LPHN3 expression (Arcos-Burgos et al., 2010).

ADHD etiology is very complex and not yet well understood. There are most likely many genes that play a small role in ADHD. This idea of a polygenetic disorder magnifies the difficulty of precisely determining the root cause of ADHD. The brains of people with ADHD have many structural and volume differences including the frontal, parietal, occipital, and temporal lobes, as well as, the caudate, cerebellum, and regions of the corpus callosum. These structural and genetic differences play a role in how neurotransmitters interact in the brain leading to ADHD symptoms.

Pharmaceutical Treatment

According to the American Academy of Pediatrics (2011), treatment for children with ADHD should include both behavior therapy and the use of an appropriate medication. Medications used to treat ADHD can be divided into two categories: stimulant medications and non-stimulant medications. In the United States the number of people being prescribed ADHD medication has increased from 1.2 percent to 3.5 percent since the 1970s (Singh, 2010).
Stimulant medications are split into two classes: amphetamines and methylphenidate, with methylphenidate being the most commonly used (American Academy of Child & Adolescent Psychiatry and American Psychiatric Association, 2013; Dela Pena et al., 2013). Non-stimulant medications can also be split into two classes: norepinephrine uptake inhibitors and alpha adrenergic agents (American Academy of Child & Adolescent Psychiatry and American Psychiatric Association, 2013). Stimulant medication have a long history of use going back to 1937. When Charles Bradly first studied ADHD and the effects of amphetamines on children with the disorder (Kar, 2013). Non-stimulant medication are relatively new having only been approved by the FDA for the treatment of ADHD since 2002 (American Academy of Child & Adolescent Psychiatry and American Psychiatric Association, 2013).

Methylphenidate has both a quick release and an extended release, and can be administered by pill, transdermal patch, chewable tablets, and liquid form (American Academy of Child & Adolescent Psychiatry and American Psychiatric Association, 2013). Some of the different forms of methylphenidate include methylphenidate (Ritalin), extended release methylphenidate (Ritalin LA), dexamethylphenidate (Focalin), extended release dexamethylphenidate (Focalin XR), Daytrana methylphenidate in a transdermal patch, and Quillivant XR an extended release liquid form of methylphenidate (American Academy of Child & Adolescent Psychiatry and American Psychiatric Association, 2013). Methylphenidate works by blocking dopamine and noradrenaline transporters that remove extracellular dopamine and noradrenaline from the synapse resulting in an increase in the amount of dopamine and noradrenaline remaining in the synapse (Dela Pena et al., 2013; Hodgkins, 2012). Eighty five to ninety percent of prescriptions being written for methylphenidate are for ADHD (Ryan et al., 2011). Methylphenidate is extremely fast acting with positive effects being seen in as little at 15
minutes and lasting from 4 to 12 hours depending on rate of release (Ryan et al., 2001). The most common side effects of methylphenidate are tiredness, appetite loss, irritability, insomnia, and anxiousness (Hodgkins, 2012).

Amphetamines are the first class of drug to have been used in studying ADHD (Kar, 2013). There are several types of amphetamines currently used to treat ADHD including both quick and extended release forms. The main amphetamines being used are mixed amphetamine salts (Adderall), extended release mixed amphetamine salts (Adderall XR), dextroamphetamine (Dexedrine), and lisdexamfetamine (Vyvanse) (American Academy of Child & Adolescent Psychiatry and American Psychiatric Association, 2013). Amphetamines like methylphenidate block the reuptake of dopamine and noradrenaline, however amphetamines also inhibit the reuptake of 5-hydroxytryptamine also known as serotonin (Hodgkins, 2012). The positive effects of amphetamines can be seen in 30 to 45 minutes with the effects lasting 3 to 12 hours depending on the rate of release (Hodgkins, 2012). The most common side effects include appetite loss, headache, and insomnia (Sibley, Kuriyan, Evens, Waxmonsky, & Smith, 2014).

Methylphenidate and amphetamines are often studied together, because of the similarities in their mode of action and their effect. Stimulant medications have are very effective with 75%-80% positive effect on the treatment of ADHD symptoms (Ryan et al., 2011). Ryan et al., (2011) also point out that since stimulants are fast acting the therapeutic effects are often seen within minutes of taking the medication. Stimulant medications have been shown to have a positive effect on task performance and self-reported motivation in children (Groen, Tucha, Wijers, & Althaus, 2013). Groen et al., (2013) found that children treated with methylphenidate responded to feedback similarly compared to typically developing children suggesting that methylphenidate helps to normalize these responses. Improvements in attention span, impulse
control, and decreased hyperactivity have been consistently reported by both parents and teachers of ADHD children treated with stimulant medication (Ryan et al., 2011). Studies have shown that medication treatment improves academic performance, with students scoring between 2.9 and 5.4 points higher on standardized tests depending on how long the child had been medicated (Ryan et al., 2011). Ryan et al., (2011) did however point out that improvements seen on standardized tests were not enough to eliminate the gap between typical children and those with ADHD. Currie, Stabile, and Jones (2014) found stimulate medications to have no significant effect on academic performance, and even suggested an increase in grade repetition and a decrease in math scores. However, most studies using stimulant medications to treat ADHD show positive outcomes with improvements in observed behavior and in clinical diagnostic tests. In fact there is some evidence the splenial area of the brain may normalize with long term treatment of stimulant medication (Schnoebelen, Semrud-Clikeman, & Pliszka, 2010).

There are several possible adverse side effects associated with stimulant medication, though most can be managed so that treatment need not stop (Cortese et al., 2013). Ryan et al. (2011) placed the side effects associated with stimulant medications into three categories: common side effects, more serious side effects, and rare side effects as shown in Table 1. Loss of appetite is one of the most common side effects of stimulant medications. Loss of appetite has been shown to be a likely cause of growth delay associated with stimulant medications (Cortese, 2013). Cortese (2013) indicate that growth delay is attenuated over time and after discontinuing treatment there is an accelerated growth rate which adjusts for the delayed growth in weight and height. Insomnia is another common side effect reported by those taking stimulant medications (Singh et al., 2010). Increased blood pressure and heart rate have been seen, but they are usually
minor elevations and there is no evidence of long term cardiovascular damage caused by stimulant medication (Cortese et al., 2013).

<table>
<thead>
<tr>
<th>Common Side Effects</th>
<th>More Serious Side Effects</th>
<th>Rare Side Effects</th>
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<tbody>
<tr>
<td>Blurred vision</td>
<td>Difficulty urinating</td>
<td>Chest pain</td>
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<tr>
<td>Constipation</td>
<td>Fast/pounding/irregular heartbeat</td>
<td>Confusion</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Mental/mood changes</td>
<td>Easy bruising/bleeding</td>
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<tr>
<td>Dizziness</td>
<td>Significant unexplained weight loss</td>
<td>Extreme tiredness</td>
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<tr>
<td>Dry mouth</td>
<td>Uncontrolled movements</td>
<td>Fainting</td>
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<tr>
<td>Fever</td>
<td>Verbal tics</td>
<td>Fast/pounding/irregular heartbeat</td>
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<tr>
<td>Headache</td>
<td></td>
<td>Signs of infection</td>
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<tr>
<td>Irritability</td>
<td></td>
<td>Jaw/left arm pain</td>
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<tr>
<td>Lightheadedness</td>
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<td>Persistent sore throat</td>
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<tr>
<td>Loss of appetite</td>
<td></td>
<td>Shortness of breath</td>
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<tr>
<td>Nausea/vomiting</td>
<td></td>
<td>Severe headache</td>
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<tr>
<td>Nervousness</td>
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<td>Seizures</td>
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<tr>
<td>Stomach pain</td>
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<td>Slurred speed</td>
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<td>Trouble sleeping</td>
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<td>Swelling of the ankles/feet</td>
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<tr>
<td>Weight Loss</td>
<td></td>
<td>Weakness on one side of the body</td>
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Table 1: List of side effects of Stimulant medications.

One of the other major concerns of stimulant medications is the potential for abuse and addiction. Stimulant medications increase dopamine concentrations in the areas of the brain associated with substance abuse (Chang et al., 2014). Those with ADHD have a 1.5 times higher risk for substance abuse and a three times higher chance of nicotine dependence (Cortese et al., 2013). This increased risk is part of the concern about abuse and addiction of stimulant medication. When studying rats Dela Pena et al. (2013) found the rats had a consistent and sustained self-administration of stimulant medication showing a potential to develop dependency. However, Chang et al. (2014) found that children with ADHD treated with stimulant medication for three years were 31% less likely to be involved with substance abuse. These two findings are not necessarily contradictory. Stimulant medication can reduce the risk
of using other drugs and addictive substances yet still have a potential to be addictive. Thus, it is important that clinicians monitor their patients for abuse (Chang et al., 2014). Changing the pharmacokinetics of simulant medications such as using extended release is one way to help avoid abuse of the medication. Using medications that do not become bioavailable until after they have been ingested is another method use to try to avoid misuse (Sibley et al., 2014). After studying nearly 40,000 individuals over a four year period Chang et al. (2014) concluded there was no evidence stimulant medications lead to increased substance abuse and may actually reduce the rate of abuse.

Non-stimulant medication are relatively new in comparison to stimulant medication in treating ADHD. Stimulant medications were the only FDA approved pharmaceutical treatment for ADHD until 2002 (American Academy of Child & Adolescent Psychiatry and American Psychiatric Association, 2013). Non-stimulant medication are divided into two classes norepinephrine uptake inhibitor atomoxetine (Strattera) and alpha adrenergic agents including extended release guanfacine (Intuniv) and extended release clonidine (Kapvay) (American Academy of Child & Adolescent Psychiatry and American Psychiatric Association, 2013).

Atomoxetine was the first FDA approved non-stimulant medication for treating ADHD (Rains & Scanhill, 2006). Atomoxetine is similar to tricyclic antidepressants, but considered to be safer (Sibley et al., 2014). According to Sibley et al. (2014) atomoxetine has been shown to improve ADHD symptoms, but not to the same degree as stimulant medications. Atomoxetine takes longer to show the therapeutic effect. Atomoxetine works by inhibiting norepinephrine reuptake which increases the amount of norepinephrine in the brain (Rains & Scanhill, 2006). The most common side effects are decreased appetite and weight loss, but headache, upper
abdominal pain, nausea, irritability, dizziness, and somnolence have also be observed (Rains & Scahill, 2006).

Clonidine and guanfacine work by blocking the firing of norepinephrine and help to regulate the adrenergic system (Rains & Scahill, 2006). Guanfacine also acts on the prefrontal cortex by stimulating norepinephrine receptors (Rains & Scahill, 2006). Both of these drugs have been shown to improve the functioning of ADHD children when being used in concert with methylphenidate (Rains & Scahill, 2006; Sibley et al., 2014). However, they have not been very effective on their own. Drowsiness is the most common side effect with both clonidine and guanfacine but there are very few other side effects (Corteses et al., 2013).

Stimulant medications are very effective for treating ADHD, helping with attention, focus, and hyperactivity. Singh et al. (2010) found that young people reported feeling that stimulant medication help them improve social behaviors, and their relationships with peers. Young people also reported improvements in school, relationships with parents and siblings, self-confidence, and self-esteem (Singh et al., 2010). Stimulant medications are an effective treatment for ADHD even when the positive outcomes are weighed against the possible side effects and potential for abuse. Non-stimulant medication tend to have fewer side effects, but are not as effective.

Nutrition

Attention-deficit disorder has a very complex etiology including genetics, and brain structure and function. It is well known that genetics by themselves do not tell the entire story of what genes are expressed, but that environmental factors play a role in gene expression. Environmental factors may influence the effects of ADHD by as much as 20-30% making them very important in the expression and severity of the disorder (Verlaet et al., 2014). Some of the environmental factors that have been found to influence ADHD include low socioeconomic
class, family dysfunction, foster placement, low birth weight, premature birth, and prenatal alcohol or tobacco smoke exposure (Verlaet et al., 2014). Another major environmental factor is nutrition. Nutrition has long been suspected of influencing the symptoms of ADHD. In fact dietary changes are the most commonly used alternative therapies for ADHD (Karpouzis, & Bonello, 2012). Areas that have been identified as contributors to ADHD are the intake of food additives such as artificial food coloring and preservatives, vitamin and mineral deficiencies, and the influence of omega 3 and omega 6 fatty acids. It has also been long suspected that sugar intake may play a role in increased hyperactivity in children with ADHD.

Dr. Benjamin Feingold an allergist and pediatrician was one of the first to suggest the influence diet had on the hyperactivity of children with ADHD (Schwing, 2009). Dr. Feingold stated the removal of artificial colors and from a child’s diet would benefit the child by the reduction and possible elimination of ADHD related symptoms (Eagle, 2014). The Feingold diet was a diet free of certain food additives, especially azo dye food colors, and naturally occurring salicylates, an aspirin-like compound found in many fruits and some vegetables (Stevenson, 2009). Feingold claimed that these dietary changes benefitted about 50% of children with his diet (Schwing, 2009). In 1983, a meta-analysis of the Feingold diet found the diet’s effect size too small to be of value, creating uncertainty in the benefit of dietary treatment of ADHD (Nigg, Lewis, Edinger, & Falk, 2012).

The uncertainty of the effects of artificial food colors remained until Schab and Trinh (2004) performed another meta-analysis of the previous twenty years of research. Schab and Trinh (2004) concluded that artificial food colors had a significant effect on the hyperactivity of children with ADHD. This finding reignited the artificial food color argument. There is some evidence that artificial food colors and some preservatives may increase the hyperactivity of
children even if they have no history of ADHD (Verlaet et al., 2014). Verlaet et al (2014) indicate there is strong evidence that at least a subgroup of children with ADHD would benefit from a diet free of artificial food color. Nigg et al (2012) indicate that as many as 30% of children with ADHD may benefit from restricting artificial food colors. Nigg et al (2012) did point out that when only FDA approved food colors were considered the results were not consistent and they may not have the same negative effects. There has even been some evidence that artificial food colors may have a positive effect in some subgroups of children with ADHD (Eagle, 2014).

Sugar is often associated with ADHD and increased hyperactivity in children. Some studies have indicated as many as 24% of children can benefit from a reduced sugar intake, though restricting sugar intake is less effective than medication (Schwing, 2015). This finding however is controversial. Kim and Chang (2011) concluded there was no link between sugar intake and behavior in children with ADHD. Kim and Chang (2011) based their conclusion on findings indicating sugar intake had no influence on behavior and learning of children in Korea with ADHD. Johnson et al (2011) put forth the idea that chronic excessive sugar intake leads to a decrease in dopamine receptors and dopamine receptor-mediated signaling. This decrease in dopamine receptors and signaling then leads to the development of ADHD. The hypothesis put forth by Johnson et al (2011) is based on two main ideas. First, excessive sucrose intake increases the amount of dopamine released. The chronic increase of dopamine leads to a desensitization of dopamine-stimulated responses. Johnson et al (2011) also point out the majority of studies that show no association between sugar intake and ADHD symptoms are comparing sugar to artificial sweeteners, suggesting artificial sweeteners may have the same
effect as increased sugar intake. It may not be an acute reaction to increased sugar intake, but a prolonged exposure to higher amounts of sugar that exacerbates ADHD symptoms.

Iron and zinc deficiencies have been associated with increased ADHD symptoms (Oner et al., 2010; Rucklidge et al., 2014). Iron is closely associated with dopamine metabolism. Brains with lower iron levels have been shown to have decreased numbers of dopamine receptors and transporters (Oner et al., 2010). There is evidence linking ADHD with other disorders associated with inflammation such as, atopic eczema (Rucklidge et al., 2013). Blood ferritin levels indicate iron status and can also reflect reduced inflammation possibly improving ADHD symptoms (Rucklidge et al., 2013). Oner et al (2010) showed an association with low ferritin levels and hyperactivity. There has been limited research treating iron deficiency with ferrous sulfate that indicate a significant benefit for children with ADHD, but more research is needed associating iron studies with ADHD (Bloch & Mulqueen, 2014).

Low zinc levels in children have been associated with ADHD diagnosis (Bloch & Mulqueen, 2014). Bloch and Mulqueen (2014) point out that symptoms of zinc deficiency include inattention, jitters, and delayed cognitive development all of which are similar to ADHD symptoms. Low zinc levels have been associated with hyperactivity, increased anxiety, and conduct problems, however lower zinc levels were not associated with learning problems (Oner et al., 2010). Oner et al (2010) suggested this finding indicated that zinc levels are linked closer to the hyperactivity and impulsiveness aspect of ADHD rather than the inattention aspect. Zinc is a dopamine transporter inhibitor. Low zinc levels have been linked to low synaptic dopamine levels (Oner et al., 2010). Zinc supplementation has had mixed results reflected through the effects on ADHD scores, one study showing benefits on hyperactivity and impulsiveness, and another study showing no effects (Ghanizadeh & Berk, 2013). There is some evidence that using
zinc in combination with stimulant medications will help to improve ADHD symptoms and possibly lead to lower dose requirements, with as much as a 37% reduction in the dose of medication (Bloch & Mulqueen, 2014).

Fatty acid intake has become an area of high interest in treating ADHD, because fatty acids have been linked to neurological development (Karpousiz & Bonello, 2012). In particular omega-3 and omega-6 fatty acids have been linked to behavioral and cognitive development (Stevenson, 2010). Stevenson (2010) also pointed out that eating oily fish, a good source of omega-3 fatty acids, during early pregnancy had a positive effect on hyperactivity of the child at age nine. Children with ADHD have been shown to have consistently lower blood levels of omega-3 fatty acids compared to normally developing children (Hawkey & Nigg, 2014). There is also evidence that fatty acid abnormalities may effect adult behavioral disorders. Furthermore, omega-3 fatty acids have been linked mood disorders and impulsivity (Richardson, 2006). These links between fatty acids and ADHD have made them one of the largest areas of study in regards to nutritional therapies for ADHD.

Most studies have shown positive effects from the treatment of ADHD with omega-3 and omega-6 fatty acids with results varying from strong to slight improvements (Barragan, Breuer, & Dopfner, 2014; Hawkey & Nigg, 2014). Barragan et al (2014) compared treatment with omega-3 and omega-6 fatty acids alone, with methylphenidate alone, and with a combination of methylphenidate and omega-3 and omega-6 fatty acids. They found that the fatty acid treatment alone improved ADHD scores by 60%, methylphenidate alone improved scores by 80%, and the combination treatment improved scores by 93%. Hawkey and Nigg (2014) did not report such strong results, but did state that fatty acid intake has a reliable significant effect on ADHD symptoms. Richardson (2006) agrees that supplementing the diet of children diagnosed with
ADHD with omega-3 fatty acids can alleviate symptoms. Omega-3 fatty acid treatment has been shown to be more effective in treating hyperactivity and impulsivity than inattention (Barragan et al., 2014; Hawkey & Nigg, 2014; Richardson, 2006). Supplementation of omega-3 fatty acids have been shown to be safe with little to no side effect, and may provide other positive health benefits such as improved lipid profiles (Manor et al., 2013). Even with the many positive studies on fatty acids, the outcomes are not totally consistent and some contrary result have been seen indicating a need for more study (Karpouzis & Bonello, 2012).

Nutrition is a key component of all areas of health including those associated with ADHD. Good nutrition will help to improve any health problem while a poor diet may deteriorate function and health. Junk food diets or diets with high amounts of chocolate, chips, and larger amounts of sugar have been associated with hyperactivity (Karpouzis & Bonello, 2012). Karpouzis and Bonello (2012) also point out the western-style diet or a diet high in takeout foods, processed meats, high-fat dairy products, and soft drinks contribute to ADHD. While healthy diets that are high in whole grains, fruit, vegetables, legumes, and fish do not have the same connection with ADHD (Karpouzis & Bonello, 2012). In support of this ADHD has an increased association with obesity, as children with ADHD have shown to have as much as twice the proclivity for being in the top 85% of BMI (Johnson et al., 2011). All of this evidence points to a need to manage diet, whether by supplementing to correct for deficiencies or merely eating healthy it may improve ADHD symptoms.

Discussion

ADHD is multifactorial, consequently it is difficult to isolate the cause. The genetics of ADHD are just beginning to be understood and there is much more to learn. As ADHD genetics are better understood it should lead to enhanced treatment options. Arcos-Burgos et al. (2010) indicate that certain genes associated with ADHD may also be of use in determining if a
medication will be effective in treating ADHD. Genes associated with ADHD may also be of use in predicting what side effects may be seen with specific medications (Johnson et al., 2013). It is becoming clear that as the understanding of ADHD genetics improves treatments will become more effective.

Insight into the underlying genetics will also help to more fully understand the brain areas associated with ADHD and what effect changes in those areas of the brain may have. Using the various imaging techniques it has become clear there are many structural and volume differences in the brains of those with ADHD. These structural differences probably play a key role in the functional problems in dopamine signaling among those with ADHD. As these structural differences are better understood it should assist development of treatments focusing on the functional issues they cause.

Stimulant medications are the most commonly used treatments for ADHD, because they have a positive effect on the symptoms of ADHD for 75 to 80% of those treated (Ryan et al., 2011). Consequently stimulant medications have become the first line of ADHD treatment. Both classes of stimulant medications have been shown to be equally effective in treating ADHD symptoms, but methylphenidate has a lower rate of adverse effects (Hodgkins et al., 2012). It is common practice to try the other class of stimulant medication if one class of stimulant medication is ineffective (Hodgkins et al., 2012). Side effects and addiction are two of the major concerns associated with stimulant medications. Side effects and lack of effectiveness are the main reasons for those with ADHD to stop using their medication (Toomey, Sox, Rusinak, & Finkelstein, 2015). Knowing what leads those with ADHD to discontinue medication use may help find alternative treatment options. Those options may be designed to reduce or possibly eliminate the need for medication.
One of the major options that has been looked for at least fifty years is nutrition. It is intuitive to consider nutrition as everything ingested will have some effect on the body. As with any medication some effects will be positive and some will be negative, making it important to consider both things that should be eliminated from or added to the diet. Artificial food color and some preservatives have been shown to effect the hyperactivity of children with ADHD, and though these conclusions can be disputed there is enough evidence to continue studying the effects of these additives (Nigg et al., 2012; Schab & Trinh, 2004). Artificial food color and preservatives do not offer any nutritional value, they are just additives. Avoiding these food additives even if they have not been shown beyond doubt to increase hyperactivity may still be beneficial.

Supplementation of certain nutrients, including iron, zinc, and omega-3 and omega-6 fatty acids, has been shown to be beneficial in treating ADHD. Fatty acids have been the most frequently studied nutrient in treating ADHD and have shown promising results with as high as 60% improvement on ADHD scores (Barragan et al., 2014). Omega-3 fatty acids have been associated with improvement of overall health including reducing the risk of heart disease and stroke. In addition to the other positive health benefits associated with omega-3 fatty acids, they are very safe as there are little to no side effects (Barragan et al., 2014). Iron and zinc have not been as conclusive when showing positive effects as fatty acids have, but there is enough positive results to continue studying them.

When treating a complex disorder like ADHD it is best to look at the individual as a whole as well as all possible aspects involved with the disorder. Hodgkins et al. (2011) indicate that medication with behavior therapy provides superior outcomes to medication alone. Barragan et al. (2014) were able to show improvement in the reduction of ADHD symptoms with a
combination of methylphenidate and an omega-3 and omega-6 supplementation regimen with a 93% improvement over a twelve month period. Both these studies indicate that combining treatment methods improves outcomes for those with ADHD. Exercise has been shown to improve performance on attention orientated task, as well as, improving social behavior, motor skills, strength, and neuropsychological parameters (Silva et al., 2015; Kamp, Sperlich, & Holmberg 2014). All of these areas of treatment including medications, nutrition, behavior therapy, and exercise have been shown to be effective in treating ADHD. Studies that combined different treatments have been shown more effective in reducing ADHD symptoms than individual treatments. It would make sense that a treatment plan focused on all aspects of an individual with ADHD including multiple treatment approaches would have the most benefit.

Holistic treatment methods need further research.

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