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Explanation of the Dependency of the Efficacy of ADHD Treatments on the Age of the Recipient

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ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is a highly prevalent neuropsychiatric disorder, affecting people of all age groups. Several treatment methods have proven to be effective in ameliorating ADHD symptoms, most falling under the categories of stimulants, non-stimulants and non-pharmacological. However, many experimental studies have shown that the efficacy of certain ADHD treatments is dependent on the age of the subject. In this paper, I will be providing insight into possible explanations of this phenomenon. By understanding this, not only can we better understand the changes that occur in the brain with age, but also the disorder itself and possible treatment methods.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neuropsychiatric disorder where patients typically exhibit symptoms of inattention, impulsivity and hyperactivity (Caye et al., 2019). ADHD is considered the most common neurobiological disorder, with 5% of adolescents and children and 2.5% of adults affected globally. Out of the 5% affected children, 65% have persisting impairing symptoms of ADHD that continue into adulthood (de Crescenzo et al., 2017). Children with ADHD have proven to have an increased risk of impaired academic performance, accidental injuries and tense relationships with family and friends (Caye et al., 2019). As such, adolescents with ADHD, in general, have a higher rate of grade retention, teenage pregnancy, and drug abuse (Caye et al., 2019). Due to its proven negative impact on people in general, as well as its astounding prevalence, ADHD is considered psychological morbidity and social disadvantage to children and, in extension, adolescents and adults (Hodgson et al., 2014). This is all the more reason to conduct experimental research in an attempt to better understand this disruptive, enduring and widespread disorder.

Diagnosis of ADHD in children usually requires the patient to exhibit at least five out of nine symptoms of impulsivity, hyperactivity or inattention according to the Diagnostic and Statistical Manual of Mental Disorders (de Crescenzo et al., 2017). However, such diagnostic criteria often varies with doctors' personal opinions. For example, some may require the ADHD symptoms to be expressed consistently throughout different social scenarios. Additionally, many clinicians rely on interviews with people who live in close quarters with the patient to assess ADHD symptoms, as patients themselves often undergo recall bias which twists the onset, severity and persistence of the symptoms(de Crescenzo et al., 2017). After an individual's symptoms and possible comorbid conditions are assessed holistically, treatments are tailored to their specific situation and usually consist of psychostimulants, non-stimulants, non-pharmacological medication or a combination of a few of them. (de Crescenzo et al., 2017)

Despite the amount of research done on ADHD growing exponentially throughout the past few decades, the specific aetiology of ADHD still remains unclear, although, there are factors that may contribute to a higher risk of ADHD. However, these may be correlations, not direct causes. It is possible that, like many neuropsychiatric disorders, genetic risk plays a role in causing ADHD(Thapar et al., 2013). According to a

study that analysed ADHD genetic risk by observing the prevalence of ADHD in biological and adoptive families, relatives directly related to ADHD patients are two to eight times more likely to show symptoms of ADHD than relatives of unaffected individuals (Faraone et al., 2005). However, this connection between heritability and the presence of ADHD symptoms by no means eliminates the possible effect of environmental causes, which are difficult to analyse due to obstacles posed by differences in patient diagnosis and symptoms(Faraone et al., 2005). That being said, one factor has been identified as a significant environmental factor by multiple research teams: parental and child dispositions(Rutter et al., 2006). This can include prenatal exposure to maternal alcohol, cigarettes or even childhood social rejection. Due to the various uncertainties in the aetiology of ADHD, the trial and error method is heavily relied on to identify possible treatment methods, whereby multiple possible solutions are tested to find the most effective one, instead of finding a method based solely on the understanding of the mechanisms (Thapar et al., 2013). Throughout the decades, various stimulants, non-stimulants and non-pharmacological treatments like behavioural therapy and dietary treatments have proven to be effective in lessening ADHD symptoms. However, studies have shown that the efficacy of individual treatment methods is different in certain age groups. Given this phenomenon, the mechanisms behind it still remain unclear, which is exactly the question that will be addressed. By understanding the underlying mechanisms, not only can we better understand the changes that occur in the brain with age, but also the disorder itself and possible treatment methods.

Pharmacological Treatments

After decades of experimental research, pharmacological treatments for ADHD remain the most widely accepted effective treatment method. According to a study on pharmacological treatments for children and adolescents in the United States, 90% of all children with ADHD reportedly undergo pharmacological treatment(Danielson et al., 2018). Pharmacological treatments are usually categorised into stimulant and non-stimulant medications. The most frequently prescribed medications are two psychostimulants, methylphenidate (MPH) and amphetamines (AMP). Only if these psychostimulants prove to be ineffective or intolerant for the patient, will second-line medications like atomoxetine (ATX), clonidine (CLO) and guanfacine (GFC) be prescribed. (Caye et al., 2019)

Stimulants

Of the popular pharmacological treatment options for ADHD, stimulant-based treatments are considered the relatively more efficacious method. In a double-blind study testing the efficacy of stimulants on ADHD treatments in children and adults, 65% to 75% proved to be clinical responders. Clinical responders refer to subjects who, to some extent, show an increase of the desired effect in a study. To put this in context, about two-thirds of the subjects given stimulants showed a reduction of ADHD-related symptoms. On the other hand, only 4% to 30% of subjects tested with placebo were clinical responders.

Though the specific mechanism driving stimulant efficacy on ADHD is still unknown, it is thought to essentially increase norepinephrine and dopamine levels. Norepinephrine and dopamine are usually associated with blood pressure control and motor control respectively, however, they have proved to enhance the ability to maintain attention, which is a significant symptom of ADHD (Ulke et al., 2019).

It is clear that the medications act primarily on catecholamine pathways (Caye et al., 2019). First-line medications, typically psychostimulants like MPH and AMP, block the reuptake of dopamine into the presynaptic neuron which, in turn, blocks the reuptake of norepinephrine. Norepinephrine and dopamine reuptake transporters are inhibited. This increases the availability of dopamine and norepinephrine and further increases the overall level of extraneuronal catecholamines (Kolar et al., 2008), which affects frontocortical activity(Kolar et al., 2008). In short, it can be seen as a dopamine reuptake and presynaptic norepinephrine inhibitor (Caye

et al., 2019). As shown in Fig 1, the AMP enters the trace amine-associated receptor 1 (TAAR1), which phosphorylates the Dopamine transporter. This phosphorylated transporter will either be absorbed by the presynaptic neuron, blocking the reuptake of dopamine or reverse the transport of dopamine back into the synapse. This mechanism is thought to increase dopamine and norepinephrine levels, allowing more capacity for self-control and attentiveness.

Second-line medications like ATX are noradrenaline reuptake inhibitors and block the protein that transports noradrenaline from the synapse back into the pre-synaptic neuron, which increases the concentration of norepinephrine, lessening ADHD-related symptoms. CLO and GFC act as alpha-2 receptor agonists that activate noradrenaline neurotransmitters, causing the locus coeruleus to produce and transport noradrenaline. This increased noradrenaline activity stimulates brain activity in the prefrontal cortex(Caye et al., 2019).

Though different stimulants may work slightly differently, the basic mechanism for ADHD treatment via stimulants is that they increase the effects of dopamine and/or norepinephrine usually by blocking their reuptake, or acting as an artificial trigger (agonist) of their receptors. This allows more capacity for self-regulation of attention, a typical ADHD symptom.

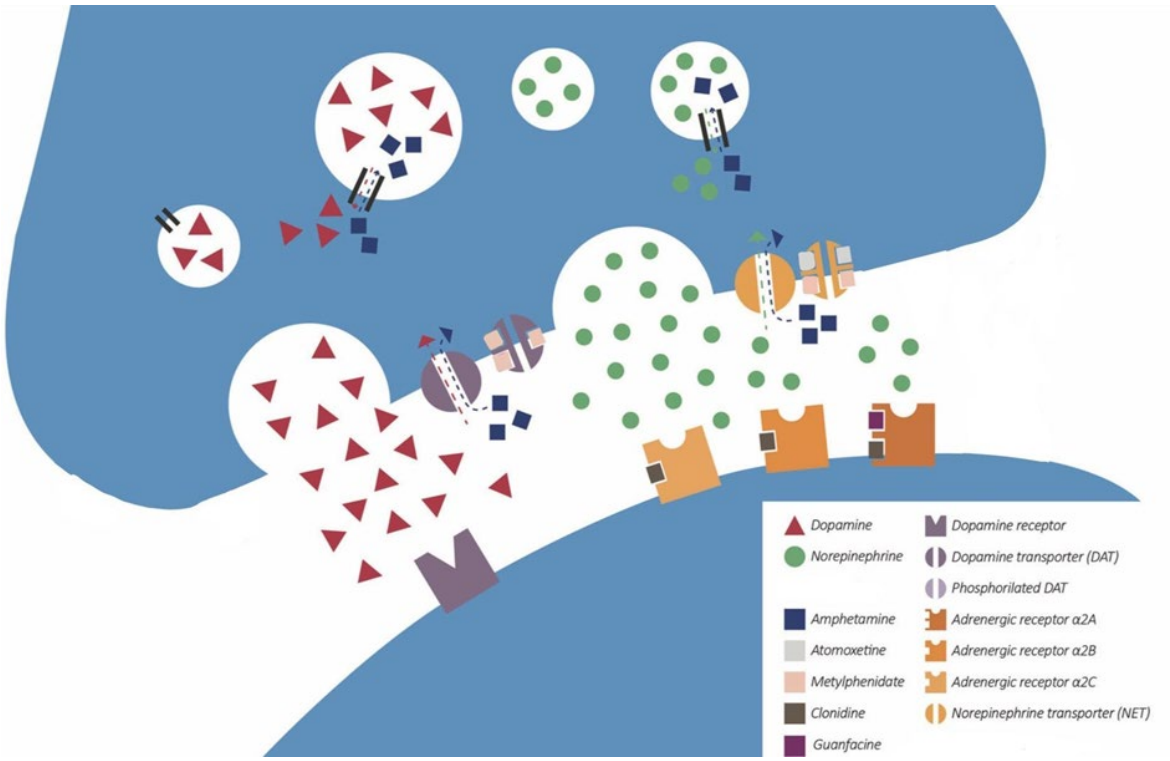

Figure 1. A synapse showing neurotransmitters, reuptake inhibitors and receptors and the proposed mechanisms of action for the medications commonly used to treat ADHD(Caye et al., 2019).

Although the mechanisms of action behind the medications remain somewhat uncertain, their efficacy has proven to be high. A multisite controlled study examined the effects of treatment by MPH specifically on aggression, a common ADHD symptom. The parents, teachers and clinicians observed the changes in aggression-related behaviour of the subjects, after which they individually gave a rating that reflects the size of the effect. A higher rating corresponds to a larger difference in frequency or intensity of aggression-related behaviour, which in turn corresponds with higher efficacy and vice versa. If the data given by the parents, clinicians and teachers (if applicable) didn't differ by a significant factor, then an average is taken of the three numbers. However, if a large discrepancy is present, then they will be discussed and additional testing and observation will take place if necessary. Once a consensus is reached, only then can the data be viewed as significant and

unbiased. The purpose of this conjoined review is to minimize bias from the subject. The results were that the group with a mean age of 8.8 years had a comparatively higher overall rating of 1.396, whereas the group with a mean age of 14.4 had a lower rating of 0.957. This discrepancy in results between the children and adolescent age groups could possibly be explained by the following study.

A study was performed to determine the changes in synapses as the brain ages using electron microscope analysis to examine the effects of age on synapses from the frontal cortex of Rhesus monkey brains. The results show that there is no change in the length of the synaptic junction. However, there is a 30% loss of both excitatory and inhibitory synapses in layers 2/ 3 as the subject's age is from 5 to 30 years(Peters et al., 2008). Though there are limitations regarding whether synapses in Rhesus monkey brains are comparable to humans, the correlation of synapse loss still could explain the lower efficacy of adolescents compared to children. MPH is thought to lessen ADHD symptoms by blocking the reuptake of dopamine and norepinephrine, which increases dopamine and norepinephrine levels. However, with fewer synapses to begin with, dopamine and norepinephrine levels would supposedly decrease as well. Because ADHD tends to correlate with reduced levels of dopamine and norepinephrine activity, this would likely cause an increase in the frequency and intensity of ADHD symptoms.

Nevertheless, it is noteworthy that there is still a lot that is yet to be understood in the field, not only due to the lack of experimental research but also because of the discrepancies regarding whether or not there is an effect of ageing on synapse loss. Though there are a number of studies that draw conclusions consistent with the study done on Rhesus monkeys mentioned above, there are a few that do not. For example, according to a study that examined 21 normal human brains ranging from aged 2-16, there is no significant loss of synapses from layers 2/ 3 and 5 of the prefrontal cortex (Peter R., 1979). Such differences in results could be due to delay in post-mortem, different methods of counting synapses or perhaps unknown factors(Peter R., 1979). It is acknowledged that there are limitations regarding the age of Rhesus monkeys compared to the human test subjects.

A double-blind study was conducted on 27 adults and adolescents diagnosed with ADHD, whereby the efficacy of mixed amphetamine salts extended-release capsules (MAS XR) on the reduction of ADHD symptoms was tested(Spencer et al., 2008). After a 4-week placebo-controlled study, the research team reported that there was a statistically significant advantage in the efficacy of the treatment in adolescents compared to adults and the placebo group.

To eliminate the possibility of treatment using MAS XR having a significant discrepancy in efficacy as compared to MPH mentioned above, a number of journals were reviewed. All stimulant medications work similarly in lessening ADHD symptoms, and the mechanism behind MAS XR is no exception. MAS XR is composed of a number of different stimulants (amphetamine aspartate monohydrate, amphetamine sulfate, dextroamphetamine saccharate, dextroamphetamine) and has the advantage of having a rapid onset of action of 1.5 hours, significantly faster than other drugs(Weisler, 2005). Well-controlled clinical studies also show its extended duration of action and effect of treatment relief for at least 12 hours(Weisler, 2005).

A team of researchers used MRI neuromelanin imaging to assess activation in the locus coeruleus (LC) in adolescents and adults(Hämmerer et al., 2018). The neuromelanin-sensitive MRI detects the activation of LC through the detection of neuromelanin, which is produced when dopamine goes through melanogenesis(Cassidy et al., 2019). The results prove that adults have poorer LC structural integrity compared to adolescents and children. This would likely in turn decrease the volume of noradrenaline produced because of the causal relationship between noradrenaline production and LC integrity. With lower noradrenaline levels, an ADHD patient's self-control and self-regulation abilities would also decrease. Though there is no definite explanation for the lower efficacy of MAS XR in adults, this could be a possibility.

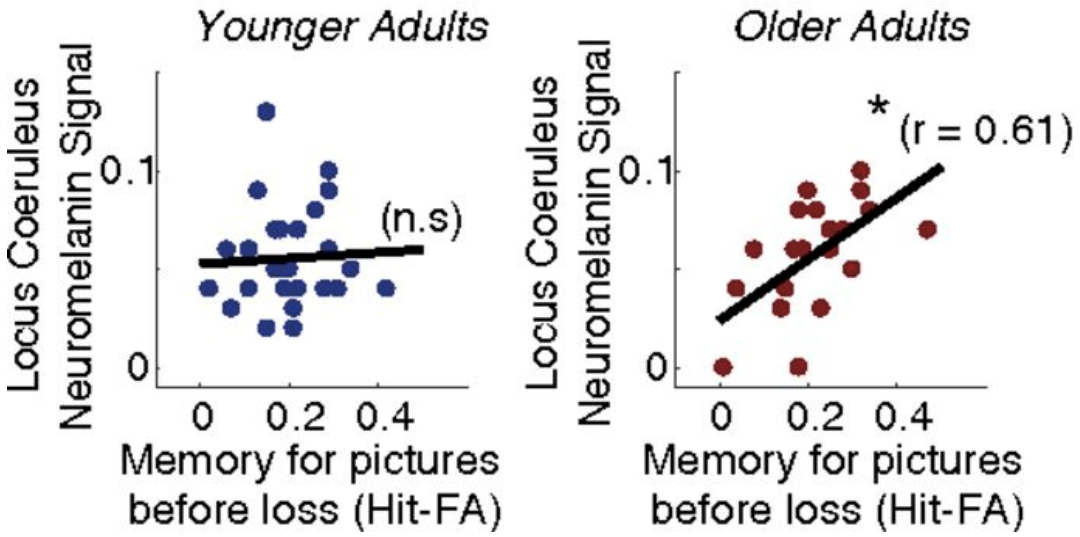

Figure 2. "Better memory for scene stimuli before losses was observed in individuals with larger NM signals in the LC. This suggests a positive link between LC integrity and emotional memory capacity in older adults." (Hämmerer et al., 2018)

Interestingly, researchers associate a decrease in LC integrity with declining cognitive abilities, such as memory. Their research showed that the LC integrity diminishes with age and along with this, their cognitive abilities are reduced as well. This then suggests that a decrease in noradrenaline is directly correlated to a decrease in cognitive abilities. Though low cognition is not a common ADHD symptom, children with ADHD are known to have impaired cognitive development typically caused by inattention and hyperactivity which disrupts learning. As these children grow up and eventually age, these impaired cognitive abilities may not still pose as a hindrance to their daily lives, but they might still alter the results of a study measuring the effects of medication on such symptoms.

Non-stimulants

In the world of ADHD treatment, it's a given that stimulants are the first-line treatment. Only when stimulants prove to be ineffective or have intolerable side effects (approximately 10-30% of patients) will clinicians turn to the second line of treatment: non-stimulants. Non-stimulant treatments are second-line medications because they typically have a lower efficacy rate across all age groups despite their lower risk of addiction and low incidence rate (Li et al., 2017). Also, most non-stimulants have only recently been approved by the FDA, therefore, there are very limited studies that investigate their long-term effects. This uncertainty deters clinicians from prescribing them as first-line medications. Results of studies have also shown that non-stimulants are less capable of short-term efficacy (Štuhec et al., 2015). The mechanism behind non-stimulants is essentially the same as one of the stimulants explained above, where norepinephrine reuptake inhibitors increase norepinephrine, which controls motor control and is involved in working memory, attention and other executive functions (Umehara et al., 2013). This decreases horizontal locomotion and causes higher levels of dopamine and norepinephrine. However, this former can perhaps be considered situational as it has only been noticed in a study done on hypertensive rats.

So far, there are only approximately four large-scale, randomized, double-blind studies done on the efficacy of ATX on ADHD symptoms. One was done on boys aged 7 to 15 years and girls aged 7 to 9 years who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnostic criteria for ADHD (KRATOCHVIL et al., 2002). The results of the study were presented as T-scores, a transformation of the raw score based on normative data, with a mean of 50 and a change of 10 points would constitute one standard

deviation. Based on parent-rated ADHD RS Total T scores, patients' symptom severity at study entry averaged approximately 2.7 standard deviations above age and gender norms. With this rating system, symptom severity can be estimated relative to age and gender expectations for normal children.

The results showed that ATX allowed patients to have an average of 49% decrease in inattentive and hyperactive-impulsive symptoms, with the baseline and endpoint being 39.4 and 20.0 respectively on the scale used by the researchers.

In another ADHD study, researchers conducted two identical randomized, double-blind, placebo-controlled, multisite studies that also tested the efficacy of ATX, but on 536 adults (individuals over the age of 18) instead (McEwen et al., 2016; Michelson et al., 2003). Similar to the study mentioned before, individuals had to meet the DSM-IV-defined ADHD criteria to be eligible for the study. This 10-week study focused on the comparison between ATX and placebo to prove ATX efficacy. It used the Conners' Adult ADHD Rating Scale to present its results, making it more standardized and easily quantifiable. The study reports that ATX proved to reduce symptoms of attention deficit and hyperactivity by a statistically significant factor as compared to the placebo group. However, despite this indicated efficacy, it only reduces approximately 37% of the symptoms as reported by the study, which is slightly lower than its efficacy on children as mentioned in the previous study.

Findings in glucocorticoids, a class of hormones commonly associated with physiological stress, showed that acute stress increased the number of NMDA and AMPA receptors expressed in the prefrontal cortex (McEwen et al., 2016). This, in turn, increased the expression of NMDAR and AMPAR subunits which enhanced mechanisms associated with glutamate, a neurotransmitter that binds to NMDA and AMPA receptors. These mechanisms typically have to do with prefrontal cortex-dependent memory processes or cognitive learning and spatial learning. This effect would be especially noticeable in older individuals where basal cortisol levels are higher (McEwen et al., 2016). However, more in-depth research showed that chronic stress surprisingly significantly reduces the expression of AMPA and NMDA receptors and, subsequently, reduces AMPA and NMDA-dependent synaptic transmission. With the decreased glutamate levels that come with this, cognitive abilities like solving puzzles may decrease. It is logical to conclude that as we age, the likelihood of having chronic stress increases. Therefore, it is possible that the reason behind the decreased efficacy of ATX in adults is that the AMPA and NMDA receptor expression has decreased.

The underexpression of AMPA and NMDA receptors was tested on medical students who reportedly had continuously high GPAs and scored high on a 10-item perceived stress scale. Some individuals showed low performance on a mental flexibility test as well as impaired functional connectivity of the PFC on an fMRI. However, these effects proved to be reversible, for the abnormal results of the fMRI and mental flexibility test were gone after the students had a one-month vacation. Nonetheless, the reduced functional connectivity and reduced cognitive abilities shown were confirmed by similar research done on young adult rat brains(McEwen et al., 2016),

Researchers also used an animal model to conclude that chronic stress causes the shrinkage of dendrites (McEwen et al., 2016). Though it is untested, it is possible that this shrinkage would either increase the length of the synapse, making it more difficult for neurotransmitters to act on post-synaptic terminals. Either way, this could explain the lower efficacy of ATX on adults, as many of them are likely to have endured chronic stress.

Both the effects of decreased expression of AMPA and NMDA receptors and the shrinkage of dendrites may be associated with ADHD because though the precise aetiology of ADHD is unknown, experimental research has shown that ADHD is associated with decreased volume or functionality of white and grey matter in the brain, which then causes decreased cognitive abilities and attention.

Non-Pharmacological Treatments

Non-pharmacological treatments to suppress ADHD symptoms usually include behavioural and psychosocial modification, cognitive training, and dietary treatments. Because these treatments usually affect the patient in milder and more subtle ways than pharmaceuticals, they are often used in toddlers, children and adolescents. Furthermore, some patients may take second-line non-stimulant medications instead of stimulants because of their lower chance of abuse. However, most non-stimulants also have lower efficacy, therefore, some clinicians may ask for a combined treatment of non-pharmacological treatments and non-stimulant medication to raise the chances of suppressing ADHD symptoms.

Though there is still a lot to be learned, it is thought that oxidative stress contributes to the likelihood of ADHD in an individual. Oxidative stress occurs when there is an imbalance between antioxidants and free radicals in the body. Free radicals are molecules that have an uneven number of valence electrons and reactive oxygen species (ROS) are considered a subset of free radicals because not only do they have an uneven number of outer shell electrons, but they also contain oxygen. This quality allows them to react readily with other molecules because they want to let go of their extra outer shell electrons to form a full octet, which is more energetically favourable. This process of losing electrons is called oxidation. When oxidation occurs in a rapid and uncontrolled manner, this leads to oxidative stress. However, the body has adapted ways to deal with this; there are certain mechanisms that are antioxidative and prevent oxidative stress from happening. For example, a high oxygen potential between intracellular and extracellular compartments encourages the diffusion of the excess oxygen down a concentration gradient (Verlaet et al., 2018). There are also certain antioxidants that are enzymatic and non-enzymatic produced by the body that re-establishes homeostasis.

The oxidative stress that occurs when these antioxidant mechanisms fail to decrease oxygen levels is suspected to contribute to ADHD. Due to the high metabolic rate of the brain, oxidative stress can easily cause the peroxidation of membrane lipids and membrane-associated proteins like neurotransmitter receptors (Verlaet et al., 2018). The peroxidation of membrane lipids decreases the fluidity within the plasma membrane and alters the regulation of neurotransmitter receptor levels that would otherwise stay constant. This change in neurotransmitter receptor levels can sometimes interfere with dopamine synthesis. Also, dopamine is easily oxidised when antioxidant levels are low due to its reactive nature. Oxidized dopamine produces aminochrome which causes cytotoxicity (Segura-Aguilar & Huenchuguala, 2018; Verlaet et al., 2018). This in turn could cause damage to the prefrontal cortex and basal ganglia, sections of the brain associated with attention(Verlaet et al., 2018). This, therefore, could worsen or potentially cause certain ADHD symptoms like attention deficit.

In response to the issue of imbalanced antioxidants and ROS, an antioxidant extracted from the French pine tree bark, pycnogenol has been studied as a treatment for ADHD (Tenenbaum et al., 2002). This natural compound was developed by the French Pine tree as a mechanism to protect itself from damaging sunlight. Ultraviolet radiation causes the release of inflammatory cytokines from cells, which triggers the formation of reactive oxygen species (ROS) that damage lipids, proteins, and DNA. Plants, having to be exposed to high amounts of ultraviolet radiation, developed the ability to produce antioxidants to minimize permanent damage (Tenenbaum et al., 2002).

A double-blind study on 61 children aged 9-14 years old was conducted to test the effect of pycnogenol on ADHD symptoms. The subjects were given 1mg/kg body weight of either pycnogenol or placebo every day for 1 month. The results were recorded by teachers and parents who rated the subjects according to symptoms of attention-deficits and hyperactivity as well as visual-motoric coordination and concentration. After the 1 month study, the research showed significant improvement, however, these improvements were only temporary and washed out after one month. Further research showed that the group who took pycnogenol had a decrease in biomarkers of oxidative damage as compared to the placebo group. This is, therefore, an indicator of the higher efficacy of the drug in the adolescent age group (Trebatická et al., 2006).

In addition to studies done on children, another similar study in a randomized, double-blind, placebo-controlled, crossover study tested the efficacy of pycnogenol compared to a placebo group and MPH, Tenenbaum et al., 2002 studied 24 adults with ADHD. At the beginning and end of the administration of drugs, ratings

were given by the subjects themselves as well as their significant others to reflect the changes in ADHD-related symptoms. The subjects were given 1mg/lb body weight of MPH or pycnogenol per day for 3 weeks. The results showed, however, that there were no improvements when subjects took MPH or pycnogenol as compared to the placebo group. A possible explanation is both the subjects who took MPH or pycnogenol and the placebo group were clinical respondents, making it difficult to observe the effect of the drug. However, an explanation for this low efficacy in the adult age group is suspected to have to do with experimental technique instead of flaws in pycnogenol. It is possible that the pycnogenol has to be administered for longer than 3 weeks in adults to have significant clinical benefits. Or the dosage of pycnogenol administered is too low for an adult. Flaws in the sample could be too small a sample size or the sample was too heterogeneous (Simpson et al., 2019).

Conclusion

There are a number of possible explanations for the discrepancy in the efficacy of treatments within different age groups as shown by experimental studies, all of which correlate to affecting ADHD symptoms. The explanation of the effect of stimulants mentioned includes diminishing LC integrity as well as cognitive abilities and worsening ADHD symptoms. From non-stimulants, the loss of synapses and the shortening of dendrites cause decreased levels of dopamine and norepinephrine. From non-pharmacological methods, the lack of clinical respondents is thought to be affected by the experimental method implemented. Nonetheless, with current technology, it is difficult to determine with certainty the explanation behind the difference in efficacy of the treatment methods.

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