

Bachelor Degree Project



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COMMON TREATMENTS OF ATTENTION DEFICIT/HYPERACTIVITY DISORDER

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I hereby certify that all material in this final year project which is not my own work has been identified and that no work is included for which a degree has already been conferred on me.

Signature: _____

Abstract:

Attention-deficit/hyperactivity disorder (ADHD) is a well-known and much debated neurological disorder. The core symptoms consist of a lacking ability to maintain focus, hyperactivity and a motoric restlessness. It is a neurological disorder, with its causes under much debate, although this essay identifies some important brain areas and transmitter systems. The aim of this essay is to give an overview of the available treatments for children with ADHD in the form of the two largest groups of treatments; pharmacological treatments and psychosocial treatments. The conclusion found is that pharmacological treatments are more effective at reducing the core symptoms of ADHD, while psychosocial treatments are more effective at improving the development of social functioning, suggesting a combination to be the superior choice.

Keywords: Attention deficit/hyperactivity disorder, Methylphenidate, Amphetamine, Psychosocial treatments.

RUNNING HEAD: Treatments of ADHD

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Introduction

This essay will be on attention deficit/hyperactivity disorder (ADHD), which is a common disorder among children and for a long time believed to only affect children and be outgrown in adolescence. It has since been discovered that the previous acting out was in many cases simply replaced by less visible symptoms (Wolraich Et al., 2005), which sometimes persists even into adulthood (Resnick, 2005). The amount of people affected is hard to estimate and different studies present different numbers, the most common estimate in children range from 3% to up to 11% (Ellison-Wright, Ellison-Wright & Bullmore, 2008; Mayes, Bagwell & Erkulwater, 2008; Daley, 2005). This essay will focus mainly on the treatment options for children, reviewing and comparing the two main groups of treatment; pharmacological and psychosocial.

The core symptoms of ADHD are considered to consist of problems with maintaining focused attention, impulsivity and motoric restlessness (Daley, 2005). Results from intelligence-tests have indicated a generally lower IQ in children with ADHD, although this has been dismissed as flawed results, due to the symptoms of ADHD causing lower scores on tests in general (Bidwell, McClernon & Kollins, 2011). There are some variations of the combinations of the core symptoms and therefore the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) divides ADHD into 3 groups,

predominantly inattentive, predominantly hyperactive and combined ADHD (Vaughan, Roberts, & Needelman, 2009; Mayes, Bagwell & Erkulwater, 2008; Daley, 2005). Worth mentioning is that low self-esteem is also common among children with ADHD, although it is not considered a core symptom (Vaughan, Roberts, & Needelman, 2009).

The aim of this essay is to give an overview of the treatment options for children who suffer from ADHD by examining and comparing the two main treatment options, pharmacological treatments and psychosocial treatments. The articles used were chosen for their relevance to that aim and their availability, since even though there is an abundance of articles on pharmacological treatments, there are surprisingly few on psychosocial treatments.

First this essay will briefly discuss some of the background and related topics, such as how ADHD is diagnosed, and after that go into a bit more detail of what the neurological basis of ADHD is, to try to give a clearer picture of where the problems originate or at least give an account of what is known in that area so far. Two sections are used to discuss this, a section that is focused on the physical differences in the brain of someone with ADHD and a section describing the so called Dopamine Transfer Deficit-theory. After that the largest group of treatment will be discussed, pharmacological, both generally and with detailed

discussion of the main substances used. This will be matched with a section on the second largest group of treatments, psychosocial, with the most commonly used techniques discussed thoroughly. The essay will end with a comparison and evaluation of the two groups and some conclusions of which method of treatment is the better one or if they might be better used in conjunction with each other.

Background

When a child is suspected of suffering from ADHD, the first to report the signs are usually the parents and/or teachers. When such a situation arises, the child is taken to be examined by a pediatric neurologist, who interviews the child, the parents and the teacher/s in accordance with structured interviews specifically produced to extract the relevant information. The information from these interviews usually form the basis of the information used to set the diagnosis by comparing that information with the list of diagnostic criteria, which can be found in the appendix (Nass, 2006).

Two points in the list of diagnostic criteria are in my opinion important to take note of. The first is that the severity of the symptoms must be inappropriate for the developmental level of the child and the symptoms must be disruptive in the two settings used for the diagnosis, usually the school and the home. This is all the help the list of

criteria gives in differentiating between a child who is just troublesome and a child who really has ADHD (American Psychiatric Association, 1995).

The second point is that the symptoms must not be better explained by another diagnosis (American Psychiatric Association, 1995), which might be worthwhile to keep in mind since ADHD is commonly comorbid with a variety of other mental disorders and symptoms (Efron, Hazell & Anderson, 2011; Wilens, & Fusillo, 2007; Daley, 2005; Wolraich Et al., 2005).

Other methods can be used to give the neurologist stronger indications whether the diagnosis is correct or not, for example tests of executive functions such as IQ-tests and memory tasks, however they do not predict that the child has ADHD reliably enough for a diagnosis, only that he or she has problems similar of someone with ADHD (Nass, 2006).

ADHD is not an entirely uncontroversial diagnosis, with some researchers doubting its very existence (Tait, 2008), or at least doubting that the extent of the disorder is as large as the extent of pharmacological treatment (Graham, 2008; Mayes, Bagwell & Erkulwater, 2008). Tait (2008) wrote a philosophical article in which he attempted to show some of the logical fallacies displayed by the proponents of ADHD. Despite this article and other critiques (Graham, 2008; Mayes, Bagwell & Erkulwater, 2008), ADHD is a widely accepted neurological diagnosis (Tripp & Wickens, 2009; Mayes, Bagwell & Erkulwater, 2008; Levya, Hay, & Bennett, 2006; Daley, 2005).

ADHD is defined as a neurological condition (Ellison-Wright Et al., 2008), since it is assumed that neurological deficits, mainly in the frontal regions, are the causes of the disorder (Graham, 2008), however the specific causes are under much debate. Despite this, statistics show a highly probable heritability (Tripp & Wickens, 2009; Levya, Hay, & Bennett, 2006; Daley, 2005) sometimes measured to be as high as 77% (Banerjee, Middleton & Faraone, 2007).

There are many different genes being pointed to as important for ADHD in different ways, suggesting the heritable effect comes from a collection of genes each doing a small thing, rather than a few causing all the symptoms on their own (Tripp & Wickens, 2009).

There are also several environmental factors increasing the risk. These are much debated as well, but among them counts diet (Curtis & Patel, 2008; Daley, 2005), exposure to toxins, pregnancy and delivery complications as well as fetal exposure to alcohol and smoking (Banerjee, Middleton & Faraone, 2007). Diet has been much discussed in popular media, but many studies indicate it might play a much smaller role than believed. ADHD can rarely, however, be explained solely by genes or environment, but usually a combination of the two (Banerjee, Middleton & Faraone, 2007). With the many risk factors ADHD might be considered a difficult disorder to treat, without resorting to stimulant medication (Daley, 2005), but the appropriateness of giving so many young

children drugs has been questioned (Graham, 2008; Mayes, Bagwell & Erkulwater, 2008; Daley, 2005).

It has been theorized that ADHD is not just a cognitive dysfunction, but a motivational style, where the child attempts to avoid delay by giving rash responses (Bidwell, McClernon & Kollins, 2011; Daley, 2005). This came about through the observation that many of the experiments on ADHD-children were confounded by delay. A two-part experiment was conducted by Sonuga-Bark and colleagues first in the traditional manner where the next trial began as soon as the first one ended, and then a second time under time constraint, with a fixed time for each part, to prevent any time gain from impulsive decision-making. The first experiment showed ADHD-children making more errors than non-ADHD-children, the second however showed no difference between children with ADHD and those without (Daley, 2005). It has also been shown that children with ADHD are more sensitive to the delay of rewards (Tripp & Wickens, 2009) which is related to the functioning of the dopaminergic systems (Tripp & Wickens, 2008) which will be discussed later in this essay.

Neuroanatomy of ADHD

The causes of ADHD are a somewhat controversial topic. According to Tripp and Wickens (2009) the fact that ADHD is diagnosed by behavioral cues instead of physical tests can produce test groups that are less homogenous than test groups

for other conditions, which leads some researchers to question if there really is one unitary cause. If there is not, then ADHD is a collection of different disorders diagnosed as the same. If so, there is a need for finding the nuances and differences to divide the disorders from each other. There is also a possibility that there is one underlying cause that manifests itself in different forms and as the research stands at the moment, one cannot know for sure (Tripp & Wickens, 2009).

The research is because of this in some cases a bit inconsistent, making it hard to get a good overview of the neural correlations of ADHD. These inconsistencies have been discussed in recent years and have been attempted to be resolved by arguing that one should try to find which areas are the most radically different in children with ADHD compared to controls. This was done in a meta-analysis article by Valera, Faraone, Murray & Seidman (2006), which showed that even though the frontostriatal areas are the most significant, and indeed the most common area to research in connection to ADHD (Cherkasova & Hechtman, 2009; Popovic, Bhattacharya, & Sivaswamy, 2009; Tripp & Wickens, 2009; Valera, Faraone, Murray & Seidman, 2006), other areas should also be taken a closer look at, such as the cerebellum.

Even so, one of the most common finds in studies investigating the anatomical brain structure of ADHD is a reduction in total brain volume as well as more specific

volume reductions in caudate nucleus, prefrontal cortex white matter, corpus callosum and the cerebellar vermis (Tripp & Wickens, 2009).

As previously mentioned, the frontostriatal circuitry is often thought to be very closely linked to ADHD (Efron, Hazell & Anderson, 2011; Cherkasova & Hechtman, 2009; Tripp & Wickens, 2009; Valera Et al., 2006). It is involved in the inhibiting of impulses and the maintaining of habits (Chudasama & Robbins, 2006). It includes the dorsolateral prefrontal cortex, the ventrolateral prefrontal cortex, the dorsal anterior cingulate cortex, the caudate nucleus and the putamen (Cherkasova & Hechtman, 2009).

Structurally studies investigating the brain volume in children with ADHD have found prefrontal volume reduction, caudate nucleus and pallidum volume reduction (Cherkasova & Hechtman, 2009), and cortical thickness reduction (Cherkasova & Hechtman, 2009; Tripp & Wickens, 2009), as well as a delay in cortical maturation into adolescence. A significant regional grey matter reduction has also been shown in the right putamen-globus pallidus region (Cherkasova & Hechtman, 2009).

The frontostriatal circuitry is not the only areas of interest, however. Cherkasova and Hechtman (2009) have in their review of neuroimaging of ADHD found other important regions.

The cerebellum has been shown to perform many

different functions, not limited to primarily motor functions as traditionally believed, and a lot of these functions are important for ADHD (Bidwell, McClernon & Kollins, 2011; Cherkasova & Hechtman, 2009; Popovic, Bhattacharya, & Sivaswamy, 2009), such as temporal information processing, motor sequencing and planning, working memory, shifting of attention, implicit learning, emotional regulation, and executive functions (Cherkasova & Hechtman, 2009).

Structurally there have been many reports of reductions in posterior inferior lobules of the cerebellar vermis (VIII to X) in children with ADHD and some reports of reduction in lobules VI, VII and an overall volume reduction in the right cerebellum. Something to notice, according to Cherkasova and Hechtman (2009), is that the amount of studies on cerebellar volume in children with ADHD are few and despite the seeming agreement between the existing studies, more research need to be done on the topic.

The parietal areas are also discussed by Cherkasova and Hechtman (2009) as important for ADHD, due to their connection to functional attention. An important aspect to keep in mind when investigating the parietal areas is the diversity of the functions of the different parts.

Studies on the structural differences for children with ADHD have to some extent disagreed to what those differences actually are. The most common finds are overall reduction of the parietal lobe volume, reduced amounts of grey

matter, reduced amounts of white matter and reduced cortical thickness. Despite this there have been a few reports of inferior parietal grey matter increase (Cherkasova & Hechtman, 2009).

Finally, the temporal areas are also interesting in connection to ADHD, partly since impairment in linguistic processing have been reported in children with ADHD and the temporal areas play a key role in linguistic information processing, but also since some of the subcortical parts of the temporal areas, such as the amygdala and hippocampus, are thought to be involved in the processing of reward information and children with ADHD might vary from children without ADHD in the responsiveness to rewards and punishments (Cherkasova & Hechtman, 2009).

Studies on the structure of the temporal lobes in children with ADHD show reduced total temporal lobe volume, reduced grey matter volume and reduced cortical thickness. One study also found the hippocampus to be enlarged and the volume of the basolateral amygdala reduced (Cherkasova & Hechtman, 2009).

Dopamine Transfer Deficit

It has for a while been suspected that problems with the dopamine production are an important part of the biological foundation of ADHD. Tripp and Wickens (2008) theorize that children with ADHD suffer from what they refer

to as Dopamine Transfer Deficit (DTD) and that this condition is a possible partial cause of the symptoms of ADHD.

The theory of DTD is closely related to the findings surrounding the reaction children with ADHD have on reinforcement and delay of rewards, namely that they have trouble with it. The reason for this, according to Tripp and Wickens (2008), is that for a child without ADHD the target behavior, the behavior the child is later rewarded for, gives a response in the dopaminergic system. The dopamine cells in substantia nigra and ventral tegmental area are especially involved, also the striatum has in animal studies been found to activate in parallel to the reinforcement of an action and the nucleus accumbens in parallel to reward anticipation. For a child with ADHD on the other hand, the dopaminergic response to the target behavior is significantly reduced. These target behaviors function as cues for the later reward and the timing of the cue and reward, and nature of the cue and reward have been found to affect the firing rate of the dopamine cells across the learning session, in a manner consistent with contemporary learning theories (Tripp & Wickens, 2008).

The DTD theory posits that another difference in dopaminergic functioning between children with and children without ADHD should be that when a child without ADHD is learning, the early learning process should be characterized by a weak dopamine release in response to the cue, but a stronger response to the reward. Later in the learning process, the

response to the cue should get increasingly stronger while the response to the actual reward weakens. In this way the dopamine cell response is supposedly transferred from the reward to the cue. This process should also become faster at adapting to new cued stimuli as the amount of such previously learned behavior increase (Tripp & Wickens, 2008).

Contrary, for a child with ADHD, already the early learning process should have a weaker response to the cue, compared to the child without ADHD, while the response to the actual reward is comparable. Later in the learning process for the child with ADHD, there should still be a weak response to the cue and a strong response to the reward. This is at the moment untested, however, since brain imaging techniques cannot differentiate between different specific neurotransmitters (Tripp & Wickens, 2008).

Timing is an important aspect for the proper functioning of dopamine reinforcement on a cellular level. The release of dopamine must be within a very short time interval, described by Tripp and Wickens (2008) as a sub-second, and the theory is that the cues for a reward function to grant the dopamine release within the appropriate time interval, reinforcing the behavior even when the reward is delayed or discontinuous. This is proposed as the reason children with ADHD have trouble with delay, they do not get the needed immediate dopamine release (Tripp & Wickens, 2008).

In the context of the theory of DTD some of the behavioral symptoms of the diagnostic criteria in DSM-IV, which can be found in the appendix, can be can be biologically explained, although some cannot, indicating that the theory is only a partial solution to the causes of ADHD. Of the symptoms for inattention, "often does not give close attention to details or makes careless mistakes in schoolwork, work, or other activities", "often has trouble keeping attention on tasks or play activities" and "is often easily distracted by external stimuli" are examples of off-task behavior, which can be explained by underdeveloped dopamine responses to attending. According to Tripp and Wickens (2008), on-task behavior is maintained in children without ADHD by continuous reinforcement for attending by their previously learned dopamine anticipatory responses. Since children with ADHD develop less such anticipatory responses, they are instead reinforced by the instant reward of off-task stimuli.

Two more symptoms described by the DSM-IV that can be explained by DTD are "often does not follow instructions and fails to finish schoolwork, chores, or duties in the workplace" and "often avoids, dislikes, or does not want to do things that take a lot of mental effort for a long period of time". These symptoms can be explained by sensitivity to delayed reward. The four symptoms not mentioned cannot be satisfactory explained by the DTD theory, since they involve other primary psychological processes, which at best can be

indirectly linked to dopaminergic systems (Tripp & Wickens, 2008).

Regarding hyperactivity/impulsivity four symptoms can be explained by the DTD. The first is "often gets up from seat in the classroom or in other situations when remaining in seat for a long period of time is expected", which can be explained by lack of dopamine reinforcement for remaining in seat, similarly to the explanations for previously discussed symptoms of inattention. The symptoms of "often has trouble waiting one's turn", "often blurts out answers before questions have been finished" and "often interrupts or intrudes on others" can be explained by sensitivity to the innate delay of reward in the situations. The other hyperactivity symptoms are not directly explained by the DTD theory, however, might be explained by other consequences of altered dopamine responses, such as motor activating effects due to dopamine exciting striatal neurons (Tripp & Wickens, 2008).

According to Heal, Smith and Findling (2011) there is a very noteworthy connection between the dopaminergic system and the adrenergic system. Dopamine transporter neurons are fewer in the pre-frontal cortex, making it difficult to increase the dopamine efflux in that area. However, when norepinephrine efflux is increased dopamine can be transported in the norepinephrine reuptake transporter system into the

prefrontal cortex, because of the relatively low selectivity of the reuptake transporters. This is not as effective anywhere other than the pre-frontal cortex though, due to it being much more effective to simply increase the dopamine efflux of that area directly (Heal, Smith & Findling, 2011).

Concluding this section it is worth to note that if the DTD theory is correct, then it is possible to suffer from DTD without actually having ADHD, according to Tripp and Wickens (2008), due to only five and four symptoms being present in each category respectively and six being the required. However, drugs that increase efflux of dopamine, such as Methylphenidate and Amphetamine which will be discussed next, would be effective at improving the symptoms of both DTD and ADHD alike (Tripp and Wickens, 2008).

Pharmacological Treatments

Pharmacological treatments are by far the most common way to manage ADHD. It has been stated that about 90% of children diagnosed with ADHD will receive some form of medication. The reasons for not medicating a child with ADHD can vary wildly, those found to be among the most common are:

The cost of the medication is too much for the family to afford, the child does not respond to the medication, the side effects are outweighing the improvements of the medication and parents not accepting pharmacological treatment (Vaughan, Roberts, & Needelman, 2009).

The different medications are commonly divided into stimulants and non-stimulants, where stimulants are the most commonly used and often considered the most effective at reducing the core symptoms of ADHD. Non-stimulants on the other hand are mainly used to medicate the children who for some reason or another cannot take the stimulant medications. An example of such a reason could be allergic reactions to the specific substances (Vaughan, Roberts, & Needelman, 2009).

When trying out which substance would be the most fitting for a specific child, about 80% of the children respond to the first substance they are introduced to, however there can be some trouble with managing side-effects (Vaughan, Roberts, & Needelman, 2009). Insomnia (Vaughan, Roberts, & Needelman, 2009; Stein, Weiss, & Leventhal, 2007) and loss of appetite are common for stimulants, but affective flattening, mood disturbances, headaches, abdominal pain, lethargy, and fatigue are also possible. A somewhat rarer side-effect is a slightly increased pulse and blood pressure, although the amount increased is considered not to be significant unless there is a genetic history of cardiovascular problems (Vaughan, Roberts, & Needelman, 2009). There have been reports of children dying suddenly and unexplainably, which has been linked to the use of stimulants, although this is such a rare occurrence that the odds of it happening are not even calculable (Vitiello, & Towbin, 2009).

When looking at the long term effects of stimulants,

one of the few supposed side-effects found is a decrease in height and weight when reaching adolescence. However, there have been theories of children with ADHD having a different growth trajectory than other children of the same age, which, if true, would suggest the growth difference not to be a side effect at all. There is at this time not enough information on the subject to indicate one view over the other (Vaughan, Roberts, & Needelman, 2009).

Stimulant Medications

Stimulants have been suggested by the evidence to be effective for about 2 thirds of the children with ADHD who try them. They grant a variety of short term improvements in addition to, as previously stated, being considered the most effective at reducing the core symptoms of inattention, hyperactivity and impulsivity. Academic productivity and test scores also improve in children with ADHD with stimulant treatment (Vaughan, Roberts, & Needelman, 2009).

To use stimulants as a treatment for a disorder characterized by hyperactivity and inattention has by some been viewed as paradoxical, and some stimulants have even been marketed to have a "paradoxical effect" (Graham, 2008, p. 90). Despite this, the research has consistently shown stimulants to improve concentration for children with ADHD (Vaughan, Roberts, & Needelman, 2009) and even, to a lesser extent, those who do not have ADHD, but show similar behaviors (Graham, 2008). This is however not a surprising finding if

Tripp and Wickens (2008) are correct regarding their Dopamine Transfer Deficit theory.

Since the stimulants can be used recreationally in higher doses, there is always a risk for abuse (Ghaffari, 2009; Volkow & Swanson, 2008; Fone & Nutt, 2005). Increased dopamine efflux is known to reinforce drug use (Volkow, Fowler, Wang & Swanson, 2004), so worried parents have often wondered whether introducing their child to stimulants increases the risk of them becoming addicts later in life. While it has been found to be statistically true that substance use disorder is more common among adults with ADHD since childhood, the available research does not indicate a connection between the use of stimulant medication and substance use disorders later in life, although there have also been indications that adolescents who have not been previously treated for ADHD suffer a slightly higher risk of developing substance use disorders (Ghaffari, 2009; Volkow & Swanson, 2008).

Stimulant medication comes in many variants and forms, trying to tailor the medication to the needs of the child and the child's environment. The active ingredients, however, are nearly always either methylphenidate or amphetamine. The choice of specific medication is especially important if the child has a co-morbidity, which might sometimes require another medication and create the risk of adverse combined side effects (Heal, Cheetham & Smith, 2009;

Vaughan, Roberts, & Needelman, 2009).

Methylphenidate

The most common of the active ingredients in ADHD-medication in Europe and one of the most thoroughly tested medications for ADHD is methylphenidate. It is a dopamine and noradrenaline uptake inhibitor and when discussing ADHD it is important to know that it has been shown to substantially increase the efflux of dopamine in striatal areas (Bidwell, McClernon & Kollins, 2011; Heal, Smith & Findling, 2011) and prefrontal cortex (Heal, Smith & Findling, 2011), which as previously mentioned is important for the functions of ADHD, especially if the Dopamine Transfer Deficit theory is correct (Tripp & Wickens, 2008).

The common medications contain D-threo-isomer methylphenidate, also known as D-methylphenidate, or a 50/50 mixture of D-methylphenidate and L-threo-isomer methylphenidate, also known as L-methylphenidate. Such a 50/50 mixture of two mirroring isomers is known as racemic. The majority of the effect of the DL-methylphenidate medications is believed to come from the D-methylphenidate, due to research showing it to be about ten times as potent as L-methylphenidate. Methylphenidate was originally introduced as a mix of two racemic compounds, the DL-threo-methylphenidate mentioned above and the DL-erythro-methylphenidate, which was later found out to not affect the central nervous system at all and was therefore discontinued (Heal, Smith & Findling,

2011).

When used in medications, the effect of methylphenidate can last about 3-4 hours or even up to 12 hours, all depending on whether it uses a delayed delivery system or if the dose is immediate release. When treating with the immediate release pills, the child must take the medication 2-3 times per day, which for many is not ideal (Vaughan, Roberts, & Needelman, 2009).

Several long-acting alternatives exist, with different delivery systems. Some examples are as follows:

Metadate CD and Ritalin LA which contain 30% and 50% immediate release methylphenidate respectively and also 70% and 50% respectively of delayed release methylphenidate beads. Their coverage is about 8 hours (Vaughan, Roberts, & Needelman, 2009).

Focaline XR, an extended release form of focaline, also has 50% each of immediate and delayed release doses (Vaughan, Roberts, & Needelman, 2009).

Ritalin SR, Metadate ER and Methylin ER are single-pulse sustained release products of methylphenidate. They are coated with a wax matrix, which must be swallowed whole to preserve the long-acting properties (Vaughan, Roberts, & Needelman, 2009).

Daytrana is a patch with methylphenidate, delivering the drug through the skin, which is applied once per day. For children unable to swallow pills or have gastrointestinal

side-effects, Daytrana is ideal. Unfortunately the side-effects of skin redness and irritation are fairly common, which sometimes makes some parents opt for some other kind of treatment (Vaughan, Roberts, & Needelman, 2009).

Amphetamines

Amphetamine based stimulants are a less common way to treat ADHD in Europe, however in the US are just as common as methylphenidate (Heal, Smith & Findling, 2011). They are considered to be slightly more effective than methylphenidate (Faraone & Buitelaar, 2010). The list of different variants of amphetamine that has been shown to be effective for the treatment of ADHD is as follows; D-amphetamine, L-amphetamine, racemic amphetamine, Adderall and lisdexamphetamine (Heal, Smith & Findling, 2011).

Amphetamine based medication functions by stimulating the release of monoamines, which is a group of neurotransmitters, most notably containing dopamine and norepinephrine (Bidwell, McClernon & Kollins, 2011; Heal, Smith & Findling, 2011). Amphetamine as a compound is also structurally related to dopamine and norepinephrine (Heal, Smith & Findling, 2011). This is of course important in relation to the Dopamine Transfer Deficit Theory (Tripp & Wickens, 2008).

Comparing the therapeutic effectiveness of amphetamine based medications with non-stimulant medications, there are a few studies showing results in favor of

amphetamines, although the area needs more research (Heal, Smith & Findling, 2011). Below follows a few examples of Amphetamine-based medications:

Adderall contains a mix of 50% of the slightly outdated L-isomer, or L-amphetamine, and 50% of the nowadays most common D-isomer, or D-amphetamine (Heal, Smith & Findling, 2011). Adderall XR is the extended release version of Adderall, with 50% immediate release and 50% delayed in beads. It is designed to mimic the effect of taking two immediate release Adderall's with a 4 hour interval (Vaughan, Roberts, & Needelman, 2009).

Vyvanse, also known as lisdexamphetamine, is the first stimulant to be a prodrug, which means it is inactive upon ingestion and activates due to chemical processes in the intestines. The d-amphetamine is covalently bound to l-lysine, and becomes active d-amphetamine when it is hydrolyzed. Since hydrolysis is rate-limited, the process is slow and predictable, which of course is desirable in a long acting medication (Bidwell, McClernon & Kollins, 2011; Cheetham & Smith, 2009; Popovic, Bhattacharya, & Sivaswamy, 2009; Vaughan, Roberts, & Needelman, 2009). It has been well tested and found to be safe for children and adults, although research is lacking for its use in adolescents and it should not be used by pregnant or breastfeeding women (Popovic, Bhattacharya, & Sivaswamy, 2009).

Non-stimulant Medication

While stimulants are considered the most effective direct treatment of ADHD, there are, as mentioned before, sometimes reasons for not treating a child with them, such as allergies or lack of response to the treatment. When stimulant treatment is no longer an option there is still a wide array of non-stimulant options to choose from, which also often have an effect that lasts throughout the day, a feature even delayed release stimulants have a difficult time matching (Vaughan, Roberts, & Needelman, 2009). Non-stimulants also generally have less risk of abuse, due to most often being unable to create the euphoric sensation associated with recreational use (Ghaffari, 2009).

Since what can be considered a non-stimulant drug with positive effects on ADHD is a quite loose definition, and therefore creates a large amount of obscure drugs with little research on their effects on ADHD, the rest of this section will focus on presenting the most common and important non-stimulants used for treatment of ADHD.

Bupropion is both used as an anti-depressant, marketed as Wellbutrin, and an aid to quit smoking, marketed as Zyban, which has been indicated to be effective against ADHD. It is not entirely known how the drug works, but it is believed to indirectly inhibit norepinephrine and dopamine reuptake. Compared to other dopamine reuptake inhibitors, it is not very strong. It has been shown to affect prefrontal

cortex, striatum and nucleus accumbens, indicating it to be effective in the treatment of ADHD. Stimulants are still much more effective, although bupropion might be a sound alternative, considering the much lower risk of abuse compared to stimulants and especially for children in which bupropion have shown more improvement than in adolescents and adults (Heal, Smith & Findling, 2011).

Irritability, insomnia and loss of appetite are common side effects of bupropion and rashes, edemas and seizures are rare, although seizures have been linked to higher doses, eating disorders and previous history of seizures (Heal, Smith & Findling, 2011; Vaughan, Roberts, & Needelman, 2009).

Modafinil, or Provigil, is a drug usually used for treating narcolepsy, stimulating the cortex without a widespread activation of the central nervous system, but it has also been shown to improve ADHD symptoms. In a positron emission tomography experiment Modafinil was shown to affect the striatum and thalamus of monkeys and striatum of humans (Heal, Smith & Findling, 2011; Heal, Cheetham & Smith, 2009). In microdialysis it has been shown to increase dopamine amounts in the nucleus accumbens of rats and the striata of dogs and monkeys (Heal, Smith & Findling, 2011; Heal, Cheetham & Smith, 2009).

No direct comparison between stimulants and Modafinil has been made, so there is no real knowledge of its relative

effectiveness in relation to stimulants, although it is likely to be less effective than stimulants. Its abuse potential is low, although it has been found to be reinforcing in monkeys and humans in high doses. Despite this it is not approved for use in the US due to one of the rare side effects being rashes characteristic of Stevens-Johnson syndrome (Heal, Smith & Findling, 2011; Vaughan, Roberts, & Needelman, 2009).

Atomoxetine, or Strattera, is a selective noradrenergic reuptake inhibitor and the first non-stimulant drug to be approved for use in the US for ages 6 and up (Bidwell, McClernon & Kollins, 2011; Heal, Smith & Findling, 2011; Graham, Seth, & Coghill, 2007). Atomoxetine synergizes with the structure of the prefrontal cortex, and increase dopamine in that area (Bidwell, McClernon & Kollins, 2011; Heal, Smith & Findling, 2011), which is key to its usefulness in ADHD treatment. Unfortunately, since the effect of Atomoxetine is so specific to the prefrontal areas, other areas might not be treated as well, which is believed to be the reason stimulants have been found more effective (Heal, Smith & Findling, 2011; Heal, Cheetham & Smith, 2009).

Dosing of Atomoxetine is based upon weight of the recipient and the improvements, both social and core symptoms, is dependent on correct dosage. There is a dose ceiling, meaning after a certain dose, the effects of the drug do not increase. Most common side effect is loss of appetite, although mood liability and sedation has been observed. One

downside to Atomoxetine is that it can take up to 4-6 weeks before the effects of the drug start to emerge, which may limit its usefulness in certain circumstances (Heal, Smith & Findling, 2011; Vaughan, Roberts, & Needelman, 2009).

Clonidine mimics the functions of norepinephrine by stimulating all three subtypes (A, B and C) of alpha-adrenergic receptors in the pre-frontal cortex (Bidwell, McClernon & Kollins, 2011). It is most often used to treat hypertension, but is also used for treating ADHD, tic disorders and ADHD related sleep disturbances. For the treatment of ADHD it is effective against hyperactivity and impulsivity, but has limited effect on attention. It has been found to have a halftime of about 5 hours in children and common side effect is sedation or sometime hypotension, although hypertension can be the result of a sudden withdrawal. There is also a version of Clonidine on a patch (Vaughan, Roberts, & Needelman, 2009).

Guanfacine is an anti-hypertension medicine, similar to Clonidine, but has been shown to improve both attention and hyperactivity (Bidwell, McClernon & Kollins, 2011; Vaughan, Roberts, & Needelman, 2009). It also mimics norepinephrine by stimulating the pre-frontal cortex, but more specifically and more effectively the alpha-adrenergic receptors of subtype A, which strengthens the connectivity in the pre-frontal cortex (Bidwell, McClernon & Kollins, 2011). For being a non-stimulant drug it is unusually effective at treating

hyperactivity and impulsivity, almost rivaling stimulants. Treating inattention with guanfacine is not as effective however and has comparable effect to other non-stimulants (Heal, Smith & Findling, 2011).

Open label trials over two years with the extended release version of guanfacine, Intuniv, revealed a discontinuation rate of more than 80%. 12,5% reported lack of efficiency to be the reason, however the ones who completed the entire trials reported a maintained efficiency over the period (Heal, Smith & Findling, 2011).

The most common side effect of guanfacine is sedation, although some small changes in blood pressure have been observed (Vaughan, Roberts, & Needelman, 2009).

Venlafaxine is an antidepressant which has been studied as a treatment for ADHD, although unfortunately mostly in adults. It is a serotonin and norepinephrine reuptake inhibitor, known side effects are abdominal pain, restlessness, loss of appetite, increased appetite, insomnia, vomiting, nausea, somnolence and headaches (Amiri, Farhang, Ghoreishizadeh, Malek & Mohammadzadeh, 2012; Zarinara Et al., 2010).

The active ingredient in cigarettes, nicotine, has long been known to improve various cognitive aspects in humans, such as attention (Bidwell, McClernon & Kollins, 2011; Swan & Lessov-Schlaggar, 2007). Only recently, however, has nicotine been considered as a treatment option for ADHD. This

is slightly controversial since statistics show that individuals with ADHD are at risk to start smoking at a younger age and have more trouble quitting. In the brain, receptors that accept nicotine are found in nearly every region, where they modulate the function of other transmitter systems. At the moment, there are no approved nicotine treatments for ADHD, however it is researched with hope to be used in the future (Bidwell, McClernon & Kollins, 2011). Despite these positive features, the physical side-effects, such as raised heart-rate and blood pressure, might make nicotine undesirable as a treatment (Swan & Lessov-Schlaggar, 2007).

Despite the success of many of the pharmacological agents to relieve symptoms of ADHD, one must not forget that they do not cure ADHD. Since the results from the famous multimodal treatment study of children with ADHD (commonly referred to as the MTA) gave strong indications that psychosocial treatments are inferior to pharmacological treatments in treating the core symptoms of ADHD, most of the research on ADHD has been on pharmacology and the use of pharmacological treatments has been the first pick of treatments for clinicians and many researchers seem to consider psychosocial treatments obsolete (Heal, Cheetham & Smith, 2009; Pelham & Fabiano, 2008; MTA Cooperative Group, 1999).

Not all researchers agree however that the MTA was

the last nail in the coffin for psychosocial treatments, and still think they have a place as a complement to the pharmacological solutions (Pelham & Fabiano, 2008; Chronis, Jones & Raggi, 2006).

Psychosocial Treatments

There are a vast number of psychosocial therapies for the treatment of ADHD out there, the problem being that many of them simply do not have any scientific foundation for their claims to improve the core symptoms of ADHD (Fabiano, Pelham, Coles, Gnagy, Chronis-Tuscano & O'Connor, 2009; Heal, Cheetham & Smith, 2009; Pelham & Fabiano, 2008).

Since there rarely are clear and exact definitions of what activities a psychosocial treatment must or do contain, they are often presented in groups, this section will discuss the most common and most scientifically supported groups of treatment.

Psychosocial treatments are very delicate and there is a great need to tailor-make the treatment to the developmental level and behavioral dysfunctions of the child. Much of the work in psychosocial treatments is spent on educating the parents on the workings of ADHD and the correct way to parent a child with ADHD, in part since statistics show that many parents of children with ADHD suffer from some kind of psychopathology themselves, but also in part since the responses parents develop to deal with the behaviors of a child with ADHD might be counterproductive (Chronis, Jones &

Raggi, 2006).

There are reasons to consider complementing stimulant treatments with psychosocial treatments, even when stimulants would work fine, such as to improve the parent-child relationship, which can be quite strained by the child's behavior and parents lack of knowledge of the disorder, and to improve social skills. Drugs are great for improving core symptoms, but sometimes more is required (Chronis, Jones & Raggi, 2006). Important to note also is that during the MTA (multimodal treatment study of children with ADHD) parents reported being most satisfied with the combined stimulant and behavioral treatments (Chronis, Jones & Raggi, 2006; MTA Cooperative Group, 1999).

Family-Based Interventions

Psychosocial treatments are often spoken of as interventions and as one of the settings used in a diagnosis is often the home, that group is referred to as the family-based interventions. As mentioned, parents sometimes develop strategies for dealing with disobedient children that are very counterproductive, especially when the child suffers from ADHD and learning to deal with the stress, understanding the disorder and learning better ways to handle the child's inappropriate behavior are necessary for a functioning home-life (Chronis, Jones & Raggi, 2006). Due to the similarity of the behavior, I find it probable that disobedient children would also benefit from having these strategies taught to

their parents, although this is never clearly stated by Chronis, Jones and Raggi (2006).

Behavioral Parent Training is the most common form of home-based interventions based on social learning techniques and in it parents learn to see the signs and consequences of a child's behavior, to respond appropriately and bring about better consequences, to reinforce positive behavior by praise and positive attention and decrease negative behavior by use of approved discipline techniques, such as planned ignoring, time out or removal of privileges (Daly, Creed, Xanthopoulos, & Brown, 2007; Chronis, Jones & Raggi, 2006). It has a solid scientific foundation of studies supporting its effects, especially at improving the parent-child relationship (Pelham & Fabiano, 2008; Chronis, Jones & Raggi, 2006).

School-Based Interventions

The second setting most often used for diagnosing is the school setting, where school-based interventions are put in. Also, since the school-behavior is typically the setting where symptoms are seen the most, and reflected in academic performance, it is a vital setting to try to improve in (Chronis, Jones & Raggi, 2006).

Classroom Behavioral Management interventions is a form of school-based intervention where the teacher gets educated generally on the disorder and then more specifically in the needs of the child and also learns proper behavior

modification strategies and discipline techniques, much in the same manner as Behavioral Parent Training, but with more classroom adapted alternatives, an example of which is the daily report card, often referred to as the DRC (Pelham & Fabiano, 2008; Daly Et al., 2007; Chronis, Jones & Raggi, 2006).

The daily report card is a reinforcement method where specific goals are set on how the child behaves in class and the child is then rewarded at home for how well the goals were met. It is important that the goals set are always challenging, but not impossible for the child to meet, and as such increase successively as the child approaches the normative behavior of a same aged child. At the same time, the daily report card informs parents of the progress of the child's behavior and performance in the school setting, giving them a chance to give further reinforcement if appropriate. The developmental level of the child determines the amount of goals and frequency of the feedback, tailoring the method to suit the child. It might for example be suitable to have fewer goals and more frequent reinforcement and feedback regarding a younger and more impulsive child, than an older child or adolescent (Chronis, Jones & Raggi, 2006).

Academic interventions are another kind of school-based interventions, which instead of targeting the disrupting behavior in the classroom focuses on improving the academic performances by manipulating instructions and materials in the

academic setting. This is of course important due to the fact that ADHD is very strongly associated with weaker academic performances and is known to often be co-morbid with a variety of learning disabilities (Chronis, Jones & Raggi, 2006).

Chronis, Jones & Raggi (2006) mentions a number of common academic interventions. One which is not specifically named is to target homework problems by structuring of the homework time, using of goals and reinforcement and a collaborative effort between the parents and the teacher. This kind of intervention has been studied and shown to produce good results (Chronis, Jones & Raggi, 2006).

Another is Task and Instructional Modifications in which the task the child is supposed to perform is divided into smaller subunits, length of task is reduced, goals are set to shorter time intervals, more stimulating variant of the task is used, meaning for example adding color or texture, and/or the instructions are giving in an individually adapted way, depending on the child's preferred learning style (Chronis, Jones & Raggi, 2006).

Computer-Assisted Instruction means altering the form of the task, which can be done in several different ways. Specific instructional objectives can be presented, essential material can be highlighted, multiple sensory modalities can be used, information can be divided into smaller chunks and feedback on response accuracy can be immediately provided (Daly Et al., 2007; Chronis, Jones & Raggi, 2006).

Related to Computer-Assisted Instruction is the so called Working Memory Training. Not actually an academic intervention, it focuses more on improving the inattentive symptoms of ADHD, by practicing the use of working memory in a computer program. Successive increases in difficulty challenges the child and it has been shown in a few studies to be effective, though it is a very new method and there has been relatively little research on it (Bidwell, McClernon & Kollins, 2011).

Strategy training means teaching the child strategies to handle academic situations, such as taking notes, completing homework, studying skills and procedures for self-reinforcement (Chronis, Jones & Raggi, 2006).

The final academic intervention mentioned by Chronis, Jones & Raggi (2006) is peer tutoring, where another child provides assistance, instruction and feedback, which improves academic and social skills (Chronis, Jones & Raggi, 2006).

Unfortunately, very few studies have investigated the results of academic interventions, although the ones that have found them to be effective. Worth to note is that most of these studies took place in a classroom environment, introducing many confounding's which makes it difficult to draw any conclusions from the studies. All in all, more investigation into the area is needed (Chronis, Jones & Raggi, 2006).

Peer Interventions

Since children with ADHD suffers a greater risk of developing poor social skills and becoming social outcasts due to their hyperactive and often aggressive behavior, there is a need to target peer relationships in the treatment (Chronis, Jones & Raggi, 2006).

Social skills training is one of the more common treatments in this category, and focus on the development and reinforcement of behavior and skills that are socially acceptable and appropriate, such as cooperation and communication. Though such an intervention seems logically sound, there is little evidence that it actually improves the behavior of the children (Pelham & Fabiano, 2008; Chronis, Jones & Raggi, 2006). There has been some support for a positive effect when combined with other social treatments, most notably a study combining parent training and social skills training showing positive results, although the study has yet to be replicated (Chronis, Jones & Raggi, 2006).

Summer treatment program for children with ADHD (commonly referred to as STP) is an eight-week intensive combination of several evidence-based techniques and treatments, such as group-based parent training, a daily report card, social skills training, sports skills training and problem solving skills training. These treatments are used both in an academic and recreational setting, to improve the child's interaction with adults and peers, academic

performances and self-efficacy (Chronis, Jones & Raggi, 2006). The summer treatment program is well supported in the literature as an effective treatment for ADHD; even the MTA supported it as a viable treatment option (Pelham & Fabiano, 2008; Daly Et al., 2007; Chronis, Jones & Raggi, 2006; MTA Cooperative Group, 1999).

Combined Pharmacological and Psychosocial Treatment

Quite few studies have investigated the effects of combining pharmacological and psychosocial treatments, the biggest one being the MTA. It consisted of a 14 month treatment in one of 4 treatment groups, psychosocial treatments (referred to as behavioral treatments), pharmacological treatments (referred to as medical management), combined treatments and community comparison group, which meant they could choose whether to stay untreated or get the treatment offered in their community. A third of the participants in the community comparison group did not receive any treatment, most of the other two thirds received medication (Chronis, Jones & Raggi, 2006; MTA Cooperative Group, 1999).

The MTA showed that medical treatments were just as effective as combined treatment at reducing the core symptoms of ADHD and the behavioral group had no incremental effects (Daly Et al., 2007; Chronis, Jones & Raggi, 2006), which by some has been taken to indicate that psychosocial treatments are largely ineffective (Heal, Cheetham & Smith, 2009; Pelham & Fabiano, 2008). Despite this, combined treatments were rated

the highest by parents and showed more improvement on social skills and parent-child relationships (Chronis, Jones & Raggi, 2006; MTA Cooperative Group, 1999).

Discussion

The research on ADHD is, at the moment, very one-sided. This is easily seen when searching for articles, and is also mentioned in some reviews as a problem (Efron, Hazell & Anderson, 2011). Pharmacological treatment options are researched very intensively and extensively while other areas, such as psychosocial treatments for example, are left to only a handful of dedicated (perhaps even zealous) researchers. This makes trying to review, discuss and compare the different treatment options for ADHD a difficult task in that it is very difficult to discern whether or not the conclusions regarding the standing of psychosocial treatments drawn in various articles are valid or not. There does not seem to be a solid comparable foundation for claiming either pharmacological treatments or psychosocial treatments to be the clearly better alternative when there is so much debate over the conclusions of the most important studies discussing the subject, such as the MTA. Heal, Cheetham and Smith (2009), for example, claim the MTA proved psychosocial treatments ineffective and stating that as the reason to research pharmacology, while Chronis, Jones and Raggi (2006) point to the same study claiming it to show the value of psychosocial treatments combined with pharmacological treatment, which they consider reason enough

to research psychosocial treatments. These slight biases to one's own research might be inescapable, but makes it difficult to discern the direction research should take, although at the heart of the problem lies, in my opinion, the overweight of research on the pharmacological side, making me inclined to say there is a need of more research in psychosocial treatment and especially in comparing and combining the two treatment groups.

So, in the discussion of which treatment option is better for treating ADHD, the consensus seem to simply be that stimulant treatments are superior, due to the quick, cheap and effective impact they have on the core symptoms of ADHD. This, however, is the view of the researchers researching pharmacological treatments of ADHD, making the conclusion sound a little bit as a biased opinion, as already discussed a moment ago. As also stated there, studies of the opposing view do not claim such rigorous conclusion, here illustrated by a statement by Pelham & Fabiano (2008):

"Many reviews have concluded that medication is more effective than behavior modification. Notably, these reviews have all based their conclusions on the small number of large, between-group studies in the literature – most prominently the MTA." (Pelham & Fabiano, 2008, p. 185)

This indicates that perhaps psychosocial treatments should not be taken entirely out of the count, even though

stimulant treatments are more effective in treating core symptoms.

Conclusions

I think it seems likely that the best and most appropriate general treatment option would be the combined treatment, where the psychosocial treatments can be taken to full benefit with the aid of stimulants, or other pharmacological treatments. This might not be entirely practical however, since children with ADHD are a very heterogeneous group and it might be a lost cause to find a singular treatment method to suit all needs. The conclusion of this essay is that treatment should always be suited to the needs of the specific child, unless one is forced to discuss the matter generally, in which case the best course of action seems to be a combined treatment option.

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comparison trial. *Human Psychopharmacology: Clinical and Experimental*, 25, 530-535.

Appendix

A. Either 1 or 2:

1. Six or more of the following symptoms of **inattention** have been present for at least 6 months to a point that is disruptive and inappropriate for developmental level:

Inattention

- a. Often does not give close attention to details or makes careless mistakes in schoolwork, work, or other activities.
- b. Often has trouble keeping attention on tasks or play activities.
- c. Often does not seem to listen when spoken to directly.
- d. Often does not follow instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behaviour or failure to understand instructions).
- e. Often has trouble organizing tasks and activities.
- f. Often avoids, dislikes, or does not want to do things that take a lot of mental effort for a long period of time (such as schoolwork or homework).
- g. Often loses things needed for tasks and activities (e.g. toys, school assignments, pencils, books, or tools).
- h. Is often easily distracted by external stimuli.
- i. Is often forgetful in daily activities.

2. Six or more of the following symptoms of **hyperactivity-impulsivity** have been present for at least 6 months to an

extent that is disruptive and inappropriate for developmental level:

Hyperactivity

- a. Often fidgets with hands or feet or squirms in seat.
- b. Often gets up from seat in the classroom or in other situations when remaining in seat for a long period of time is expected.
- c. Often runs about or climbs when and where it is not appropriate (adolescents or adults may feel very restless).
- d. Often has trouble playing or enjoying leisure activities quietly.
- e. Is often 'on the go' or often acts as if 'driven by a motor'.
- f. Often talks excessively.

Impulsivity

- g. Often blurts out answers before questions have been finished.
- h. Often has trouble waiting one's turn.
- i. Often interrupts or intrudes on others (e.g., butts into conversations or games).

B. Some symptoms of hyperactivity/impulsivity or inattention that cause impairment were present before age 7 years.

C. Some impairment from the symptoms is present in two or more settings (e.g. at school/work and at home).

D. There must be clear evidence of significant impairment in social, school, or work functioning.

E. The symptoms do not happen only during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and the symptoms are not better accounted for by another mental disorder (e.g. Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).

(American Psychiatric association, 1994, p. 47-49).