Controversies over Attention-Deficit/Hyperactivity Disorder

Bachelor thesis

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Annotation

This bachelor thesis discusses the matter of attention-deficit/hyperactivity disorder which is one the most studied mental disorders today. Regarding its rich history of development it elicits many controversies over the diagnosis itself, diagnostic criteria and treatment as well. First of all it deals with the basic characteristics of what the disorders is, what are the diagnostic criteria according to DSM-IV and ICQ-10 and most importantly how do we treat this disorder, which is the topic that evokes the most discussions. The three main questions that I am intruding to answer in the last chapter are, are there comprehensive diagnostic criteria and methods for diagnosing ADHD does the use of stimulants for treatment beget later substance abuse/use, and is the use of stimulants the cause of sudden deaths? The goal of this thesis is to find answers to these questions using and analysing studies, meta-analysis and reviews of literature accomplished by American and British researchers.

Keywords

Attention-deficit/hyperactivity disorder · inattention · impulsivity · hyperactivity · stimulant · methylphenidate · amphetamine · sudden death · substance use disorder

Abbreviations

Declaration

I declare that I worked out the presented paper myself and that I used only below mentioned resources. At the same time I agree that this work can be made available both in a relevant library of The Charles University and through the electronic database of university dissertations in the depository of The Charles University, and used for study purposes in accordance with the copyright law.

In Prague, the 30th of June

Eva Hartmannová
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Introduction

Attention-Deficit/Hyperactivity Disorder is one of the most studied disorders today. It went through great changes since it has been first discovered in 1902 that concern its diagnostic criteria, etiology and also its treatment and there are still new aspects emerging.

My interest in this disorder has been elicited by meeting some of these children during my 6 years’ pedagogical experience, which led to a deeper research of this disorder. At the beginning I was looking for some methods that would help me manage these children, but as I found out more and more about this matter, I started to realize there are many more issues that need to be perused.

As I made my way through a great number of books, articles and web pages, I discovered there are several controversial issues that elicit stormy discussions among public, parents, clinicians and specialists and decided to find out more about these controversies and try to get to the root of them, which later led me to choose this search as the topic of my thesis.

The first chapter is presenting all the important controversies that caught my eye and that arise from the different views of this disorder and which caused in following chapters an urge to describe this disorder in detail, including its history of development. I felt that it is very important to know first what this disorder is about, what are the main characteristic, core symptoms and most importantly what treatments are used for managing it, as these are the matters that evoke greatest controversies.

There have been concerns about the diagnosis itself and questions like, is it really a disorder, are the clinicians conducting adequate diagnosis and are there sufficient diagnostic criteria and methods, are falling on us from everywhere. Even more fuss and disagreements are apparently around the use of medicaments, particularly stimulants, as a fundamental part of the treatment of children with ADHD. And the last but not least is the concern about the sudden death of children using stimulants, particularly Ritalin. These controversies and questions led me to settle 3 main questions that I would like to answer in the third chapter deriving from individual studies, meta-analysis and reviews of literature accomplished by American and British researchers which will sow the seed for figuring out the separate controversies.

The main questions I will be intruding in are:

Are there comprehensive diagnostic criteria and methods for diagnosing ADHD?
Does the use of stimulants for treatment beget later substance abuse/use?
Is the use of stimulants the cause of sudden deaths?

The goal of this thesis is to give the readers an idea about what this disorder is and what is going on around it, and to find satisfying answers to the questions initiated above supporting them with the analysis of the studies.

To some people it might seem as insignificant such attention to one of the mental disorders when we have so many of them, but I can assure you that as this disorder is “spreading among the children almost like a pandemic plague”, you never know when you’ll bump into one of them and you should get ready for an unstoppable tornado that sometimes causes more trouble than a bag of flies. If you want to find out where this tornado comes from and how it could be stopped before it causes calamity in his and others life, keep on reading.
1. Opening into the matter

Attention-deficit/hyperactivity disorder (further ADHD) seems to be a term that we all heard once somewhere, but most of us will find ourselves in a situation when we are not able to open the right drawer in our memory and find the right information about this matter. Even if we located it, we would soon find out that the information that we hold is incomplete and fragmentary. As a matter of fact it is not that much our fault, because even the specialists devoted to this field differ in their opinions concerning ADHD, its etiology, symptoms and therapy. ADHD is the most discussed and studied disorder nowadays and the development of this disorder throughout the 20th century creates a very breeding ground for many controversies.

1.1 Controversies over ADHD and its treatment

The discrepancies begin with the diagnosis itself. Some people feel that even diagnosing children with this disorder is mistaken and they think that it is a way how to deal with children that are hard to handle in school or elsewhere. Some groups like Church of Scientology and some specialists claim that the whole idea of ADHD is a “myth” and that it is not correct to label children in this way.

Doctor Fred Baughman is one of the specialists that don’t consider ADD/ADHD a disease and he calls it a fraud. Dr. Baughman is an adult & child neurologist, he has been running his private practice for 35 years and is experienced, as he says, in making diagnosis of “real” diseases. He claims that:

“They made a list of the most common symptoms of emotional discomfiture of children; those which bother teachers and parents most, and in a stroke that could not be more devoid of science or Hippocratic motive - termed them a “disease”. “ (Baughman, 2001) He also says that the number of children diagnosed with ADHD has grown from 500 thousand in 1985 to between 5 and 7 million in 2001, and he asks himself what is the cause of it, is it possible, that the number could have risen with such a great speed in such a short period of time? According to his opinion ADHD was created by psychiatric/pharmaceutical cartel, in order to have somebody to prescribe stimulants to. These stimulants, as Ritalin (methylphenindate), Dexedrine (dextro/amphetamine), Aderall (mixed dextro/ and levo/amphetamine) and Gradumet, and Desoxyn (both methamphetamine) belonging into
Schedule II are dangerous and addictive. Doctor Bauhman warns public, that it has been betrayed and victimized, and he demands immediate stop of drugging children.

If we consider ADHD a disorder, the next difficulty that appears, is the diagnosis of it and evaluating children. It is crucial to establish diagnostic criteria and methods for ADHD that are reliable and valid and that will avoid misdiagnosing, which would have serious consequences. There are concerns that the physicians do not perform thorough and sufficient evaluations before starting the treatment.

The most widely spread and contemporary concerns relate to the use of medicaments, primarily of stimulants, as a treatment of ADHD. The shocking fact that frightens many people is the dramatic increase of production and use of Ritalin, which raises questions for the cause of it. Is it because of the change of diagnostic criteria, or improved physicians’ recognition of the disorder, or more evidence of the effectiveness of stimulants, or prescription for profit? Doubts concerning using stimulants as part of the treatment are enormous. Another one says, stimulants are amphetamines, which are proved to be addictive and we want to treat our children with these? The question is if the use of stimulants begets later substance abuse and/or drugs use.

Another issue that makes parents’ eyes wild with terror is cases of sudden death. When you google the term ADHD you will find web pages as www.RitalinDeath.com that warn parents against letting their children be treated by stimulants particularly Ritalin, as they are convinced that it was the cause of their children’s deaths. They refer to the statement which was presented at the National Institutes of Health Consensus on ADHD: "We do not have an independent, valid test for ADHD, and there is no data to indicate that ADHD is due to a brain malfunction"1. According to them ADHD, ADD and other labels are not true diseases and even the psychiatrist are not able to find common and unambiguous diagnostic criteria. In spite of this they are still prescribing medications as Ritalin to the children that supposedly suffer from these diseases.

Mr. Lawrence Smith is a father of Matthew W. Smith, who died after using Ritalin for seven years (age 7-14) and the main reason why he wrote this article is that he wants to warn parents of other children not to succumb the pressure of school managements and doctors to put their children on medication.

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1 This statement was issued by National Institute of Health (NIH) at the National Institutes of Health Consensus Conference in 1998.
According to Dr. Ljuba Dragovic, the chief pathologist in Oakland County Michigan, Matthew died of long term use of methylphenidate. His heart showed clear signs of small vessel damage, which was caused by using stimulant drugs. His heart was also bigger than usual, but the parents didn’t know about any preexisting heart disease or defect and they learned that anyway this wouldn’t be noticed by standard tests necessary for prescription, which are blood work, listening to the heart, questions about school behavior, sleeping and eating habits. They weren’t informed of other important tests, which could have been done, and could have saved their son’s life.

Mr. Smith was forced by the school to put Matthew on Ritalin and he assumed that it was caused by school employees wanting to have easier manageable children and he also considered as a possible cause the fact, that when schools label a child as having learning disorder, they receive additional state and federal funding for each child, each semester. Could it be a matter of money? He feels that his rights were violated and that he wasn’t informed well enough not only about the risk of using stimulant and their side-effects, but also about the alternatives, that could be causing his son’s behavior, for example undiagnosed allergies or food sensitivities. “These mental illnesses are scientifically unfounded with no scientific validity what so ever. The dopamine theory is nothing more than wishful thinking on the part of psychiatry and the pharmaceutical industry.” (Smith, 2001)

The use of Ritalin constricts and gets the veins and arteries very small which makes it hard for the heart to pump blood throughout the body. The extra force it takes to circulate blood causes high blood pressure and damage to the heart.

There are many other drugs that are given to children for ADD and ADHD with different names. Amphetamine-type drugs such as Adderall, Concreta, Metadate, Ritalin and Dexedrine also antidepressant type drugs, Selective Serotonin Reuptake Inhibitors (SSRI), such as Prozac, Zoloft, Paxil and Luvox and the new selective norepinephrine reuptake inhibitors like Strattera which can cause serious side effects.

These can include seizures, cardiac problems such as arrhythmias, hypertension, heart failure and even death. These drugs can also cause emotional symptoms such as psychosis, agitation, aggression, hostility, anxiety and hallucinations.
When you read this article written by a parent whose child died it makes you wonder, what are we doing to our children? Is it really necessary to use these medications? And are they really the cause of deaths of these children?

The thing that surprised me when I examined this web page, was that on the sides of these articles were advertisements for alternative treatment of ADHD like homeopathy, drug free ADHD treatment, or The Whole Food Farmacy which suppose to make a new person of you, or offers for Hair Analysis Test & a Food Allergy Test to find causes for ADD/ADHD symptoms. On one hand they criticize the pharmaceutical industry for forcing the physicians to prescribe medications and on the other hand they advertise and offer other and of course better possibilities. If I was thinking in the same way that they do, I would probably accuse them of creating this web page just to promote these different alternatives.

Of course we could just add this to a grieve of a parent overwhelmed by a lost of his child, but the problem is that **these opinions are in a great number being published and showed in the media and it creates a very confusing climate for the general public and elicits fears by the physicians, parents and educators.** (Goldman, 1997, pg. 1101)

As I have showed above there are many questions that need to be answered and in the following chapters, I would like to give the reader a clear view of these issues supporting my conclusions with reliable sources of information.

### 1.2 The transitions of ADHD in last 100 years

The history of ADHD is very complicated and complex process of various stands, concepts and theories. Its history has to be factored in while dealing with this subject, because it demonstrates that many current views of its nature arose a long time ago and they reappeared throughout the 20th century as the clinicians and examiners struggled to find the correct answers to all their questions concerning this condition.

ADHD was first clinically examined in 1902 by **George Still.** He had observed and described 43 children from his own practice that showed symptoms that we would today be considered as caused by ADHD. He viewed these children as children with a major “**defect in moral control**”. They weren’t able to change their responses and behavior even after a punishment, which would normally prevent a child from doing it again. The moral control was believed to be the process of comparison between, what the child wants and what he
knows as good of all, which Still named “moral consciousness”. These children seemed to be missing this as if they weren’t able to learn from their previous experiences.

“Still concluded that a defect in moral control could arise as a function of three distinct impairments: “(1) defect of cognitive relation to the environment; (2) defect of moral consciousness; (3) defect in inhibitory volition” (p. 1011).” (Barkley, 2006, p.4) He assumed that the lower levels would affect the levels above and through them the moral control of behavior. Still also noticed that there were a greater number of males than females (3:1) among these children, that the disorder typically appeared in early childhood and that most of his observed patients were physically handicapped. They also tended to accidents as their careless behavior sometimes caused them or somebody in their surroundings an injury. He noted that alcoholism, criminality, depression and suicide are more common among biological relatives of these children. Some of these children sustained a brain damage and some of them suffered from tic disorders, which was probably the first time when tics and ADHD were considered as comorbid condition. He determined that the lack of moral control is possible to be inherited or caused by some neurological deficiency. It is almost unbelievable, how many factors, that would be used in later recognition of this disorder, he noted.

An epidemic of encephalitis during 1917-1918 which caused brain damage and resulted in behavioral problems that would fit the characteristics of ADHD, led to connection of the brain damage with behavioral pathology. Birth trauma, measles, lead toxicity, epilepsy and head injury were investigated in association with these behavioral impairments and terms like “organic driveness” (Kahn & Cohen, 1934) and „restlessness“ syndrome (Childers, 1935; Levin, 1938) were used. “It would be several decades before investigators would attempt to parse out the separate contributions of intellectual delay, learning disabilities, or other neuropsychological deficits to the maladjustment of these children.” (Barkley, 2006, p.6) The brain damage theory was supported by comparison of behavior of these children and primates with frontal lobe lesions. Levin used these findings to claim that the restlessness in children might be caused by defect in the forebrain structures, which was used much later by many other investigators (Barkley, 1997; Ferguson, Koon & Dickey, 1986). The displays of hyperactivity were considered as a result of poor parenting and this conclusion did appear several times during the next 50 years.

In the 1950s most of these children were put in psychiatric facilities as they were believed to suffer from some type of brain damage. Strauss & Lehtinen (1947) actually
believed that children with these behavioral characteristics have a brain damage, even though it wasn’t detected, and they used the term “brain-injured child”. Because of the absence of evidence of brain damage a term “minimal brain damage” and later “minimal brain dysfunction” (MBD) were developed and used in 1950s and 1960s. The recommendations made by Strauss & Lehtinen affected the special educational services adopted later in U.S. public schools, like classes of fewer children, plain look of classes etc., that are in milder version taken place even in contemporary educational plans for children with ADHD. These arrangements even though they had a weak scientific support have an important historical value.

In 1937 the stimulants were first used as a treatment of children with ADHD and the improvements of their behavioral problems and academic performances led to a spreading use of these medicaments, which continues till now.

In the 1950s a several studies took place, of which the most famous is the one done by Laufer et al (1957). These authors called ADHD a “hyperkinetic impulse disorder” and they asserted that the central nervous system deficit was in the thalamic area and that the children with ADHD have a lower threshold for stimulation. By this time was ADHD generally considered as a brain damage syndrome, even though the evidence of brain damage was weak. The milestones of the treatment were educational classrooms with reduced stimulation and the use of stimulants was on the rise.

In the 1950s and 1960s slowly appeared critics of MBD and its neurological roots and in some cases the blame was entirely put on parental and family factors, which resulted from the psychoanalytic theory (Hertzig, Bortner, & Birch, 1969). The term “MBD” was eventually replaced by new labels as “dyslexia”, “language disorder”, “learning disability” and “hyperactivity”. After this the attention shifted to hyperactivity and it led to the birth of hyperactivity syndrome (Chess, 1960). It was recognized that hyperactivity is a behavioral syndrome that can have organic origins but not necessarily. It was believed that hyperactivity diminishes by adolescence and this believe endured till 1980s. The diagnosis of hyperactivity first appeared in terminology in the Diagnostic and Statistical Manual of Mental Disorders (DSM II; American Psychiatric Association, 1968) and it said: “The disorder characterized by overactivity, restlessness, distractibility, and short attention span, especially in young children; the behavior usually diminishes by adolescence” (APA, 1968, p.50).
Different paths of North America and Europe particularly Great Britain occurred. In North America hyperactivity became a behavioral syndrome, characterized by higher-than-normal levels of activity unlike in Great Britain were paradigm of brain damage continued into the 1970s.

By 1969 the prevailing view was that hyperactivity is a brain dysfunction syndrome but not as a matter of brain damage, but more likely dysfunction of brain mechanisms. The symptoms were determined as the most leading one was consider excessive activity level or hyperactivity. “The recommended treatments now consisted of short-term treatment with stimulant medication and psychotherapy, in addition to the minimum-stimulation types of classrooms recommended in earlier years.” (Barkley, 2006, p.9)

The 1970s were a very productive period, where many studies were carried out and the results were that hyperactivity was not considered as the only behavioral deficit with hyperactive children, but that lack of attention and impulse control also played big part relating to this disorder. The influence of brain damage was minimized, but importance of other brain mechanisms, such as underactivity, brain neurotransmitter deficiencies (Wender, 1971), or neurological immaturity (Kinsbourne, 1977), grew. There was also a great discussion about potential environmental causes, particularly diet and child rearing. The treatments that were being recommended, were not only stimulant medication, but also special education program, classroom behavior modification, dietary management, and parent training in child management skills. More attention was paid to disturbed social relations and the positive impact of stimulants in modifying these social conflicts. “However, the sizable discrepancy between North American and European views of the disorder remained: North American professionals continued to recognize the disorder as more common, in need of medication, and more likely to be an attention deficit, while those in Europe continued to view it as uncommon, defined by severe overactivity, and associated with brain damage.” (Barkley, 2006, p.19) The 1970s were an important period also because of the fact that the same symptoms recognized by children with ADHD, were found by adults, which was in discrepancy with the assertion that ADHD diminishes before adolescence.

By the end of 1980s during which the diagnosis of ADHD went through many changes, it was viewed as a developmentally disabling condition. Researches led to the understanding that it is a chronic condition of a biological nature, that is heritable and
that has a huge effect on the academic success, and social behavior of these children, but they also realized that the environmental, particularly familial, factors have a great influence on the final outcome. In the field of treatment they wagered on cooperation of multiple methods and professional disciplines, which would have to take place for a longer period and would have to be re-evaluated regularly as the changes in prognosis of the disorder had to be followed. The range of treatment was extended to cover parental disturbances and family dysfunction, and children’s anger control and social skills. Several studies indicated the use of tricyclic antidepressants and antihypertensive medications.

Even though there was a great progress in the scientific and professional fields, the general public was frightened by the increasing use of stimulants as a treatment of the disorder. The situation was partially soothed by establishment of several associations of parents, which undertook to moderate this boom and to make the education of these children the national political priority. These associations were trying to provide the general public with more precise information about the disorder and its treatment and they hoped that this would help them to realize that even though this disorder is of biological origins the social environment has a great impact on the development of it, and that it is not only the matter of bad parenting or some diet.

During the 1990s the course was changed back to neurological and genetic factors, which were again thought to have more influence than social or environmental ones. It was generally agreed that both these factors impact this condition somehow, but as for the causation the former ones were being preferred. The evidence of social impact let to a view that the environment influences the child individually. Behavioral inhibition was considered characteristic and it was used as a symptom that distinguished ADHD from other mental and developmental disorders (Barkley, 1997; Nigg, 2001; Pennington & Ozonoff, 1996; Chachar, Tannock, & Logan, 1993) and caused the association of ADHD with disruptive development of self-regulation.

One of the most important things that happened in this period was the evolution of 3 subtypes: subtype of ADHD with inattention without hyperactive-impulsive behavior, subtype with hyperactive-impulsive behavior and subtype with combined behavior. Great deal of follow-up studies of people diagnosed with ADHD in childhood confirmed the contention of pervasiveness of the symptom into adulthood with the exception of transformation of some of them. The use of stimulants regarding its effectiveness was further increasing and even though the results of multimethod intensive psychosocial
intervention programs were weak, the treatment was a combination of medication with psychosocial and educational treatment programs as in the 1980s. It is unbelievable how big was the influence and political activity of patient and family support organizations, such as CHADD\(^2\), which caused greater awareness of the disorder, as well as the emergence of controversies over its existence, definition, and treatment with stimulants.

\(^2\) CHADD – Children and Adults with ADHD
2. The characteristics of ADHD

ADHD is according to the American specialists a neuropsychiatric syndrome (Goldman et al, 1997), a neurobehavioral disorder (Wilens et al, 2003) and also a chronic condition (Subcommittee on ADHD, 2001) with the onset in early childhood, which usually is diagnosed during the first years of grade school. In most of the cases it is very probable that it will endure through adolescence into adulthood.

2.1 Diagnostic criteria

Clinicians and other specialists endeavor to diagnose in as many cases as they can, because once a diagnosis is determined, the adequate treatment can take place. To help them with the diagnoses the diagnostic manuals were created. Nowadays exist and are used two main classifications, Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV), created and edited by American Psychiatric Association in 1994 and International Classification of Diseases, 10th Revision (ICD-10) done by World Health Organization in 1994.

The diagnostic criteria for ADHD according to DSM-IV are as follows:

To diagnose ADHD it must meet 6 criteria of inattention symptoms or 6 criteria of hyperactive/impulsive symptoms for 6 months to a degree that is maladaptive. It must have onset prior to age 7. The impairment has to be present in 2 or more settings and the examiner must have a clear evidence of clinically significant impairment in social, academic or occupational functioning. Before diagnosing ADHD it must be made certain that the behavior of the child isn’t caused by any other disorder or disease.

A Inattention

a) often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
b) often has difficulty sustaining attention in task or play activities
c) often does not seem to listen when spoken to directly
d) often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
e) often has difficulty organizing his tasks and activities
f) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
g) often loses things necessary for tasks or activities (e.g. toys, school assignments, pencils, books, or tools).
h) is often easily distracted by extraneous stimuli
i) is often forgetful in daily activities

**B Hyperactivity**
a) often fidgets with hands or feet or squirms in seat
b) often leaves a seat in classroom or in other situations in which remaining seated is expected
c) often runs about or walks on excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feeling of restlessness)
d) often has difficulty playing and engaging in leisure activities quietly
e) is often “on the go” or often acts as if “driven by a motor”
f) often talks excessively

**C Impulsivity**
g) often blurts out answers before questions have been completed
h) often has difficulty awaiting his turn
i) often interrupts or intrudes on others (e.g. butts into conversations or games)

**Based on these criteria, three types of ADHD are identified:**

1. ADHD, Combined Type: if both criteria 1A and 1B are met for the past 6 months
2. ADHD, Predominantly Inattentive Type: if criterion 1A is met but criterion 1B is not met for the past six months
3. ADHD, Predominantly Hyperactive-Impulsive Type: if Criterion 1B is met but Criterion 1A is not met for the past six months.

**The diagnostic criteria of hyperkinetic disorder according to ICD-10 as follows:**

“Note: The research diagnosis of hyperkinetic disorder requires the definite presence of abnormal levels of inattention and restlessness that are pervasive across situations and
persistent over time, that can be demonstrated by direct observation, and that are not caused by other disorders such as autism or affective disorders.

Eventually, assessment instruments should develop to the point where it is possible to take a quantitative cut-off score on reliable valid and standardised measures of hyperactive behaviour in the home and classroom, corresponding to the 95th percentile on both measures. Such criteria would then replace G1 and G2 below.

**G1. Demonstrable abnormality of attention, activity and impulsivity at home**, for the age and developmental level of the child, as evidenced by (1), (2) and (3):

(1) at least three of the following **attention problems**:
(a) short duration of spontaneous activities;
(b) often leaving play activities unfinished;
(c) over-frequent changes between activities;
(d) undue lack of persistence at tasks set by adults;
(e) unduly high distractibility during study e.g. homework or reading assignment;

(2) plus at least three of the following **activity problems**:
(a) very often runs about or climbs excessively in situations where it is inappropriate; seems unable to remain still;
(b) markedly excessive fidgeting & wriggling during spontaneous activities;
(c) markedly excessive activity in situations expecting relative stillness (e.g. mealtimes, travel, visiting, church);
(d) often leaves seat in classroom or other situations when remaining seated is expected;
(e) often has difficulty playing quietly.

(3) plus at least one of the following **impulsivity problems**:
(a) often has difficulty awaiting turns in games or group situations;
(b) often interrupts or intrudes on others (e.g. butts in to others' conversations or games);
(c) often burts out answers to questions before questions have been completed.
(d) without consideration of social usage and restrictions talks excessively
G2. Demonstrable abnormality of attention and activity at school or nursery (if applicable), for the age and developmental level of the child, as evidenced by both (1) and (2):

(1) at least two of the following attention problems:
(a) undue lack of persistence at tasks;
(b) unduly high distractibility, i.e. often orienting towards extrinsic stimuli;
(c) over-frequent changes between activities when choice is allowed;
(d) excessively short duration of play activities;

(2) and by at least three of the following activity problems:
(a) continuous (or almost continuous) and excessive motor restlessness (running, jumping, etc.) in situations allowing free activity;
(b) markedly excessive fidgeting and wriggling in structured situations;
(c) excessive levels of off-task activity during tasks;
(d) unduly often out of seat when required to be sitting;
(e) often has difficulty playing quietly.

G3. Directly observed abnormality of attention or activity. This must be excessive for the child's age and developmental level. The evidence may be any of the following:

(1) direct observation of the criteria in G1 or G2 above, i.e. not solely the report of parent or teacher;

(2) observation of abnormal levels of motor activity, or off-task behaviour, or lack of persistence in activities, in a setting outside home or school (e.g. clinic or laboratory);

(3) significant impairment of performance on psychometric tests of attention.” (ICD-10, 1994, p.187-190)

Even though it might not seem like it there are differences between diagnostic criteria in these manuals. The ones that concern ADHD are two. DSM-IV classifies feature “often talks excessively” as a symptom of hyperactivity whilst ICD-10 classifies similar, but more accurate behavior, thus “talks excessively without consideration of social usage and restrictions”, as a symptom of impulsivity. However the most significant difference is that DSM-IV requires the six (or more) symptoms of hyperactivity/impulsivity linger for at least 6 months to a degree that is maladaptive and isn’t corresponding with the developmental level in order to diagnose ADHD. Since there are embraced 6 symptoms of hyperactivity (and 3 symptoms of impulsivity), it is possible, that even children without
symptoms of insufficient control of impulsivity can complete the diagnostic criteria for ADHD. This finding is of a great importance if only for the reason that recent scientific course tends to regard the insufficient control of impulsivity to the core symptom of ADHD.

These differences between diagnostic criteria of ICD-10 and DSM-IV cause that more children are being diagnosed with ADHD when the DSM-IV diagnostic criteria are used than when the ICD-10 are followed. These two groups overlap but in compliance with ICD-10 smaller group with more serious symptoms is diagnosed. If the DSM-IV diagnostic criteria are used, it means that more children who need care and who might not fit into ICD-10 will be treated. It’s also a fact that most international studies and in particular most big and well established studies work with patients diagnosed in accordance with DSM-IV diagnostic criteria. If the clinicians in European countries want to use outcomes of these studies, they will have to apply them to a same clinical population, thus to a population diagnosed in compliance with DSM-IV. (Munden, Arcelus, 1999)

2.2.1 Symptoms

The symptoms of ADHD fall into three main area, as was pointed out above, hyperactivity, impulsivity and inattention. These symptoms are long-lasting and occur in more settings.

Many small children are very active and they might seem to us as hyperactive, but the level of activity grows till the age of three and then it gradually falls. Children with ADHD are often very active already in the womb before birth and they usually cry a lot and can’t sleep much. Parents of these children are usually quite exhausted and gloomy, but even though it might disturb the early relationships it usually isn’t the case. The problem is that it influences the relationships with other children. Some children act silly in a group of children to get their attention but still they don’t fit in, sometimes they damage other children’s toys etc. without meaning to, they might play roughly in the playground and hurt somebody. Other children may feel that the child with ADHD is bossy, silly, clumsy, too rough or will make their team lose. So they’ll avoid the child in the play ground and won’t invite him to their homes to play. This can make the child feel rejected and develop low self-esteem. Isolation in the playground can also make him more at risk of being bullied or becoming a bully himself.
The real trouble begins when they start going to school, where they are asked to remain at one place and to pay attention, which is sometimes almost impossible for them. They often leave their seats, shout, tease classmates and disturb them from tasks, they are often distract, often forget and loose things for class which leads to angry teachers and classmates rejecting them.

The problem of impulsivity is that these children aren’t able to control their reactions to signals, stimuli or events that don’t relate to what they are doing at the moments. This opinion was presented and procured by Professor Russell A. Barkley, prominent American specialist on ADHD. (Munden, Arcelus, 1999) Their impulsive behavior is quite dangerous, for example stepping into the street without looking. They quite often do hazardous things like jumping from an unsafe height just to show off in front of others. As hyperactivity it brings problems into the social matter of making and keeping friends. They barge into games and conversations, speak without thinking and say inappropriate things and their moods are volatile so other children don’t know what to expect from them. They have a short fuse and lash out when frustrated.

The inattention isn’t as noticeable as hyperactivity and impulsivity but it causes great problems with learning and not only in school, but with learning of practical and motoric skills and also communication skills. The gist of the problem is that they aren’t able to pay attention to anything for time long enough to grasp it.

All these three main symptoms can seriously affect the ability to learn. ADHDs’ frequent comorbid are specific learning disorders. They often fall behind the rest of the class as their disorder complicates everything, they can’t concentrate as long as their classmates, noise and surrounding movement distracts them and sometimes they overhear and important information or teachers’ instructions, no wonder they can’t catch up to the rest of the class.

2.2.2 Etiology

The origin of ADHD is primarily influenced by genetic factors however the nongenetic factors play its role during the development of the disorder. The development can also be buttressed or on the contrary suppressed by the environment in which the child is being raised.

**Genetic factors.** The heredity is according to existing studies the main etiological factor. It was proved by studies of adoptive children and their biological and adoptive parents, and
of monovular twins, which showed that in 80-90% of the cases (Munden, Arcelus, 1999, p.52), where one of them had ADHD, the other one suffered from this disorder too. The researches also showed that if a man is diagnosed with ADHD the probability of passing the disorder on to his children is five times greater. There are a great number of genetic studies nowadays that are trying to detect which genes, the so called candidate genes, are responsible for the genesis of ADHD. A great importance is attached to an innate genetic defect that affects metabolism and function of dopamine and noradrenalin, thus substances, which mediate the transfer of signals in different part of the brain.

Into the group of **nongenetic factors** fall perinatal complications and injuries, e.g. smoking and drinking during pregnancy, abortive, prolonged or in any other way complicated birth, head injuries primarily in the prefrontal area. Very popular in the 1980s were speculation about the impact of ecological factors such as increased fall-out of heavy metals or radiation, which affect the activity of neurotransmitters and the rate of flow of blood in the prefrontal and motoric cortex. But the researches didn’t really validate these hypotheses therefore they were dropped. (Drtílková, 2007; Malá, 2000)

There is a danger that the symptoms of ADHD will be further developed by unsuitable family environment along with discordant and unstable relationships, neglect of the child, inappropriate and unreasonable punishments, and disorganized daily regime. Behavior might get worse as a result of certain stressful event, such as divorce of the parents, death of a beloved person, relocation, transition into another school or other traumatic experience. (Drtílková, 2008, p.47-48)

### 2.2.3 Epidemiology and prevalence

When we bare ourselves in the issue of prevalence, we will very quickly notice that it differs almost study by study. Most studies oscillate in the boundary of 2-12% among school-aged children (Hort et al, 2000, p.308), e.g. Wilens et al (2003) states the prevalence of 4-9% among youths, Goldman et al (1997) 3-6% among the school-aged population, the Clinical practice Guideline authored by Subcommittee on ADHD and Committee on Quality Improvement (2001) quotes a prevalence of 4-12% among school-aged children, but it is no exception if the number is lower or higher. These differences are caused by the variety of population being studied and by different diagnostic methods. The divergence between The United States and Europe arises from the use of different diagnostic manuals,

3 An example of these various results can be seen in the table in Supplement no.2.
as American physicians and psychiatrist follow the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (1994) created by American Psychiatric Association and the Europeans International Classification of Diseases, 10. Revision (1994), including different diagnostic criteria as was written above.

To the increase of cases of ADHD in The United State Goldman et al states that: “The evolution of criteria from DSM-III to DSM-IV, although based on a progressively larger empirical base, has broadened the case definition, so that more children appear to be affected. This is largely a function of the increased emphasis on attentional problems as opposed to a more narrow focus on hyperactivity in earlier diagnostic sets.” (Goldman et al, 1997, p.1102)

**2.2 The treatment of ADHD**

Even though it was believed in the past that this disorder will diminish by adolescence and we came to know that it is a chronic condition we have never found a cure for this disorder. What we have found are several treatments that can effectively assist with its management. The specialists came to agree that the most important thing is to inform and educate the family and school staff about the nature of the disorder so they would know what they are dealing with. Among all the treatments that the specialists put into use the one that stood up in effectiveness are stimulant medications, which are methylphenidate known as Ritalin, dexamphetamine known as Dexedrine, Adderall, and in rare cases, pemoline known as Cylert. In some cases it was proved that tricyclic antidepressants, in particular desipramine, help with managing symptoms of the disorder, but not just that they also aid in managing co-existing symptoms of mood disorder or anxiety, even though they are not as effective as stimulants. The use of clonidine was rather stopped because its effects are not clear apart from its well-known sedation effects. Some patients might require a combination of these medications or even other because of the co-existence of other mental disorders besides ADHD.

Psychological treatments, such as behavioral therapy and parent training in child behavior management methods, show only short-term improvements and mostly just in these settings that are included in the management program. Recent studies indicated that once the treatment of medications is terminated the improvement may not endure. It follows that the treatments of ADHD must often be combined and must be maintained over long periods of time so as to sustain the initial treatment effects.
2.2.1 Pharmacotherapy

Pharmacotherapy is one of the methods of treatment of ADHD. It should be used rather for children with medium acute and acute level of this disorder and the prescription should be preceded by quite thorough examination and careful diagnose. The treatment should be in motion under a watchful eye of a clinician whose cooperation with the child and his parents is unconditional. If the child is prescribed a medication, he has to be given adequate information of the purpose and reason why he should be taking them. The clinician should hear out the child as to prevent the child to think that the medications are a punishment. If certain medication doesn’t show the longed effects, a change of medications or their combination should be considered.

As was mentioned above the medications used for treatment of ADHD are primarily stimulants, particularly Ritalin, and also Dexedrine, Adderall and Cylert, tricyclic antidepressants, in particular desipramine, and in some cases antihypertensive, such as clonidin or propranolol. To the best of our knowledge the major problem in the attention system in the brain of a person who has the diagnosis of ADHD is a difference in their dopamine system. Current research shows there about 13 different genes that vary from the so-called normal genes that are involved in making up what we call the attention deficits. This is reflected in the fact that there is not enough dopamine around to support the system to work in a consistent and predictable manner. It follows that these medications are used for correcting this deficit and its associated problems like anxiety, depressed and demoralized mood, overactive startle response, and the many problems with aggression.

2.2.2.1 Stimulants

The use of stimulant medications is the easiest and most accurate route and the one that has proven to be the most efficacious for the greatest number of children with the diagnosis of ADHD. The most frequently used stimulant is Ritalin, a derivative of amphetamine, as are the used Dexedrine (dextroamphetamine) and Adderall (racemic mixture of amphetamines). The main impact that Ritalin has is that it decreases hyperactivity and impulsivity and increases the span of attention. Children are less aggressive and more obedient, and they react positively to instructions and orders. Since they listen to instructions they make fewer mistakes and they aren’t as forgetful. The quality of their performance and behavior is better which further influences relationships with others and may lead to a higher self-esteem. Yet, after this rapid improvement long journey awaits the
child during which he has to learn how to manage all the things that weren’t possible before. He has to learn skills like making friends, devoting himself to his hobby etc. Naturally the degree of improvements greatly varies among the treated children and a big complication is the fact that the medication has to be taken regularly for a long period of time which might cause a lot of practical and emotional problems.

A great advantage of Ritalin is its short time of action. Its effects are evident in 15 to 20 minutes, and it reaches the maximum in about an hour. The effects last about 4 hours which means that the medication needs to be taken regularly approximately every 4 hours. It is very important to create carefully planed schedule of usage of the medication considering the rate of processing, situation, in which the child is, and also the possibility of taking the medication at school.

Unfortunately it has as almost every medication adverse effects, but these are mild, of short duration and they also depend on dosing and timing adjustments (Brown et al, 2005). The most common are sleeplessness (insomnia), decreased appetite associated with weight loss, sometimes nervousness, stomachache, nausea, vomiting, which should fade out in some time, occasionally headaches, drowsiness, dizziness, some children might be irritated or weepy.

**Dexedrine** doesn’t have any substantial advantage or disadvantage compare to Ritalin, but it can be used by children who doesn’t react to Ritalin and its effect on the brain lasts longer so the number of dosage can be cut down. As for the side effect it has the same ones as Ritalin.

**Cylert** is a long acting medication that takes a while to get to its therapeutic action so it doesn’t have an immediate effect like Ritalin or Dexedrine and there have been cases of sudden deaths due to liver failure. The pros and cons aren’t sufficiently compared yet and so it is considered controversial as a first line treatment and recommended only as a second line treatment.

(Train, 1996, p.47-50; Elliott, Place, 1998, p.60-71; Munden, Arcelus, 1999, p.75-81)

**Concerta** is a recently developed form of methylphenidate that uses capsules which release the effectual substance gradually for 12 hours which entails that it necessary to use only one capsule in the morning. The effect of Concerta is noticeable after quite short time and the fluctuation of effectual substance during the day in plasma is missing. (Drtílková, 2007, p.72)
2.2.2.2 Antidepressants

To children that do not react or react badly to stimulants are prescribed antidepressants, in particular tricyclic antidepressants such as impramin (Tofranil), desiprimin (Noraprimin) and amytriptylene (Elavil). They effectively reduce the core symptoms of ADHD, even though not as effectively as stimulants, and due to their sedative effect, they downgrade the quality of learning. On the other hand they might be very effective for children suffering from anxiety and depression, because antidepressant will reduce its symptoms.

Since they don’t metabolize as fast as stimulants, they work all day which means that they have to be taken only once a day.

The side effects are mostly only mouth dryness and constipation, but rashes, hypertension, confusion, seizures and changes of heart rhythm might appear in rare cases. It follows that ECG (electrocardiogram) should be done before and also during treatment as should the blood pressure and the pulse be taken.

(Train, 1996, p.47-50; Elliott, Place, 1998, p.60-71; Munden, Arcelus, 1999, p.75-82)

One of the newer antidepressants bupropion known as Wellbutrin was thought to be a wonder drug at the time of its release as it could serve as a replacement of Ritalin. It blocks the reuptake of dopamine and should have been an effective alternative to the stimulants. It is long acting and it was claimed to have fewer side effects than the tricyclics. Unfortunately, the effectiveness in clinical settings didn’t prove as it was hoped. It works well in about 50% of cases but has many more side effects than any of the previously mentioned choices. There is a new slow-release preparation of this medication that wasn’t tested well enough to make conclusions, but it seems that it could be easier for patients to use, though effectiveness is still very variable.

2.2.2.3 Antihypertensive

Antihypertensive, particularly clonidin, proved in some cases to be effective. They are often used in the afternoon to manage the core symptoms of ADHD without causing sleeplessness that stimulants often produce. This medicament might be very helpful in managing ADHD combined with comorbidities such as tics or Tourett syndrome and in those rare cases, when stimulants worsen motor tics.
There are of course possible side effects like mouth dryness, falloff, nausea, dizziness and rarely a rash. It also requires carefulness when prescribing it to patients with depressions. (Munden, Arcelus, 1999, pg.83-84)

2.2.2.4 New preparation

The new preparation for treatment of ADHD is an atomoxetine known as Strattera that is available recently in The United States (licensed by the FDA in November 2002) and some other countries. It is a selective presynaptic norepinephrine transporter and primarily affects the nor-adrenalin system in the brain even though it isn’t a stimulant, which eliminates the possible danger of abuse. According to the latest studies its effects are comparable with the effects of Ritalin and Concerta. The advantage of this preparation is its long action for 24 hours, even though its onset of action is slower. Strattera was also found effective in cases of ADHD combined with tic disorder, sleep and anxiety disorder where the stimulants failed.

The side effects might be a bit higher blood pressure and accelerated pulse, and reduction of appetite, but these effects aren’t for most of the patients clinically important. The liver tests are recommended during the treatment. Longitudinal studies, which would monitor the effects of this preparation from childhood all the way to adulthood, aren’t at disposal yet. (Drtílková, 2007; Brown et al, )

2.2.2 Behavioral therapy

Treating such a condition as ADHD is doesn’t require only treatment by medications, which represses the core symptoms. These children need more than that. They are feeling alone, because their peers and classmates keep a distance from them due to their behavior and even when the behavior changes, it is a long, demanding process to find a way how to get closer to them. The medications also don’t help the children with their academic performance. The children are not the only ones who need help. Their parents are often blamed for not being able to handle them and the other parents and people around them view them as incapable and bad parents. Similar feelings are experienced by the teachers who are often feeling incompetent to educate children as they don’t see any results of their effort. It follows that the therapy shouldn’t include only children but also their parents and possibly their teachers.
That is why it is very efficient to use behavioral therapy which is based on the use of principles of learning to change the undesirable reactions and behavioral patterns to the desirable ones. The cornerstone of this method is that the therapist uses specific examples from the child’s life and his goal is to make the child understand them and be able to use them while dealing with difficulties that appear in everyday life. There are several techniques that help to control undesirable behavior and the most useful are ABC analysis\(^4\) and positive reinforcement.

The ABC analysis is based on the fact that the manifestations of most behavioral patterns are influenced by antecedent events, which are the ones that precede it, and by consequent events, that follow it. The change of the antecedence and consequence can result into a reduction of the behavior. The therapist asks the parents to note the events, which forego and follow the behavior and then he with cooperation with the parents creates a scheme, which shows how the child behaves under certain circumstances. It also helps the parents to become aware of their own reactions to the child’s behavior and of the hidden goal of it. If the parents don’t realize the true intention they can easily slip into strengthening the undesirable behavior. The therapist in cooperation with the parents will be trying to change some of the events happening before and after the behavior, which may lead to a change in behavior of the child.

Positive reinforcement is a very effective way how to change the child’s behavior. The reactions to impulsions and certain behavior are more repeated and stronger, if they are followed by a reward. The first step is to very thoroughly explain to the child what we expect from him and what we mean by the term good behavior and bad behavior. The child also has to realize the consequences of his behavior and what the reward will be if he behaves well. Every good behavior has to be praised or rewarded and it has to be done right after it happens. The rewards must correspond with the age and interest of the child as to stay motivating. If the child is behaving badly we should in some measure try not to respond to it, because the child might loose the will to improve if he is in trouble all the time. It is also very helpful if the parents don’t expose the child to unnecessarily stressful situations. The punishments are not overly recommended as their effect is not really positive. On the other hand a reasonable time-out can serve our target. The child is taken to a quiet place without distractions where he has to stay for a precisely determined time.

\(^4\) ABC procedure – antecedent-behavior-consequence response
**Family therapy** is mostly used in families, where the problems arise from unclear and indistinct communication, and in families with tense relationships. The ADHD is considered as a problem of the whole family not just the child and the attention is shifted from the causes to the improvement of communication and understanding among members of the family with the goal of helping them find their own solution of the problems, that were caused by ADHD a other factors. Parents can participate in parent management training which is held in individual or group setting and its function is to decrease disruptive behavior, increase parents’ self-confidence and decrease family stress.

These children are quiet often very poor self-observers and frequently lack insight into why they behave the way they do. To help the child understand the events around him, it might be considered suitable to use **one-to-one therapy** that can help the child to reveal its thoughts, feelings, relationships and experience from privacy. This therapy has to be performed only by an experienced and well educated therapist, because it requires specific knowledge, skills and well-founded insight into the matter.

(Munden, Areclus, 1999, p. 87-95)

Very specific method is **EEG biofeedback** based on the recording of brain activity which is during the therapy transferred into a simple videogame whose course can be operated by changes of psychic state evoked by occurrence of desirable or undesirable brain activity. The appearance of desirable activity is rewarded by a success in the game or by a different signal. Repeated training theoretically helps the brain to function in the desired frequency zone, which might lead to a better mental performance and by the children with ADHD it might have a good impact on behavior, learning and attention. *American Academy of Pediatrics* (AAP) doesn’t classify EEG biofeedback as a fully proved and effective therapy of ADHD and it is considered to be experimental. However, in some cases it helps in training the attention, concentration and relaxation and in these cases it can be used as a supplementary technique. (Drtilková, 2007, p. 78-79)

**2.2.3 Combined therapy**

Combined therapy is the combination of medication and behavioral treatment, which includes the monthly titration, parent group and individual sessions, teacher consultation, summer treatment program (STP) and the classroom aide. This therapy was compared very unique study accomplished by MTA Cooperative Group called A 14-Month Randomized Clinical Trial of Treatment Strategies for ADHD with medication management, behavioral
therapy and community care and the results were that for most of ADHD symptoms combined treatment and medication management showed significantly greater improvement than behavioral treatment and community care. The combined and medication management differed in oppositional/aggressive symptoms, internalizing symptoms, teacher-rated social skills, parent-child relation, and reading achievement. The MTA Group says: “Our combined treatment did not yield significantly greater benefits than medication management for core ADHD symptom, but may have provided modest advantages for non-ADHD symptom and positive functioning outcomes.

3. The analysis of individual studies

The question of ADHD being a myth or a real disease is easily answered. As it is a neurobiological disorder proving its existence is a matter of scientific research and an abundant prove was given by many professional researches and their writings for example
by Dr. Russel Barkley, Dr. Sam Goldstein and others who have consistently identified a group of individuals who have trouble with concentration, impulse control and hyperactivity. Even though the name, diagnostic criteria and prevalence had changed several times over the past decades, the same symptoms were found again and again in the same combination. This disorder which is today called ADHD was recognized as a disability by the courts, the United States Department of Education, the Office of Civil Rights, the National Institutes of Health, and all major professional medical, psychiatric, psychological, and educational associations in The United States.

It follows that there is no doubt about existence of this disorder and actually when you look at all the data that are proving its validity, you will find out that they are much more compelling than data for most mental disorders.

### 3.1 Sufficient diagnosis

As every mental disorder ADHD has to be carefully diagnosed as the misdiagnosing or overdiagnosing can have inauspicious consequences, which leads us to another controversial issue. Concerns have been raised whether the clinicians are performing enough evaluations before prescribing medication. As the Council Report (Goldman et al, 1998) deals with this problem, it states that the diagnostic criteria (DSM-IV) are sufficient and reliable, the thing is that the clinicians should be well informed also about the normal development to make comparison, they should diagnose ADHD if the behavior is occurring in at least two settings (e.g. in school, at home) and they should eliminate any other diagnose that could have similar symptoms. If they keep these three basic rules there shouldn’t occur any misdiagnoses. “The overall approach to diagnosis may involve (1) a comprehensive interview with the child’s adult caregivers; (2) a mental status examination of the child; (3) a medical evaluation for general health and neurologic status; (4) a cognitive assessment of ability and achievement; (5) use of ADHD-focused parent and teacher rating scales; and (6) school report and other adjunctive evaluations if necessary (speech, language assessment etc.) depending on clinical findings.” (Goldman, 1998,p.1102)

As you can see above the diagnosis should be a complex process of several steps performed by a skilled clinician that should lead to a correct diagnosis.
The Subcommittee on ADHD and Committee on Quality Improvement in cooperation with other specialist, such as neurologist, psychologist, child psychiatrists, epidemiologist etc. compiled a Clinical Practice Guideline: Treatment of the School-Aged Child With ADHD (2001) to provide the clinicians with a secure material that could serve as a framework for making decisions while treating children between 6 and 12 of age with ADHD without major coexisting conditions. (Subcommittee on ADHD, 2001)

“The Guideline contains the following recommendations for the treatment of a child diagnosed with ADHD:

- Primary care clinicians should establish a treatment program that recognizes ADHD as a chronic condition.
- The treating clinicians, parents, and child, in collaboration with school personnel, should specify appropriate target outcomes to guide management.
- The clinician should recommend stimulant medication and/or behavior therapy as appropriate to improve target outcomes in children with ADHD.
- When the selected management for a child with ADHD has not met target outcomes, clinicians should evaluate the original diagnosis, use of all appropriate treatments, adherence to the treatment plan, and presence of coexisting conditions.
- The clinician should periodically provide a systematic follow up for the child with ADHD. Monitoring should be directed to target outcomes and adverse effects, with information gathered from parents, teachers, and the child.” (p.1033)

Treating children with medication has been, and continues to be the subject of a great controversy. Even in the face of years of scientific research, advances in understanding how these medications work, and significant improvement in the quality of life for millions around the world, there are still those who question, doubt, and attack the role that medication provides in the treatment of ADHD.

Some people are embittered and scared because there are more and more children diagnosed with ADHD which of course leads to more children being treated by medicaments particularly stimulants, as these are the fundamental part of the treatment. The first cause of this is that the criteria in DSM-IV had been broadened in comparison with DSM-III5, so more children seem to be affected and there has been a

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5 The diagnostic criteria DSM-III, DSM-III-R and DSM-IV are introduced in Supplement 1
shift from the emphasis on hyperactivity (DSM-III) to a stress on attentional problems, which also results in more girls being diagnosed with ADHD, as their manifestations of hyperactivity and impulsivity aren’t as noticeable and recognized as the boys’. (Goldman, 1998) The extent of diagnosis is also caused by a better acquaintance of parents, teachers and clinicians.

The concern about highly increased production (2 000 kg in 1986 to 9 000 kg in 1995) and prescription of methylphenidates to children in The United States isn’t caused just by an increase of children diagnosed with ADHD but we have to realize that the DEA\textsuperscript{6} production quota is a gross estimate, which includes FDA\textsuperscript{7} estimates of need, some drug inventories, exports and industry sales expectations. These medicaments are also used by adults, are prescribed as a treatment for other conditions, for example narcolepsy, and sometimes received by geriatric patients to help them with problems as memory functioning. So people are mistaken to think that all the produced stimulants are used for children.

3.2 The abuse/ use of drugs

Even though the efficacy of stimulants is well substantiated there are still concerns that the use in childhood and youth can increase the risk for substance use disorder (SUD). These allegations might have serious consequences as the stimulants are fundamental in the treatment of ADHD and the families and clinicians would have to decide if the improvement provided by these medications is worth risking later SUD. On the other hand if they decrease the risk of SUD they could serve as prevention.

In this chapter I will present 4 studies that engage in researching the relationship between stimulant therapy and subsequent SUD in children and youths with ADHD. These studies compare the samples of medicated subjects with ADHD, non-medicated with ADHD and subjects without ADHD to find out if any of the characteristics of these study groups influence the risk of later development of SUD and how.

To unravel this issue I chose following studies:

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Main issue</th>
<th>Secondary issue</th>
<th>Results</th>
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<tbody>
<tr>
<td>DEA - Drug Enforcement Administration</td>
<td>FDA - Food and Drug Administration</td>
<td></td>
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<tr>
<td>Author(s)</td>
<td>Study Description</td>
<td>Hypothesis</td>
<td>Findings</td>
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<tr>
<td>Biederman et al, 1999</td>
<td>The relation of psychotropic medications used for treatment of ADHD and SUD</td>
<td>Comorbid Conduct disorder</td>
<td>Unmedicated subjects with ADHD – increased risk for SUD</td>
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<td></td>
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<td>Medicated subjects with ADHD – Reduced risk for SUD</td>
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<td></td>
<td>No statistical interaction between CD and ADHD – CD increased risk for SUD</td>
</tr>
<tr>
<td>Barkley et al, 2003</td>
<td>Effect of stimulant treatment in childhood on substance use, dependence and abuse by young adulthood</td>
<td>Sensitization hypothesis</td>
<td>No evidence of stimulant treatment in childhood associated with risk for adolescent or adult substance use or of having substance dependence or abuse disorder</td>
</tr>
<tr>
<td>Wilens et al, 2003</td>
<td>Meta-analysis – the relationship between stimulant therapy and subsequent SUD in youths with ADHD</td>
<td>ADHD and risk of cigarette smoking</td>
<td>Almost 2-fold reduction in risk for SUD in youths treated pharmacologically compare with non-treated youths with ADHD</td>
</tr>
<tr>
<td>Lambert et al, 1998</td>
<td>Longitudinal study – the relation of stimulant therapy and SUD</td>
<td>Sensitization hypothesis</td>
<td>A greater risk for SUD for subjects medicated with stimulants</td>
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<tr>
<td></td>
<td></td>
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<td>Increased risk for nicotine dependence, cocaine dependence.</td>
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These studies have been chosen for their accessibility, validity and reliability. Their objectives are significant for making a conclusion that will prove the notions of the general public and some clinicians that pharmacotherapy, particularly stimulant therapy begets later SUD, wrong.

**Biederman et al (1999)** compiled a study titled *Pharmacotherapy of ADHD Reduces Risk for Substance Use Disorder*, which was one of the first studies to assess the supposed link between pharmacology and SUD. The study objectives were to assess the risk for SUD associated with previous use of psychotropic medication. It was a longitudinal follow-up study of psychiatrically and pediactically referred boys with ADHD taking to account the occurrence of *conduct disorder* (CD), which is well documented risk factor for SUD.

This study examined three opposed hypothesis:
1. A null hypothesis that psychotropics would have no effect on the development of SUD in children with ADHD.

2. The second one assumes that the exposure to pharmacotherapy will be associated with higher risk for SUD in general and stimulant abuse in particular.

3. The third hypothesis is based on supposition that SUD might be caused by an attempt of children and adolescents with ADHD to self-medicate themselves. It assumes that pharmacological management would diminish the risk of SUD by controlling the core features of ADHD and promoting adaptive behavior and academic success.

As the primary sample they used subjects from a longitudinal family genetic study of ADHD\(^8\) and during the cleaning of the sample, the girls were excluded from the study and only subjects who were 15 and more were included. Even though the sample was downsized to males older than fifteen, it eliminated the potential confounding by the variables of the original sample.

The diagnoses of SUD were made in compliance with DSM-III-R and by independent structured interviews with the mothers and direct interviews with the children, that at the baseline and in the 1-year follow-up determined the lifetime history of psychopathology and then the assessment obtained in the 4-year follow-up reflected the interval since the previous assessment. The diagnoses were analyzed as any SUD, alcohol abuse or dependence (A/D), marijuana A/D, hallucinogen A/D, stimulants A/D, and cocaine A/D. Tobacco A/D was collected only at the follow-up assessments.\(^9\)

The final sample consisted of 56 medicated subject with ADHD, 19 nonmedicated subject with ADHD, and 137 non-ADHD subjects. The findings weren’t associated with CD in the ADHD groups or with SUD in the control study.

The researchers used **multiple logistic regression** to create models which estimated the **relative risk** (OR – odds ratio)\(^10\) for each type of SUD associated with ADHD and with being exposed to pharmacotherapy. “The **cumulative incidence** of SUD during follow-up was predicted from a model containing terms for ADHD, medication status, age at follow-

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9. The Prevalence of SUD Subtypes can be found in Supplement no.3.

10. The Adjusted Effect of ADHD and Pharmacotherapy on SUD Incidence can be found in Supplement no.4.
up, socioeconomic status (SES), diagnosis of SUD at baseline, and history of SUD in subjects’ parents.” (Biederman, 1999, p.3)

The results showed that the unmedicated subjects with ADHD were at a significantly increased risk for any SUD at follow-up compared with non-ADHD control subjects. The subjects with ADHD medicated at baseline were at a significantly reduced risk for any SUD outcome at follow-up compared with nonmedicated subjects with ADHD. “As expected, CD and parental SUD were also associated with a significant increased risk for an SUD. However there was no statistical interaction between CD and ADHD or medication status indicating that the effect of medication status in subjects with ADHD on subsequent SUD was not modified by the presence of CD.” (Biederman, 1999, p.3)

(Bidereman, 1999, p.1-5)

Does Stimulant Therapy of Attention-Deficit/Hyperactivity Disorder Beget later Substance Abuse? A Meta-analytic Review of Literature, is a study done by Wilens et al (2003). It is a meta-analysis that evaluates the relationship between stimulant therapy and subsequent SUD in youths with ADHD in general and than separately on alcohol or drug use disorders. This method was used because it evaluates whether the total evidence across all available studies provides evidence for statistical significance. A search of literature was the first step of this study and it yield 6 studies, 2 with follow-up in adolescence and 6 in young adulthood, that provided a sample of 674 medicated subjects and 360 unmedicated subjects who were followed for at least 4 years and of which 97% were treated with stimulants.

The hypotheses were actually the same as in the previous study as it was carried out by almost the same group of researchers.

The study calculated odds ratio (OR) for each study and it showed the protective effect of pharmacotherapy on drug abuse and dependence. The overall OR indicates an almost 2-fold reduction in risk for SUD in youths treated with medicaments compared with non-medicated youths with ADHD.

Results of this study provides compelling evidence that, contrary to assertions in the popular media, pharmacotherapy with stimulants for ADHD does not lead to SUD but instead seems to have protective effects for adverse SUD outcomes in youths with ADHD.

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11 Table of ORs presented as a Supplement no.5.
It is important to remark that the study didn’t fined difference of the risk for SUD between medicated youths with ADHD and non-ADHD controls.

It should be also noted that the protective effect of ADHD pharmacotherapy reducing SUD is weaker in adulthood relative to adolescence, but it could be caused by lack of medication during adolescence.

Even though some studies say that ADHD is a risk factor for cigarette smoking in children and adults, and others even connect smoking with stimulant use, the aggregative literature leans towards the notion, that ADHD in not related to and increased risk for subsequent cigarette or tobacco abuse.

“The mechanism by which ADHD stimulant pharmacotherapy protects against SUD remains unclear.” (p.183) The reason might be that it reduces ADHD symptoms, demoralization, poor self-esteem and academic/occupational failure, which are associated independently with SUD risk. It could be a result of parents who search help for their children with ADHD having a bigger interest in them, being of a higher socioeconomic status or investing more in children’s education success.

These finding should reassure parents that it is safe to use stimulants because they don’t increase the risk for later SUD which could serve as a template for other mental health disorders and could affect a large group of adolescents and young adults that have trouble with SUD. Of course that as every study even this one has its limitations for example not enough research data or appearance of confounds. “Despite these limitations, a meta-analysis of the available literature indicates that stimulant therapy of ADHD does not increase the risk for subsequent SUD but seems to have a protective effect.” (p.184)

A longitudinal study, *Does the Treatment of ADHD with Stimulants Contribute to Drug Use/Abuse? A 13-Year Prospective Study*, accomplished by Barkley et al (2003) seeks the goal to give answers to public concerns that stimulants may cause later drug use/abuse. The concern arises from a conjecture that stimulant such as methylphenidate are chemically similar to cocaine and that is why they have a potential for abuse and addiction, but it is proved that these two drugs have quite different pharmacokinetic properties. Another conjecture that nourishes this concern is the potential for stimulant use to lead to increased sensitization to later stimulant exposure. It means that the more they use stimulants the more they crave them. It is hard to say if it is true, because children get medicament orally, in small doses, and for a long period of time.
This longitudinal study focused on the effect of stimulant treatment in childhood on substance used, dependence, and abuse by young adulthood. "If the stimulant sensitization hypothesis is correct, then duration of stimulant use in childhood should have a significant relationship with extent of cocaine and other stimulant abuse by young adulthood, even after controlling for these other mediating variables." (p.99)

The original sample consisted of 158 hyperactive children and 81 normal children in a control group. These children were first evaluated in 1979 to 1980 when they were ages 4 to 12 years. Majority of these subjects (hyperactive 123, normal 66) were evaluated again in 1987 and 1988 when they were ages 12 to 20 years and then again in 1992 to 1996 when they were ages 19 to 25 years. These children were evaluated by Hyperactivity Index of the Revised Conner Parent Rating Scale and the Weiss-Peters Activity Rating Scale, they had to have high score on Home Situations Questionnaire indicating significant behavioral problems in at least 6 of the 14 situations and a parent and/or teacher complaint of poor sustained attention, poor impulse control, and excessive activity level.

The subjects were evaluated again when they were 15 and 21. At the adolescent follow-up (15) the researchers interviewed the parents about disruptive behavior disorders of their adolescents (ADHD, CD), about history of mental health and medication treatment, history of antisocial behavior and illegal drug use, and educational history. They again collected the rating scales of behavioral adjustment from parents and also the adolescents. Rating scales concerning behavioral adjustment were also collected from parents and adolescents and the last faze of the process was and interview with the adolescents, where they asked them if they had ever used various illegal substances.

At the young adult follow-up they used to evaluate them a batter of measures that assessed the self reports of psychiatric disorders, history of mental health treatments, history of adaptive functioning in education, occupation, dating, sexual activity, driving, etc., and history of antisocial activities and drug use. Then the battery of psychological test and rating scales followed.

At the adolescent follow-up the parents were asked about what medications have their children been taken and for how long. Among the hyperactivity children there were 98 receiving stimulants and 21 had not, they received d-amphetamine or pemoline or their combination. None of the control children had been treated with stimulants. The total duration of stimulant use for the treated children was 40.2 months with a range up to 156 months.
At the young adult follow-up was detected that 22% of hyperactivity group were treated with stimulants during high school for 26.6 months in average. “Only 7 of the hyperactive group (5%) were currently being treated with stimulants at the young adult follow-up.” (p.100)

The next step was a split into two groups from which one had and the other had not been treated with stimulants in childhood. To compare these 2 groups they used the \( \chi^2 \) analyses on the part that self-reported if they had used any of 10 illegal or illicit drugs (cigarettes, alcohol, marijuana, hashish, cocaine, heroin, hallucinogens, unprescribed stimulants, sedatives or tranquilizers). The results showed that these 2 groups didn’t differ significantly in their frequency of having tried any of these drugs. It follows that all \( \chi^2 \) tests were nonsignificant. Next they, provided that the sensitization hypothesis goes for all forms of stimulant use or abuse, combined cocaine with amphetamines use, calculated if each subject had ever tried any form of these stimulants, and they found out that the groups didn’t differ on the outcome either.

Barkley et al as Lambert et al compared 2 categories of children who had been taken stimulants for >1 and <1 year, but there weren’t any significant differences between these two groups on the proportion of adolescents who had tried each of the medication or other drug like cocaine or unprescribed amphetamines.

The same analysis was accomplished for those who had been treated in high school with stimulants and the only significant correlation was for cocaine which after taking conduct disorders into consideration became insignificant. “The two groups were then compared on the proportions that had ever taken any of these substances. Those results appear in Table 4. Again, the groups differed significantly only in the proportion that had ever tried cocaine and, as a result, those who had ever tried any stimulant. Hyperactive individuals who had been treated with stimulants in high school were more likely to have ever tried cocaine. As above, a logistic regression analysis was the used to determine whether stimulant treatment in high school contributed to risk for any cocaine use after controlling for severity of ADHD and conduct problems in childhood and ADHD and CD at adolescence and at adult outcome. When stimulant treatment was treated as a dimensional variable (duration in months) it did not make a significant contribution in this analysis. The contribution of both current severity of ADHD and CD symptom was marginally significant. However, when stimulant treatment in high school was treated as a categorical variable (no/yes), the contribution of both lifetime CD symptoms and high school stimulant treatment was significant.” (p. 103-104)
The final conclusions say that they did find no evidence that stimulant treatment in childhood or during high school is associated with risk for adolescent or adult substance use. They also didn’t find that duration of such treatment would influence later substance use or abuse disorders. “The greater risk for using cocaine in adulthood among children or adolescents who had been treated with stimulants found here was largely explained by severity of current CD symptoms, a previously well-established risk factor for substance use and abuse among hyperactive/ADHD probands.” (p.107) This study admits that the stimulant treatment for 1 year and more in childhood may have protective effects to risk of a hallucinogen abuse disorder in adulthood and it suggests that the clinician probably shouldn’t be afraid of prescribing stimulants to children with ADHD as it isn’t predisposing those children to later drug use, dependence, or abuse.

(Barkley et al, 2003, p.97-109)

Lambert et al carried out a follow up study into adulthood, called Prospective study of tobacco smoking and substance dependencies among samples of ADHD and non-ADHD participants (1998), which findings are in contrast with other studies, because it found a relationship between stimulant treatment in childhood and later drug use or abuse. As for cigarette smoking in adulthood they found an increased risk for nicotine dependence, also cocaine dependence, and possibly stimulant dependence disorders.

In the initial report they divided their sample into groups according to duration of stimulant treatment to the ones who never used stimulants, used stimulants 1 year or less, and more than 1 year. In the additional analyses of the same sample, the subjects fall in a large group of normal children and then they were divided to groups according to stimulant treatment history. The results were even more serious as they found that the risk for cocaine dependence is significant and that it was likely to develop a stimulant dependence disorder in adulthood. The authors concluded that taking stimulants in childhood predisposes to nicotine use in adulthood and to a small degree to cocaine and stimulant dependence, possibly supporting the stimulant sensitization hypothesis.

These results are attackable as there were many comorbid disorders associated with ADHD, such as oppositional disorder, conduct disorder, learning disabilities and major depression, all these might be influencing the risk of abuse/use of drugs, as for conduct disorder it has been proved to be a great risk factor. Both these reports failed to examine and control for the impact of severity of current ADHD and especially current or lifetime symptoms of CD on drug use and abuse at adulthood.
No parent loves the idea of using medications for their children but these behavioral problems aren’t going to disappear by themselves and they might influence the whole life of the child as you could have seen in the previous chapters. It is no wonder that parents are scared of using stimulants for their children as they fall into the same category as cocaine and are proved to have abuse/use potential. It shouldn’t surprise us that so many concerns are appearing in the media and that so many people are protesting against the use of these medicaments for children with ADHD, but as you could realize while reading the aforementioned and described longitudinal studies there is no prove that stimulants beget later substance use/abuse or that they increase the risk for it, it was actually found that the use of these medicaments for treatment of these children has a protective effect for adverse SUD outcomes and that on the contrary the children who aren’t treated are at a significantly greater risk of SUD, as studies (e.g. Wilens, 2003) showed untreated ADHD is a significant risk factor for SUD even after considering the comorbid conduct disorders.

These findings, however, need further investigation as does the mechanisms by which ADHD stimulant pharmacotherapy protects against SUD, which are still quite unclear. There are several factors as a reduction of ADHD symptoms, demoralization, poor self-esteem and academic failure, that are associated with SUD risk, that could be having this positive impact. It could also be put in favor of the parents, because the fact that they search help for their children might be a sign of greater interest in them a more solicitude, they also might be of higher socioeconomic status or invest more in their children’s education success. It’s a question that is hanging in the air and is a potential theme for future studies.

The fact it was proven that the stimulants don’t increase the risk for later SUD is of a great importance because it can help diminish parents’ fear of using these medicaments, clinicians’ fear to prescribe them and educators’ fear to give the pills to children during school. But first the general public should be thoroughly informed about these findings and the results should get into a popular awareness, which is much complicated by the enormous number of articles in various newspapers, magazines and of course mostly on the
internet, that malign the mind of many parents and clinicians and that “warn” better say scare parents. Much more effort will have to be put into this process.

### 3.3 Stimulants as a cause of sudden death

Sudden death is the most frightening thought for all parents, just imagine that you would search for information about a medication that was prescribed to your child by a clinician and the first information that would get to you would be that it can cause sudden death of your child. Would you let your child be treated for several years with such a medicament, probably not, but that is a mistake.

On the basis of these concerns US Food and Drug Administration (FDA) raised a concern about potential cardiovascular safety of stimulants and was considering marking the stimulants with a “black-box” warning on the risk for sudden death (SD), which led to an public atmosphere of high anxiety and it made it difficult to explain to the parents and public that the things are not as hot.

To find an answer to a question, if stimulant therapy increases risk of SD or actually causes it, we have to first assess if the risk of SD in individuals taking stimulants is higher than risk of general population. Next important thing is to find out if there is evidence for biological plausibility that the use of stimulants has cardiovascular outcomes. (Wilens, 2006)

SD occurs at a stable rate in the general population, which is for children and adolescent between 0.6 and 6 in 100 000 per year and it increases with age. “SD is presumed to be of cardiac origin in half of the cases, with structural heart defects (e.g. idiopathic hypertrophic subaortic stenosis) accounting for the majority of abnormalities identified, followed by anomalous origin of cardiac vessels and aortic dissection and rupture.” (Wilens, 2006, p.1216)

If we want to find out what is the risk of SD for children treated with stimulants we must compare it with the risk in similarly aged individuals in the general population. The FDA Psychopharmacology Pediatric Advisory Board in 2006 came to a conclusion that stimulant medications don’t present an excessive cardiovascular risk in children and adolescents, the only risk is in patients that suffer from an underlying heart defects.

During the years 1999-2003 were reported 25 cases of SD among patients treated with stimulants. It was detected that vast of these patients that suffered SD during treatment
with stimulants had autopsies and the results were that 8 of 12 cases using amphetamine and 4 of 7 using methylphenidate had a structural cardiac defect, most commonly hypertrophic cardiomyopathies, which were most probably the underlying cause of SD.

“Nevertheless, the risk and distribution of the cardiac dysfunction and structural abnormalities reported in patients receiving stimulants are strikingly similar to the characteristics of SD reported in the general population.” (Wilens, 2006, p.1217)

There is a growing number of studies evaluating the short- and long-term effects of stimulants on cardiovascular parameters in children, adolescents and adults with ADHD who are taking stimulants. These studies work with healthy subjects without known preexisting cardiac anomalies and they enduringly register only a small, statistically significant, but not clinically meaningful increase in blood pressure and pulse as well as minimal changer during electrocardiography.

The question is what the physiologic effect of stimulants is. They are actually catecholaminergic and have sympathomimetic character that can affect rate, cardiac conduction, and repolarization and rhythmicity of the heart. However not all catecholaminergic agents have the same effect and stimulants are the ones with milder effect than the rest, e.g. isoproterenol. Stimulants affect heart rate and contractility but their effects are predictable and they rarely reach tachycardia (140 beat per minute in children).

The conclusion is that existing data of SD in children, adolescents and adults treated with stimulants prove it extremely rare. It is still unclear if the risk for SD is higher by these patients then in the general population, but the autopsies of patients who suffered SD during treatment of stimulants didn’t show anything different from the general population. So as the FDA says there is no causality. “Whether the stimulants interact with “vulnerable” patients such as those with presumed preexisting cardiac disease to create rhythm disturbances remain unclear, and if these disturbances are operant, they are probably occurring at an extremely low baseline rate.” (p. 1217)

Wilens (2006) says that we have to weight the risks of leaving ADHD untreated. He thinks it would be a mistake, because it is proved that ADHD itself leads to risk for substantial comorbidity, including academic, occupational, and interpersonal failure, criminality and injuries and to more car accidents and that patients with untreated ADHD are at greater risk of cigarette smoking and substance use/abuse. All these factors can cause death so it is much more dangerous to not treat ADHD than to treat it with stimulants when we don’t have evidence that it causes SD.
Even though stimulant therapy wasn’t identified as associated with SD before starting therapy with medicaments the family history of SD should be checked and it should also be found out if there were or are any syncopes, palpitations, chest pain, or dizziness of unknown origin, especially during exercise. Important is also to examine blood pressure and pulse before and during treatment. “Other than clinical history and unusual physical examination, there is no good way to screen for occult structural cardiac disease.” (p. 1218) If the patients demonstrate any aforementioned symptoms further examination should take place. (Wilens, 2006, p.1215-1219)

As you could have seen above there is no evidence that using stimulants as a treatment of ADHD increases risk of SD or causes it and to prevent it the clinicians should carry out thorough examination of the child and his personal and family history to try to discover the possibility of hidden cardiovascular defect. Otherwise there is no other reason why stimulants that have been proved by so many studies to be the most affected treatment for ADHD shouldn’t be used, and it would have much more serious consequences if the children with ADHD weren’t treated at all.
Conclusions

As I wrote at the beginning of this thesis and as you could have read in previous chapters, Attention-Deficit/Hyperactivity Disorder is a very complicated disorder so we probably shouldn’t be surprised that such a subject elicits severe discussions, raises concerns and questions.

The realness of this diagnose has been proved by many clinicians and there is no doubt about its existence.

The number of children diagnosed with this disorder is not higher because teachers are trying to label difficult children, but it is caused by widening the case definition from DSM-III to DSM-IV which is used now, when a shift from emphasizing hyperactivity to putting forward attentional problems took place. It is also a matter of better understanding and widely spread knowledge of it, better acquaintance of clinicians, teachers and parents with this disorder.

There are sufficient diagnostic criteria and methods to diagnose this disorder but the clinicians have to accomplish a thorough examination of the child, gain information from several sources so they could evaluate the child in different settings and they have to eliminate the possibility of another disorder that could be imitating very similar symptoms.

As for the substance use/abuse that is thought to be caused by using stimulant therapy, it has been well proved that it actually doesn’t beget later substance use/abuse but even that it has a protective effect. On the other hand children with untreated ADHD are at much greater risk than treated and normal children.

The last concern related to sudden death caused by use of stimulants, isn’t based on sufficient evidence and the rates of SD among children with ADHD don’t differ from the ones of general population. It is again untreated ADHD that is a danger for children and adolescents with ADHD as the lack of help causes poor self-esteem, disturbed social relationships among family, peers and others, worse academic or occupational performance, all aspects leading to pathologies that can in the worst end lead to death.

There is much more to be discovered and proved and there is still a need of additional studies that would help us unravel this tight knot.
References

- Goldman, L.S, MD; Genel, M., MD; Bezman, R.J., MD; Slanetz, P.J., MD, MPH (1997): *Diagnosis and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents.* Chicago: American Medical Association.


Glossary

- **Etiology** – The cause of a particular disorder, or the study of the causes of disorders in general.

- **Conduct disorder** – A mental disorder of childhood or adolescence characterized by repetitive and persistent violations of the right of others and of social norms and rules, including bullying, aggressive or threatening behavior towards people or animals, deliberate destruction of property, deceitfulness, or theft, with the behavior causing significant impairment in social, academic, or occupational functioning.

- **Confidence interval** – In statistics, a range of values bounded by confidence limits within which there is a specified probability that the true value of a population parameter is expected, with a specified level of confidence, to lie. By convention, the 95 and 99 per cent confidence intervals are most used.

- **Dependence** – A psychological and sometimes physical state of reliance on a substance, especially on a narcotic drug such as cocaine or heroin, but also on everyday drugs such as nicotine, caffeine, or alcohol, characterized by a compulsion to take the drug in order to experience its effect and generally also withdrawal and tolerance.

- **Hyperactivity** – Abnormal or pathological overactivity.

- **Learning disability** – A generic name for disorders characterized by substantial deficits in scholastic or academic skills, including reading disorder, mathematics disorder, and disorder of written expression.

- **Stimulant drug** – Any drug that increases or tends to increase the activity of a system or organ of the body, especially one that increases or speeds up the activity of the central nervous system by boosting catecholamine transmission, producing an exaggeration of the characteristic features of alert wakefulness, and that in high dosages can cause hallucinations, convulsions and death. Also called a *psychoanaleptic drug*, a *psychomotor stimulant*, or a *psychostimulant*. A common street name for stimulant drugs in general is *uppers*.

- **Randomized controlled trial** – A research design used for testing the effectiveness of a drug, or any other type of treatment, in which research participants are assigned randomly to treatment and control or placebo groups and the differences in outcomes are compared.
• **Standard deviation** – In descriptive statistics, a measure of the degree of dispersion, variability, or scatter in a set of scores, expressed in the same units as the scores themselves, defined as the square root of the variance.

• **Substance abuse** – A maladaptive use of a drug, resulting in impairment of functioning or distress, as manifested by: a failure to perform adequately at home, school or work; repeated drug use in dangerous circumstances, such as when driving or operating machinery; repeated police arrests; or serious marital or interpersonal problems caused or exacerbated by the drug use.

• **Substance-related disorders** – A class of mental disorders resulting from drug use (including alcohol), side-effects of medication, or exposure to toxins. There are 11 groups of substances specifically discussed in DSM-IV: alcohol; amphetamines and related sympathomimetics; caffeine; cannabis; cocaine; hallucinogens; inhalants; nicotine; opiates; hallucinogens; phencyclidine and related drugs; and sedatives, hypnotics, or anxiolytics.

• **Substance use disorders (SUD)** – A class of substance-related disorders.

• **Symptom** – A subjective indication of a disorder reported by an afflicted person rather than being observed by an examiner.

• **Syndrome** – A pattern of signs and symptom that tend to occur and may indicate a common origin, course, familial pattern, or indicate treatment of particular disorder.
List of supplements

**Supplement no.1**: Diagnostic Criteria for ADHD Across Versions of the Diagnostic and Statistical Manual (table)

**Supplement no.2**: Prevalence Studies of Attention-Deficit/Hyperactivity Disorder (table)

**Supplement no.3**: Prevalence of SUD subtypes (table)

**Supplement no.4**: The Adjusted Effect of ADHD and Pharmacotherapy on SUD Incidence (table)

**Supplement no.5**: Studies That Examined the Impact of ADHD Pharmacotherapy on Later Substance Use Disorder (table)
## Supplements
### Supplement no. 1:

<table>
<thead>
<tr>
<th>TABLE 2. Diagnostic Criteria for ADHD Across Versions of the Diagnostic and Statistical Manual</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DSM-III-R</strong></td>
</tr>
<tr>
<td>A. Inattention, at least three of the following:</td>
</tr>
<tr>
<td>1. Often fails to finish tasks that he or she starts</td>
</tr>
<tr>
<td>2. Often doesn’t seem to listen</td>
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<tr>
<td>3. Easily distracted</td>
</tr>
<tr>
<td>4. Has difficulty concentrating on schoolwork or other tasks</td>
</tr>
<tr>
<td>5. Requires sustained attention</td>
</tr>
<tr>
<td>6. Has difficulty sticking to play activities</td>
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<tr>
<td>B. Impulsivity, at least three of the following:</td>
</tr>
<tr>
<td>1. Acts before thinking</td>
</tr>
<tr>
<td>2. Shifts excessively from one activity to another</td>
</tr>
<tr>
<td>3. Has difficulty organizing work (this not being due to cognitive impairment)</td>
</tr>
<tr>
<td>4. Needs a lot of supervision</td>
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<tr>
<td>5. Frequently calls out in class</td>
</tr>
<tr>
<td>6. Has difficulty awaiting turn in games or group situations</td>
</tr>
<tr>
<td>C. Hyperactivity, at least two of the following:</td>
</tr>
<tr>
<td>1. Runs about or climbs excessively</td>
</tr>
<tr>
<td>2. Has difficulty sitting still or fidgets excessively</td>
</tr>
<tr>
<td>3. Has difficulty staying seated</td>
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<tr>
<td>4. Moves about excessively during sleep</td>
</tr>
<tr>
<td>5. Is always “on the go” or acts as if “driven by a motor”</td>
</tr>
<tr>
<td>D. Onset before the age of 7</td>
</tr>
<tr>
<td>E. Duration of at least 6 months</td>
</tr>
<tr>
<td>F. Not due to schizophrenia, affective disorder, or severe or profound mental retardation</td>
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### DSM-IV-TR

<table>
<thead>
<tr>
<th><strong>A. Either (1) or (2):</strong></th>
</tr>
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<tbody>
<tr>
<td>(1) Six (or more) of the following symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:</td>
</tr>
<tr>
<td>(a) Often fails to give close attention to details and makes careless mistakes in schoolwork, work, or other activities</td>
</tr>
<tr>
<td>(b) Often has difficulty sustaining attention in tasks or play activities</td>
</tr>
<tr>
<td>(c) Often does not seem to listen when spoken to directly</td>
</tr>
<tr>
<td>(d) Often does not follow through on instructions and fails to finish schoolwork, chores, or other tasks in the workplace (not due to oppositional behavior) or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)</td>
</tr>
<tr>
<td>(e) Often has difficulty organizing tasks and activities</td>
</tr>
<tr>
<td>(f) Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)</td>
</tr>
<tr>
<td>(g) Often loses things necessary for tasks or activities (eg, toys, school assignments, pencils, books, or tools)</td>
</tr>
<tr>
<td>(h) Is often easily distracted by extraneous stimuli</td>
</tr>
<tr>
<td>(i) Is often forgetful in daily activities</td>
</tr>
</tbody>
</table>

| **B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years** |

| **C. Some impairment from the symptoms is present in two or more settings (eg, at school or work) and at home** |

| **D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning** |

| **E. The symptoms do not occur exclusively during the course of a pervasive developmental disorder, schizophrenia, or another psychotic disorder and are not better accounted for by another mental disorder (eg, mood disorder, anxiety disorder, obsessive-compulsive disorder, or a personality disorder)** |

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52
Supplement no.2:

Table 2.—Prevalence Studies of Attention-Deficit/Hyperactivity Disorder

<table>
<thead>
<tr>
<th>Site</th>
<th>Source, y</th>
<th>Criteria*</th>
<th>Prevalence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Zealand</td>
<td>Anderson et al.21, 1987</td>
<td>DSM-III</td>
<td>6.7</td>
</tr>
<tr>
<td>New York, NY</td>
<td>Cohen,26, 1988</td>
<td>DSM-III</td>
<td>3.6</td>
</tr>
<tr>
<td>Ontario</td>
<td>Szatmari et al.27, 1989</td>
<td>DSM-III</td>
<td>8.3</td>
</tr>
<tr>
<td>Puerto Rico</td>
<td>Bird et al.28, 1988</td>
<td>DSM-III</td>
<td>9.5-16.1</td>
</tr>
<tr>
<td>US inner city</td>
<td>Newcorn et al.29, 1989</td>
<td>DSM-III†</td>
<td>12.3</td>
</tr>
<tr>
<td>Pittsburgh, Pa</td>
<td>Costello et al.30, 1988</td>
<td>DSM-III-R</td>
<td>2.6</td>
</tr>
<tr>
<td>Iowa</td>
<td>Lindgren et al.31, 1990</td>
<td>DSM-III‡</td>
<td>2.8</td>
</tr>
<tr>
<td>Germany</td>
<td>Baumgarten et al.32, 1995</td>
<td>DSM-III</td>
<td>9.6</td>
</tr>
<tr>
<td>Mannheim, Germany</td>
<td>Isser et al.34, 1990</td>
<td>DSM-III-R</td>
<td>4.2</td>
</tr>
<tr>
<td>United States</td>
<td>Pelham et al.35, 1992</td>
<td>DSM-III-R</td>
<td>2.5-4.0</td>
</tr>
<tr>
<td>Tennessee</td>
<td>Wolk et al.36, 1996</td>
<td>DSM-III-R</td>
<td>7.3</td>
</tr>
<tr>
<td>United States</td>
<td>Shaffer et al.37, 1996</td>
<td>DSM-III-R</td>
<td>4.1</td>
</tr>
</tbody>
</table>

†Prevalence of 18.9% using DSM-III-R.
‡Prevalence of 6.1% using DSM-III-R.
§Prevalence of 8.0% primarily inattentive, 3.9% primarily hyperactive, 4.8% combined (17.8% total) using DSM-IV.

(Goldman, 1998, p.1102)

Supplement no.3

TABLE 1. Prevalence of SUD Subtypes

<table>
<thead>
<tr>
<th></th>
<th>Medicated ADHD N = 56</th>
<th>Non-medicated ADHD N = 19</th>
<th>Non-ADHD N = 137</th>
<th>$\chi^2$ (df)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline SUD†</td>
<td>0 (0)</td>
<td>7 (37)</td>
<td>18 (13)</td>
<td>19.2‡</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Alcohol A/D</td>
<td>0 (0)</td>
<td>7 (37)</td>
<td>15 (11)</td>
<td>20.7‡</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Marijuana A/D</td>
<td>0 (0)</td>
<td>4 (21)</td>
<td>8 (6)</td>
<td>11.7‡</td>
<td>.001</td>
</tr>
<tr>
<td>Hallucinogen A/D</td>
<td>0 (0)</td>
<td>4 (21)</td>
<td>4 (3)</td>
<td>17.9‡</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Stimulant A/D</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td>2 (1)</td>
<td>12.6‡</td>
<td>.2</td>
</tr>
<tr>
<td>Cocaine A/D</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (1)</td>
<td>1.3‡</td>
<td>.6</td>
</tr>
<tr>
<td>Follow-up SUD†</td>
<td>14 (25)</td>
<td>14 (75)</td>
<td>25 (16)</td>
<td>19.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Alcohol A/D</td>
<td>12 (21)</td>
<td>13 (68)</td>
<td>21 (13)</td>
<td>20.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Marijuana A/D</td>
<td>9 (16)</td>
<td>8 (42)</td>
<td>11 (8)</td>
<td>13.6†</td>
<td>.001</td>
</tr>
<tr>
<td>Hallucinogen A/D</td>
<td>4 (7)</td>
<td>3 (16)</td>
<td>5 (4)</td>
<td>4.7</td>
<td>.09</td>
</tr>
<tr>
<td>Stimulant A/D</td>
<td>1 (2)</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>5.8‡</td>
<td>.06</td>
</tr>
<tr>
<td>Cocaine A/D</td>
<td>1 (2)</td>
<td>3 (16)</td>
<td>2 (1)</td>
<td>8.2</td>
<td>.02</td>
</tr>
<tr>
<td>Follow-up tobacco A/D</td>
<td>19 (34)</td>
<td>6 (32)</td>
<td>22 (16)</td>
<td>8.8</td>
<td>.012</td>
</tr>
</tbody>
</table>

* Logistic regression model using robust estimates of variance to account for familial associations between siblings.
† SUD subtypes are not mutually exclusive.
‡ Uncorrected P value reported because regression model would not converge due to cell with zero observations.

(Biederman et al, 1999, p.3)
Supplement no.4:

**TABLE 2. The Adjusted Effect of ADHD and Pharmacotherapy on SUD Incidence**

<table>
<thead>
<tr>
<th></th>
<th>Unmedicated ADHD Versus Controls</th>
<th>Medicated ADHD Versus Unmedicated ADHD</th>
<th>Baseline CD(+) Versus Baseline CD (−)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Any SUD at follow-up</td>
<td>6.3 (1.8-21.4)</td>
<td>0.15* (0.04-0.6)</td>
<td>5.5 (2.0-15.3)</td>
</tr>
<tr>
<td>Alcohol A/D†</td>
<td>5.8 (1.7-19.3)</td>
<td>0.16 (0.05-0.57)</td>
<td>4.9 (1.8-13.5)</td>
</tr>
<tr>
<td>Marijuana A/D</td>
<td>3.1 (0.8-12.5)</td>
<td>0.42 (0.11-1.7)</td>
<td>5.4 (1.7-16.9)</td>
</tr>
<tr>
<td>Hallucinogen A/D</td>
<td>1.0 (0.1-9.3)</td>
<td>0.76 (0.12-5.0)</td>
<td>9.0 (1.7-46.9)</td>
</tr>
<tr>
<td>Cocaine/stimulant A/D</td>
<td>7.5 (0.3-163.8)</td>
<td>0.2 (0.02-2.1)</td>
<td>3.0 (0.2-48.3)</td>
</tr>
<tr>
<td>Tobacco A/D</td>
<td>0.85 (0.15-4.8)</td>
<td>2.4 (0.5-12.3)</td>
<td>4.4 (1.5-12.7)</td>
</tr>
</tbody>
</table>

* ORs < 1 indicate a protective effect, i.e., that the odds of SUD were smaller in the medicated than in the unmedicated ADHD groups.
† A/D, abuse or dependence.

From separate logistic regression models predicting each SUD subtype as the dependent variable and the following baseline characteristics as independent variables: ADHD, Medication for ADHD, Conduct disorder, age, SES, any SUD at baseline, and parental history of SUD. For simplicity only the results from the terms of most interest (ADHD, Medication for ADHD, & CD) are presented. Underlining indicates P value < .01 according to Wald’s χ² using robust estimates of variance to account for familial associations between siblings.

(Biederman, et al, 1999, p.3)

Supplement no.5

**TABLE 2. Studies That Examined the Impact of ADHD Pharmacotherapy on Later Substance Use Disorders**

<table>
<thead>
<tr>
<th>Study</th>
<th>Protective Effect (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td>Meta-analysis of drug studies</td>
<td></td>
</tr>
<tr>
<td>Lambert†</td>
<td>0.47</td>
</tr>
<tr>
<td>Biederman†</td>
<td>3.9</td>
</tr>
<tr>
<td>Huss*</td>
<td>2.2</td>
</tr>
<tr>
<td>Loney†</td>
<td>1.1</td>
</tr>
<tr>
<td>Molina††</td>
<td>4.6</td>
</tr>
<tr>
<td>Barkley</td>
<td>0.83</td>
</tr>
<tr>
<td>Meta-analysis of alcohol studies</td>
<td></td>
</tr>
<tr>
<td>Lambert†</td>
<td>0.6</td>
</tr>
<tr>
<td>Biederman†</td>
<td>8.1</td>
</tr>
<tr>
<td>Loney†</td>
<td>3.6</td>
</tr>
<tr>
<td>Molina††</td>
<td>6.6</td>
</tr>
<tr>
<td>Barkley</td>
<td>0.98</td>
</tr>
</tbody>
</table>

The OR measures the increase in the odds of not having an SUD outcome between medicated and unmedicated youths with ADHD. ORs > 1 indicate a protective effect of pharmacotherapy on SUD outcome. The larger the OR, the greater the protective effect of pharmacotherapy on SUD outcome.

(Wilens et al, 2003, p.182)