Recent Advances in Management of Attention- Deficit /Hyperactivity Disorder

An essay submitted for partial fulfillment of Master Degree in Neuropsychiatry

By

Maged Abd Elmaksoud Elesely

M.B.B.Ch.

Under Supervision of

Professor Dr. Taha Kamel Taha

Professor of Neuropsychiatry

Ain Shams University

Professor Dr. Nahed Salah El-Din Ahmed

Professor of Neuropsychiatry

Ain Shams University

Dr. Naglaa Mohamed El Khayat

Assistant professor of Neuropsychiatry

Ain Shams University

Faculty of Medicine

Ain Shams University

2010

ACKNOWLEDGEMENT

Praise to "*Allah*", the Most Gracious and the Most Merciful Who Guides Me to the Right Way

I wish to express my sincere gratitude and gratefulness to ***Professor Dr. Taha Kamel Taha***, Professor of Neuropsychiatry, Ain Shams University, for his kind supervision and constant encouragement. In fact, it has been a great honor to work under his supervision.

I am greatly indebted and appreciating to ***Professor Dr. Nahed Salah El-Din Ahmed***, Professor of Neuropsychiatry, Ain Shams University. Her Useful suggestions, generous help and enthusiastic cooperation have made it possible to complete this work.

I would like to thank ***Dr. Naglaa Mohamed El Khayat, Assistant professor of Neuropsychiatry, Ain Shams University*** for her honest help and continuous advice, and guidance all through the work.

CONTENTS

LIST OF ABBREVIATIONS

5HT	Serotonin
ADD (H)	Attention deficit disorder-with or without hyperactivity
ADHD	Attention deficit hyperactivity disorder
ADHD NOS	Attention deficit hyperactivity disorder not otherwise specified
AMP	Amphetamine
ASRS	Adult self report scale
CAARS	Conners adult ADHD rating scale
CBT	Cognitive behavioral therapy
CD	Conduct disorder
COWAT	Color word association test
CPT	Continuous performance test
DA	Dopamine
DSM	Diagnostic and statistical manual of mental disorders
DSM-IV-TR	Diagnostic and statistical manual of mental disorders text revision
EEG	Electroencephalogram
EPI	Epinephrine
*f*MRI	Functional magnetic resonance imaging
ICD 10	International classification of diseases, 10^{th} edition
MAO	Mono amino oxidase
MAOI	Mono amine oxidase inhibitor
MDD	Major depressive disorder
MPH	Methylphenidate
MRI	Magnetic resonance imaging
NE	Norepinephrine
ODD	Oppositional defiant disorder
PDD	Pervasive developmental disorder
PET	Perfusion emission tomography
SNRI	Selective norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
WAIS	Wechsler adult intelligence scale
WCST	Wisconsin cad sorting test
WRAAS	Wender-Reimherr attention deficit disorder scale

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a common and impairing neuropsychiatric disorder affecting 6 to 9 percent of school-aged children **(Biederman, 1998)** and 5 percent of adults **(Goldman et al, 1998)**.

Although ADHD was first identified in children in the 19th century, adult ADHD wasn't described in the literature until 1976, when **Wood et al. (1976)** showed evidence of response to stimulants in a group of adults who presented with the same symptoms as ADHD children.

ADHD is a heterogeneous behavioral disorder with multiple possible etiologies. The most important risk factor for ADHD is genes. Central nervous system insults, environmental factors are risk factors **(Biederman et al, 1995)**.

The presumed pathophysiology of ADHD is an abnormality in central dopaminergic and noradrenergic tone, and the only pharmacotherapy that have been shown to be effective in both children and adults have been those affecting these 2 neurotransmitters **(Biederman &Spencer, 1999)**.

The neuroimaging investigations of the brain dopamine transporter (DAT) using Positron Emission Tomography **(PET)** proved that differences in DAT levels are unlikely to be the primary abnormality in ADHD and that lower-than-normal DA release further characterizes individuals with ADHD. However, the finding of a positive correlation between DAT and inattention

symptoms supports the mechanism of action of stimulant medications **(Volkow et al, 2007)**.

The neural networks of attention include the prefrontal cortex, the parietal cortex, the cingulate gyrus, the limbic structures such as amygdala-hippocampus, the basal ganglia, the thalamus, the reticular formation, and the cerebellum **(Seidman et al, 2006)**.

The neuroanatomical findings of (ADHD) are becoming increasingly better defined by a growing body of evidence from Magnetic Resonance Imaging studies (MRI). Total brain size of children with ADHD appears reduced by up to 5%, and the surface area of anterior regions of the corpus callosum is reduced, as are right prefrontal, caudate, and cerebellar volumes **(Durston et al, 2004)**.

A child with ADHD faces a difficult but not insurmountable task ahead. In order to achieve his or her full potential he or she should receive guidance, and understanding from parents and the public education system. Symptoms of ADHD include difficulty sustaining attention, forgetfulness, distractibility, hyperactivity, and problems with impulse control. According to the diagnostic and statistical manual of mental disorders [DSM-IV-TR], there are three patterns of behavior that indicate ADHD. People with ADHD may show several signs of being consistently inattentive .They may have a pattern of being hyperactive and impulsive far more than others of their age, or they may show all three types of behavior. This means that there are three subtypes of ADHD recognized by professionals. These are the predominantly

hyperactive-impulsive type [that does not show significant inattention]; the predominantly inattentive type [that does not show significant hyperactive-impulsive behavior], sometimes called ADD; and the combined type [that displays both inattentive and hyperactive impulsive symptoms] **(APA, 2000)**.

Pharmacologic interventions have been the mainstay of the treatment of ADHD for decades, with hundreds of well-controlled studies documenting the safety and efficacy of this approach to treatment in both children and adults **(Conners, 2002)**.

About 80 percent of children who need medication for ADHD still need it as teenager's. Over 50 percent need medication as adults **(Wilens et al, 2004)**.

Stimulants medications as methylphenidate and amphetamine, and their various isomers, have been shown to provide the greatest efficacy compared with non stimulant medications **(Faraone et al, 2006)**.

Despite this demonstrated efficacy, there are limitations to many available pharmacologic interventions for ADHD. For example, evidence suggests that adherence to medication regimens for treating ADHD is disappointingly low; with 12-month adherence rates for stimulants hovering around 20% and it was found that adherence rates tended to be somewhat better with newer extended-release stimulant formulations vs. shorter-acting stimulants. Fortunately, many of the new and emerging pharmacologic options address some of these limitations of the traditional mainstays of ADHD treatment **(Hodgkins et al, 2006)**. Moreover, stimulant agents used to treat ADHD have a demonstrated abuse potential and some patients

experience idiosyncratic side effects that preclude the use of stimulant drugs **(Kollins 2003)**.

Psychological therapies use to treat ADHD include psychoeducational input, behavior therapy, cognitive behavioral therapy (CBT), interpersonal psychotherapy (IPT), family therapy, school-based interventions, social skills training, and parent management training.

Parent training and education have been found to have short term benefits. Family therapy has shown to be of little use in the treatment of ADHD, though it may be worth noting that parents of children with ADHD are more likely to divorce than parents of children without ADHD, particularly when their children are under the age of 8 years **(Pliszka, 2007).**

Aim of the work

1. To review different modalities in pathogenesis and diagnosis of ADHD

2. To review the recent and updated effective treatments for ADHD

HISTORY, NEUROBIOLOGY AND PATHOPHYSIOLGY OF ADHD

History of ADHD

ADHD is a neurobehavioral developmental disorder. **(Zwi et al, 2005)**. It is the most commonly diagnosed psychiatric disorder in children affecting about 3 to 5% of children globally with symptoms starting before seven years of age (**Nair et al., 2006)**. It is characterized by a persistent pattern of impulsiveness and inattention, with or without a component of hyperactivity **(Biederman et al., 2008)**. ADHD is diagnosed twice as frequently in boys as in girls, though studies suggest this discrepancy may be due to subjective bias. ADHD is generally a chronic disorder with 30 to 50% of those individuals diagnosed in childhood continuing to have symptoms into adulthood. As they mature, adolescents and adults with ADHD are likely to develop coping mechanisms to compensate for their impairment. (**Gentile 2004 and Bálint et al, 2008).** Four percent of American adults are estimated to live with ADHD **(Stern, 2008)**.

The first documented disorder relating to impulsiveness was by Still, This was in Britain. He called this disorder "Defect of Moral Control" and he believed that the diagnosed individual had a medical disorder beyond their control. The next documentation of was in 1922. Here, the symptoms associate with ADHD were given the name "Post-Encephalitic Behavior Disorder. In 1937, Dr. Charles Bradley introduced the use of stimulants in children who were hyperactive. Still found it interesting that stimulants were thought of to treat hyperactive children when they were already bouncing off the walls. While it is true that stimulants calm hyperactive kids down, how did

someone hypothesize that this would occur? In 1956, Ritalin was introduced as the drug of choice to treat hyperactivity **(Londrie, 2006; Schonwald, 2006).** In the early 1960s, the disorder was called "Minimal Brain Dysfunction". At the end of the decade, though, the name of the disorder was changed to "Hyperkinetic Disorder of Childhood" **(Londrie, 2006)**.

New symptoms were added to the disorder. Along with hyperactivity, added symptoms were lack of focus and spaceyness associated with impulsiveness. Impulsiveness now included verbal, cognitive and motor impulsiveness**.**, the disorder was given its current name of Attention Deficit Disorder (ADD) , with or without hyperactivity. This was documented in the DSM-III put out by the American Psychiatric Association (APA). ADD and ADHD were two different diagnoses. The American Psychiatric Association noted that this was a medical diagnosis, and not purely psychological. They also noted that ADHD could cause behavioral issues (**Londrie, 2006**).

In 1996, a new medication called Adderall was approved by the FDA for the treatment of ADHD. After a period of time, it was deemed to be better at treating the disorder since it lasted longer and was easier to come down off of. **(William and Crook 1996)**. In 1999, other medications were added to treat ADHD such as Concerta and Focalin**.** (**American Academy of Child and Adolescent Psychiatry, 1999)**. In 2003, Strattera was introduced as the first ADHD medication that was not a stimulant. This drug acted like an antidepressant, but increased the amount of norepinephrine in the brain **(Tom, Pharm, 2003)**.

It may be helpful to understand that "ADD" and "ADHD" are the same thing, and constitute a single syndrome, with several important and distinctive variations. The clinical definition of "ADHD" dates to the mid-20th century, but was known by other names. Physicians developed a diagnosis for a set of

conditions variously referred to as "minimal brain damage", "minimal brain dysfunction", "learning/behavioral disabilities" and "hyperactivity". Some of these labels became problematic as knowledge expanded. For example, as awareness grew that many children with no indication of brain damage also displayed the syndrome, the label which included the words "brain damage" did not seem appropriate. The DSM-II (1968) began to call it "Hyperkinetic Reaction of Childhood" even though the professionals were aware that many of the children so diagnosed exhibited attention deficits without any signs of hyperactivity. In 1980, the DSM-III introduced "ADD (Attention-Deficit Disorder) with or without hyperactivity." That terminology (ADD) technically expired with the revision in 1987 to ADHD in the DSM-III-R **(Parrillo, 2009**). In the DSM-IV, published in 1994, ADHD with sub-types was presented. The DSM-IV-TR was released in 2000, primarily to correct factual errors and make changes to reflect recent research; ADHD was largely unchanged **(Polanczyk, et al., 2007)**.

Under the DSM-IV, within the ADHD syndrome, there are three sub-types, including one which lacks the hyperactivity component. Approximately one-third of people with ADHD have the predominantly inattentive type (ADHD-I), meaning that they do not have the hyperactive or overactive behavior components of the other ADHD subtypes (Fig. 1).

ADHD terminology still objectionable to many. There is some preference for using the ADHD-I and ADD terminology when describing individuals lacking the hyperactivity component, especially among older adolescents and adults who find the term "hyperactive" inaccurate, inappropriate and even derogatory **(Polanczyk, et al., 2007)**.

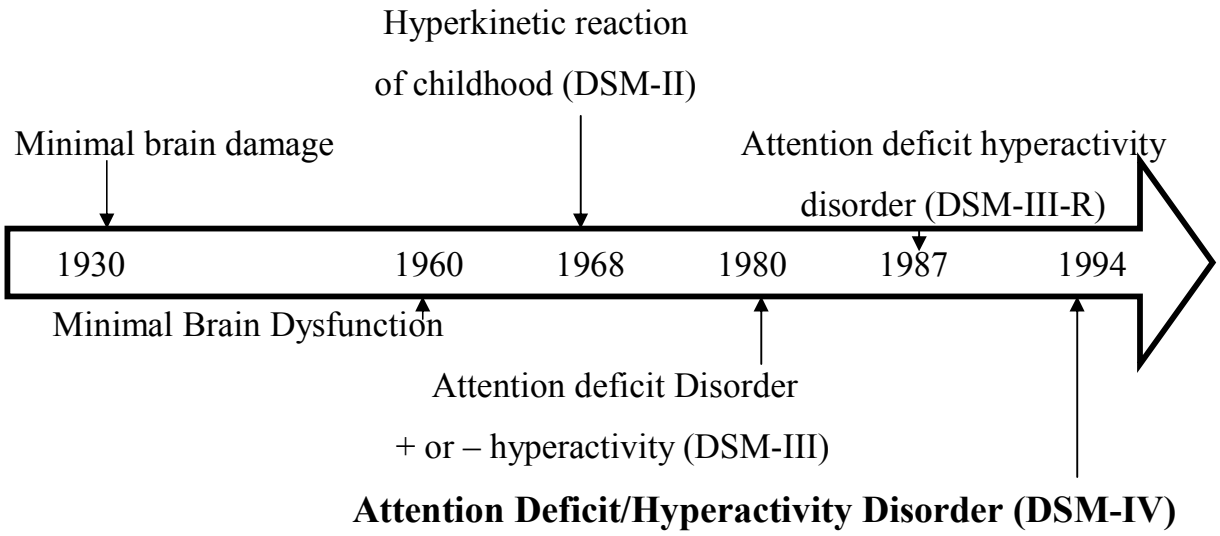

Fig. (1): Historical Timeline **(Nigg, et al., 2002)**

Neurobiology of ADHD

The data on the neurobiological substrate of ADHD are derived from neuropsychological, neuroimaging and neurotransmitter studies. ADHD is caused by neurological rather than parental, social, or emotional causes. The cause of (ADHD) has been linked with the brain's chemical system, not it's structure. Thus, (ADHD) is a problem with brain chemistry - not brain damage or injury **(Riesgo, et al., 2004)**.

The brain uses multiple chemical substances for operation, regulation, and communication. These chemicals, called "neurotransmitters", serve various functions in the brain. Three neurotransmitters have been linked to behavioral and emotional conditions: Dopamine, Serotonin, and Norepinephrine (Fig.2). If we imagine using a "dipstick", like the dipstick used to check oil/transmission fluid levels in automobile, we might be able to check the neurotransmitter levels in brain, finding which neurotransmitters are low, within the normal range, or high. Low levels of serotonin, for example, are linked with clinical depression and for that reason, modern antidepressant medication increases the availability of the serotonin neurotransmitter in the brain **(Joseph, 2009)**.

Attention-Deficit Hyperactivity Disorder (ADHD) appears related to two neurotransmitters - Dopamine and Norepinephrine. Neurotransmitters are used by the brain to stimulate or repress stimulation in brain cells. To pay proper attention, the brain must be adequately stimulated. To have proper control of our impulses, areas of the brain must be adequately controlled, repressed, or slowed down. In ADHD children, both systems of stimulation and repression are not working correctly. Some studies suggest that ADHD