Assessment and Diagnosis of ADHD

Joseph Biederman, MD
Professor of Psychiatry
Harvard Medical School
Chief, Clinical and Research Programs in Pediatric Psychopharmacology and Adult ADHD
Director, Bressler Program for Autism Spectrum Disorders
Massachusetts General Hospital
History of ADHD

1902 - George Still described ADHD

1937 – Bradley* Benzedrine

1955 – MPH Created

1960 – Minimal Brain Dysfunction

1966 – Clements listed attention as a deficit in children

1980 – Attention Deficit Disorder + or – Hyperactivity (DSM-III)

1987 – Attention Deficit Hyperactivity Disorder (DSM-III-R)

1994 – DSM-IV updated criteria

2013 – DSM-V updated criteria

* Bradley (1937) original conceptualization of ADHD involved testing of response stimulant.

ADHD: Etiology

ADHD is a heterogeneous behavioral disorder with multiple possible etiologies.

- Neuroanatomic and Neurochemical causes
- CNS insults
- Genetic origins
- Environmental factors
Worldwide Prevalence of ADHD in Children

Prevalence of ADHD (%)

USA

N.Y., Mich., Wis.
North Carolina
Virginia
Missouri
Oregon
Minnesota
Tennessee
Iowa
Pittsburgh
New York City
Puerto Rico

Ex USA

Spain
New Zealand
Canada
Ireland
United Kingdom
Israel
Switzerland
Netherlands/Belgium
Germany
Ukraine
Brazil
Japan
New Zealand
Netherlands
China
India

Prevalence of ADHD (%)

Faraone SV et al. (2003), World Psychiatry 2(2):104-113
Key findings

Data from the National Health Interview Survey, 1998–2009

- The percentage of children ever diagnosed with attention deficit hyperactivity disorder (ADHD) increased from 7% to 9% from 1998–2000 through 2007–2009.

- ADHD prevalence trends varied by race and ethnicity. Differences between groups narrowed from 1998 through 2009; however, Mexican children had consistently lower ADHD prevalence than other racial or ethnic groups.

- From 1998 through 2009, ADHD prevalence increased to 10% for children with family income less than 100% of the poverty level and to 11% for those with family income between 100% and 199% of the poverty level.

- From 1998 through 2009, ADHD prevalence rose to 10% in the Midwest and South regions of the United States.

Akinbami et al. NCHS Data Brief No. 70, August 2011

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Adherence in ADHD is Dismal

• Only 13% of patients consistently take their medication one year out.

- Within 2 to 3 months, a majority of patients with ADHD have stopped taking medication consistently.
- Patients renewed their monthly prescriptions about 2 to 3 times per year.

Psychopharmacology Course 2017
Percent of Children with ADHD who Renewed their First Stimulant Rx at Partners Healthcare: An EMR Review

<table>
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<th># of patients</th>
<th># of patients who refilled a prescription for ≥1 medication</th>
<th>% of patients who refilled</th>
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<td>2,685</td>
<td>1,537</td>
<td>57%</td>
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Patients who refilled a prescription for ≥1 medication
Poor adherence occurs despite the well documented morbidity of ADHD, the marked efficacy and safety of stimulants as well as the fact that ADHD symptoms return rapidly when the medication is not taken.
Long Delays in the Initiation of Treatment (n=1498)

Age of Onset of Diagnosis: 3.3
Age of Onset of Treatment: 7.8

p < 0.001

MGH Pediatric Psychopharmacology Clinic
Diagnosis of ADHD

- Diagnosis is based on clinical assessment of symptoms, associated impairment and age of onset
- No test is available
- Symptoms are subjective, as well as developmentally and context sensitive
ADHD: Core Symptom Areas

Inattention

Impulsivity/Hyperactivity
ADHD: DSM-V Criteria

Inattention

Six or more of the following – manifested *often*:

- Inattention to details/ makes careless mistakes
- Difficulty sustaining attention
- Seems not to listen
- Fails to finish tasks
- Difficulty organizing
- Avoids tasks requiring sustained attention
- Loses things
- Easily distracted
- Forgetful

DSM-V, 2013
ADHD: DSM-V Criteria

Impulsivity/Hyperactivity

Six or more of the following – manifested often:

**Impulsivity**
- Blurs out answer before question is finished
- Difficulty awaiting turn
- Interrupts or intrudes on others

**Hyperactivity**
- Fidgets
- Unable to stay seated
- Inappropriate running/climbing (restlessness)
- Difficulty in engaging in leisure activities quietly
- “On the go”
- Talks excessively
ADHD
Variation in Symptoms

- Pervasiveness
- Frequency of Occurrence
- Degree of Impairment

Symptoms Vary in
Course of ADHD Symptoms Over Time by Sex: A Growth Curve Model

Age by Sex Interaction: NS

Biederman et al. 2009

Psychopharmacology Course 2017
The age-dependent decline and persistence of attention-deficit/hyperactivity disorder throughout the lifetime. Follow-up studies have assessed children with attention-deficit/hyperactivity disorder (ADHD) at multiple time points after their initial diagnosis. Although they document an age-dependent decline in ADHD symptoms, ADHD is also a highly persistent disorder when defined by the persistence of functional impairment or the persistence of subthreshold (three or fewer) impairing symptoms. By contrast, many patients remit full diagnostic criteria.
ADHD: Course of the Disorder

Hyperactivity

Impulsivity

Inattention

Time
ADHD as a Brain Disorder
Attention-deficit/hyperactivity disorder

Stephen V. Faraone¹,², Philip Asherson³, Tobias Banaschewski⁴, Joseph Biederman⁵, Jan K. Buitelaar⁶, Josep Antoni Ramos-Quiroga⁷—⁹, Luis Augusto Rohde¹⁰,¹¹, Edmund J. S. Sonuga-Barke¹²,¹³, Rosemary Tannock¹⁴,¹⁵ and Barbara Franke¹⁶

Abstract | Attention-deficit/hyperactivity disorder (ADHD) is a persistent neurodevelopmental disorder that affects 5% of children and adolescents and 2.5% of adults worldwide. Throughout an individual’s lifetime, ADHD can increase the risk of other psychiatric disorders, educational and occupational failure, accidents, criminality, social disability and addictions. No single risk factor is necessary or sufficient to cause ADHD. In most cases ADHD arises from several genetic and environmental risk factors that each have a small individual effect and act together to increase susceptibility. The multifactorial causation of ADHD is consistent with the heterogeneity of the disorder, which is shown by its extensive psychiatric co-morbidity, its multiple domains of neurocognitive impairment and the wide range of structural and functional brain anomalies associated with it. The diagnosis of ADHD is reliable and valid when evaluated with standard criteria for psychiatric disorders. Rating scales and clinical interviews facilitate diagnosis and aid screening. The expression of symptoms varies as a function of patient developmental stage and social and academic contexts. Although there are no curative treatments for ADHD, evidenced-based treatments can markedly reduce its symptoms and associated impairments. For example, medications are efficacious and normally well tolerated, and various non-pharmacological approaches are also valuable. Ongoing clinical and neurobiological research holds the promise of advancing diagnostic and therapeutic approaches to ADHD.

For an illustrated summary of this Primer, visit: http://go.nature.com/l6jiwl
The DLPC is linked to WM, the VMPFC to complex decision making and strategic planning, and the parietal cortex to attention.

The executive control and cortico-cerebellar networks coordinate EFs.

The VMPFC, OFC & ventral striatum are the brain network associated with anticipation and reward.

The frontal and parietal cortices and the thalamus support attentional functioning.

Negative correlations between the DMN and the frontoparietal control network are weaker in patients with ADHD.
Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: a cross-sectional mega-analysis


**Interpretation** With the largest dataset to date, we add new knowledge about bilateral amygdala, accumbens, and hippocampus reductions in ADHD. We extend the brain maturation delay theory for ADHD to include subcortical structures and refute medication effects on brain volume suggested by earlier meta-analyses. Lifespan analyses suggest that, in the absence of well powered longitudinal studies, the ENIGMA cross-sectional sample across six decades of ages provides a means to generate hypotheses about lifespan trajectories in brain phenotypes.

Effect of Psychostimulants on Brain Structure and Function in ADHD: A Qualitative Literature Review of Magnetic Resonance Imaging–Based Neuroimaging Studies

Thomas J. Spencer, MD; Ariel Brown, PhD; Larry J. Seidman, PhD; Eve M. Valera, PhD; Nikos Makris, MD; Alexandra Lomedico, BA; Stephen V. Faraone, PhD; and Joseph Biederman, MD
ADHD Imaging Studies Summary

- Neuroimaging studies confirm that brain abnormalities in fronto-subcortical networks are associated with ADHD
- Neuroimaging techniques are not valid tools for ADHD diagnosis; imaging measures are not sensitive or specific enough to be used for diagnostic purposes
- Treatment attenuates neural deficits

Spencer et al. *J Clin Psychiatry* 2013 Sep;74(9):902-17
ADHD as Neurobiological Disorder

Catecholamine Dysregulation
Frontosubcortical Networks and Catecholamines

- Dopaminergic and noradrenergic dysregulation abnormalities in frontosubcortical pathways
- Medications that are effective in ADHD are either dopaminergic or noradrenergic

Human Brain
Brain Stem

- Substantia nigra tegmentum (dopamine) to diencephalon and cerebrum
- Locus ceruleus (norepinephrine) to cerebellum
- Raphe nuclei (serotonin) to cord

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ATTENTION DEFICIT: IS IT IN THE GENES?
ADHD: Genetics

Twin Studies

Family Studies

Genetic Basis of ADHD

Adoption Studies

Molecular Genetics
Family Studies

ADHD in first-degree family members of children with ADHD

- Morrison & Stewart (1971)
- Cantwell (1972)
- Biederman et al. (1990)
Mean Heritability of ADHD in Youth = .75
Genetics of ADHD

22q11.2 deletion syndrome
  Jacobsen syndrome (deletions of the end of 11q)
  Turner syndrome (X0)
  Klinefelter syndrome (XXY)

16p13.11
  15q11–15q11.2 region containing
  nicotinic a7 acetylcholine
  receptor subunit gene
  Rare point mutations expected
  from sequencing studies

Monoamine systems
  genes
  Neurite outgrowth
  genes

Figure 3 | Genetics of attention-deficit/hyperactivity disorder. Common variants explain approximately 40% of the heritability of attention-deficit/hyperactivity disorder but, compared with rarer causes, individual common variants have much smaller effects on the expression of the disorder.

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The Dopamine Story...

Presynaptic Neuron

Dopamine Transporter (DAT)

Dopamine

Methylphenidate (MPH)

Dopamine Receptor (DRD4)
New Results from Genomewide Association Studies (GWAS)

Number of ADHD GWAS Samples

- Y2012
- Y2014
- Q4_2015
- Q1_2019

Faraone et al, 2015
Preliminary ADHD meta-analysis
18,284 cases 33,836 controls

Preliminary analyses suggest eight genome-wide significant loci

PGC ADHD/iPSYCH-SSI-Broad Collaboration
Maternal Smoking During Pregnancy: Results in Children


- **History of Maternal Smoking (%):**
  - **22%** (N=140) with ADHD
  - **8%** (N=120) Controls

- *P*=0.04, controlling for SES, parental ADHD, and parental IQ

- *P*=0.002
ADHD Diagnostic Considerations

Inattention

Comorbidity

Impulsivity/Hyperactivity
Cumulative Morbidity Risks for Psychiatric Disorders in ADHD and Control Probands


*Psychopharmacology Course 2017*
Accidents and Near Misses

*Indicates $P<0.05$ after controlling for gender, age, time of day and the age*ADHD interaction

(Reimer et al., submitted)
During the five surprise events, drivers in the medication group were 67% less likely to have a collision than drivers in the placebo group.

**LDX = lisdexamfetamine dimesylate**

Biederman et al. 2011 submitted
Association Between Medication Use for Attention-Deficit/ Hyperactivity Disorder and Risk of Motor Vehicle Crashes

DESIGN, SETTING, AND PARTICIPANTS For this study, a US national cohort of patients with ADHD (n = 2,319,450) was identified from commercial health insurance claims between January 1, 2005, and December 31, 2014, and followed up for emergency department visits for MVCs. The study used within-individual analyses to compare the risk of MVCs during

CONCLUSIONS AND RELEVANCE Among patients with ADHD, rates of MVCs were lower during periods when they received ADHD medication. Considering the high prevalence of ADHD and its association with MVCs, these findings warrant attention to this prevalent and preventable cause of mortality and morbidity.

ADHD (n = 2,319,450) was identified from commercial health insurance claims between January 1, 2005, and December 31, 2014, and followed up for emergency department visits for MVCs. The study used within-individual analyses to compare the risk of MVCs during months in which patients received ADHD medication with the risk of MVCs during months in which they did not receive ADHD medication.

EXPOSURES Dispensed prescription of ADHD medications.

MAIN OUTCOMES AND MEASURES Emergency department visits for MVCs.
ADHD: Impact on Family

Parents of children with ADHD experience higher levels of

- Stress
- Self-blame
- Social isolation
- Depression
- Marital discord

Status of 144 Caregivers at any time after Diagnosis of Child’s ADHD

- Changed Work Status: 39%
- Unchanged Work Status: 63%

Noe et al. 1999
Impairment in ADHD

- Parent stress
- Family conflict
- Accidents and injuries
- Smoking and substance abuse
- Legal difficulties
- Poor peer relationships
- School failure
- Psychiatric comorbidity
- Accidents and injuries
- Family conflict
- Parent stress
Is ADHD a **Serious** Public Health Concern?

- Prevalence
- Impairment
- Treatment Effectiveness
- Chronicity
Summary

• ADHD is a neurobehavioral disorder with a:
  – Complex etiology
  – Neurobiologic basis
  – Strong genetic component

• ADHD
  – Affects millions of people of both genders
  – Persists through adolescence and adulthood in a high percentage of cases
  – Can have negative impact on multiple areas of functioning
  – ADHD is a highly treatable disorder
QUESTIONS ?