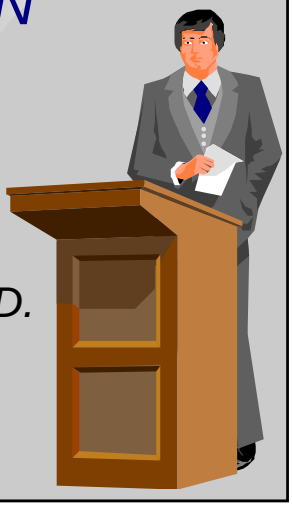
ADD: NEW DEVELOPMENTS AND ITS ROLE IN DYSLEXIA



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HISTORY AND NOMENCLATURE

- *1902: "Fidgety Phil" (Lancet)*
- *1902 (Still): Inattention and overactivity as a defect in moral control*
- *1904 (Myer): Traumatic Insanity (Inattention & impulsivity following brain trauma)*
- *1920: Inattention, restlessness, overactivity, impulsivity, learning disabilities in post-encephalitic children and adolescents (encephalitis lethargica)*
- *1930's:Minimal Brain Damage/Dysfunction*

HISTORY AND NOMENCLATURE

- *1968 (DSM II): Hyperkinetic Reaction of Childhood (**H**yperactivity, **I**mpulsivity, **D**istractibility, **E**xcitability)*
- *1980 (DSM III): Attention Deficit Disorder (ADD)*
  - *with Hyperactivity (ADDH)*
  - *without Hyperactivity (ADDnoH)*
  - *Residual Type*
- *1987 (DSM III-R): Attention Deficit Hyperactivity Disorder (ADHD)*

  (grouped under Disruptive Behavior Disorders)

HISTORY AND NOMENCLATURE

- *1994 (DSM IV): Attention Deficit Hyperactivity Disorder (grouped under Attention-Deficit and Disruptive Behavior Disorders)*
  - *Combined Type (50-75%)*
  - *Predominantly Inattentive Type (20-30%)*
  - *Predominantly Hyperactive-Impulsive Type (<15%)*

– *Prevalence in school age children: 3-5%*

HISTORY AND NOMENCLATURE

- *DSM IV-TR: Three major criteria*
  - *Inattention or hyperactivity (6/9 symptoms)*
  - *Impairment in two functional settings (e.g. work, school, home)*
  - *Symptoms date back to early childhood*

RECENT EMPHASES

- *1. Continuation into adolescence and adulthood*
- *2. Subtypes; role of gender influences*
- *3. Neurobiology*
- *4. Differential diagnosis*
- *5. Comorbidity*
  - *other psychiatric/behavioral disorders*
  - *learning disabilities*
- *6. Neuropsychological dysfunction*
- *7. Treatment*

ADOLESCENCE AND ADULTHOOD

MYTH: *ADHD will be outgrown and medication can be discontinued at puberty.*

FACT: *30-70% of children with ADHD become adults with ADHD*

ADHD IN ADOLESCENCE

- *impaired school performance*
- *increased risk of delinquency*
- *impaired social relationships*
- *impaired family interactions*
- *substance abuse, Conduct Disorder, Oppositional-Defiant Disorder*

ADHD IN ADULTHOOD

- *High levels of dysfunction despite syndromatic remission (school & job failures, unstable personal lives, lower socioeconomic status, traffic accidents and violations)*
- *More even gender distribution*
- *Increased lifetime incidence of multiple neuropsychiatric disorders, but comorbidity does not contribute significantly to disability*
- *Attentional problems evolve into executive function deficits (multi-tasking, time mgmt)*

ADHD IN ADULTHOOD

Attenuation of symptoms with age:

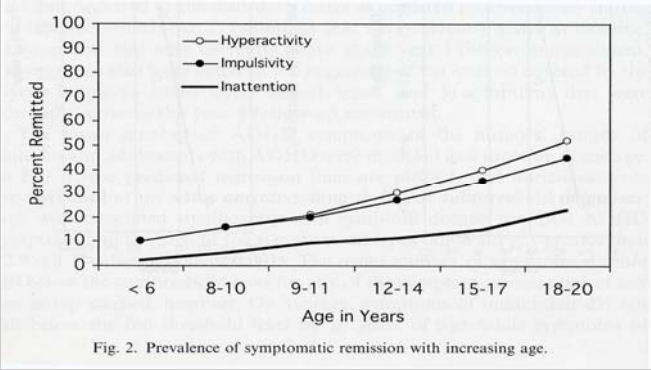


Fig. 2. Prevalence of symptomatic remission with increasing age.

ADHD IN ADULTHOOD

- *Comorbid neuropsychiatric disorders*
  - *Antisocial Personality Disorder*
  - *Major Depression, Dysthymia*
  - *Bipolar Disorder - originates in childhood*
  - *>2 Anxiety disorders*
  - *Tic disorders*
  - *Alcohol dependence (women)*
  - *Drug dependence (men)*
  - *Learning disability (dyslexia, auditory processing)*

ADHD IN ADULTHOOD

- *Substance Abuse*
  - *Increased risk in ADHD typically not expressed until adulthood*
  - *Medication for ADHD during childhood significantly decreases risk in adolescents (Biederman et.al., 1999)*
    - *Unmedicated: 75%*
    - *Medicated: 25%*
    - *Controls: 18%*

SUBTYPES

- ***1. Residual Type***
  - *Diagnosis (Wender)*
    - *i. Childhood history of ADD*
    - *ii. Presence of ADD in adulthood characterized by :*
      - *persistent motor activity*
      - *attention deficits*
      - *affective lability*
      - *inability to complete tasks*
      - *hot temper, short-lived explosive outbursts*
      - *impulsivity*
      - *stress intolerance*

SUBTYPES

Gender Influence

(Overall male:female = 4-9:1)

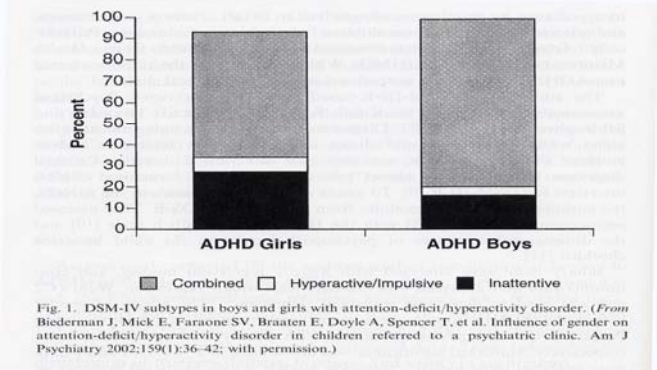


Fig. 1. DSM-IV subtypes in boys and girls with attention-deficit/hyperactivity disorder. (*From* Biederman J, Mick E, Faraone SV, Braaten E, Doyle A, Spencer T, et al. Influence of gender on attention-deficit/hyperactivity disorder in children referred to a psychiatric clinic. Am J Psychiatry 2002;159(1):36–42; with permission.)

SUBTYPES

- ***2. ADD without Hyperactivity (ADDnoH)***
  - *1/7 children with ADD, relatively more girls*
  - *academic under achievement, especially math*
  - *high incidence (60%) of developmental reading or arithmetic disorder*
  - *apathy, psychomotor slowness, inconsistent STM, decreased rapid naming*
  - *increased anxiety and shyness (internalizing)*
  - *less impulsivity and motor activity (externalizing)*
  - *absence of Conduct Disorder diagnosis*

NEUROBIOLOGY

- ***1. Genetics***
  - *Substantial genetic component established in twin studies. Heritability comparison:*
    - *ADHD: 0.8*
    - *Height: 0.95*
    - *Schizophrenia: 0.75*
  - *Several genes may be involved*
  - *Recent focus on dopamine transporter gene (DAT)and D4 dopamine receptor gene (DRD4)*
    - *abnormal expression in ADHD adults*
    - *action directly affected by stimulants*

NEUROBIOLOGY

- *Environmental agents implicated in expression of genetic vulnerability including:*
  - *Psychosocial stressors*
  - *Toxic insults*
  - *Brain damage*
- *Familial ADHD more likely to persist into adolescence and adulthood*
  - *57% prevalence of ADHD in children of adults with ADHD*

NEUROBIOLOGY

- ***2. Neuroanatomy***
  - *Basic principle: a network of brain areas contributes to attentional/executive processes and behavioral self-regulation*
  - *Key areas include*
    - ***Dorsolateral prefrontal cortex** (planning, attentional focus, working memory)*
    - ***Basal ganglia** (executive functions, dopaminergic)*
    - ***Cingulate cortex** (motivation, response selection and inhibition)*
    - ***Lateral prefrontal and parietal cortices** (sustained and directed attention)*
    - ***Brain stem reticular activating system** (attentional tone and filtering of interference)*

NEUROBIOLOGY

- *MRI findings (juvenile subjects): smaller prefrontal cortex and caudate; abnormalities in globus pallidus and corpus callosum, reduced cerebellar volume*
- *Functional scans (adult subjects): decreased activity in striatum, prefrontal cortex and dorsal anterior cingulate cortex (medial frontal lobe)*
- *Neuroimaging not yet diagnostic*

NEUROBIOLOGY

- ***3. Neurochemistry***
  - *no single neurotransmitter hypothesis suffices*
  - *theories based on noradrenergic or dopaminergic defects still being advanced but clinical data inconsistent*
- ***4. Early toxic exposure, e.g. Fetal Alcohol Syndrome***

DIFFERENTIAL DIAGNOSIS

- *1. Depression (Inattentive subtype)*
- *2. Mania (Combined subtype)*
- *3. Primary disorder of vigilance*
- *4. Narcolepsy*
- *5. Learning disorders*
- *6. Conduct Disorder, Oppositional Defiant Disorder (Hyperactive subtype)*
- *7. Acquired focal neurological deficits causing neglect and/or inattention*

COMORBID DISORDERS

- *1. Conduct Disorder (30-50%)*
- *2. Oppositional Defiant Disorder (35%)*
- *3. Mood Disorders & Anxiety Disorders (15-75%)*
- *4. Learning Disorders (50-80%)*
- *5. Tourette's Syndrome (60% with ADD)*
- *6. Mental Retardation (3-4 X normal IQ)*
- *7. Borderline Personality (25% with ADD)*
- *8. Anxiety Disorders (25%)*

The nature of the comorbidity may delineate subgroups differing in risk factors, clinical course and pharmacological response.

NEUROPSYCHOLGICAL DYSFUNCTION

- *Deficits in attention, executive functions (decision making, self-monitoring, impulse control, response inhibition, planning, working memory)*
- *In children, strongly influenced by comorbid learning disabilities, especially reading and arithmetic (approx 30% of ADHD children)*
- *Implicates prefrontal cortex and connections, primarily to striatum (caudate, globus pallidus)*

NEUROPSYCHOLGICAL DYSFUNCTION

- *Not diagnostic of ADHD; i.e. approx 50% do not have dysfunction*
- *Not explained by comorbid psychiatric disorders*
- *Findings are similar in boys and girls*
- *Adults: milder but similar cognitive domains*

NEUROPSYCHOLGICAL DYSFUNCTION

- *Test instruments that consistently differentiate adult ADHD from controls:*
  - *Continuous Performance Test (but not TOVA)*
  - *Stroop Color-Word Interference Test*
  - *Trail Making*
  - *Controlled Word Association Test (FAS)*
  - *WAIS-R, WAIS III*

TREATMENT-MEDICATION

- *Stimulants are efficacious in 70% of children and adolescents; probably similar for adults at equipotent daily doses*
- *Improvement reflected in behavior, self-esteem, cognition and social/family functioning*
- *Studies largely focus on latency age, Caucasian boys and have rarely assessed comorbid psychiatric disorders such as anxiety and depression*

TREATMENT-MEDICATION

- *First line treatment choices*
  - *1. Methylphenidate*
  - *2. Dextroamphetamine*

The Official TCR ADHD Medication Comparison Chart

Medication	Dose	Available Doses	Duration of Action	Can be Split?	Generic Available?	Year FDA-Approved	Company	Notes
Methylphenidates								
Short-acting								
Ritalin	5-30 mg BID	10, 20	3-4 h	yes	yes	1956	Novartis	
Focalin	2.5-10 mg BID	2.5, 5, 10	3-4 h	yes	no	2001	Novartis	D-enantiomer of Ritalin
Methylin	5-30 mg BID	5,10,20	3-4 h	yes	"branded generic" of Ritalin	?	Mallinckrodt	
Methylin CT	5-30 mg BID	2.5, 5, 10	3-4 h	yes	no	2004	Mallinckrodt	Chewable
Methylin Oral Solution	5-30 mg BID	5 mg/5ml, 10mg/5ml	3-4 h	NA	no	2004	Mallinckrodt	Clear, grape-flavored liquid
Intermediate-acting								
Ritalin SR	20-60 mg q AM	20	4-8 h	no	yes	1960s	Novartis	Continuous release (less predictable because of wax matrix)
Metadate ER	20-60 mg q AM	10, 20	4-8 h	no	"branded generic" of Ritalin SR	1999	UCB	Continuous release (less predictable because of wax matrix)
Methylin ER	20-60 mg q AM	10, 20	4-8 h	no	"branded generic" of Ritalin SR	2000	Mallinckrodt	Hydrophilic polymer, so possibly more continuous than others in category
Long-acting								
Concerta	18-56 mg q AM	18, 27, 36, 54	12 h	no	no	2000	Alza	Initial bolus, then continuous
Metadate CD	20-60 mg q AM	10, 20, 30	8 h	can be sprinkled	no	2001	UCB	Mimics BID dosing; beads
Ritalin LA	20-60 mg q AM	20, 30, 40	8-12 h	can be sprinkled	no	2002	Novartis	Mimics BID dosing; beads
Amphetamines								
Short-acting								
Dexedrine	5-20 mg BID	5	3-5 h	yes	yes	1958	GSK	dextroamphetamine
Dextrostat	5-20 mg BID	5, 10	3-5 h	yes	"branded generic" of Dexedrine	1960s	Shire	dextroamphetamine
Desoxyn	5-10 mg BID	5	3-5 h	yes	yes	1943	Abbott	methamphetamine
Intermediate-acting								
Adderall	5-30 mg BID or 5-60 mg q AM	5, 10, 20, 30	4-8 h	yes, can be crushed	yes	1996	Shire	Mixed salt of l- and d-amphetamine
Long-acting								
Dexedrine Spansules	20 mg q AM	5, 10, 15	8-12 h	no	yes	1960s	GSK	Initial bolus, then continuous; beads
Adderall XR	5-30 mg q AM	5, 10, 15, 20, 25, 30	8-12 h	no	no	2001	Shire	Mixed salt of l- and d-amphetamine; beads; mimics BID dosing
Non-stimulant								
Strattera	0.5 mg/kg-1.2 mg/kg	5, 10, 18, 25, 40, 60	24 h	no	no	2003	Lilly	atomoxetine

TREATMENT-MEDICATION

- 3. Pemoline (CYLERT) (long acting but less effective)
- 4. Antidepressants
  - tricyclics (desipramine)
  - SSRI's (PROZAC , ZOLOFT, PAXIL, CELEXA, LEXAPRO)
  - bupropion (WELLBUTRIN, SR, XL)

TREATMENT-MEDICATION

- 5. Atomoxetine (STRATTERA)
  - selective norepinephrine reuptake inhibitor (SNRI)
  - first nonstimulant to be approved by FDA for ADHD
  - superior to placebo, comparable to MPH in limited studies to date
  - potential interactions with SSRI's
  - adverse effects
    - Children: GI, somnolence, increased BP and pulse
    - Adults: GI, dry mouth, insomnia, sexual dysfunction

TREATMENT-MEDICATION

- *Recent controversies*
  - *SSRI antidepressants (and all others by association): black box warning re suicidal ideation in children and adolescents*
  - *Adderall XR: sudden death*
    - *Sales suspended by Health Canada, but not by FDA*
    - *Interpretation of data subject to multiple poorly assessed factors*

TREATMENT - OTHER

- *The MTA Cooperative Group (Multimodal Treatment Study of Children with ADHD)*
  - *Co-sponsored by NIMH and Department of Education in 1992-3 and published in 1999 (Arch. Gen. Psychiatry)*
  - *Intended to address public concerns about use of stimulants in children*
  - *14 month study with 579 children aged 7-9.9 years*
  - *4 treatment groups*
    - *1. Medication alone (dose titration, monthly visits)*
    - *2. Intensive behavioral treatment (child, parent, school)*
    - *3. Combined*
    - *4. Standard community care*

TREATMENT - OTHER

- *Results*
  - *All groups had significant improvement*
  - *Groups 1 and 3 had significantly greater improvement than 2 and 4*
  - *Groups 1 and 3 did not differ with respect to core ADHD symptoms*
  - *But only Group 3 was superior to 2 and 4 in such measures as oppositional and aggressive symptoms, internalizing symptoms, social skills, parent-child relations, reading achievement*

ADHD AND DYSLEXIA

- *1. Definition of Learning Disability (LD)*
  - *"...a disorder in one or more of the basic psychological processes involved in understanding or in using language, spoken or written, which disorder may manifest itself in an imperfect ability to listen, think, speak, read, write, spell, or to do mathematical calculations. (Education for all Handicapped Children Act of 1975)*
  - *..a heterogeneous group of disorders manifested by significant difficulties in the acquisition and use of listening, speaking, reading, writing, reasoning, or mathematical abilities. These disorders are intrinsic to the individual and presumed to be due to central nervous system dysfunction. National Joint Committee on Learning Disabilities, 1987)*

ADHD AND DYSLEXIA

- *2. 50-80% of children with ADHD have LD*
  - *reading disorders (RD) most common: 25-40% of children with ADHD (RD) have RD (ADHD)*
- *3. Specific cognitive deficits (Willcutt, et. al., 2000-2001)*
  - *RD: phonological processing, verbal working memory*
  - *ADHD: executive function deficits*
  - *RD+ADHD: all of the above, generally greater severity*

ADHD AND DYSLEXIA

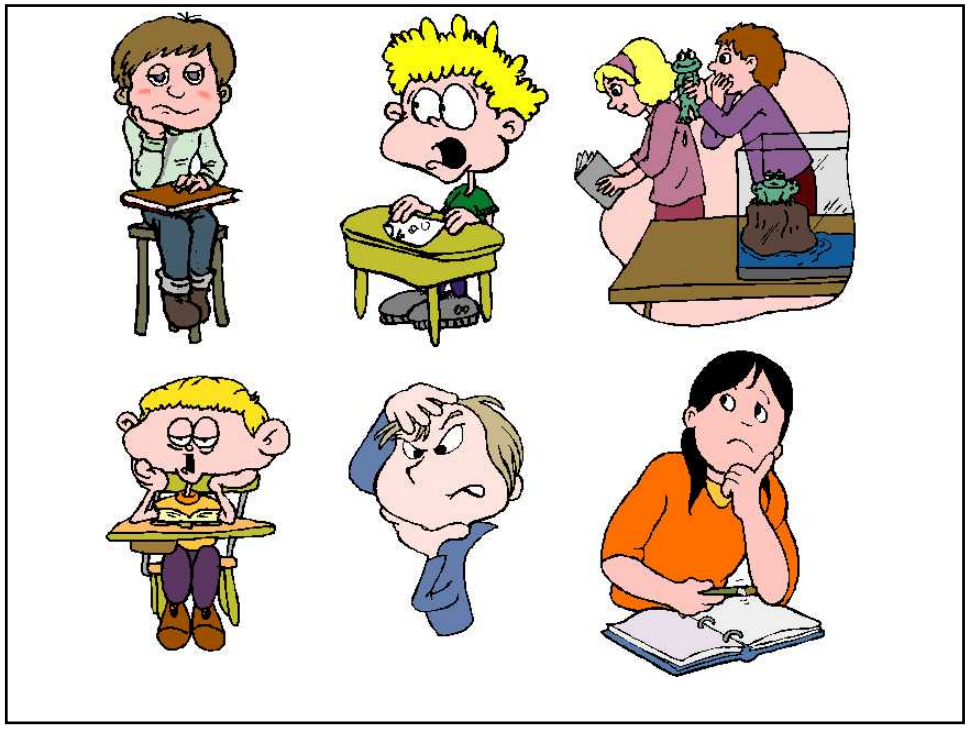
- *4. Recent genetic studies (Willcutt et.al., 2002)*
  - *Both ADHD and RD are highly heritable*
  - *Bivariate linkage for ADHD with 3 measures of reading difficulty*
  - *Comorbidity may be due in part to pleiotropic effects of a trait locus on chromosome 6p*
  - *RD correlates most strongly with inattentive subtype of ADHD*

ADHD AND DYSLEXIA

- *5. Psychiatric Comorbidity*
  - *RD associated with increased emotional and behavioral disorders*
    - *Male: externalizing disorders (ODD, CD, aggressivity)*
    - *Female: internalizing disorders (depression, anxiety, social withdrawal)*
  - *However, externalizing disorders are mediated by comorbid ADHD*

ADHD AND DYSLEXIA

- *6. Basic Conclusions*
  - *Hyperactivity in ADHD is not a reaction to educational failure*
  - *ADHD does not cause reading disorders*
  - *Comorbidity is not due to neurological insults, socioeconomic disadvantages or early language difficulties*
  - *Common genetic factors probably underlie ADHD and RD, exerting independent influences on each*



MEDICATION

BEHAVIOR THERAPY

READING REMEDIATION