

a LANGE medical book

CURRENT

Diagnosis & Treatment

Psychiatry

second edition

Edited by

Michael H. Ebert, MD

*Associate Dean for Veterans Affairs and Professor of Psychiatry, Yale University School of Medicine
Chief of Staff, VA Connecticut Healthcare System
West Haven, Connecticut*

Barry Nurcombe, MD

*Professor of Child and Adolescent Psychiatry,
Departments of Pediatric Medicine and Psychiatry and
Neuroscience*

University of Western Australia, Perth, Western Australia

Professor Emeritus of Psychiatry

University of Queensland, Herston, Queensland, Australia

Vanderbilt University School of Medicine

Nashville, Tennessee

Peter T. Loosen, MD, FRCPS

*Professor Emeritus of Psychiatry
Department of Psychiatry
Vanderbilt University School of Medicine
Nashville, Tennessee*

James F. Leckman, MD

*Neison Harris Professor of Child Psychiatry, Pediatrics,
and Psychology*

Director of Research

Yale Child Study Center

Yale University School of Medicine

New Haven, Connecticut

BRITISH LIBRARY
DOCUMENT SUPPLY CENTRE

09 MAY 2008

m08/.

20564

**Mc
Graw
Hill** Medical

New York Chicago San Francisco Lisbon London Madrid
Mexico City Milan New Delhi San Juan Seoul Singapore Sydney Toronto

SHIRE EX. 2046
KVK v. SHIRE
IPR 2018-00200

**DOCKET
ALARM**

Find authenticated court documents without watermarks at docketalarm.com.

Current Diagnosis & Treatment: Psychiatry, Second Edition

Copyright © 2008 by The McGraw-Hill Companies, Inc. All rights reserved. Printed in the United States of America. Except as permitted under the United States Copyright Act of 1976, no part of this publication may be reproduced or distributed in any form or by any means, or stored in a data base or retrieval system, without the prior written permission of the publisher.

1 2 3 4 5 6 7 8 9 Doc/Doc 0 9 8

ISBN 978-0-07-142292-5

MHID 0-07-142292-7

ISSN 1528-1124

Notice

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The authors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

This book was set in Times Roman by Aptara, Inc.

The editors were Anne M. Sydor and Kim J. Davis.

The production supervisor was Thomas Kowalczyk.

Project management was provided by Vageesh Sharma, Aptara.

The cover designer was Mary McKeon.

The art director was Margaret Webster-Shapiro.

Cover inset photos, clockwise from upper left, provided by Medipics/Alamy; Gabe Palmer/Alamy; PHOTOTAKE Inc./Alamy.

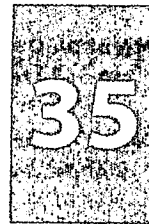
R R Donnelley & Sons, Inc. was the printer and binder.

This book is printed on acid-free paper.

International Edition ISBN 0-07-121271-X

Copyright © 2008. Exclusive rights by The McGraw-Hill Companies, Inc., for manufacture and export. This book cannot be re-exported from the country to which it is consigned by McGraw-Hill. The International Edition is not available in North America.

Attention-Deficit Hyperactivity Disorder



Thomas Spencer, MD



ESSENTIALS OF DIAGNOSIS

DSM-IV-TR Diagnostic Criteria

Attention-Deficit/Hyperactivity Disorder

A. Either (1) or (2):

(1) *Sx (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:*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 tasks 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 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

(2) Six (or more) of the following symptoms of **hyperactivity-impulsivity** have persisted for at least 6 months to a degree that is mal-

adaptive and inconsistent with developmental level: Hyperactivity

- (j) Often fidgets with hands or feet or squirms in seat
- (k) Often leaves seat in classroom or in other situations in which remaining seated is expected
- (l) Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
- (m) Often has difficulty playing or engaging in leisure activities quietly
- (n) Is often "on the go" or often acts as if "driven by a motor"
- (o) Often talks excessively

Impulsivity

- (g) Often blurts out answers before questions have been completed
- (h) Often has difficulty awaiting turn
- (i) Often interrupts or intrudes on others (e.g., butts into conversations or games)

- 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 (e.g., 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 other Psychotic Disorder and are not better accounted for by another mental disorder (e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).

Code based on type:

Attention-Deficit/Hyperactivity Disorder, Combined Type: if both Criteria A1 and A2 are met for the past 6 months

Attention-Deficit/Hyperactivity Disorder, Predominantly Inattentive Type: if Criterion A1 is met but Criterion A2 is not met for the past 6 months

Attention-Deficit/Hyperactivity Disorder, Predominantly Hyperactive-Impulsive Type: if Criterion A2 is met but Criterion A1 is not met for the past 6 months

General Considerations

A. EPIDEMIOLOGY

Attention-deficit hyperactivity disorder (ADHD) is the most common emotional, cognitive, and behavioral disorder treated in youth. It is a major clinical and public health problem because of its associated morbidity and disability in children, adolescents, and adults. Data from cross-sectional, retrospective, and follow-up studies indicate that youth with ADHD are at risk for developing other psychiatric difficulties in childhood, adolescence, and adulthood including delinquency as well as mood, anxiety, and substance-use disorders.

Early definitions, such as the Hyperkinetic Reaction of Childhood in DSM-II, placed the greatest emphasis on motoric hyperactivity and overt impulsivity as hallmarks of the disorder. The DSM-III represented a paradigm shift as it began to emphasize inattention as a significant component of the disorder. DSM-IV now defines three subtypes of ADHD: predominantly inattentive, predominantly hyperactive-impulsive, and a combined subtype. Criteria for each DSM-IV subtype require six or greater of nine symptoms in each respective category. There are four additional criteria that include age of onset by 7 years, ADHD-specific adaptive impairments, pervasiveness, and separation from other existing conditions. The combined subtype is the most commonly represented subgroup accounting for from 50% to 75% of all ADHD individuals, followed by the inattentive subtype (20–30%), and the hyperactive-impulsive subtype (less than 15%).

Epidemiologic studies indicate that ADHD is a prevalent disorder affecting from 4% to 7% of children worldwide including the United States, New Zealand/Australia, Germany, and Brazil. Although previously thought to remit largely in adolescence, a growing literature supports the persistence of the disorder and/or associated impairment into adulthood in a majority of cases.

Prevalence estimates of childhood ADHD in the United States are estimated to be 5–8%. Estimates

vary predictably depending on methodology. Definitions that require both symptom dimensions (hyperactivity/impulsivity and inattention) are more restrictive than those that require only one of these dimensions. Thus, estimates based on pre-DSM III definitions or the ICD codes of hyperkinetic disorder produce lower estimates. In addition the surveys that estimate based on symptoms alone and do not include impairment yield higher estimates. As recently by Faraone et al. (2003), other factors that affect apparent prevalence estimates include pervasiveness criteria, informants (teacher, parent, child), use of rating scales versus clinical interviews as well as ascertainment issues. Community samples have higher rates than school samples.

Gender and age of the sample also affect estimates prevalence. Girls more commonly have the inattentive type and also less commonly have accompanying ODD/CD, disruptive disorders, factors leading to lower rates of diagnosis. The original descriptions were derived from a child-focused perspective, and do not reflect what are thought to be more salient aspects of adult ADHD: the executive function disorders of poor organization, poor time management, and memory disturbance associated with academic and occupational failure. The lack of appropriate description of adult symptoms may reduce the true prevalence of ADHD in adulthood.

B. ETIOLOGY

Biological adversity—Several biologic factors have been proposed as contributors to ADHD, including food additives/diet, lead contamination, cigarette and alcohol exposure, maternal smoking during pregnancy, and low-birth weight. Although the Feingold diet for ADHD was popularized by the media and accepted by many parents, systematic studies showed that this diet was ineffective and that food additives do not cause this disorder. Several investigators have shown that lead contamination can cause symptoms of ADHD. However, lead does not account for the majority of ADHD cases, and many children with high-lead exposure do not develop ADHD. An emerging literature documents that maternal smoking and alcohol exposure during pregnancy, low-birth weight, and psychosocial adversity are additional independent risk factors for ADHD.

Pregnancy and delivery complications (i.e., toxemia, eclampsia, poor maternal health, maternal age, fetal postmaturity, duration of labor, fetal distress, low-birth weight, antepartum hemorrhage) appear to have a predisposition for ADHD. Several studies documented that maternal smoking during pregnancy is an independent risk factor for ADHD.

Psychosocial adversity—Findings of recent studies stress the importance of adverse family-environment variables as risk factors for ADHD. In particular, chronic

family conflict, decreased family cohesion, and exposure to parental psychopathology (particularly maternal) are more common in ADHD families compared with control families. It is important to note that, although many studies provide powerful evidence for the importance of psychosocial adversity in ADHD, such factors tend to emerge as universal predictors of children's adaptive functioning and emotional health, rather than specific predictors of ADHD. As such, they can be conceptualized as nonspecific triggers of an underlying predisposition or as modifiers of the course of illness.

C. GENETICS

Because ADHD is believed to be highly genetic, studies of twins have been used to establish its heritability or the degree to which this disorder is influenced by genetic factors. Based on numerous studies of twins, which varied considerably in methodology and definitions of ADHD, the mean heritability for ADHD was shown to be 77%. Seven candidate genes show statistically significant evidence of association with ADHD on the basis of the pooled odds ratio (1.18–1.46) across studies: DRD4, DRD5, DAT, DBH, 5-HTT, HTR1B, and SNAP-25.

Clinical Findings

A. SIGNS & SYMPTOMS

The diagnosis of ADHD is made by careful clinical history. A child with ADHD is characterized by a considerable degree of inattentiveness, distractibility, impulsivity, and often hyperactivity that is inappropriate for the developmental stage of the child. Other common symptoms include low-frustration tolerance, shifting activities frequently, difficulty organizing, and daydreaming. These symptoms are usually pervasive; however, they may not all occur in all settings. Adults must have childhood-onset, persistent, and current symptoms of ADHD to be diagnosed with the disorder. Adults with ADHD often present with marked inattention, distractibility, organization difficulties and poor efficiency, which culminate in life histories of academic and occupational failure.

B. RATING SCALES

Rating scales are extremely helpful in documenting the individual profile of ADHD symptoms as well as assessing the response to treatments. It is important to emphasize that they should not be used for diagnosis without careful clinical confirmation and elicitation of the other criteria necessary for diagnosis. Although neuropsychological testing is not relied upon to diagnose ADHD it may serve to identify particular weaknesses within ADHD or specific learning disabilities co-occurring with ADHD.

Rating scales are available for all age groups and can be useful in assessing and monitoring home, academic and occupational performance. Increasingly, there has been a congruence of opinion in this area with a number of the most widely used scales consisting of Likert ratings of the existing DSM-IV criteria. There are two types of scales in wide use, the so-called "narrow" scales that are specific for ADHD and "broad" scales that measure additional dimensions including comorbidity. The broad scales are useful for separating straightforward and complex cases, and the narrow scales are most useful for honing in on exclusively ADHD dimensions both diagnosis and to monitor specific responses to treatment. In looking to the future, there are proposals to expand the set of diagnostic symptoms to include executive functions (such as time management and multitasking) especially in older individuals.

C. PSYCHOLOGICAL TESTING

Psychological testing is not necessary for the routine diagnosis of ADHD and does not readily distinguish children with and without ADHD. Nonetheless, psychometric testing can be valuable in narrowing the differential diagnosis and identifying comorbid learning difficulties. Many children with ADHD have difficulties with abstract reasoning, mental flexibility, planning, and working memory, a collection of skills broadly categorized as executive functioning skills. They can also present with verbal and nonverbal performance skills and/or visual-spatial processing deficits. In such circumstances, neuropsychological assessments can be valuable and may help to clarify the diagnosis. Children with learning, language, visual-motor, or auditory processing problems usually perform poorly only in their particular problem area, whereas children with ADHD may perform poorly in several areas of evaluation.

Laboratory Findings

Nonroutine laboratory studies are not indicated unless the history or physical examination is suggestive of seizures, neurodevelopmental regression, or localizing neurologic signs, or if an acute or chronic medical disorder is suspected.

NEUROIMAGING

The neurobiology of ADHD is not completely understood, although imbalances in dopaminergic and noradrenergic systems have been implicated in the core symptoms that characterize this disorder. Many brain regions are candidates for impaired functioning in ADHD. Prefrontal hypotheses in ADHD have primarily involved the dorsolateral prefrontal cortex, associated with organizational, planning, working memory, and attentional

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.