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ADHD and the Disruptive Behavior Disorders

Elena B. Metcalf, M.D.*

Abstract Although it has now been reclassified as a Neurodevelopmental Disorder, Attention Deficit/Hyperactivity Disorder (ADHD) frequently overlaps with the Disruptive, Impulse Control, and Conduct Disorders such as Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD), forming a heterogeneous group of childhood onset behavioral disorders that have traditionally been lumped together as Disruptive Behavior Disorders (DBD). These frequently comorbid disorders cause significant disturbance and distress within the child's environment, usually school and/or family, as well as causing severe developmental and psychosocial dysfunction for the individual. ADHD is characterized by symptoms of inattention, impulsivity and hyperactivity, ODD by hostility, anger, argumentativeness, defiance, and CD by aggression, deceitfulness, and violation of rights of others. The DBDs play an enormous social role because they represent a high risk for developmental trajectories that harbor psychosocial, economic, psychiatric, and criminal morbidity across the lifespan and have significant socioeconomic and health impact on a national level (1). The DBDs may share comorbidities and some etiologic and pathophysiologic characteristics, however, their clinical manifestations, developmental trajectories, and biologic substrates are distinct.

The explosion of neurobiological literature about the Disruptive Behavior Disorders, most specifically on ADHD, reflects the complex, fluid, and often-contradictory manifestations of brain-behavior relationships. This complexity is enhanced further by the accumulating research demonstrating significant differences in manifestations according to age, cognitive status, gender, comorbidities, psychosocial context, and treatment response. There is an enormous degree of individual variation shaped by the transaction of biological and environmental factors, which again has major implications for prevention and diagnostic and therapeutic interventions. For practical purposes, the current discussion will focus on each condition separately.

Keywords Disruptive behavior disorders · ADHD · Comorbidity · Gender · Preschool · Children · Conduct disorder · Psychopharmacology · Prevention

18.1. Attention Deficit/Hyperactivity Disorder

18.1.1. Description

ADHD is a complex neurodevelopmental syndrome characterized by developmentally inappropriate dysregulation of attention, impulse control, and hyperactivity, which is discrepant to the developmental status and cognitive competence of the individual. Commonly seen associated symptoms are perceptual and motor coordination problems and affective dysregulation. It is the most common neurodevelopmental disorder diagnosed in children, manifesting usually in the preschool years and thought to affect up to 5.4 million children in the US (2). It is a chronic and usually lifelong condition, persists in the majority of cases into adolescence and adulthood, and is estimated to have an adult prevalence of about 4% (3). Hyperactivity and impulsivity and emotional dysregulation are the most obvious and impairing symptoms in early childhood because of their stressful effects on family,

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E.B. Metcalf, M.D. (✉)
Fellow, Department of Psychiatry, Division of Child and Adolescent Psychiatry, University of Minnesota School of Medicine, Minneapolis, MN, USA
e-mail: metca058@umn.edu

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social, and preschool functioning. As the individual matures, hyperactivity usually diminishes, but internal restlessness, impatience, impulsivity, and attentional problems, as well as distractibility and forgetfulness, persist and impede development on all functional levels. There is often a striking discrepancy between cognitive potential and emotional and behavioral immaturity, which leads to peer rejection and poor self-esteem, which are major predictors of negative social outcome. The significance of the syndrome lies in the fact that not only do the ADHD symptoms by themselves block individual self-realization, but, in the majority of cases, they are associated with comorbid disorders. Depending on personality and psychosocial factors, they can lead to lifelong maladaptations and economic, social, and emotional adversity. The economic impact associated with ADHD in adults is calculated to be between $87 and $138 billion/year through reduced productivity and salary loss alone (4).

Because of its high prevalence and because of the evidence that early diagnosis and treatment clearly diminish the adverse impacts of ADHD (5), the American Academy of Child and Adolescent Psychiatry (AACAP) has recommended that all children presenting for mental health and behavioral disorders be screened for ADHD (6). And because the vast majority of children with ADHD are treated by primary care physicians rather than psychiatrists, the American Academy of Pediatrics (AAP) has developed guidelines for diagnosis and treatment of ADHD in the primary care setting (7).

The core features of ADHD are considered to be deficits of "executive function", i.e., dysfunctions of working memory and response inhibition to inappropriate actions, thoughts, and feelings; impaired attention, planning, impulse control, mental flexibility, and activity regulation (8). These deficiencies unfold throughout the lifespan with shifting symptomatology and consequences depending on age, gender, cognitive and comorbid status, and social context. ADHD is characterized by a high rate of comorbidities with other neuropsychological disorders such as language or learning disabilities, as well as with psychiatric disorders, which results not only in more severe and complex lifetime impairment for the individual, but increases the enormous burden of ADHD for society as a whole (3, 9). Besides the obvious effects on educational, vocational, and psychosocial outcomes, ADHD is also associated with increased medical morbidity and costs in accidents, hospitalizations, substance abuse, and teen pregnancy (10). Nationally, $21–$44 billion are spent each year in incremental health care costs for children with ADHD, with an additional $15–$25 billion in excess educational costs (4). Depending on personality and psychosocial factors, only a minority of persons diagnosed with ADHD in childhood show a benign life trajectory. Despite this bleak picture, there are many individuals who have managed to achieve star status despite or perhaps even because of the vagaries associated with this condition. Leonardo DaVinci, Wolfgang Amadeus Mozart, Benjamin Franklin, Thomas Edison, Albert Einstein, Abraham Lincoln, John F. Kennedy, and champion swimmer Michael Phelps, to name just a few of a long list of iconic figures, have been described with symptoms of ADHD. Clearly the factors that shape positive as well as negative outcome need as much exploration as the syndrome itself.

Historically, a clinical picture compatible with ADHD has been described for millennia and undergone a series of labels based on etiologic and functional conceptualizations. From Hippocrates, who in 500 BC described the symptoms as the result of an imbalance of humors, to the description by Still in 1902 of a genetic "moral defect" of inhibition (11), to its reframing as a disorder of attention as the core deficit, the syndrome continues to be conceptually a moving target. This is exceptionally true for the current state of affairs, where the understanding of ADHD as an executive function disorder has been broadened to contemplate a more global disorder of neurodevelopment. It is moreover becoming increasingly evident that what we clinically call ADHD is in fact the manifestations of many different disorders of multiple underlying neurobiological pathways.

ADHD is a perfect example of the nature−nurture controversy. On the one hand, it is a validated psychiatric diagnosis (12), on the other, it continues to be controversial because its symptoms are qualitatively within the spectrum of normal human behavior and temperament and attain pathological significance only at their extremes (13). Although diagnosis continues to be based on clinical indicators of impairment, ADHD is associated with objective neuropsychological deficits, changes in brain volume, and increased slow wave electroencephalograms (14). It is controversial because as a developmental disorder it evolves transactionally from conception within a social as well as biological context, so that ADHD symptoms may both cause and be manifestations of social, medical, emotional, and other neurodevelopmental conditions. It is diagnostically further complicated by the fact that the symptoms show a great deal of intraindividual variation and inconsistency and are experienced and described more by relevant persons in the child's (or adult's) environment than subjectively experienced by the child him/herself. In other words, the objective symptoms, the subjective bias of the "eye of the beholder" (teacher, parent, spouse, etc.), and the cultural and specific context that defines abnormality and impairment must be taken into consideration.

18.1.2. ADHD Criteria in DSM-5

There has been an explosion of information about psychosocial, biologic, and neuropsychological correlates of ADHD and other neuropsychiatric disorders gained in the last 15 years. Although there is now an FDA approved brain-wave test for ADHD, it remains defined and diagnosed by behavioral manifestations rather than laboratory tests. There are some variations among diagnostic systems defining ADHD, including the World Health Organization International Classification of Diseases (ICD 10), and DAMP (Disorder of Attention, Motor control and Perception, a system used primarily in Scandinavia) (15). However, The Diagnostic and Statistical Manual of Mental Disorders (DSM) classification system (16) is the prevalent system in the US and in

international research. The DSM diagnostic criteria for ADHD represent a somewhat surgical approach to dissecting the actual clinical phenomenology of ADHD from its complex manifestations and context. The DSM-5 Criteria are based on extensive field trials of ADHD symptoms, in which two behavioral dimensions may be identified, one associated with inattention and cognitive disorganization, and the other with impulsivity and hyperactivity, occurring alone or in combination.

There are several areas of discussion associated with criteria ABCD, regarding the age of onset, the occurrence across contexts, and the exclusionary criteria (17).

Criterion A: The minimum number of symptoms necessary for diagnosing older adolescents (>17 years) and adults has been decreased from 6 to 5, reflecting typical evolution of the disorder with age and development.

Criterion B: Age of onset has been increased to 12 years, a change from the previous DSM version, which stipulated onset prior to age four. This change conveys the importance of clinical presentation in childhood, while reflecting the difficulties in establishing precise age of onset retrospectively. While children who are disruptive, impulsive, and hyperactive are usually identified in their preschool years, diagnosis of children with predominantly inattentive symptoms may be delayed because inattention and cognitive disorganization may not be noticed in the preschool and early elementary years. These symptoms often become impairing only when academic and organizational demands accelerate in the later school grades or even in adulthood.

Criterion C: Cross-situational impairment is required for diagnosis but may not be consistently observed; for instance, behavioral dysregulation, oppositionality, and aggression may be obvious at home from toddlerhood, but may be well controlled in a structured and developmentally effective preschool or daycare environment. Children with ADHD have low adaptability and are often exquisitely sensitive to the "goodness of fit" with their physical environment, teachers, parents, siblings, and peers, which may be reflected in the often highly disparate behavior ratings one finds between teachers and parents, and between teachers from one grade to the next (18, 19).

Criterion D refers to the requirement for clear evidence of functional impairment. The core impairments in ADHD are academic underachievement and poor peer relationships due to peer rejection. The presence and degree of functional impairment is clinically more relevant than the absolute number of ADHD symptoms, and has higher predictive significance for outcome (20). Gordon and colleagues (20), in an analysis of four longitudinal epidemiologic studies of ADHD, pointed out that in all four studies, the link between impairment and symptoms was weak, with DSM symptoms predicting at most 25% of the variance of impairment. Accordingly, prevalence rates were found to diminish when impairment criteria were applied. On the other hand, ADHD with significant impairment may be underdiagnosed if impairment is ignored and symptom counts do not meet threshold levels, which is frequently the case for adolescent and adult ADHD (20).

Criterion E: The exclusionary criteria have been revised to permit codiagnosis of ADHD with Autism Spectrum Disorders. Close attention must be paid to differential diagnosis given the frequent overlap of impulsivity, hyperactivity, and attentional dysregulation in other neurodevelopmental, mood, anxiety, and impulse-control disorders (21), and the frequent comorbidity of mood disorders with ADHD (9). This overlap will be discussed further in the section about comorbidities.

The DSM-5 symptom checklists are prefaced with the requirement that the behaviors interfere with functioning and development. The adequacy of the family, social, and school environment as well as age and cognitive-adaptive status of the child therefore need to be taken into consideration in order to assess how the child's ADHD symptoms are related to the environment, and if behavioral or academic expectations are appropriate for the age and development of the child. This is especially relevant when preschoolers and toddlers present with difficult behavior. Neurodevelopmental delays in toddlers and preschoolers are frequently associated with behavioral dysregulation, poor frustration tolerance, impulsivity, and avoidance behaviors and may mimic early signs of ADHD (22). On the other hand, inexperienced, stressed, emotionally dysregulated, or isolated parents may misinterpret the normal developmental agenda of increased autonomy and exploratory drive in young children as hyperactivity and ADHD (23). The parental expectations, socioemotional health, and possible observation bias of the caretakers must therefore be considered, and observations of less involved individuals included in the behavioral assessment of very young children. It is important to remember that there is an increased frequency of socioeconomic adversity and neuropsychiatric disorders in other family members of children with ADHD, which increases the risk for maladaptation and persistence of disruptive symptoms from early into later childhood and adolescence, and for the development of behavioral and emotional comorbidities (24).

18.1.2.1. Inattentive vs. Hyperactive-Impulsive Symptom Spectrum

Considerable clinical and neuropsychological differences exist between the inattentive and hyperactive presentations, indicating the heterogeneity underlying the diagnosis. Differences are found with respect to gender distribution, functional impairments, comorbidities, and pharmacologic response (25, 26). Hyperactivity is the symptom driving behavioral impairment and comorbidity with ODD, whereas attention problems drive academic impairment (27, 28). The combined type has the worst of both worlds, showing both academic impairment and ODD symptoms in about 50%, and is the most common presentation in both genders (28). The hyperactive-impulsive presentation is usually not associated with academic problems, and in fact is correlated with above average academic performance in a significant proportion (27). However, about 30% of children are behaviorally at risk because of associated ODD symptoms (27).

The predominantly inattentive form of ADHD (ADHD-I) is characterized largely by symptoms of cognitive dysfunction, underarousal, poor working memory, slow cognitive tempo, forgetfulness, and avoidance of mental effort (29). These children are usually older at diagnosis, more likely to be female, and are more likely to have comorbid internalizing rather than externalizing disorders, learning disabilities, and speech and language problems (26, 29). Children demonstrating predominantly inattentive behavior are socially impaired because of withdrawn behavior rather than impulsive intrusiveness. There is low comorbidity between inattentive ADHD and ODD symptoms. Community samples have found that a higher proportion of girls have the inattentive subtype than the other two subtypes (1:2), and in referred samples, inattention is found twice as frequently in girls than boys (30). Because inattentive children are not disruptive, problems may go unnoticed; they are underreferred, and often only identified when comorbidities or academic problems emerge.

18.1.3. Epidemiology

18.1.3.1. Prevalence

ADHD is the most commonly diagnosed neurobehavioral disorder of childhood. Prevalence rates vary from 3 to 12% in large epidemiologic studies, with 6.7–7.5% appearing to be the most consistent range. The most recent National Survey of Children's Health, conducted by the CDC in 2007, and based on telephone interviews with over 100,000 families, reported 9.5% (5.4 million) US children, age 4–17, that had ever had a diagnosis of ADHD. The rate in boys was reported to be 13.2%, versus 5.6% in girls. The rates increased with age: 6.6% in children less than 11 years; 11.2% in children 11–14 years old, and 13.6% in 15–17 year olds. There were large prevalence differences by state, with the lowest rate (5.6%) in Nevada, and the highest (15.6%) in North Carolina. There was no significant difference between white and black respondents (9.9% vs. 10.1%, respectively), however rates in multiracial children (14.2%) were higher than for other racial groups. Hispanics reported rates almost half those of non-Hispanics (5.6% vs. 10.5%) (2).

A 2007 systematic review and metaregression analysis of 102 studies from all world regions (31) found a pooled international prevalence rate of 5.29%. ADHD has been identified as a clinical diagnostic entity in all countries studied, but rates vary according to diagnostic criteria, source of information, requirement of impairment for diagnosis, and geographic origin of the study. Rates based on geographic location of the population were only significantly different between the US and Africa. The fact that ADHD rates are higher in inner cities and populations below the poverty level indicates the contribution of psychosocial adversity to syndrome development, which was already demonstrated by Rutter in the Isle of Wight studies in the 1970s (32). Epidemiologic data clearly associate socioeconomic and demographic factors with the diagnosis of ADHD, i.e., family characteristics such as less likely to live with father, more likely to be poor, school characteristics such as older teachers, and higher expectations for school performance (33).

It is important to stress that Checklist studies lead to false elevations of prevalence rates and can only be used as an estimate of deviance from the norm in a particular population. Checklist studies do not rate the prevalence of ADHD using diagnostic criteria. Instead, rating scales only establish a level of statistical deviance from the normative population. Population prevalence rates established by checklist criteria are often far higher than prevalence rates reported for more stringent diagnostic criteria (20).

18.1.3.2. Gender

Historically, most of the clinical description, epidemiology, and prevalence literature has been focused on latency age boys. ADHD in boys manifests with more disruptive and externalizing behaviors than girls, so that the rate of referral and diagnosis in boys has been much higher, possibly skewing epidemiologic as well as clinical data. Girls with ADHD are underreferred, which is strikingly illustrated by the fact that prevalence rates for ADHD in community samples show a >2:1 male:female ratio, but the ratio of boys to girls referred to clinics may be as high as 10:1 (28). This referral and treatment discrepancy is highly significant because girls with ADHD are just as much at risk for adverse long-term functional outcomes as boys with ADHD as they progress into adolescence and adulthood (34). Although for most aspects of female ADHD, it is not gender, but ADHD, that accounts for functional impairment, the clinical picture differs somewhat from that of boys with ADHD in that ADHD girls have less disruptive and externalizing behaviors and higher rates of internalizing symptoms and more cognitive impairment than boys. Both genders appear to be equally vulnerable to ADHD risk conferred by psychosocial adversity (30, 34). However, boys may be more vulnerable to involvement with deviant peers (35).

In the Massachusetts General Hospital Study of Gender Differences (36), a longitudinal study following both clinic and community cohorts, the predominant subtype for both genders in both community and referred settings was the combined subtype. However, the inattentive subtype was identified in twice as many girls as boys in the clinic population. In both community and referred subjects, boys and girls showed significant and comparable impairments in psychosocial, educational, and emotional

domains. At 5-year follow-up at an average age of about 17 years, the girls with ADHD had rates of antisocial, anxiety, mood, and substance abuse disorders comparable to boys with ADHD, and significantly higher than female controls. A nonsignificant trend to eating disorders also appeared in this population in adolescence. Girls with ADHD in this study differed from boys in one surprising aspect, namely that in adolescence they showed a higher vulnerability to substance abuse than boys with ADHD, even though they had less impairments earlier on. A longitudinal study of girls with ADHD followed from childhood to adolescence found disruptive-oppositional ADHD symptoms and peer rejection in girls to be predictive of later substance abuse and internalizing disorders (37). Girls with ADHD are at high risk for early sexual activity and unplanned pregnancy. Longitudinal studies into adulthood confirm that the persistence of ADHD symptoms and continued strong association with depression and anxiety is similar for both genders, with a higher risk for substance abuse disorders and antisocial personality disorders in men (38).

18.1.3.3. Age

18.1.3.3.1. Infants

Most studies of ADHD are limited to children in middle childhood (6–12 years). However, data are becoming available about the developmental precursors of psychopathology from infancy and toddlerhood, although the DSM classification system is poorly suited for these age groups. Neuroimaging studies suggest that structural variations may be present in infancy that are associated with later executive functioning impairment (39). Models of temperament conceptually overlap the dimensions of behavioral and affective self-regulation associated with ADHD, and the "difficult-temperament" infant may represent a bridge between infant risk and development of ADHD (40).

Auerbach (41) examined temperament differences and neurodevelopmental immaturity in male newborns at familial risk for ADHD using factors derived from the Brazelton Neonatal Behavior Assessment Scale (NBAS) (42). Newborns at risk for ADHD showed risk factors not only on indices associated with temperament, namely poor state organization (irritability, problems self-quieting), but also on measures of motor maturity and autonomic stability. At 7 months of age, a subcohort of this genetically at-risk group showed decreased interest in block play, higher activity, and increased anger reactivity. These authors assert that symptoms are subtle, possibly nonspecific, and their predictive value for later ADHD or psychopathology could be a function of the interaction with caretaking environments.

Other studies have found disorganized, insecure attachment, emotional dysregulation, and sleep problems in infancy correlated with hyperactivity, ADHD, and conduct disorders at early school age (23, 43, 44). The infant behaviors may be mediated by negative parenting and/or parental psychopathology, specifically maternal depression. Hostile parenting by mothers of sons appears to be a risk factor for later ODD and conduct disorder, whereas maternal depression is more strongly associated with ADHD (45, 46). A construct of parental–child interaction that may be a mediating factor for these effects is the presence and quality of parental, i.e., maternal responsiveness. Parental responsiveness can be operationalized and indicates the parent's sensitivity and adaptation to the child's signals, states, and needs. Maternal responsiveness may not protect against the development of ADHD, however, it does appear to protect against the codevelopment of ODD/CD (45). Maternal responsiveness is also strongly associated with language development in early childhood, which, in turn affects behavior regulation (47). In fact, distractibility in early childhood as a precursor of hyperactivity in middle childhood may be determined more by caregiving and contextual factors than biological and temperamental factors (48).

This reality was aptly summarized by Erickson, who observed: "The infant age of development is based on establishment of basic trust derived from earliest experience and is dependent on the quality of the maternal relationship" (49). And to follow with Michael Rutter: "The impression of lasting effects stems from the very high probability that a poor early upbringing will be followed by a poor later upbringing. The persistence of behavioral sequelae is largely a consequence of the persistence of the damaging experiences" (50).

18.1.3.3.2. Preschoolers

ADHD may be suspected when developmentally appropriate activity and impulsivity characteristic for toddlers and early preschoolers becomes extreme or persists beyond the toddler and early preschool period. However, in about 50% of cases considered to be at risk for ADHD, symptoms do not persist, and only 5–10% of preschoolers with concerns about inattention actually continue on to develop ADHD (51). Prevalence rates for ADHD in preschoolers are quite inconsistent, depending on methods and clinic vs. community populations. The range is from about 2% in primary care pediatrics to 5.7% in community to 59% in psychiatric referral clinics (52). There is often a significant discrepancy between parent and teacher evaluations. For example, in one Japanese study, parents reported a prevalence of 31.1% of ADHD symptoms, while teachers thought only 4.3% of these children met diagnostic criteria (53). In the Canadian nationwide survey of children 0–7 years, children's behavior was rated by their mothers at 2 and again at 7 years, with 7% of children showing persistence of hyperactivity at 7 years. The persistence was associated with male gender, maternal prenatal smoking, maternal depression, and hostile parenting (54).

At this age persistent behavioral ADHD symptoms may indicate a host of disparate problems, from medical problems, such as gastro-esophageal reflux, to environmental disruption and parenting effects, to the emotional and cognitive response to developmental frustration, to autism spectrum disorders (ASD). Disrupted sleep patterns or reduced sleep quality are associated with overactivity, anger, aggression, impulsivity, tantrums, and annoying behaviors, and these problems often resolve when the underlying sleep problem is corrected (55). Toddlers and preschoolers with language delay are often very frustrated, distractible, disruptive, emotionally dysregulated, and physically expressive. Language may improve dramatically with skilled speech-language therapy and results in equally dramatic emotional and behavioral stabilizations. In contrast, impulsive, hyperactive, inattentive, and distractible behaviors are common in preschoolers with autism spectrum disorders, but it is the lack of communicative and social intent and stereotypical behaviors that should raise concerns that one may be dealing primarily with an ASD rather than ADHD. Furthermore, cognitive deficits may underlie and mimic ADHD symptoms (22). Preschoolers usually love the individual attention and activities of testing situations as long as they are able to understand and perform the requested tasks. They may do fine behaviorally and be attentive as long as they are not requested to perform tasks that are difficult for them. However, when increased task complexity such as in imitative drawing or block activities, language testing, and other cognitive challenges results in avoidance behavior, distractibility, and inattentiveness, verbal and nonverbal cognitive deficits should be ruled out.

Preschoolers with ADHD show deficits and differences from control children in intellectual, sensory, and motor performance that go beyond the core symptoms of ADHD (22). Although similar deficits have been found in school-age children with ADHD, there is a paucity of data about developmental delays in preschoolers with ADHD. However, it is important to remember that ADHD, ASD, cognitive-adaptive, and language disorders have common interfaces at this age, and may only reveal their separate identities and diagnoses with time and with appropriate interventions.

18.1.3.3.3. Middle Childhood

By middle childhood the behavioral, cognitive, and emotional streams become more separable and diagnostically recognizable. Academic underachievement and problems with social competence and acceptance emerge as the most salient impairments. Awareness of being different begins to affect the child's self-esteem, especially as it is often the result of peer rejection or name-calling. Behavioral dysregulation persists, but dysfunctions in cognition, sensory and motor, and affective domains become more evident (17, 56).

There are many ways in which ADHD children differ from their unaffected peers. Causal connections, story comprehension, and time perception are deficient compared to controls (57, 58). Children with ADHD show restricted cognitive flexibility (59), which may manifest as stubbornness, oppositionality, or avoidance behavior. Cognitive disorganization, impaired working memory, poor reading comprehension, and procrastination emerge in middle childhood, and affect academic performance and especially homework activities (17). They have difficulty starting and completing tasks and have difficulty self-monitoring (60). They are often clumsy with complex fine motor tasks (61), and in visual-motor integration, which manifests in poor handwriting and impairment in written schoolwork. Adaptive function in daily living skills, such as maintaining personal hygiene or taking on household responsibilities, is immature relative to cognitive levels (62). Although they are inattentive and distractible with chores, homework and even on the sportsfield, they may spend hours transfixed watching television or playing computer and video games. They are emotionally and behaviorally very context dependent (57), for instance may do very well with one teacher, but may be oppositional and resistant to another. They are emotionally dysregulated, attention seeking, difficult to satisfy, tend to overreact to current and anticipated experience, and are especially intolerant of disappointment and negative experience (63).

A frequent complaint of parents is emotional and behavioral immaturity, such as silliness and inappropriateness, a preference for playmates, activities, and toys that are considerably below age and cognitive level, and a remarkable lack of insight into their own behavior, while being extremely sensitive to rejection and criticism.

However, it is very important to acknowledge that their emotions go both ways: they are also often very affectionate, enthusiastic, generous, forgiving, eager to please, very responsive to individual attention especially from other adults, and are often deeply hurt and baffled by the rejection they experience from their peers.

Academic failure due to core ADHD symptoms and associated cognitive, language, and learning disabilities, which are found in 30–50% (9), lead to poor self-esteem and acting-out behavior, conflictual family, and peer relationships and increase the risk for depression. Peer rejection may happen already to hyperactive, intrusive, impulsive preschoolers, but becomes much more evident and perceived by middle childhood, where it quickly leads to loss of self-esteem and confidence. Half of children with ADHD suffer from peer rejection, which appears to be the primary mediator for the relationship between ADHD and depression in both younger and older children with ADHD, and is a powerful predictive factor for depression in adult ADHD, particularly in women (64). Academic performance in fact may not be an issue in a bright child with ADHD, but whose impulsive and unmodulated social approach may lead to significant impairment in family and peer relationships from early childhood. Academic underachievement and peer rejection in association with ADHD convey separate but additive risk for developing of internalizing and externalizing behaviors, substance abuse disorders, and school and occupational failure in adolescence and adulthood (65).

Erik Erikson refers to middle childhood as the stage that is determined developmentally by the conflict between industry and inferiority: "the child's danger, at this stage, lies in a sense of inadequacy and inferiority. If he despairs of his tools and skills or of his status among his tool partners, he may be discouraged from the identification with them and with a section of the tool world" (49).

18.1.3.3.4. Adolescence

In the transition from childhood to adulthood, powerful changes occur in physical development, sexuality, peer and family relationships, and cognitive, moral, and emotional development. In previously emotionally healthy children, this transition is not as tempestuous as lore would have it. However, adolescence increases the risk for emergence or consolidation of previously latent, cognitive, behavioral, and emotional problems, which appears to be driven by genetic-biologic factors and shaped by family and peer relationships and academic performance. The persistence of ADHD into adolescence is also strongly associated with familial occurrence, psychosocial adversity, and preexisting psychiatric comorbidity (24, 66). Impairing symptoms continue into adolescence in 60–85% with only a small minority showing remission. Hyperactivity decreases, but inattentiveness and impulsivity persist (56). Comorbidities with anxiety disorders, depression, and dysthymia increase from the already high rate of about 30% in middle childhood to 35 and 50% respectively by mid-adolescence. Adolescent-onset mania may be suspected in depressed children with chronic irritability and explosiveness (9). Quality of life is affected in all domains: 50–70% of children with ADHD have few or no friends, the school dropout rate is estimated at 32–40%, and the college completion rate 5–10% (10, 67, 68). Adolescents with ADHD are at a twofold to fourfold risk compared with normative peers to be involved in automobile accidents (69); other risk-taking behaviors are increased, such as unprotected sex, with an increased teen pregnancy and STD rate in some studies (10). Eating disorders present a risk in girls with ADHD who are experiencing academic and peer problems, probably as a result of seeking peer acceptance and impulsive behavior (64). ADHD has also been correlated with bulimia in obese adolescents of both genders, independently of mood disorders (70).

The increased rate of psychiatric disorders in adolescence is multifactorial, driven on the one hand by familial predisposition, physical change, and environmental stressors and on the other by adolescent-specific cognitive and affective development, increased introspection, and self-appraisal (71). Sociocultural factors play a strong role in shaping the course of adolescence, so that coping mechanisms as well as issues such as school attendance and dropout rates, adolescent sexual behavior, substance use, and problems with the criminal justice system, must be considered in context, rather than solely being the results of individual pathology.

18.1.3.3.5. Adults

Although this discussion about ADHD is restricted to children, mention of adult ADHD is appropriate, since a significant portion of the parents of children with ADHD themselves have ADHD and associated comorbidities. Frequently it is the child's evaluation and treatment that leads to the parents' realization of their own disability, and frequently the first step in treating the child is addressing the parents' problems. Although adults may not meet full symptom criteria, it appears that impairing ADHD symptomatology persists into adulthood in about 65% of childhood diagnosed ADHD (4). There also is a subgroup of adults whose symptoms did not appear or result in impairment until later childhood who nevertheless meet all other diagnostic criteria and show significant impairment (72). The adult prevalence is estimated to be between 4–5% (3, 4).

The majority of adults have significant psychosocial dysfunction, including lower educational and occupational status, have fewer friends, sire more children in early adulthood, and have higher divorce rates than controls (1, 10, 72, 73). They are at substantially higher risk for antisocial personality disorders, and mood and anxiety disorders, and for behavior leading to arrest. In fact, reported prevalence of ADHD among incarcerated males may be as high as 40%, and is highly associated with learning disabilities and affective disorders (74).

18.1.4. Comorbidity

Comorbidities with at least one neurodevelopmental or psychiatric disorder occur in at least 80% of persons with ADHD, and 60% have two or more comorbidities (9). The greater the number of comorbidities, the more severely the cognitive and psychosocial functions of the individual are affected (75). Awareness of this high likelihood of comorbidity, and diagnosis and interventions has the same urgency as treatment of ADHD in order to decrease the severe psychosocial stressors that are the inevitable consequences for the child and his/her family (76). There is virtually no research literature that explicitly describes the development and course of children with "pure" ADHD, which clearly exist and could in fact represent a specific subcategory of ADHD that deserves investigation.

18.1.4.1. ADHD and Other Neurodevelopmental Disorders

Children with ADHD are different cognitively as well as affectively from children without ADHD. About 30–50% of children with ADHD have other neurodevelopmental disorders such as dyslexia and language disorders. It appears that such co-occurrences are not based on single factor linear causality, such as attentional dysfunction leading to impaired perceptual processing which then leads to reading disorders. It appears instead that they may be etiologically multifactorial, in that disparate conditions share genetic and cognitive traits that account for their co-occurrence (77). The surprisingly high rate of 25–40% comorbidity of ADHD with dyslexia is an example of such a putative genetic pleiotropy, in which one gene may exert effects on different cognitive functions.

Speech-language delay and disorders occur in 30–50% of children with ADHD (78), and frequently precede the development of reading disorders. The etiologic complexity of these comorbidities is illustrated by the fact that both language and reading development are strongly affected by environmental-caretaker factors as well as genetic factors (79). Language disorders that persist into adolescence are in and of themselves associated with higher degrees of cognitive, behavioral, and emotional disturbances (80), as is the nonverbal learning disability or right hemisphere syndrome, which is frequently associated with ADHD and is characterized by average language ability but difficulty with social cognition, and deficits in visual-integrative, mathematics, and graphomotor competence (81).

Children with Autism Spectrum Disorders have a 20–50% rate of comorbid ADHD as well as the characteristic social-communication deficits (82). Developmental coordination disorder is identified in about 50% of children with ADHD, and indicates more severe cognitive involvement as well as psychopathology. Conversely, virtually all children with movement problems are at risk for problems in attention, learning, and psychosocial adjustment (83). About 55% of children with Tourette's syndrome have comorbid ADHD (84).

Children with mental retardation have similar prevalence rates of ADHD as children with typical intelligence. However, the concurrence of ADHD increases the severity of functional cognitive impairment (82).

18.1.4.2. Psychiatric Comorbidity

18.1.4.2.1. Mood and Anxiety Disorders

Mood and anxiety disorders frequently have symptoms of inattention, impulsivity, and hyperactivity that may be misdiagnosed as ADHD. However, at least 25% of children with ADHD are thought to have comorbid anxiety and close to 50% may have mood disorders, including dysthymia and Major Depression (9). Community and psychiatric referral cohorts show the same rate of comorbidities, and in both, the prevalence of comorbidities increase markedly with age. The Massachusetts Longitudinal studies of children with ADHD found that 29% of 11 year olds with ADHD met criteria for depression, which increased to 45% by mid-adolescence, compared to 2–5% of controls. The association of Bipolar Disorder to ADHD is as yet somewhat unclear, but it is thought that early hyperactivity may actually represent a developmental precursor to mania for a significant number of children with ADHD. In the Massachusetts cohort, 11% were found to have mania at baseline, characterized by severe chronic irritability, aggression, and explosiveness, which increased to 12% after 4 years. Lifetime prevalence of ADHD in bipolar adults is estimated at 9.5%, with onset of mood symptoms an average of 4 years earlier (13.9 vs. 18 years old) than in patients with bipolar disorder alone (85). Anxiety disorders were found in 28% at baseline of 11 years, and increased to 35% in middle adolescence, compared to 5% and 9% respectively in normals. Characteristically, anxiety (generalized anxiety, separation anxiety) and depression are found concurrently in ADHD. The severity and degree of impairment is mediated by a number of comorbid conditions, family-genetic factors, and age of onset (86), i.e., the earlier the onset, the more severe the manifestations.

An interesting diagnostic dilemma exists between ADHD and Posttraumatic Stress Disorder, especially in communities that experience high levels of community or domestic violence. Clinicians must be attentive to significant overlap of ADHD symptoms with PTSD arousal symptoms (PTSD criteria E for older children or criteria D for children under 6): irritable behavior, angry outbursts, reckless behavior, hypervigilance, exaggerated startle response, concentration problems, and sleep disturbance. It is often difficult to elicit a clear history of trauma; whereas parents and schools are likely to report behavior problems. The two disorders are phenomenologically, diagnostically, and neurobiologically independent disorders, which can coexist and combine to exacerbate stress-reactivity (87).

18.1.4.2.2. Risk Factors in Psychiatric Comorbidity

As with other neurobehavioral disorders, the development of depression and anxiety in childhood and adolescence is associated with genetic, prenatal, and early infant and childhood biological and experiential factors (86, 88). It is in this context quite striking that the role of mothers in the development of behavioral disorders is well researched, whereas the presence and role of

fathers as contributing to or protective of mental disorders has received little attention until recently (89). The importance of prenatal and early childhood environmental/psychosocial contributions to childhood mental health and developmental disorders cannot be stressed enough, since prevention and early intervention are realistic goals for many of the identified risk factors (90).

Prenatal maternal stress, substance use, anxiety, and depression are associated with risk to the cognitive and affective-behavioral development in their children, mediated by alterations in the maternal HPA and, in the case of substance use, on the direct effects of teratogens on the developing brain. Postnatal environment, which includes psychosocial adversity (low income, social isolation, marital stress, absent fathers, intrafamily hostility), parental psychopathology, and caretaking behaviors are risk factors for the development of externalizing and internalizing disorders in the offspring.

However, anxiety disorders in parents have a higher specificity for development of anxiety in their children (86) than other disorders, which is mediated by overprotective, controlling, and negative parenting. Child factors that are associated with the development of anxiety are biobehavioral dysregulation in infancy, overreactivity and developmental delays in the preschool period (91), and resulting vicious cycles of anxiety, impaired peer relationships, and further developmental and academic failure. Development and persistence of depression is less specific to the particular parental psychopathology, but associated with similar prenatal and postnatal risk factors as well as with the presence of depression in the mother during later childhood (46). The cumulative effects of poor peer relationships and academic impairments represent the specific risk factors for the development of depression in ADHD (64, 86).

18.1.4.2.3. ADHD and Oppositional Defiant Disorder

ODD can be identified in about 40–60% of children with ADHD, predominantly combined type, in about 30% with the predominantly hyperactive type and is rarely reported in ADHD-Inattentive type (9). Children with ODD are disobedient toward authority figures, often easily angered, negative, vindictive, very controlling, and easily provoked by their peers. Children with depression, bipolar, and anxiety disorders may demonstrate similar symptoms. Such symptoms may occur as a reaction to stress or abuse. Despite severely oppositional behavior toward adults, behavior toward peers may be quite peaceful. Symptoms may emerge as early as in toddlerhood to preschool age and are strongly associated with maternal depression, decreased maternal responsivity, and negative parenting practices in early childhood (23, 46). In preschoolers, ODD behavior may be severe at home, often especially toward the mother and siblings, but not evident in a well-managed structured preschool environment. When ODD persists into later childhood and adolescence, a high rate of active maternal depression, helplessness and overreactivity (92–94), and paternal negativity are contributing factors (86), and oppositional behavior spills over into the school setting. Fathers of children with ODD have an increased rate of substance abuse, negative parenting, a childhood history of ADHD, and current anxiety disorder (94). ODD is associated with intense family conflict (95), that is especially virulent in adolescence and potentiates the negative effects of core ADHD behaviors (96, 97). ODD may be comorbid with Conduct Disorder as well as ADHD, but ODD does not develop into later Conduct Disorder if the latter was not already present in earlier childhood (92). Conduct disorder is clearly separable from both ADHD and ODD, and will be discussed separately.

18.1.4.2.4. ADHD-Plus

Symptoms of ADHD can be found as a specific manifestation of neurological involvement or as secondary symptoms of systemic disorders. First, identifying an underlying medical condition is imperative for appropriate etiological treatment. Secondly, if ADHD is a manifestation of or occurs comorbidly in chronic systemic or neurologic illness, pharmacologic treatment may considerably improve quality of life. ADHD symptoms, in association with cognitive and learning disorders are frequent in: posttraumatic and postinfectious encephalopathy, fetal alcohol exposure, chronic lead poisoning, cerebral palsy, prematurity, neuromuscular disorders, especially myotonic dystrophy, neurofibromatosis, fragile X, Turner, Klinefelter, and Williams Syndromes, seizure disorders, congenital brain anomalies, metabolic disorders, as well as in a host of less prevalent neurogenetic syndromes (98).

Any chronic illness, anemia, asthma, allergies, heart conditions, renal disease, metabolic dysregulation such as in diabetes or thyroid disease, chronic gastrointestinal problems, nutritional deficiencies, and other disorders causing chronic fatigue, inattentiveness, and behavioral symptoms such as restlessness may mimic ADHD and should be considered in the presence of leading physical symptoms. Chronic hypoxia, as in congenital heart disease (CHD) and Sleep Disordered Breathing, have actually been shown to be causal for ADHD (99). Studies have shown clinically significant improvement in attentional symptoms as measured by continuous performance tests following tonsillectomy (100).

Furthermore, many medications have side effects that may affect attention and cognitive processing in some children, most significantly antipsychotics, anticonvulsants, steroids, antihypertensives, bronchodilators, and antihistamines.

18.1.5. Neuropsychology

Neuropsychological theories regarding a hyperactive, impulsive, and inattentive childhood behavioral syndrome have a long-standing history dating to the latter part of the nineteenth and early part of the 20th century (12, 101). Neuropsychological dysfunction in ADHD has since been increasingly well-characterized and documented. In the 1990s, the availability of enhanced brain imaging and measurement techniques served as a catalyst to rapid advancements in the field, with much of the research over the last decades focusing on the delineation of executive functioning and inhibitory deficits in the disorder (8, 102, 103). As seen from a neuropsychological perspective, many functional processes fall under the rubric of executive functions, including set shifting, planning, inhibition, and working memory. Primarily concerned with goal-directed and problem-solving behavior, executive functions are thought to play a role in a wide range of adaptive and goal-directed behaviors, including context-specific action selection (102, 104). Problems with behavioral inhibition, conceptualized as the ability to strategically or effortfully inhibit an automatic or on-going response, have been suggested by Barkley (8) to be the primary deficit in ADHD, with inhibitory impairments leading to inadequate time for execution of other executive functions—particularly, working memory, self-regulation (e.g., of affect, motivation, and arousal), internalization of speech, and reconstitution (analysis and synthesis).

Research to date has widely supported the presence of both behavioral inhibition and executive functioning deficits in the combined subtype of the disorder (105–107). A meta-analysis by Willcutt and colleagues identified difficulties with response inhibition, vigilance, working memory, and planning to be the most robust ADHD-related impairments. Imaging studies have linked executive and inhibitory impairments to dysfunction in multiple distributed prefrontal-striatal neural networks, particularly right prefrontal cortex (especially the inferior frontal gyrus), anterior cingulate, caudate, and thalamus (108–110). However, whether response inhibition deficits—or even executive functioning or prefrontal cortex deficits more broadly—constitute the core or primary deficit in ADHD remains under considerable debate (111, 112). For instance, attention and arousal factors (e.g., variable performance and slower responding) are likely to also contribute to response inhibition deficits (113). In addition, meta-analytic studies suggest that despite findings of moderate group deficits on executive measures, many children with ADHD do not demonstrate executive impairments on any given measure. Nigg and colleagues, for instance, found that although approximately 80% of children with ADHD exhibit impairments on at least one executive functioning measure, no more than 50% of children with ADHD demonstrated impairments on any one particular executive measure and only ten percent of children had generalized/global impairments across executive functioning measures (i.e., on five or more executive functioning measures) (114). The implicit conclusion from such findings is that children with ADHD likely comprise a heterogeneous group consisting of etiologically distinct subtypes, with multiple or distinct etiological pathways that lead to similar behavioral (i.e., descriptive)-level phenotypes (as documented by the DSM-5).

The considerable neuropsychological heterogeneity among children diagnosed with ADHD has moved the field towards a search for "endophenotypes" to bridge ADHD behavioral symptoms, neuropsychological impairments, and underlying genetic or neurobiological etiologies and to explain differences in symptom clusters, comorbid diagnoses, and patterns of neuropsychological and cognitive deficits (114, 115). This approach aims to identify possible pathways to disorder—including potentially numerous genetic and environmental influences—and attempts to improve upon the DSM's behaviorally-based taxonomy by increasing specificity of the ADHD construct. This alteration in focus has produced a resurgence of interest in alternate theories of ADHD, especially those that posit neuropsychologically distinct subtypes with multiple pathways to disorder (116–118). For instance, Sergeant and colleagues' cognitive-energetic state regulation theory of ADHD (119) posits arousal (i.e., phasic alertness), activation (i.e., response readiness), and effort impairments—linked to right-lateralized noradrenergic and left-lateralized dopaminergic neural networks, respectively—to constitute the primary deficits in ADHD, with specific impairments possible in one or more of these three energetic "pools". Other prominent theories of ADHD argue the disorder to result from temporal processing deficits (120, 121), abnormalities in reinforcement-response mechanism (e.g., reward circuitry) (122), or interactions between altered reinforcement-response mechanisms and environmental factors such as social-learning, environmental conditioning, and altered appetitive or motivational systems (123) that produce "delay aversion" (124, 125).

A few additional points are relevant to current neuropsychological findings in ADHD. Patterns of impairment in the inattentive subtype of the disorder remain relatively underspecified, with the limited existing studies finding no convincing evidence for subtype differences (126). This research may, however, be confounded by the DSM taxonomy, which lumps together children without hyperactivity (many of whom are actually underactive) and those whose hyperactivity problems are "subthreshold" for the combined subtype of the disorder. This distinction is important, since some evidence suggests that children with "sluggish cognitive tempo" (e.g., inconsistent alertness and underactivity) may represent an etiologically distinct neuropsychological subtype of ADHD (127). Also as yet relatively underspecified are neuropsychological pathways towards comorbidity in ADHD. Temperamental vulnerabilities (e.g., negative emotionality), for instance, may predict development of comorbid oppositional or antisocial behavior disorders in ADHD independently of cognitive deficits (117, 118). Likewise, ADHD-related

neurocognitive impairments may predispose children towards the development of comorbid learning disabilities (128, 129). Finally, identification of the developmental trajectory of neurocognitive impairments remains in its early stages, but studies to date support the presence of impairments identifiable as early as preschool (116, 130) that persist into adulthood, despite the waning of behavioral symptoms such as hyperactivity and impulsivity (131–133).

18.1.6. Pathophysiology

The dominant hypothesis for the pathophysiology of ADHD is that of prefrontal cortical dysfunction, which is mediated by abnormalities of catecholaminergic neurotransmission in the catecholamine-rich fronto-striatal-cerebellar networks, which are the putative neural substrates for inhibitory and attentional control. The hypothesis is supported by the treatment effectiveness of stimulants, which increase the availability of extracellular catecholamines by inhibiting their reuptake from the synaptic cleft into the presynaptic terminals. Further, an increasing number of neuroimaging studies have captured structural and functional abnormalities in fronto-cortical and fronto-subcortical networks that persist in to adulthood. For example, a study of medication naïve young adults with a childhood ADHD diagnosis showed dysfunction in latero-fronto-striato-parietal regions relative to controls during sustained attention, as well as in ventromedial orbitofrontal regions during reward, suggesting dysfunctions in cognitive-attentional as well as motivational neural networks (134). The brain deficits in ADHD appear to be multisystemic, and are likely the result of differential disruptions that may occur during the development of the brain in fronto-striatal-cerebellar-parietal circuits, and may account for the inconsistency of clinical as well as of neuropsychological, morphological, and neuroimaging findings. As Casey points out, "cognitive (and neural) processes are intrinsically linked deficits in one system, and are likely to affect others in secondary ways, especially in a dynamically changing system such as the developing child with ADHD" (135).

18.1.6.1. Neuroimaging

Anatomic evidence for involvement of the frontal-striatal-cerebellar circuits is based on volumetric studies which demonstrate differences of the cerebellar vermis, caudate, putamen, and globus pallidus morphology in ADHD subjects compared to controls, as well as frontal lobe differences, with smaller volumes described of medial frontal areas including the cingulate, prefrontal, premotor, and motor cortex (136). In contrast to finding volumetric changes in discrete regions, Castellanos (137) found cerebrum and cerebellum as a whole to be smaller in all mapped regions in children and adolescents with combined type ADHD, rather than showing localized changes in fronto-striatal volumes. These differences were not affected by symptom severity, physical growth, handedness, or cognitive-comorbid parameters and remained consistent over different ages, except for a "normalization" of caudate size in adolescent probands, which was speculated to reflect the decrease in motor activity with adolescence in normal as well as hyperactivity-impulsivity in ADHD children. Significantly, morphologic changes were the same for children on stimulants as for untreated children. fMRI studies demonstrate activation differences in attention processing tasks in striatal-frontal networks (138), and in inhibitory-control tasks of cingulate, ventrolateral, and dorsolateral prefrontal cortex between ADHD and controls, but, comparable to Castellanos' findings, no differences were identified between treated and stimulant-naive ADHD subjects. (110, 139). Acute methylphenidate challenge enhances brain activity on fMRI, but this response to methylphenidate is inconsistent, not reflected in clinical test performance, and does not correspond to the fMRI activation patterns between ADHD probands and controls (138).

Affective response and mood disturbances in ADHD are thought to be correlated with volumetric differences in amygdalar regions found in children with combined ADHD and are interpreted to represent alterations in interconnectivity between amygdalar nuclei and the Prefrontal Cortex (PFC). Differences in hippocampal volume are speculated to account for differences in delay aversion and stimulus-seeking behavior (140). Further evidence for frontal involvement are EEG studies demonstrating cortical slowing (141, 142), and enhancement of Theta activity in frontal quadrants in ADHD, with males having more generalized and females having localized frontal changes (143). These EEG changes are the basis of the FDA approved Neuropsychiatric EEG-Based Assessment aid, which computes the ratio of theta and beta brain waves over a 15-minute period (144). In a blinded, prospective, multicenter study, EEG identified ADHD with 87% sensitivity and 94% specificity. Because EEG cannot identify comorbidities or alternative diagnoses, it is not recommended as a substitute for clinical evaluation (145).

It is unclear how specific neuroimaging findings are to ADHD and how much they overlap with other forms of neuropathology. It appears likely that structural-functional relationships are bidirectional, and affected by developmental and environmental factors (136). Given the clinical as well as neuropsychological heterogeneity of ADHD more definite conclusions require investigation of population samples that are defined by phenotypical homogeneity with regard to cognitive, behavioral, comorbid, and medication response characteristics.

18.1.6.2. Neuromodulators

ADHD symptoms appear to be mediated by alterations of the availability and effect of the catecholamines dopamine, and norepinephrine, which activate the circuitry and projections between the prefrontal cortex (PFC), basal ganglia, and cerebellum. Moderate levels of these catecholamines enhance, and high levels inhibit PFC function. Localization and effect of dopamine is dependent on the type of dopamine receptors that are activated, of which D-1, D-2, and D-4 receptors are the major groups. D-1-type receptors are concentrated in the PFC and their stimulation has a "U" shaped effect on PFC function, e.g., enhances working memory and attention regulation at lower levels of dopamine, but impairs it at high levels, such as with stress. Much less is known about dopamine-2-type receptor dysfunction, which appears to be associated with schizophrenia, and while there is some evidence for genotypic overlap of ADHD and schizotypy, the role of D-2 activity in ADHD remains to be clarified. D4 receptors are actually activated by norepinephrine rather than dopamine and appear to inhibit GABAergic (inhibitory) activity in PFC pyramidal cells; stimulation of D4 receptors consequently increases pyramidal cell firing. It appears that D4-receptor dysfunction, which results in increased GABA activity in the PFC with decreased pyramidal cell firing, may be associated with ADHD (146–148).

Norepinephrine receptor activity may enhance or impair PFC depending on receptor type. Activation of the postsynaptic alpha-2A receptor has enhancing effects and its agonist guanfacine improves executive functions in the PFC. Stress increases norepinephrine release at alpha-1 receptors, which has detrimental effects on PFC function. High alpha-1 activity may be associated with mania and schizophrenia, worsening with stimulants, and is blocked pharmacologically by antipsychotics (149).

18.1.7. Etiology

The many changes the concept of ADHD has undergone over time reflect different ideas about its causes. There is a point of view that considers what is called ADHD not to be a neuropathologically defined entity, but a mental construct for behavioral dysfunctional symptoms that represent a final common pathway of etiologically heterogeneous conditions. A monocausal model has given way to a transactional developmental model, in which individual factors (i.e., genetic vulnerabilities, temperament, and intelligence) interact with biologic and psychosocial factors throughout the lifespan. Recent research has returned focus on and specified the significance of the physical and social environment during gestation, infancy, and early childhood in shaping the neurodevelopmental substrate out of which mental and physical health as well as pathology, evolve (23, 90). This research gives support to the feasibility of prevention or at least mitigation of physical as well as mental disorders.

18.1.7.1. Genetics

Given the transactional conception of ADHD, the vulnerability to develop the behavioral and cognitive features associated with ADHD is highly familial. Based on epidemiologic, family, twin, adoption, and case–control studies, the heritability is considered to be between 60 and 80% (149, 150). The phenotype of ADHD is highly variable, and implies complex interactions of multiple genetic, biologic, and environmental factors. ADHD is most likely a polygenic condition, which implies the interaction of multiple alleles in the expression of ADHD, and a high if less expressive presence of such alleles in the nonafflicted population, which increases the difficulty of identifying pathogenic polymorphisms. Studies relating neuropsychological and behavioral markers to known candidate genes have led to inconsistent results (149, 150). Consequently, clinical, neuropsychological, epidemiological, and pharmacological patterns are sought as identifiers of distinct heritable subtypes that then can be researched systematically with molecular genetic methods (150, 151). Chromosomal regions containing potential ADHD predisposing loci, including 5p, 6q, 7p, 11q, 16p, and 17p, have been identified through family-based linkage studies (152). However, data associating ADHD with identifiable susceptibility genes is contradictory and still far from providing any clinically applicable consequences.

Because of the marked therapeutic effect of stimulants in ADHD, which is attributed to the inhibition of dopamine transporter (DAT) and increase of functional availability of extracellular dopamine, molecular genetic investigations have largely focused on identifying candidate genes associated with alterations of dopamine transporter and receptor (DRD) mechanisms. For example, associations were found with DAT1, DRD4, synaptosomal-associated protein of 25 kDa (SNAP25), brain serotonin transporter (5HTT), serotonin receptor 1B (HTR1B), and dopamine-beta-hydroxylase (DBH) (153). Meta-analysis examining 5 top candidate genes, all implicated in synaptic transmission and plasticity [brain-derived neurotrophic factor (BDNF), HTR1B, norepinephrine transporter gene (SLC6A2), SLC6A4, and SNAP25] found only the SNAP25 variant showing an association with ADHD. SNAP25 decreases Ca^{2+} responsiveness at glutamatergic synapses (150). A meta-analysis of 113 genetic studies by Bobb, Castellanos, and colleagues (154) supports a definite but modest role for dopamine D4 and D5 receptors, and dopamine and serotonin transporter genes in ADHD. An association of the DRD4 7- repeat allele with ADHD has been replicated

and a longitudinal study has confirmed this association in ADHD with higher cognitive function and better long-term outcome than other forms of ADHD (155).

A different approach to genetic specification suggests differentiating the phenotypes of ADHD by using dimensional as well as categorical diagnostic criteria as well as refining the subtypes as a workable path to identifying associations with susceptibility genes, for instance in differentiating susceptibility genes for different comorbidities with ADHD (156). This approach is related to the concept of "endophenotype," which has resurfaced as a way to organize and classify the mediators of genetic-phenotype relationships into operational subtypes, such as through specific neuropsychological profiles or biological markers that themselves are heritable (157). However attempts to prove that specific neuropsychological deficits play this role in children with ADHD and their unaffected family members have been unsuccessful or limited at best (115).

An example of the genotype-phenotype linkage approach is Barkley and colleagues' study of the clinical phenotypes associated with identified susceptibility genes in children with ADHD and controls enrolled in the Rochester Longitudinal Study (158). The investigation included a wide spectrum of behavioral and neuropsychological measures and identified a group of children with ADHD that demonstrated numerous behavioral main effects associated with a heterozygous DAT1 polymorphism. This group was distinguished by more severe and pervasive behavioral problems and consequences, whose effect size increased from childhood into adulthood, whereas neuropsychological tests of executive function did not associate with susceptibility genes or with distinguishing behavioral symptoms (158). Barkley makes an argument for studying the "extended phenotype" of ADHD, which he describes as the distal effect of the genotype on social relations, family, and occupational performance. Barkley conceptualizes this "extended phenotype" as being a genetically and biographically relevant endophenotype, determining the life trajectory with at least as much validity as endophenotypes identified by specific neuropsychological constellations.

In summary, the molecular genetics of ADHD supports polymorphisms in dopaminergic transporter and receptor genes, but also implies involvement of other neurotransmitter systems. Phenomenologically defined "endophenotypes" are sought as heritable mediators between genotype and phenotype to explain the heterogeneity of ADHD, but so far are only theoretical constructs. The available data does not support a unitary cause for ADHD but indicates significant polygenetic heterogeneity (159).

18.1.7.2. Physical Environmental Factors

There are many studies demonstrating the effect of early environmental adversity and influences on developmental outcome (23, 90). ADHD symptoms are frequently embedded in a spectrum of cognitive, behavioral, and physical sequelae that are strongly mediated by psychosocial and genetic variables. The following section briefly outlines the most salient environmental factors that have been etiologically associated with ADHD. Based on current knowledge, many cases of ADHD and associated neurodevelopmental disorders could be prevented or mitigated with individual as well as public health interventions.

Factors that are unequivocally associated with the etiology of ADHD are maternal smoking and alcohol use during pregnancy as well as exposure to other environmental toxins, nutritional deficiencies, prematurity, and maternal stress. However, any agent that crosses the blood-brain barrier may affect neurodevelopment. Exposure levels that have no effects in adults may have a significant impact on the developing brain. Direct behavioral effects of single agents are difficult to disentangle from the interaction with genetic, other environmental, and socio-familial factors that are frequently involved (160).

18.1.7.2.1. Prenatal Smoking

Epidemiologic and animal studies provide strong support that in-utero exposures to maternal smoking and alcohol are associated with increased risk for persistent behavioral and cognitive effects in the offspring. Smoking occurs in up to 25% of US pregnancies and increases the risk for ADHD by a factor of 2.5–3.5, when corrected for other biological and psychosocial variables (161). Most epidemiologic studies have focused on ADHD-combined type and externalizing disorders and found a strong association with prenatal smoking and nicotine exposure (162), but a careful case-control study of 100 middle-class children with ADHD-Inattentive type found an odds-ratio of 3.44 for ADHD if mothers smoked more than 10 cigarettes/day compared to mothers who did not smoke. Smoking was also associated with lower IQ scores and an increased rate of anxiety disorders in this nonreferred cohort. There was a higher prevalence of mothers with ADHD in the smoking group, demonstrating the cumulative risk of environmental and genetic factors (163).

Smoking has developmental and morphologic effects through multiple pathways, including increased CO, decreased oxygenation, cadmium accumulation, vasoconstrictive, and nicotinergic effects. The effect on the brain occurs through nicotinic effects on cholinergic neurotransmission, and on neuronal migration, replication, and differentiation early in brain development (164). Smoking alters the maternal HPA-axis and increases fetal cortisol exposure, which affects neurotransmission in cortical, hippocampal, and limbic systems, and has been shown to increase fetal ACTH, which has long-term effects on stress reactivity and behavior of the offspring (165). Increased prenatal cortisol exposure is associated with long-lasting behavioral effects that

include not only ADHD but anxiety and depression (166). Genetically mediated susceptibility to the effects of prenatal smoking has been demonstrated by the increased prevalence and severity of ADHD in children with both DAT1 and DAT4 polymorphisms who were exposed to prenatal smoking as compared to exposed children with either or no polymorphism (167).

18.1.7.2.2. Prenatal Alcohol Exposure

The teratogenetic effects on multiple organ systems of prenatal alcohol exposure, which is estimated to occur in 20–30% of pregnancies in the US, are well known (168). It is estimated that 2–5% of younger school children in the United States and Western Europe have Fetal Alcohol Spectrum Disorder (a composite of full-blown Fetal Alcohol Syndrome, Alcohol Related Neurodevelopmental Disorder, and Alcohol Related Birth Defects) (169). Alcohol affects neuronal migration, myelination, and neuronogenesis. Direct behavioral teratogenicity is demonstrated in animal studies showing specific attentional dysfunction with fetal alcohol exposure. Indirect effects are through dysregulation of the maternal HPA-axis and cortisol levels with effects on fetal brain development and function (170–172).

ADHD has been reported in 50–80% of individuals with prenatal alcohol exposure, and usually occurs within a spectrum of significant cognitive and behavioral deficits (173). The neuropsychological profile of FASD is subtly different than in ADHD without alcohol exposure in terms of executive functioning, spatial working memory, encoding, and set-shifting (174, 175). Further clarification of the neurodevelopmental differences between FASD and ADHD may have treatment implications, as stimulants are often less effective in treating attention and impulse control problems in alcohol exposed children (176).

In maternal Alcohol Use Disorder (AUD), the effects of polysubstance use, especially smoking, dose-response effects, genetic susceptibility, cognitive impairment, and nutritional and environmental factors mediate the behavioral outcomes, so that the behavioral risk conferred by the prenatal exposure alone is difficult to determine. Psychosocial confounders, particularly maternal psychopathology and male gender of the child, account for a much higher proportion of the behavioral variance than alcohol itself (168). However, even minimal amounts of prenatal alcohol exposure within an adverse social environment potentiate the behavioral risk when compared to controls. Aggressive and hyperactive behaviors are seen at 7 years of age after as little as 0.5 oz/week of fetal alcohol exposure when other factors are accounted for (168). In a "Children of Twins" study, comparing the offspring of twin pairs that were discordant for alcohol use, Knopik concludes that genetic factors (i.e., maternal ADHD, which leads to maternal AUD) act independently of alcohol exposure, and represent a cumulative risk for ADHD with alcohol exposure (177).

18.1.7.2.3. Environmental Pollutants

The neurotoxic effects of lead and mercury are well researched and include hyperactivity and attentional deficits. Exposure of the developing brain to cadmium (through prenatal and secondary smoking, industrial waste, and diet), manganese (as supplement, in soy products, and as octane enhancer in gasoline), PCBs (the latter affecting thyroid function), and agricultural and household pesticides causes neurobehavioral deficits including hyperactivity and attentional dysfunction, which have been demonstrated in epidemiologic samples as well as in animal studies. Research on the developmental effects of the thousands of other common environmental pollutants is lacking. Environmental pollutants, genetic susceptibility, nutritional deficits, and psychosocial risk factors frequently occur simultaneously and may enhance or modify their interactions, so that it is extremely difficult to determine the effect of single factors (90, 178).

18.1.7.2.4. Nutritional and Micronutrient Deficiencies

Nutritional and micronutrient deficiencies in infants, children, and women of childbearing age have a profound impact on global health and are not restricted to the developing world. Brain, behavior, and cognitive development are affected by both protein-energy malnutrition (PEM) and micronutrient deficiencies during the course of early brain development and are etiologically associated with deficits in cognitive function and ADHD (179, 180). Globally, about 25% of children have stunted growth due to malnutrition, and in the US clinical malnutrition affects about 10% of poor children (181, 182). In a longitudinal study of a Barbadian birth cohort, Galler and Ramsay reported a 60% incidence of persistent ADHD in children followed to at least age 18 years who had protein-energy malnutrition only in the first year of life, but not later, compared to a 15% incidence in controls (183). However, in the developed world, children with systemic disorders that affect feeding or absorption of nutrients, for instance cerebral palsy or celiac disease, may also suffer nutritional deficits that may cause neurodevelopmental compromise. Maintaining appropriate and adequate nutrition during periods of rapid brain growth and neuromotor development is therefore crucial in infants with nutritional deficiencies of all causes.

Iron deficiency is the most common micronutrient deficiency worldwide affecting 1.2 billion people and is most prevalent in infants, children, and women of childbearing age. It is also common in the US: 13% of 1-year-olds, 5% of 2-year-olds, and

9–11% of adolescent and young adult women are shown to have iron deficiency, of which only 2–5% had iron deficiency anemia (184). Multiple studies show attentional, memory, and learning impairment in anemic and nonanemic iron deficiency in infancy, childhood, and adolescence. Iron fulfills multiple roles in brain function, including mitochondrial electron transport, neurotransmitter synthesis, and cortical, and hippocampal development. Iron deficiency in infancy has lasting effects throughout childhood and adolescence, but correction during infancy improves cognitive and behavioral effects. Correction of iron deficiency diagnosed in school-age and older children has also been shown to normalize the cognitive-behavioral effects (185).

Long-Chain-Polyunsaturated essential fatty acids, specifically Omega-3 FAs, have been studied not only in terms of cardiac and immunologic effects but also for their role in brain development and function. Omega-3 FAs are structural elements of cell membranes, neurotransmitters and substrates of signaling molecules, and modulators in the regulation of gene expression and have played a central role in the evolution of the brain (186). Omega-3 FAs cannot be synthesized by the body and are derived entirely from the diet. Marginal or deficient Omega-3 status during pregnancy and in early infancy has been associated with increased susceptibility to bipolar disorder and depression (187). The increased risk for ADHD and schizophrenia in persons born prematurely is thought to be the result of delayed grey matter maturation associated with decreased Omega-3 fatty acid accrual (187). Abnormalities of fatty acid metabolism have been shown in subgroups of children with ADHD who demonstrated symptoms of fatty acid dysfunction, i.e., increased thirst and dry skin (188).

18.1.7.2.5. Other Dietary Factors

18.1.7.2.5.1. Obesity Risks

The well-known worldwide increase in obesity, especially relevant in pregnant women, is associated with an increase in gestational diabetes and metabolic syndrome, which is associated with increased and lasting risk for metabolic and neurologic problems in the offspring. At this time there is no evidence for a direct causal relationship between obesity during pregnancy and ADHD.

Increasing evidence, however, points to a significant association between ADHD and obesity (189). Three mechanisms underlying the association between ADHD and obesity have been proposed: (1) obesity and/or factors associated with it (such as sleep-disordered breathing and deficits in arousal/alertness) manifest as ADHD-like symptoms; (2) ADHD and obesity share common genetics and neurobiological dysfunctions, involving the dopaminergic and, possibly, other systems (e.g., brain-derived neurotropic factor, melanocortin-4-receptor); and (3) impulsivity and inattention of ADHD contribute to weight gain via dysregulated eating patterns. This association was confirmed in a recent study by Cortese et al., which found men diagnosed as children with ADHD were twice as likely to be obese in a 33-year follow-up study compared to men who were not diagnosed with the condition (190).

18.1.7.2.5.2. Food Reactivity and ADHD

Ever since Feingold published his observations in 1977 that a salicylate-free diet originally intended to treat salicylate-induced asthma also improved symptoms of hyperactivity (191), the discussion of a possible dietary role in behavioral disturbance and specifically in ADHD has been highly partisan, with objectivity becoming a victim of beliefs and biases on both sides of the issue. Recent meta-analyses reviewing 35 years of data have done little to clarify the issues (192). Diets purported to reduce symptoms associated with ADHD include sugar-restricted, additive/preservative free, allergen-free (elimination) diets, and a non-Western "healthy" diet high in fiber, folate, and omega-3 fatty acids. Controlled studies failed to confirm the effectiveness of the Feingold additive and salicylate-free diet. Nevertheless, a small subgroup of children do seem to respond adversely to additives and preservatives administered as a challenge, suggesting that combination antigen and additive-free diet may be appropriate for children with sensitivities to food antigens or allergens and to dyes (about 8% of children with ADHD) (192, 193). Atopic children with ADHD have a significantly higher response rate to elimination diets than nonatopic children. Foods most commonly implicated include dairy, wheat, egg, chocolate, nuts, and citrus fruits. Skin tests for allergic reactivity are not reliable, and behavioral improvements may lag 2 weeks after elimination of the offending food (193).

Meta-analysis of 16 studies concluded that sugar does not usually affect the behavior or cognitive performance of children, nor does aspartame or saccharine, although, as was the case with food dyes, there may be a small group of "sugar-responders" for whom aggressive or hyperactive behavior correlate with daily sugar intake. Reactive hypoglycemia is a plausible cause of transient increase in beta activity in fronto-temporal areas, associated with exacerbation of ADHD symptoms, and can be ameliorated by a low glycemic-index diet (193).

The Australian Raine study examined the relationship between dietary patterns and ADHD in a population-based cohort of live births followed until age 14. This study found an association between ADHD and higher intake of fat, sugar, and sodium (the typical "Western" diet), while diets rich in fish, fruits, vegetables, and whole grains ("healthy" diet) were not associated with ADHD diagnosis (194).

The pathophysiological mechanisms underlying behavioral food reactivity are not known. The role of diet and nutrition certainly is not settled at this point and deserves further exploration.

18.1.7.3. Prematurity

The occurrence of premature delivery is itself highly complex and multifactorial. Multiple physical and environmental factors place enormous demands on the premature brain, and even in the absence of significant neurologic or physical sequelae, many children remain small, have mild neurologic dysfunctions or dyspraxia, and "soft" morbidities that nonetheless may have significant effects on cognitive and especially psychosocial function (195). In addition, family factors, such as parental anxiety and overprotectiveness may affect cognitive and emotional development. Children born with low birth weights are at an increased risk for ADHD and other behavioral, psychiatric, and cognitive disorders. Neuronal cell death associated with multiple assaults on the immature brain, as well as reduced essential fatty acid availability, may be some of the causative factors involved. Other factors may be increased maternal stress and cortisol levels. The risk for ADHD was found to be increased by a factor of 2.46 in a meta-analysis of premature outcomes (196), and longitudinal studies found an incidence of ADHD of at least 23% of otherwise neurologically and cognitively intact very low birth weight (VLBW) children at follow-up, although even weights of less than 2,500 g already present an independent risk for ADHD (196). Psychosocial factors mediate the severity of the developmental sequelae on behavior and cognition. Lawson carefully examined focused attention at 7 months of age in neurologically intact VLBW infants and found correlations of focused (as compared to casual) attention with cognitive as well as hyperactivity measures at 5 years of age, with risk mediated by male gender, gestational age, and maternal education (197). Other longitudinal studies have shown strong relationships between VLBW, cognitive deficits, emotional dysregulation, and lower SES at 2 years (198), and internalizing problems, peer rejection, and inattention in late adolescence (199).

In summary, prematurity and low birth weight are associated with an increased risk for ADHD and behavioral-psychiatric disorders in neurologically and cognitively intact children. Risk is mediated by gender, age, and SES/maternal education. Early anticipatory guidance should start in infancy to mitigate psychiatric and behavioral morbidity.

18.1.7.4. Chronic Hypoxia

Chronic, even mild degrees of oxygen desaturation may cause cognitive and attentional dysfunction. Cyanotic Congenital Heart Disease (CHD) and Sleep Disordered Breathing are both relatively common. The evidence is robust that the hypoxia associated with both is causative for ADHD (99). Cyanotic CHD is well known to be associated with neurodevelopmental delays. Sleep disordered breathing, such as in adenoidal hyperplasia or respiratory allergies, causes significant oxygen desaturation, ADHD, and decreased IQ. Seemingly innocuous and mundane factors such as infant seating and carriers may restrict respiratory activity and should be seen as potential sources of harmful oxygen desaturation (99).

18.1.7.5. Psychosocial Factors

As already discussed, psychosocial factors play a pervasive role in the development of ADHD. The stage is set already before birth, in that maternal mental health and stress have direct and indirect physical effects on the fetus, which may last into adulthood. After birth, the responsiveness of the primary caretakers to the infant appears to be the crucial factor that shapes and gives direction to the development of attention, perception, cognition, attachment, emotionality, and beginning sense of self of the infant. This process is beautifully described by Daniel Stern (200) and continues to be validated by infant research. Maternal responsiveness may be fragile or inconsistent: depression, anxiety, ADHD, substance abuse, multiple children, and economic pressures may interfere with the intent or ability to provide the emotional and cognitive stimulation and reciprocity necessary for normal development. Attention deficit may in fact, in some cases, be a deficit of attention. Child factors that may inhibit maternal reciprocity are also significant, such as poor maternal-child temperamental "fit," child illness with increased internal distractibility due to pain or discomfort, sensory overreactivity, etc. Other family environmental factors that contribute to later comorbidities with depression and oppositional defiant behavior may be paternal psychopathology, hostile parenting, and a chaotic family environment. Boys are rated by their parents as being more intentional and in control of their disruptive behavior than girls, and are at higher risk for being the object of hostile parenting and harsh discipline, which may be a factor leading to increased oppositionality in boys already present by preschool age (201). Low SES and family stressors are high risk factors for development of antisocial behavior in hyperactive boys, and predictive of negative adolescent peer group affiliation (gangs) already by kindergarten age (202).

The Fragile Families and Child Wellbeing Study, a multicenter study of almost 3,000 children followed from birth to 3 years, examined the cumulative effect of maternal mental health, substance use, and domestic violence at 1 year after the child's birth on child behavior at 3 years as measured by the Child Behavior Checklist (CBCL) (203). 50% of mothers had at least one adversity factor. Prevalence of child aggression, anxiety, and attention problems were between 18 and 20% in children whose mothers were depressed, anxious, or abused and increased highly significantly with cumulative maternal problems, with anxiety showing the greatest increase. Prevalence rates for all problems were much higher in families below the poverty line and lower SES

than higher SES. However, the effect of increased maternal problems on the children was the same across SES groups (203). This study demonstrates the high correlation with and cumulative effect of maternal and child problems. Unfortunately, there is no information about the factors that were associated with positive child outcomes (about 75%) in this study.

18.1.7.6. Electronic Media

TV viewing during infancy and toddlerhood has been shown in several studies to be associated with significantly increased risk for ADHD by school age (204, 205). TV watching in infants, whose brains are undergoing rapid synaptogenesis, and have high plasticity relative to experience and stimulation, may interfere with normal perceptual and cognitive development, especially in the presence of perceptual or cognitive vulnerabilities. It is also known that adult TV watching decreases the attention given to the child. This may play a significant role in environmental and social deprivation for children whose mothers are depressed and isolated (206). In older children, an association between time spent playing video games, school performance, and symptoms of ADHD inattentive type has been found (207). Swing and colleagues (208) used a longitudinal design to show that the amount of time spent watching TV or playing video games was positively related to greater attention problems. This was true even when earlier attention problems and gender were statistically controlled, ruling out the possibility that the association between screen media use and attention problems is merely the result of children with attention problems being especially attracted to screen media. Screen time was associated with attention problems in both middle childhood and late adolescent/early adult samples (208).

18.1.8. Evaluation

Since the majority of children with ADHD are treated by their primary care physicians, the American Academy of Pediatrics has issued guidelines for evaluation and management of ADHD which are virtually congruent with the preliminary guidelines by the American Academy of Child and Adolescent Psychiatry (6, 7).

Screening for ADHD should be a part of any child's mental health assessment. Any child presenting with symptoms of impulsivity, hyperactivity, and attentional dysfunction should have a thorough evaluation for ADHD. Assessment needs to be based on DSM-criteria and includes information from parents or caregivers, classroom teacher, or other school professionals, regarding the core symptoms of ADHD in various settings, the age of onset, duration of symptoms, and degree of functional impairment. Since ADHD increases and becomes more virulent with psychosocial adversity and comorbidities, information about preceding and ongoing social/familial stressors and family and emotional functioning should be obtained.

18.1.8.1. The Diagnostic Interview

The diagnostic interview with the parents as well as interview with the child, and, if possible, observation in a challenging situation, are central to the evaluation. The parents and child should be interviewed separately in order to allow free expression of concerns, avoid further injury to self-esteem, and divulge confidential information from both. A thorough medical history including prenatal and perinatal and family history is important for the consideration of etiologic factors, rule out medical conditions, and to assess risk for specific comorbidities. Developmental, educational, and daycare information, as well as social history, provide essential contextual information.

The interview with the verbal child/adolescent may lead to sometimes unexpected insight into the child's emotional state, and perception of self, peer, and family relationships and should serve to rule out significant social, thought, or emotional problems.

The physical and neurological examination should be made with respect to ruling out associated or underlying medical conditions, which are, in effect, infrequent. However, in about 50% of children with ADHD one finds indication of mild neurological dysfunction, such as abnormal neurologic soft signs, decreased muscle tone, motor planning problems, and sensory differences, which may significantly affect fine and gross motor activities. These findings are important for treatment planning. Laboratory evaluations are not useful unless clinically indicated.

A short developmental screening session with preschoolers often is a window into behavioral, cognitive, and emotional vulnerabilities. Avoidance, inattention, distractibility, or oppositionality on developmental testing are often signs of developmental incompetence rather than of a primary attention deficit.

18.1.8.2. Behavior Rating Scales

The diagnostic interviews should be augmented with information from school, teachers, and other caregivers and should include standardized ADHD specific rating scales from parents and teachers (ADHD IV, SNAP-IV-R, Vanderbilt ADHD Rating Scales, AcTers, Conners' Rating Scales-Revised), and broadband behavior rating scales that screen for associated behavioral-emotional

dysfunction in the home and school environment (BASC, CBCL Parent, caregiver-teacher report forms). Adolescent self-reports are available for the major screening systems (209). Several of these scales are free and in the public domain and can be downloaded (209). Children with ADHD usually have better behavioral control in structured situations, so that there may be significant differences between classroom, playground, and home behavior. Discrepancies between teacher and parent behavior ratings are common and do not necessarily challenge the diagnosis, but show that different aspects of the underlying condition manifest in different environments. Emotional-behavioral issues may be more pronounced at home, whereas inattention/distractibility is more evident in school. Children with ADHD may be likened to the proverbial "canaries in the coal mine" and quickly display problems with environmental "fit". Children with LD without ADHD usually are not disruptive or inattentive outside of the challenging situations.

Behavior rating scales are important adjuncts in the evaluation process for ADHD but should not be used as the basis for making the diagnosis. It should also be remembered that they reflect subjective evaluations of the child and may be colored by the emotional state, expectations, and experience of the evaluator.

18.1.8.3. Developmental/Psychological Assessments

Since ADHD is defined as a significant discrepancy of attention, impulsivity, and activity relative to developmental age, screening and if indicated evaluation of cognitive-adaptive status, communication-language, visual-motor integration, social-adaptive, as well as hearing and vision should be performed in the child suspected of having ADHD.

A formal psychoeducational evaluation assessing intelligence, memory, executive function, visual-motor integration, and achievement with standard methods may be necessary in the academically or behaviorally underperforming school-age child to rule out learning discrepancies relative to cognitive potential, which may also include giftedness. A psychoeducational evaluation can be performed free of charge by the school system for any child in a given district, provided that there is an indication. Specific speech-language and occupational therapy evaluations may be indicated to rule out a language disorder, which co-occurs in approximately 25% of children with ADHD.

In older students and adults, evaluations become more problematical because of the need to have childhood behavior information (possibly from the patient's parent or sibling) as well as current behavioral descriptors, such as from the spouse or employer.

The evaluation should explicitly identify vulnerabilities and impairments, i.e., academic, social, emotional, behavioral, and comorbidities. However, in addition to impairments, it is important to identify strengths, competencies, talents, and other self-esteem and resilience building factors that may be integrated into the comprehensive treatment plan.

18.1.9. Treatment

ADHD is a chronic disorder, therefore quality of life considerations of the child within his or her family, school, and peer context should be at the center of treatment planning. Similarly to other chronic conditions, a holistic approach needs to include lifestyle as well as medication management. Short-term and long-term treatment goals need to be specified relative to specific target symptoms, and academic and social goals need to be balanced. Educating the child and the family, engaging them as partners, and addressing both child and family generated problems is the first step. It is important to remember that at least 25% of children with ADHD also have a parent with ADHD, and that other mental disorders are increased in these families. Quite frequently, the diagnosis of the child leads to the parent's recognition of their own impairment and seeking treatment for themselves. Comorbidities need to be treated with the same urgency as ADHD, with stabilization of any acute conditions such as manic episodes, given priority.

The treatment plan should consider medication and/ or behavioral therapy as appropriate. Target outcomes should be defined and if not achieved within a given period of time, the diagnosis, comorbidities, compliance, and treatment appropriateness should be re-evaluated. A systematic follow-up needs to be pursued, and target outcomes and adverse effects should be monitored with information gathered from teachers, parents, and the patient.

18.1.9.1. Behavioral and Educational Treatments

Medication management is at the center of ADHD treatment, but supportive interventions should be considered in any child at risk for or with manifestations of ADHD. Intensive behavior management interventions within the school and home setting are shown to be sufficient in decreasing core symptoms in milder cases of ADHD, and should be considered in such cases before pharmacological treatment is begun. Consistent behavior management decreases dosage requirements when medication proves necessary (210), although short-term treatment does not appear to offer any benefit beyond that obtained by optimal medication management (211).

Behavioral treatments are especially relevant in preschool ADHD, where skilled early behavioral intervention may redirect an otherwise high-risk developmental trajectory and medication treatment may not be desired, effective, or associated with unacceptable side effects (212). Behavior management in older children does not change the core symptoms of ADHD, but it changes parenting style and effectiveness. Parenting-family training can give parents the skills to be active and authoritative agents in their children's development and behavior and to avoid the combination of helpless defeatism, hostile parenting, and chaotic overreactivity that gives rise to and maintains externalizing behavior (213, 214).

Parent training and /or developmental preschools may be available through the State Early Intervention or school systems and should be vigorously sought at the earliest possible moment. Providers who deal with young children need to be knowledgeable about state and community resources. Early Head Start, a good daycare, or preschool may provide an emotionally neutral environment, which may relieve stress for the child as well as the family and improve family interactions.

Educational interventions: School children with ADHD without learning disabilities are eligible for individualized accommodations under section 504 of the 1973 Rehabilitation Act which is a civil rights law that prohibits discrimination against individuals with disabilities and emphasizes regular class placement with behavioral and pedagogic modifications. It is unfunded but federally mandated. Children with ADHD and comorbid learning disabilities are eligible for special education and an Individualized Education Plan (IEP) under the federally funded Individuals with Disabilities Education Act, which is mandated to provide more extensive services to children with disorders of learning and encompasses modification under section 504.

Tutoring may be extremely helpful in children with specific LD and ADHD. Being able to read at grade level by third grade is associated with increased resilience in light of other developmental risk factors. ADHD behavior that is highly associated with a learning disability may resolve if the LD is successfully addressed. Social skills interventions for ADHD may be provided within the school setting but usually are obtained privately. Social skills and behavior management training in the context of ADHD summer camps improve core ADHD symptoms as well as social coping and insight and are available in some communities as academic laboratory settings. It is quite obvious that behavior management interventions require more financial and personal cost than medication management. Health insurance frequently does not pay for the intensive parenting counseling that is initially required, and parents must be willing to develop the skills, change their own behavior, and adopt a long-term perspective for success. Behavior management is similar to medication management in that it is effective only as long as it is utilized, i.e., it has no curative potential, but it does, however, teach self-control, social skills, and coping strategies (215).

18.1.9.2. Pharmacologic Treatment

18.1.9.2.1. Stimulants

In 1937 Bradley reported that amphetamine dramatically improved behavior, emotionality, and academic performance in institutionalized children with normal cognition but severely disruptive behavior (216). Amphetamines (AMP) were not routinely used in ADHD until the less potent stimulant methylphenidate (Ritalin) became available in the 1960s. Since then methylphenidate (MPH) has become the most frequently utilized and studied psychotropic agent in children, and stimulants have become the gold standard for treatment effectiveness in ADHD (217). Stimulants are by far the most popular medications for ADHD because of their large margin of safety, effectiveness, short half-lives with easily observed treatment response, and ease of administration. Side effects are low, and there is little attenuation over time.

Improvement of prefrontal cognitive tasks in "normal" as well as ADHD subjects with low doses of methylphenidate is the basis for improvement of clinical symptoms. Stimulants affect norepinephrine and dopamine release predominantly in the prefrontal cortex and fronto-striatal circuits by inhibiting the reuptake, and enhancing the release of these catecholamines at the synaptic cleft, as well as by blocking the dopamine transporter and enhancing extracellular dopamine (147).

Given the neuropathological heterogeneity of ADHD, the effectiveness of stimulants on the core symptoms in the majority of cases is surprisingly simple. Stimulants improve cognitive and academic performance as well as the core symptoms of impulsivity, hyperactivity, and attentional dysregulation. Stimulants are effective in improving ODD and CD symptoms even in the absence of ADHD symptoms (147). Stimulants are effective in all ages starting with preschoolers (218). The effects are similar in children and adults with and without ADHD and are therefore neither diagnostic nor specific. Treatment has been shown to have major effects on quality of life: Stimulant treatment is associated with less grade retention, lower school dropout rates, less absenteeism, lower rates of substance abuse, and improved reading scores (5). Hundreds of randomized short-term trials have shown stimulants to be effective in 50–75% of children with ADHD with relatively few side effects. However, the application of the outcomes of clinical research trials vs. the outcome in community settings is problematic, because clinical research trials have a strong sample bias compared to community conditions, excluding many factors that confound community treatment such as comorbid conditions and poor compliance. The distinction between *efficacy*, as used in controlled clinical research trials, vs. *effectiveness* of a treatment, i.e., the treatment response under usual clinical conditions, should therefore be kept in mind. Quality of life measures should also be considered when assessing treatment response (219).

Compared to the abundance of short-term randomized trials of stimulants, mostly of methylphenidate, comparatively few long-term studies have been completed. The benchmark of long-term clinical trials has been the Multimodal Treatments Study of Children with ADHD (MTA) (220), a multicenter randomized prospective study which compared community (including pharmacological) treatment, intensive pharmacological (mostly methylphenidate), and behavioral treatments alone and in combination with pharmacological treatment, over the course of 14 months in 579 children. The study found that compared to behavioral and community treatments, pharmacological treatment alone was superior to all other conditions in treating core ADHD symptoms. However, combination treatment was more effective than pharmacologic treatment alone in improving associated oppositional/aggressive and internalizing symptoms, especially comorbid anxiety, teacher-rated social skills, parent-child relations, and reading achievement (220). While there has been an explosion of research in neurodevelopmental disorders, mostly in the realm of genetics and neuroimaging, this study remains the foundation of clinical practice.

The community counterpart to the MTA has been the medication arm of the Rochester Epidemiology Project (5, 11). The long-term safety and effectiveness of stimulant treatment in a community setting was investigated in 283 children with research identified ADHD, whose treatment data were available from a median age of 9 years, with a median duration of 33 months and range from school entry until high school graduation. Seventy-three percent showed a favorable response rate to stimulants. About 22% of children had side effects with a higher rate of side effects for dextroamphetamine than MPH (5).

Treatment effects have been studied predominantly in latency age boys, but similar effectiveness in girls, adolescents, and adults has been demonstrated (5, 220). Effects are also similar across subtypes in most studies, with some showing greater responsiveness of the inattentive subtype to lower doses. However, outcomes are not always consistent: other studies show improved hyperactivity and impulsivity with less response of attention problems. The Preschool ADHD Treatments Study (PATS), a combination of blinded randomized and open label study of 1 year's duration in children, age 3–5 years, demonstrated that stimulants are also efficacious in preschoolers, who tended to require lower doses and had an increased incidence of side effects (218).

18.1.9.2.1.1. Stimulant Forms

Methylphenidate, its D-isomer (dexmethylphenidate, Focalin), mixed amphetamine salts (MAS-Adderall) and D-Amphetamine are the most frequently used stimulants and are available in short acting (4 hour), intermediate (8 hour), and sustained release (12 hour) forms. Amphetamines are about twice as potent as methylphenidate. The effect size of stimulants, i.e., the difference between drug and placebo effects, is 0.8–1 and provides a comparison measure between different medications for ADHD. Dosage and frequency requirements are highly individualistic and depend only in part on the size and weight of the child. It is therefore recommended to start low and titrate upward depending on treatment goals. Dosage for MPH preparations range from 0.3 to 2 mg/kg/day, with half of that for Focalin (D-isomer of MPH) and amphetamine preparations (221).

When beginning stimulant treatment, it is important to consider the target symptoms, i.e., under what conditions does the child need medication and for how long (school, homework, sports, etc.)? Timing is important also in observing the child for effects and side effects at peak level as well as possible withdrawal/rebound symptoms at trough, and allows for adjustment of medication to daily routines, meals, and bedtimes.

Short-acting MPH/MAS/D-amphetamine onset is after about 30 minutes and duration of effect is about 3–5 hours. Short-acting methylphenidate is now available in liquid form for children who have difficulty swallowing pills. Intermediate preparations (Metadate CD, Ritalin LA) onset is after about 1 hour and duration about 8 hours. Sustained release preparations (OROS-Methylphenidate/Adderall XR MAS/lisdexamphetamine) have an onset of about 1 hour, with a duration effect of up to 12 hours. Intermediate and long-acting preparations vary with respect to the immediate release component, which is 50% and 25% respectively, and may need an initial low-dose short-acting "booster". The type of delivery system, whether beaded in capsules, in a wax matrix or osmotic release form, affect absorption and availability. Once per day sustained release dosing is desirable because it improves compliance, is less conspicuous, has less abuse potential, and the effect is smoother with less "roller coaster" response from changes in levels (222–224).

A MPH dermal patch (multipolymeric adhesive system, Daytrana), releasing 10–30 mg of MPH over a 9 hour period, is approved for children 6–12 years and can be practical in children who are not able to take oral medications. It has been found safe and effective in short-term studies (225). There are anecdotal reports of local and systemic sensitization, however, which is a risk with all topical medications. Heat sensitivity of the patch needs to be considered.

Dosage requirements of stimulants vary with the individual as well as with the context. Children with prenatal substance exposures often require higher stimulant doses and are more difficult to manage medically. Behavioral interventions modify medication effects. Pelham has observed that stimulant effectiveness plateaus at lower doses under conditions of consistent behavior management and a structured environment, whereas higher doses are more likely to be required in less optimal circumstances (210).

Maintenance of a structured, daytime routine with adequate nutrition and sleep, as well as physical exercise, (which in some studies has shown to improve executive function), provides the physical requirements to optimize medication effects.

18.1.9.2.1.2. Stimulants in Comorbid Conditions

Stimulants are effective for ADHD symptoms in multiple comorbid conditions including sequelae of brain injury and other static encephalopathies; in ADHD symptoms associated with Autism Spectrum Disorders; and in mental retardation with ADHD. Careful stimulant treatment may be very effective and is not contraindicated in well-controlled seizure disorders with comorbid ADHD (226). In ADHD with comorbid tic disorders, stimulants are not a contraindication when carefully monitored (227), but should be discontinued if tics worsen or do not stabilize with alpha-adrenergic agonists (clonidine, guanfacine) (228), which have shown effectiveness in tic disorders.

Stimulants may not be as effective in treating core symptoms of ADHD when there are significant comorbidities with anxiety or mood disorders. Under these conditions, single or combination treatments with atomoxetine have been shown to be effective in some patients (229). Alternatively, SSRIs, buproprion, or tricyclic antidepressants may be helpful. The tricyclics have significant alpha-adrenergic effects but require very close monitoring because of cardiac toxicity. Stimulants should not be used in severe anxiety disorders. There is some indication that stimulants may precipitate manic episodes in previously not identified bipolar disorder, but may be used in ADHD/bipolar co-occurrence after mood stabilization (230).

18.1.9.2.1.3. Stimulant Side Effects

Stimulants have a high margin of safety. Most side effects are a result of CNS-action of stimulants and therefore behavioral or emotional. However, stomach and headache are frequent, usually mild, and of short duration. Absorption is affected by calcium and citric acid, but not by other foods, so that stomach aches can be ameliorated when stimulants are taken with a meal. Appetite suppression is frequent and chronic, but can be compensated with a good breakfast, dinner, and bedtime snack. Children should have a snack when levels are declining after short or intermediate dosages in order to prevent the convergence of hunger and rebound/withdrawal symptoms. Sleep problems are often associated with ADHD, but stimulants may also interfere with sleep if given too late in the day. Sleep hygiene, melatonin or clonidine, and a carbohydrate- rich bedtime snack may help with sleep onset. Lack of adequate and restful sleep may worsen ADHD symptoms and emotional reactivity.

Stimulants are activating and therefore may increase anxiety. Rarely stimulants may precipitate a psychotic reaction (231). Social withdrawal, emotional and activity constriction, and obsessive-compulsive behavior may be a sign of overmedication and should lead to dosage adjustment. In some children, increasing hyperactivity may be a sign of overmedication rather than undermedication. "Roller coaster" and withdrawal effects are seen more often on short-acting than intermediate or long-acting stimulants. They are usually of short duration and consist of whininess, sadness, and irritability. A nutritious snack and "quiet time" or physical activity usually can bridge this period. However, some children may withdraw or rebound with significant aggression, which may necessitate a stimulant switch or alternate medication or augmentation with an alpha-adrenergic agonist (clonidine, guanfacine). It is important to observe behavioral changes with regard to expected peak or declining levels.

Transient tics may occur as a result of stimulant treatment and usually resolve after change in dosage, discontinuation, or change to alternative drugs (228). Contrary to public opinion, stimulants do not promote substance abuse and in fact, show a protective effect to nonalcohol substance use when compared to persons with ADHD who have not been treated (232).

Occasionally stimulants cause increased diuresis and enuresis due to a minor diuretic effect. Priapism can occur. Bone-marrow suppression and leukopenia occur very rarely. There are no established recommendations regarding monitoring of CBC.

18.1.9.2.1.3.1. Cardiac Effects

Stimulants do have cardiovascular effects, and may decrease heart rate and increase diastolic and systolic blood pressure at standard therapeutic doses (233). Although cases of sudden cardiac death have been reported, increased risk is not supported by clinical data (234): sudden death on Adderall is calculated as 0.5:100,000 patient years as compared to 1.3–8.5:100,000 patient years in the general pediatric population. Sudden death in children is most often caused by fatal arrhythmias due to congenital heart diseases, such as long QT syndrome and hypertrophic cardiomyopathy. Five of the 12 reported cases of sudden cardiac death while taking stimulants had unrecognized underlying structural heart disease. While screening for a family history of sudden cardiac death is prudent, the American Academy of Pediatrics and American Academy of Child and Adolescent Psychiatry no longer recommend the routine use of EKG before beginning stimulant therapy (235). The combination of the cardiotropic alpha-adrenergic drugs and stimulants should be carefully monitored for hypotension and arrhythmias or bradycardia.

Tricyclic antidepressants and MAO inhibitors should not be given with MPH because the latter increases TCA levels, increasing the risk of cardiotoxicity or hypertension. Stimulants are contraindicated in significant arrhythmias, hypertension, liver disease, severe anxiety, and drug-seeking behavior (234).

18.1.9.2.1.3.2. Stimulants and Growth

The effect of stimulants on growth has been a topic of controversy for some time. Although the Preschool ADHD Treatment Study, which monitored children over 12 months of stimulant treatment, found that linear growth decelerated by 20% of

expected growth in 1 year, with a moderate effect on weight (236), studies in older children show insignificant decreases in growth velocity and weight gain on MPH and MAS as well as on long-acting stimulants in school-age children (237). No information is currently available on the long-term growth trajectories of children started on stimulants as preschoolers; stimulant use in preschoolers needs precise justification. Depending on symptom severity, continuous year-round dosage may be warranted, but in cases of growth plateau, drug holidays can provide crucial opportunities for catch up growth. Although growth suppression is independent of weight loss, in very young children, careful management of dosing times to provide for adequate mealtimes is important to allow adequate nutrition.

18.1.9.2.2. Nonstimulant Medications

Fifty to seventy percent of children respond to stimulants, but alternate medications and nonpharmacological and supportive interventions are necessary for the other 30–50% who do not.

18.1.9.2.2.1. Atomoxetine

Atomoxetine (Strattera) is a norepinephrine reuptake inhibitor. Its benefits include no abuse potential, no motor or tic activation, and it does not interfere with sleep. However its effect size is significantly less than that of stimulants at 0.6–0.72. Full effect is reached after 4–6 weeks (and possibly longer) of therapy. Dose is 0.5 mg/kg/day in one or two divided doses, effects last for 24 hours, which is very useful for children who have significant attentional problems in the morning. Atomoxetine may be more effective in treating core symptoms of ADHD in stimulant naive children rather than in those previously on stimulants. It may be used in conjunction with a stimulant when longer duration without sleep deprivation is needed. Atomoxetine is showing some advantage in children with ADHD and comorbid anxiety or depression; however, comedication with a stimulant may be necessary to improve core symptoms. Side effects are appetite suppression, GI upset, somnolence, occasional irritability, and aggression. Cardiac side effects, i.e., increased blood pressure and tachycardia have been reported. Suicidal ideations have been reported in 5/1357 children on atomoxetine, leading to a Federal Drug Administration black box warning (238).

18.1.9.2.2.2. Modafinil

Modafinil (Provigil) (221), originally indicated for narcolepsy, is not FDA approved for treatment of ADHD. Its mechanism of action is thought to be through diffuse cortical activation via adrenergic systems as well as through thalamic and reticular activation system attenuation. It also has a low abuse potential. It has an effect size of 0.7 after titration to a full dose after 7–9 days to an average dose of 300–400 mg/day. Side effects are headache, appetite suppression, nervousness, and sleep disturbance.

18.1.9.2.2.3. Alpha-2 Adrenergic Agonists

The antihypertensive drugs clonidine and guanfacine (221) inhibit catecholamine release, affect basal adrenergic tone, and improve prefrontal cortex function. They may be used alone or in conjunction with stimulants and are effective in impulsivity, hyperactivity, aggression, especially in young children, and in treating ADHD associated sleep disorders (239). Guanfacine is effective in tic disorders with ADHD, alone or in combination with stimulants (228). Behavioral effectiveness may not be observable for 4–6 weeks. Side effects of sedation and irritability may be significant initially, more so with clonidine than guanfacine. The potential for hypotension and bradycardia require EKG and blood pressure monitoring. Both medications are available in long-acting formulations (marketed as Intuniv and Kapvay) for once-daily dosing.

18.1.9.2.2.4. Antidepressants

The tricyclic antidepressants desipramine and nortriptyline have excellent effectiveness in improving the core symptoms of ADHD, and ADHD with comorbid tic disorders due to their noradrenergic effects (148). However, they have a narrow margin of safety because of their significant accumulation in cardiac as well as brain tissue, with a significant risk of cardiotoxicity resulting in conduction abnormalities, increased heart rate, and increased blood pressure. Effects are observed after about 4 weeks, dosages must be carefully titrated, and blood levels and cardiac response monitored with frequent EKGs. TCAs have significant anticholinergic side effects, often cause weight gain and gastrointestinal problems. Their use for ADHD has decreased sharply after reports of sudden cardiac death in several children (240).

Bupropion is an antidepressant with noradrenergic and dopaminergic neurotransmission effects. Several double-blind controlled studies have showed some efficacy in treating children and adolescents for ADHD, though results were less robust than those typically seen with stimulants (241–245). Caution should be used in those at risk for seizures.

18.1.9.3. Nonpharmacologic Treatments of Core ADHD Symptoms

Nonpharmacological treatments may need to be considered when medication response is associated with significant side effects, lack of improvement, or when pharmacologic treatment is undesirable for other reasons. Nonpharmacological treatments that have been subjected to accepted research trials are biofeedback paradigms and dietary interventions in selected populations. These interventions may be effective by themselves or within a multimodal treatment context. Many alternative and complementary treatments of ADHD that reflect cultural as well as scientific approaches are in use and cannot be discussed here. Given the fact that there are many pathways that lead to ADHD, heterogeneity of effective interventions is conceivable. A critical but open mind should be maintained toward novel approaches.

18.1.9.3.1. Biofeedback Modalities

Neurofeedback is a method of self-regulation that has been widely clinically utilized in combination with or as an "alternative" to pharmacologic treatment, especially in Australia and Europe. Neurofeedback is based on the pathophysiological model of cortical hypoarousal, which is demonstrated in neuroimaging modalities and may also be observed in quantitative EEG studies by the relative dominance of slow (theta) waves over alpha and beta waves in the frontal and prefrontal cortex in the majority of patients with ADHD (142, 143). Suppression of slow and increased production of faster brain-wave activity is achieved by operant conditioning using differing EEG feedback protocols that are determined by ADHD subtype. Thirty to fifty sessions are usually required. The results of several controlled group studies indicate that EEG biofeedback may be effective in treating the core behavioral symptoms as well as successful on the continuance performance test (CPT), cognitive, emotional, and academic performance in ADHD, either alone or in conjunction with stimulants. Improvements in these parameters has allowed reduction of stimulant doses and has persisted up to 1 year after conclusion of the NF treatment and after complete discontinuation of stimulant treatment (246). Randomized double-blind placebo controlled studies have shown similar results on behavioral and neuropsychologic parameters as well as activation of cortical areas known to be underactive in ADHD. Strehl and colleagues reported a controlled study of EEG-biofeedback in self-regulation of Slow Cortical Potentials with persistent improvement in ADHD core symptoms as well as neuropsychological parameters (247). However, methodological questions remain whether the actual agents of change are the biofeedback paradigm or contextual factors (142).

Significant improvement of hyperactivity with Actigraph-biofeedback has also been reported (248). The interactive metronome (249), a biofeedback paradigm based on synchronization of hand and foot movements with auditory stimuli, originally used in enhancing performance in sports, and widely used in movement disorders, has been shown to improve attentional and academic performance in one double-blind placebo controlled study (249).

18.1.9.3.2. Elimination Diets and Dietary Supplements

Based on the research of the last 35 years, it is difficult to dismiss summarily the findings that some children with ADHD respond favorably to individualized elimination diets (192). Behavioral improvement is more likely with appropriate elimination diets in individuals with atopic histories, family history of migraine, and a family history of food reactivity (192); younger children also seem to be more responsive. Specific target behaviors may include sleep and mood disturbances in addition to typical ADHD symptoms. Proven or suspected antigens as well as food colorings and preservatives should be eliminated for at least 3 months with monitoring of target behaviors. Challenges should then be tried for the individual suspected foods. A partial blinding may be carried out by not informing teachers or therapists. Nutritional counseling and referral to support groups is often advisable. The family must understand that dietary management requires a great deal of commitment on a long-term basis. Dietary management should be under the direction of a knowledgeable physician.

Children with ADHD have been found to have low levels of long-chain polyunsaturated fatty acids in their plasma and red blood cells, compared with controls (192). The double-blind placebo controlled Oxford-Durham study found that Omega 3:6-essential fatty acids (EFA) supplementation improved manifestations of ADHD as well as reading and spelling in children with Developmental Coordination Disorder, reading disorders, and associated ADHD symptoms, without affecting motor coordination (250). Other studies have failed to show any benefit from Omega-3 supplementation (251). For review see (252).

Low serum ferritin has been correlated with baseline inattention, hyperactivity, and impulsivity, and also with the dose of amphetamine required to optimize clinical response, indicating that iron supplementation may be worthy of further exploration. Some studies have also shown benefit in ADHD from zinc supplementation (192).

18.1.9.4. Prevention

Considering the vast implications of ADHD for the individual as well as for society, and the fact that a good deal is known about risk factors for ADHD, it is surprising that very little emphasis is placed on prevention. Addressing the socioeconomic adversity within which ADHD and other neurobehavioral disorders flourish is a challenge to public health and political institutions.

However, the practitioner in primary care as well as the mental health provider who deals with children, parents, and women of childbearing age has the opportunity and obligation to inform about prevention, early intervention, and steps that can be taken to modify known genetic and environmental risk factors, as well as to treat manifest developmental and mental disorders. Prevention should address prepregnancy and pregnancy physical health, optimize chronic illness management, stress avoidance of toxins (i.e., smoking, lead, alcohol, mercury), and emphasize optimal nutrition. Essential fatty acids (EFAs) occupy a special role because they are essential for fetal neurodevelopment, may be protective for mood disorders, but are seriously deficient in the average American diet, which provides only 20–60% of the recommended daily dose. Mental health factors frequently are interactive with physical factors, and depression, isolation, and psychosocial stress contribute to adverse pregnancy outcome and fetal neurodevelopmental problems. Postnatal preventive measures again include optimal nutrition for the infant, child, and lactating mother, and enabling and maximizing caretaker-child responsiveness and interaction. This includes early recognition and treatment of postpartum depression and of the overall high incidence (20%) of maternal depression. Anticipatory guidance includes supporting the parent's understanding of the infants and child's developmental needs and capabilities, and addressing ADHD in parents and other family members. Early interventions for developmental and behavioral problems should be encouraged rather than adopting a "wait and see" attitude. Avoiding active and passive TV and video exposure during the first 2 years and limiting it afterwards, as recommended by the American Academy of Pediatrics, promoting social and physical activity, and providing parental and caretaker responsiveness may not eliminate ADHD, but provide the background for optimal emotional and cognitive development within the constraints of genetic predispositions, and mitigate the risk for development of psychiatric comorbidities.

In the child that is at high risk for or has manifest ADHD, supportive interventions are important for improving self-esteem and peer and family relationships, which can buffer the negative effects of ADHD on psychosocial functioning. Peer friendships, extracurricular activities (sports, arts, scouting, etc.), social-altruistic engagement, and parent involvement in school activities improve self-esteem and self-concept. An adult mentor outside of the nuclear family ("Big Brother/Sister", teacher, godparent, etc.) can be crucial especially for adolescents and especially in families that have multiple risk factors (253). Family activities and rituals, as well as stable daily routines help to provide the external emotional and temporal stability that is often very fragile in children with ADHD.

18.2. Oppositional Defiant Disorder (ODD)

ODD is one of the most commonly encountered clinical disorders in children and adolescents, characterized by a persistent pattern of angry or irritable mood, argumentative or defiant behavior, and vindictiveness that exceeds behavioral expectations for the individual's developmental level, gender, and culture. The severity of the disorder is linked to the pervasiveness of the behaviors across multiple settings.

18.2.1. Epidemiology

Prevalence studies have indicated a rate of 1–16%, depending on criteria and assessment methods used, with an average of 3.3%. There is a slight predominance in boys, with a male-female ratio of 1.4:1 prior to adolescence. Prevalence is consistent across cultural and ethnic groups, and onset is usually by age 8 (254).

18.2.2. Etiology

There is no unifying theory of etiology for ODD. High levels of emotional reactivity and poor frustration tolerance are temperamental factors associated with development of ODD. Harsh, inconsistent, and neglectful parenting practices are often implicated in causal theories. Neurobiological markers have not successfully distinguished ODD from Conduct Disorder. Baseline underarousal has consistently been found in youth with ODD, and exogenous biological factors may be implicated. Attachment theorists have suggested that oppositional behavior can develop in the face of an unresponsive parent. Aggressive children underutilize pertinent social cues, misattribute hostile intent to peers, generate fewer solutions to problems, and expect to be rewarded for aggressive responses. Although environmental factors such as poverty, lack of structure, and community violence have been posited as contributing factors; in fact, socio-economic status appears to be responsible for <1% of variance. However, intrafamilial social processes such as lack of parental supervision, lack of positive parental involvement, inconsistent discipline practices, and outright child abuse have been consistently implicated in the pathogenesis of disruptive behaviors (255).

18.2.3. Comorbidities

About 14% of children, adolescents, and adults with ODD also meet criteria for ADHD; 14% have a comorbid anxiety disorder, and 9% have comorbid depression (256). Persons with predominantly angry/irritable mood symptoms are at increased risk for mood disorders, while predominantly defiant/vindictive individuals frequently progress to conduct disorder. Learning disabilities, language disorders, and substance use disorders are also considered common comorbidities, although specific numbers are lacking. Oppositional behavior is sometimes used to manage anxiety, and is also frequently observed in autism spectrum disorders (255).

18.2.4. Prognosis

Approximately 67% of children will no longer meet criteria for diagnosis after 3 years. Early onset of symptoms is associated with worse prognosis, and 30% of these children progress to conduct disorder. Comorbidity with ADHD confers worse prognosis, with a greater range and persistence of problem behaviors, higher rates of peer rejection, and worse academic performance.

18.2.5. Treatment

18.2.5.1. Parent Training

The greatest degree of evidence supports parent management strategies targeting social skills, conflict resolution, and anger management, and training to improve parents' ability to handle disruptive behavior (257). The basic principles include: (1) reduce positive reinforcement of disruptive behavior; (2) increase reinforcement of prosocial and compliant behavior; (3) apply consequences for disruptive behavior; (4) make parental response predictable, contingent, and immediate. These interventions address the coercive response to parental demands and ways parents unwittingly reinforce the child's noncompliance (258).

18.2.5.2. Other therapies

Evidence supports programs such as Head Start, home visitation to high-risk families, and school-based programs as having a modest preventative effect for ODD (255). For severe cases, day treatment and residential treatment facilities may be necessary, always giving preference for the least restrictive treatment setting. Short-term, "inoculation" interventions (such as "boot camps") have not been shown to be effective and can even reinforce a fear-aggression reaction if children are exposed to frightening situations without providing behavioral alternatives (255).

18.2.5.3. Role of Medication in ODD

In the event of comorbid ADHD, treatment with stimulants or nonstimulants may improve oppositional behavior. Both typical and atypical antipsychotics have been shown to be helpful for treating aggression (259).

18.3. Intermittent Explosive Disorder

Intermittent Explosive Disorder, or IED, consists of a pattern of aggressive outbursts that typically last for only a few minutes and can involve either frequent (i.e., twice weekly) verbal or nondestructive physical aggression, or at least three outbursts of aggression that result in property destruction or physical injury over the course of a year. The outbursts are impulsive (rather than premeditated), usually come "out of the blue" or in response to a minor provocation, and appear grossly out of proportion to the alleged trigger (260).

Five to seven percent of the US population is estimated to display recurrent, problematic, impulsive aggression (261). Age of onset is typically in adolescence, and the course of the disorder tends to be relatively stable for up to two decades. Research has identified serotonergic abnormalities, especially in the anterior cingulate and orbitofrontal cortex, with higher amplitude amygdala response to anger stimuli on fMRI than in controls (260). There appears to be a higher prevalence in first-degree relatives (32%) and twins, suggesting a substantial genetic influence for impulsive aggression (262). Significant psychological correlates have also been found, with affected individuals demonstrating elevated relational aggression, more hostile attribution bias, greater affective lability and affective intensity, and a greater degree of immature defense mechanisms such as acting out, dissociation, projection, and rationalization. A history of trauma, especially in childhood, is frequently elicited (260).

The disorder is frequently comorbid with mood, anxiety, substance use, and personality disorders, as well as being frequently seen in individuals with ADHD (17.2%), ODD (21.6%), or Conduct Disorder (19.3%) (260). An IED diagnosis is not compatible, however, with a diagnosis of Disruptive mood dysregulation disorder, which always has onset in childhood and is characterized by a persistently negative mood state, not just during aggressive outbursts.

Preliminary medication trials with fluoxetine, divalproex, or oxcarbazepine have all been shown to reduce impulsive aggression, as has CBT, although additional research is needed regarding treatment of this disorder (260).

18.4. Conduct Disorder

18.4.1. Definition

Conduct disorder consists of a constellation of symptoms whereby rights of others are repeatedly violated. This comprises serious aggressive and antisocial behaviors such as bullying, initiating physical fights, physical cruelty to people and animals, fire setting and deliberately destroying others' properties, stealing, and serious violations of parental and school rules. This disturbance in behavior causes clinically significant impairment in social, academic, or occupational functioning.

18.4.2. Epidemiology

Three to five percent of preadolescent boys and 6–8% of adolescent boys meet criteria for conduct disorder. Boys outnumber girls 4:1 prior to adolescence to about 2:1 in adolescence (263). The Ontario Child Health Study indicated that for ages 4–16 years, 5.5% suffered from conduct disorder. Life-course persistent (LCP) versus adolescence-limited antisocial behavior are two examples of developmental pathways to antisocial or violent behavior.

LCP accounts for 5–8% of the offender populations which have an early onset involving serious crime and continue into adulthood. Twenty-five percent of adolescence-limited offenders continue their delinquent behavior into adulthood. These late starters may offend with peers but behave well in school and at home (264).

DSM-5 distinguishes between three subtypes of conduct disorder based on the age of onset. In childhood onset type, there is onset of at least one criterion characteristic of conduct disorder prior to age 10 years. These children begin showing mild conduct problems as early as preschool or early elementary school and their behavioral problems tend to increase in rate and severity throughout childhood and into adolescence.

The second type is the adolescence-onset conduct disorder in which there is absence of any criterion characteristic of conduct disorder prior to age 10 years. These youth do not show any significant behavioral problems in childhood. It is with the onset of adolescence that they begin to exhibit significant antisocial and delinquent behaviors.

Unspecified onset can be used when criteria for conduct disorder are met, but there is not enough information to determine if symptom onset was before or after 10 years of age.

Additional specifiers indicate a lack of prosocial emotions, such as remorse or guilt, lack of empathy, lack of concern about performance, and shallow or deficient affect.

18.4.3. Genetics

The Iowa Adoption cohorts have demonstrated that the degree of adoptee aggressiveness and conduct disorder has a significant genetic component. Cadoret et al. (265) followed the lead that the neurotransmitter serotonin or polymorphisms in the serotonin transporter gene (5HTT) were important sources of variability in "externalizing" behaviors such as aggression, conduct disorder, and attention deficit hyperactivity disorder. They genotyped a subgroup of adoptees ($n=87$) at high risk of these disorders with respect to the serotonin-transporter-linked promoter region (5HT-TLPR) polymorphism and used ordinal logistic regression to conduct an associated study. One type of interaction with the long variant of 5HT-TLPR increased externalizing behaviors in individuals with antisocial biologic parentage. A second interaction with one or more 5HT-TLPR short variants appeared to increase externalizing behaviors in conjunction with a genetic diathesis for alcoholism. It was also demonstrated that male individuals with a short variant were more likely to have higher symptom counts for conduct disorder, aggression, and ADHD. Their results supported the hypothesis that gene-biological family history interactions are involved in the externalizing behaviors studied.

Dick and colleagues (266) did a genome-wide screen for genes influencing conduct disorder. Their results suggest that regions on chromosomes 19 and 2 may contain genes conferring risk to conduct disorder. Interestingly the same region on chromosome 2 has also been linked to alcohol dependence in this sample (266). Childhood conduct disorder is known to be associated with the susceptibility for future alcohol problems. These findings suggest that some of the genes contributing to alcohol dependence in adulthood may also contribute to conduct disorder in childhood.

18.4.4. Risk Factors

There are several risk factors that contribute to the outcome of conduct disorder (267). Genes and intergenerational transmission and familial aggregation of antisocial behavior play a part in the development of conduct disorder. Studies have shown that there is an aggregation of disruptive and antisocial behaviors in families. It has also been demonstrated that a history of parental antisocial behavior disorder is associated with a preadolescent onset of conduct disorder. Cortisol levels were lower among sons of fathers with a childhood history of conduct disorder that progressed to antisocial personality disorder than those without a history. Testosterone has also been associated with aggression, including the early onset of aggression (267).

There is a link between underarousal of the autonomic nervous system and conduct disorder. Evidence has shown an association between low heart rate and conduct disorder and higher heart rate and anxiety, also seen in girls. A higher skin conductance has been found in individuals who avoid criminal behavior despite a paternal history of criminality. It has been hypothesized that these are markers of anxiety that play a role in inhibiting children from engaging in disruptive or criminal behavior (267).

Maternal smoking has also been linked to conduct disorder in boys, particularly with onset before puberty. Parent substance abuse, pregnancy, and birth complications have also been linked to disruptive behavior disorders. High levels of environmental toxins, such as lead, have been associated with greater parent and teacher ratings of aggressiveness, delinquency scores, and greater somatic complaints.

It has been seen that by adolescence, delinquent peers contribute greatly to the spread of delinquency and antisocial behaviors. Youth with conduct disorder are frequently rejected by prosocial peers and they tend to become more attached to youth with longer criminal histories. Males are more likely to be arrested for violent crimes and females for truancy, prostitution, running away, or underage drinking (264).

Potential links have been identified between temperament, antisocial behavior, and conduct disorder. Two temperamental types have been found. Type 1 is the callous unempathetic type, which appears to be unrelated to parenting and family context. Type 2 is the reactive, externalizing, antisocial child and is often associated with conduct disorder and negative parenting (268).

A modest to moderate link has been suggested between empathy and prosocial behavior. Boys and girls with conduct disorder are lower in empathy and the identification of interpersonal cues than those without conduct disorder.

Low IQ is associated with low achievement and school failure, both of which are related to later antisocial behavior. High verbal IQ was related to a decrease in conduct disorder symptoms over time only for boys in a clinic-referred sample without a parent with antisocial personality disorder (267).

Reading disorder may be associated with abnormal language processing within the left temporal cortex and has been linked to conduct disorder (267).

There has been a strong association between poverty and crime and disruptive behaviors. Disruptive behaviors among both boys and girls have been linked with poor and disadvantaged neighborhoods. Several other community factors are predictive of later violence such as availability of drugs, exposure to violence, and low SES. Youth in late adolescence with conduct disorder reported experiencing greater stress and engaging in more maladaptive coping strategies (267).

18.4.5. Protective Factors

Findings have indicated that outcomes are mediated by the interaction between protective elements and risk factors. Protection against antisocial behaviors is determined by high IQ, easy temperament, the ability to relate well to others, good work habits at school, areas of competence outside school, and a good relationship with at least one parent or other important adult. A school atmosphere that fosters success, responsibility, and self-discipline as well as selection of a nondelinquent peer is vital in protecting against continuing criminal activity (269).

18.4.6. Neurobiological Findings

Many previous brain-imaging studies in adults with antisocial behavior have shown functional and morphologic brain abnormalities. Sterzer et al. (270) used functional magnetic resonance imaging to test whether the impaired emotional responsiveness of adolescents with antisocial conduct disorder would be reflected by abnormal neural responses to negative affective stimuli. They compared brain activations in response to passive viewing of affect-laden pictures in conduct disorder patients to those in normal control subjects. The main effects for negative-neutral affective valence included activations in the amygdala and hippocampus, ventral extrastriate visual cortex, and the intraparietal sulcus bilaterally.

Kruesi et al. (271) compared regional brain volumes from magnetic resonance imaging scans from 10 youths with early onset conduct disorder and 10 healthy controls to determine whether prefrontal or temporal lobe brain volumes differed in the two groups. Results showed that subjects with conduct disorder had significantly reduced right temporal lobe and right temporal gray matter volumes. The prefrontal volumes in subjects with conduct disorder were 16% smaller than in controls, but the

difference did not reach statistical significance. It was also seen that early onset conduct disorder without substance abuse comorbidity was also significantly associated with small right temporal gray matter volumes.

Bussing et al. (272) conducted a study to examine a community sample of 12 children with combined subtype ADHD (ages 8–12 years, 7 with conduct disorder) and 19 healthy controls matched for age, gender, handedness, and poverty. Measurements of the left and total posterior, superior, and inferior lobes of the cerebellar vermis indicated smaller volumes for both pure ADHD and comorbid children compared to the controls. The results suggested ADHD and ADHD comorbid with conduct disorder have similar cerebellar morphology.

18.4.7. Treatment

It has been seen that no single intervention is effective against severe conduct disorder. Each dysfunctional domain needs to be targeted by multimodal interventions and this treatment must be delivered long enough to make a difference. Programs such as Head Start may help prevent delinquency in conduct disorder in preschool-aged children where poverty, perinatal complications, maternal attachment problems, temperamental traits, and parental education are risk factors. Such programs provide children with stimulation, parents with education, and parental support in crisis (269).

In the treatment of conduct disorder in school-aged children, both parenting skills training and training for the child are effective. The intervention should be aimed for the child, the family, as well as the school.

Adolescence is a time when internal self-regulation assumes more importance. Henggeler's Mutisystemic Therapy treats adolescents with conduct disorder in their psychosocial environment and family interventions (269). Augmentation of treatment is done by targeting social skills, conflict resolution, and anger management.

The childhood-onset group of conduct disorder has a history of behavior problems early in development and is at risk for the most severe and aggressive pattern of behaviors in adolescence and adulthood. Early interventions that are comprehensive and target multiple risk factors are found to be more effective. Families and Schools Together (FAST Track) Program involves multiple component interventions such as: (1) Parenting interventions that teach parents appropriate behavior management skills, (2) helping children develop anger control and problem-solving skills using a cognitive behavior intervention, (3) helping teachers use more effective behavior management using classroom interventions, (4) academic tutoring, and (5) home visits to support family functioning (263).

18.4.7.1. Pharmacotherapy

Medications are recommended only for treatment of target symptoms and comorbid disorders. Mood stabilizers, typical and atypical antipsychotics, alpha agonists, and the stimulants have been found to be useful in the treatment of children and adolescents with conduct disorder. Findling et al found that aggressive children with conduct disorder may benefit from quetiapine (273). Lithium was found to be safe and efficacious for the short-term treatment of aggressive inpatient children and adolescents with conduct disorder. Haloperidol was also found to be useful but lithium was better tolerated than haloperidol (267).

Risperidone and methylphenidate were also found to be superior to placebo in treating conduct disorder. Although no studies have demonstrated their superior efficacy in conduct disorder, antidepressants, lithium carbonate, carbamazepine, and propranolol are used in clinical practice. Clonidine and guanfacine are often used for their effect on reducing aggression and impulsivity (267). Donovan et al. found divalproex to be an efficacious treatment for explosive temper and mood lability in conduct disorder (274).

There are clear indications for hospitalization in children and adolescents who exhibit potential for imminent risk to self or others and show aggressive behavior or imminent deterioration in medical status (269). Inpatient, partial-hospitalization and residential treatment should include therapeutic milieu, family involvement, individual and group therapy, vocational training, treatment of comorbid disorders, and ongoing coordination with school, social services, and the juvenile justice system.

18.5. Summary

The explosion of neurobiological literature on ADHD and the Disruptive Behavior Disorders reflects the complex, fluid, and often-contradictory manifestations of brain–behavior relationships. This complexity is enhanced further by the accumulating research demonstrating significant differences in manifestations according to age, cognitive status, gender, comorbidities, psychosocial context, and treatment response. There is an enormous degree of individual variation shaped by the transaction of biological and environmental factors, which again has major implications for prevention and diagnostic and therapeutic interventions. ADHD has a high, though polygenic, heritability, with clinical expression strongly mediated by environmental and

familial factors. ADHD and CD appear to be genetically distinct, whereas ODD evolves within the context of ADHD. ADHD demonstrates extremely high affiliations with other neurodevelopmental and mental disorders. Research has expanded the conceptualization of ADHD as a primary disorder of frontal-striatal cognitive systems to include affective and motor regulatory pathways and to question the validity and utility of "executive function" deficits as the sole core dysfunctions. ADHD manifests from early childhood and persists in most cases throughout the lifespan. Evaluation and management of the individual needs to acknowledge the co-occurrence of ADHD with learning disorders, anxiety, and mood disorders, which are the basis for the high degree of psychosocial morbidity. Despite the etiological, neuropsychological, and clinical complexity, psychostimulant treatment can help to attenuate some of the most detrimental psychosocial effects that occur when left untreated. Alternative drugs are available in patients who cannot use stimulants, and behavioral and psychosocial interventions should be included as supportive treatments, especially in young children. Prevention and early intervention are feasible, given that there are clear causal relationships, such as toxic exposures (prenatal exposure to smoking, alcohol, lead, etc.), parental psychopathology, and environmental and lifestyle stressors that can be eliminated or modified if appropriate intervention is sought and available.

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