CONTINUING MEDICAL EDUCATION

Attention-Deficit/Hyperactivity Disorder

A Current Overview

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SUMMARY

Background: Attention-deficit/hyperactivity disorder (ADHD) is a common, early-onset, persistent developmental disorder of childhood and adolescence, with a prevalence of approximately 5%.

Methods: This article is based on publications retrieved by a selective search in PubMed with an emphasis on pertinent guidelines and systematic reviews.

Results: At least 75% of affected children and adolescents develop a comorbid disorder, which impedes diagnosis and treatment and worsens prognosis. The etiology of ADHD is complex and heterogeneous, involving a major genetic component and diverse neurobiological alterations. Prenatal environmental factors also seem to elevate the risk of ADHD. The mainstays of treatment are psychoeducation, behavioral therapy, and psychoactive drugs, which generally have only mild side effects, such as insomnia or decreased appetite. The indication for treatment in the individual case is based on severity, comorbidity, previous therapy attempts, and the familial, social, and educational framework conditions.

Conclusion: Translational research is needed to clarify the etiology of ADHD. Epidemiological studies published since 1987 do not reveal any increase in the prevalence of ADHD among children and adolescents. Improved diagnosis necessitates an evidence-based and need-adapted approach to treatment.

▶ Cite this as:
Banaschewski T, Becker K, Döpfner M, Holtmann M, Rösler M, Romanos M: Attention-deficit/hyperactivity disorder—a current overview. Dtsch Arztebl Int 2017; 114: 149–59. DOI: 10.3238/arztebl.2017.0149

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Attention-deficit/hyperactivity disorder (ADHD; according to the DSM-5) (1) and hyperkinetic disorder (HKD; according to the ICD-10) (2) describe a childhood-onset developmental disturbance that persists for at least six months and across different situations, and comprises the three core symptoms inattentiveness, impulsivity, and/or motor unrest. These core symptoms are present to an extent beyond what would be expected for the patient's age, developmental level, and intelligence. To diagnose the disorder, clinically relevant functional psychosocial impairment must be present in different settings, e.g., family, school, or work. In the general population, these core symptoms are dimensionally distributed along a continuum, the upper end of which constitutes clinically relevant ADHD symptoms (e1). In this selective review, we focus on meta-analyses, systematic reviews, large registry studies, and randomized controlled trials. The aim is to provide the reader with an evidence-based overview of the developmental trajectories in ADHD, the various and often controversial treatment options, and the current state of etiological research.

Classification

The two most commonly used nosological classification systems worldwide, the ICD-10 and the DSM-5, are broadly consistent in their operationalizations of the various symptoms of ADHD, but differ with respect to subtypes and additional criteria. The "subtypes" defined in the DSM-IV have been attenuated to "presentations" in the DSM-5, due to their temporal instability and frequent developmentally dependent changes from one category to another (e2, e3). The DSM-5 is the first classification system to define specific features of ADHD in adults, reducing the number of symptoms necessary for diagnosis from the age of 17, due to the

Core symptoms

The core symptoms of ADHD and HKD are inattentiveness, impulsivity, and/or motor unrest.

fact that functional impairment can persist or worsen with age despite an age-dependent reduction of symptoms (e3, e4). Moreover, the age of onset criterion has been raised to 12 in the DSM-5, as an older age of onset (between 7 and 12 years) was found to show no effect on clinical manifestation, symptom severity, nature and extent of comorbid disorders, neuropsychological findings and functional impairment, progression or treatment response (e5).

Epidemiology

ADHD as defined by the DSM-IV criteria has a worldwide epidemiological prevalence of 5.3% [5.01%–5.56%] and is thus one of the most common mental illnesses in childhood and adolescence (3, e5). Use of the stricter ICD-10 research criteria leads to lower prevalence estimates of approximately 1–2% (e6–e8). According to the DSM-IV criteria, around 2.5% of the general adult population suffers from ADHD (4). The higher prevalence in males is more pronounced in clinical samples (3–4 : 1) than in epidemiological studies (2 : 1). ADHD is associated with a lower socio-economic status (e9). Although the rate of diagnosis has risen markedly around the world in recent decades, currently lying at approximately 4% of children and adolescents in Germany, epidemiological studies have shown no change in the worldwide population-based prevalence of 5.3% over the last 30 years (6). Rising rates of diagnosis are thus not due to a real increase in prevalence, but rather to improved diagnosis or to an increase in functional impairment (5, 6, e10).

Developmental psychopathology

Symptom levels vary across different areas of life and according to the extent of external demands. In this respect, situations that require attention, sitting still, and impulse control are often the first in which the symptoms are experienced as causing impairment (e.g., classroom behavior, homework, chair-circle activities, etc.). Marked motor unrest before the age of four years, however, is very hard to distinguish from a variant of normal behavior. Moreover, the novelty of a situation, a high specific motivation or expectation of a reward, and strong external behavioral control can reduce symptoms in certain situations, but not in a long-lasting manner. Thus, a lack of symptoms in a circumscribed observational situation does not automatically rule out the diagnosis. In children of elementary-school age, inattentiveness becomes increasingly evident and causes greater impairment as the external demands increase. Motor unrest often lessens from adolescence onward and is often reduced to a subjectively unpleasant inner feeling of restlessness and drive, while difficulties such as inattentiveness, deficient planning ability, and impulsivity often persist (5). In adulthood, the core symptoms of ADHD may be accompanied more prominently by symptoms of emotional dysregulation, including reduced frustration tolerance, irritability, and marked mood swings (7, 8, e11).

Prospective longitudinal studies have shown a continuous reduction of the core symptoms over the lifespan. Generally speaking, only around 5–15% of patients continue to completely fulfill the diagnostic criteria for ADHD in adulthood, although persistent symptoms or functional impairment remain in approximately 70% (3, e12); however, findings vary widely across studies due to methodological differences and other reasons. Comorbid disorders may be more prominent than ADHD itself and dominate the clinical picture. A positive family history of ADHD, unfavorable psychosocial conditions (severe early childhood deprivation, psychopathology in one or both parents), severe core symptoms, and comorbid mental illnesses (particularly conduct disorders and depressive disorders) are risk factors for an unfavorable course and for the persistence of the disorder (9, e13–e16).

ADHD is associated with psychosocial functional impairment and a markedly reduced subjective health-related quality of life (10, 11). Children with ADHD are about four times less likely than their peers to obtain a college degree, and attain a lower socio-economic status on average (12). Their relationships with parents, siblings, peers, and partners are often conflict-ridden (10, 12). Their risk of delinquent behavior is elevated by a factor of 2–3 (12, e17). From preschool age up to age 13, the risk of suicidal ideation is almost 6 times higher than in their peers (e18), and they show a four-fold-increased lifetime risk of suicide (13, e17, e19); the severity of ADHD is correlated with the frequency of suicidality (e19). Accident-proneness, particularly regarding road traffic accidents, is the major reason for the 50% increase in mortality seen among persons with ADHD across all age groups (9, 11).

Although, according to the definition of ADHD, the disorder first manifests in childhood, more recent longitudinal cohort studies suggest that symptoms can also begin (or become clinically relevant) in adulthood

Epidemiology

ADHD has a worldwide epidemiological prevalence of 5.3% [5.01%–5.56%] according to the DSM-IV criteria and is thus one of the most common mental illnesses in childhood and adolescence.

Developmental psychopathology

Prospective longitudinal studies have shown a continuous reduction of the core symptoms of ADHD as patients grow older.

(14, e20, e21). The interpretation of these findings is currently a matter of debate (e21). One possible explanation is that protective factors prevent an early clinical manifestation of the disorder, and symptoms only become evident once the individual is subjected to the greater demands of adulthood.

Developmentally dependent trajectories of comorbidity

Approximately 75% of persons with ADHD have an additional mental disorder and around 60% have multiple comorbid mental disorders; this can adversely affect prognosis and may necessitate specific therapeutic measures (15). Circumscribed developmental disorders (motor function, language, scholastic skills), anxiety disorders, tic disorders, and oppositional-defiant disorder emerge early in child development (16). In contrast, depressive disorders and severe conduct disorders often emerge later on, toward the end of the elementary school years and during the transition to adolescence. From adolescence onward, such disorders are often associated with substance abuse and dependence (odds ratios [OR] 1.7 and 2.5, respectively) (12) and with the development of personality disorders (8, e22, e23). Approximately one in four children receiving treatment for ADHD also have an affective disorder (15, 16), while over half of all adults with ADHD have clinical depression (2.3-fold increased risk) (12, e24). Thus, the age-dependent development of comorbid disorders often occurs in specific sequential steps (e.g., from oppositional disorders, through conduct disorder, to depression with increased suicidality), particularly as comorbid disorders constitute specific risk factors for the development of further mental disorders (16).

Pathophysiology

Genetics

ADHD tends to run in families. First-degree relatives have a five- to tenfold increased risk of developing ADHD (e25, e26, 17). Twin studies have revealed a high degree of heritability: 70–80% of the phenotypic variance is attributable to genetic factors, sometimes in interaction with environmental factors (epigenetic changes in gene expression due to specific environmental factors) (17). The remaining variance is explained by pre-, peri-, and postnatal environmental factors that twin siblings do not share. Shared environmental effects are of secondary importance. Meta-analyses of candidate gene studies have shown that genes encoding the receptors and transporters of the catecholaminergic and serotonergic neurotransmitter systems play a role in the etiology of the disorder (17, 18). Genome-wide association studies have revealed many other potential risk variants, and their findings suggest that some 40% of the genetically determined variance is due to common variants (i.e., variants with a frequency higher than 5%), which alone only increase the risk to a small degree *(Table 1)* (19, 20). Rare risk alleles (frequency <1%) and copy-number variants also elevate the risk; they can have relatively strong effects on individuals or within a single family, but account for only a small amount of the variance in the overall population; nicotinergic and glutamatergic systems and genes regulating neural development and synaptogenesis also play a role in the etiology of ADHD (21, 22). Moreover, there are a number of genetic syndromes which are known to be associated with the symptoms of ADHD, including fragile X syndrome, microdeletion 22q11 syndrome, tuberous sclerosis, and Williams–Beuren syndrome (11, 23).

Environmental risk factors

Epidemiological studies have shown associations between ADHD and various environmental factors. These primarily include pre- and perinatal risk factors (maternal stress, smoking or alcohol consumption during pregnancy, low birth weight, prematurity), environmental toxins (organophosphates, polychlorinated biphenyls, lead), unfavorable psychosocial conditions (severe early-childhood deprivation, maternal hostility), and dietetic factors (11, 23). The causal role of most of these putative environmental risk factors has not yet been proven: The variables are not randomly distributed in the population and the observed associations may be due to confounding factors and selection effects. Moreover, for some variables, causality may lie in the opposite direction, as ADHD itself may lead to increased exposure to certain environmental factors (11, 23, e27).

Multiple studies have shown that negative mother–child interactions can be a result (but not a cause) of ADHD symptoms in early childhood, but that maternal hostility negatively influences symptoms in the further course of the disorder (e28, e29). The associations of ADHD with prenatal exposure to maternal stress and maternal smoking seem to be partially due to confounding factors, although the association of ADHD with low birth weight, prematurity and lead

Developmentally dependent comorbidities

Depressive disorders and severe conduct disorders often arise toward the end of the elementary school years and during the transition to adolescence.

Environmental risk factors

These include the following: maternal stress, cigarette smoking or alcohol consumption during pregnancy, low birth weight, prematurity, environmental toxins, unfavorable psychosocial conditions, and dietetic factors.

TABLE 1

Some genetic associations with pooled risk elevation for ADHD (pooled odds ratio) that have been confirmed in meta-analyses*

Gene	Gene product	Variant / risk allele	Pooled odds ratio
DRD4	Sopamine D4 receptor	VNTR in exon 3/ 5-repeat allele	1.33
		VNTR in exon 3/ 7-repeat allele	1.68
		Polymorphism in promoter/T allele	1.21
DRD5	Dopamine D5 receptor	Dinucleotide repeat/ 148-bp allele	1.23
DAT1	Dopamine transporter	VNTR in exon 8/ 3-repeat allele	1.25
		VNTR in 3-UTR/ 10-repeat allele	1.17
		Polymorphism in 3'-UTR/G allele	1.20
5HTT	Serotonin transporter	5HTTLPR/ long allele	1.31
HTR1B	Serotonin 1B receptor	Polymorphism in exon 1/G allele	1.11

ADHD, attention-deficit/hyperactivity disorder; bp, base pair; UTR, untranslated region; VNTR, variable number tandem repeat
*modified from (17, 18, 20)

exposure is probably not explained by confounding variables; they make only a small contribution to the overall variance, however (23, 24, e29–e31). By contrast, the causal role of severe early childhood deprivation has been demonstrated (25, e32).

Neuropsychology

In group comparisons, studies have shown various neuropsychological impairments in the area of executive functions (inhibitory control, working memory, planning ability) and non-executive functions (regulation of activation and arousal, temporal processing, memory, reaction-time variability). Motivational processes and learning mechanisms are also affected, e.g., an aversion to delayed rewards and reduced behavioral control and error processing mechanisms. However, these impairments and their profile are not specific to ADHD (26, e33, e34); as they show only medium effect sizes, there is considerable overlap with healthy control subjects. Only about half of all persons with ADHD have marked neuropsychological impairment. Currently, it is unclear whether the associated abnormalities are of causal relevance or should rather be seen as epi-phenomena of the etiological mechanisms (26–28, e34, e35).

Structural and functional brain abnormalities

Global brain volume is reduced by 3–5%, with the gray matter preferentially affected (29, e36, e37). More marked volume loss, correlated with the severity of the symptoms of ADHD, is seen in the prefrontal areas, the basal ganglia, and the cerebellum (29, e36). Cortical maturation is delayed, particularly in the prefrontal areas (e38). These abnormalities develop to differing degrees across brain regions and patient populations. The persistence of ADHD symptoms into adulthood is correlated with the persistence of these neuroanatomical abnormalities (e39). Functional imaging reveals hypoactive activation patterns in the prefrontal cortical areas, the anterior cingulate gyrus, and associated parietal, striatal, and cerebellar structures (29, 30, e38, e40, e41).

The pathophysiological mechanisms of ADHD are not yet adequately understood. On the basis of the available study findings, ADHD is presumed to be multifactorial in most cases. Genetic factors and early environmental risk factors that interact in complex ways to affect the structural and functional development of the brain play a major role and account for a

Structural and functional brain abnormalities

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Diagnostic evaluation

The diagnostic evaluation integrates information from a detailed developmental history and family history, a psychological diagnostic evaluation, and a physical diagnostic evaluation including a differential diagnostic evaluation.

high degree of etiological heterogeneity. Each individual factor accounts for only a small part of the variance, i.e., each one is relevant only to a small percentage of affected persons or else has only a weak effect. The risk factors that have been identified are not specific for ADHD; they elevate the risk of other mental illnesses as well, and they also increase the extent of subclinical ADHD symptoms in healthy persons without ADHD. These findings support the hypothesis that ADHD represents one end of a dimension of traits that is continuously distributed in the general population. Its multifactorial etiology corresponds to the heterogeneous overall profile of cerebral structural abnormalities and functional neuropsychological and psychopathological disturbances (11, 23).

Diagnostic evaluation

Like all other neuropsychiatric disorders, ADHD is diagnosed on a clinical basis. No biomarker has yet been found with adequate sensitivity and specificity. Nonetheless, ADHD can be reliably diagnosed if the diagnostic criteria are carefully scrutinized and differential diagnoses are excluded.

The diagnostic evaluation integrates information from a detailed developmental history and family history, a psychological diagnostic evaluation, and a physical diagnostic evaluation including a differential diagnostic evaluation. If the patient is a child or adolescent, the current clinical symptoms and their severity in multiple areas of life are primarily assessed through information from the parents and/or other adults who interact with the child. Information from multiple observers who deal with the patient in different areas of life should always be considered. In adulthood, the diagnostic evaluation is based mainly on talking with the patient, although information from family members or third parties (e.g., school report cards) can be helpful. Useful diagnostic aids include structured or semi-structured interviews and checklists to assist in clinical judgments, and disorder-specific questionnaires to determine how the patient is viewed by parents and teachers, as well as by him- or herself. Such questionnaires are now available in German for the diagnosis of ADHD in children, adolescents, and adults according to either the ICD-10 or the DSM-5 (e.g., DISYPS-III, IDA) (e42, e43) *(eTable)*. For diagnosis, the symptoms must have led to a marked impairment of the patient's performance and/or functioning in the social environment. In ADHD/HKD, the degree of severity of the core symptoms is not simply a function of the affected person's age and developmental state. Questionnaires and checklists enable inexpensive, systematic, and standardized data collection from multiple areas of life but may yield misleading findings. If discrepancies in the assessment of the patient remain, it may help to try to resolve these with the aid of more information, which can be obtained over the telephone (e.g., from teachers or carers) or in further face-to-face conversation (e.g., with the patient's grandparents). Persons filling out questionnaires are often reluctant to give answers that cast the child in a negative light, or they may have other personal reasons for giving a modified answer *(eTable)*.

The diagnostic evaluation can also be supplemented with psychological tests, which are necessary when certain specific differential-diagnostic questions have to be answered. About half of all persons with ADHD have normal neurocognitive test findings despite marked core symptoms of the disorder (e33, e34). Reduced intelligence must be ruled out; a valid intelligence assessment (e.g. with the WISC, or with another test such as the CFT-20R for a preliminary assessment) is an obligate component of a comprehensive diagnostic evaluation.

Laboratory tests and ancillary tests can be helpful for the investigation of possibly underlying somatic disease (e.g., thyroid disease, disturbances of sight and hearing, organic sleep disorders, drug-induced disorders) or in differential diagnosis (e.g., to distinguish ADHD from absence epilepsy).

ADHD often needs to be distinguished from a conduct disorder or depression. Very careful distinctions must be drawn between the core symptoms of ADHD (impaired concentration, impulsivity, hyperactivity) and the dissocial and aggressive symptoms that characterize conduct disorder. Further observation over time can clarify whether an observed lack of ability to concentrate combined with heightened irritability is primarily or entirely due to a depressive mood disturbance, rather than being a chronic manifestation of ADHD. Other, less common and very rare differential diagnoses include attachment disorders and schizophrenic and bipolar prodromes.

The clinician must make the diagnosis in the light of all the findings, and not merely on the basis of questionnaires or behavior observation in a test setting in the absence of a thorough developmental history. Differential diagnoses must be considered and ruled out.

Aids for the assessment of ADHD patients

Remaining discrepancies in the assessment of the patient may be resolved with the aid of further information obtained over the telephone (e.g., from teachers or carers) or in face-to-face conversation (e.g., with the patient's grandparents).

Differential diagnosis

ADHD often needs to be distinguished from a conduct disorder or depression. The core symptoms of ADHD can be difficult to distinguish from those of a conduct disorder.

TABLE 2

Non-pharmacological interventions—efficacy with respect to ADHD core manifestations

Interventions	Effect strength, OR [95% CI]		Remarks
	Unblinded	Blinded	
Dietetic interventions			
Elimination diet (32)	1.48 [0.35; 2.61]	0.51 [−0.02; 1.04]	Statistically insignificant effect in blinded assessment
No artificial coloring (32)	0.32 [0.06; 0.58]	0.42 [0.13; 0.70]	Statistically significant, moderately strong effect in selected cohorts in blinded assessment
Unsaturated fatty acid supplementation (32)	0.21 [0.05; 0.36]	0.16 [0.01; 0.31]	Statistically significant but clinically irrelevant effect in blinded assessment
Psychological interventions			
Cognitive training (32, 35)	0.64 [0.33; 0.95] 0.37 [0.09; 0.66]	0.24 [−0.24; 0.72] 0.20 [0.01; 0.40]	Meta-analysis 1: No statistically significant effect in blinded assessment (32) Meta-analysis 2: Improvement of working memory in blinded assessment (verbal: 0.52 [0.24; 0.80]; visual: 0.47 [0.23; 0.70]) and small but significant effect on ADHD core manifestations (35)
Neurofeedback (32, 34)	0.59 [0.31; 0.87]	0.29 [−0.02; 0.62]	In blinded assessment, no statistically significant effect when all studies are included (32); nonetheless, an exploratory secondary analysis (34) reveals a moderately strong, statistically significant effect with the use of a standardized neurofeedback protocol (0.36 [0.04; 0.69])
Behavioral therapy (32, 33)	0.40 [0.20; 0.60]	0.02 [−0.30; 0.34]	In blinded assessment, no statistically significant reduction of ADHD core manifestations (32), but (33) there is significant improvement in positive parenting behavior (0.63 [0.47; 0.7]), reduction in negative parenting behavior (0.43 [0.24; 0.62]), and reduction of abnormal conduct (0.31 [0.05; 0.57])

ADHD, attention-deficit/hyperactivity disorder; OR, odds ratio; CI, confidence interval

Nor can the diagnosis of ADHD be made or excluded solely on the basis of psychological testing. The lack of essential information, e.g., prohibition of contact with the school, weakens the validity of the diagnosis.

Treatment

ADHD is generally treated in the outpatient setting. If outpatient treatment fails due to poor compliance, inadequate family resources, difficult drug adjustments, or impending expulsion from school, it may be necessary to conduct partial or full inpatient treatment. Certain differential diagnostic questions or a complex burden of comorbidities constitute further possible reasons for inpatient treatment.

Treatment guidelines from Germany and abroad now recommend a combination of multiple, individually adapted treatment components (multimodal treatment) (31, e6, e62). The foundation of all therapeutic interventions is psychoeducation to impart information about the disorder and potential treatment approaches to the parents, as well as to the child or adolescent patient in an age-appropriate manner. Cognitive behavioral therapy techniques are also used, in both individual and group settings:

- In childhood and adolescence: parent training, interventions in kindergarten and in school, e.g., a therapy program for children with problematic hyperkinetic and oppositional behavior (e63).
- In adulthood: specific psychotherapy manuals.

An unblinded assessment showed low to moderate effects on the core ADHD symptoms, which remained stable even after the end of treatment (32). However, so far, significant effects have not been conclusively demonstrated in blinded assessment (32). By contrast, blinded assessment has revealed positive effects on parental child-rearing behavior, problems of conduct, and the functional level of the affected children (33).

Treatment

ADHD is usually treated on an outpatient basis.

Therapeutic intervention

The foundation of all therapeutic interventions is psychoeducation to impart information about the disorder and potential treatment approaches to the parents, as well as to the child or adolescent patient in an age-appropriate manner.

TABLE 3

Approved substances in Germany for the treatment of attention-deficit/hyperactivity disorder

	Substance class	Typical dose range	Effect strength	Number needed to treat	Adverse effects	Remarks
Methylphenidate (MPH)	Psychostimulant	0.3–1.0 mg/kg BW	0.8–1.0	ca. 2.5 (e81)	On average, mild increase in blood pressure and heart rate; appetite suppression, weight loss, abdominal pain, headache, difficulty falling asleep, insomnia, emotional irritability, intensification of tic manifestations if already present	Drug of first choice; sustained-release preparations are available (e81, e82)
Dexamfetamine	Psychostimulant	0.1–0.5 mg/kg BW	0.8–1.0	ca. 2 (e82)		Efficacy and tolerability comparable to that of MPH; approved if MPH is not sufficiently effective (e81, e82)
Lisdexamfetamine	Psychostimulant	30–70 mg	Ø 1.0			Prodrug with prolonged effect; approved in Germany if the response to MPH is inadequate (e83)
Atomoxetine	Selective norepinephrine reuptake inhibitor (SNRI)	1.2 mg/kg BW	0.5–0.7	ca. 4 (e84)	On average, mild increase in blood pressure and heart rate; mild shortening of QTc, dry mouth, appetite suppression, weight loss, gastrointestinal symptoms, dizziness, headache, drowsiness, fatigue, sedation	Drug of first choice in the presence of a comorbid tic, anxiety, or substance disorder; otherwise, drug of second choice (e84)
Guanfacine	Central α_2-agonist	1–5 mg	0.6	ca. 4 (e85)	Fatigue, sedation, somnolence, mild lowering of blood pressure and heart rate, mild QTc prolongation	Sustained-release preparation available as a drug of second choice if MPH is ineffective or poorly tolerated; metabolized by CYP3A4 (e85, e86)

BW, body weight

Meta-analyses have shown that food supplementation with unsaturated fatty acids has a weakly statistically significant but clinically irrelevant effect on the core symptoms of ADHD (32). Nor are any other dietetic measures generally of therapeutic use. The utility of neurofeedback as part of a multimodal overall treatment plan remains unclear (34). So far, an insufficient number of studies with high-quality training protocols have been performed. Such studies would probably yield better results than other approaches *(Table 2)*.

Alongside these treatments, pharmacotherapy *(Table 3)* is a further essential component of ADHD treatment. The efficacy and tolerability of treatment with stimulants have been demonstrated repeatedly in many meta-analyses, e.g., that of the National Institute of Excellence (e6). A recent Cochrane Review (36) cast doubt on the quality of the evidence supporting the efficacy of methylphenidate. This review, however, was widely criticized by experts around the world and aroused vigorous debate due to its unusually strict categorizations of bias, questionable inclusion criteria, methodological errors, and an inadmissible clinical interpretation of the data (36, 37, e64–e69).

Randomized trials on the long-term efficacy of treating ADHD with stimulants cannot be performed for ethical reasons. The last three decades have seen a marked rise in the number of studies on the long-term results of treatment (e70, e71). Longitudinal studies of brain development (e36, e72, e73) have revealed a structural normalization of brain development under treatment with stimulants. The findings of Scandinavian registry studies that have been adjusted for potential confounding factors suggest that drug treatment for ADHD reduces the risk of delinquent behavior (38), substance abuse (e74), suicidal behavior (e75),

Positive effects

Cognitive behavioral therapy techniques have positive effects on parental child-rearing behavior, problems of conduct, and the functional level of the affected children.

Pharmacotherapy

Pharmacotherapy is an essential component of the treatment of ADHD.

and accidents (e76) to a statistically significant and clinically relevant extent. Further studies have also shown a reduction of functional impairment and an improvement in health-related quality of life (e77). In general, (drug) treatment leads to a more favorable temporal course of the core symptoms, associated psychiatric disorders, and relevant functional impairments, even though a fully normal state still cannot be achieved in most cases (e71, e78, e79).

The decision for drug treatment should be made only after careful consideration in all cases, as should the further decisions about when to treat, for what duration, and at what dosage. Behavioral therapy is always preferable to drug therapy for preschool children and for school-age children with only mild symptoms. Primary treatment with drugs is indicated from school age onward in the case of pronounced and situationally independent ADHD symptoms that are causing marked functional impairment (e6). Moreover, there is evidence to support primary drug treatment for some children with moderate ADHD symptoms. For adults with ADHD, drugs are the first line of treatment (e80). Patients must be followed up regularly over the long term to check for possible side effects of drug treatment; in particular, their blood pressure, heart rate, height, and weight should be regularly monitored (39). The effect of treatment should also be monitored with regular brief periods of discontinuation of the drug, generally once per year (39).

For the treatment of associated mental disorders, further psychotherapeutic interventions on the basis of behavioral therapy, family systems therapy, or depth psychology may be helpful. Drugs may also be useful to treat certain comorbid psychiatric problems such as depression, tic disorders, and obsessive-compulsive disorder.

Overview

ADHD is a developmental disorder that has not become any more prevalent in the general population in recent decades but that has nonetheless become increasingly well recognized. As it leads to functional impairment in multiple areas of life, is often associated with the development of comorbid mental disorders, and can have lifelong adverse consequences for the patient, ADHD requires early, need- and age-adapted treatment consisting of psychoeducation, behavioral therapy, and treatment with psychoactive drugs. There are effective methods of treatment for both the core and accompanying symptoms of ADHD. As part of the nationwide research network on mental illness supported by the German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung, BMBF), the ESCAlife Association (a German acronym for "evidence-based, multilevel care of ADHD over a lifetime"; www.esca-life.org) is now studying the efficacy and cost-effectiveness of individualized and stepwise multimodal treatment programs for ADHD and is trying to identify predictors of the individual response to treatment.

Primary drug treatment

Primary treatment with drugs is indicated from school age onward if pronounced and situationally independent ADHD symptoms are present that are causing marked functional impairment.

Conflict of interest statement

Prof. Banaschewski has served as a paid consultant for Lilly, Medice, Novartis, Shire, Otsuka, and Actelion. He has received payment for publications from Hogrefe, Thieme, CIP Medien, and Oxford University Press. He has served as a paid consulting medical expert for Hexal. He has received reimbursement of meeting participation fees and of travel and accommodation expenses from Shire, Medice, and Novartis and has also been paid by these firms for organizing continuing medical education events. He has received financial and material support from Viforpharma for a research project that he initiated.

Prof. Becker has received consultant's fees and reimbursement of meeting participation fees and of travel and accommodation expenses from Lilly, as well as scientific lecture honoraria from Shire.

Prof. Döpfner has served as a paid consultant for Medice, Shire, Lilly, and Vifor. He has received payment for publications from Hogrefe, Huber, Guilford, and Kohlhammer. He has received reimbursement of meeting participation fees and of travel and accommodation expenses as well as scientific lecture honoraria from Shire, Medice, Lilly, and Vifor. He has received financial support for a research project that he initiated from Vifor, Medice, Lilly, Novartis, and Shire, as well as material support from Vifor, Medice, Lilly, and Shire.

Prof. Holtmann has served as a paid consultant for Lilly Deutschland, Shire, and Medice. He has received reimbursement of travel and accommodation expenses from Medice and Shire and lecture honoraria from Medice, Shire, Lilly, and neuroConn.

Prof. Rösler receives royalties from Hogrefe Verlag. He serves as a paid consultant for Medice, Shire, and Lilly. He has received lecture honoraria from Medice and Shire. He has received financial support for a research project that he initiated from Vifor and material support for the performance of clinical trials from Medice.

Prof. Romanos has served as a paid consultant for AOK Baden–Württemberg.

Manuscript submitted on 1 August 2016, revised version accepted on 11 January 2017.

Translated from the original German by Ethan Taub, M.D.

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This CME unit can be accessed until 28 May 2017, and earlier CME units until the dates indicated:

– "Pulmonary Hypertension" (Issue 5/2017) until 30 April 2017,

– "Hepatitis C" (Issue 1–2/2017) until 2 April 2017.

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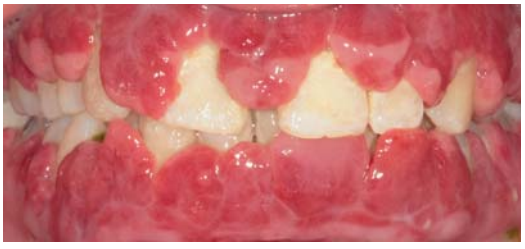
Supplementary material
For eReferences please refer to:
www.aerzteblatt-international.de/ref0917

eTable:
www.aerzteblatt-international.de/17m0149

CLINICAL SNAPSHOT

Is Idiopathic Always Idiopathic? What the Teeth Can Tell Us



The initial findings: gingival hyperplasia

A 25-year-old woman presented to the periodontology clinic of the dental hospital because of generalized hyperplastic swelling of the gingiva. Her fasting blood sugar was normal (01/2013: 97 mg/dL), but her inflammatory parameters were elevated (01/ 2013: ESR 90 mm/hr, CRP 1.9 mg/dL, WBC 11.1/nL). Her body-mass index (BMI) was over 30. As there was no other evidence of systemic illness and her medication use was unknown, the initially presumed diagnosis was of idiopathic gingival hyperplasia associated with chronic periodontitis. Systematic non-surgical periodontal treatment along with adjuvant antibiotics led to moderate improvement, but the hyperplasia did not resolve. Repeated laboratory testing one year later revealed an elevated fasting blood sugar (03/2014: 204 mg/dL) and an HbA_{1c} value of 9.5%. Antidiabetic treatment and continued local mechanical treatment led to the near-total resolution of gingival hyperplasia.

We conclude from this case that patients who present with gingival hyperplasia should undergo intensified diagnostic testing for diabetes mellitus even if their initial fasting blood sugar is normal.

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Conflict of interest statement
The authors state that they have no conflict of interest.

Translated from the original German by Ethan Taub, MD.

Cite this as:
Friedmann A, Becker M, Heppner J: Is idiopathic always idiopathic? What the teeth can tell us. Dtsch Arztebl Int 2017; 114: 158. DOI: 10.3238/arztebl.2017.0158

Please answer the following questions to participate in our certified Continuing Medical Education program. Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

What is the worldwide epidemiological prevalence of attention-deficit/hyperactivity disorder (ADHD) in childhood and adolescence, according to the DSM-IV criteria?

a) Approximately 1.8%
b) Approximately 2.7%
c) Approximately 3.9%
d) Approximately 5.3%
e) Approximately 7.1%

Question 2

The diagnosis of hyperkinetic disorder (HKD) according to the ICD-10 requires the fulfillment of certain diagnostic criteria. Which of the following is an obligate criterion?

a) Persistent, situationally independent symptoms for at least 12 months
b) At least average intelligence
c) Exclusion of dyslexia
d) Demonstration of at least one underlying neuropsychological abnormality (e.g., aversion to delayed reward, high reaction time variability)
e) The extent of the core symptoms is beyond that expected for the patient's age and state of development

Question 3

Which of the following is an essential part of a comprehensive diagnostic work-up for ADHD?

a) Complete blood count
b) Intelligence test
c) Positron-emission tomography scan of the brain
d) Rorschach test
e) Mobility test

Question 4

Which of the following is a risk factor for a severe course of ADHD and elevates the probability that the disorder will persist?

a) An unfavorable psychosocial environment
b) A negative family history of ADHD
c) Core symptoms of only mild intensity
d) Female sex
e) High intelligence

Question 5

Persons with ADHD have a higher mortality than the general population for multiple reasons, including accident-proneness and a higher suicide rate. By what amount is the mortality of persons with ADHD elevated?

a) 10%
b) 30%
c) 50%
d) 70%
e) 90%

Question 6

By what factor is the risk of ADHD elevated among first-degree relatives of persons with ADHD?

a) 5- to 10-fold
b) 10- to 15-fold
c) 15- to 20-fold
d) 20- to 25-fold
e) 25- to 30-fold

Question 7

What mental or psychosomatic comorbidity of ADHD tends to arise early in child development?

a) Oppositional defiant disorder
b) Functional abdominal complaints
c) Depression
d) Schizophrenia
e) Anorexia nervosa

Question 8

What environmental factor have epidemiological studies shown to be associated with ADHD in childhood?

a) Cannabis consumption by the patient
b) High educational level of the parents
c) Being an only child
d) Extensive television-watching
e) Intrauterine nicotine exposure

Question 9

Which of the following is the foundation of appropriate therapeutic intervention for ADHD?

a) Psychoeducation
b) Confrontation therapy
c) Aggression training
d) Autogenic training
e) Jacobsen relaxation exercises

Question 10

Which of the following drugs (among others) can be used to treat ADHD if the patient does not respond to methylphenidate?

a) Promethazine
b) Lisdexamfetamine
c) Clomethiazole
d) Olanzapine
e) Haloperidol

Supplementary material to:

Attention-Deficit/Hyperactivity Disorder

A Current Overview

By Tobias Banaschewski, Katja Becker, Manfred Döpfner, Martin Holtmann, Michael Rösler, and Marcel Romanos

Dtsch Arztebl Int 2017; 114: 149–59. DOI: 10.3238/arztebl.2017.0149

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eTABLE 1

Diagnostic instruments

Clinical interviews and diagnosis systems (incl. questionnaires)	Age range	Reference
– Kiddie-SADS	6–18 years	(e44)
– Kinder-DIPS	6–18 years	(e45)
– DISYPS-III (DCL-ADHS, ILF-EXTERNAL, FBB-ADHS, SBB-ADHS)	From 11 years onward	(e46)
– HASE	Adults	(e47)
– IDA	Adults	(e43)
Further ADHD-specific questionnaires		
– Conners 3	6–18 years	(e48)
– Conners scales for adults	> 18 years	(e87)
Questionnaires on comorbid depression		
– DIKJ	8–15 years	(e49)
– BDI-II	From 13 years onward	(e50)
– DTGA	Preschool and elementary school age	(e51)
Questionnaires on comorbid anxiety disorder		
– PHOKI	8–18 years	(e52)
– SPAIK	8–16 years	(e53)
Questionnaires on comorbid conduct disorder		
– FAVK	9–14 years	(e54)
Questionnaires on comorbid tic disorder		
– FBB-TIC / SBB-TIC	Adults/ 11–18 years	(e46)
Questionnaires on comorbid obsessive-compulsive disorder		
– CY-BOCS (interview)	6–17 years	(e55)
– Y-BOCS (interview)		(e56)
– OCI	Adults	(e57)
Questionnaires on comorbid autism spectrum disorder		
– FSK	From 4 years onward	(e58)
– MBAS		(e59)
– ADI-R	From 2 years onward	(e60)
– ADOS-2	From 12 months onward	(e61)