Long version of the interdisciplinary evidence- and consensus-based (S3) guideline "Attention-Deficit/Hyperactivity Disorder (ADHD) in children, adolescents and adults"

AWMF Registration No. 028-045

The responsible, participating Scientific Societies

dgkjp
Deutsche Gesellschaft für
Kinder- und Jugendpsychiatrie,
Psychosomatik und Psychotherapie e.V.

Ψ DGPPN
Deutsche Gesellschaft
für Psychiatrie und Psychotherapie,
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I. Introduction

1. Preamble

The present Practice Guideline applies to all children, adolescents and adults with Attention-Deficit/Hyperactivity Disorder (ADHD) [diagnosed according to DSM-5: ADHD (314); or ICD-10: Hyperkinetic disorders (F90) or Attention-Deficit Disorder without Hyperactivity (F98.8)] of every degree of severity. The Guideline equally applies to children, adolescents and adults who exhibit a clinically relevant degree of symptom severity, but do not meet the full diagnostic criteria, regardless of the type and extent of possible comorbidities.

The Practice Guideline is intended for application in all areas of prevention, diagnostics and treatment of ADHD in children, adolescents and adults at all outpatient, partial inpatient and inpatient healthcare facilities while targeting those professional groups involved in the diagnosis of children, adolescents and adults with mental disorders or special needs or who offer therapy to individuals with ADHD or counsel ADHD patients and their families (including managed self-help groups and counselling centers). This Practice Guideline was primarily written for specialists[1] in child and juvenile psychiatry and psychotherapy, specialists in pediatrics and adolescent medicine (particular those focused on neuropediatrics), specialists in psychiatry and psychotherapy, specialists in neurology as well as psychological psychotherapists and child and adolescent psychotherapists. Additional addressees include specialists in psychosomatic medicine, physicians with an additional qualification in psychotherapy, general practitioners, psychologists, neuropsychologists, school psychologists, teachers, special needs teachers, remedial teachers, social educators, occupational therapists, speech therapists, social workers, specialized nurses, learning therapists, music therapists, motopedists, mototherapists, educational counseling centers and other professional groups involved in the diagnosis and management of ADHD patients. In addition, this Practice Guideline can be used by those affected and their family members as a source of fundamental information and is intended to inform the public about good diagnostic and therapeutic methodologies. Indirect users include Medical Associations and Chambers of Psychotherapists, social administrations, social agencies, youth welfare institutions, care offices, governmental employment bureaus, decision-makers and cost bearers within the healthcare system, courts and expert opinion writers.

All in all, the interdisciplinary evidence- and consensus-based (S3) Practice Guideline on "Attention-Deficit/Hyperactivity Disorder (ADHD) in Children, Adolescents and Adults" (AWMF Registration No. 028-045) is comprised of a Short Version listing the recommendations, this Long Version itself and a Guideline Method Report. Among others, the Method Report describes the methodology used to

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[1] Although the generic masculine form has been used throughout this Clinical Practice Guideline and the Method Report for the sake of easier readability, all instances refer equally to all genders.

draft this Practice Guideline and handle conflicts of interest, while also disclosing the financial support provided for its creation.

Under every gray-highlighted recommendation in both the short and the long versions, you will find an assessment of the quality of evidence and the grade of recommendation, whenever an expert consensus was not reached. A detailed derivation of the evidence can be found in Chapter 2 of this long version.

As described in the Practice Guideline Method Report, two rounds of voting were held for each recommendation: All mandate holders from the participating professional associations who had no conflicts of interest (COI) voted in the first round and then all of the mandate holders voted in a second round. The results of the voting can also be found after every recommendation. There were several exceptions to the recommendations and/or chapters where it can be assumed that specific COIs had no impact. When one and/or two rounds of voting took place, respectively, it was Professor Kopp of the AWMF who undertook the assessment.

Although the masculine form has been used throughout this Practice Guideline for the sake of easier readability, all instances refer equally to all genders.

2. Introduction

2.1. Definition of ADHD

Characterized by a consistent pattern of the three hallmark symptoms of inattention, impulsivity and hyperactivity, Attention-Deficit/Hyperactivity Disorder (ADHD) is recognized as one of the most common mental disorders in children and adolescents. These symptoms present abnormally in terms of age and developmental stage, occur in different circumstances and cause significant suffering and/or limitations in the ability to function socially, academically or professionally. In many patients, the disorder and its associated functional limitations persist into adulthood. In the context of this guideline, the term ADHD is meant to include Attention-Deficit/Hyperactivity Disorder (ADHD), as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [1] as well as the clinical pictures classified as hyperkinetic (conduct) disorders (HKD) in ICD-10 [WHO: International Statistical Classification of Diseases and Related Health Problems, last update 2, 3].

2.2. History

A combination of the symptoms of motor restlessness, behavioral anomalies and concentration difficulties was initially described by Melchior Adam Weikard in 1775 [4]. In 1937, Bradley [5] was the first to notice that amphetamines (Benzedrine) led to a reduction in symptoms in children with severe behavioral disorders. The commonly used international classification systems DSM and ICD have operationalized the disorder differently in their various revisions. In the 1940s, the term "minimal brain damage" (MBD) was first introduced as a putative cause of hyperkinetic, impulsive and inattentive behavioral disorders. In 1962, this term was replaced by the concept "minimal cerebral dysfunction" (MCD). Coinciding with the introduction of DSM-III in 1980, these symptoms were classified as Attention-Deficit Disorder (ADD) with or without hyperactivity, before the clinical picture was finally classified as Attention-Deficit/Hyperactivity Disorder (ADHD) by DSM-IV in 1994, and then by DSM-5 starting in 2013. In ICD-9 [6], the constellation of symptoms was defined as hyperkinetic syndrome and then, with the introduction of ICD-10, under the category of hyperkinetic conduct disorders.

By means of the imaging techniques available in the 1980s, structural changes in the brain associated with ADHD were visualized for the first time. Twin studies demonstrated a high degree of heritability, as a result of which genetic questions have increasingly become the focus of research projects. Subsequently, new insights were gained into the genetic changes in ADHD at the molecular biological level. Thanks to the many long-term epidemiological and clinical studies, we now know more about

what contributes to the etiology of the disorder, which treatments are effective, and what limitations may affect the lives of ADHD patients [7].

Although the existing classification systems undertake a categorical assignment of ADHD presentations, there is a broad consensus in the scientific community that the core symptoms of ADHD are more likely to be extreme manifestations of characteristic dimensions continuously distributed across the population.

2.3.   Epidemiology

The prevalence of ADHD is age-dependent and varies according to the diagnostic criteria and information sources used to assess the symptoms. International epidemiological studies have shown that the worldwide prevalence found in children and adolescents is 5.3% (95% CI 5.01 – 5.56), with no significant differences existing internationally [7-9]. In Germany, the frequency of ADHD diagnoses reported by parents is around 5%, according to the KiGGS study by the Robert Koch Institute [10]. In adults, a prevalence of 2.5% (95% CI 2.1 – 3.1) was ascertained by a meta-analysis of six studies applying DSM-IV criteria [11].

2.4.   Age-related changes in symptomatological manifestations

The symptoms of ADHD show development-dependent changes such that the various symptomatological dimensions can be present in varying manifestations across the different age levels. For example, pronounced restlessness and hyperactivity are the hallmark symptoms in most preschool children affected with ADHD. To a large extent, by school age, children with ADHD will stand out in situations where they are expected to sit still. From adolescence onwards, hyperactivity often no longer manifests itself in increased physical activity but rather as a form of inner restlessness or agitation. This inner form of restlessness also persists into adulthood. Similarly, the symptom of inattention shows a developmental aspect. The disturbance of attention is particularly evident in school-aged children who are essentially required to work in a focused and concentrated manner while disrupted concentration can be observed and identified directly during the lessons. Thanks to developmental advancement, these children's attention span improves with increasing age, but often remains reduced compared to their non-ADHD peers. This lowered attentiveness can still significantly limit the everyday lives of those affected, even well into adulthood. Likewise, impulsivity will usually decrease with age; over the long term, however, it continues to cause major interference with day-to-day functioning.

Consistent with this development-dependent decrease in typical symptoms of ADHD, its prevalence rate continues to decline from childhood and adolescence into adulthood. Nevertheless, about 50% to 80% of those affected in childhood also present with ADHD symptoms as adults, with one third even exhibiting the full-blown picture of the disorder [12].

2.5.   Impairments of functioning, quality of life and participation

ADHD is associated with numerous functional impairments, which are significant risk factors impacting the further course of the disorder. Functional impairments not only include problems in school, training, educational and professional settings but also social difficulties within the family, in interactions with peers and partners in relationships. Longitudinal studies have shown that adults affected with ADHD have lower levels of education, income and socioeconomic status, exhibit increased risk behaviors, get involved in traffic accidents more often and tend to be more likely to break the law. The quality of life of ADHD sufferers is thus comparatively impaired, with the greatest differences being found in the areas of educational and professional performance as well as in psychosocial contexts [7].

2.6.   Etiology

The pathogenic factors causing ADHD are heterogeneous and have not yet been fully clarified. It is clear that multiple influences interacting with one another are involved in the etiology of ADHD. First and foremost, a decisive role is played by genetic predispositions and pre-, peri- and early postnatal environmental factors that affect the structural and functional development of the brain.

2.7.   Genetic influences

Family investigations show that ADHD often runs in families. First-degree relatives are two to eight times more at risk of developing ADHD [13, 14], and siblings or parents of affected children have a risk of between 10% and 35% [15, 16]. Adoption and twin studies have shown that clustering in families is largely attributable to genetic factors. A meta-analysis of 20 twin studies showed an average heritability of 0.76, i.e. 76% of the phenotypic variance can be explained by genetic factors and their interaction with environmental factors [13].

Candidate gene association studies of the catecholaminergic neurotransmitter system found robust relationships between ADHD and a polymorphism in exon III of the dopamine D4 receptor gene [17, 18], a VNTR polymorphism in the 3'-untranslated region of the dopamine transporter (DAT1) gene [19], a VNTR variant in the 5' region of the dopamine receptor D5 gene [19, 20] as well as

polymorphisms in the promoter region of the serotonin transporter gene (5-HTTLPR) [13] and in exon I of the serotonin receptor 1B (HTR1B)[19] and in the SNAP -25 gene as well [13]. However, the corresponding risk alleles only slightly increase the risk of developing ADHD. More recent genome-wide association studies to identify other risk variants have identified additional candidate genes [21, 22]. According to the current state of knowledge, numerous interacting gene variants are involved in the etiology of ADHD. One part of the genetically determined variance seems to be explained by frequent variants, which are not pathological per se and, by themselves, only cause a small increase in risk. On the other hand, rare gene variants, which were also found in autism and schizophrenia, seem to be involved in the etiology of ADHD as well [23-26]. Although these variants contribute stronger effects individually or within one family, each only explains a small part of the variance in the overall population. In summary, the results of genetic studies support the theory that ADHD is an expression of a genetically (co-)determined neuronal development disorder.

2.8.   Environmental risks

Research into the contribution of environmental factors to the pathogenesis of ADHD [27, 28] is methodologically difficult due to its heterogeneous etiology involving different development pathways and the uncertain causality of environmental factors. This can be illustrated, for example, by nicotine exposure—a long discussed risk factor during pregnancy. It is unclear to what extent the two to four times higher risk that children of smokers will develop ADHD [29-31] can be better explained by confounding factors of smoking during pregnancy than by causal teratogenic effects on the fetus in utero [32]. In addition to possible direct damage to the fetus from noxious agents, a lack of or insufficient care of the unborn child can lead to various indirect damage, thereby increasing the risk of premature birth [33]. In addition, there are common genetic predispositions connecting tobacco addiction and ADHD as well as common environmental risks [34, 35].

A similar picture emerges on alcohol use during pregnancy [36]. Other environmental toxins are also suspected of being involved in the etiology of the disorder. In addition, a higher excretion rate of metabolites of organic phosphates in the urine (DAP) of children with ADHD was found [37, 38]. Polychlorinated biphenyls (PCBs) or the lead content in children's blood have also been associated with ADHD [39, 40]. So far, however, the toxins mentioned only partially explain the variance in ADHD and their causal relevance remains unclear. The situation is similar in terms of certain nutritional factors (e.g. artificial food colors, preservatives etc.) [41]. However, there does not appear to be a consistent picture here either, where exposure necessarily leads to increased ADHD symptoms.

Furthermore, prematurity and low birth weight are discussed as prenatal risk factors for ADHD. With a mean risk ratio of 2.64, the association between the former and ADHD suggests a particular

prominence [42], although it currently appears to be seen only as a correlative. Also, the influence of mediating factors such as organic risks or substance use, the monitoring of which has so far mostly been neglected, needs to be clarified [43].

Moreover, studies have shown that postnatal factors such as aversive psychosocial conditions can play a role. Thus, a fairly consistent picture emerges of how early deprivation influences the development of ADHD, where extreme levels of neglect can have a particularly ADHD-favoring effect. This was evidenced in studies on Romanian orphans during childhood [44] and adolescence [45]. Interestingly, this association remains even into early adulthood, particularly with regard to the inattentive subtype [46]. The association between institutionalization and ADHD has also been demonstrated in other populations [47-51], indicating a dose effect and that the association becomes stronger as a function of the duration of deprivation [52, 53].

In addition, children with ADHD are often found to come from a background with adverse psychosocial conditions, such as parental mental illness[54], negative parenting [55, 56], but above all reduced maternal sensitivity [57, 58] and a lower degree of family support [59]. However, this again begs the question as to the extent that such psychosocial stresses are a causal factor in the development of ADHD or should merely be seen as a reaction to the child's behavior in terms of an evocative gene-environment correlation. Accordingly, it is likely that parents' negative reaction to the child's genetically influenced behavior thereby reinforces it and/or actually induces antisocial behavior. Interestingly, positive parenting behavior, particularly from the mother, seems to be a protective influence against ADHD; this proving especially true in subjects with a familial risk [60].

Low socioeconomic status is another factor that is discussed [61]. While the association between low socioeconomic status (SES) and conduct disorders is fairly clear [62, 63], the link to ADHD has recently moved into the spotlight. Population-based cohort studies have accordingly shown that a low family income in early childhood (up to the age of 5) is associated with an increased risk of ADHD [64]. However, such effects are rather non-specific and reflect a variety of risk factors, such as possible malnutrition, parenting behavior or exposure to substances [62]. It is interesting that this relationship seems to be explained by inter-familial conflict and parental attachment behavior, but not by smoking during pregnancy [65]. All in all, drawing conclusions about a causal link between environmental risks and ADHD should be viewed as tentative. The causal attribution regarding the etiology of ADHD is made more difficult by a lack of randomized controlled studies as well as by confounding factors like genes and environment, on the one hand, and various environmental influences, on the other. This requires further research, for example, using longitudinal, quasi-experimental and/or genetically informative designs.

2.9.   Gene-environment interactions

Several studies suggest that genetic factors and environmental influences interact in a complex way to contribute to the pathophysiological mechanisms of ADHD development [66]. On the one hand, environmental factors can, for example, affect the transcription of certain genes, while genetic pre-disposition can increase the risk vis-à-vis specific environmental influences on the other [39]. Studies of gene-environment interactions in ADHD have so far mainly focused on the interaction between negative environments and polymorphisms in the dopaminergic and serotonergic system. For example, two independent studies have shown that poorer mother-child interaction contributes to increased externalization of symptoms in carriers of the 7-repeat alleles of the dopamine D4 receptor gene (DRD4 exon III VNTR) subtype in both preschool children [67] and adolescents[68]. Similarly, this interaction pattern is also observed in prenatal [69-71] and postnatal environments [72-75], and thus represents the most consistent findings in the context of gene-environment interaction in ADHD. Furthermore, there was also an interaction between the variation of mini-satellites (variable number of tandem repeats; VNTR) in the dopamine transporter gene (DAT1 3′UTR) and psychosocial stresses on ADHD, whereby carriers of the 10-repeat variant showed more inattention, hyperactivity and impulsivity with increased stress [76]. This interplay was also demonstrated in girls who were abused [77] and institutionalized Romanian children who suffered early deprivation [78].

In the serotonergic system, length polymorphism in the promoter region of the serotonin transporter-linked promoter gene (5-HTTLPR) has been most frequently investigated. Overall, replications were achieved with psychosocial but not with prenatal factors [79]. For example, this interactive relationship in ADHD patients was demonstrated in a recently published study. Accordingly, carriers of the S-allele showed a more positive correlation between critical life events and the severity of ADHD compared to LL-homozygotes, which primarily affected the hyperactive-impulsive dimension [80] and was mediated by the amount of gray matter in frontal areas such as the anterior cingulum [81]. Considering the prominent variants mentioned above, it is interesting that this relationship could not be demonstrated in the dopaminergic system [82]. This pattern of interaction also occurred with regard to intrusive parenting behavior in institutionalized children [83], an adverse childhood in delinquents [84] and the presence of inter-familial conflict, whereby the latter primarily affected the inattentive type [85]. However, the findings do not appear to be consistent with those of an earlier meta-analysis in which the L allele was identified as a risk variant [19]. In conclusion, the interactions between genetic factors and environmental risks have been insufficiently researched to date and should be regarded as preliminary given the paucity of positive findings. The approach to the interplay between the adverse environment and the variation in a candidate gene thus far pursued does not seem to reflect the complex picture of ADHD adequately.

2.10. Structural and functional hallmarks in the brain

Several studies have shown that children with ADHD have a smaller whole-brain volume compared to healthy control children [86] and that mainly the gray matter was reduced, but not the white matter [87]. More pronounced volume reductions associated with the severity of the symptoms are present in the various prefrontal areas, the caudate nucleus and the cerebellum [88-90]. Functional hallmarks were also found in children with ADHD in whom frontal brain regions are consistently hypoactive and altered activation patterns were found in the anterior cingulum, the prefrontal cortex and in associated parietal, striatal and cerebellar structures [91, 92]. By contrast, increased activation was shown in regions associated with visual, spatial and motor processing, thus suggesting different processing mechanisms [66].

Notwithstanding the above, no specific brain-resident structural and functional features have been identified to date. It is clear that there are group-level differences compared to children without ADHD, although the findings have so far been very heterogeneous. To date, brain-resident structural and functional features have neither been adequate nor necessary requirements for an ADHD diagnosis [66]. It is also not yet clear as to what extent structural and functional features in the brain are the causes or consequences of the symptoms.

Other peculiarities were found in spontaneous or resting EEG recordings. Here, ADHD patients consistently showed a pattern with increased slow and reduced fast activity [93]. Studies investigating event-related potentials (ERP) have demonstrated differences in early attention orientation, inhibition processes, action control and error handling processes [94]. Accordingly, there are differences in all phases of information processing. The hypothesis that catecholaminergic neurotransmitter systems are pathophysiologically significant has not been only confirmed by studies on animal models [95] and by the effectiveness of psychostimulants in ADHD patients [96], but also by the fact that frontal-subcortical control loops (control of motor skills, attention and executive functions) are involved [66].

2.11. Neuropsychological findings

Patients with ADHD exhibited neuropsychological peculiarities in a group comparison with healthy control subjects. The findings revealed impaired executive functions [97], including motor inhibitory control [98]. In addition, basal neuronal processes are impaired with early and automated phases of information processing also being disrupted, for instance [99]. Patients with ADHD also show changed motivational and impaired learning processes (e.g. aversion to delayed gratification; reduced action control and error handling mechanisms) [95, 100]. However, the effect sizes are only in the

medium range, suggesting that there is a considerable overlap with healthy control subjects [66]. In addition, these impairments are not specific to ADHD, but are also found in other disorders.

2.12.   Temperament traits

Temperament traits can be the first precursor symptoms of ADHD [101] or can increase the risk in an existing predisposition [102]. It has been shown that increased activity levels in infants and toddlers are an indicator of the early onset of ADHD [103]. Compared to other infants of the same age, those who later develop ADHD sometimes already showed increased regulatory disorders such as excessive crying, sleep disorders or feeding problems [104] in infancy along with increased levels of negative emotionality (e.g. angry, whiny moods). The ability to exercise effortful control is less pronounced [105-108]. These deficits in the ability to self-regulate emotions may likewise be an early precursor of ADHD symptoms and involved in the development of aggressive behaviors [109].

2.13.   Diagnosis of ADHD

In order to diagnose HKD or ADHD, the diagnostic criteria provided in the ICD-10 or DSM-5 classification systems must be met. The presence of at least moderate functional impairments is also required. The symptoms (hyperactivity, inattentiveness and impulsivity) and the resulting functional impairments should be manifest in several domains of everyday life. If the symptoms only occur in one domain of everyday life (e.g. only at school/work or in the family), this may be an indication of other mental disorders (e.g. adjustment disorders due to stress in the family or at school) that need to be examined for a differential diagnosis.

2.14.   Differences between the ICD-10 and DSM-5 classification systems

ICD and DSM use different terms to describe the ADHD symptom cluster. In ICD-10, published by the World Health Organization (WHO), it is referred to as "hyperkinetic disorder", whereby all three key symptoms – inattention, impulsivity and hyperactivity – must be present (F90.0 "Disturbance of activity and attention"). If there is a coexisting conduct disorder, the diagnosis is "Hyperkinetic conduct disorder" (F90.1).

The DSM-5, published by the American Psychiatric Association (APA), distinguishes three types of ADHD presentations: predominantly inattentive, hyperactive-impulsive and combined type.

Compared to DSM-IV [110], three essential diagnostic criteria for ADHD have changed in DSM-5:
1.) The age at onset of the disorder was increased from before seven years to before twelve years

2.) from the age of 17, only five symptoms of inattention and hyperactivity/impulsivity should be present, instead of six or more

3.) ADHD can also occur with autism spectrum disorder; this is no longer an exclusion criterion [7].

In addition, DSM-5 cites examples of the corresponding symptoms to better elucidate the age-related changes in symptoms and thus ensure better detection of symptoms in adults.

The studies on which this Practice Guideline is based applied the criteria for HKD according to ICD-10 and DSM-IV for ADHD, respectively. A review of the transferability of the study results to DSM-5 findings in patients who only meet DSM-5, but not DSM-IV criteria is still pending.

Table 1: Differences in diagnostic criteria for ADHD according to ICD-10 and DSM-5

	Symptoms of "Disturbance of activity and attention" according to **ICD-10**	Symptoms of "Attention-Deficit/ Hyperactivity Disorder" according to **DSM-5**
Inattention	**For at least 6 months, at least 6** of the following symptoms of inattention have persisted to a degree that is maladaptive and inconsistent with the developmental level of the child who • Often fails to give close attention to details or makes careless errors in schoolwork, work or other activities • Often fails to sustain attention in tasks or play activities • Often appears not to listen to what is being said to him or her • Often fails to follow through on instructions or to finish schoolwork, chores or duties in the workplace (not because of oppositional behavior or failure to understand instructions) • Is often impaired in organizing tasks and activities • Often avoids or strongly dislikes tasks, such as homework, that require sustained	**A. Six** (**age 17 or older: five)** or more of the following symptoms of inattention have persisted for **at least 6 months** to a degree that is maladaptive and inconsistent with the developmental level of the child who • Often fails to give close attention to details or makes careless mistakes in schoolwork, at work or during other activities • Often has difficulty sustaining attention in tasks or play activities • Often does not seem to listen when spoken to directly • Often does not follow through on instructions and fails to finish schoolwork, chores or duties in the workplace • Often has difficulty organizing tasks and activities • Often avoids, dislikes or is

	mental effort	reluctant to engage in tasks that require sustained mental effort
	• Often loses things necessary for certain tasks and activities, such as school assignments, pencils, books, toys or tools • Is often easily distracted by external stimuli • Is often forgetful in the course of daily activities.	• Often loses things necessary for tasks and activities (e.g. school materials, pencils, books, tools…) • Is often easily distracted by extraneous stimuli • Is often forgetful in daily activities.
Hyperactivity	**For at least 6 months, at least 3 of the following symptoms of hyperactivity** persist to a degree that is maladaptive and inconsistent with the developmental level of the child who • Often fidgets with hands or feet or squirms on seat • Leaves seat in classroom or in other situations in which remaining seated is expected • Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, only feelings of restlessness may be present) • Is often unduly noisy in playing or has difficulty in engaging quietly in leisure activities • Exhibits a persistent pattern of excessive motor activity that is not substantially modified by social context or demands.	**Six** (**age 17 or older: five**) or more of the following symptoms of hyperactivity and impulsivity have persisted for **at least 6 months** to a degree that is inconsistent with the developmental level and that negatively impacts directly on social and academic/occupational activities: • Often fidgets with or taps hands or feet or squirms in seat • Often leaves seat in situations when remaining seated is expected • Often runs about or climbs in situations where it is inappropriate (Note: In adolescents or adults, may be limited to feeling restless) • Often unable to play or take part in leisure activities quietly • Is often "on the go" acting as if "driven by a motor" • Often talks excessively.
Impulsivity	**For at least 6 months, at least 1** of the following symptoms of impulsivity persists to a degree that is maladaptive and inconsistent with the developmental level of the child who • Often blurts out answers before questions have been completed	• Often blurts out an answer before

	- Often fails to wait in lines or await turns in games or group situations - Often interrupts or intrudes on others (e.g. butts into others' conversations or games) - Often talks excessively without appropriate response to social constraints.	- a question has been completed - Often has trouble waiting his/her turn - Often interrupts or intrudes on others (e.g. butts into conversations or games).
	Additional criteria:	Additional criteria:
	1. Onset of the disorder is no later than the age of **seven** years. 2. Criteria should be met for more than one setting, e.g. there should be a combination of inattention and hyperactivity both at home and at school or at school and in another place where the children can be observed, e.g. a hospital. (The evidence of symptoms in different settings usually requires information from more than one source. Parents' reports on classroom behavior are usually insufficient). 3. The symptoms (inattention, hyperactivity and impulsivity) cause clinically significant distress or impairment in social, academic or occupational functioning. 4. The patient does **not** meet criteria for **pervasive developmental disorder (F84.-),** a manic episode (F30.-), a depressive episode (F32.-) or an anxiety disorder (F41.-).	B. Several inattentive or hyperactive-impulsive symptoms were present before age **12** years. C. Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (e.g. at home, school or work; with friends or relatives; in other activities). D. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, school or work functioning. E. The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (e.g. mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).

2.15. Differential diagnosis

The key symptoms of inattention, motor restlessness and increased impulsivity indicative of ADHD can similarly be attributed to other disorders. Impaired concentration is a non-specific symptom and occurs regularly in many mental disorders like depression or in somatic diseases such as absence

seizures or thyroid conditions. Inattention can also be a symptom of anxiety disorders. However, this inattention is due to rumination or concern, rather than to a state of being easily distracted, as is the case with ADHD. A general aversion to tasks that require attention can be found in oppositional defiant disorder. The primary symptoms of oppositional defiant disorder are hostility and negativity, which do not result from general difficulties in maintaining attention, and therefore must be differentiated diagnostically from ADHD. In individuals with certain learning disorders or intellectual impairments, symptoms such as inattention or hyperactivity can also arise from a lack of interest, limited skills (and the resulting frustration). However, these are limited to school settings and therefore do not occur during non-intellectual tasks.

Hyperkinetic symptoms are found in adjustment disorders, conduct disorders or can be caused by adverse drug reactions. They should likewise be differentiated from stereotyped movement disorders, in which repetitive motor behaviors are a predominant symptom (autism spectrum disorders). Multiple motor tics can usually be well-differentiated from the generalized motor restlessness of ADHD by prolonged observation.

Disturbances of impulse control can also be found in obsessive-compulsive disorders or personality disorders. In individuals with personality disorders, disorganization, a lack of social distancing or emotional and cognitive dysregulation may, at first glance, resemble ADHD symptoms. However, there are also very specific features (deviations in the characteristic inner experience and behavior patterns by those affected from culturally expected and accepted standards/norms in the areas of cognition, affectivity, impulse control and satisfaction of needs as well as interpersonal relationships), which indicate a personality disorder. A high level of recurrent behavioral outbursts arising from the failure to control aggressive impulses is an essential criterion of the "Intermittent explosive disorder" (new in DSM-5), problems with attention, however, do not occur. Furthermore, physical aggression against property, animals or other people is absent in ADHD, but is a hallmark of "intermittent explosive disorder".

Difficulties in social behavior, often resulting from the key symptoms of ADHD, are to be distinguished from social disinterest, social withdrawal and the inability to recognize facial and vocal communication signs of an autism spectrum disorder. Also, in the case of socially disinhibited behavior, a disinhibited social engagement disorder (DSM-5 diagnosis) should be considered, especially if there is a prior history of social neglect or deprivation. If there is, however, constant irritability and low frustration tolerance, the likely diagnosis is a "disruptive mood dysregulation disorder" – new in DSM-5. Individual symptoms that also occur with ADHD can emerge as a result of family difficulties, bullying or abuse.

In addition, there are mental disorders that temporarily show symptoms within clearly defined time frames that also occur in ADHD (e.g. bipolar disorders, psychotic disorders, substance use disorders) or that can be differentiated from ADHD by their onset of symptoms (e.g. neurocognitive disorders). In these cases, a thorough medical history regarding the development of symptoms is crucial. For example, a depressive disorder to be differentiated by differential diagnosis can also be a comorbid disorder if the concentration disorder had already persisted before the depressive episode occurred and did not present for the first time as an epiphenomenon of the depression.

Comprehensive exclusion diagnostics include physical and neurological examination that is at least of an orientational nature including a cursory examination of hearing and eyesight. An electroencephalogram (EEG) should be ordered if the patient's medical history and clinical examination suggest a seizure disorder. Distinguishing the aforementioned differential diagnoses from ADHD requires qualified diagnostics and can be difficult in isolated cases. Therefore, it should also be taken into account that all differential diagnoses can also occur as comorbid disorders.

2.16. Coexisting disorders

In very few cases does an ADHD diagnosis occur in isolation. Up to 85% of those affected by ADHD have an additional comorbid mental illness [111] and, in 60% of cases, multiple comorbidities [112]. The extent varies according to age.

Comorbidities in childhood

The highest comorbidity rate (50%) in childhood occurs with oppositional defiant disorder, whereas 30-50% of those affected by ADHD also have a pronounced conduct disorder [113]. Children under the age of 12 with an oppositional defiant disorder commonly also have ADHD [114, 115]. ICD-10 classifies this comorbidity as a separate diagnosis of "Hyperkinetic conduct disorder" (F 90.1) that has proved to be valid [112]. It is known that both disorders have the same genetic etiology, but the underlying environmental factors have not yet been very specifically defined. ADHD is also considered to be a risk factor for the development of conduct disorders (CD) [116]. Conversely, a comorbid conduct disorder adds to a stability of the ADHD symptoms as well as to more pronounced hyperactivity and attention problems [114], thus representing a risk factor for the further progression [112]. In addition, the socio-economic status of this subgroup is lower than that of children with isolated ADHD [117].

The common occurrence of a mood (affective) disorder with ADHD is somewhat less common. Comorbid anxiety disorders are present in up to 25%, depressive disorders in 15%-20% [111, 118].

Particularly in anxiety disorders, it is assumed that there are common environmental factors that co-contribute to both pathologies [112]. Depression, by contrast, has a common familial vulnerability, especially amongst girls [119]. An anxiety disorder, especially a depressive disorder, frequently only develops as a result of ADHD [120]. Failure in school and increasing social difficulties with peers contribute to low self-esteem and thus promote the development of a mood (affective) disorder [121].

The comorbidity between ADHD and bipolar disorders has been discussed as controversial. Studies on comorbidities with ADHD [122, 123] and the usual treatment for ADHD with stimulants or tricyclics, where no triggering of a manic episode has been reported to date [124], suggest the conclusion that the comorbidity rate of the two disorders is extremely low and only very rarely do they occur concurrently [112]. It is therefore much more important to conduct a proper differential diagnostic work-up and differentiate adequately between the symptoms of ADHD and bipolar disorders [125]. With the publication of DSM-5, a new diagnosis of disruptive mood dysregulation disorder was introduced that is characterized by the hallmarks of constant irritability and low frustration tolerance. Many children with this diagnosis also meet the criteria for ADHD, which should then be diagnosed separately.

In ADHD, learning difficulties occur as a comorbid disorder in 10%-25% [121]. This includes language development disorders, delayed expressive speech ability, reading and writing disorders (dyslexia) or isolated dyscalculia [126, 127]. Particularly in the presence of dyslexia concurrent with ADHD, the problems in school—often already present due to ADHD—are exacerbated [121]. Studies [128] have also shown that the intellectual performance of children with ADHD was reduced by seven to 15 IQ points, although this was mostly only observed in children with attention-deficit disorder without hyperactivity [126]. Population studies have moreover shown that developmental disorders are 5-10 times more common in children with ADHD than in children without ADHD [129]. Furthermore, weaknesses in many areas of neuropsychological functional domains are associated with ADHD, e.g. in executive functions, processing speed and motivation [130]. In addition, difficulties in sensorimotor areas occur, such as problems with handwriting, awkwardness, poor performance in sports and significant delays in reaching motor milestones. Many of these children also meet the criteria for a developmental coordination disorder [131]. A tic disorder co-occurs concomitantly in up to 30% of children with ADHD [132]. Up to 70% of patients with Tourette syndrome have an ADHD that preceded the development of the tic disorder [133, 134]. The etiology of the two disorders is presumed to be a hypersensitivity of dopamine metabolism in the neostriatum [135]. Especially in terms of social interaction [112], it is difficult to differentiate between autism spectrum disorder and ADHD when symptoms of the two disorders occur comorbidly [136-139], given that they both commonly manifest social perception difficulties in social perception [112]. Studies also show that both disorders share a part of the genetic variance [140]. Using DSM-5, it is now possible to render both diagnoses, with a profound developmental disorder no longer being considered an exclusion criterion for ADHD.

Children with ADHD also have more problems falling asleep and sleeping through the night [141]. In addition, more and more studies are reporting an increased prevalence in allergies and atopic conditions (asthma, neurodermatitis, atopic rhinitis, urticaria) in conjunction with ADHD [142].

Comorbidities in adolescence and adulthood

The frequency of conduct disorders—the most common comorbidity in childhood— decreases from adolescence to adulthood. In 25% of cases at most does delinquency or anti-social behavior in the form of anti-social personality persist into adulthood. Substance dependence, such as smoking or drug use [143], usually manifest more frequently during the course of the disorder [144]. Substance abuse in ADHD mainly occurs in connection with a conduct disorder [145]. Adolescents with ADHD start smoking earlier and consume more tobacco in total than their peers [146]. There is also an increased rate of alcohol abuse and addiction amongst ADHD sufferers in adulthood; conversely, ADHD is also present in more adults with an addiction disorder [147]. As several studies have shown, treatment with stimulants can reduce the risk of developing substance dependence [148-150].

The comorbidity rate with mood (affective) disorders varies greatly between 10%-78% for unipolar depression and between 3%-14% for bipolar affective disorder [151]. It is important to differentiate the symptom of attention-deficit diagnostically from depression and hyperactivity as well as to separate impulsivity clearly from mania. Unipolar depression presents concurrent with ADHD in 7.6% and with bipolar affective disorders in 6% of cases. The course of a bipolar disorder is often more severe with comorbid ADHD [151].

Eating disorders are other comorbid conditions that occur with a greater frequency in adulthood. Borderline personality disorder is also suspected to be a comorbidity of ADHD. However, the symptoms of impulsivity, affectivity and aspects of managing relationships are similar to ADHD and should therefore be well explored, especially in terms of the differential diagnosis. Accordingly, borderline personality disorder can, in fact, be viewed as a differential diagnosis rather than a comorbid disease [112]. Studies also found an association between ADHD and obesity in adulthood [152].

Health economic aspects of ADHD

Not only ADHD itself, but all its comorbidities and interrelated problems incur considerable personal, economic and social costs. This section shall primarily focus on the medical costs of ADHD and the cost-effectiveness of potential treatment options for the disorder. Personal costs in terms of limitations in quality of life and participation have already been presented in Chapter 2.5. When considering the

economic impact of ADHD, a distinction can be made between the direct costs that arise from diagnostic and therapeutic measures and the indirect costs caused by those affected themselves and their family members due to illness-related restrictions on work and the associated loss of productivity.

According to the Nordbaden database [153, 154], the direct costs for statutory health insurance for a 7- to 9-year-old patient with ADHD in 2003 were €622, of which €182 were for medication. During the same period, a patient comparable in age, gender and health insurance affiliation incurred healthcare costs of €244, (of which €77 were for medication). For the outpatient care of ADHD patients, health insurance costs of at least €190 million per year were incurred in 2003 and a further €70 million per year were required for days in the hospital during inpatient treatment [155]. On top of this come further costs incurred by family members who utilize up to 60% more medical services [156]. According to the results of the "multimodal treatment of ADHD" (MTA) study [157], the most cost-effective treatment option was intensive drug therapy with stimulants, especially methylphenidate (including long-acting products [158]), supervised by specialized physicians [157]. These findings were also confirmed for Germany [159, 160]. Atomoxetine, a drug with a similar efficacy to methylphenidate, is a drug of second choice due to its higher costs [158]. Behavioral therapy alone performed poorly compared to pharmacological treatments [161]. However, the aforementioned results that primarily favor drug therapy should be interpreted with caution. It was the medicines that mostly performed much better because of the defined evaluation period of one year maximum and the emphasis on improvement in key symptoms [156]. By contrast, the cost-effectiveness of behavioral therapy in combination with medication was demonstrated for comorbid diseases [162].

Indirect costs of ADHD mostly arise from increased family stress amongst the parents of affected children due to reduced occupational productivity, increased absence from work, reduced working hours or giving up work altogether [163]. According to data from the USA, the annual indirect costs for businesses (estimated on prevalence projections) were more than US$ 30 billion [164]. The loss of productivity of 500 US households with an adult with ADHD was also investigated. The productivity-related loss of income was US$ 77 billion a year [165].

Overall, US data indicated that the economic costs of ADHD are comparable to the consequences of alcohol abuse (approx. US$ 83 billion) or addiction disorders (approx. US$ 58 billion) [156]. The direct costs exceed by far the indirect ones and are therefore of considerable economic relevance.

3. Further need for research

Scientific publications on the subject of ADHD continue to rise annually. For the first time in 2014, the number of ADHD publications listed in PubMed exceeded 2000 per year (see Figure 1). By the end of 2017, a total of 319 meta-analyses had been published on the topic of ADHD.

Figure 1: Number of publications listed in PubMed (in general) and meta-analyses (in particular) on the topic of ADHD (title/abstract) per year in the last 10 years.

These scientific publications have made a considerable contribution to a better understanding of the complexity and heterogeneity of this disorder and its management. Despite a considerable increase in knowledge and understanding, open questions remain while there is a further need for research in the areas of etiology, diagnosis, epidemiology, clinical course, subgroups and therapy (expanded according to [166]). In addition to content issues, we also need to design smarter, more powerful and innovative studies with well-defined large sample populations for the scientific investigation of various aspects of ADHD in general alongside well-designed longitudinal studies in particular [166]. This requires large interworking research networks, not only across the different specialties with both basic scientists and clinical researchers, but also between clinical researchers and their medical and psychological colleagues in clinical practice. Affected patients of different age groups and their families [166] should be covered as well as the different social settings (kindergarten, school, occupational and professional training, workplace).

It is essential to identify important research areas in the field of ADHD for future studies as well. The purpose hereby served is not only to develop optimal trial designs for large research networks, but likewise to convince politicians and third-party donors who finance these socially and healthcare-relevant networks of the need for these studies and of their far-reaching significance for individuals with ADHD, their families and society on the whole. In addition to questions that are interesting from a scientific perspective, the question also arises about issues, not yet addressed but relevant to individuals with ADHD, educators, teachers and personnel in healthcare, youth welfare and the justice system (expanded according to [167]).

3.1.   Further research needs in etiology and diagnostics

Although numerous studies have examined biological, genetic and environmental factors in the etiology of ADHD alongside individual biological factors combined with environmental factors [168], the complex interplay between genes (gene variations) and other biological and environmental factors has not yet been sufficiently researched. It is a known fact that environmental risk factors interact with genetic (risk) factors, covariate with genetic factors or are the main factors themselves (see also Chapter 1.1. Diagnosis). Conversely, genetic factors can interact or covariate with environmental factors or are the main factors. Indeed, gene-environment interaction studies are complicated by the many different genetic-biological risk factors and variations in the similarly interlinked environmental factors.

In addition, comorbid disorders should be fully included in study designs (e.g. comorbidity in oppositional defiant disorder (ODD)). Various studies have previously paid too little attention to the important role that the timing of the examination and therefore the correct age (development status) play in data collection. This is because there are certain time windows for the valid and useful recording of certain basic deficits and specific symptoms during developmental processes (e.g. Pauli-Pott & Becker, 2015). Studies covering larger age groups are not equally applicable across all age groups and the outcomes documented are not automatically generalizable. Moreover, outcomes of studies that mainly include male ADHD patients do not automatically apply to girls, female adolescents or women affected by ADHD. Improved identification of underlying pathophysiological ADHD mechanisms in the future is also relevant because of its potential to develop new, more specific treatment goals and methods, to identify potential biomarkers of diagnostic and/or prognostic relevance as well as to derive more specific primary and secondary prevention strategies [166].

Scientific evidence that leads to clear recommendations for reliable and economical screening instruments in pediatric and general medical practice for different age groups would be helpful in diagnosing ADHD. Another important topic would be to establish best practices for dealing with data

from varying multiple information sources (self-rated, parent-, teacher-, observer-reported assessments, behavioral observations) and to derive recommendations for diagnosing ADHD therefrom.

3.2. Further research needs for therapy and disease management as well as overriding challenges of research on ADHD

Although self-help is undoubtedly of clinical importance (see also Chapter 1.7 Self-help), further research on its effectiveness in ADHD is needed, given the paucity of relevant evaluation studies to date. The same applies to therapeutic measures such as psychoeducation or occupational therapy interventions. Also, the effects of (ADHD) specific support for pupils with ADHD from teachers in the regular school system have not yet been examined [167]. Furthermore, there is a need for studies on the effects of individualized, stepwise adaptive multimodal treatment with flexible, patient-oriented, adaptive designs in the different age groups. There is a lack of comparative studies on ADHD-specific pharmacotherapy and on drug combination therapy (benefits, adverse drug reactions, costs) as well as on pharmacotherapy in certain subgroups, e.g. ADHD patients with additional addiction problems.

ADHD is a complex disorder with a high level of heterogeneity with regard to etiology (including underlying risk factors), symptoms and basic deficits, comorbid mental and organic disorders or symptoms, the clinical courses (persistent versus non-persistent) and responses to therapy. In addition, as mentioned above, it is necessary to examine specific questions for different age groups separately (as some questions only make sense in certain age groups and development phases) and to consider gender differences. The scientifically relevant question as to whether or not a particular intervention has a demonstrable effect in ADHD has been and continues to be frequently posed. Guided by the extant pivotal study outcomes and meta-analyses, future emphasis should be on how to answer the question of more accurately defining and characterizing those subgroups that would benefit from the method investigated. For example, meta-analyses produced barely significant results for the effectiveness of cognitive training in children and adolescents with ADHD. However, the question remains unanswered as to which group of individuals affected by ADHD, e.g. children with well-diagnosed and documented specific executive function deficits, can benefit from which specific type of cognitive training. The same applies, for example, to neurofeedback studies. To date, there is (still) insufficient evidence for the effectiveness of standard neurofeedback in the treatment of ADHD. Given the heterogeneity of ADHD, however, it is perhaps unlikely that a standard neurofeedback intervention will be equally effective for all ADHD sufferers. Alongside double-blind controlled designs as standards of good research, neurofeedback, to the future, researchers should aim to more

effectively answer the question as to which neurofeedback training is the most beneficial for which subgroup and which subgroups best lend themselves to documentation and objective diagnosis. The same applies to specific training programs to treat ADHD, including its underlying basic deficits, e.g. problems with working memory, inhibition control deficits, delay aversion. In this conflagration, it has not yet been fully elucidated whether specific training programs aimed at improving the previously diagnosed basic deficits in the group of ADHD patients with those specific problems in that domain will ameliorate these basic deficits or improve functional performance while achieving a reduction in ADHD severity as well. This question should moreover be examined across the different age groups. Whether or not transcranial direct-current stimulation [169, 170] is an effective treatment for subgroups of adolescents and adults with ADHD also requires further study.

Overall, there is a need for large-scale studies to directly compare the different therapy modules (with and without medication), combination therapies and pharmacological combination treatments in addition to the need for longitudinal studies on the long-term effectiveness of various therapy modules and the course of ADHD. Likewise, studies on compliance and adherence are necessary, as this knowledge would be important for improving therapies as well.

3.3. Summary and Outlook

In summary, this all leads to the following need for further research or to the fact that the following 25 complex issues[2] have not yet been adequately resolved (modified and supplemented according to) [166, 167, 171]:

- Gender differences in etiology, comorbid disorders, course of the disorder and response to therapy
- Effects of (ADHD) specific individual teacher support on ADHD in schoolchildren attending regular classes
- Effects of individualized, stepwise adaptive multimodal treatment in different age groups
- Comparative pharmacotherapeutic studies (head-to-head studies) of various drugs approved for the treatment of ADHD
- Prospective studies on the combination treatment of various ADHD medications as well as long-term studies on the progress of patients with ADHD who no longer take medication
- Effects of ADHD medication in the subgroup of ADHD patients with comorbid addiction or increased substance use
- Effects of intensive, parent-specific programs for parents of children with ADHD

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[2] The order of the list of further research needs is arbitrary and does *not* reflect any priorities in ranking.

- Effects of self-help
- Effects of specific psychoeducation
- Capture of non-compliance rates in various ADHD therapies and the need for studies on achieving and improving adherence to therapeutic interventions in the management of ADHD
- Effectiveness of psychosocial (including psychotherapeutic) treatment programs (alone or combined with pharmacotherapy); the effectiveness of multimodal therapy in toddlers and preschool children (age < 6 years) with ADHD or externalizing behavioral problems; a comparison of different therapy programs (head-to-head) also in this age group; studies on the long-term outcome of these interventions
- Effectiveness of specific (including computer-based) training programs on specific basic deficits presumably underlying the diagnosis of ADHD, such as problems with working memory, inhibition control deficits or delay aversion in children, adolescents and adults with ADHD and diagnosed difficulties in the aforementioned basic deficits mentioned. On the one hand, it would be interesting to learn more about the effectiveness on post-training performance in these basic deficits and on ADHD symptoms and functional levels on the other.
- Effectiveness of different multimodal interventions alone or combined with pharmacotherapy in childhood, adolescence and adulthood, as well as effects in specific subgroups
- Long-term outcomes after psychosocial (including psychotherapeutic) and/or pharmacological ADHD therapy versus an appropriate comparator group, including capture of educational qualifications, occupational training and professional success
- Identification of other predictors, moderators and mediators of treatment outcomes in specific forms of therapy. To date, results are available on variants in treatment outcomes based on specific socio-demographic factors (such as low socioeconomic status, gender, ethnicity) and clinical indices (such as comorbid mental disorders, ADHD subgroups, developmental delays, comorbid partial performance disorders or weaknesses)
- Study outcome measurements of specific ADHD therapies should also encompass general functional levels (according to the Clinical Global Impairment Scale), quality of life, participation and measurements of specific functional levels in the academic and social-emotional domains
- Studies on variances in the case identification and prevalence of ADHD across different geographic regions, age groups, settings and cultures alongside studies on the causes and consequences of these variations regarding access to support systems and outcomes
- Effectiveness of transcranial direct-current stimulation in ADHD therapy
- Identification of the best diagnostic procedure for integrating information from different (multiple) information sources

- Studies on ADHD diagnosed in adulthood without previous ADHD symptoms in childhood
- Validation studies of the most reliable and concurrently economical screening instruments for use in pediatric and general practice to identify cases of possible ADHD early
- Better studies on different development pathways of individuals with ADHD over a lifespan (with identification of predictors) and large, multicenter longitudinal studies with neuroscientific (e.g. MRI, potential biomarkers still need to be identified) and neurocognitive (e.g. basic deficits, comorbid disorders) data
- Studies on benefits, risks (undesirable effects) and costs of non-pharmacological therapies for ADHD in different age groups (with blind study designs as a required quality standard)
- Studies on improved transition of patients with persistent ADHD coming of age when moving from child and adolescent psychiatric, psychotherapeutic or pediatric care to adult psychiatric or psychotherapeutic treatment
- Integration of "Big Data" study results in science and clinical practice.

All in all, there is an urgent need for multicenter, high-quality studies on the individualized, age-specific and adaptive treatment of ADHD across different age groups, taking into account specific subgroups and using flexible designs aligned with the clinical course.

To cite one example: As part of the German research network on mental illnesses, financed by the Federal Ministry of Education and Research (BMBF) – a multicenter research association consisting of both child and adolescent psychiatric and (adult) psychiatric centers – is currently evaluating an "Evidence-based, Stepped Care of ADHD Along the Life-span" (ESCAlife; www.esca-life.org). Amongst other things, the efficiency and effectiveness of individualized and stepped multimodal treatment programs is examined and attempts are made to identify predictors for individualized therapeutic response to optimize treatment strategies.

What are needed in addition to new, innovative designs, a high-quality capturing of ADHD symptoms and associated factors [Clinical Global Impression (CGI), functional level in various domains such as school, education, training, job, family and peer group, friendships and quality of life] and of neurobiological factors is good collaboration between the various specialist disciplines of child and adolescent psychiatry, pediatrics, psychiatry, child and adolescent psychotherapists and psychological psychotherapists; outpatient clinics, hospitals and clinicians in private practice; cooperation with schools, basic scientists with clinicians etc.). Moreover, appropriately setup third-party funded programs aimed at solving scientific and care-provision-related issues are needed to improve prevention, early detection and, most importantly, the therapy and clinical course of ADHD across the different age groups.

II. Recommendations with comments and derivation of the evidence

1. Recommendations with comments

The recommendations in this Practice Guideline are graded using the symbols shown in Table 2. In addition to the symbols, the wording of the recommendation also reflects the respective grade of recommendation. Further information can be found in the Practice Guideline Method Report in Chapter 5.2.3.

Table 2: **Recommendation grading (according to AWMF, 2012)**

Strength of	Description	Wording	Symbol
A	Strong recommendation	Shall/shall not	⇑⇑
B	Positive recommendation	Should/should not	⇑
0	Open recommendation	Can be considered/ can be rejected	⇔
CCP*	Good Clinical Practice		-

CCP* ("Clinical consensus point" or expert consensus): Recommended as "good clinical practice point" as a treatment standard reached by consensus and based on the clinical experience of the Guideline Group members where no experimental scientific research is possible or pursued.

1.1. Diagnosis

In order to make a diagnosis of ADHD, the symptoms of hyperactivity, impulsivity and/or inattention must meet the ICD-10 or DSM-5 criteria (see also "Diagnostic decision tree for HKD (ICD-10) and ADHD (DSM-5)" in Appendix III.1.). These include at least moderate impairments in relationships, performance, activities and participation. The symptoms and the resulting functional impairments must be present in several domains of everyday life. If the symptoms are only present in one domain of everyday life (e.g. only at school/work or in the family), this can be an indication of other mental disorders that need to be investigated in terms of a differential diagnosis.

The diagnosis must be coded according to ICD-10 for the provision of billable medical care/psychotherapy under the statutory health insurance scheme in Germany [2]. In contrast to ICD-10 (F90.0), DSM-5 differentiates between different presentations. Presumably, ICD-11 will adopt this

presentation classification. However, the DSM-5 classification can also be reflected in ICD-10 (see Decision Tree for Diagnosis Criteria, Annex III.1.).

1.1.1. Who should undergo diagnostics for ADHD?

The possibility of an underlying ADHD should be considered and appropriate diagnostic tests ordered in children, adolescents and adults with developmental, learning/performance or behavioral problems or other mental disorders (see II.1.1.9.) and signs of impaired attention, concentration or increased restlessness or impulsivity.

Notes on the evidence in Section: II.2.1.1.

Consensus recommendation: Without COI 100% – all 100%

Quality of evidence: Moderate

Grade of recommendation: Recommendation, ↑, B

1.1.2. Who should diagnose ADHD?

In **children and adolescents,** the diagnosis of ADHD should be made by a specialist in child and adolescent psychiatry and psychotherapy, a child and adolescent psychotherapist or a psychological psychotherapist with additional qualifications for children and adolescents, or by a specialist in pediatric and adolescent medicine with experience and expertise in the diagnosis of ADHD.

In **adults**, the diagnostic clarification should be carried out by a specialist in psychiatry and psychotherapy, a specialist in neurology, a specialist in psychosomatic medicine, physicians with certification in psychotherapy or psychological psychotherapists. If there are indications of coexisting mental disorders or physical illnesses, or if it seems necessary to differentiate them from other mental disorders or somatic illnesses, a referral to a specialist from the relevant discipline should be made if the options available for diagnostics and treatment are insufficient.

Notes on the evidence in Section: II.2.1.2.

Consensus recommendation: All 96.3% (only one round of voting[3])

If the diagnosis is made by a child and youth psychotherapist or by a psychological psychotherapist, the mandatory physical examination according to II.1.1.3 should additionally be carried out by a physician.

Notes on the evidence in Section: II.2.1.2.

Consensus recommendation: Without COI 93.3% – all 92.6%

Quality of evidence: Expert consensus

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[3] There was only one round of voting for this recommendation. An explanation can be found in the Preamble.

Commentary on the recommendation:

In **children and adolescents**, the diagnostic clarification of ADHD should be carried out by a doctor or psychotherapist with the appropriate developmental psychopathological expertise; this is because a profound knowledge of the development-specific manifestations of ADHD symptoms and its comorbidities is not only required to diagnostically classify the condition but particularly to render a differential diagnosis against other related disorders.

Similarly, the diagnosis of ADHD in **adults** should be carried out by a physician or by a psychotherapist with appropriate psychopathological expertise; this is because a profound knowledge of the manifestations of ADHD symptoms and its comorbidities is not only required to diagnostically classify the condition but essential to rendering a differential diagnosis against other related disorders of adulthood in the various domains of everyday life.

Dissenting opinions expressed by the BVDN & BVDP

Who should diagnose ADHD?

According to the current (model) regulations on continuing medical education of the German Medical Association that govern the board-certification of specialists in psychiatry and psychotherapy to allow them to also treat children and adolescents, it is possible for a specialist in psychiatry or in psychiatry and psychotherapy or a neurologist with experience and expertise in diagnosing ADHD to diagnose ADHD in older children and adolescents. The details of the dissenting opinions and the reasoning can be found in the Appendix under point III.8.1., p. 160.

Steering Committee commentary on dissenting opinions

The still currently valid (model) regulations on continuing medical education of the German Medical Association are merely recommendatory in nature when applied to the state medical associations. Each physician is only legally bound by the regulations on continuing medical education governing the state medical association of which he is a member. In general, the regulations on continuing medical education of the state medical associations do not mandate continuing medical education periods in the fields of child and adolescent psychiatry, psychotherapy or pediatrics.

1.1.3. Which diagnostic tests should be used routinely?

The diagnosis should be made on the basis of:
- A comprehensive structured assessment of the patient and—especially for children and adolescents—of their reference persons (especially the parents, but if possible the teacher/educator, including written reports and report cards) to:

a) Current presentation of ADHD symptoms (type, frequency, intensity) in different domains of everyday life (family, school, leisure) and the situational variability in these domains of everyday life (e.g. homework, family activities)

b) Resulting limitations on functionality (e.g. in relationships, performance, participation)

c) Current coexisting psychological symptoms/disorders or physical illnesses

d) Current and previous environments, resources and stresses in the family and in kindergarten/school or at work, including the mental and physical health of the reference persons

e) The history of the disorder-specific development (e.g. start and course of the symptoms) against the background of the general development history including relevant pretreatments

f) The resources, wishes and needs of the patient and their reference persons

g) The family history, particularly with evidence of ADHD in parents/siblings/children.

Notes on the evidence in Section: II.2.1.3.

Consensus recommendation: Without COI 95.5% – all 96.3%

- The behavioral observation reported by the patient and – in the case of children and adolescents – of the patient-parent interaction during the examination situation (ADHD symptoms do not necessarily need to occur)

- The psychopathological assessment of the patient based on explored and observed symptoms

- The physical and particularly the neurological examination assessing the level of development.

Notes on the evidence in Section: II.2.1.3.

Consensus recommendation: Without COI 95.7% – all 96.3%

Quality of evidence: Expert consensus

Dissenting vote from the DGPs along with the reasoning can be found in the Appendix under point III.8.4., p. 170 - 173.

Commentary on the recommendation:

For taking a structured medical history, it is recommended that the diagnostician be familiar with at least one standardized structured interview and use it as guidance.

1.1.4. How important are patients' self-assessments?

Alongside the crucial importance of reports given by parents and other reference persons for the assessment of ADHD symptoms in childhood, the inner experience of the child or adolescent should also be taken into account when assessing the clinical significance and impairment caused by their ADHD symptoms. In adults, the assessment is based primarily on the result of the diagnostic interview, as is the case with other mental disorders. The information should be compared with those of close reference persons, if available.

Notes on the evidence in Section: II.2.1.4.

Consensus recommendation: Without COI 100% – all 100%

Quality of evidence: Expert consensus

1.1.5. How important is the use of questionnaires and behavioral observations in diagnosing ADHD?

Although the diagnosis should not be made solely on the basis of questionnaires or behavioral observations, questionnaires are helpful for parents, teachers or patients (see list of psychometrically investigated procedures for the detection of ADHD in German, Appendix III.4.) and should also be used for in-depth exploration of ADHD or coexisting symptoms.

Behavioral observations made outside of the actual examination situation (e.g. at school) are useful and should be carried out, especially if symptoms cannot be conclusively explored.

Notes on the evidence in Section: II.2.1.5.

Consensus agreement: Without COI 90.48% – all 92.31%

Quality of evidence: Expert consensus

1.1.6. How important is the use of psychological tests in the context of neuropsychological, developmental and performance-related diagnostic assessment?

The diagnosis of ADHD should neither be made nor excluded solely on the basis of psychological tests. However, psychological tests can be used to supplement a diagnostic assessment and are necessary to answer specific questions (e.g. if there is a suspicion of academic overchallenging, diminished intelligence, developmental disorders or specific neuropsychological disorders). Behavioral observations during the psychological test assessment can provide additional information about the presence of ADHD symptoms. However, ADHD symptoms do not necessarily have to occur during the examination.

Notes on the evidence in Section: II.2.1.6.

Consensus recommendation: Without COI 100% – all 100%

Quality of evidence: Expert consensus

1.1.7. What are the importance of laboratory tests and technical diagnostic procedures?

Checking laboratory parameters routinely is not required for the diagnosis of ADHD. Any laboratory tests and technical diagnostic procedures should be carried out prior to elective pharmacotherapy, if they are important for diagnosing possibly underlying somatic diseases or for the differential diagnosis.

Notes on the evidence in Section: II.2.1.7.

Consensus recommendation: Without COI 100% – all 100%

Quality of evidence: Expert consensus

1.1.8. Are there any age-specific features that should be considered in the diagnostic process?

The diagnostic process should take into account age-specific symptom peculiarities in the different age groups:

- The diagnosis of ADHD should not be made in children under the age of three years.
- In children aged three to four years, the diagnosis cannot usually be made with sufficient certainty.
- In preschool children, the diagnosis should generally only be made if the symptoms are very pronounced.
- In younger children, very pronounced restlessness, impulsiveness, distractibility and regulation disorders can be risk factors for the development of ADHD.
- The younger the children, the more difficult it is to differentiate them from normal variations.
- In adolescence and adulthood, the reduction in hyperactivity that often occurs during puberty must be considered.

Other mental disorders must be differentiated in terms of differential diagnosis or considered as coexisting disorders.

Notes on the evidence in Section: II.2.1.8.

Consensus recommendation: Without COI 87.0% – all 88.9%

Quality of evidence: Expert consensus

1.1.9. Which mental disorders or somatic diseases are differential diagnoses of ADHD?

Hyperactivity-impulsivity and inattention can also occur in other mental disorders, but they have additional features that usually do not occur in ADHD.

The following should be considered:

- Conduct disorders (CD), which may be accompanied by refusal to complete tasks that

require sustained mental effort

- Stereotyped movement disorders (isolated or in the context of autism spectrum disorders or mental retardation), which can be accompanied by an increased motor restlessness
- Tic and Tourette's disorders, which can be characterized by sudden, irresistible movements
- Specific developmental disorder of motor function and learning disorders that may be associated with inattention
- Diminished intelligence, where overchallenging can trigger symptoms of ADHD
- Autism spectrum disorders, in which inattention or even impulsivity can be triggered by autistic symptoms
- Relationship/attachment disorder with disinhibition, in which socially uninhibited impulsive behavior occurs
- Generalized Anxiety Disorder (GAD), which may include inattention and restlessness related to anxiety
- Depressive disorders that can cause problems with concentration
- Bipolar disorders, in which episodic over-activity, impulsivity and concentration problems occur
- Disruptive mood regulation disorders, in which impulsivity occurs in the context of irritability
- Substance use disorders in which symptoms of ADHD can be triggered by substance use
- Personality disorders, in which symptoms of disorganization, social pushiness, as well as emotional and cognitive dysregulation can occur
- Psychotic disorders, in the course of which ADHD symptoms can also occur
- Drug-induced disorders, for example with bronchospasmolytic agents
- Fatigue and inattention in the presence sleep disorders (including sleep apnea)
- Hyperarousal in post-traumatic stress disorder (PTSD).

Consensus recommendation: Without COI 90.91% – all 92%

Organic diseases can trigger behaviors that are misinterpreted as ADHD symptoms:
- Visual or hearing disorders that are misinterpreted as inattention
- Seizure disorders that are misinterpreted as inattention or motor restlessness
- Thyroid dysfunction.

Consensus recommendation: Without COI 90.9% – all 92.3%

Organic diseases can also trigger symptoms of ADHD and should also be diagnosed, e.g. epilepsy, fragile X syndrome, 22q11 deletion syndrome, neurofibromatosis type 1, fetal alcohol spectrum disorder (FASD).

Disorders to be ruled out in the differential diagnosis can also occur as coexisting disorders (see II.1.1.10.).

Notes on the evidence in Section: II.2.1.9.

Consensus recommendation: Without COI 100% – all 96.3%

Quality of evidence: Expert consensus

1.1.10. Which common coexisting disorders deserve special consideration?

Coexisting disorders occur frequently, can have an adverse effect on the prognosis and require special therapeutic measures.

The disorders that occur with the greatest frequency include oppositional defiant behavior (in children) and other conduct disorders, tic disorders, specific developmental disorders (of motor function, language, scholastic skills), anxiety disorders, depressive disorders, autism spectrum disorders and, from adolescence onward, substance use disorders and personality disorders; these should be monitored, diagnosed based on the appropriate evidence and treated according to the respective guidelines.

Notes on the evidence in Section: II.2.1.10.

Consensus recommendation: Without COI 100% – all 100%

Quality of evidence: Moderate

Grade of recommendation: Strong recommendation, ↑↑, A

1.2. Intervention algorithm

See also the differential therapeutic decision trees for children, adolescents and adults in the Appendix (III.2 and III.3).

1.2.1. How should the individual treatment option be selected?

For children, adolescents and adults with ADHD who meet the diagnostic criteria, it is important to clarify which treatment options are possible (informed decision) and also which are desired and supported by the patient and his reference persons (shared decision-making).

When selecting therapy, personal factors (e.g. level of suffering), environmental factors, the severity of the disorder and the coexisting disorder as well as participation should be taken into account.

Notes on the evidence in Section: II.2.2.

Consensus recommendation: All 88.9% (only one round of voting[3])

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[3] There was only one round of voting for this recommendation. An explanation can be found in the Preamble.

Quality of evidence: Expert consensus

1.2.2. How should the treatment be planned?

1. The treatment of ADHD should be carried out as part of a multimodal comprehensive therapeutic concept (treatment plan), whereby psychosocial (including psychotherapeutic) and pharmacological as well as complementary interventions can be combined, depending on the individual symptoms, the functional level, the participation as well as the preferences of the patient and their environment.

2. In general, comprehensive psychoeducation[4] should be offered, where patients and their relevant reference persons are educated about ADHD, individual disorder concepts are developed and treatment options are presented with the aim of enabling shared decision-making.

3. Children under the age of six years should primarily receive psychosocial[5] (including psychotherapeutic) interventions. Pharmacotherapy for ADHD symptoms should not be offered before the age of three.

4. In mild ADHD, the primary intervention should be psychosocial (including psychotherapy). In individual cases, pharmacotherapy can also be offered if residual ADHD symptoms require treatment.

5. In moderate ADHD, following extensive psychoeducation, either intensive psychosocial (including intensive psychotherapeutic) intervention, pharmacological treatment or a combination of both should be offered, depending on the patient's specific situation, their environment, the preferences of the patient and their relevant reference persons as well as on treatment resources.

6. In severe ADHD, pharmacotherapy should primarily be offered after intensive psychoeducation. A parallel intensive psychosocial (including psychotherapeutic) intervention can be integrated into pharmacotherapy. Depending on the course of pharmacotherapy, psychosocial (including psychotherapeutic) interventions should be offered in the event of residual ADHD symptoms that require treatment.

Consensus recommendation: All 76.9% (only one round of voting[3])

7. Coexisting disorders should be treated in accordance with practice guidelines. When deciding which disorder should be treated first, the severity of the disorder, amongst others, should be considered.

Consensus recommendation: All 100% (only one round of voting[3])

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[4] The definition of "psychoeducation" used here can be found in the commentary on this recommendation.

[5] The definition of "psychosocial" used here can be found in the commentary on this recommendation.

Notes on the evidence in Section: II.2.2.

Quality of evidence: Expert consensus

Some dissenting votes from the BVKJ and bkj and bvvp on this recommendation as well as associated reasoning and commentary can be found in the Appendix under point III.8.2., p. 161 – 164 and III.8.3., p. 164 – 170.

Comments on the recommendation:

Treatment planning:

For **children and adolescents,** treatment planning should be carried out by a specialist in child and adolescent psychiatry and psychotherapy, or a child and adolescent psychotherapist, or by a clinical psychotherapist with additional qualifications in working with children and adolescents, or a specialist in pediatric and adolescent medicine with experience and expertise in the treatment of ADHD.

In **adults,** treatment planning should be undertaken by a specialist in psychiatry and psychotherapy, a specialist in neurology, a specialist in psychosomatic medicine, physicians with certification in psychotherapy or psychological psychotherapists.

If, in addition to the core symptoms of ADHD, resulting impairments of functioning, quality of life and participation occur, or if there are specific psychosocial stress factors, the patient and his reference persons should be advised of adjuvant and supportive psychotherapeutic and pharmacological treatment options. These symptoms should then be treated in accordance with the relevant practice guideline.

Severity classification:

Mild:

In addition to the symptoms required for the diagnosis, no others occur at all or with a mild frequency and only lead to minor impairments in the domains of social, academic or professional functioning.

Moderate:

The severity of symptoms and functional impairments range between "mild" and "severe", i.e. despite only mild symptoms, the symptoms result in a clear functional impairment or, despite only a current presentation of minor impairments in the domains of social, academic or occupational functioning, the symptoms present are clearly in excess of those required for rendering the diagnosis.

Severe:

The number of symptoms is clearly in excess of those required for rendering the diagnosis or several symptoms that are particularly severe, are present, or the symptoms result in marked impairment in social, academic or occupational functioning.

The degree of severity (mild, moderate and severe) was classified according to DSM-5. Both the symptom severity and the degree of functional impairment are used to define the severity grade. Please note that the diagnosis checklist for ADHD (DCL-ADHD) based on the diagnostic system for mental disorders according to ICD-10 and DSM-5 in children and adolescents [172] was used to determine the clinical severity in children and adolescents. This checklist contains both a determination of the degree of severity of each individual symptom as well as an assessment of functional impairment.

Several studies agree that ADHD is best seen as a dimensional disorder (and not as a categorical unit). This has now become very well supported scientifically by twin studies on heritability [173-176], confirmatory factor analyses [177-180] and psychometric analyses, such as Item Response Theory [181].

To this extent, a grading of symptom severity is easily justified and using the DSM-5 classification into mild, moderate and strong ADHD symptoms constitutes the most straightforward grading method. The degree of severity is based on the clinical assessment that takes account of symptom severity, the functional level and the psychosocial conditions of the patient. Such clinical assessment can be documented using the Clinical Global Impression Scale (CGI; [182]), which has proven to be reliable and sensitive to change in research (cf. [183]). The grade of severity can also be ascertained from parent-, educator- and teacher-rated assessments, obtained using questionnaires (e.g. [172, 184]), but also on the basis of clinical assessments, for example via the diagnostic checklist for ADHD [172, 185]. The scales and subscales for ADHD (e.g. for inattention and for hyperactivity-impulsivity), which have been developed on the basis of these instruments, show very good reliability and factorial validity. Additionally, these methods also offer scales for capturing functional limitations in the assessments reported by parents, teachers, the patients themselves as well as by clinicians.

The overall conclusion is that the grading of ADHD symptoms can be empirically justified. The derivation of the empirical evidence for the intervention algorithms is described in Chapter II.2.2. (p. 92 f.).

Similar to the guidelines of the American Academy of Child and Adolescent Psychiatry and the American Academy of Pediatrics, the recently published update of the NICE guideline comes to the conclusion that the use of pharmacotherapy is recommended for managing ADHD, regardless of its degree of severity. As such, the recommendation in the German guidelines regarding the use of

pharmacotherapy must be regarded as conservative. Notwithstanding the fact that the effects of psychosocial interventions are deemed to be moderate—at least by the unblinded assessments commonly used in routine care—the recommendation of giving higher priority to psychosocial interventions when the severity is mild would still appear well justified.

Pharmacotherapy in preschool children

Pharmacotherapy for preschool children (three to six years) mentioned in point 3 should only be undertaken by a physician with specialized knowledge in behavioral disorders in this age group (see II.1.4.1). Based on current study data, the effects of pharmacotherapy on brain development in children of pre-school age is thought to be rather favorable. Possible impacts on weight and longitudinal growth are addressed in Recommendations 1.4.6.5. and II.1.4.6.6., and in the Derivation of the Evidence (II.2.4.2.1 and II.2.4.3.1.1.). In general, study results provide conclusions at the group level. In some individual cases and in severe ADHD, an individual risk-benefit assessment is therefore necessary.

Definition of psychosocial interventions

Psychosocial interventions include mindful, planned psychological, psychotherapeutic and social interventions that have been learned during training and are aimed at reducing ADHD or comorbid mental disorders. Psychosocial interventions can be intended for the patient or their reference persons (e.g. parents, teachers, partner) or involve the patient's immediate or wider environment (family, daycare center, school, workplace, community). Psychosocial interventions can be delivered by different professional groups as long as they have the appropriate qualifications, for example psychologists, psychotherapists, doctors, educators, occupational therapists or social workers.

Definition of psychoeducation

Psychoeducation or psychoeducational interventions encompass the education and counseling of patients or their reference persons about the disorder, its causes, clinical course and intervention options. Besides providing didactically communicated information about possible impairments, focus should also be placed on individual strengths and resources, e.g. special athletic skills, spontaneity, sociability or creativity in order to enable these items to be experienced by the patient and their psychosocial environment. This informational content is worked up with the patient together with their reference persons to develop an individualized disorder concept relating to the presumed causes, and the likely course of the symptoms in the particular individual's case. In addition, specific strategies are developed for coping with the problems and their consequences in the various domains of the patient's everyday life. Psychoeducation forms the basis of all further psychosocial (including

psychotherapeutic) and pharmacological interventions and provides those affected with information that makes "shared decision making" (SDM) possible. Intensive psychosocial (including psychotherapeutic) interventions also include the delivery of interventions that go beyond psychoeducational counseling and, for instance, include concrete and detailed instructions to the parents or other reference persons on how to change the way they interact with the patient. This also includes interventions to modify the cognitive trajectory (including attitudes), emotions and actions of reference persons and patient while giving both parties concrete therapeutic tasks.

As part of the multimodal treatment plan, described in point II.1.2.2, interventional objectives in the domains of activities and participation should be prioritized. These defined objectives should be discussed with the person concerned and their family members.

1.2.3. What procedures should be adopted if there is no response to the therapeutic measures?

If the therapeutic measures, be they pharmacological or non-pharmacological, e.g. parent training, psychosocial (including psychotherapeutic) interventions, have only little or no effect at all, the practitioner should review:

In general:

- Whether the diagnostic criteria for ADHD are met
- Whether the poor therapeutic response can possibly be explained by underlying coexisting disorders/diseases
- How patients and guardians are attuned to the therapeutic interventions used
- To what extent guardians/other caregivers support the patient's treatment and the patient is motivated to receive treatment
- Whether the fear of stigmatization affects acceptance of the therapy.

Additionally by pharmacotherapy:

- How regularly the medication was taken, whether there were any adverse reactions and how the patient's adherence to the treatment can be assessed in this context
- Whether the medication was prescribed and taken in a sufficient dose and at the appropriate frequency throughout the day.

Notes on the evidence in Section: II.2.2.

Consensus recommendation: Without COI 100% – all 100%

Quality of evidence: Expert consensus

1.2.4. How should ongoing coexisting disorders or problems be dealt with?

If pharmacotherapy or non-pharmacological therapy is successful in treating the core ADHD symptoms, together with the patient and their reference persons, it should be assessed whether coexisting disorders or problems are ongoing (e.g. aggressive behavior, anxieties or learning difficulties). An individualized treatment plan should be drawn up and appropriate measures initiated to address these accompanying difficulties.

Notes on the evidence in Section: II.2.2.

Consensus recommendation: Without COI 100% (one abstention) - all 100% (one abstention)

Quality of evidence: Expert consensus

1.3. Interventions on a psychological-psychotherapeutic level (psychoeducation, psychosocial interventions, psychotherapy, neurofeedback), diets

1.3.1. Psychosocial interventions

1.3.1.1. Preventative psychosocial interventions that do not require diagnostic confirmation

1.3.1.1.1. Which preventative psychosocial interventions are recommended?

Advice on appropriate parenting behavior and influence of teachers (including parent training, educator training) should also be offered to children with expansive behavior problems (e.g. oppositional behavior, increased restlessness, clear distractibility) even if the criteria for an ADHD diagnosis are not (yet) fulfilled or have not been clarified. In this context, interventions that generally aim to strengthen parenting behavior and have a more preventive character should additionally be offered and/or training sessions that have proven effective in children with aggressive behavior (see Appendix III.5 German-language prevention programs recommended by the Steering Committee).

Notes on the evidence in Section: II.2.3.1 and the evidence table in the Method Report, Appendix 11.4.1.

Consensus recommendation: Without COI 100% – all 100%

Quality of evidence: Expert consensus

1.3.1.2. Psychosocial interventions in preschool children with ADHD

1.3.1.2.1. Which psychosocial (including psychotherapeutic) interventions should be used in preschool children with ADHD (approx. three to six years)?

1.3.1.2.1.1. Parents of children with ADHD that are under school-age should be offered parental training/education/counseling (including psychoeducation) as the primary intervention. The intervention can also be offered as guided self-help. The aim of these interventions is to improve

parents' understanding of the symptoms, optimize their parenting behavior and reduce expansive behavioral problems including the ADHD symptoms and psychosocial impairments of the child in the home environment.

Notes on the evidence in Section: II.2.3.1 and the evidence table in the Method Report, Appendix 11.4.1.

Consensus recommendation: Without COI 95% – all 96.3%

Quality of evidence: High

Grade of recommendation: Strong recommendation, ↑↑, A

Dissenting opinion 4 of bkj and bvvp and the associated reasoning can be found in the Appendix under point III.8.3., p. 166 - 167.

Commentary on the recommendation:

A guide to dealing with difficult everyday situations and aids for parents to acquire skills to support significant activities and to cope with developmental tasks that the child will face offer the parents real help in the upbringing of the child.

1.3.1.2.1.2.   As ADHD symptoms also occur in the kindergarten/at the daycare center, educators should be offered training in behavioral therapy (educator training) or advice. These interventions aim to improve educators' understanding of the symptoms, to optimize their teaching methods against the backdrop of ADHD symptoms and to reduce expansive behavior problems, including ADHD symptoms such as the child's psychosocial impairment in the environment of the kindergarten or daycare center.

Notes on the evidence in Section: II.2.3.1 and the evidence table in the Method Report, Appendix 11.4.1.

Consensus recommendation: Without COI 95% – all 88.9%

Quality of evidence: Moderate

Grade of recommendation: Recommendation, ↑, B

Commentary on the recommendation:

As part of the training, the educators should also be given options and direct suggestions how they can effectively support the acquisition of skills to deal with important developmental tasks the child will face, and how to promote the affected child's satisfactory participation in everyday life at the kindergarten/daycare center. In addition, the educators will also be advised on how to optimize the spatial environment in such a way that the affected child can act and participate more successfully.

1.3.1.2.1.3.   Here, programs that were primarily developed for children with oppositional or aggressive behavior should also be used. These programs can also be applied absent the formal diagnosis of a conduct disorder.

Notes on the evidence in Section: II.2.3.1 and the evidence table in the Method Report, Appendix 11.4.1.

Consensus recommendation: Without COI 95% – all 92.6%

Quality of evidence: Moderate

Grade of recommendation: Recommendation, ↑, B

1.3.1.2.1.4. Child-centered interventions (training sessions) to improve the intensity and endurance of playing and keeping occupied or to practice the routine actions of everyday life can be offered as adjunctive measure, but are usually not sufficient alone.

Notes on the evidence in Section: II.2.3.1 and the evidence table in the Method Report, Appendix 11.4.1.

Consensus recommendation: Without COI 95% – all 92.6%

Quality of evidence: Low

Grade of recommendation: Recommendation open, ↔, 0

Commentary on the recommendation:

These training courses can also be used additionally for acquiring skills in important everyday activities and for coping with developmental tasks the child will face. To ensure their generalization and transfer into everyday life, child-centered interventions should always be carried out in combination with parent-centered interventions.

1.3.1.2.2.   Which training format (individual versus group) should be offered to parents/educators for preschool children with ADHD?

Parents' and educators' group or individual training sessions that were developed specifically for the treatment of children with ADHD or with oppositional aggressive behaviors should be accessible to parents and other reference persons; in this context, group trainings have been better evaluated. Therefore, group training should be preferred if possible.

However, individual training may be preferred because of the complexity of the child's or the family's problems or for organizational reasons (e.g. because parent groups do not take place).

Notes on the evidence in Section: II.2.3.1 and the evidence table in the Method Report, Appendix 11.4.1.

Consensus recommendation: Without COI 90% – all 88.9%

Quality of evidence: Expert consensus

1.3.1.2.3. How should parent training be carried out in preschool children with ADHD?

Parent training in a **group format** should:

- Involve both parents as far as possible and be beneficial for the child
- Not include more than 10-12 parents in a group, whereby a smaller group size can help intensify group work
- Be based on social learning theory and teaching behavior modification methods including resource-oriented approaches to improve relationships
- Include psychoeducation and cognitive methods as well as methods of model learning, behavioral exercises and feedback in order to modify parenting behavior
- Be carried out in accordance with the specifications of an evaluated and established training manual in order to ensure consistent implementation of the training manual (see Appendix III.5 with evidence-based manuals in German for psychosocial (including psychotherapeutic) interventions in children and adolescents with ADHD and their reference persons).

The treatment usually consists of 10 to 16 sessions, each lasting 90 to 120 minutes.

Notes on the evidence in Section: II.2.3.1 and the evidence table in the Method Report, Appendix 11.4.1.

Consensus recommendation: Without COI 85% – all 84.6%

Parent training in an **individual format** should:

- Involve both parents (or other important educators) and benefit the child as much as possible; parent behavior training practice should also involve the child
- Be based on the social learning theory (similar to parent training in the group format (see above), apply comparable methods and be carried out according to the specifications of an evaluated and established training manual to ensure consistent implementation of the training manual (see Appendix III.5 with evidence-based manuals in German for psychosocial (including psychotherapeutic) interventions in children and adolescents with ADHD and their reference persons).

This training usually consist of at least 8 to 10 sessions lasting 45 to 90 minutes, although longer treatments may also be indicated.

Notes on the evidence in Section: II.2.3.1 and the evidence table in the Method Report, Appendix 11.4.1.

Consensus recommendation: Without COI 85% – all 85.2%

Quality of evidence: Expert consensus

Commentary on the recommendation:

The individual parent training courses mentioned in the recommendation can also be carried out as interventions in the home environment. Here, parents who are particularly stressed may be better cared for than with outpatient therapy, and the generalization of newly acquired skills in daily life is probably better, as the newly acquired behaviors can be practiced in their natural environment.

1.3.1.2.4. Under what conditions should counseling or training courses for educators of preschool children with ADHD (educator training) be carried out?

If pronounced ADHD symptoms also occur in kindergarten (which is usually the case), then, in addition to parent training, advice or training for educators of children with ADHD (educator training) should be carried out parallel to and oriented towards parent training/parent education in individual or group format. Here, structured interventions at group level (e.g. strict group rules) should also be considered (see Appendix III.5 with evidence-based manuals in German for psychosocial (including psychotherapeutic) interventions in children and adolescents with ADHD and their reference persons). Individual training may be preferred due to the complexity of the child's problem or in the kindergarten setting, or for organizational reasons (e.g. because educator training groups are not taking place).

Notes on the evidence in Section: II.2.3.1 and the evidence table in the Method Report, Appendix 11.4.1.

Consensus recommendation: Without COI 95% – all 96.3%

Quality of evidence: Low

Grade of recommendation: Recommendation, ↑, B

Commentary on the recommendation:

The above-mentioned counseling or training for educators of children with ADHD in pre-school age children (educator training) can also be carried out on-site.

1.3.1.2.5. How should child-centered interventions be delivered in pre-school age children with ADHD and which child-centered interventions are recommended?

If the symptoms of ADHD also occur in therapy situations or during activities to support early development, child-centered interventions can be delivered as adjuncts to parent training; here, the aim is to improve the child's intensity and endurance of playing and keeping occupied, to practice routine actions and cope with upcoming developmental tasks. Here, particular attention should be paid to

general changes in the child's behavior in daily life. In addition, child-centered interventions can be used to reduce developmental deficits, defiant behavior and other behavioral or emotional problems.

Notes on the evidence in Section: II.2.3.1 and the evidence table in the Method Report, Appendix 11.4.1.

Consensus recommendation: Without COI 84.2% – all 80.77%

Quality of evidence: Expert consensus

Dissenting vote 5 of bkj and bvvp and the associated reasoning can be found in the Appendix under point III.8.3., p. 167 - 168

1.3.1.2.6. What further measures should be considered after completing psychosocial (including psychotherapeutic) interventions in pre-school children with ADHD?

If the entire outpatient treatment could successfully improve ADHD symptoms and the associated functional limitations, the following aspects should be considered:

- Before finishing therapy, it should be checked if there are any residual coexisting abnormalities that require treatment and, if so, a new treatment plan should be developed. Here, the child, their parents or other educators and siblings should be involved.
- After starting school, it is important to check whether ADHD symptoms and associated impairments reoccur.

If the ADHD symptoms and their associated functional limitations cannot be successfully reduced by overall outpatient management (including comprehensive psychotherapy), then the treatment administered should be reviewed and thought given to more extensive interventions, even including outpatient youth welfare measures, if appropriate as an emergency solution. In case these are not sufficient, (partial) inpatient youth welfare measures or (partial) inpatient hospital treatments should be considered.

Notes on the evidence in Section: II.2.3.1 and the evidence table in the Method Report, Appendix 11.4.1.

Consensus recommendation: Without COI 100% – all 100%

Quality of evidence: Expert consensus

Commentary on the recommendation:

After completing psychosocial interventions in pre-school age children with ADHD, the follow-up measures listed in the recommendation may address comorbid disorders in the child (e.g. developmental disorders, delayed development in toilet training, emotional disorders) or stressful conditions in the child's environment (e.g. partner conflicts, mental health problems in another family member). Here, outpatient youth welfare measures can also be considered. If these are not sufficient,

(partial) inpatient youth welfare measures or (partial) inpatient hospital treatments should be considered (see Chapter II.1.5).

1.3.1.3. Psychosocial interventions in school-age children and adolescents with ADHD

1.3.1.3.1. Which psychosocial (including psychotherapeutic) interventions should be carried out in school-age children and adolescents with ADHD and mild to moderate functional impairment?

1.3.1.3.1.1. If the schoolchild/adolescent with ADHD has slight to moderate functional impairment, the parents or other key educators should be offered parent counseling/training/education (including psychoeducation) in the individual or group format. The intervention can also be offered as guided self-help. The aim of these interventions is to improve parents' understanding of the symptoms, optimize their parenting behavior and reduce expansive behavioral problems including the ADHD symptoms and psychosocial impairments of the child in the home environment.

Notes on the evidence in Section: II.2.3.1 and the evidence table in the Method Report, Appendix 11.4.1.

Consensus recommendation: Without COI 94.7% – all 92.3%

Quality of evidence: Moderate

Grade of recommendation: Recommendation, ↑, B

Commentary on the recommendation:

A guide to dealing with difficult everyday situations and tools for parents to acquire skills to support important activities and to cope effectively with developmental tasks that the child will face, offer the parents practical assistance in the upbringing of the child.

1.3.1.3.1.2. If the ADHD symptoms also occur in the school environment, teacher training/teacher education should be carried out in parallel to and oriented towards parent training/parent education, in the individual or group format, or teacher training in behavior therapy. The aim of these interventions is to improve educators' understanding of the symptoms, optimize their pedagogical behavior in dealing with ADHD symptoms and reduce expansive behavioral problems including the ADHD symptoms and psychosocial impairments of the child or adolescent in the school environment.

Notes on the evidence in Section: II.2.3.1 and the evidence table in the Method Report, Appendix 11.4.1.

Consensus recommendation: Without COI 89.47% – all 88.46%

Quality of evidence: Moderate

Grade of recommendation: Recommendation, ↑, B

1.3.1.3.1.3   Parent training and school-centered interventions can be supplemented by cognitive-behavioral therapy of the child/adolescent (training in organizational skills, self-management training, self-instructional training, social skills training). However, treating the child/adolescent alone is usually not enough.

Notes on the evidence in Section: II.2.3.1 and the evidence table in the Method Report, Appendix 11.4.1.

Consensus recommendation: Without COI 89.74% – all 88.46%

Quality of evidence: Moderate

Grade of recommendation: Recommendation open, ↔, 0

Dissenting opinion 6 of bkj and bvp and the associated reasoning can be found in the Appendix under point III.8.3., p. 168 – 169.

Commentary on the recommendation:

This training can usually be carried out by therapists who have received extensive training in child behavior therapy, i.e. child and adolescent psychotherapists, psychological psychotherapists or physicians with appropriate additional qualifications in child behavior therapy.

1.3.1.3.2.   What format, intensity and content of training (teacher support) should parents/teachers of school age children and adolescents be offered?

Recommendations on the format, intensity and content of parent and educator training for children with ADHD at pre-school age (see recommendations II.1.3.1.2) should also be applied to the training of parents/teachers (teacher counseling) of school-age children and adolescents. As with preschool children, methods based on social learning theory according to the specifications of an evaluated and established training manual, are recommended for children from school age onwards (see Appendix III.5).

If the interventions are carried out individually, the child, and especially the adolescent, should be actively involved. In adolescents, family interventions should be carried out in order to reduce parent-adolescent conflict.

Notes on the evidence in Section: II.2.3.1 and the evidence table in the Method Report, Appendix 11.4.1.

Consensus recommendation: Without COI 89.47% – all 88.46%

Quality of evidence: Expert consensus

Commentary on the recommendation:

The above-mentioned training for parents and teachers (teacher counseling) of children and adolescents from school-age can also be carried out on-site.

1.3.1.3.3. How should interventions be delivered in the school environment where school-age children with ADHD are present?

If pronounced ADHD symptoms also occur in the school environment (which is usually the case), then teacher training/teacher education should be carried out parallel to and oriented to parent training/parent education in individual or group format respectively teacher counseling. The teacher should at least be provided with written material about the content of parent training. The interventions should be carried out according to the specifications of an evaluated and established training manual (see Appendix III.5).

Notes on the evidence in Section: II.2.3.1 and the evidence table in the Method Report, Appendix 11.4.1.

Consensus recommendation: Without COI 89.47% – all 88.46%

Quality of evidence: Low

Grade of recommendation: Recommendation, ↑, B

1.3.1.3.4. What are the goals of cognitive behavioral therapy for children/adolescents with ADHD from school-age onwards?

If a child/adolescent undergoes cognitive behavioral therapy in individual or group format, a broad spectrum of possible treatment goals should be considered, including the improvement of social skills in contact with peers, problem solving ability, impulse and self-control, listening skills and organizational and self-management skills as well as skills to control emotions and express them adequately. Active learning strategies should be practiced and rewards introduced aimed at using learning strategies and achieving learning goals.

In order to ensure consistent implementation of the training manual, the interventions should be carried out according to the specifications of an evaluated and established training manual (see Appendix III.5).

Notes on the evidence in Section: II.2.3.1 and the evidence table in the Method Report, Appendix 11.4.1.

Consensus recommendation: Without COI 89.47% – all 88.46%

Quality of evidence: Low

Grade of recommendation: Recommendation, ↑, B

Commentary on the recommendation:

In the aforementioned cognitive behavioral therapy for school-age children/adolescents with ADHD, therapeutic homework should be used to support the transfer of acquired skills into daily life. In addition to the recommended cognitive-behavioral therapy, psychodynamic treatments are also carried out that do not yet have sufficiently high quality of evidence for the outcomes and are therefore not recommended in these evidence-based guidelines. If psychodynamic therapy for the child/adolescent is delivered as an individual or a group-based therapy, a broad spectrum of possible treatment goals is considered. Such goals include:

- Development/strengthening of the ego functions with the aim of achieving better mood and impulse control
- Strengthening the ability to control and express emotional stress and state of mind
- Stabilizing self-esteem
- Developing social skills further (conflict and problem solving, age-appropriate forms of contact and relationship building with peers and other generations).

Where appropriate, active tools for organizing and structuring everyday (school) life should be included. Here, it is important to strengthen the child's/adolescent's own initiative.

1.3.1.3.5. What further measures should be considered when treating school age children and adolescents with ADHD?

If the overall treatment successfully reduces ADHD symptoms and their associated functional limitations, then the following aspects should be considered:
- Before finishing the treatment, it is important to evaluate whether there are any residual coexistent symptoms requiring treatment and, if so, a new treatment plan should be developed. Here, the child, parents or other educators, as well as siblings, should be involved.
- If the symptoms of ADHD and the associated functional limitations cannot be successfully reduced by the overall outpatient management (including extensive psychotherapy), the treatment should be reviewed and further interventions including, if necessary, outpatient youth welfare measures, should be considered and carried out. In case these are not sufficient, (partial) inpatient youth welfare measures or (partial) inpatient hospital treatments should be considered.

Notes on the evidence in Section: II.2.3.1 and the evidence table in the Method Report, Appendix 11.4.1.

Consensus: Without COI 89.47% – all 92.31%

Quality of evidence: Expert consensus

Commentary on the recommendation:

After completing the psychosocial (including psychotherapeutic) interventions in children and adolescents with ADHD from school age onward, the above-mentioned follow-up measures may address comorbid disorders (e.g. depressive disorders, dissocial disorders, tic disorders) or stressful conditions in their environment (e.g. partner conflicts, mental disorders in another family member). Here, outpatient youth welfare measures can also be considered. In case these are not sufficient, (partial) inpatient youth welfare measures or (partial) inpatient hospital treatments (see Chapter II.1.5.) should be considered.

1.3.1.3.6. Which psychosocial (including psychotherapeutic) interventions should be carried out in school-age children and adolescents with ADHD and moderate to severe functional impairment?

In schoolchildren and adolescents with moderate to severe functional impairments who do not receive pharmacotherapy (see Chapter II.1.4.) (e.g. due to a lack of efficacy, lack of adherence, excessive adverse drug reactions or rejection by the parents or the child/adolescent) or who have residual ADHD symptoms despite optimized pharmacotherapy, the same psychosocial (including psychotherapeutic) interventions should be provided as for children and adolescents with mild to moderate ADHD.

If patients or reference persons refuse the indicated pharmacotherapy due to reservations and fears, these attitudes can be addressed within the psychoeducational scope. Treating poor medication adherence can also be the goal of psychoeducational interventions.

If pharmacological or psychosocial (including psychotherapeutic) interventions were effective in reducing the symptoms in children and adolescents with moderate to severe ADHD, it is important to check if potential residual symptoms and problems still exist and indications for further psychosocial (including psychotherapeutic) interventions to treat these should be reviewed.

Notes on the evidence in Section: II.2.3.1 and the evidence table in the Method Report, Appendix 11.4.1.

Consensus recommendation: Without COI 84.21% – all 84.62%

Quality of evidence: Expert consensus

Dissenting opinion 7 of bkj and bvp and the associated reasoning can be found in the Appendix under point III.8.3., p. 169 - 170.

1.3.1.4. Psychosocial interventions in adults with ADHD

1.3.1.4.1.   What are the general goals of psychosocial interventions in adults with ADHD?

Psychosocial (including psychotherapeutic) interventions in adults with ADHD are intended to provide information about ADHD as well as to increase acceptance of the disorder—a requirement for behavioral changes—to develop coping strategies and to improve everyday functions. The aim should be to reduce the symptoms of ADHD and commonly occurring coexisting symptoms such as depression, anxiety or problems with self-esteem.

Notes on the evidence in Section: II.2.3.2 and the evidence table in the Method Report, Appendix 11.4.2.

Consensus recommendation: Without COI 100% – all 100%

Quality of evidence: Expert consensus

1.3.1.4.2.   Who should be considered for psychosocial interventions?

Psychosocial (including psychotherapeutic) treatment should be offered in particular to people who:
- Were first diagnosed in adulthood and are in the process of accepting and gaining insight into the recent diagnosis
- After being fully informed, decide against commencing medication
- Still show symptoms and/or functional impairments on drug treatment
- Have contraindications to drug treatment
- Have difficulty accepting the diagnosis and/or adhering to drug treatment
- Have few symptoms and where psychosocial (including psychotherapeutic) interventions are considered sufficient to treat minor or moderate functional limitations in everyday life.

Notes on the evidence in Section: II.2.3.2 and the evidence table in the Method Report, Appendix 11.4.2.

Consensus recommendation: Without COI 94.12% – all 95.45%

Quality of evidence: Moderate

Grade of recommendation: Strong recommendation, ↑↑, A

1.3.1.4.3.   What psychosocial interventions should be used in adults with ADHD?

1.3.1.4.3.1.   Psychoeducation should be offered to everyone who has been diagnosed with ADHD in adulthood. Psychoeducation should be used as a basic strategy for all interventions in adults with ADHD. Psychoeducation is intended to help convey an adequate understanding of the disease. The cause of the disorder should be made clear to the patient and an understanding of the symptoms and the associated functional restrictions should be conveyed. The main strategies for alleviating the effects of ADHD and the treatment options should be explained.

Notes on the evidence in Section: II.2.3.2 and the evidence table in the Method Report, Appendix 11.4.2.

Consensus recommendation: Without COI 94.74% – all 88.46%

Quality of evidence: Expert consensus

Dissenting opinion 8 of bkj and bvvp and their associated reasons can be found in the Appendix under Point III.8.3. p. 169.

Commentary on the recommendation:

For the definition of "psychoeducation", see Commentary on recommendation II.1.2.2.

1.3.1.4.3.2.   If psychotherapy is indicated, cognitive behavioral therapy should be provided. Cognitive behavioral therapy (CBT) is intended to help with the development of strategies and the learning of practical techniques that contribute to a reduction of the effects of ADHD symptoms on everyday functions, e.g. teaching skills in problem solving, techniques for reducing distractibility and skills in dealing with stress. Furthermore, dysfunctional cognitions, acquired over the lifespan, should be recognized and reviewed.

Notes on the evidence in Section: II.2.3.2 and the evidence table in the Method Report, Appendix 11.4.2.

Consensus recommendation: Without COI 78.95% – all 80.77%

Quality of evidence: Moderate

Grade of recommendation: Recommendation, ↑, B

Commentary on the recommendation:

In addition to the classic cognitive behavioral therapy (CBT) mentioned in the recommendation, there are other psychosocial interventions that can be used in the treatment of adults with ADHD:

Metacognitive Therapy (MCT) is based on the cognitive behavioral therapy and is intended to improve time management as well as organizational skills in ADHD and to reduce depressogenic cognitive patterns and fear-avoidance cognitions.

"Reasoning & Rehabilitation" therapy is intended to practice prosocial behavior as well as to improve the symptoms of ADHD.

Skill trainings are based on CBT and include elements of dialectical behavioral therapy. They are intended to facilitate improved control of ADHD symptoms and emotion regulation.

Mindfulness-based Cognitive Therapy (MBCT) is designed to improve attention processes and stress regulation in ADHD.

Coaching should be used as a supportive intervention. The goal should be to help adults with ADHD to identify and access their own strengths, but also to overcome their problems and cope with everyday tasks.

1.3.1.4.4. In what format should psychosocial interventions be offered in adults with ADHD?

Psychosocial (including psychotherapeutic) interventions should be offered in the form of group-based or individual treatment.

Notes on the evidence in Section: II.2.3.2 and the evidence table in the Method Report, Appendix 11.4.2.

Consensus recommendation: Without COI 94.74% – all 100% [6]

Quality of evidence: Low

Grade of recommendation: Recommendation, ↑, B

1.3.2. Neurofeedback

1.3.2.1. When can neurofeedback be used as a treatment option for ADHD?

Neurofeedback, as per standard training protocol, can also be used as part of a treatment plan for ADHD in children > six years and in adolescents if this does not delay or prevent another, more effective therapy.

Notes on the evidence in Section: II.2.3.3 and the evidence table in the Method Report, Appendix 11.4.3.

Consensus recommendation: Without COI 87.5% – all 84.0% [6]

Quality of evidence: Moderate

Grade of recommendation: Recommendation open, ↔, 0

1.3.2.2. How should neurofeedback be carried out in ADHD?

If neurofeedback is employed, it should:

- Be practiced using fully evaluated protocols; these include feedback of the theta/beta ratio over the fronto-central region, the sensorimotor rhythm (SMR) over the motor cortex or the slow

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[6] The presentation of the voting result is correct. Mandate holders of the first round of voting voted differently in the second round of voting.

cortical potentials (SCP) over the parietal region. "QEEG-based" protocols with other frequency ranges and electrode positions should not be used

- Include principles of learning theory and transfer exercises to apply the learning to everyday life
- Be practiced long enough (at least 25 to 30 sessions), while reviewing regularly with the child/adolescent and their parents whether continuing treatment is justified by looking for signs of initial effectiveness.

Notes on the evidence in Section: II.2.3.3 and the evidence table in the Method Report, Appendix 11.4.3.

Consensus recommendation: Without COI 91.67% – all 92.0%

Quality of evidence: Moderate

Grade of recommendation: Strong recommendation, ↑↑, A

Commentary on the recommendation:

Since neurofeedback is an intervention based on behavioral therapy, practicing therapists should be qualified in behavioral therapy and have a thorough knowledge of the standard neurofeedback training protocols (e.g. at https://www.akademie-neurofeedback.de/ausbildung/biofeedback-therapeut/). Similar to other types of interventions, supervision and intervision are additionally considered indispensable. There is currently no formalized training that leads to a qualification for carrying out neurofeedback.

1.3.3. Dietary interventions

1.3.3.1. What should the patient be told about nutrition in general?

The practitioner should advise patients of all ages and their family members about the importance and value of a balanced diet, whole-food nutrition and regular exercise or sport.

Notes on the evidence in Section: II.2.3.4.

Consensus recommendation: Without COI 95.45% – all 100%[6]

Grade of recommendation: Expert consensus

1.3.3.2. What should be considered with regard to artificial food colorings?

Trying to avoid artificial colorings or other nutritional supplements as part of the diet can prove helpful for individual patients. However, this should not be carried out as a general intervention in children, adolescents or in adults with ADHD.

Notes on the evidence in Section: II.2.3.4.

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[6] The presentation of the voting result is correct. Mandate holders of the first round of voting voted differently in the second round of voting.

Consensus recommendation: Without COI 95.65% – all 96.0%

Quality of evidence: High

Grade of recommendation: Strong recommendation, ↑↑, A

1.3.3.3. What should be considered regarding elimination diets?

1.3.3.3.1.   The medical history of children and adolescents with ADHD should also include the question as to whether certain foods or beverages influence the symptoms (especially hyperactivity). If there are any indications of possible connections in this context, parents, caregivers or those affected should be encouraged to keep a diary of food/drink consumption and the clinical course of ADHD symptoms for a few days. If this supports a link between certain foods and behavior, a referral to a dietitian should be offered. The further relevant procedure (e.g. the omission of certain foods) should include a joint agreement between the nutritional counselor, the primary care physician and the parents or caregivers.

Notes on the evidence in Section: II.2.3.4.

Consensus recommendation: Without COI 95.45% – all 100%[6]

Quality of evidence: Moderate

Grade of recommendation: Recommendation, ↑, B

1.3.3.3.2.   In this context, the parents or reference persons of children or adolescents with ADHD should be advised that there are no studies on the long-term effectiveness of eliminating certain foods, that there is only limited evidence of short-term benefits of such diets and that possible deficiency symptoms and late sequelae can be expected.

Notes on the evidence in Section: II.2.3.4.

Consensus recommendation: Without COI 100% – all 100%

Quality of evidence: Moderate

Grade of recommendation: Recommendation, ↑, B

1.3.3.4. Can omega 3/omega 6 fatty acids be recommended for the treatment of ADHD?

Contrary to previous findings, which indicated a positive but quantitatively small effect of omega-3 and omega-6 fatty acids for the treatment of ADHD in children, adolescents and adults, according to current knowledge (NICE 2016), no recommendation for dietary supplements using these substances is given.

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[6] The presentation of the voting result is correct. Mandate holders of the first round of voting voted differently in the second round of voting.

Notes on the evidence in Section: II.2.3.4.

Consensus recommendation: Without COI 100% – all 100%

Quality of evidence: Moderate

Grade of recommendation: Recommendation open, ↔, 0

1.4. Pharmacological Interventions

Which patients should receive pharmacotherapy?

The indication for pharmacological interventions can be found in the Chapter Intervention Algorithms, Recommendation II.1.2.2.

A variety of different factors should be considered when rendering the indication for pharmacotherapy, including the patient's age, the severity of symptoms and the severity of impairment they cause in the various domains of everyday life; consideration should also be given to the preferences of the family and the patient as well as the effectiveness of any psychosocial (including psychotherapeutic) interventions initiated thus far. In toddlers or pre-school age children with ADHD age three years and older, pharmacotherapeutic interventions should only be considered cautiously due to insufficient existing evidence, and after exhausting all non-pharmacotherapeutic options such as, for example, parent training (see below). In school-age children, the recommendation for pharmacotherapy as part of the overall therapeutic strategy particularly depends on the severity of symptoms and the preference of the respective patient and their family. If the symptoms are severe and clearly cause impairments, patients and their families should be advised to undergo primary pharmacotherapy, after having exhausted extensive psychoeducation, provided this does not contradict the expectations and wishes of those affected. Even in moderately severe symptoms or impairments, such an intervention can be indicated if the patient and their family prefer a pharmacotherapy option. The same applies if previously initiated non-drug therapies lack efficiency. In contrast, based on the available evidence, pharmacotherapy (in addition to psychoeducation) is considered to be the primary therapy option in adults, even with mild and moderate symptoms and impairments (provided this reflects the patient's preference).

1.4.1. Who should carry out drug treatment?

- Any drug treatment should only be initiated and supervised by an appropriately qualified specialist in pediatric and adolescent medicine, child and adolescent psychiatry and psychotherapy, neurology, neurology and/or psychiatry or psychiatry and psychotherapy or by a medical psychotherapist. They should have knowledge in the field of ADHD and in monitoring pharmacotherapeutic treatment.

- For children aged three to six, the prescribing should be made by a doctor with expertise in behavioral disorders in this age group.

- The decision to commence drug therapy should only be taken once a reliable diagnosis, based on a comprehensive medical history and examination, has been made.

- After the patient has been established on an effective dose by the respective specialists, general practitioners can also issue repeat prescriptions and carry out follow-up monitoring in exceptional cases. In order to check the effectiveness or rather the need for ongoing treatment or to adjust the dose according to need, however, regular reviews by the specialists responsible for supervising the treatment should still continue.

Notes on the evidence in the evidence table in the Method Report, Appendix 11.4.4.

Consensus recommendation: Without COI 92.86% – all 91.3%

Quality of evidence: Expert consensus

Commentary on the recommendation:

Prescribing physicians should be familiar with the legal requirements and regulations that apply in connection with the prescription of stimulants, which are subject to the Narcotic Drugs Act (statutory provision).

Pharmacological treatment of children and adolescents with ADHD should be carried out by specialized healthcare professionals (specialists in child and juvenile psychiatry and psychotherapy, as well as physicians with expertise in child and youth psychiatry; qualified specialists in child and adolescent medicine).

For adults with ADHD, pharmacological treatment should be given by physicians with expertise in ADHD, psychopharmacotherapy and comorbidities that often occur in adults.

1.4.2. Which drugs are recommended for the treatment?

If drug treatment is indicated, stimulants (methylphenidate, amphetamine and lisdexamfetamine), atomoxetine and guanfacine should be considered as possible options for treating ADHD. The current approval status should be noted.

Notes on the evidence in Section II.2.4.1 and the evidence table in the Method Report, Appendix 11.4.4

Consensus recommendation: Without COI 91.67% – all 91.3%

Quality of evidence: High

Grade of recommendation: Strong recommendation, ↑↑, A

1.4.3. What criteria should be used to select the right medication?

1.4.3.1. When deciding on pharmacotherapy, the choice of active ingredient and/or the pharmaceutical form, the following aspects should be considered:

- Approval status
- The desired duration of action and expected efficacy profile
- The varying profiles of adverse drug reactions
- Presence of specific coexisting disorders/diseases (e.g. tic disorders, epileptic syndromes); for the particulars of the respective drug choice, see II.1.4.5
- Special circumstances that could affect the patient's adherence to medication, e.g. stigmatization of a child or adolescent if a short-acting drug needs to be taken during the school day (see II.1.4.5.2)
- The risk of the substance being misused by the patient or the medication being passed on to third parties (II.1.4.3.2 and II.1.4.5)
- The preferences of the patient and, where applicable, their guardians.

Notes on the evidence in Section II.2.4.2 and the evidence table in the Method Report, Appendix 11.4.4

Consensus recommendation: Without COI 100% – all 100%

Quality of evidence: Expert consensus

1.4.3.2. The pharmacological treatment of patients with ADHD, who also have a substance abuse or substance addiction problem, should be carried out by a specialist with expertise in the treatment of ADHD and addiction.

Notes on the evidence in Section II.2.4.2 and the evidence table in the Method Report, Appendix 11.4.4

Consensus recommendation: Without COI 100% – all 100%

Quality of evidence: Expert consensus

1.4.4. Which examinations should be carried out before starting pharmacotherapy?

1.4.4.1. Before starting pharmacotherapy, a renewed physical and neurological examination should be considered. It is important to ask specifically about symptoms that could indicate cardiovascular disease (e.g. syncope or unexplained shortness of breath) and about potential family history that could indicate a predisposition to cardiovascular disease.

Notes on the evidence in Section II.2.4.2 and the evidence table in the Method Report, Appendix 11.4.4

Consensus recommendation: Without COI 100% – all 100%

Quality of evidence: Expert consensus

1.4.4.2. Prior to commencing any medication, at least basic checks such as pulse rate and blood pressure as well as the patient's body weight and height should be carried out and their respective percentiles calculated for children as well as adolescents.

Notes on the evidence in Section II.2.4.2 and the evidence table in the Method Report, Appendix 11.4.4

Consensus recommendation: All 100% (only one round of voting[3])

Quality of evidence: Expert consensus

1.4.4.3. An ECG should be recorded and, if necessary, a consultation with a cardiologist or pediatric cardiologist should be sought if there is evidence of cardiovascular disease from past medical history or physical examination or if there is a family predisposition.

Notes on the evidence in Section II.2.4.2 and the evidence table in the Method Report, Appendix 11.4.4

Consensus recommendation: All 96.0% (only one round of voting[3])

Quality of evidence: Expert consensus

Commentary on the recommendation:

The screening examinations focus on commonly occurring and relevant adverse reactions (see II.2.4.1.). Given that increases in pulse rate and blood pressure, decreased appetite and effects on longitudinal growth are some of the most common adverse reactions, it is recommended that standard measurements of pulse rate, blood pressure, body weight and height are performed; the corresponding age percentiles for children and adolescents should also be determined. Since other adverse reactions are less common, a standard examination prior to commencing drug therapy is not recommended. This need only be carried out in individual cases if the medical history/family history or corresponding family predisposition is indicative of cardiovascular disease.

1.4.5. What should be considered when selecting a drug for an individual patient?

1.4.5.1. When the decision is made to start medication, the practitioner should, whilst taking relevant contraindications into account

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[3] There was only one round of voting for this recommendation. An explanation can be found in the Preamble.

- Initiate ADHD treatment with stimulants in patients who have no relevant comorbidities.

Consensus agreement: Without COI 95% – all 96.15%

Commentary on the recommendation:

Initial treatment with an approved amphetamine products [Attentin® (dexamfetamine sulfate), Elvanse® (lisdexamfetamine)] is seen as an unapproved use, if treatment with methylphenidate was not attempted initially.

"Off-label use" means the use of an approved drug for not-approved or not-yet-approved conditions, in particular when using an approved drug outside the indications for which it was approved by the national or European regulatory authorities (definition by the German Federal Joint Committee, G-BA). The following criteria must be met for off-label use of drugs in clinical practice:

- Proven efficacy
- Favorable risk-benefit profile
- Lack of alternatives, i.e. therapeutic trial setting.

Furthermore, the treating physician has a particular obligation to inform the patient about possible consequences (no manufacturer liability, etc.). Joint decision making is necessary. Thus, "off-label use" is only permitted for serious illnesses if there is no alternative treatment. Based on current scientific knowledge, there must be a reasonable prospect that the treatment will be successful.

- For patients with ADHD and coexisting conduct disorders or antisocial personality disorders also choose initial treatment with stimulants.

Consensus agreement: Without COI 100% – all 100%

- For patients with ADHD and coexisting tic disorders, choose stimulants or alternatively atomoxetine or guanfacine.

Consensus agreement: Without COI 95% – all 96.15%

Commentary on the recommendation:

Initiating treatment with Intuniv® (guanfacine) is only approved for children and adolescents aged 6-17 years if treatment with stimulants is contraindicated, is not tolerated or has proven to be ineffective.

- In patients with ADHD and coexisting anxiety disorder, choose stimulants or alternatively atomoxetine.

Consensus agreement: Without COI 100% – all 100%

- In patients with ADHD and substance use with an increased risk of improper use of the medication, choose long-acting stimulants or alternatively atomoxetine or guanfacine.

Consensus agreement: Without COI 100% – all 100%

- In patients for whom treatment with one stimulant has proven ineffective despite receiving the maximum tolerable dose, choose another stimulant, i.e. atomoxetine or guanfacine.

Consensus agreement: Without COI 95% – all 96.15%

Notes on the evidence in Section II.2.4.3 and the evidence table in the Method Report, Appendix 11.4.4

Quality of evidence: High

Grade of recommendation: Strong recommendation, ↑↑, A

Commentary on the recommendation (as per end of 2017):

In Germany, there are essentially four different active substances for the treatment of children and adolescents with ADHD with a large number of drugs derived from them and approved for oral use. Frequently, two groups are distinguished: The stimulants (methylphenidate and dexamfetamine) on the one hand, and the non-stimulants (atomoxetine and guanfacine) on the other. The stimulants represent marketable and prescription narcotics according to the German Narcotic Drugs Act.

Treatment must be carried out under the supervision of a specialist in conduct disorders in children and the diagnosis of ADHD must have been made on a comprehensive medical history, an examination of the patient and according to currently valid criteria (DSM or ICD-10) and not be based solely on the presence of one or several symptoms.

There are, however, relevant differences in the Summary of Product Characteristics that need to be considered when selecting a suitable drug in clinical practice. Thus, the active substances methylphenidate and atomoxetine are generally approved for the treatment of ADHD, while dexamfetamine is only approved after clinically unsatisfactory treatment with methylphenidate, and guanfacine only after clinically unsatisfactory treatment with stimulants.

Methylphenidate is available as immediate-release and sustained-release presentation. There are various generics, all of which contain the same active substance, but differ in part with regard to fillers and additives. This results in differences in the release of the active substance and the duration of

action, particularly in the case of the extended-release dosage forms. This can be relevant when selecting a preparation or switching to a different one and can be of clinical benefit to the patient. Atomoxetine (Strattera®), a selective norepinephrine reuptake inhibitor, is approved as an alternative treatment. The first generic preparations were approved in the United States in 2017.

Two pharmacologically related products from the amphetamine substance group are approved for the treatment of ADHD in children and adolescents from the age of six years, if the response to previous treatment with methylphenidate is considered to be clinically inadequate. Dexamfetamine sulfate (Attentin®) and lisdexamfetamine dimesylate (Elvanse®) represent different presentations of the active substance dexamfetamine.

Guanfacine (Intuniv®), a pharmacological derivative of the anticholinergic agent clonidine, has also been approved in Germany since January 2016. A requirement for the use as an 'approved application', is that treatment with stimulants is contraindicated, is not tolerated or has proven to be ineffective.

Treatment of adults from the age of 18 can be started with two methylphenidate products exerting delayed releases of action (Medikinet adult®, Ritalin adult®). These drugs may also be prescribed to elderly individuals. Nevertheless, according to the G-BA requirements, they should not be prescribed to senior citizens. Yet, a clear age cut-off delineating the age, from which prescriptions should no longer be written, was not defined.

Treatment of ADHD in adults can also be started with atomoxetine. Its Summary of Product Characteristics states that its use for treating patients from the age of 65 has not been systematically evaluated. This suggests that patients in this age group should only be treated with atomoxetine after an especially critical evaluation of its indication. Treatment with OROS methylphenidate during adolescence can be continued into adulthood.

Further information on individual products can be found in the respectively current prescribing information on each drug. The authors explicitly state that they make no warranty of any kind for the information provided herein and waive all liability arising from incorrect, incomplete or outdated particulars.

1.4.5.2. When prescribing stimulants for patients with ADHD, long-acting drugs can be considered for the following reasons:
• Greater ease of use, including simplified medication intake

- Improved adherence

- Avoiding possible stigmatization (e.g. by not taking medication in school)

Depending on the demands during the day, the different pharmacokinetic profiles of long-acting preparations should be taken into account.

Alternatively, immediate release products, for example, can be considered for the following reasons:

- More precise dose adjustments during the initial titration phase of the medication

- Greater flexibility in dose schedule is required

Notes on the evidence in Section II.2.4.3 and the evidence table in the Method Report, Appendix 11.4.4

Consensus recommendation: Without COI 100% + one abstention – all 100% + one abstention

Quality of evidence: Moderate

Grade of recommendation: Recommendation, ↑, B

Commentary on the recommendation:

Efforts should be made to ensure that the patient and reference persons strictly adhere to the instructions during the dose titration phase, regardless of the respective active substance, so that they take personal responsibility for changing doses and that their understanding of the drug is strengthened. The aim is to treat with the lowest possible dose. This will also reduce or prevent problems with adverse reactions (loss of appetite, sleep disturbance, low mood, sadness). Under these conditions and assuming a low starting dose, the dose can be gradually increased until no further clinically significant improvement in the symptoms (e.g. core symptoms, but also in terms of a change in problem behavior) can be achieved and the adverse reactions remain tolerable. The permitted maximum daily dose of the individual preparations should be considered and only exceeded in justified exceptional cases. It should be noted that this would be classified as an off-label use.

1.4.5.3. If several drug options are regarded as equivalent, the most cost-efficient preparation should be chosen first.

Notes on the evidence in Section II.2.4.3 and the evidence table in the Method Report, Appendix 11.4.4

Consensus recommendation: Without COI 95% – all 88%

Quality of evidence: Expert consensus

1.4.5.4. Antipsychotics should not be used to treat ADHD without the presence of other associated disorders.

Notes on the evidence in Section II.2.4.3 and the evidence table in the Method Report, Appendix 11.4.4

Consensus recommendation: Without COI 100% – all 100%

Quality of evidence: Expert consensus

1.4.5.5. A combination of different active substances can be considered in patients with ADHD whose symptoms do not respond to stimulants (methylphenidate, dexamfetamine), atomoxetine or guanfacine, or in patients where the medication mentioned, leads to intolerable undesirable effects.

Notes on the evidence in Section II.2.4.3 and the evidence table in the Method Report, Appendix 11.4.4

Consensus agreement: Without COI 94.12% – all 90.91%

Quality of evidence: Expert consensus

1.4.5.6. In patients with ADHD and severe impulse control disorder and aggressive behavior, short-term additional administration of atypical neuroleptics combined with psychosocial (including psychotherapeutic) interventions can be considered to reduce these symptoms.

Notes on the evidence in Section II.2.4.3 and the evidence table in the Method Report, Appendix 11.4.4

Consensus agreement: Without COI 95% – all 96.15%

Quality of evidence: Expert consensus

Commentary on the recommendation:

The additional administration of atypical neuroleptics is usually classified as an off-label use.

An exception to this is the use of risperidone, for the short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorders in children from the age of five years and adolescents with below-average intellectual function or intellectual disability who were diagnosed according to the DSM-IV criteria and where the severity of aggressive or other disruptive behaviors requires pharmacological treatment.

1.4.5.7. Based on evidence to date, a recommendation for the use of additional drugs (e.g. SSRI, modafinil, selegiline, bupropion) for the treatment of ADHD is currently not possible.

Notes on the evidence in Section II.2.4.3 and the evidence table in the Method Report, Appendix 11.4.4

Consensus agreement: Without COI 100% – all 100%

Quality of evidence: Expert consensus

Commentary on the recommendation:

SSRIs, modafinil, selegiline and bupropion are not approved for the treatment of ADHD (off label).

1.4.5.8. Cannabis should not be used to treat ADHD.

Notes on the evidence in Section II.2.4.3 and the evidence table in the Method Report, Appendix 11.4.4

Consensus agreement: Without COI 100% – all 100%

Quality of evidence: Expert consensus

1.4.6. What should be considered in the course of drug treatment?

1.4.6.1. When commencing medication with stimulants, atomoxetine or guanfacine, each change in the dose (besides checking the effectiveness on ADHD symptoms) should be closely monitored, e.g. on a weekly basis, by interviewing the patient and/or caregivers and by documenting the occurrence of undesirable effects.

Notes on the evidence in Section II.2.4.4 and the evidence table in the Method Report, Appendix 11.4.4

Consensus agreement: Without COI 100% – all 100%

Quality of evidence: Expert consensus

1.4.6.2. Regular follow-ups on the effectiveness and recording of adverse drug reactions are also necessary over the further course of treatment. Whether further treatment is indicated should be checked at least every six months.

Notes on the evidence in Section II.2.4.4 and the evidence table in the Method Report, Appendix 11.4.4

Consensus agreement: Without COI 95% – all 96.15%

Quality of evidence: Expert consensus

Commentary on the recommendation:

The following options may result from the indication review mentioned in the recommendation, which should then be implemented in the further course of treatment:

- Medication continues as before
- Medication is reduced/increased
- Medication is discontinued

- Medication is discontinued and other medication is chosen
- Medication is combined with another drug

1.4.6.3. Once a year, the indication for continuation of pharmacological treatment should be reviewed as part of a treatment-free period.

Notes on the evidence in Section II.2.4.4 and the evidence table in the Method Report, Appendix 11.4.4

Consensus agreement: Without COI 85% – all 88.46%

Quality of evidence: Majority approval of the experts

1.4.6.4. In addition to the practitioner's clinical assessment, standardized instruments (self-rating and parent/teacher rating) such as questionnaires should be used to record the symptoms and/or assess possible adverse reactions of pharmacological treatment (see list of German-language psychometrical procedures for documenting ADHD, Appendix III.4).

Notes on the evidence in Section II.2.4.4 and the evidence table in the Method Report, Appendix 11.4.4

Consensus agreement: Without COI 95% – all 92.31%

Quality of evidence: Expert consensus

1.4.6.5. During treatment, regardless of the choice of medication
- The height of children and adolescents should be measured and documented approx. every six months
- Patients of all ages should have their body weight measured and documented, initially approx. after three and six months from starting medication, and then approx. every six months
- Corresponding age percentiles should be determined in children and adolescents with regard to body weight and height.

Notes on the evidence in Section II.2.4.4 and the evidence table in the Method Report, Appendix 11.4.4

Consensus recommendation: Without COI 100% – all 96.15%

Quality of evidence: Expert consensus

1.4.6.6. If a significant impairment in longitudinal growth occurs linked to pharmacological treatment with stimulants, the treatment should be temporarily interrupted, e.g. during school holidays to allow

the patient's growth to "catch up" if there are no other more important clinical contraindications to be considered.

Notes on the evidence in Section II.2.4.4 and the evidence table in the Method Report, Appendix 11.4.4

Consensus agreement: Without COI 100% – all 92.31%

Quality of evidence: Expert consensus

1.4.6.7. In patients of all ages, pulse and blood pressure should be checked each time the dose is adjusted or approx. every six months as part of routine examinations and compared with age-appropriate normal values (see Appendix III.7). When treating with guanfacine, pulse and blood pressure should be closely monitored due to possible bradycardia and hypotension. Patients should also be examined for signs and symptoms of somnolence. Guanfacine should be discontinued gradually to avoid a reactive increase in blood pressure and heart rate.

Notes on the evidence in Section II.2.4.4 and the evidence table in the Method Report, Appendix 11.4.4

Consensus recommendation: Without COI 100% – all 100%

Quality of evidence: Expert consensus

1.4.6.8. Damage to the liver is a rare undesirable effect of treatment with atomoxetine. Liver-specific laboratory tests are not required as part of routine examinations. If there is evidence of liver damage, the medication must be discontinued immediately and appropriate examinations arranged.

Notes on the evidence in Section II.2.4.4 and the evidence table in the Method Report, Appendix 11.4.4

Consensus recommendation: Without COI 94.74% – all 96.15%

Quality of evidence: Expert consensus

1.4.6.9. In the case of treatment with stimulants, therapists, legal guardians and other caregivers should take note of the risk of drug misuse.

Notes on the evidence in Section II.2.4.4 and the evidence table in the Method Report, Appendix 11.4.4

Consensus recommendation: Without COI 100% – all 100%

Quality of evidence: Expert consensus

1.4.6.10. Adolescents and adults treated with atomoxetine should be regularly asked about adverse effects on sexual dysfunctions (erection or ejaculatory problems) and dysmenorrhea.

Notes on the evidence in Section II.2.4.4 and the evidence table in the Method Report, Appendix 11.4.4

Consensus recommendation: Without COI 100% – all 96.15%

Quality of evidence: Expert consensus

1.4.6.11. Patients exhibiting resting tachycardia, arrhythmia or increased systolic blood pressure (> 95th percentile, see Appendix III.7) on repeated examination dates during pharmacological treatment, should have their dose reduced and be referred to a pediatric cardiologist or cardiologist.

Notes on the evidence in Section II.2.4.4 and the evidence table in the Method Report, Appendix 11.4.4

Consensus recommendation: Without COI 95% – all 96.15%

Quality of evidence: Expert consensus

Commentary on the recommendation:

A definition of hypertension with the corresponding cut-offs can be found in Appendix IV.6.

1.4.6.12. Whenever psychotic symptoms (e.g. delusions/hallucinations) manifest in patients of all age groups during treatment with stimulants, the respective drug should be discontinued and the patient submitted to careful psychiatric re-examination.

Notes on the evidence in Section II.2.4.4 and the evidence table in the Method Report, Appendix 11.4.4

Consensus recommendation: Without COI 100% – all 100%

Quality of evidence: Expert consensus

1.4.6.13. If any new seizures or an exacerbation of known epilepsy occur in patients on treatment with stimulants or atomoxetine, the drug should be discontinued immediately and the further procedure discussed with a neuropediatrician/neurologist.

Notes on the evidence in Section II.2.4.4 and the evidence table in the Method Report, Appendix 11.4.4

Consensus recommendation: Without COI 100% – all 100%

Quality of evidence: Expert consensus

Commentary on the recommendation:

Epilepsy per se is not a contraindication for treatment with stimulants or atomoxetine as there is no evidence that these lower the central nervous seizure threshold (see II.2.4.1.).

1.4.6.14.   If tics occur during treatment with stimulants, the practitioner should consider:

- Whether the tics are related to the medication or whether the symptoms increase or subside as part of the natural course of an existing tic disorder or

- Whether the impairment due to the tics outweighs the positive effects of the pharmacological treatment for ADHD. In cases where the tics are related to the medication, the dose should be reduced or the medication discontinued and, as appropriate, treatment with guanfacine or atomoxetine be given.

Notes on the evidence in Section II.2.4.4 and the evidence table in the Method Report, Appendix 11.4.4

Consensus recommendation: Without COI 100% – all 100%

Quality of evidence: Expert consensus

1.4.6.15.   In patients with known anxiety symptoms, medication with stimulants can potentiate anxieties. If this is the case, reducing the dose or switching to atomoxetine or guanfacine can be considered. Comorbid anxiety symptoms should be treated in accordance with practice guidelines.

Notes on the evidence in Section II.2.4.4 and the evidence table in the Method Report, Appendix 11.4.4

Consensus recommendation: Without COI 100% – all 100% (one abstention)

Quality of evidence: Expert consensus

1.4.7. What needs to be considered with regard to drug adherence?

Lack of adherence to ADHD treatment in childhood, adolescence and adulthood is a common phenomenon. Non-adherence can be associated with the persistence of ADHD symptoms and the resulting impairments.

1.4.7.1. Medication adherence should be checked regularly.

Notes on the evidence in Section II.2.4.4.

Consensus recommendation: Without COI 100% – all 100%

Quality of evidence: Low

Grade of recommendation: Recommendation, ↑, B

1.4.7.2. It should be kept in mind that non-adherence can indicate a rejection of this form of therapy.

Notes on the evidence in Section II.2.4.4.

Consensus recommendation: Without COI 70% – all 61.54%

Quality of evidence: Majority approval by the experts

Commentary on the recommendation:

A critical evaluation of the patient's motivation should be included in the verification of adherence. In older children and especially in adolescents, it should be borne in mind that they may wish to take the medication in order to avoid certain psychological stresses that often go hand in hand with high academic demands. Here, there is a risk that certain developmental stages in the experience of self-efficacy, the development of frustration tolerance as well as in overcoming difficulties are more encumbered for children and adolescents.

1.4.7.3. The adherence to medication during the course of treatment should be assessed in a mutual discussion and based on the regularity in which prescriptions are requested.

Notes on the evidence in Section II.2.4.4.

Consensus recommendation: Without COI 100% – all 100%

Quality of evidence: Expert consensus

1.4.7.4. If there are signs of poor medication adherence, the causes should be elucidated and broken down individually. Possible solutions should be developed as part of shared decision making.

Notes on the evidence in Section II.2.4.4.

Consensus recommendation: Without COI 100% – all 100%

Quality of evidence: Expert consensus

Commentary on the recommendation:

The lack of medication adherence mentioned in the recommendation may also be an expression of the patient's resistance to pharmacological treatment. Because stimulants are highly effective drugs that interfere with neurotransmitter metabolism in the brain and thus change the individual's self-experience, a possible protest/reservation against or even rejection of the medication must be met with respect for the patient's right to self-determination. Particularly in children, careful psychological evaluation is required, because children are less able to convey their feelings easily given the status of their cognitive and emotional development.

1.5. Inpatient and partial inpatient therapy, youth welfare measures and rehabilitation[3]

1.5.1. When are inpatient and partial inpatient therapies and measures indicated in children, adolescents and young people?

The diagnosis and treatment of ADHD in childhood and adolescence should generally be carried out on an outpatient basis. Inpatient or partial inpatient therapies (in hospitals, youth welfare or rehabilitation facilities), if necessary with admission/treatment of parents, or home treatment in the natural environment may be considered after unsuccessful outpatient therapy or if outpatient therapy is unlikely to be successful. The latter may be the case, for example:

- In particularly severe ADHD symptoms
- In particularly severe coexisting disorders (including acute endangerment of self or others)
- When very few resources are available in the family, kindergarten or at school or
- In particularly unfavorable psychosocial conditions.

In the case of permanently insufficient resources in the family or very pronounced symptoms (including coexisting conditions) that cannot be sufficiently reduced by outpatient or short-term inpatient treatment, then the option of using longer-term outpatient, day-patient or inpatient youth welfare measures can be weighed.

Notes on the evidence in Section II.2.5.

Consensus recommendation: 100%

Quality of evidence: Low

Grade of recommendation: Recommendation, ↑, B

1.5.2. Under what conditions are inpatient and partial inpatient therapies and measures indicated in adults?

The diagnosis and treatment of ADHD in adults should generally be carried out on an outpatient basis. Inpatient or partial inpatient therapies (in hospitals or rehabilitation facilities) or home treatment in the natural environment may be considered after unsuccessful outpatient therapy or if outpatient therapy is unlikely to be successful.

The latter may be the case, for example

- For particularly severe ADHD symptoms
- In particularly severe coexisting disorders (including acute endangerment of self or others)

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[3] From this chapter on, there was only one round of voting for each recommendation. An explanation can be found in the Preamble.

- In particularly unfavorable psychosocial conditions.

Notes on the evidence in Section II.2.5.

Consensus recommendation: 100%

Quality of evidence: Low

Grade of recommendation: Recommendation, ↑, B

1.6. Transition

1.6.1. Which patients should be transitioned to further treatment in adulthood and who should initiate this?

Patients with ADHD in the transition phase should be offered a referral to a secondary care physician/psychotherapist if debilitating ADHD symptoms are ongoing and/or other coexisting disorders that require treatment are present.

Notes on the evidence in Section II.2.6.

Consensus recommendation: All 100%

Quality of evidence: Expert consensus

Commentary on the recommendation:

The German medical societies DGKJP and DGPPN have published a joint Key Issues Paper on the topic of transition. In line with the international definition of transition in the health sector by (cf. Mayr et al. [186]) both societies understand transitioning as "…*the targeted support of the transition process in the sense of coordinating suppliers and ensuring supply continuity on the path from youth centered to adult-oriented care...*" (cf. Key Issues Paper at: http://www.dgkjp.de/stellungnahmen-positionspapiere/stellungnahmen-2016/396-uebergang-zwischen-jugend-und-erwachsenenalter-herausforderungen-fuer-die-transitionspsychiatrie).

1.6.2. How should transition work?

If treatment needs to be continued, ADHD patients should be re-examined during the transition phase in order to facilitate smoother transitioning and provide the secondary care physicians/psychotherapists with comprehensive information about their medical history, course of treatment and current clinical picture. While transitioning, a discussion between the previous physicians/psychotherapists and those continuing therapy should be facilitated. The ADHD patient in the transition phase should receive comprehensive information about the provision of care in adult settings.

Notes on the evidence in Section II.2.6.

Consensus recommendation: All 100%

Quality of evidence: Expert consensus

1.6.3. Which primary measures should be taken by the physicians/psychotherapists continuing therapy?

The physicians/psychotherapists taking over and continuing treatment should give the ADHD patient perform an initial comprehensive examination that includes the documentation of the individual's educational, occupational and social functioning level. In addition, any coexisting conditions, especially any personality disorders, drug abuse and emotional regulation disorder should conclusively be assessed.

Notes on the evidence in Section II.2.6.

Consensus recommendation: All 100%

Quality of evidence: Expert consensus

1.7. Self-help

1.7.1. How can self-help be incorporated into treatment?

Specialists who care for patients with ADHD should know the regional and national ADHD self-help groups and inform patients and their family members about any offers and support options. Visiting a self-help group or a family support group can also be helpful for those affected.

Notes on the evidence in Section II.2.7.

Consensus recommendation: All 100%

Quality of evidence: Expert consensus

2. Derivation of evidence

2.1. Diagnosis

NICE [187, 188] conducts systematic reviews and meta-analyses of empirical studies on the validity of the diagnosis of ADHD and comes to the following conclusions:

- Symptoms that describe hyperactive, impulsive and inattentive behavior form common clusters in childhood and adolescence, and can be distinguished from other symptom clusters, although they often coexist with other ones.
- ADHD symptoms can be seen along a continuum in the general population.
- ADHD can be distinguished from the normal range by the number and severity of symptoms and by their association with a significant degree of impairment.

- Assessing the extent of impairment caused by symptoms is of particular importance, since a specific cut-off at which symptom severity causes impairment is generally hard to ascertain.

- Children and adolescents with ADHD suffer impairments in psychological, social and educational/occupational settings.

- In the greater number of cases, ADHD symptoms persist from childhood into adulthood, where a significant minority will carry forward the diagnosis of ADHD, although, in the majority of such cases, subclinical symptoms associated with significant impairments will still be detectable.

- The symptom spectrum can change in adulthood, with inattention being more dominant than hyperactive-impulsive symptoms.

- There is evidence that both genetic and environmental factors play a role in the etiology of ADHD. The diversity in the etiology of the disorder is unknown. Current evidence suggests multiple risk factors with each having minor effects.

- The complex interaction between genetic and environmental factors has not been well researched to date. Environmental risk factors can interact or show covariation with genetic factors or have significant effects. Equally, genetic factors can interact or show covariation with environmental factors or have significant effects as well. In each individual case, an interplay of various factors must be assumed.

- At the group level, associations of ADHD symptoms with certain genetic, environmental risks and neurobiological changes have been proven, but these relationships are too weak to develop diagnostic tests for individual cases.

- The diagnosis remains descriptive at the behavioral level and can only be causally related to certain neurobiological or environmental factors in rare cases.

- Hyperkinetic disorder as classified in ICD-10 is a narrow subtype of the combined presentation of ADHD according to DSM-IV and DSM-5. In ICD-10, a more cross-situational and more disruptive form of the disorder is described. Both concepts are useful.

- There is only limited evidence for differing concepts of ADHD in children and adults. However, age-related variations in the clinical presentation are documented. These age-related variations are not yet reflected in the current diagnostic criteria of ICD-10 and DSM-5. All current methods of capturing ADHD have their own limitations. Therefore, a flexible deployment of diagnostic procedures is needed and the severity of impairment caused by the symptoms must be taken into account each time a diagnosis is made.

These key statements continue to be applicable without restriction. Findings obtained using German-language diagnostic procedures support these statements. It has also been demonstrated for the German-speaking countries (1) that symptoms of ADHD can be distinguished from other mental disorders based on parent, teacher and clinical ratings, (2) that ADHD symptoms can be described

along a continuum in the general population, (3) that a specific symptom severity cut-off where impairment occurs, cannot be generally ascertained and that (4) children, adolescents and adults with ADHD exhibit impaired functioning in psychological, social, educational and occupational settings [178, 185, 189-194].

With regard to individual recommendations, the following empirical evidence can be applied:

2.1.1. Who should undergo diagnostics for ADHD?

Problems in development, learning/performance and conduct manifesting as expansive behavioral disorders occur with an increased frequency in ADHD [118, 195, 196]; therefore, the possibility of an underlying ADHD should be considered and appropriate diagnostics carried out whenever these anomalies are present. The same applies if there are signs of at least mild ADHD symptoms, since there is a continuum from mild to very pronounced symptoms [196].

2.1.2. Who should diagnose ADHD?

There is no empirical evidence for this; but given the complexity of diagnostics and differential diagnostics, it is obvious that sufficient professional qualifications are required to diagnose ADHD.

2.1.3. Which diagnostic measures should be deployed routinely?

As with the diagnosis of all mental disorders, diagnostic measures should focus on the clinical exploration of typical symptoms, on behavioral observations in the examination situation and on the psychopathological assessment of the patient based on the explored and observed symptoms. The focus during childhood and adolescence is initially on the exploration of the parents, since SIGN [197] deems the parental reports about the current psychopathology of the child to be an accurate means of assessments [198, 199]. However, SIGN [197] also acknowledges that psychological abnormalities in the parents can influence the reliability of parental reports about the child's behavior [200-202]. Therefore, the examiner's assessment of the parents' information, including all information, is of great importance for the psychopathological findings report.

Patient-reported information is also important, because information from parents and patients captured in structured clinical interviews and on questionnaires correlates, at best, in the middle range [196, 203]; this is not only due to the different anchors on which respondents base their judgment but equally because parents do not always have insight into all domains of their child's everyday life [185]. According to SIGN [197], studies show that children and adolescents do not always accurately

assess externalizing symptoms. However, they may be better at assessing internalizing symptoms, such as anxiety and depression [121, 204].

On this exploration, information from educators/teachers is additionally important; this is because information from parents and educators/teachers correlates, at best, in the middle range – a finding particularly exposed by questionnaire studies [196, 205, 206]. In addition, educators/teachers can observe patients in domains of everyday life that are very important for assessing the patient's functional performance and behavior in group situations only partially accessible to parents.

In addition to the current ADHD symptoms, it is also important to explore the resulting functional impairments, seeing as both symptoms and impairments are necessary prerequisites for diagnosis and therapy planning. Current and previous environments, resources and stresses in the family and in kindergarten/school or at work, including the mental and physical health of the reference persons, can influence the symptoms of ADHD and the choice of therapy; therefore, the exploration should capture the appropriate information [121, 187].

In adulthood, the diagnostic assessment is based primarily on information provided by the patient during the exploration. No studies have proven that data from additional external medical histories have a higher diagnostic accuracy. Nevertheless, parental information can be helpful in adults with ADHD symptoms to answer the question whether ADHD symptoms were already present in childhood. In a follow-up study on children with ADHD in adulthood, only 78% were diagnosed with childhood ADHD according to their self-reported data [207]. However, it was also shown that the information provided by parents and adults with ADHD exhibits limited consistency and that there is no additional benefit gained in terms of diagnostic accuracy by including the information provided by parents [208]. School report cards may contain evidence of childhood ADHD symptoms, but there are no studies to prove the diagnostic validity of such documents.

A physical and neurological examination is indicated because it helps to identify physical problems, the basis of ADHD symptoms and any possible contraindications to pharmacological interventions (cf. [197]). However, according to SIGN, [197] neurological signs and minor morphological anomalies can neither rule out nor confirm the diagnosis of ADHD. Although many SIGN studies [197] show a slightly higher number of neurological hallmarks in hyperactive children, the usefulness of this association for the diagnosis of ADHD has not been established [209, 210]. Similarly, minor morphological anomalies are of no diagnostic significance for ADHD [211]. Nevertheless, screening for neurological signs and minor morphological anomalies is part of the physical examination [197].

2.1.4. How important are patients' self-assessments?

The report of parents, teachers and other reference persons is of crucial importance for the assessment of ADHD symptoms in childhood. This is because the reports of older children and adolescents regarding their own behavior also often deviate from the assessments of other observers, possibly due to the tendencies of those affected to dissimulate as well as to perceive their own behavior differently [189, 196, 203]. In adulthood, the patient is the most important source of information. However, the information provided by reference persons can help validate the patient's information.

2.1.5. How important is the use of questionnaires and behavioral observations in diagnosing ADHD?

Questionnaires can provide important additional information, but they cannot replace clinical exploration. This is because an assessment of behavior as being abnormal requires a clinical estimation based on a preferably concrete description (or observation) of the behavior, which is usually not captured on questionnaires. Not only are the anchors on which respondents base their judgment reflected when behaviors are assessed as abnormal on questionnaires, but these anchors may also be distorted by the rater's own psychological burdens. Therefore, some studies show that patient's behavior is judged to be less abnormal by clinical assessments than by parent-rated assessments [185]. Questionnaires can also be used to document coexisting symptoms. The behavioral observation reported by the patient in the examination situation can provide additional information, whereby - according to SIGN [197] - it is important to consider that children show less abnormal behavior in new situations, e.g. when presenting in a practice or hospital, or when an observer comes to school [212]. Therefore, unremarkable behavior in an examination situation is not a definitive criterion for excluding an ADHD diagnosis. Behavioral observations made outside of the actual examination situation (e.g. at school) are valuable and should be carried out, especially if symptoms cannot be conclusively explored.

2.1.6. What is the significance of psychological tests?

ADHD cannot be diagnosed or excluded solely on the basis of psychological tests alone since, according to SIGN [197], neuropsychological tests for attention and concentration do not differentiate reliably between ADHD and other mental disorders or abnormal behavior [121, 213, 214]. Indeed, children and adolescents with ADHD often exhibit specific developmental disorders with an increased frequency alongside persistent performance problems in adulthood [215, 216] that need to be clarified using developmental, intelligence and performance diagnostic testing methods [121].

2.1.7. What is the importance of laboratory tests and technical diagnostic studies?

There is no specific biological marker for ADHD [187, 217]. Therefore, the diagnosis must be based exclusively on exploration and psychopathological assessment. Laboratory and technical diagnostic studies can, however, be important for diagnosing possibly underlying somatic diseases or for the differential diagnosis.

2.1.8. Are there any age-specific peculiarities that should be addressed by diagnostics?

According to the ADHD guideline by the AAP [218], the diagnosis of ADHD can be made with reasonable certainty from the age of four; risk factors for the development of ADHD can include very pronounced restlessness, impulsivity and distractibility alongside regulatory disorders in the first years of life [205, 219-223].

A decrease in symptoms, particularly hyperactivity, which often occurs must be taken into account in adolescents [224]. From adolescence onwards, it is important to diagnostically differentiate from other mental disorders; other coexisting conditions and risks must also be taken into account (e.g. substance abuse, emotionally unstable personality disorder, psychosis, risky sexual behavior [189, 225]). Symptoms of emotional dysregulation are common in adulthood [226].

2.1.9. Which mental disorders or somatic diseases are considered in the differential diagnosis of ADHD?

The differential diagnosis is oriented on DSM-5 and ICD-10.

2.1.10. Which commonly coexisting disorders should be considered in particular?

Coexisting disorders occur frequently, can have adverse effects on the prognosis and require special therapeutic measures. The disorders that occur with the greatest frequency include oppositional defiant behavior and other conduct disorders, tic and Tourette disorders, specific developmental disorders (of motor function, language, scholastic skills), anxiety disorders, depressive disorders, autism spectrum disorders and, from adolescence onward, substance use disorders and personality disorders [195, 227].

2.2. Intervention algorithms

In general, both the NICE source guidelines [187] and those of the European Guidelines Group on ADHD [228] recommend psychosocial interventions based on behavioral therapy primarily for children under the age of six years and for those with mild to moderate functional impairment due to ADHD symptoms from the age of six years. Pharmacotherapy should be offered from the age of six years, mainly for children with severely pronounced functional impairment. The present Practice

Guideline deviates from this algorithm insofar as it does not primarily recommend psychosocial interventions for children from the age of six years with moderate symptoms or functional impairment. Rather, psychosocial interventions and/or pharmacotherapy are recommended in equal measure.

Meta-analyses have shown a high efficacy and tolerance of pharmacotherapy in treating core symptoms; however, more recent meta-analyses with blind assessments were unable to demonstrate any effectiveness of psychosocial interventions [229, 230]. The benefits of pharmacotherapy on the symptoms of ADHD are therefore significantly higher than those of psychosocial interventions. Based on these new meta-analyses, the Evidence Update [231] and the 6-year Surveillance Review by NICE [232] concluded that parent training can be useful for parents, but may have a limited impact on ADHD symptoms and behavior outside the family. These results convinced them to re-examine the guideline. The guideline is currently being revised.

In general, the effects of pharmacotherapy on the symptoms of ADHD can be estimated to be at least twice as high as the effects of psychosocial interventions [233]. Thus, the recommendation for primary pharmacotherapy for more severe symptoms is well founded. However, greater effects from pharmacotherapy compared to psychosocial interventions on functional impairments have not been consistently proven. For example, the MTA study, where the raters were not blinded, clearly demonstrated that pharmacotherapy was superior in improving ADHD symptoms, but not in improving psychosocial functioning levels compared to behavioral therapy [234].

Although the severity of ADHD symptoms in the MTA study was not a moderator for the effectiveness of behavioral interventions [235],—i.e. it could not be proven that behavioral therapy had fewer effects in children with more severe symptoms—pharmacotherapy can be expected to have greater effects on more severe symptoms. For example, in a reanalysis of the MTA study, Santosh et al. [236] found greater effects from pharmacotherapy in patients with an HKD diagnosis as defined in ICD-10, compared to patients who did not meet these diagnostic criteria but did meet the criteria for ADHD as defined in DSM-IV. However, the effects in this analysis were also significantly influenced by the fact that patients with comorbid anxiety disorder (in whom behavioral therapy achieved relatively good benefits) were also excluded from the diagnosis of HKD when using ICD criteria.

2.3. Interventions on a psychological-psychotherapeutic level (psychoeducation, psychosocial interventions, psychotherapy, neurofeedback), diets

2.3.1. Derivation of the level of evidence and grade of recommendation for psychosocial interventions in children and adolescents with ADHD

In general, a large number of empirical studies on the effectiveness of psychosocial interventions in children and adolescents with ADHD symptoms are now available, although many of these studies have methodological flaws that make it difficult to assess the respective results. There is also a large heterogeneity of psychosocial interventions in terms of the type of intervention and its intensity. This makes it considerably difficult to integrate empirical study results and to aggregate them in meta-analyses. In this respect, studies on the effectiveness of psychosocial interventions differ from the studies on the efficacy of pharmacotherapy. In addition to meta-analyses, the presentation of the empirical evidence must therefore also rely more heavily on individual studies than when deriving empirical evidence from pharmacotherapy. The main methodological problems in studies on the effectiveness of psychosocial interventions are:

1. Inconsistent study samples regarding the categorical diagnoses.
2. Little experimental control, for example, due to a lack of randomization.
3. Blinding is difficult to achieve, which is why measurement variables are increasingly used in the hope of reducing subjectivity. However, these create other methodological problems.

2.3.1.1. Derivation of the level of evidence and the grade of recommendation for preventive psychosocial interventions that do not require diagnostic verification

Preventive psychosocial interventions for children with externalizing behavior problems (e.g. oppositional behavior, increased restlessness, significant distractibility), which have not yet met the criteria for an ADHD diagnosis, do not differ methodologically from psychosocial interventions in children with ADHD. The meta-analyses used in Chap. II.2.3.1.2 and II.2.3.1.3 often include not only children diagnosed with ADHD, but also children with prominent ADHD symptoms who do not meet the diagnostic criteria for ADHD as well as children with oppositional behavioral problems. This particularly applies to parent training sessions and kindergarten- or school-based interventions. In German-speaking countries, the parent and educator training sessions on indicated prevention as well as guided self-help programs for parents were developed and evaluated on sample populations that included both children with ADHD and those with externalizing disorders (and at risk of developing ADHD). The studies proved the effectiveness of these interventions and are rated as "moderate" for the quality of evidence and as "recommendation" for the grade of recommendation.

Therefore, as per Chap. II.2.3.1.3, the quality of evidence has been rated as "moderate" and the grade of recommendation as "recommendation" for the effectiveness of preventive psychosocial interventions in children at risk of developing disruptive behavioral disorders, including ADHD. The interventional forms include indicated prevention by parent training, educator training/interventions in the kindergarten and programs for guided self-help for parents.

2.3.1.2. Derivation of the level of evidence and the grade of recommendation for psychosocial interventions in pre-school age children with ADHD

2.3.1.2.1.   Evidence from source guidelines

The NICE guidelines [187] identified two studies [237, 238] on the effectiveness of parent training, based on social learning theory (in an individual and group format) as psychosocial interventions in pre-school age children with ADHD (approx. three to six years old). Based on these studies, the guidelines conclude that parent training for children with ADHD is effective. The NICE guidelines likewise point out that the NICE analyses on the effectiveness of parent training for patients with conduct disorders showed parent training for preschool-age children to be effective, thereby concluding that these results are likely to apply to children with ADHD because of the substantial overlap between the two groups. The 3-year Review [239], the Evidence Update [231] and the 6-year Surveillance Review [232] all list further studies that prove the effects of parent training in preschool-age children with ADHD [240-242]. This additional evidence supports the previous recommendations.

The AAP clinical practice guidelines [218] refer to the meta-analysis by Charach et al. [243], which summarized the results of eight high-quality studies on the effectiveness of parent training for preschool-age children with disruptive behavioral problems (i.e. oppositional, aggressive, impulsive and hyperkinetic-inattentive behavioral problems) [237, 238, 242, 244-247]. These studies showed medium effects on disruptive behavior (SMD = -0.68 (95% confidence interval: -0.88 to -0.47) (see also [243]). In summary, it was established that parent training is effective in treating preschool-age children with disruptive behavioral problems and also has benefits with regard to ADHD symptoms. These studies additionally showed long-term effects for up to two years, including on the symptoms of ADHD. The meta-analysis by Charach et al. [243, 248] also summarized the results of five studies on the effectiveness of parent training combined with interventions in kindergarten for preschool-age children with disruptive behavioral problems [249-255]. Altogether, these indicated that additional counseling sessions for educators of preschool-age children from a lower socio-economic background are helpful, but not for children from families with a higher socio-economic background. Two studies [254, 255] examined the effects of combined parent and educator training as well as patient-centered interventions and showed that all behavioral interventions were effective. It was also demonstrated that interventions with parents attending at least eight sessions were more effective than those where

parents attended fewer sessions. The AAP clinical practice guidelines therefore concluded that evidence-based behavioral therapy interventions implemented by educators or parents should be the first-choice therapy for preschool-age children aged four to five years. The AAP clinical practice guideline assigns this recommendation the level of evidence A and the grade of recommendation: strong recommendation. In the AWMF nomenclature, this corresponds to the level of evidence "high" and the grade of recommendation "strong".

The SIGN guidelines [197] summarize three RCTs [237, 238, 240] which consistently showed that parent training conducted by qualified trainers can improve symptoms of ADHD that stabilize over a one year period. In contrast, parent training conducted by unqualified trainers proved to be ineffective. The recommendations derived from this Practice Guideline suggest that parents of preschool-age children with ADHD symptoms should receive training programs and that these programs should be offered by a qualified trainer. The SIGN guideline assigns this recommendation the level of evidence 1+ and the grade of recommendation: B. In the AWMF nomenclature, this corresponds to the level of evidence "high" and the recommendation grade "Can".

2.3.1.2.2.   Evidence from recent meta-analyses and studies

Several meta-analyses and single studies (see evidence tables for Psychosocial Interventions in Children and Adolescents in Appendix 11.4.1 of the Method Report) have been published in recent years, which have not yet been included in the source guidelines and their updates or are only mentioned briefly. Also, German-language publications are not usually included in international guidelines and meta-analyses.

Meta-Analyses. Daley et al. [230] (see 2.3.1.3) found in the updated meta-analysis by Sonuga-Barke et al. [229] of randomized control group studies on children and adolescents with ADHD (across the entire age range) and found positive effects of behavioral parent training in unblinded assessments (mainly from parents) but not in blinded assessments (mainly from teacher assessments). They also found positive effects when they looked at unblinded and blinded assessments of oppositional and aggressive symptoms and parenting behavior. In younger children (preschool-aged), more positive effects were found across several domains.

Single Studies. Abikoff et al. [256] (see evidence tables "Psychosocial Interventions in Children and Adolescents in Appendix 11.4.1 in the Method Report) compared the effects of training delivered in the family home for the parents of preschool-age children with ADHD constructively targeting ADHD-related dysfunctions versus a clinic-based parenting intervention designed for treating noncompliant behavior in young children. Both training programs showed significant effects on the ADHD symptoms, as assessed by the parents, and on oppositional behavior, which also stabilized over

the follow-up period, but no effects were found when looking at the educator's assessment. In addition, no significant differences between the two interventions could be proven.

In German-speaking countries, the effectiveness of parent group training and educator group training (Prevention Program for Externalizing Problem Behavior, PEP [257]) was examined in several studies on preschool-age children with externalizing behavior problems (including ADHD symptoms and the full picture of ADHD) (see Appendix III.5).

The effectiveness of parent training as guided self-help for parents of children with external behavioral problems (including ADHD) is shown in a meta-analysis of eleven randomized controlled studies [258], which nearly all examined its effectiveness in parents of pre-school age children as well as the effects in reducing external behavioral problems as assessed by the parents (but not in behavioral observation), and in improving parenting behavior, mood and reducing stress on parents (see Appendix III.5). There are only a small number of individual case analyses of child-centered interventions with limited methodological quality or small sample sizes that suggest that ADHD symptoms can be reduced (see Appendix III.5).

2.3.1.2.3.   Summary assessment of the level of evidence and derivation of the grades of recommendation

Overall, the effectiveness of parent training for pre-school age children is judged as high level of evidence and educational training/interventions in kindergarten, at least for pre-school age children with disruptive behavior disorders (including ADHD) and with the risk of developing disruptive behavior disorders (including ADHD), as 'moderate' level of evidence. The effectiveness of child-centered interventions can still be judged a "low" level of evidence. These levels of evidence were assigned to the corresponding recommendations of II.1.3.1.2.

Based on the assessment of the level of evidence and according to the recommendation grades specified in the source guidelines, a 'strong' recommendation grade can be derived for the implementation of parent training for preschool-age children with ADHD or with increased symptoms of ADHD. For the implementation of kindergarten-centered interventions the recommendation grade is 'recommendation' and for the implementation of additional child-centered interventions the recommendation grade is 'open recommendation'.

For all further recommendations regarding the implementation of these interventions, there is either little or only few direct empirical evidence from individual studies or the evidence can only be derived indirectly from studies or, for the corresponding recommendation, experimental scientific studies are

not possible. The level of evidence is classified as an expert consensus and a recommendation grade is not specified.

2.3.1.3. Derivation of the quality of evidence and grade of recommendation for psychosocial interventions in preschool children with ADHD

2.3.1.3.1. Evidence from source guidelines

The NICE guidelines [187] identified eight RCTs [259-266] on the effectiveness of parent training and patient-based interventions (in individual and group format) as psychosocial interventions in children and adolescents with ADHD from school-age (up to the age of 13 years) and concluded, on the basis of these studies, that these interventions have moderate effects on children with ADHD with regard to ADHD symptoms as assessed by parents, and oppositional defiant disorder both for children without pharmacotherapy and for those who also receive pharmacotherapy in parallel. The NICE guidelines also point out from their analyses on the effectiveness of parent training for patients with conduct disorders, that parent training for school children proved to be effective and, based on the significant overlap between the two groups, concluded that these results are also likely to apply to children with ADHD. Four studies [261, 265-267] described positive effects of psychological patient-centered interventions (cognitive behavioral therapy/social skills training) on the core symptoms of ADHD, aggressive behavior, social competence or self-efficacy. None of the included studies examined the effects in adolescents from the age of 13 years. However, according to NICE, interventions used in older children are also likely to be effective in adolescents.

The Evidence Update [231] and the 6-year Surveillance Review [232] by NICE list new studies on (a) parent training, (b) telephone-based parent training, (c) patient-centered interventions, and (d) school-centered interventions:

(a) Parent training. The Cochrane meta-analysis by Zwi et al. [268] examined the effectiveness of parent training in reducing ADHD symptoms and associated problems in children aged between five and 18 years. A total of five studies (284 patients) were assessed, comparing all parent training with treatment as usual. With regard to aggressive-oppositional and rule-breaking behavior, no significant effect could be found (SMD −0.32, 95% CI −0.83 to 0.18, p = 0.21; 3 studies, n = 190). With regard to internalizing behavioral abnormalities, a significant effect was found (SMD = −0.48, 95% CI −0.84 to −0.13, p = 0.0074; 2 studies, n = 142). With regard to parents' perception of the child's behavior, a significant effect was demonstrated in the parent stress indices (average difference [MD] = − 10.52, 95% CI −20.55 to −0.48, p = 0.04). Sonuga-Barke et al. [229] carried out a meta-analysis of non-pharmacological interventions to reduce ADHD in children and adolescents. Of the 54 RCTs (n = 3154), 15 (n = 1041) were related to behavioral parent-based interventions (eight studies), combined

parent training and child-centered interventions (four studies), combined parent and teacher training as well as child-centered interventions (two studies) and one study related to child training only (n = 18). Behavioral therapeutic interventions had significant effects when the assessments of ADHD symptoms were unblinded (mainly assessed by parents) (SMD = 0.40, 95% CI 0.20 to 0.60, p = 0.0001), but not in blinded assessments. However, behavioral therapeutic interventions differed considerably in terms of the intensity and duration of therapy. Daley et al. [230] updated the meta-analysis by Sonuga-Barke et al. [229] of randomized control group studies of children and adolescents with ADHD (across the entire age range) and found positive effects of behavioral interventions (mainly behavioral parent training) in unblinded assessments (mainly from parents) but not in blinded assessments (mainly teacher assessments). They also found positive effects when they looked at unblinded and blinded assessments of oppositional and aggressive symptoms and parenting behavior.

The Evidence Update [231] and the 6-year Surveillance Review [232] concluded from these new meta-analyses that this new evidence suggests that parent training may be useful for parents but has only limited impact on ADHD symptoms and behavior outside the family surroundings; additional predicates were that further research is needed and that the indication of parent training as a first-line intervention should be re-evaluated. The guideline is currently being revised.

(b) Telephone-based parent training. The study by McGrath et al. [269] demonstrated the effectiveness of telephone-based self-help for parents of children with ADHD in follow-up studies. Although the study is not directly applicable to Great Britain and thus initially has no influence on the NICE guideline, according to NICE [231], however, the evidence suggests that telephone-based parent training could be effective. Additionally, the advantages of this form of intervention are highlighted.

(c) Patient-centered interventions In an RCT, Abikoff et al. [256] tested the effectiveness of patient-based and parent-based behavioral interventions (20 hours) to improve problems with organization, time management and planning in 158 children aged eight to eleven years with ADHD. Both interventions showed pronounced effects on the improvement of organizational skills, with patient-based interventions being superior. Regarding other measures of success, both interventions were equally effective and the therapeutic effects were stable over a period of two years. In an RCT, Langberg et al. [270] reviewed the effectiveness of behavioral interventions (in school) to improve organizational skills in school and for homework. Positive effects on organizational skills were found in the parent-rated assessment.

NICE [231] concludes that both studies demonstrate the importance of training for improving organizational skills in order to improve the functioning of children with ADHD.

(d) School-centered interventions. Mikami et al. [271] investigated the effect of a four-week summer training program with a token reward system to improve compliant behaviors and adjunctive components to encourage the inclusion of children with ADHD in the classroom. The study showed additional effects of the interventions in improving the integration of children with ADHD into the school class. NICE [231] concludes that this study highlights the importance of interventions that affect the whole class to improve the social integration of children with ADHD.

The AAP guidelines [218] refer to the systematic reviews by Pelham et al. [272, 273] and emphasize that the variety of interventions and success parameters place more demands on meta-analyses of studies on the effectiveness of these interventions and that the long-term effects of behavioral therapy are still unclear. This clinical practice guideline refers to the MTA study results and point out the greater benefits from combined behavioral and pharmacotherapy in this study compared to pharmacotherapy alone [162]. The AAP guidelines therefore classify the evidence-based behavioral interventions, carried out by parents or teachers, as level of evidence "B" and grade of recommendation "Strong". In the AWMF nomenclature, this corresponds to the level of evidence: "moderate" and grade of recommendation "strong".

The SIGN guidelines [197] analyzed six RCTs on the effectiveness of parent training for children under the age of twelve years [264, 266, 274-277], which show that parent training reduces comorbid aggressive behaviors and internalizing problems but has no added benefit over medication or routine clinical care on core ADHD symptoms. Improvements in the family usually do not transfer to the school environment. The MTA study [278] demonstrated additional effects of psychosocial interventions on oppositional and aggressive behavior, internalizing behavioral problems, social competence, parent-child relationships and reading skills. An RCT [279] showed effects of behavioral interventions for parents, children and teachers in children with ADHD of the inattentive subtype. Linked to this, this Practice Guideline recommends conducting behavioral therapeutic interventions in children under the age of twelve years with ADHD and comorbid symptoms of oppositional or aggressive behavior to reduce comorbid symptoms. In the nomenclature of the SIGN guideline, the studies this recommendation is based on are assigned to the level of evidence 1+ and the grade of recommendation: A. This corresponds to the level of evidence in the AWMF nomenclature: "high" and the grade of recommendation "strong".

Regarding school-based interventions, the SIGN guidelines refer to the meta-analysis by DuPaul and Tanya [280], which proves that methods of contingency management and support measures are superior to cognitive therapies (e.g. self-instruction training) (evidence level 1+ = high). Studies show that the effects often disappear when the intervention is stopped and that, although the target behavior of an intervention is improved, the symptoms of ADHD are not necessarily improved [281]. Further

studies show that smaller class sizes, the use of special support rooms, direct instructions and involvement of the whole class can improve the concentration of pupils with ADHD [282].

2.3.1.3.2. Evidence from recent meta-analyses and studies

Several meta-analyses have been published in recent years that have not yet been included in the source guidelines and their updates or are only mentioned briefly. Also, publications in the German-language are usually not included in international guidelines and meta-analyses.

Meta-Analyses: Cortese et al. [283] conducted another update of the meta-analysis by Sonuga-Barke et al. [229] of randomized control group studies on (mainly computer-assisted) cognitive training in 759 children and adolescents with ADHD and found significant effects on ADHD symptoms (SMD=0.37; 95% CI 0.09 to 0.66) reported by mainly unblinded raters who were the most familiar with the treatment setting (mainly parents). These effects decreased when presumed blinded measures were used, but still just reached significance (SMD=0.20; 95% CI 0.01 to 0.40). Significant effects were found in tests on working memory (verbal: SMD=0.52, CI 0.24 to 0.80; visual: SMD=0.47, CI 0.23 to 0.70) and in executive functions (SMD=0.35, CI 0.08 to 0.61), as assessed by parents. Rapport et al. (2013) examined 25 studies on the effectiveness of cognitive training in children with ADHD and found that short-term memory training had moderate effects on short-term memory (d = 0.63), whilst attention training did not significantly improve attention performance and that training to improve executive functions did not have significant effects on cognitive functions. Generalization effects on academic performance, blinded behavioral assessments or other cognitive performance were either not significant or negligible. Unblinded raters describe larger effects (d = 0.48) compared to blinded raters and objective tests. The authors conclude that the expectations that cognitive training improves academic performance, cognitive functions and behavior will not be confirmed by the meta-analyses. However, it is still unclear whether children with well-documented deficits in executive functions can benefit from such interventions.

DuPaul et al. [284] carried out a meta-analysis of 60 outcome studies (in between-subjects, within-subjects, and single-subject experimental designs) on the effectiveness of school-based behavioral therapy interventions in children with ADHD. For the studies with between-subjects experimental designs, the effect sizes of d = 0.43 (95% CI -0.36 to 1.21) for improvements in academic performance (two studies) and the effect sizes of d = 0.18 (95% CI -0.62 to 0.98) for improvements in behavioral abnormalities were both not significant. For the within-subject studies, significant effect sizes of d = 0.42 (95% CI 0.09 to 0.93) for improvements in academic performance (ten studies) and also significant effect sizes of d = 0.72 (95% CI 0.13 to 1.30) for improvements in behavioral disorders (15 studies) were found. Even stronger effects were found in the individual case studies. In moderator

analyses, positive effects on both outcome measures were associated with contingency management, cognitive-behavioral interventions and with measures to promote school performance.

Richard et al. [285] provided a systematic overview of a total of 37 English and German-language studies on school-based, class-centered, teacher-centered and student-centered interventions in ADHD. Sibley et al. [286] conducted a systematic review of the effectiveness of psychosocial and pharmacological interventions in adolescents (from the age of ten years) with ADHD, including all controlled studies. The authors identified 22 studies (since 1999) on behavioral therapy in adolescents and found medium effect sizes for the reduction of ADHD symptoms SMD = 0.49; 80% CI 0.45 to 0.52) and oppositional behavior (SMD=0.34; 80% CI 0.32 to 0.36). Different functional impairments showed effect sizes between SMD = 0.31 (n = 1 study, no CI) and SMD = 1.20 (80% CI 0.94 to 1.47).

Chan et al. [287] provided a systematic overview of the effectiveness of psychosocial interventions (mainly treatment involving behavioral and cognitive methods as well as skill training, involving the patient, parents and the teacher) in adolescents with ADHD (ten RCTs). Five studies reported a reduction in inattention (Cohen's d = 0.3 to 1.42) and a decrease in hyperactivity-impulsivity (d= -1.03) was found in two studies. According to parent-rated assessments, group cognitive behavioral therapy leads to a greater reduction in ADHD symptoms (group mean difference, −9.11 points [95% CI, −11.48 points to −6.75 points]; Cohen's d = 8.4; p < .001) [288]. These extremely high effect sizes are due to exceptionally small variances and are therefore not very meaningful. However, according to Chan et al. [287], the most significant changes were achieved by measures that reduce functional impairments (e.g. completion of homework, improvement in organizational skills).

In German-speaking countries, the effectiveness of the Treatment Program for Hyperkinetic and Oppositional Problem Behavior (THOP) for children [113], which combines parent-centered, kindergarten and school-centered as well as patient-centered behavioral therapy, was examined in schoolchildren and adolescents with externalizing behavioral problems (including ADHD symptoms and the full clinical picture of ADHD) (see Appendix III.5). Several non-randomized control group studies of parents of schoolchildren with ADHD and other externalizing behavioral problems to investigate the effectiveness of parent training in form of guided self-help were also carried out in German-speaking countries (see Appendix III.5). Dose et al. [289] (see evidence tables on Psychosocial Interventions in Children and Adolescents in Appendix 11.4.1 of the Method Report) were also able to show in an RCT that the program can achieve further improvements in ADHD symptoms and functional impairments in patients with ADHD who were already receiving stimulant therapy but still showed other ADHD symptoms.

There are only a few and poorly conducted studies from German-speaking countries on the isolating effects of child-centered interventions, also at school age (see Appendix III.5). The effectiveness of School-based Coaching for Teachers of Children with Disruptive Behavior Problems (SCEP) [290] was demonstrated in a randomized control group study [291].

2.3.1.3.3. Summary assessment of the level of evidence and derivation of the grades of recommendation

Overall, both the effectiveness of parent training for children and adolescents and school-based interventions state the level of evidence as 'moderate'. Based on recent studies [256, 270] on the effectiveness of interventions for improving organizational skills, the effectiveness of patient-centered interventions was evaluated as level of evidence 'moderate'. These levels of evidence were assigned to the corresponding recommendations of II.1.3.1.3.

Based on the assessment of the levels of evidence and on the grades of recommendation specified in the source guidelines, the recommendation grade 'recommendation' can be given for the implementation of parent training, school-centered interventions and for the implementation of additional patient-centered interventions (including social competence training). Due to the overall heterogeneous findings on the effectiveness of patient-centered interventions, which—insofar as significant—show predominantly minor effects on ADHD symptoms, the recommendations in II.1.3.1.3. also add that these interventions are generally not sufficient as an adequate treatment of ADHD.

For all further recommendations regarding the implementation of these interventions, either little or no direct empirical evidence can be found in individual studies or the evidence can only be derived indirectly from studies or experimental scientific studies are not possible for the corresponding recommendation. The level of evidence is therefore defined as 'low' with the recommendation grade 'recommendation' or classified as an expert consensus.

2.3.1.4. Derivation of the level of evidence and grades of recommendation for psychosocial interventions in adults with ADHD

2.3.1.4.1. Evidence from source guidelines

The NICE guidelines emphasize the clinical consensus that particularly behavioral therapy seems to be appropriate for the treatment of adults with ADHD. The NICE guidelines [187] identified a randomized controlled trial on the effectiveness of psychosocial interventions in adults with ADHD [292]. Here, a small group of adults with ADHD already receiving medication (n = 16) were treated

with additional cognitive behavioral therapy (CBT) in an individual setting. The results of the study can be interpreted that CBT reduced symptoms of anxiety associated with ADHD in adults receiving pharmacological treatment. Furthermore, the assessment by an independent rater showed a moderately positive effect on the symptoms of ADHD, but this was not statistically significant. The NICE guidelines also base their analysis on a non-randomized study with patients on a waiting list as a control group, in which 41 patients were treated with a CBT-based group treatment program [293]. The CBT group showed a statistically significant gain in knowledge about ADHD, self-efficacy and self-esteem compared to the control group. In addition, the study concluded that group settings have a positive effect. Studies on the cost-benefit analysis of psychosocial interventions in adult ADHD do not exist. Based on a NICE analysis, individual behavioral therapy was assessed as not being cost-beneficial; in contrast, group CBT had a more favorable cost-benefit ratio.

2.3.1.4.2. Evidence from recent meta-analyses and controlled studies (including German-language studies)

Four controlled studies [294-297] and two systematic reviews/meta-analyses [298, 299] were published by September 2016 after the NICE guidelines have been updated (see evidence tables for Psychosocial Interventions in Children and Adolescents in Appendix 11.4.1 of the Method Report) and yielded the following results: In drug-treated adult patients with ADHD, CBT leads to a significant reduction in self-assessed (d = .46, p <.001) and externally assessed ADHD symptoms (d = .65, p <.001) (n = 95) compared to treatment as usual [296]. These effects were stable during the follow-up. However, the study shows a high dropout rate of almost 50%. The study results support previous findings on the effectiveness of CBT compared to treatment as usual in medicated patients with residual ADHD [292].

A randomized large multicenter study (n = 433) [294] showed no differences between cognitive-behavioral group therapy, based on dialectical behavioral therapy, compared with active clinical management (CM) with regard to ADHD symptoms (ADHD index, Conners adult ADHD rating scale), whilst methylphenidate treatment was significantly superior to placebo. No significant differences between the groups were found with regard to depression. After 52 weeks, group psychotherapy was superior to CM from a global clinical perspective; assessment of the general effectiveness of the treatment as a possible measure of coping with daily life was superior to CM at each measuring time point.

Mindfulness-based cognitive therapy (MBCT) led to a reduction in ADHD symptoms compared to a waiting list control group (n = 61) [295]. These clinical changes correlated to changed event-related potentials. Information regarding blinding is missing in the publication. A controlled study on web-

based cognitive behavioral therapy with and without treatment support compared to a waiting list control group (n = 45, [297]) can only be interpreted very cautiously due to methodological shortcomings, such as a lack of external assessment. Recommendations cannot be derived from this.

In a meta-analysis, cognitive behavioral therapy in adults with ADHD was superior, compared to waiting list control conditions, while showing a moderate to high effect size. When compared to an active control condition, small to moderate effect sizes were seen [299]. The meta-analysis by Jensen et al. [298] showed that cognitive behavioral therapy was effective in reducing ADHD symptoms following self-assessment by the patients, but not when evaluated by the clinician. Depression and anxiety symptoms were significantly reduced in self-reported and clinician ratings. The authors of both meta-analyses rated the quality of the studies included as poor. The meta-analyses were evaluated according to GRADE criteria (see evidence tables for Psychosocial Interventions in Children and Adolescents in Appendix 11.4.1 of the Method Report).

2.3.2. Neurofeedback

Several meta-analyses are available as an evidence base for the evaluation of neurofeedback (NF) in the treatment of children with ADHD. The first meta-analysis [300] of ten prospective, controlled studies with 467 patients found medium to large effect sizes (ES) for all three areas of core ADHD symptoms (ES inattention = 0.81; 95% CI: 0.39, 1.23, ES hyperactivity = 0.40; 95% CI: 0.05, 0.75, ES impulsivity = 0.69; 95% CI: 0.34; 1.03). More training sessions correlated with greater improvement in attention problems (r = .550, p = 0.04). A second meta-analysis [229] with a stricter methodological approach comprised eight randomized studies and showed a significant effect of NF on the overall symptoms of ADHD (ES = 0.59 [0.31-0.87]) in parent-rated assessments or by presumably unblinded raters. The trend of this effect was reduced to a statistical trend when only presumably blinded evaluations were included (ES = 0.30; 95% CI: -0.02-0.61). Studies with NF protocols that were not generally accepted were also included in this study. The meta-analysis of five studies [301] again showed significant effects of NF compared to control conditions in, presumably unblinded, parent assessments (ES ADHD total value = 0.49 [0.74, 0.24]), ES inattention = 0.46 [0.76, 0.15]), ES hyperactivity/impulsivity = 0.34 [-0.59, 0.09]). In addition, the blinded assessment by teachers also saw significant positive effects on inattention (ES = 0.30 [0.58, 0.03]). Cortese et al. [302] examined in an update of the meta-analysis by Sonuga-Barke et al. [229] 17 studies with 567 children and adolescents with ADHD, where all studies by Sonuga-Barke et al. (2013), Micoulaud-Franchi et al. (2014) and additional RCTs were included. They found moderate to small but significant effects of neurofeedback on inattention, hyperactivity-impulsivity and overall ADHD symptoms mainly based on unblinded assessments by people familiar with the intervention (usually parent-rated assessment) (standardized mean difference [SMD] overall symptoms = 0.35, 95% CI = 0.59, 0.11; SMD

inattention = 0.34, 95% CI = 0.58, 0.09; SMD hyperactivity/impulsivity = 0.23, 95% CI = 0.40, 0.06). These effect sizes are maintained if the analysis is limited to frequency band training (SMD overall symptoms = 0.37; SMD inattention = 0.33; SMD hyperactivity/impulsivity = 0.26). Too few studies were available for a separate analysis of slow cortical potentials neurofeedback or for a comparison of different training protocols. When only studies with active control conditions or sham feedback, as a comparison, were included in the analyses, the effects were hardly significant for hyperactivity/impulsivity (SMD = 0.21, 95% CI = 0.42, 0.01), but not for the rest of the symptom cluster. Electrophysiological evidence of changes due to neurofeedback was found in three out of five studies.

Cortese et al.[302] also explored what influence the quality of the applied neurofeedback had and found that studies that followed a well-designed standard training protocol had stronger and more significant effects. They were guided by the criteria for standard neurofeedback presented by Arns et al. [303]. These include the use of training protocols such as the feedback of the theta/beta ratio over the fronto-central region, the sensorimotor rhythm (SMR) over the motor cortex or the slow cortical potentials (SCP) over the parietal region. Trainings using other frequency bands and "QEEG-based" protocols with partly other electrode positions, is not validated and therefore considered unsuitable for routine use. The authors also consider the principles of learning theory and transfer exercises to apply what has been learned to everyday life as essential elements. The evaluation of seven studies that met these criteria showed higher effect sizes for most measures of change. Moreover, in three of these studies, the evaluations were blinded and showed a significant effect on the overall symptoms of ADHD (SMD = 0.36, 95% CI = 0.04, 0.69).

Based on the evidence described above, the present Practice Guideline makes an open recommendation for the implementation of neurofeedback as per standard training protocol within the framework of a treatment plan, provided that this does not delay or prevent another more effective therapy. If neurofeedback is used in the treatment of ADHD, the requirements for performing neurofeedback training, as listed in the recommendation in II.1.3.2.2., should be implemented. Neurofeedback cannot currently be recommended for general routine use since despite indications of the effectiveness of standard neurofeedback, there is currently insufficient evidence from well-controlled studies for its use in the treatment of children and adolescents with ADHD.

There is a lack of controlled studies and meta-analyses on neurofeedback in adults with ADHD. After all, neurofeedback is used clinically in adults with epilepsy [304], and an uncontrolled study in adults with ADHD showed a partial specific effect of slow cortical potentials (SCP) neurofeedback, since the subgroup of self-regulation learners showed greater long-term symptom reduction than non-learners [305].

2.3.3. Dietary interventions

2.3.3.1. What should the patient be told about nutrition in general?

Dietary interventions are widely used in patients with ADHD. On the one hand, the interventions summarized under this heading include adding certain dietary supplements to the nutritional regimen (e.g. long-chain, polyunsaturated fatty acids), while omitting specific food ingredients (such as artificial coloring). Other dietary interventions may involve fundamental changes in the composition of the patient's diet. However, to date the question of the effectiveness of the mentioned interventions has not been sufficiently answered in scientific studies. Changes in eating and drinking behavior can be influenced by many different factors, and it is also methodologically difficult to ensure that the subjects, their families and the practitioners are blinded during the study. Since some dietary measures have significant restrictions, e.g. with regard to the selection of possible foods, ensuring compliance in this context can be difficult and challenging, especially when applied to young patients. As a result, there are only few studies on this topic that meet the necessary qualitative study requirements. The evidence base, which our recommendations are based on, is discussed below. Whenever a change in diet is introduced, it is important to consider carefully if this could cause potential malnutrition as well as compliance problems.

2.3.3.2. What needs to be considered regarding artificial food coloring?

As early as 1976, the group around Conners described a significant difference between the effect of a "Feingold" diet (elimination of artificial coloring and natural salicylates from food) and a "placebo" diet on the symptoms of ADHD patients. However, the generalization of this result seemed questionable due to methodological problems; a similarly designed study [306] could also not replicate the results. Further studies that followed showed that this diet was superior to placebo [307], although this result could not be replicated on another sample [308]. More recently, Nigg et al., amongst others, [41] conducted a meta-analysis on the effects on ADHD symptoms induced by omitting synthetic food color additives and preservatives from the diet. Effect sizes of 0.29 were found for the dietary intervention after pooling the information provided by parents, teachers and observers, but no reliable effects of such a diet could be demonstrated. The authors concluded from their results that a subgroup of ADHD patients might benefit from such a dietary intervention, although the previous data do not allow conclusions regarding possible predictors of successful therapeutic outcomes. Another meta-analysis of the effectiveness of non-pharmacological interventions in children and adolescents with ADHD by Sonuga-Barke et al. [229] included assessments of various dietary interventions made by raters "closest to the therapeutic setting" (especially parents) as well as the ratings by largely blinded raters such as teachers. When restricting the analysis to studies (n = 8) on dietary elimination of

artificial coloring and preservatives, significant effects were found in both assessment groups. However, large methodological and qualitative differences between the different studies as well as a possible preselection of patients (in the sense of including patients with known food sensitivities in particular) were also pointed out. This work has not led to any changes in the current recommendations when evaluated by the authors of the NICE update, [231] no relevant work has been added since then.

2.3.3.3. What needs to be considered with regard to elimination diets?

An alternative approach to omitting certain food additives is to assume that there are individual food intolerances in a group of children with ADHD that affect the severity of the symptoms. In this context, an open study design was initially used in most cases [309, 310] to identify individual foods that were not tolerated by affected children, then these provoking foods (e.g. milk protein, white flour, citrus fruits, eggs, but also colorings or preservatives) were subsequently reintroduced in a double-blind cross-over design. It was shown here that some of the children affected benefited from an elimination diet based on individual intolerance, at least in the short term. Further studies [311, 312] looked at the effectiveness of an oligoantigenic diet (elimination of foods with the most common intolerance as recommended by Eggers et al., 1985), compared to a blinded "placebo" condition in different patient populations. These studies also showed an (albeit slight) advantage of the elimination diet over the control condition. Despite these weak, albeit fundamentally positive results, elimination diets should also take into account the undesirable effects that may occur (challenge for families, stigmatization of the affected child, possible deficiency symptoms). Therefore, such dietary interventions should only be performed if there are indications of intolerance to certain foods and under professional supervision and guidance.

2.3.3.4. Can omega 3/omega 6 fatty acids be recommended for the treatment of ADHD?

Long-chain unsaturated fatty acids play an important role, among others, in the development of nerve cells and their membranes. A deficit in these substances (either due to a restrictive diet or an excessive proportion of saturated fatty acids with competitive inhibition of enzymes) is associated with various neurological or psychological disorders. Dietary supplements that can be purchased usually consist of different compositions of omega-3 and omega-6 fatty acids, which differ from one another in terms of their chemical properties and possibly also their effects on a physiological level. This also creates difficulties with regard to the comparability of most of the studies carried out to date, as different preparations were always used. Until the publication of the NICE guideline, [187] the evidence on which the recommendations were based was rather heterogeneous, which is why a supplementation of food with long-chain unsaturated fatty acids in children, adolescents and adults with ADHD could not be recommended. Since then, research efforts have been intensified on various sides in order to shed

more light on this issue. A Cochrane review by Gillies et al. [313] published in 2012, showed evidence of superiority of a combined dietary supplement with omega-3 and omega-6 fatty acids compared to placebo in improving core ADHD symptoms. In general, however, methodological flaws in the studies included (e.g. in relation to randomization processes) were again pointed out, as were difficulties with blinding, especially of the omega-3 preparations (due to the specific smell and taste of fish oil). In the context of the aforementioned meta-analysis by Sonuga-Barke et al. [229], significant effects of dietary supplementation with long-chain unsaturated fatty acids on the ADHD core symptoms were found, both in the assessments by the "most direct" raters involved in therapy (such as parents) and in the assessments by largely blinded raters (e.g. teachers); but here too the heterogeneous quality of the studies included was pointed out. In a further meta-analysis from 2014, Hawkey et Nigg [314] were able to prove that children and adolescents with ADHD have a reduced blood level of omega-3 fatty acids, compared to healthy children, and positive effects of dietary supplementation with these fatty acids on ADHD symptoms were also reported. In the recent NICE Update, however, [315] the authors who conducted a systematic review of the literature up to the end of 2015, report on the treatment of ADHD symptoms with omega-3 and omega-6 fatty acids. They concluded that no short or long-term effects of unsaturated fatty acid preparations on ADHD symptoms or academic ability in the individuals examined can be proven. There is only a slight superiority of the preparations compared to placebo in terms of an improvement in the general functional level after three months of treatment, but this is rated as marginal. There is no evidence of potential damage or side effects due to the fatty acid preparations. However, since these were not systematically recorded by most of the studies included, potential damage from such treatment cannot be excluded. On the basis of the evidence presented, NICE concluded that due to a lack of effectiveness of omega-3 and omega-6 fatty acids on ADHD symptoms and academic achievement, this group of dietary supplements should not be recommended for the treatment of ADHD.

2.4. Pharmacological Interventions

The effectiveness of stimulants in treating attention-deficit/hyperactivity disorder (ADHD) was already discovered more than 70 years ago. Bradley (1937) found that academic performance and social behavior of hypermotoric children improved significantly using d,/l-amphetamine[5]. In the following decades, the effectiveness and tolerability of stimulants for the treatment of children and adolescents with ADHD was tested in more than 180 controlled clinical studies.

2.4.1. Which preparations are recommended for the treatment?

2.4.1.1. Stimulants

Since then, various stimulants with immediate or delayed release have been approved in most European countries as part of a comprehensive treatment regimen for children from the age of six years and for adolescents, when non-pharmacological treatments alone prove to be insufficient. In Germany, various methylphenidate (MPH) preparations with immediate or delayed release action are approved as first-choice drug for children and adolescents with ADHD. Immediate release *d*-amphetamine sulfate (AMF: Attentin®) received approval in 2012 as a short-acting amphetamine for the treatment of children and adolescents with ADHD. In 2013, the AMF prodrug lisdexamfetamine dimesylate (LDX; Elvanse®) was approved as the first long-acting AMF preparation for the treatment of children and adolescents from the age of six years provided there was an insufficient clinical response to previous MPH treatment.

The central mechanism of action of stimulants is that they inhibit the reuptake of dopamine and norepinephrine in the presynapsis by blocking the dopamine transporters; this is reversible after discontinuation and acts as a dopamine agonist [316]. Amphetamines also increase the release of monoamines into the synaptic cleft [317]. D-methylphenidate is pharmacologically the more effective enantiomer that, contrary to l-methylphenidate, specifically binds to the dopamine transporter in animal models. In contrast, the contribution of l-methylphenidate to effectiveness is still unclear [318]. The therapeutic effect of LDX is based on the effect of *d*-AMF, released after enzymatic cleavage in the cytosol of erythrocytes. The exact action mechanisms of stimulants, however, are not yet known and could vary in different areas of the brain and between children, adolescents and adults.

In Germany, pharmacological treatment for adults has only been available since 2011 when a delayed-release methylphenidate was approved. In other countries, such as in the USA or Canada, pharmacological treatment for adults has been possible for many years. Meanwhile, two delayed-release MPH preparations have been approved for the primary treatment of adult ADHD; another MPH with extended-release action (OROS MPH) can be used to continue treatment started in childhood and adolescence. Immediate-release methylphenidate formulations are not approved for adults.

Systematic meta-analyses and reviews, including meta-analyses by the renowned National Institute of Clinical Excellence (NICE) [319], have reported the effectiveness of methylphenidate and dexamfetamine in reducing ADHD core symptoms in children and adolescents as consistently medium to large with effect sizes mainly in the range of 0.8-1 [233, 243, 248, 319-329]; the strongest effects

were seen for attention, distractibility, impulsiveness, motor hyperactivity and social behavior in the classroom as well as in the interaction with parents and peers.

The effectiveness and tolerability of MPH in the treatment of ADHD in children and adolescents was also examined in a Cochrane review [330], which includes several meta-analyses based on 185 randomized placebo-controlled double-blind studies with 12,245 patients, based primarily on the teacher's assessment. A parallel group design (n = 5111) was used in 38 studies and 147 studies (n = 7134) used a cross-over design. The authors calculated an average effect size of 0.77 (95% confidence interval 0.90 - 0.64) for the reduction of ADHD symptoms (based on a total of 19 studies). They also found an average effect size of 0.87 for a reduction in behavioral problems, based on teachers' assessments.

When the review was revisited, it found that four of the 19 studies included in the effect size calculation did not test MPH against placebo, but examined the effectiveness of a combination treatment; these studies compared the use of clonidine + MPH vs. clonidine [331], parent training + MPH vs. parent training [332], behavior therapy + MPH vs. MPH [333, 334] . The analysis also included the Preschool ADHD Treatment Study [335], which examined the effectiveness of MPH in children aged 3 to 6 years; in this age range, MPH is not only an off-label indication, but is on average also less effective. After excluding these four studies mentioned above, the calculated age-adjusted effect size was 0.89 (95% confidence interval 0.79 - 1.01). This effect size was consistent with the previous literature and also corresponds to the effect size calculated in the Cochrane review that included all 75 studies and examined the reduction in ADHD symptoms based on teachers' assessments (n = 6344; effect size: 0.91).

According to the **NICE Guidelines [187]**, the quality of evidence for the effectiveness of stimulants in treating core ADHD symptoms was assessed as "moderate" (dexamfetamine) to "'high" (methylphenidate). The **SIGN Guidelines [197]** and the **AAP Guidelines [218]** rated the quality of evidence as "high".

The Cochrane review reached a deviating conclusion [330] and assessed the quality of evidence for the effectiveness of MPH in the treatment of core ADHD symptoms in children and adolescents as 'very low'. The authors criticized all the meta-analyses and reviews previously identified by them, explicitly including the NICE meta-analyses [319] that examined the effectiveness and safety of MPH treatment in children and adolescents as having significant methodological weaknesses. The methodological quality of all 185 studies included in the Cochrane review was compromised by a high risk of systematic errors. Thus, there is a considerable discrepancy between the quality assessments of the same studies by NICE ("moderate to high quality") and by the Cochrane authors ("very low").

However, the assessment of the risk of bias used in the Cochrane review does not stringently follow the criteria and domains specified in the Cochrane Handbook [336]. Storebo et al. [330] added an eighth dimension, that of "conflict of interest", whereby all studies financed by the pharmaceutical industry or whose study investigator declared potential conflicts of interest, regardless of their scientific quality, were placed under general suspicion and rated as having a high risk of bias, even if no objections were found in all other assessment criteria. Furthermore, they classified each study where the assessment of one of the domains was judged as unclear as having a high risk of bias overall. For 74 studies, there was no high risk of bias in any domain; for a further 42 studies, a high risk of bias was coded only for conflict of interest. In seven studies, the risk of bias in all domains was assessed as low, but the authors of the Cochrane review nevertheless postulated a high risk of bias. Overall, the risk of bias is not properly assessed and the conclusion regarding the assessment of the evidence for the effectiveness of MPH for the treatment of children and adolescents with ADHD is therefore inadequate.

The efficacy and tolerability of lisdexamfetamine (LDX) in the treatment of children and adolescents with ADHD was examined in three European, multicenter, double-blind, placebo-controlled, non-crossover studies, which were summarized by Stuhec et al. [337] in a meta-analysis. Here, LDX was highly effective in reducing ADHD symptoms compared to placebo (SMD = -1.28, 95% CI; -1.84, -0.71). A meta-analysis by Maneeton et al. [338] showed that lisdexamfetamine was significantly superior to placebo in terms of improving core ADHD symptoms (ADHD-RS IV) (weighted mean difference (95% CI) -15.20 (-19.95, -10.46) I^2 = 94%) but treatment discontinuation rates due to adverse events did not differ significantly between LDX and placebo (RR (95% CI) 1.99 (0.70, 5.64), I^2 = 0%). The meta-analysis was based on five RCTs with a total population of 1,016 children and adolescents with ADHD and a treatment duration of four to eleven weeks.

A nine-week comparative study between LDX and atomoxetine (ATX) in children and adolescent with ADHD, who had previously responded inadequately to methylphenidate treatment, showed that patients with LDX responded faster (LDX mean time to first clinical response (95% CI) 12.0 d (8.0-16.0)) vs. ATX (21.0 days (15.0-23.0)) and LDX after nine weeks led to a more significant reduction in core ADHD symptoms than ATX (ADHD-RS total score, difference in least-squares mean change from baseline -6.5 (-9.3 to -3.6), p <0.001 effect size 0.53) [339].

All of the above-mentioned studies showed that ADHD patients not only showed an improvement in their core symptoms but also in their functional levels. A secondary analysis of the MTA study [236] revealed that children with severe ADHD symptoms benefited significantly more from medication than children with mild or moderate ADHD symptoms (high quality of evidence).

A meta-analysis [340] of a total of 36 studies showed that treatment with MPH improved various neuropsychological impairments associated with ADHD, such as executive functions (working memory, inhibitory ability) and non-executive functions (non-executive memory processes, such as recognition, reaction speed and reaction time variability), [341] showing a moderate effect size (high quality of evidence).

Another meta-analysis, [342] based on 23 studies, compared the effectiveness of stimulants (amphetamine and methylphenidate) in reducing core symptoms in children and adolescents with ADHD; the results suggest a moderately higher effect size of the amphetamine preparations; according to NICE, the results of direct comparative studies do not provide reliable evidence that one of the two substances is more effective. However, the studies show a preferential response to methylphenidate or amphetamine in a significant minority of affected children and adolescents [343-345].

Swedish registry studies suggest that pharmacological treatment for ADHD (especially with stimulants) significantly reduces the risks of delinquent behavior [346], substance abuse [347] and suicidal behavior [348]. The results that suggest a reduction in accidents due to pharmacological treatment for ADHD are of great importance [349]. In a Swedish registry study of 17,408 people with ADHD, an increased risk of traffic accidents involving men and women was found, compared to individuals without ADHD (HR 1.47 and 1.45, respectively). A reduction of 42% in the risk of accidents was recorded for male ADHD patients on medication. No such connection has been described for women [347]. The significance of these findings lies in the considerably increased risk of premature death for people with ADHD. In a Danish registry study of 1.9 million people, of whom 32,061 suffered from ADHD, an increased mortality rate ratio (MRR) of 1.5 was found for ADHD without other significant coexisting disorders. If there were additional disorders such as addictions and conduct disorders, the mortality risk increased even further [350]. The most common cause of premature death were accidents.

Further studies show a reduction in functional impairments and an improvement in health-related quality of life [351]. A systematic review and meta-analysis by Prasad et al., based on 43 studies (n = 2110) examining the effectiveness of stimulants [352] in improving school achievements in schoolchildren with ADHD, found evidence of improvement in working behavior; however, in contrast to other studies [353] there was no clear evidence of an improvement in school achievements.

Data on the long-term effectiveness of stimulant therapy is limited. According to the SIGN guidelines [197] the MTA study [354] and the study by Gillberg et al. [355] documented a longer lasting (up to 24 months) effect on the core symptoms. Finally, the long-term (more than 24-month) effectiveness of

pharmacotherapy and non-pharmacological ADHD treatment on functional impairments and health-related quality of life was finally summarized by Shaw et al. [356] in a systematic review. According to NICE, this work provides evidence that the treatment of ADHD has a positive long-term effect in many different domains, although normalization is rarely achieved. Similar results can be found in an overview by Fredriksen et al. [357]. In addition to controlled, randomized studies, naturalistic observational studies were also taken into account. Therapy with stimulants showed positive effects on functional progress.

The effectiveness of pharmacotherapy with stimulants and behavioral therapy was compared in the "Multimodal Treatment Study of Children with ADHD" by the National Institute of Mental Health (NIMH). In this study, a total of 579 children with ADHD aged 7-9 years were treated over 14 months and provided with carefully monitored pharmacotherapy involving monthly half-hour consultations and intensive psychoeducation, intensive behavioral interventions, a combination of both treatments or with routine visits to primary care. The results after 14 months showed that all treatment measures can reduce core symptoms, but that intensive behavioral interventions and normal primary care are generally inferior to carefully monitored and closely managed pharmacotherapy [278, 358]. Combined therapy had no significant additional effects on the core symptoms compared to pharmacotherapy. However, behavioral therapeutic interventions improved aggressive behaviors, social skills and parent-child relationships just as effectively as pharmacotherapy. There were also slight advantages in this regard with combination treatment [278, 358]. According to the MTA results, families with low socioeconomic status in particular seem to benefit from combined treatment, whereas for families with higher socioeconomic status no difference was found between careful pharmacological treatment and combination therapy [359].

Data on ADHD studies in adults has improved significantly in recent years, although it has not yet reached the diversity of therapeutic studies of children and adolescents. There are seven meta-analyses that investigated the effectiveness of methylphenidate in adults with ADHD. The meta-analyses by Faraone et al. [360], Koesters et al. [361] and Castells et al. [362] investigated studies that related exclusively to treatment with MPH, while the meta-analyses by Meszaros et al. [363], Faraone and Glatt [322], Linderkamp et Lauth [364] and Cunill et al. [365] looked at studies on the use of modafinil and bupropion in addition to methylphenidate, amphetamine and atomoxetine. Other substances considered in these meta-analyses were paroxetine, nicotine and desipramine. When focusing on the three MPH meta-analyses, it can be concluded that MPH shows a significant effect on ADHD core symptoms such as attention deficit, hyperactivity and impulsivity. The effect sizes in these three studies vary between 0.42 [361] 0.56 [362] and 0.9 [360]. The observed effect sizes in adults are somewhat below the effect sizes in children and adolescents. The effect sizes shown here

with regard to core ADHD symptoms are based on the examiner's assessment. If the effect sizes are calculated based on patient self-assessments, they are somewhat lower [322, 366].

In addition to the effectiveness of MPH on the classic ADHD psychopathology of inattention, hyperactivity and impulsivity, various controlled studies have also shown a moderate effect on phenomena of emotional dysregulation [226, 367]. Factors that may influence the effect of MPH have been regularly studied. In the meta-analyses by Faraone et al. [360] and Castells et al. [362], higher daily MPH doses were associated with higher effect sizes. These findings were not confirmed in studies by Koesters et al. [361] and Faraone and Glatt [322].

A study of 419 adults with ADHD, similar to the MTA study in children, was carried out by Philipsen et al. [294] to compare different therapeutic interventions. Patients were divided into 4 treatment arms: MPH with sustained release and clinical management, dialectical behavior therapy (DBT) with MPH with sustained release, DBT and placebo, clinical management and placebo. History data collected over a period of 3 and 12 months have been evaluated and published. A reduction in ADHD psychopathology was observed in all four treatment arms. The result showed a superiority of the treatment in the groups that had received MPH.

There are no further evidence-based guidelines for the adult sector apart from the NICE reference guideline. With regard to the importance of MPH therapy, NICE states that treatment with MPH is classified as a "first-line treatment".

2.4.1.2. Atomoxetine & Guanfacine

Other substances approved for the treatment of ADHD: the selective norepinephrine reuptake inhibitor atomoxetine (ATX, Strattera®) and the alpha2A-adrenergic agonist guanfacine (Intuniv®). In 2016, guanfacine prolonged-release (GXR, Intuniv®) was approved as an alpha2A-adrenergic agonist to treat children and adolescents with ADHD for whom treatment with stimulants is contraindicated, not tolerated or has proven to be ineffective.

Atomoxetine inhibits the presynaptic uptake of norepinephrine by the norepinephrine transporter, thereby increasing the amount available in the synaptic cleft. As a selective norepinephrine reuptake inhibitor, it indirectly influences dopamine activity in the prefrontal cortex, but not in the striatum and nucleus accumbens. ATX is primarily metabolized by the CYP2D6 isoenzyme; therefore, the dose needs to be adjusted in patients with a slow CYP2D6 metabolism or when taking CYP2D6 inhibitors such as fluoxetine or paroxetine. The use of ATX is permitted for adults as part of a differentiated treatment plan if MPH is not sufficiently effective or not tolerated.

The effectiveness of ATX to treat core ADHD symptoms in children and adolescents—with moderate effect sizes between 0.5-0.7—has been consistently demonstrated in several randomized, placebo-controlled studies [187, 197]. In comparison to MPH, ATX has a lower effect size on the core symptoms. Accordingly, a large randomized, placebo-controlled, direct comparative study of ATX and MPH-ER (Concerta®), which included 635 children and adolescents with ADHD, showed higher response rates and greater efficacy for MPH-ER compared to ATX [368]. About one third of patients showed a preferred response to one of the two substances (about half of these patients responded preferentially to MPH or ATX). The proportion of patients who ended the study prematurely, however, was higher for ATX than for MPH. Overall, direct comparative studies on the effectiveness of MPH and ATX suggest a more favorable benefit-risk profile for MPH.

In the most comprehensive meta-analysis on the effectiveness and safety of ATX in treating children and adolescents to date [369], with a total of 3,928 study participants, ATX proved to be effective as compared to placebo with a pooled effect size of 0.64. The effects were similar on all core ADHD symptoms, but were weakened when pretreatment with stimulants was given.

With regard to the effectiveness of ATX on ADHD symptoms in adults, the meta-analysis by Cunill et al. [370] shall be referred, which included twelve controlled trials, involving 3,375 patients. ATX proved to be superior in reducing ADHD symptoms compared to placebo. The effect sizes were moderate (clinician: 0.40, patient self-assessment: (0.33). The NICE [187] guidelines recommend prescribing ATX in adults if MPH is not effective or not tolerated. The discontinuation rate under ATX was higher than in the placebo group. Almost 50% of patients on ATX discontinued therapy. Compared to the discontinuation rate of placebo patients, the odds ratio was 1.39 (1.17 - 1.64).

Guanfacine is an agonist of alpha2A-adrenergic receptors that modulate noradrenergic signaling in the prefrontal cortex and in the basal ganglia [371]. There is also evidence that the substance affects dendritic plasticity in the prefrontal cortex. Guanfacine is metabolized by CYP3A4/5. As a result, guanfacine levels may rise when CYP 3A4/5 inhibitors are taken. In contrast, guanfacine levels decrease when CYP3A4/5 inducers are taken, e.g. rifampicin and valproic acid.

When using guanfacine prolonged-release, therapeutic benefits (e.g. stable 24-hour effect when a single dose is administered) must be weighed against risks in terms of higher rates of adverse effects, especially from the fatigue cluster (SSF = somnolence, sedation, fatigue). Furthermore, undesirable effects such as orthostatic problems and bradycardia must also be considered, especially in the early stages of treatment. There is a delay of two to three weeks before treatment effects are seen; this is significantly later compared to the effects of stimulants, but a few weeks earlier compared to atomoxetine.

The effectiveness and tolerability of guanfacine in treating ADHD in children and adolescents was examined in a meta-analysis by Ruggiero et al. [372]. The meta-analysis included seven RCTs with a total population of 1,752 children and adolescents. The duration of treatment varied between 6 and 16 weeks. 59.0% of the study participants responded to guanfacine (CGI-I score ≤ 2) compared to 33.3% on placebo (pooled OR 3.2, 95% CI 2.4-4.1). Somnolence (OR 4.9), sedation (OR 2.8) and fatigue (OR 2.2) were the adverse events with the greatest risk of occurrence in the guanfacine vs. the placebo group. Discontinuation rates due to adverse events were 9.5% with guanfacine and 2% with placebo (OR 4.16; 95% CI 1.10-15.64).

Newcorn et al. [373] evaluated the long-term maintenance of guanfacine efficacy in an initially open study with a 26-week, randomized, placebo-controlled withdrawal phase after 13 weeks. 528 participants were included. Recurrence rates were significantly lower in patients on guanfacine (49.3%) than on placebo (64.9%) (p = 0.006). Wilens et al. [374] evaluated the safety and efficacy of guanfacine in adolescents (aged 13-17 years) in a 13-week dose-optimized RCT; 314 participants were randomized. Participants receiving guanfacine showed significant reduction in core ADHD symptoms (ADHD-RS total score) compared to placebo (least squares mean score change, -24.55 (GXR) versus -18.53 (placebo); effect size 0.52; p <0.001).

The efficacy of guanfacine both with regard to core ADHD symptoms and to functioning levels in children with ADHD was shown, regardless of the time of intake of the substance [375, 376].
Compared to the above-mentioned meta-analysis, these more recent studies on guanfacine did not reveal any significant new aspects regarding the side effect and safety profile. In addition to the aforementioned fatigue cluster (SSF = somnolence, sedation, fatigue), especially hypotension, bradycardia and weight gain are frequent adverse events that require monitoring.
In Germany, guanfacine has been approved for the treatment of ADHD in children and adolescents aged 6-17 years for whom treatment with stimulants is contraindicated, not tolerated or has proven to be ineffective.

The substances d-amphetamine, lisdexamfetamine and guanfacine, approved for children and adolescents, are not licensed for the treatment of adults.

2.4.2. What criteria should be used to select the right medication?

As guanfacine extended-release has an unfavorable ratio of desired to undesirable effects, compared to stimulants, it should be considered as second-line treatment. However, if the administration of stimulants is clinically contraindicated or there are accompanying circumstances that support the use of guanfacine prolonged-release (e.g. in tic disorders or Tourette syndrome, high blood pressure or a

significant reduction in weight or dwarfism), it can also be given without prior prescription of other ADHD medications.

2.4.2.1. Stimulants (methylphenidate, dexamfetamine, lisdexamfetamine)

According to current studies, methylphenidate and amphetamine show a similar profile and comparable frequency of undesirable effects. Decreased appetite, weight loss, difficulty falling asleep, abdominal pain and headaches, and a slight increase in pulse/blood pressure are all common adverse reactions of stimulant treatment [344]. Occasionally, dysphoric mood, anxiety, irritability, drowsiness, tics and weight loss can occur. In most patients treated for ADHD, adverse reactions are mild to moderate, dose-dependent and—as a rule—tend to occur transitionally at the start of treatment [377]. Rarely, (in about 0.2% of those treated), short-term psychotic or maniform symptoms can occur [378, 379].

Findings from meta-analyses show that in children and adolescents the frequency of a reduction in appetite with MPH treatment increases by about 30% (95% CI: 18.0 - 42.6). A marked appetite reduction can be expected in approx. 10% (95% CI: 7.0 - 14.0) of treated patients (versus 1.8% (95% CI: 0.0 - 5.5) those on placebo) [328]. Similar effects are expected with amphetamine treatment. Several studies suggest that weight gain and growth can be affected during treatment [380, 381]. Analyses of growth and weight curves over time in the MTA study showed that children who had been treated with medication consistently for three years, compared to children who only received medication after 14 months and patients who were not treated at all or were not continuously treated with stimulants, had a decrease in growth and a delay in weight gain during the course of treatment. After 36 months there was an average decrease in height of 2 cm and a weight difference of 2.7 kg. It remains unclear whether these children will catch up over time. The effects on growth appear to be age- and dose-dependent, occur to the same extent with MPH and amphetamine and are usually not clinically significant [381].

Controlled studies show a – dose-dependent – potential mild increase in heart rate and blood pressure [382, 383], in most of those affected (average 1-4 mmHg systolic, 1-2 mmHg diastolic; 1-2 beats/minute), but in about 5-15% of patients it is more pronounced and leads to an increased heart rate and BP over the 95th percentile (Hammerness et al., 2011). Longer-term studies with a 24-month observation period show that these increases persist during treatment [382].

In adults, a meta-analysis [384] showed an increase in heart rate of 5.7 beats when treated with MPH or amphetamine (3.6 - 7.8). Systolic blood pressure increased on average by 2 mmHg (0.8 - 3.2). The meta-analysis was based on 10 studies with 1,839 patients, treated with stimulants. None of the studies

reported serious cardiovascular events (e.g. heart attack, atrial fibrillation, sudden cardiac death or heart defects). The proportion of treatment dropouts in the stimulant group was reported as 1.5%. It was 0.8% in the placebo control groups. This difference was not statistically significant. However, 6 studies reported cases where a clinically relevant increase in heart rate (> 90/min) under treatment with stimulants (OR = 2.75) occurred. When interpreting this data, it must be taken into account that the patients in the meta-analysis were relatively young (median 42 years). This means that these populations have a relatively low cardiovascular risk. The cardiovascular risk in older people is expected to be higher.

According to current knowledge, it can be assumed that the rate of serious cardiovascular events (sudden cardiac-related deaths, myocardial infarction, stroke) during treatment with stimulants is not higher than the rate in the untreated population. Cooper et al. [385] found no evidence of an increased risk of serious cardiovascular events in a retrospective study using healthcare plan data from children, adolescents and young adults (2-24 years; n = 1200438) (95% CI: 0.31 - 1.85). Other large studies (n = 443198 adults [386]; n = 241417 children, age: three to 17 years [387]) also found no evidence of an increase in serious cardiovascular events. A meta-analysis of various observational studies revealed consistent findings [388].

So far, there is no evidence that tic disorders are caused by treatment with stimulants [320, 389-391]. Whilst existing tic disorders do not worsen in most patients when treated with stimulants, they can be exacerbated in some patients [320, 392]. There is no evidence that stimulants lower the seizure threshold in the brain [393]. Children with ADHD and well-controlled epilepsy rarely show an increase in seizure frequency when treated with methylphenidate [377].

According to the results of a meta-analysis (five double-blind placebo-controlled studies; n = 1024), the risk of suicidal behavior was not increased in the short term [394] on medication for ADHD (ATX and MPH), according to the findings of a Swedish registry study (n = 37,936 patients with ADHD [395]) the risk was reduced with pharmacotherapy (hazard ratio: 0.81; CI: 0.70 - 0.94).

Meta-analyses of prospective cohort studies showed that patients with ADHD are about 1.5 times more likely to develop substance abuse disorders (except nicotine) and about three times more likely to become addicted to nicotine [248, 396]. The current findings show that treatment with stimulants improves the symptoms of ADHD in coexistent substance abuse disorder [397]. Another meta-analysis of 15 studies (n = 2565) also showed no evidence that treatment of ADHD with stimulants increases or decreases the risk of subsequent substance abuse or a later dependence on alcohol, cocaine, cannabis, nicotine or other substances [398]. A Swedish registry study did not show any evidence of an increased risk of substance abuse among individuals prescribed stimulant ADHD

medication [347]; actually, the rate was 31% lower among those prescribed ADHD medication compared to those untreated (hazard ratio: 0.69; 95% CI: 0.57 - 0.84).

On the other hand, there are indications that the treatment of ADHD in adults is less effective in the case of coexistent substance abuse disorders than in cases of ADHD without substance abuse disorders. The meta-analysis by Koesters et al. [361] reported an effect size of 0.08 for patients with ADHD and substance use disorders (SUD). Another meta-analysis by Castells et al. [362] also showed that coexistent SUD was associated with lower effect sizes. Present studies suggest that long- and short-acting stimulants have essentially the same effects in terms of their effectiveness and adverse effects [321, 399], but that extended-release preparations may have a lower potential for abuse.

There is only limited information on the misuse of stimulants by ADHD patients. Studies evaluating the prevalence and correlating factors of misuse and diversion of stimulants in young adults with ADHD in North America [400] reported that up to 25% of drug-treated subjects with ADHD had sold the prescribed medication or given it to third parties; about 25% of the respondents had increased their dose without a doctor's prescription. A meta-analysis shows that in the USA approximately 17% (95% CI: 0.13 - 0.23) of college students misuse stimulants [401]. No corresponding data is available for Europe.

Stimulants are contraindicated if the medical history suggests previous hypersensitivities to the drug or if monoamine oxidase inhibitors are taken at the same time (or within the previous two weeks). Caution should also be exercised when taking tricyclic antidepressants at the same time [344, 402]. Other contraindications are psychosis, severe depression, hyperthyroidism, cardiac arrhythmia, moderate to severe hypertension, angina pectoris and glaucoma. It should also be noted that methylphenidate can inhibit the metabolism of various antiepileptic drugs.

A systematic review by Coghill et al. [340], which included 35 publications, concluded that the safety and efficacy profile of LDX is comparable to that of other stimulants used to treat ADHD. The most common adverse events were reduced appetite (25-39%) and sleep disorders (11-19%). These were usually mild or moderate, however. On average, there was a slight increase in heart rate and blood pressure. Misuse of the substance was less common than with short-acting stimulants. Based on the study results, approval was given for LDX for the treatment of children and adolescents aged 6 to 18 years who have not responded sufficiently to previous MPH therapy.

Some studies suggest that better compliance can be achieved with long-acting substances [403, 404].

2.4.2.2. Atomoxetine and Guanfacine

Adverse effects with atomoxetine include headache, abdominal pain, decreased appetite, weight loss, sleep disorders, dysphoria, constipation, sedation, dizziness, nausea, dry mouth, increased heart rate and systolic/diastolic blood pressure, the extent and frequency of these adverse effects are dose-dependent and often occur only temporarily [405, 406]. In adolescent and adult men, erectile dysfunction can occur in 8% of patients [407]. In isolated cases, liver damage, including acute liver failure, that presents with elevated liver enzymes and bilirubin, as well as jaundice, have been observed [408]. Seizures are another potential risk. In double-blind clinical trials, suicidal behaviors were rare.

Patients known to be CYP2D6 poor metabolizers (7% of Caucasians) have a several-fold higher exposure to atomoxetine when compared with patients with a functional enzyme and are therefore at higher risk of adverse events.

In the most comprehensive meta-analysis on the efficacy and the side effect profile of alpha-2 adrenergic agonists to date, guanfacine prolonged-release proved to be superior to placebo (similar to clonidine), with an average effect size of 0.59. The effects were largely similar across the three core ADHD symptoms, regardless of age and gender [409]. The duration of action is stable over 24 hours, so that tablets can be taken according to a regular dosage regimen once a day, regardless of the time of day [375].

Overall, side effects are more common than with stimulants and atomoxetine, particularly in the first weeks of treatment. The spectrum of adverse events for stimulants and atomoxetine differ, whereby the fatigue cluster in particular, with somnolence (tiredness), sedation (psychological damping) and fatigue (faster exhaustion), is pronounced. Attention must also be paid to orthostatic dysregulation, bradycardia and a low blood pressure, particularly in the early stages of treatment. Guanfacine has advantages over stimulants in terms of its effect on appetite, which is not reduced, and in terms of body growth, which is not affected with guanfacine [409].

2.4.2.3. Unlicensed substances

Overall, the evidence supporting the efficacy of tricyclic antidepressants for the treatment of ADHD in children and adolescents aged 6 to 18 years is low [197, 410]; the profile of undesirable effects (especially cardiovascular effects, including potential cardiotoxicity) limits its therapeutic benefit considerably [187, 197].

In some randomized placebo-controlled trials, modafinil showed a medium effect size on reducing core ADHD symptoms [187]; a systematic review of three RCTs [411] and three further RCTs [412-414] on the effectiveness of modafinil did not provide sufficient evidence according to SIGN criteria. Overall, the evidence is at best moderate [187, 197]. Adverse effects include sleep disorders, decreased appetite, nausea, abdominal pain, headaches, emotional irritability and - very rarely - Stevens-Johnson syndrome, a potentially very serious complication. There is no evidence of the effectiveness of antipsychotic drugs or SSRIs on core ADHD symptoms [197, 319]. There is also insufficient evidence for the effectiveness of bupropion in treating ADHD core symptoms [415, 416].

In Germany, only extended-release methylphenidate (Medikinet adult®, Ritalin adult®) and atomoxetine (Strattera®) can be prescribed to adults with ADHD on a statutory health insurance prescription. Provided treatment was started before the age of 18 years, the same applies to Concerta®. D-amphetamine, lisdexamfetamine and guanfacine are drugs that have been initially approved for use in children and adolescents, but are additionally approved for adults in other countries.

In Austria, atomoxetine (Strattera), Ritalin LA and Medikinet are currently approved for initiating treatment in adults. Adolescents treated with Elvanse can continue this treatment into adulthood.
In Switzerland, atomoxetine can be used until the age of 50 years. Elvanse can be prescribed up to the age of 55 years. OROS methylphenidate, Focalin XR and Sandoz methylphenidate are approved up to the age of 65 years.

The meta-analyses on the effects of stimulants by Meszaros et al. [363], Faraone and Glatt [322], Linderkamp and Lauth [364] examined amphetamines and methylphenidates. The findings showed a largely similar efficacy of both substances. A Cochrane meta-analysis on the effects of amphetamines in adults [362] included seven randomized controlled trials with 1,091 patients. The mean study duration was eight weeks. Three substances were examined: d-amphetamine, lisdexamfetamine and mixed amphetamine salts. The mean effect size in reducing ADHD psychopathology was -0.72. Another meta-analysis with 806 patients [338] reported an effect size of 0.97. It can be assumed that amphetamines are effective, not only in children and adolescents, but also in adults. This is also reflected in the Nice [187] guidelines. Treatment with amphetamines is recommended if therapy with MPH has proven to be insufficiently effective or is not tolerated. The side effect profile in adults is no different to that in adolescents or adults receiving other stimulants. To date, there is insufficient knowledge about guanfacine treatment of adults with ADHD.

2.4.3.   What should be considered when selecting medication for an individual patient?

2.4.3.1. Age-related characteristics

2.4.3.1.1.   Special characteristics in the treatment of pre-school age children

Methylphenidate preparations are only approved in Germany and internationally from the age of six years. Data on the effectiveness and safety in pre-school age is limited. In an overview of a total of nine smaller studies on the effectiveness of methylphenidate in 206 children under the age of six years, eight of the nine studies showed that methylphenidate was effective in pre-school children [417]. The Preschool ADHD Treatment Study (PATS), a placebo-controlled, double-blind, randomized cross-over study with a 6-week MPH treatment (n = 160; ages three to five and a half years) found that stimulants were also effective in the three to six age range, but average effect sizes (0.4 - 0.8) on the core symptoms are lower in pre-school children, undesirable drug effects occur more frequently and are on average more pronounced than in school children [335, 412]; in the course of a year a reduction in growth of 1.38 cm and a reduction in weight gain of 1.3 kg was noted; the average annual growth rates were thus reduced by about 20% for height and by about 50% for weight gain [418].

Overall, the evidence of effectiveness and tolerability of MPH in pre-school children was significantly higher than that of AMF and ATX [419, 420]. Based on current evidence, NICE [421] recommends that pharmacotherapy should not be offered to children before the age of five years without a second opinion from a specialist in the treatment of children with ADHD in this age range. However, the S2k practice guideline "Psychological disorders of infancy, toddler and pre-school age", valid in Germany for this age range, recommends that pharmacotherapy (primarily with methylphenidate) can be considered as part of an overall therapeutic strategy from the age of three years but with particular caution and after detailed cost-risk assessment in each individual case. However, the non-pharmacotherapeutic options, primarily recommended for this age group, e.g. parent training, should be fully exhausted first.

2.4.3.1.2.   Special characteristics in the treatment of the elderly

ADHD can also be found in the elderly. A prevalence of 2.8% was found in a Dutch cohort study of 1,494 people aged 60 years and older. Systematic studies of treatment of this age group have so far been lacking. It should be borne in mind that age-related changes in pharmacodynamics and pharmacokinetics necessitate adjustments in pharmacological treatment. A pilot study by Manor et al. [422] indicates that the effect of MPH to treat classic ADHD psychopathology in older people is comparable to that in younger people.

2.4.3.2. Special characteristics for the treatment of coexisting disorders

2.4.3.2.1. Autism/intellectual disability

When treating hyperactivity/impulsivity in the context of autism or intellectual disability, methylphenidate can also be effective in the treatment of coexisting ADHD symptoms [327, 423]; in contrast to the high level of evidence for methylphenidate, the level of evidence for AMF is currently low [242]. However, it should be borne in mind that children with a severe intellectual disability are more likely to have undesirable effects, for example, exacerbation of ritualized and stereotyped behaviors [424-426].

2.4.3.2.2. Tics

Stimulants effectively reduce symptoms of ADHD also in children, who have both ADHD and tics, and reduce tic symptoms in around a quarter of these patients as well; the majority of those affected do not experience an increase in tic symptoms, although they may be exacerbate in some affected individuals (approx. 5 - 10%) [320, 390, 392, 427-429]. The results of the meta-analysis by Bloch et al. (2009) show that MPH tends to statistically improve coexisting tic disorders, ATX and alpha2 agonists statistically improve tic disorders significantly, whereby the effect sizes for MPH (ES = 0.28; 95% CI: -0.03 - 0.58) and ATX (ES = 0.32; 95% CI: 0.09 - 0.56) are comparable and tend to be lower than for alpha2 agonists (ES = 0.74; 95% CI: 0.44 – 1.04). In individual cases, exacerbation of tics was also observed in ATX treatment [430].

2.4.3.2.3. Anxiety Disorders/Depression

Overall, studies showed that patients with ADHD and coexisting anxiety disorders generally respond to stimulants in a similar way to patients without comorbid anxiety [278, 358, 431, 432]. A Danish registry study showed that pharmacological treatment for ADHD significantly reduced the risk of a current or future depressive disorder [287].

2.4.3.2.4. Conduct Disorder

Patients with ADHD and comorbid conduct disorders respond as well to stimulants as those without conduct disorders in terms of their ADHD symptoms [358]. A meta-analysis of 28 studies showed that stimulants also affected aggressive symptoms in ADHD patients with conduct disorders. The effects on aggressive behavior were less in patients with isolated conduct disorders [433-435].

2.4.3.2.5.   Personality disorders

Randomized controlled trials on the treatment response in patients with coexisting personality disorders are not yet available. Case-control studies [436] have shown that a general narrowing of successful treatment outcomes must not be expected in ADHD with coexisting personality disorder. However, this does not apply to cases with severe symptoms of personality disorders, e.g. in people with more than one diagnosis of personality disorder as defined in DSM-IV. In those cases, the treatment response rate was halved compared to personality disorder negative ADHD patients or to those with only one coexisting personality disorder, as defined in DSM-IV (71% vs. 38%).

2.4.4.   What should be considered in the course of pharmacological treatment?

The symptoms of ADHD and the needs of patients with ADHD can change significantly during development [7, 437]. Developmental changes affect core ADHD symptoms as well as impairments, with ADHD associated risk factors and the number of coexistent disorders [7, 438]. Due to body growth, the relation between drug dose and body weight changes in children and adolescents, so that an adjustment of pharmacological treatment may be required. Undesirable drug effects, in particular, must be taken into account (side effect profiles of the individual substances see above). Depending on the effectiveness and tolerability of the medication and taking coexistent disorders into account, it is important to decide whether the current treatment should be continued, the dose reduced or increased, to switch to a different substance, to use a combination of different substances or to discontinue medication.

Some patients experience a decrease in core ADHD symptoms [7], primarily during adolescence, so that ADHD specific therapy is no longer required. The NICE guidelines [187] therefore recommend that the need for ongoing medication is checked annually. A period without medication can help to assess whether pharmacotherapy is still indicated. This is not necessary if patients, treated with stimulants, continue to show clear ADHD symptoms before the medication takes effect and when wearing off.

2.4.5.   What needs to be considered with regard to medication adherence?

Medication adherence describes the extent to which the patient's medication intake complies with the recommendations agreed with the practitioner. The term adherence hereby replaces the previously used term compliance - since it is not just about following medical instructions (= compliance), but rather about adhering to the therapeutic goals set by the patient and the practitioner (= adherence). As ADHD is a chronic disorder that requires taking regular medication (usually daily or several times a day), medication adherence is particularly important [439-441].

There are many factors that can contribute to non-adherence to pharmacological treatment for ADHD. In addition to the effectiveness and tolerability of the medication, the subjective perceptions of patients, parents/family members regarding the disorder ("health beliefs") and pharmacological treatment ("attitudes") alongside the subjective inner experience of illness by those affected can play a role [441-444]. There is also evidence that age, gender and level of education of those affected as well as the frequency of daily medication use are important factors in assessing the risk of possible non-adherence [440, 441, 445]. Studies in adults suggest that men with a low educational level, in particular, are at risk for low medication adherence [440].

In general, the following points, amongst others, are beneficial for optimizing medication adherence:

- Comprehensive psychoeducation, including possible medication-related fears and worries
- Regular checks regarding the effectiveness and tolerability of the medication
- Preference for long-acting preparations over frequent use of short-acting preparations several times a day [439]
- Use of aids with reminder function.

2.5. Inpatient and partial inpatient therapy, youth welfare measures and rehabilitation

There is a paucity of empirical studies on the effectiveness of inpatient or partial inpatient interventions. In German-speaking countries, Döpfner et al. [446] demonstrated the effectiveness of partial inpatient for pre-school children, who have mainly externalizing abnormalities (including ADHD) and multiple developmental deficits. Ise et al. [447] have proven the effectiveness of a four-week inpatient treatment on a parent-child ward for children with pronounced parent-child interaction problems (mainly externalizing behavioral disorder, including ADHD), also with regard to ADHD symptoms and other externalizing behavioral problems.

2.6. Transition

Transition from adolescent to adult is not only associated with developmental psychopathological changes in ADHD [448], but also with an increase in the challenges that young person faces every day [449]. In addition, it should be noted that, with increasing age, the risk of developing addictions and personality disorders also increases [450, 451]. At the same time, the medical care conditions change during this sensitive phase of transition from adolescence to adulthood. Therefore, a monitored transfer of treatment to adult psychiatrists and psychotherapists, who have expertise in the treatment of

ADHD, but also in the detection and treatment of coexisting disorders, is highly relevant for the course of treatment.

In practice, changing treatment often proves problematic. This is usually necessary at the age of 21 at the latest, as information about previous diagnostic and therapeutic measures is lost. This is particularly disadvantageous in chronic disorders such as ADHD. An English study showed that treatment of adolescents with ADHD is often discontinued too early and that there is a lack of monitored transitions into the adult psychiatric/psychotherapeutic care system [452]. It is rarely possible to have the treatment of a young person transferred to an adult psychiatrist/psychotherapist without any interruption in treatment measures. It can be assumed that the transfer of health data and information about the course of treatment to the therapist treating the patient, will increase the effectiveness of further treatment. It is also not uncommon that after interrupting and resuming treatment in adulthood, documents from treatment in childhood are no longer or only partially available. In order to ensure optimal treatment of patients with ADHD during the critical phase of growing up, it is therefore necessary to closely interlink care systems for children and young people to those of adults. To date, however, there is a lack of research on how monitored transition affects the course of the disorder and the social consequences of ADHD for those affected in adulthood [453].

2.7. Self-help

Despite the undisputed clinical importance of self-help, its evaluation is still insufficient [454-456]. There are no studies specifically on the topic of self-help in ADHD. Regarding the benefits of self-help in mental illnesses, Edmunson et al. [457] showed that participation in self-help groups was associated with a significantly shorter hospital stay compared to non-participation (7 vs. 25 days) and better use of the psychiatric health services (53% vs. 23%).

Kurtz [458] observed that 82% of a total of 129 participants had managed their illness better since participating in a self-help group. Those affected coped with their illness better the longer they attended and the more they participated in the group. The qualitative study by Leung and Arthur [459] examined the effectiveness of self-help groups in the context of the rehabilitation of people recovering from mental illness and concluded that participation in a self-help group provided positive experiences for those affected, leading to changes in their everyday life and contributing to their rehabilitation. Furthermore, participation in self-help groups was also a predictor of successful disease management [460, 461].

III. Appendices

1. Diagnostic decision tree for hyperkinetic disorder (ICD-10) and ADHD (DSM-5)

Inattention, impulsivity or hyperactivity? → No → No HKD (ADHD)

↓ Yes

Can it be explained by other disorders/diseases? → Yes → Other disorder/disease

↓ No

Have all criteria for HKD (ICD-10) and/or ADHD, combined presentation (DSM-5) been met? → Yes → Have additional criteria for conduct disorders been met? → Yes → F90.1 Hyperkinetic conduct disorder (ICD-10). Two diagnoses (DSM-5): F90.0 - F91 x Conduct disorders

No → F90.0 Disturbance of activity and attention (ICD-10) and F90.0[1]) for ADHD, Combined Presentation (DSM-5)

↓ No

ADHD, predominantly inattentive presentation? → Yes → F98.8[3]) Other specified behavioral and emotional disorders with onset usually occurring in childhood and adolescence: Attention deficit disorder (ADHS, predominantly inattentive presentation) or F90.0[2]) Attention-deficit hyperactivity

↓ No

ADHD, predominantly hyperactive-impulsive presentation? → Yes → F90.8[1]), Other hyperkinetic disorders Hyperactive-impulsive symptoms (ADHD, hyperactive-impulsive presentation)

↓ No

Were HKD/ADHD criteria previously met in full? → Yes → F90.8[1]) Other hyperkinetic disorders: HKD, in partial remission ADHD, in partial remission

↓ No → Subclinical manifestation of HKD/ADHD symptoms

DSM-5: Determine current degree of severity:
- Mild
- Moderate
- Severe

1) For DSM-5 consistent with the proposal for alternative ICD-10 codes from the German translation of DSM-5 (APA/Falkai et al., 2015, p. 1219f), which corrected obvious errors in the US original. Cf. https://icd.who.int/browse10/2019/en#/F90.8;

2) According to the ICD-10 Thesaurus of diagnostic terms (IDT) of the Central Research Institute of Ambulatory Health Care in Germany (ZI) https://www.dimdi.de/dynamic/en/classifications/icd/icd-10-gm/history/icd-10-thesaurus-of-diagnostic-terms/ only in German

3) According to ICD-10 and DSM-5 consistent with the proposal for alternative ICD-10 codes from the German translation of the DSM-5 (APA/Falkai et al., 2015, p. 1219f) which corrected obvious errors in the US original. Cf. https://www.dimdi.de/static/de/klassifikationen/icd/icd-10-gm/kode-suche/htmlgm2020/block-f90-f98.htm#F90, https://www.icd10data.com/ICD10CM/Codes/F01-F99/F90-F98 versus https://icd.who.int/browse10/2019/en#/F90-F98

2. Clinical decision tree that informs differential psychosocial (including psychotherapeutic)/pharmacotherapeutic procedures for managing children/adolescents with ADHD

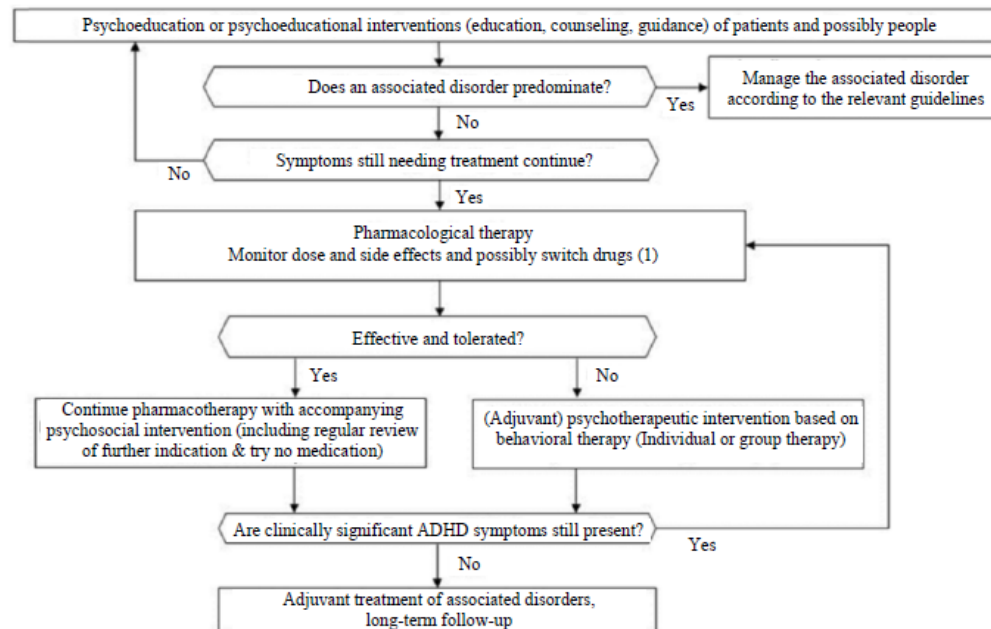| Psychoeducation or psychoeducational interventions (education, counseling, guidance) of patient, parents and educators (including case management) |

Any remaining abnormalities requiring treatment? — No → End of treatment/follow-up
↓ Yes

Does an associated disorder predominate? — Yes → Manage the associated disorder
↓ No

Is the patient < 6 years old? ← Yes[2]
↓ No

Assess grade of symptom severity/functional impairment

Sever — Moderate — Mild

No[1+2]
No[1]

Indication and preference for pharmacological
↓ Yes

Pharmacological therapy + counseling/accompanying psychosocial intervention, switch to another drug, if appropriate

Efficacious and tolerable? — No[3]
↓ Yes

Continue pharmacological therapy and accompanying psychosocial intervention (including regular review of other indication)

Indication and preference for psychosocial interventions based on behavioral therapy?
↓ Yes

Does the patient behave abnormally in the family? — Yes → Parent training/intervention in the family, additional patient-centered intervention
↓ Yes/no

Does the patient behave abnormally at the daycare center/school/workplace? — Yes → Intervention at daycare center/school/workplace; additional patient-centered intervention

Are clinically significant ADHD symptoms still present?
Yes[2]

Are clinically significant ADHD symptoms still present? — Yes

Are clinically significant ADHD symptoms still present? — No
↓ No

Additional treatment of associated disorders and long-term follow-up

1) Whenever both psychosocial interventions based on behavioral therapy as well as pharmacological therapy are neither indicated nor effective in the current settings and environments, then additional therapeutic measures (e.g. inpatient therapy) or youth welfare measures should be considered when the need for treatment is urgent.
2) Children under the age of six years should primarily receive psychosocial interventions. In individual cases, additional pharmacological therapy can be offered for residual ADHD symptoms requiring treatment. They should only be delivered by physicians with expertise in behavioral disorders of this age group. Pharmacological therapy should not be offered before the age of three (see Recommendations 1.2.2 and 1.4.1).
3) If pharmacological therapy is ineffective: Verify adherence and diagnosis.
4) If pharmacological therapy is indicated, there may also be an indication for a parallel intensive psychosocial intervention based on behavioral therapy.

3. **Clinical decision tree that informs differential psychosocial (including psychotherapeutic)/pharmacotherapeutic procedures for managing adults with ADHD**

Psychoeducation or psychoeducational interventions (education, counseling, guidance) of patients and possibly people

Does an associated disorder predominate? — Yes → Manage the associated disorder according to the relevant guidelines

No

Symptoms still needing treatment continue? — No

Yes

Pharmacological therapy
Monitor dose and side effects and possibly switch drugs (1)

Effective and tolerated?

Yes → Continue pharmacotherapy with accompanying psychosocial intervention (including regular review of further indication & try no medication)

No → (Adjuvant) psychotherapeutic intervention based on behavioral therapy (Individual or group therapy)

Are clinically significant ADHD symptoms still present? — Yes

No

Adjuvant treatment of associated disorders, long-term follow-up

1) If pharmacological therapy is ineffective: Verify adherence and diagnosis, consider inpatient treatment

4. List of German-language psychometrically investigated methods for detecting ADHD symptoms in children, adolescents and adults

Status as per May 1, 2015

Age	Clinical assessment	Parent/educator/teacher assessment	Self-assessment
3-6	• DCL-ADHS (DISYPS-III) • ILF-EXTERNAL(DISYPS-III)	• FBB-ADHS-V (DISYPS-III) • Conners EC	(not applicable)
6-10		• FBB-ADHS (DISYPS-III) • Conners 3	
11-18			SBB-ADHS (DISYPS-III)
>18	• ADHS-DC (HASE) • ADHS Interview (IDA) • CAARS-O • WRI (HASE)	(not applicable)	• ADHS-SB (HASE) • ADHS-E • CAARS-S • KATE • WR-SB • WURS-K (HASE)

ADHD-DC	ADHD Diagnostic Checklist, (HASE: Rösler et al., 2008)
ADHS-E	ADHD Screening for Adults (Schmidt and Petermann, 2013)
ADHS-SB	ADHD Self-report scale (HASE: Rösler et al., 2008)
CAARS-O	Conners' Adult ADHD Rating Scales, Observer Ratings (Christiansen et al., 2015)
CAARS-S	Conners' Adult ADHD Rating Scales, Self-report (Christiansen et al., 2015)
Conners-3	Conners' ADHD Rating Scales – 3 (Lidzba et al., 2015)
CONNERS EC	Conners' ADHD Rating Scales – Early Childhood (Harbarth et al., 2015)
DCL-ADHS	Diagnosis Checklist for ADHD from the Diagnostic System DISYPS-III (Döpfner & Görtz-Dorten, 2017)
HASE	Homburger ADHD Scales for Adults (Rösler et al., 2008)
IDA	Integrated Diagnostic Scale of adult ADHD (Retz et al., 2013)
ILF-EXTERNAL	Structured interview for externalizing symptoms from the Diagnostic System DISYPS-III (Görtz-Dorten & Döpfner, 2018)
FBB-ADHS-V	ADHD Parent and Teacher Rating Scale for preschool children from the Diagnostic System DISYPS-III (Döpfner & Görtz-Dorten, 2017)

FBB-ADHS	ADHD Parent and Teacher Rating Scale from the Diagnostic System DISYPS-III (Döpfner & Görtz-Dorten, 2017)
KATE	Cologne ADHD Test for Adults (Lauth and Minsel, 2014)
SBB-ADHS	ADHD Self-Rating Scale from the Diagnostic System DISYPS-III (Döpfner & Görtz-Dorten, 2017)
WRI	Wender-Reimherr Interview (HASE: Rösler et al., 2008)
WR-SB	Wender-Reimherr Self-Rating Questionnaire (Retz-Junginger et al., 2017)
WURS-k	Wender-Utah Rating Scale – German short version (HASE: Rösler et al., 2008)

5.   List of German-language prevention and therapy programs for managing ADHD symptoms in children and adolescents

The list contains German-language prevention and therapy programs for managing children and adolescents with ADHD that deploy methods proven to be effective in reducing ADHD symptoms by various types of German and international controlled studies. The designs of these studies included randomized trials with control groups or other types of controlled studies, such as non-randomized trials with control groups or within-subject control groups. The interventions in parent, kindergarten or school-centered settings also covered aggressive-oppositional symptoms. If the effectiveness of the therapy program was proven in international studies, there had to be at least one empirical test performed in a pre-post design (without a control group).

Evidence of effectiveness of the therapy program in the German version was assessed at the following levels

Low: At least 1 pre-post study showing significant changes in ADHD symptoms over the course of therapy.

Moderate: At least 1 controlled study, published in a peer-reviewed journal (e.g. non-randomized trial with a control group or within-subject control group), showing significant effects on ADHD symptoms (the interventions in parent-, kindergarten- or school-centered settings included aggressive-oppositional symptoms).

Good: At least 1 randomized trial with control groups, published in a peer-reviewed journal, showing significant effects on ADHD symptoms (in parent-, kindergarten- or school-centered interventions included aggressive-oppositional symptoms).

Excellent: Several studies, published in a peer-reviewed journal, showing significant effects on ADHD symptoms (in parent-, kindergarten- or school-centered interventions included aggressive-oppositional symptoms) across different samples or treatment settings (e.g. outpatient/inpatient) or with demonstration of stability; including at least 1 randomized trial with control groups.

5.1. Parent-, kindergarten-, school-centered and multimodal prevention and therapy programs

Manual	Annotation	Evidence of effectiveness of the therapy program/References
Aust-Claus, E. (2010). **ADS. Das Elterntraining.** Parent coaching manuals like the German ADS-ElternCoach are available online: OptiMind Media. Supplementary materials: Aust-Claus, E., Hammer, P.-M. (2003): ADS. Eltern als Coach. Attention-Deficit Syndrome/ADS Parent Training on DVD. OptiMind Media. Aust-Claus, E., Hammer, P. M.: ADS - Eltern als Coach (2003). Attention-Deficit Syndrome/Practical Workbook for Parents. OptiMind Media.	• Specific parent training based on behavioral therapy • Group training • Age range: Children and adolescents aged 5 to 14 years • Manuals can be purchased at: www.opti-mind.de.	**Evidence of effectiveness Low:** 1 pre-post study Moosbrugger, H., Höfling, V. (2006): Evaluationsbericht zum Wirkungsnachweis des ADS-Elterntrainings nach dem OptiMind-Konzept. http://www.opti-mind.de/fileadmin/downloads/Evaluierung_Elterntraining.pdf
Beelmann, A., Lösel, F., Jaursch, S., Bühler, A. & Kötter, C. (2007). **Elterntraining zur Förderung der Erziehungskompetenz** für emotional belastete Familien (**EFFEKT**). University Erlangen-Nürnberg; Institute for Psychology.	• Combined parent and children training; parent training oriented on Patterson	**Evidence of effectiveness Low**: Pre-post changes in the course of therapy, however, no therapy effects regarding ADHD symptoms through parent training (Kötter et al., 2011; Lösel et al., 2006) Bühler, A., Kötter, C., Jaursch, S. & Lösel, F. (2011). Prevention of familial transmission of depression: EFFEKT-E, a selective program for emotionally burdened families. Journal of Public Health, 19, 321–327. Kötter, C., Stemmler, M., Lösel, F., Bühler, A., Jaursch, S. (2011) Mittelfristige Effekte des Präventionsprogramms EFFEKT-E für emotional belastete Mütter und ihre Kinder unter besonderer Berücksichtigung psychosozialer

Manual	Annotation	Evidence of effectiveness of the therapy program/References
		Risikofaktoren. Zeitschrift für Gesundheitspsychologie 19, 122-133. Lösel, F., Beelmann, A., Stemmler, M. & Jaursch, S. (2006). Prävention von Problemen des Sozialverhaltens im Vorschulalter: Evaluation des Eltern- und Kindertrainings EFFEKT. Zeitschrift für Klinische Psychologie und Psychotherapie, 35, 79–81.
Döpfner, M., Schürmann, S. & Frölich, J. (2013). **Therapieprogramm für Kinder mit hyperkinetischem und oppositionellem Problemverhalten (THOP)**. (5th edition). Weinheim: Beltz Döpfner, M., Kinnen, C., & Halder, J. (2016). **THOP-Gruppenprogramm** für Eltern von Kindern mit ADHS-Symptomen und expansivem Problemverhalten. Manual. Weinheim: Beltz. Kinnen, C., Halder, J., & Döpfner, M. (2016). THOP-Gruppenprogramm für Eltern von Kindern mit ADHS-Symptomen und expansivem Problemverhalten. Arbeitsbuch für Eltern. Weinheim: Beltz	• Specific parent training including school- and patient-centered interventions based on behavioral therapy • Modular structured manual primarily for individual therapy; but used for group therapy as well • THOP group program developed specifically for parent groups • Age range: Children from approx. 3 to 12 years	**Evidence of effectiveness Excellent**: 7 studies: 6 (partially randomized) controlled studies, one in a partially inpatient setting, one pre-post follow-up study; long term stabilization of effects (up to 8 years) Berk, E., Plück, J. & Döpfner, M. (2008). Zufriedenheit der Eltern mit Elterngruppen auf der Grundlage des Therapieprogramms THOP in der klinischen Versorgung von Kindern mit ADHS-Symptomatik. Verhaltenstherapie mit Kindern und Jugendlichen - Zeitschrift für die psychosoziale Praxis, 4, 99-108. **(Study 1)** Döpfner M., Breuer D., Schürmann S., Wolff Metternich T., Rademacher C & Lehmkuhl G (2004). Effectiveness of an adaptive multimodal treatment in children with Attention Deficit Hyperactivity Disorder – global outcome. Eur Child & Adolesc Psychiatry 13 (Suppl. 1): I/117–I/129. **(Study 2)** Doepfner, M., Ise, E., Breuer, D., Rademacher, C., Wolff Metternich-Kaizman, T., & Schürmann, S. (2016). Long-term course after adaptive multimodal treatment for children with ADHD: An eight year follow-up. Journal of Attention Disorders (epub ahead of print). doi: 10.1177/1087054716659138. **(Study 2)** Döpfner, M., Ise, E., Wolff Metternich-Kaizman, T., Schürmann, S., Rademacher, C., & Breuer, D. (2015). Adaptive multimodal treatment for children with Attention-Deficit-/Hyperactivity Disorder: An 18 month follow-up. Child Psychiatry & Human Development, 46, 44–56. doi: 10.1007/s10578-014-0452-8 **(Study 2)** Dreisörner T. (2006). Wirksamkeit verhaltenstherapeutischer Gruppenprogramme bei Kindern mit Aufmerksamkeitsdefizit-/Hyperaktivitätsstörungen (ADHS). Kindheit und Entwicklung 15: 255-266. **(Study 3)** Ise, E., Schröder, S., Breuer, D., & Döpfner, M. (2015). Parent-child inpatient treatment for children with behavioural and emotional disorders: a multilevel analysis of within-subjects effects. BMC Psychiatry 15: 288. doi: 10.1186/s12888-015-0675-7 (**Study 4)**

Manual	Annotation	Evidence of effectiveness of the therapy program/References
		Jans et al. (2015). Does intensive multimodal treatment for maternal ADHD improve the efficacy of parent training for children with ADHD? A randomized controlled multicenter trial. J Child Psychol Psychiatry, 56, 1298 -1313. **(Study 5)**
		Lauth G.W., Kausch T.W.E. & Schlottke P.F. (2005). Effekte von eltern- und kindzentrierten Interventionen bei Hyperkinetischen Störungen. Journal Klin Psychol Psychother 34: 248-257. **(Study 6)**
		Salbach H., Lenz K., Huss M., Vogel R., Felsing D. & Lehmkuhl U. (2005). Die Wirksamkeit eines Gruppentrainings für Eltern hyperkinetischer Kinder. Ztschr Kinder-Jugendpsychiat Psychother 33: 59-68. **(Study 7)**

Manual	Annotation	Evidence of effectiveness of the therapy program/References
Döpfner, M., Schürmann, S. & Lehmkuhl, G. (2011). **Wackelpeter & Trotzkopf**. Hilfen für Eltern bei hyperkinetischem und oppositionellem Verhalten (4th revised edition). Weinheim: Beltz.	• Specific self-help manual based on behavioral therapy for self-help for parents and other caregivers • Age range: Children from 3 to 12 years • Studies partly with parenting booklets that were developed on the basis of Wackelpeter & Trotzkopf.	**Evidence of effectiveness Excellent**: 5 studies as guided self-help based on the self-help book or on parenting booklets based on it (with advice provided by telephone); 2 pre-post studies; 3 RCTs; stabilization of effects in the follow-up (up to 1 year) Dose, C., Hautmann, C., Buerger, M., Schuermann, S., Woitecki, K., & Doepfner, M. (2016). Telephone-assisted self-help for parents of children with attention-deficit/hyperactivity disorder who have residual functional impairment despite methylphenidate treatment: A randomized controlled trial. Journal of Child Psychology and Psychiatry (epub ahead of print). doi: 10.1111/jcpp.12661 **(Study 4)** Hautmann, C., & Döpfner, M. (2015). Comparison of behavioral and non-directive guided self-help for parents of children with externalizing behavior problems. European Child & Adolescent Psychiatry, 24 (Suppl. 1), S17. **(Study 5)** Ise, E., Kierfeld, F., & Döpfner, M. (2015). One-year follow-up of guided self-help for parents of preschool children with externalizing behaviour. The Journal of Primary Prevention, 36, 33-40. doi: 10.1007/s10935-014-0374-z **(Study 2)** Kierfeld, F. & Döpfner, M. (2006). Bibliotherapie als Behandlungsmöglichkeit bei Kindern mit externalen Verhaltensstörungen. Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie, 34, 377-386. **(Study 1)** Kierfeld, F., Ise, E., Hanisch, C., Görtz-Dorten, A., & Döpfner, M. (2013). Effectiveness of telephone-assisted parent-administered behavioural family Intervention for preschool children with externalizing problem behaviour: A randomized controlled trial. European Child and Adolescent Psychiatry 22, 553-565. **(Study 2)** Mokros, L., Benien, N., Mütsch, A., Kinnen, C., Schürmann, S., Wolf Metternich-Kaizman, T., Breuer, D., Hautmann, C., Ravens-Sieberer, U., Klasen, F., & Döpfner, M. (2015). Angeleitete Selbsthilfe für Eltern von Kindern mit Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung: Konzept, Inanspruchnahme und Effekte eines bundesweiten Angebotes – eine Beobachtungsstudie. Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie, 43, 275-288. **(Study 3)**
Franz, M., Gertheinrichs, T., Güttgemanns, J., Rentsch, D. (2009) **PALME - Präventives Elterntraining für alleinerziehende Mütter**.	• A preventive parental training program for single parents based on attachment theory and	**Evidence of effectiveness Low:** Pre-post changes in the course of therapy, however, no therapy effects regarding behavioral problems, minor effects on mother-child conflicts. Franz, M., Weihrauch, L., Buddenberg, T., Güttgemanns, J. Haubold, S. & Schäfer, R. Effekte eines bindungstheoretisch

Manual	Annotation	Evidence of effectiveness of the therapy program/References
Vandenhoeck & Ruprecht	psychodynamic-interactional approaches.	fundierten Gruppenprogramms für alleinerziehende Mütter und ihre Kinder: PALME. Kindheit und Entwicklung, 19, 90–101. Franz, M., Weihrauch, L., Buddenberg, T. & Scha¨fer, R. (2009). PALME: Wirksamkeit eines bindungsorientierten Elterntrainings für alleinerziehende Mütter und ihre Kinder. Psychotherapeut, 54, 357–369. Franz, M., Weihrauch, L. & Schäfer, R. (2011). PALME: A preventive parental training program for single mothers with preschool aged children. Journal of Public Health, 19, 305–319.
Kinnen, C., Rademacher, C., & Döpfner, M. (2015). **Wackelpeter & Trotzkopf in der Pubertät.** Wie Eltern und Jugendliche Konflikte gemeinsam lösen können. Weinheim: Beltz.	• Specific self-help manual based on behavioral therapy for self-help for parents and other caregivers • Study with parenting booklets that were developed on the basis of the book.	**Evidence of effectiveness Low:** Pre-post changes in the course of the intervention. Roschmann, T. (2018) Alltagswirksamkeit angeleiteter Selbsthilfe für Eltern von Jugendlichen mit ADHS. Dissertation Cologne University
Lauth, G. W., Heubeck, B. (2006). **Kompetenztraining für Eltern sozial auffälliger Kinder (KES)**: Ein Präventionsprogramm. Göttingen: Hogrefe.	• Short, specific parent training • Grouping • Age range: Children from 5 to 11 years.	**Evidence of effectiveness Low:** 3 studies: 2 pre-post studies, 1 control-group study (without effects, only pre-post changes) Konrad, G. (2002). Entwicklung und Evaluation eines Gruppentrainings für Mütter von Kindern mit Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung (ADHS). Frankfurt: Peter Lang. (**Study 1**) Lauth, G. W., Grimm, K. & Otte, T. A. (2007). Verhaltensübungen im Elterntraining. Eine Studie zur differenzierten Wirksamkeit im Elterntraining. Zeitschrift für Klinische Psychologie und Psychotherapie, 36, 26-35 (**Study 2:** Prä-Post-Veränderungen aber keine Therapieeffekte im HSQ) Grimm, K. & Mackowiak, K. (2006). Kompetenztraining für Eltern sozial auffälliger und aufmerksamkeitsgestörter Kinder (KES). Praxis der Kinderpsychologie und Kinderpsychiatrie 55, 363-383. (**Study 2:** Prä-Post-Veränderungen aber keine Therapieeffekte im HSQ) Lauth, G.W., Otte, A.T. & Heubeck, B. (2009). Effectiveness of a competence training programme for parents of socially

Manual	Annotation	Evidence of effectiveness of the therapy program/References
		disruptive children. Emotional and Behavioral Difficulties. 14, 117-126 (**Study 3**).
Lauth, G. W. (2014)**. ADHS in der Schule. Übungsprogramm für Lehrer** (2nd edition). Weinheim: Beltz.	• Teacher training with 7 modules.	**Evidence of effectiveness Low:** 2 Pre-post studies Lauth, G. W. (2014). ADHS in der Schule. Übungsprogramm für Lehrer (2nd edition). Weinheim: Beltz
Plück, J., Wieczorrek, E., Wolff Metternich, T. & Döpfner, M. (2006). **Präventionsprogramm für Expansives Problemverhalten (PEP)**. Ein Manual für Eltern- und Erziehergruppen. Göttingen: Hogrefe.	• Specific parent group and parallel educator group training on a behavioral therapy basis mainly for children aged 3 to 6 years with externalizing behaviors.	**Evidence of effectiveness: Excellent**: 3 studies (1 randomized trial with control groups (with parallel parent and educator training) and 2 within-subject control group studies (parent and educator training separately). Stabilization of effects in the follow-up (up to 1 year) Eichelberger, I., Plück, J., Hautmann, C., Hanisch, C., & Döpfner, M. (2016). Effectiveness of the Prevention Program for Externalising Problem Behaviour (PEP) in preschoolers with severe and no or mild ADHD symptoms. Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie, 44, 231-239. (**Studies 2 and 3**) Hanisch, C., Plück, J., Meyer, N., Brix, G., Freund-Braier, I., Hautmann, C. & Döpfner, M. (2006). Kurzzeiteffekte des indizierten Präventionsprogramms für Expansives Problemverhalten (PEP) auf das elterliche Erziehungsverhalten und auf das kindliche Problemverhalten Zeitschrift für Klinische Psychologie und Psychotherapie, 35(2), 117-126 (**Study 1**) Hanisch, C., Freund-Braier, I., Hautmann, C., Jänen, N., Plück, J., Brix, G., Eichelberger, I. & Döpfner, M. (2010). Detecting effects of the indicated Prevention programme for Externalizing Problem behaviour (PEP) on child symptoms, parenting, and parental quality of life in a randomised controlled trial. Behavioural and Cognitive Psychotherapy, 38, 95-112 (**Study 1**). Hanisch, C., Hautmann, C., Eichelberger, I., Plück, J., & Döpfner, M. (2010). Die klinische Signifikanz des Präventionsprogramms für Expansives Problemverhalten (PEP) im Langzeitverlauf Verhaltenstherapie 20, 265-274. (**Study 1**). Hanisch, C., Hautmann, C., Plück, J., Eichelberger, I., & Döpfner, M. (2014). The prevention program for externalizing problem behavior (PEP) improves child behaviour by reducing negative parenting: analysis of mediating processes in a randomized controlled trial. Journal of Child Psychology and Psychiatry 55, 473-484. (**Study 1**).

Manual	Annotation	Evidence of effectiveness of the therapy program/References
		Hautmann, C., Hanisch, C., Mayer, I., Plück, J. & Döpfner, M. (2008). Effectiveness of the prevention program for externalizing problem behaviour (PEP) in children with symptoms of attention-deficit/hyperactivity disorder and oppositional defiant disorder--generalization to the real world. Journal of Neural Transmission, 115 (2), 363-370. (**Study 1**).

Hautmann, C., Eichelberger, I., Hanisch, C., Plück, J., Walter, D. & Döpfner, M. (2010). The severely impaired do profit most: Short-term and long-term predictors of therapeutic change for a parent management training under routine care conditions for children with externalizing problem behavior. European Child and Adolescent Psychiatry, 19, 419-430. (**Study 2**).

Hautmann, C., Stein, P., Eichelberger, I., Hanisch, C., Plück, J., Walter, D., & Döpfner, M. (2011). The severely impaired do profit most: Differential effectiveness of a parent management training for children with externalizing behavior problems in a natural setting. Journal of Child and Family Studies 20, 424–435. (**Study 2**)

Hautmann, C., Hanisch, C., Ilka, M., Plück, J., Walter, D. & Döpfner, M. (2009). Does parent management training for children with externalizing problem behavior in routine care result in clinically significant changes? Psychotherapy Research, 19, 224 - 233. (**Study 2**).

Hautmann, C., Hoijtink, H., Eichelberger, I., Hanisch, C., Plück, J., Walter, D. & Döpfner, M. (2009). One-year follow-up of a parent management training for children with externalizing behavior problems in the real world. Behavioural and Cognitive Psychotherapy, 29, 379-396. (**Study 2**).

Hautmann, C., Hoijtink, H., Eichelberger, I., Görtz-Dorten, A., Hanisch, C., Plück, J., Walter, D., & Döpfner, M. (2013). Any indication for bias due to participation? Comparison of the effects of a parent management training rated by participating and non-participating parents. Clinical Psychology & Psychotherapy 20, 384-393. (**Study 2**)

Plück, J., Eichelberger, I., Hautmann, C., Hanisch, C., Jaenen, N., & Doepfner, M. (2015). Effectiveness of a teacher based indicated prevention program for pre-school children with externalizing problem behaviour Prevention Science, 16, 233–241. (**Study 3**) |
| Sanders, M. R., Markie-Dadds, C. & Turner, K.M.T. (2006). **Trainermanual für das Triple** | • General parent training
• Individual and group training | **Evidence of effectiveness: Excellent**: International: Meta-analyses with more than 100 studies and significant effects on changes in externalizing behavioral disorders (Sanders er al., 2014, |

Manual	Annotation	Evidence of effectiveness of the therapy program/References
P Einzeltraining. PAG Institut für Psychologie AG (Ed. of German edition). Münster: Verlag für Psychotherapie. Sanders, M. R., Turner, K.M.T. (2006). **Trainermanual für das Teen Triple P Gruppenprogramm**. PAG Institut für Psychologie AG (Ed. of German edition, 2nd revised edition). Münster: Verlag für Psychotherapie. Sanders, M. Turner, K.M.T., Markie-Dadds, C. (2009). Das Triple P–Elternarbeitsbuch. PAG Institut für Psychologie AG, (Ed. of German version, 4th edition). Münster: Verlag für Psychotherapie. Turner, K.M.T., Markie-Dadds, C. & Sanders, M. R. (2007). Trainermanual für das Triple P Gruppenprogramm. PAG Institut für Psychologie AG (Ed. of German version, 2nd edition). Münster: Verlag für Psychotherapie. Turner, K.M.T., Sanders, M. R. & Markie-Dadds, C. (2006). Beratermanual für die Triple P-Kurzberatung. PAG Institut für Psychologie AG (Ed. of German edition, 2nd revised	• Multi-level model (universal, selective, indicated prevention) • The Triple P parent workbook is a manual for self-help for parents of children at the age of 0 to 12 years. • Age range: • Children up to 12 years • Manuals are only available within the scope of continuing education.	Thomas & Zimmer-Gembeck, 2007, Nowack & Heinrichs, 20089) as well as studies on the effectiveness in children with ADHD (Bor et al., 2002, Hoath & Sanders, 2002). In German-speaking countries several RCTs on the effectiveness of Triple P as a universal prevention program with evidence of long-term effects Bor, W., Sanders, M.R. & Markie-Dadds, C. (2002). The Effects of the Triple P-Positive Parenting Program on Preschool Children With Co-Occurring Disruptive Behavior and Attentional/Hyperactive Difficulties. Journal of Abnormal Child Psychology, 30, 571–587 Eichelberger, I., Plück, J., Hanisch, C., Hautmann, C., Jänen, N., & Döpfner, M. (2010). Effekte universeller Prävention mit dem Gruppenformat des Elterntrainings Triple P auf das kindliche Problemverhalten, das elterliche Erziehungsverhalten und die psychische Belastung der Eltern. Zeitschrift für Klinische Psychologie und Psychotherapie, 39, 24- 32. Hahlweg, K., Heinrichs, N., Kuschel, A., Bertram, H. & Naumann, S. (2010). Long-term outcome of a randomized controlled universal prevention trial through a positive parenting program: is it worth the effort? Child and Adolescent Psychiatry and Mental Health, 4:14 Heinrichs, N., Hahlweg, K., Bertram, H., u.a. (2006). Die langfristige Wirksamkeit eines Elterntrainings zur universellen Prävention kindlicher Verhaltensstörungen, Ergebnisse aus Sicht der Mütter und Väter. Zeitschrift für Klinische Psychologie und Psychotherapie, 35, 82- 95. Heinrichs, N., Krüger, S., Guse, U. (2006). Der Einfluss von Anreizen auf die Rekrutierung von Eltern und auf die Effektivität eines Elterntrainings. Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie, 35, 97-108. Hoath, F.E. & Sanders, M.R. (2002) A Feasibility Study of Enhanced Group Triple P — Positive Parenting Program for Parents of Children with Attention-deficit/Hyperactivity Disorder. Behaviour Change 19, 191–206 Nowak, C. & Heinrichs, N. (2008) A Comprehensive Meta-Analysis of Triple P-Positive Parenting Program Using Hierarchical Linear Modeling: Effectiveness and Moderating Variables. Clin Child Fam Psychol Rev. Sanders, M.R., Kirby, J.N. Tellegen, C.L. & Day, J.J. (2014) The Triple P-Positive Parenting Program: A systematic

Manual	Annotation	Evidence of effectiveness of the therapy program/References
edition). Münster: Verlag für Psychotherapie.		review and meta-analysis of a multi-level system of parenting support. Clinical Psychology Review 34, 337–357 Thomas, R. & Zimmer-Gembeck, M.J. (2007) Behavioral Outcomes of Parent-Child Interaction Therapy and Triple P-Positive Parenting Program: A Review and Meta-Analysis. Journal of Abnormal Child Psychology, 5, 475-495.
Hanisch, C., Richard, S., Eichelberger, I., Greimel, L., & Döpfner, M. (2017). **Schulbasiertes Coaching bei Kindern mit expansivem Problemverhalten (SCEP).** Göttingen: Hogrefe.	• Teacher training through continuing education module and individual coaching modules	**Evidence of effectiveness Low**: 1 within-subject control group study with effects compared to waiting time (not yet published as a full article in a peer-reviewed journal) Eichelberger, I., Hanisch, C., & Döpfner, M. (2015). How effective is teacher coaching in reducing externalizing behavior problems in primary school children. European Child & Adolescent Psychiatry, 24 (Suppl. 1), S18.

5.2.   Primary patient-centered prevention and therapy regimens

Manual	Annotation	Evidence of effectiveness
Aust-Claus, E, Hammer, P.M. (2010). OptiMind. **Das ADS-Therapieprogramm für Kinder. Training für Konzentration, Kommunikation und Selbstbewusstsein**. Contains CD-ROM with materials to print out. OptiMind media.	• Individual or small group training sessions • Age range: Children from 5 to 8 years • Manual can be purchased at: • www.opti-mind.de.	**Evidence of effectiveness Low:** 1 Pre-post study Evaluierung des OptiMind-Trainingsprogramms [Evaluation of the OptiMind Training Program]. http://www.opti-mind.de/fileadmin/downloads/Evaluierung_des_OptiMind-Trainingsprogramm.pdf

Manual	Annotation	Evidence of effectiveness
Supplementary materials: Aust-Claus, E, Hammer, P.M. (2010). OptiMind - Das Konzentrationstraining für Kinder. Home exercises. Contains OptiMind media CD-ROM with materials to print out.		
Braun, S., & Döpfner, M. (2017). **Therapieprogramm zur Steigerung von Organisationsfähigkeit, Konzentration und Impulskontrolle bei Kindern mit ADHS: THOKI-ADHS**. Göttingen: Hogrefe	• Individual therapy	**Evidence of effectiveness Low:** Effects in a within-subject control group study Braun, S. (2017) Entwicklung und Evaluation des Therapieprogramms zur Steigerung von Organisationsfähigkeit, Konzentration und Impulskontrolle bei Kindern mit ADHS: THOKI-ADHS. Dissertation, Cologne University
Ettrich, C. (2004). **Konzentrationstrainings-Programm für Kinder**, Vol. 1, Vorschulalter, Vol. 2: 1. und 2. Schulklasse, Vol. 3: 3. und 4. Schulklasse. Göttingen: Vandenhoeck & Ruprecht.	• Concentration training programs for the three age groups	**Evidence of effectiveness Low:** Small control-group studies: Bergmann, G. (1996). Veränderungswerte kognitiver Parameter bei Vorschulkindern in Abhängigkeit vom Einsatz eines Konzentrations-Trainings-Programms. Diss., Leipzig University. Forker-Tutschkus, A. (1996). "Konzentrationstrainingsprogramm in Verbindung with progressiver Muskelrelaxation – Eine empirische Studie an Vorschulkindern". Diss., Leipzig University. Jeschke, B. (1996). Konzentrations-Trainings-Programm für Vorschulkinder unter Einbezug von Entspannungstechniken. Diploma Thesis. Institute of Psychology, Leipzig University. Mayer, K. (1996). Untersuchungen zu einem Konzentrations-Trainings-Programm im Vorschulalter. Diss., Leipzig University. Schuhmann, U. (1995). Konzentrationstraining im Vorschulalter – eine Möglichkeit zur Verbesserung des Erreichens der allgemeinen Schulreife. Diploma Thesis, Institute of Psychology. Leipzig University.

Manual	Annotation	Evidence of effectiveness
Jacobs, C. et al. (2013). Training für Kinder mit Aufmerksamkeitsstörungen. Das neuropsychologische Gruppenprogramm **ATTENTIONER** (3rd revised edition). Göttingen: Hogrefe.	• Group training • Age range: Children and adolescents aged 7 to 13 years	**Evidence of effectiveness Low:** 2 Pre-post studies, 1 within-subject control group study without direct comparison of the effects during waiting and therapy time. Jacobs, C., Petermann, F. (2005). Aufmerksamkeitsstörungen im Kindesalter: Konzept und Wirksamkeit des ATTENTIONER-Programms. Verhaltenstherapie und Verhaltensmedizin, 26, 317-341. Jacobs, C., Petermann, F. (2007). Aufmerksamkeitsstörungen bei Kindern – Langzeiteffekte eines neuropsychologischen Gruppenprogramms ATTENTIONER. Kindheit und Entwicklung, 16, 40-49 Jacobs, C. Petermann, F. (2008). Aufmerksamkeitstherapie bei Kindern. Langzeiteffekte des ATTENTIONERS. Zeitschrift für Kinder und Jugendpsychiatrie und Psychotherapie 36, 6, 411-417 Tischler, L., Karpinski, N., Petermann, F. (2011). Evaluation des neuropsychologischen Gruppenprogramms ATTENTIONER zur Aufmerksamkeitstherapie bei Kindern und Jugendlichen. Zeitschrift für Neuropsychologie, 22, 75–85.
Krowatschek, D. et al. (2007): **Marburger Konzentrationstraining (MKT)** für Schulkinder. (7th, unrevised edition). Dortmund: Verlag Modernes Lernen. Krowatschek, D. et al. (2010). Marburger Konzentrationstraining (MKT) für Kindergarten, Vorschule und Eingangsstufe (3rd, unchanged edition). Dortmund: Verlag Modern learning. Krowatschek, D. et al. (2007): Marburger Konzentrationstraining für Jugendliche (MKT-	• Individual or group training • 3 Manuals: Preschool children, children, adolescents • Age range 1: Kindergarten and preschool children with attention-deficit disorders and behavioral difficulties; for use in kindergarten, preschool and work with developmentally delayed children • Age range 2: School children with impulsive working style as well as slow, dreamy, always-distracted children. • Age range 3: Adolescents	**Evidence of effectiveness Low:** No clear evidence of effectiveness. Several diploma theses/dissertations with partly contradictory results. Beck, M. (1998). Therapiebaukasten oder Trainingsprogramm? In: Evaluation als Maßnahme der Qualitätssicherung. Pädagogisch-psychologische Interventionen auf dem Prüfstand. Tübingen: Dgvt-Verlag. Claes, M. (1996). Auswirkungen des Marburger Konzentrationstrainings auf das Verhalten von Mutter und Kind. Unpublished diploma thesis at Philipps Universität Marburg. Dreisörner, T. (2004). Zur Wirksamkeit von Trainings bei Kindern mit Aufmerksamkeitsstörungen. Unpublished dissertation at Göttingen University. Dröge, C. (1996). Evaluation des Marburger Verhaltenstrainings für überaktive Kinder anhand einer systematischen Verhaltensbeobachtung. Unpublished diploma thesis at the Philipps Universität Marburg. Krowatschek, G. (1996). Evaluation des Marburger Konzentrationstrainings und des Marburger Verhaltenstrainings für überaktive Kinder unter besonderer Berücksichtigung der Elternarbeit. Unpublished diploma thesis at the

Manual	Annotation	Evidence of effectiveness
J). Dortmund: Verlag Modernes Lernen.	• Therapeutic Use: accompanying parents' evenings	Philipps Universität Marburg. Witte, S. (2001). Entwicklung und Evaluation eines videogestützten Selbstinstruktionstrainings für aufmerksamkeitsgestörte Kinder. Dissertation, Göttingen University.
Lauth, G.W., Schlottke, P.F. (2009). **Training mit aufmerksamkeitsgestörten Kindern**. (6th, completely revised edition). Weinheim: Beltz, Psychologie Verlags Union.	• Individual or group setting (1-3 children) • Age range: Children aged 7 to 12 years	**Evidence for effectiveness: Moderate:** Several pre-post studies and 3 control group studies, the latter with partly contradictory results (Lauth 1996; Lauth et al., 2005: effects; Dreisörner: no effects) Dreisörner T. (2006). Wirksamkeit verhaltenstherapeutischer Gruppenprogramme bei Kindern mit Aufmerksamkeitsdefizit-/Hyperaktivitätsstörungen (ADHS). Kindheit und Entwicklung 15: 255-266. Lauth, G. W. (1996). Effizienz eines metakognitiv-strategischen Trainings bei lern- und aufmerksamkeitsbeeinträchtigten Grundschülern. Zeitschrift für Klinische Psychologie, 25, 21-32. Lauth, G. W. , Linderkamp, F. (1998). Durchführungspraktikabilität eines Trainingsprogrammes für aufmerksamkeitsgestörte Kinder. Psychologie in Erziehung und Unterricht, 45, 81-90. Lauth, G. W., Fellner, C. (1998). Evaluation eines multimodalen Therapieprogramms bei Aufmerksamkeitsdefizit-/Hyperaktivitätsstörungen über eine differenzierte Einzelfallforschung. In: Greisbach, M, Kullick, U., Souvignier, E. Von der Lernbehindertenpädagogik zur Praxis schulischer Förderung, 109-124. Lengerich: Papst Science Publishers. Lauth G.W., Kausch T.W.E. & Schlottke P.F. (2005). Effekte von eltern- und kindzentrierten Interventionen bei Hyperkinetischen Störungen. Journal Klin Psychol Psychother 34: 248-257. Linderkamp, F. (2002). Katamnestische Untersuchung zum Training mit aufmerksamkeitsgestörten Kindern. Verhaltenstherapie und Verhaltensmedizin, 23, 53-73. Naumann, K. (2000). Katamnestische Untersuchung eines kognitiv-behavioralen Therapieprogramms für aufmerksamkeitsgestörte/hyperaktive Kinder – Ein- bis Zwei-Jahres Follow-Up. Unpublished dissertation: Tübingen University.

Manual	Annotation	Evidence of effectiveness
Linderkamp, F., Hennig, T. & Schramm, S.A. (2011). ADHS bei Jugendlichen: **Das Lerntraining LeJA.** Weinheim: Beltz	• Group therapy	**Evidence for effectiveness Moderate** 1 within-subject control group study effects on ADHD symptoms as compared to a waiting list control group; however, not compared to progressive muscle relaxation Schramm, S.A., Henig, T., Linderkamp, F. (in press). Training Problem-Solving- and Organizational Skills in Adolescents with ADHD: 2006; Vogel, CL et al. Journal of Cognitive Education and Psychology
Spröber, N., Brettschneider, A., Fischer,L., Fegert, J & Grieb, J. (2013)**: SAVE-Strategien für Jugendliche mit ADHD**. Berlin: Springer	• Group therapy, 10 sessions	**Evidence of effectiveness Low:** 1 Pre-post follow-up study, within-subject control group study with changes during therapy, effects compared to waiting time not reported Fischer, L., Brettschneider, A., Kölch, M., Fegert, J.M. & Spröber, N. (2014). Individuelle Therapiezielerreichung nach Gruppentherapie „SAVE". Psychotherapeut 59 Spröber, N., Brettschneider, A., Fischer,L., Fegert, J & Grieb, J. (2013): SAVE-Strategien für Jugendliche mit ADHD. Berlin: Springer
Walter, D., & Döpfner, M. (2009). **Leistungsprobleme im Jugendalter. Therapieprogramm für Jugendliche mit Selbstwert-, Leistungs- und Beziehungsstörungen, SELBST** (hrsg. M. Döpfner, D. Walter, C. Rademacher, S. Schürmann), Vol. 2. Göttingen: Hogrefe.	• Individual therapy	**Evidence for effectiveness Moderate:** 1 within-subject control group study Walter, D., & Döpfner, M. (2007). Die Behandlung von Jugendlichen mit Leistungsstörungen mit dem Therapieprogramm SELBST- Konzept und Stabilität der Veränderungen während der Therapie. *Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie, 35*, 281-290. Walter, D., & Döpfner, M. (2007). Die Behandlung von Jugendlichen mit Leistungsstörungen mit dem Therapieprogramm SELBST – Konzept und Kasuistik. *Kindheit und Entwicklung, 16*, 163-170. Walter, D., & Döpfner, M. (2006). Die Behandlung von Jugendlichen mit Leistungsstörungen mit dem SELBST-Programm - Kurzzeiteffekte. *Verhaltenstherapie, 16*, 257-265.
Winter, B., Arasin, B. (2007). **Ergotherapeutisches Trainingsprogramm bei ADHD (ETP-ADHD)**. In: Winter, B., Arasin, B. (2007). Ergotherapie bei Kindern mit ADHS.	• Designed as individual training • Group training is possible • Age range: Primary school children	**Evidence of effectiveness Low:** 1 non-randomized control group study not published in peer-reviewed journal Arasin, B. (2009). Evaluation des Ergotherapeutischen Trainingsprogramms (ETP) bei ADHS. Inaugural dissertation

Manual	Annotation	Evidence of effectiveness
Stuttgart: Thieme.	• Child- and environment-centered interventions	for conferral of a doctoral title by the Faculty of Human Sciences at Cologne University: Cologne University.
Staufenberg, A.M., (2011). Zur **Psychoanalyse der ADHS**. Manual und Katamnese. Frankfurt a. M.: Brandes & Apsel	• Therapy founded on depth psychology	**Evidence of effectiveness Low: 1** Control group study with active control group (very short CBT, partly medication). Changes of aggressive ADHD symptoms in the course of therapy. No effects as compared to control therapy Leuzinger-Bohleber, M., Staufenberg, A., Fischmann, T. (2007). ADHS-Indikation für psychoanalytische Behandlungen? Einige klinische, konzeptuelle und empirische Überlegungen ausgehend von der Frankfurter Präventionsstudie. Praxis der Kinderpsychologie und Kinderpsychiatrie, 356 – 385. (Study 1) Laezer, K.L. (2015). Effectiveness of psychoanalytic psychotherapy without medication and behavioral treatment with or without medication in children with externalizing disorders. Journal of Infant, Child and Adolescent Psychotherapy; 14(2): 111-128, DOI: 10.1080/15289168.2015.1014991. **(Study 2)** Laezer, K.L., Tischer, I., Gaertner, B., Leuzinger-Bohleber, M. (2014): Research Report: Psychoanalytische und verhaltenstherapeutisch/medikamentöse Behandlungen von Kindern mit Desintegrationsstörungen. Ergebnisse der Frankfurter ADHS-Wirksamkeitsstudie. Analytische Kinder- und Jugendlichen-Psychotherapie, 164(4), 451-494. **(Study 2)**

5.3. Effectiveness of interventions based on depth psychology in children and adolescents

In randomized controlled studies, the effectiveness of interventions based on depth psychology could not be demonstrated in the areas of prevention or therapy. In the Frankfurt Prevention Study, an extensive prevention and intervention program at daycare centers was carried out on an unselected sample of n = 177 children aged 3-4 years (control group n = 185 children) (fortnightly supervision of the educators, weekly psychoanalytical-pedagogical offers, intensive work with parents, individual psychoanalytic therapies for children in need of therapy), in which cognitive-behavioral therapy procedures were also used (FAUSTLOS Violence Prevention Program). No effects on ADHD symptoms could be proven for the whole group (only for the subgroup of the girls) [470].

In another German study on the effectiveness of psychoanalytic treatment of children with ADHD and partly comorbid conduct disorder, a 26-month long-term outpatient psychoanalytic treatment according to Staufenberg [471] was compared with behavioral therapy and, in some cases, pharmacotherapy. In the behavioral therapy program, some patients underwent ten-day cognitive behavioral therapy [472] or six weeks of concentration training sessions as well as partly pharmacotherapy for the treatment of ADHD [473-475]. With regard to the symptoms of ADHD and aggressive/oppositional behavior, there were no differences between the two treatment groups in the clinician-, parent- and teacher-rated assessment after 38 months. The symptoms decreased similarly in both groups. The study has significant methodological flaws:

1. No randomization was carried out and the patients in both groups also had different access routes: The patients treated with behavioral therapy were referred to child and adolescent psychiatry, the psychoanalytically treated patients to a psychiatric treatment facility. In some cases, there are considerable differences in the pre-tests (with more symptomatic patients in the CBT group).
2. No intention-to-treat analysis was performed on n = 73 patients, but rather only on n = 54 children.
3. Behavioral therapy for ADHD/conduct disorder was very short and did not conform to clinical practice guidelines.
4. The effectiveness analyses on n = 54 only had the statistical power to identify large effects.

Therefore, psychoanalytic treatment based on these studies cannot be considered effective. The disorder-specific behavioral therapy programs—carried out in the German-speaking world—have

either been tested in randomized studies or are based on behavioral therapy principles that have been proven successful in international methodologically high-quality studies.

6. German-language prevention and therapy programs for the treatment of ADHD symptoms in adults

The list includes are German-language prevention and therapy programs for managing adults with ADHD symptoms that have proven effective in reducing ADHD symptoms. These studies use methods that are applied in controlled trials (randomized controlled trials or other forms of controlled studies, such as non-randomized trials with control groups, within-subject control group designs) undertaken in the German-speaking countries and internationally. If the therapy program has proven effective in international studies, in the German-speaking world there must be at least one empirical test in a pre-post design.

Evidence of effectiveness of the therapy program in the German version was assessed at the following levels:

- **Low:** At least 1 pre-post study showing significant changes in the course of therapy regarding ADHD symptoms
- **Moderate:** At least 1 controlled study, e.g. non-randomized controlled study, within-subject control group study, published in a peer-reviewed journal, showing significant effects on ADHD symptoms
- **Good:** At least 1 controlled study, published in a peer-reviewed journal showing significant effects on ADHD symptoms
- **Excellent:** Several controlled studies, published in a peer-reviewed journal, showing significant effects on ADHD symptoms in different samples or treatment settings (e.g. outpatient/inpatient) or with evidence of stability; including at least 1 randomized controlled study.

6.1. Psychological therapy manuals

Manual	Annotation	Evidence of effectiveness of the therapy program/References
Baer N, Kirsch P (2010) Training bei ADHS im Erwachsenenalter TADSE. Weinheim: Beltz Verlag	• Cognitive behavioral therapy manual • Setting: Group (can be transferred to the individual setting) • Monofocal approach target group: Individuals with ADHD (10 thematic sessions)	**Evidence of effectiveness:** Low − Nina Haible-Baer (2013) Behandlung der adulten Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung: Wirkung der Einzel- und Kombinationsbehandlung mit einem verhaltenstherapeutischen Gruppentraining und Atomoxetin. Inaugural dissertation for Conferral of a Doctoral Title in Human Biology of the Faculty of Medicine at the Justus Liebig University Giessen. http://geb.uni-giessen.de/geb/volltexte/2013/10326/pdf/HaibleBaerNina_2013_11_13.pdf
D'Amelio R, Retz W, Philipsen A, Rösler M (Ed.) (2008) Psychoedukation und Coaching bei ADHS im Erwachsenenalter. Guidance manual for patient and family groups. Munich: Urban & Fischer, Series: Im Dialog	• Psychoeducation based on cognitive behavioral therapy • Setting: Group (can be transferred to the individual setting) • Bifocal approach: Instructions for the implementation of interventions for ADHD patients (10 thematic sessions) and family members (9 thematic sessions)	**Evidence of effectiveness:** Good − [Hoxhaj E, Sadohara C, Borel P, D'Amelio R, Sobanski E, Müller H, Feige B, Matthies S & Philipsen A: Mindfulness vs psychoeducation in adult ADHD: a randomized controlled trial. *Eur Arch Psychiatry Clin Neurosci*. 2018 Jun;268(4):321-335. doi: 10.1007/s00406-018-0868-4. Epub 2018 Jan 22.
Hesslinger B, Philipsen A, Richter H (2004) Psychotherapie der ADHD im Erwachsenenalter. Göttingen: Hogrefe, Series: Therapeutische Praxis	• Cognitive behavioral therapy manual as part of DBT therapeutic principles • Setting: Group (can be transferred to the individual setting) • Monofocal approach target group: Individuals with ADHD (13 thematic sessions)	**Evidence of effectiveness:** Excellent − Hesslinger B, van Elst LT, Nyberg E, Dykierek P, Richter H, et al.: Psychotherapy of attention deficit hyperactivity disorder in adults: a pilot study using a structured skills training program. *Eur Arch Psychiatry Clin Neurosci* 2002; 252:177–184. − Philipsen A, Richter H, Peters J, Alm B, Sobanski E, et al.: Structured group psychotherapy in adults with attention deficit hyperactivity disorder. *J Nerv Ment Dis* 2007;195:1013–1019.

Manual	Annotation	Evidence of effectiveness of the therapy program/References
		− Philipsen A, Richter H, Peters J, Alm B, Sobanski E, Colla M et al. Structured Group Psychotherapy in Adults with Attention Deficit Hyperactivity Disorder – Results of an open Multicentre Study. *Journal of Nervous and Mental Disease* 2007*;195 (12):* 1013-1019. − Philipsen A, Graf E, Tebartz van Elst L, Jans T, Warnke A, Hesslinger B, Ebert D, Gerlach M, Matthies S, Colla M, Jacob C, Sobanski E, Alm B, Rösler M, Ihorst G, Gross-Lesch S, Gentschow L, Kis B, Huss M, Lieb K, Schlander M, Berger M. Evaluation of the efficacy and effectiveness of a structured disorder tailored psychotherapy in ADHD in adults: study protocol of a randomized controlled multicentre trial. Atten Defic Hyperact Disord. 2010 Dec; 2 (4): 203-12. doi: 10.1007/s12402-010-0046-7. − Philipsen A, Graf E, Jans T, Matthies S, Borel P, Colla M, Gentschow L, Langner D, Jacob C, Groß-Lesch S, Sobanski E, Alm B, Schumacher-Stien M, Roesler M, Retz W, Retz-Junginger P, Kis B, Abdel-Hamid M, Heinrich V, Huss M, Kornmann C, Bürger A, van Elst LT, Berger M. A randomized controlled multicenter trial on the multimodal treatment of adult attention-deficit hyperactivity disorder: enrollment and characteristics of the study sample. Atten Defic Hyperact Disord. 2014 Mar; 6 (1):35-47. doi: 10.1007/s12402-013-0120-z − Philipsen A, Jans T, Graf E, Matthies S, Borel P, Colla M, Gentschow L, Langner D, Jacob C, Groß-Lesch S, Sobanski E, Alm B, Schumacher-Stien M, Roesler M, Retz W, Retz-Junginger P, Kis B, Abdel-Hamid M, Heinrich V, Huss M, Kornmann C, Bürger A, Perlov E, Ihorst G, Schlander M, Berger M, Tebartz van Elst L; Comparison of Methylphenidate and Psychotherapy in Adult ADHD Study (COMPAS) Consortium. Effects of Group Psychotherapy, Individual Counseling, Methylphenidate, and Placebo in the Treatment of Adult Attention-Deficit/Hyperactivity Disorder: A Randomized Clinical Trial. JAMA Psychiatry. 2015 Dec; 72 (12):1199-210. doi: 10.1001/jamapsychiatry.2015.2146.
Lauth, GW, Minsel WR (2009) ADHS bei Erwachsenen: Diagnostik und Behandlung von Aufmerksamkeits-/Hyperaktivitäts-störungen. Göttingen: Hogrefe, Series: Therapeutische Praxis	• Specific self-help manual based on behavioral therapy for self-help for parents and other caregivers • Age range: Children from 3 to 12 years • Studies partly with parenting	**Evidence of effectiveness**: Low − Lauth GW, Breuer J, Minsel WR: Goal Attainment Scaling in der Ermittlung der Behandlungswirksamkeit bei der behavioralen Therapie von Erwachsenen mit ADHS: Eine Pilotstudie. Z Psychiatr Psychol Psychother 2010;58:45–53. − Lauth, G., Minsel, W. R., & Koch, M. (2015). Responder und Nonresponder in einer ADHS-Therapie von Erwachsenen. Zeitschrift für Psychiatrie, Psychologie

Manual	Annotation	Evidence of effectiveness of the therapy program/References
	booklets that were developed according to Wackelpeter & Trotzkopf.	und Psychotherapie, 63 (1), 39-46.
Safren SA, Perlman CA, Sprich S, Otto MW (2009) Kognitive Verhaltenstherapie der ADHS im Erwachsenenalter. (German editing by E. Sobanski, M. Schumacher-Stien & B. Alm). Berlin: Medizinisch Wissenschaftliche Verlagsgesellschaft	- Cognitive behavioral therapy manual - Setting: Individual (can be converted to the group setting) - Monofocal approach target group: Individuals with ADHD (5 thematic modules, 17 sessions in total)	**Evidence of effectiveness:** Good − Safren SA, Otto MW, Sprich S, Winett CL, Wilens TE, Biederman J: Cognitive-behavioral therapy for ADHD in medication-treated adults with continued symptoms. Behav Res Ther 2005;43: 831-842. − Safren SA, Sprich S, Mimiaga MJ, Surman C, Knouse L, Groves M, Otto MW: Cognitive Behavioral Therapy vs Relaxation With Educational Support for Medication-Treated Adults With ADHD and Persistent Symptoms. 2006; Vogel, CL et al. JAMA. 2010 Aug 25; 304 (8): 875-80.

6.2. Effectiveness of interventions in adults based on depth psychology

In randomized controlled studies, the effectiveness of interventions based on depth psychology/psychoanalysis could not be demonstrated in the areas of prevention or therapy. Therefore, the effectiveness of depth psychological and/or psychoanalytic treatment for ADHD in adulthood cannot currently be assessed. The disorder-specific behavioral therapy programs—carried out in the German-speaking world—have either been tested in randomized studies or are based on behavioral therapy principles that have proved successful in international methodologically high-quality studies.
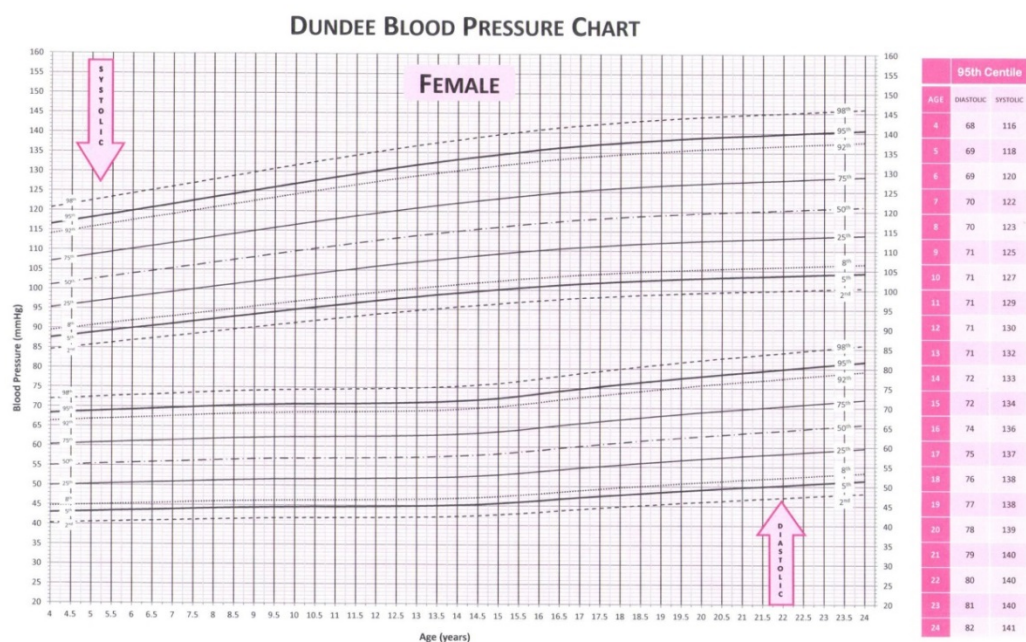
7. Definition of hypertension

(Modified according to Lurbe et al. [476]; Mancia et al. [477]; Pickering et al. [478] – adopted from the Clinical Practice Guidelines for Pediatric Cardiology, Pediatric Nephrology and Pediatrics: Arterial hypertension in childhood and adolescence (AWMF Registry No.: 023/040)

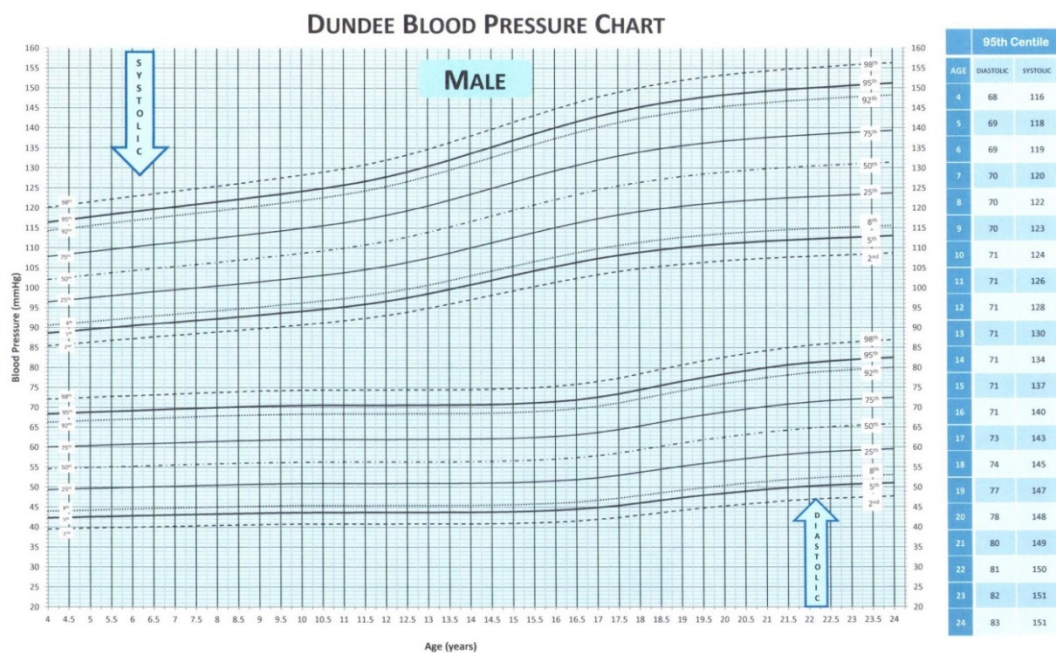|	Children and adolescents: At least 3 single measurements or long-term measurements systolic and/or diastolic	Adults: At least 3 single measurements by auscultation systolic diastolic	Adults: Long-term measurements (daily values) systolic diastolic	Adults: Long-term measurements (nightly values) systolic diastolic
Optimal	Not yet defined	< 120 and < 80	Not yet defined	Not yet defined
Normal	< 90th percentile	< 130 and < 85	< 130 and < 80	Not yet defined
High normal	90th to 94th percentile	130-139 or 85-89	130-134 or 80-84	< 120 and < 70
Hypertension 1*	95th to (99th percentile + 5 mmHg	140-159 or 90-99	≥ 135 or ≥ 85	≥ 120 or ≥ 70
Hypertension 2*	> 99th percentile + 5 mmHg	160-179 or 100-109	Not yet defined	Not yet defined
Hypertension 3*	Not yet defined	≥ 180 or ≥ 110	Not yet defined	Not yet defined

If the adult limit values are exceeded in adolescents, the lower limit value for adults should be selected.

http://www.healthcareimprovementscotland.org/our_work/mental_health/adhd_service_improvement/
stage_3_adhd_final_report.aspx:

Pan H, Cole TJ. LMSgrowth, a Microsoft Excel add-in to access growth references based on the LMS method. Version 2.74. http://www.healthforallchildren.co.uk/; 2011.

Pan H, Cole TJ. LMSgrowth, a Microsoft Excel add-in to access growth references based on the LMS method. Version 2.74. http://www.healthforallchildren.co.uk/; 2011.

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8. Feedback and dissenting votes

BDN, bkj, BVDN, BVDP, BVKJ, bvvp and DGPs have requested dissenting votes because at certain points they cannot support the general consensus of the professional societies and associations involved. According to the regulations of the Working Group of the Association of the Scientific Medical Societies (AWMF), these dissenting votes can be included in the Practice Guideline. These dissenting votes do not reflect the general consensus of the professional societies and associations involved. The received dissenting votes can be found below.

8.1. Dissenting vote from the BVDN and BVDP

Dissenting vote on point 1.1.2 "Who should carry out ADHD diagnostic tests?", wording:

According to the current Model Regulations on Continuing Medical Education of the German Medical Association, which recognizes the competence of specialists in psychiatry and psychotherapy to treat children and adolescents as well, a specialist in psychiatry, psychiatry or psychotherapy or a neurologist with training and expertise in diagnosing ADHD is also allowed to render ADHD diagnostics on older children and adolescents.

Reasoning for the dissenting vote:

1. Particularly in illnesses that tend to manifest over the entire life span of many individuals, any specialty boundaries should not be seen as inviolable, but rather integrate those involved in care beyond age limits.

2. This includes the field of psychiatry subject to the German Regulations on Continuing Medical Education (M-WBO) which knows no "downwards" age limit. Unfortunately, there are no child and adolescent psychiatrists in many rural regions. Here, child and adolescent psychiatric care must be provided by specialists in psychiatry and psychotherapy or neurologists, if necessary. As a further argument, we would also like to mention that for reasons of care provided by physicians under contract with the GKV—unlike in inpatient care—specialists in child and adolescent psychiatry and psychotherapy are allowed to treat their patients up to the age of 21.

3. The Practice Guideline classification aims to list the evidence and the evidence level for a guideline recommendation. This should take into account the real care scenarios, which on the one hand should not be firmly enshrined, while on the other hand, implementation barriers must not go unmentioned. For the content under point 1.1.2, there is only the lowest level of evidence for the expert consensus. The group of privately practicing psychiatrists and neurologists were in a

numerical minority and outvoted in the consensus process. However, together with the child and adolescent psychiatrists, child and adolescent psychotherapists in private practice, this group of privately practicing psychiatrists and neurologists provide at least 90 percent of outpatient care. Here, it is solely about ensuring good care on the basis of scientifically justified evidence.

4. Lastly, in particular with regard to the pressing problem of transition, the exclusion of these specialist groups for diagnosing and treating older children and adolescents is counterproductive.

5. In the conference on May 8, 2017, the repeated reminder that "it only involves a "should" recommendation" with a deviation potential of 40% is not helpful in our view, because the care provision is not about "deviation potentials" that will hardly be statistically detectable, but rather the effect that is achieved through such a statement is key. This seems particularly questionable given the level of evidence available (expert consensus).

Steering Committee commentary on the dissenting vote:

The still currently valid (model) regulations on continuing medical education of the German Medical Association are merely recommendatory in nature when applied to the state medical associations. Each physician is only legally bound by the regulations on continuing medical education governing the state medical association of which he is a member. In general, the regulations on continuing medical education of the state medical associations do not mandate continuing medical education periods in the fields of child and adolescent psychiatry, psychotherapy or pediatrics.

8.2.   Dissenting votes by the BVKJ
Dissenting vote 1 to 1.2.2. "How should the treatment be planned?" Point 3, wording:
Pharmacotherapy should not be given before the age of five. In this age group, recommended non-pharmacotherapeutic options such as parent training should be fully utilized.

Reasoning for the dissenting vote:
The empirical findings, in particular the long-term benefits of pharmacotherapy, are inadequate and the effects on further development are not foreseeable. Furthermore, the Practice Guideline does not specify what expertise the physician has in conduct disorders in this age group. Methylphenidate is on average less effective in preschool children with AHDS with more side effects being reported as well (Practice Guideline Long Version 2.4.3.1.1 p. 123).

Steering Committee commentary on the dissenting vote:

The present clinical practice guidelines primarily recommend psychosocial (including psychotherapeutic) interventions for children prior to the age of 6 years. Only if these have not proven to be sufficiently effective (i.e. after non-pharmacotherapeutic options have been exhausted), pharmacotherapy is recommended in individual cases with residual ADHD symptoms *requiring treatment* after careful individual risk-benefit assessment (but not in children under 3 years). Pharmacotherapy may be indicated in such cases given that pharmacotherapy has generally proven to be superior to psychosocial interventions/behavioral therapy, at least as in short-term outcomes, even in preschool children. The adverse effects of pharmacotherapy on weight and growth can, in individual cases, be easily controlled. Based on current study data, the effects of pharmacotherapy on brain development in children of pre-school age is thought to be rather favorable. In general, the benefits from pharmacotherapy and psychotherapy are not well documented regarding the long-term effects. Moreover, not treating pronounced symptoms is also associated with considerable risks. Based on current evidence, NICE [188] recommends that pharmacotherapy should not be offered to children before the age of *five* years (not six) without a second opinion from a specialist in the treatment of children with ADHD in this age range.

Dissenting vote 2 to 1.2.2. "How should the treatment be planned?" Point 3, wording:

In ADHD, following extensive psychoeducation, an intensified psychosocial (including psychotherapeutic) intervention should be offered. If these interventions are not sufficiently successful, pharmacotherapy should be offered in combination at an early stage.

Reasoning for the dissenting vote:

In these recommendations, as in the NICE guideline (p. 107) [188], we would like to point out that there is no scientific rationale linking the degree of severity to a treatment recommendation. Even though there is clear empirical evidence for the short-term efficacy of methylphenidate on the symptoms of ADHD, this contrasts with the small number of studies on long-term effects of pharmacotherapy which could not demonstrate a better prognosis for ADHD children treated exclusively with psychostimulants [see MTA study, Cologne multimodal therapy study (Döpfner et al. 2015, 2016 and Schweren et al. 2018)]. Therefore, the recommendation to offer pharmacotherapy alone for children with ADHD of moderate severity is not considered justified. The recommendation to offer medication to those for whom environmental modifications do not have sufficient effects in at least one functional domain is consistent with the long version of the NICE Guideline (p. 107) [188].

Steering Committee commentary on the dissenting vote:

It is true that the current NICE Guideline, in contrast to the previous version, no longer recommends different treatment strategies in relation to the severity grade of ADHD that was based on an expert consensus. If treatment is still indicated after the implementation of the interventions recommended as part of psychoeducation, the current version of NICE now generally recommends pharmacotherapy for ADHD, as in direct comparison, pharmacotherapy is more effective than non-pharmacological interventions [479] with the data from NICE studies showing that combination therapy does not lead to a more significant clinical improvement than monotherapy [479].

In general, the benefits from pharmacotherapy and psychotherapy are not well documented regarding the long-term effects. However, untreated ADHD has considerable risks of wide-ranging, long-term negative effects in the form of functional impairments (see also [188], p 63).

In contrast to the NICE Guideline, the present Practice Guidelines maintain the differentiation of the degree of severity and, based on expert consensus, recommend pharmacotherapy as the primary option only for those who continue to have severe symptoms after completing psychoeducation (as NICE does). However, what is contrary to NICE is that, in patients with moderate symptoms, the treatment can alternatively also be started with psychosocial interventions (including psychotherapeutic interventions) and, if mild symptoms persist after treatment with psychoeducation, then primarily psychosocial interventions (including psychotherapeutic interventions) should be initiated.

Neither does this Practice Guideline recommend offering pharmacotherapy alone to children with moderately severe ADHD. Rather, it is recommended to start with pharmacotherapy or with psychosocial interventions (including psychotherapeutic interventions) and, if they do not lead to a sufficient improvement, to then switch or combine pharmacotherapy and non-pharmacological interventions.

Pharmacotherapy combined with previous and ongoing psychoeducation may be sufficient, because a substantial proportion of patients do not have any further functional limitations or relevant ADHD symptoms whatsoever with these measures. In these cases, additional psychotherapy is not necessary. In other cases where residual ADHD symptoms or functional limitations persist in the course of pharmacotherapy, additional psychotherapy is indicated.

8.3. Dissenting Votes from bkj and bvvp

Dissenting vote 1 to 1.2.2. "How should the treatment be planned?" Point 3, wording:

If residual ADHD symptoms require treatment, additional behavioral or psychodynamic psychotherapy can be considered. Pharmacotherapy should generally be avoided due to its

unpredictable effects on weight, growth and psychosocial development. In severe ADHD, pharmacotherapy can be indicated depending on an individual risk-benefit assessment.

Reasoning for the dissenting vote:

- In children aged three to four years, often the diagnosis cannot be made with enough certainty (page 41 Long Version).
- MPH is an off-label indication for children at the age of 3-6 years; it is also generally less effective in this age range (page 110 Long Version).
- The long-term benefits of pharmacotherapy have not been substantiated.
- The younger the child, the more profound effects pharmacotherapy has on the human brain and mental structures in this vulnerable phase of development, the impact of which has not been adequately investigated.

Steering Committee commentary on the dissenting vote:

Points 3 and 4 recommend primarily psychosocial (including psychotherapeutic) interventions for mild ADHD severity or for children under the age of 6 years. The psychotherapeutic interventions also include comprehensive behavioral therapeutic approaches that are evidence-based. If these are not effective, pharmacotherapy is recommended in individual cases in the presence of residual ADHD symptoms requiring treatment (but not in children under 3 years of age). In such cases, further intense psychotherapy is not considered useful if comprehensive behavioral therapy has not been sufficiently effective. Psychodynamic psychotherapy is not recommended as it is not sufficiently evidence-based. Pharmacotherapy may be indicated in such cases given that pharmacotherapy has generally proven to be superior to psychosocial interventions/behavioral therapy, at least as in short-term outcomes, even in preschool children. The adverse effects of pharmacotherapy on weight and growth can, in individual cases, be easily controlled. In general, the benefits from pharmacotherapy and psychotherapy are not well documented regarding the long-term effects. However, the benefits of long-term therapy can be examined in individual cases.

Dissenting vote 2 to 1.22. "How should the treatment be planned?" Point 5, wording:

In moderate ADHD, intensive psychosocial (including intensive psychotherapeutic) intervention should be offered after having completed comprehensive psychoeducation. In cases of marked functional limitations, pharmacotherapy can be offered if residual ADHD symptoms of moderate severity still require treatment after other treatment options have been exhausted.

Reasoning:

In moderate severity, reference is presumably made to the degree of severity described in the long version as **"moderate".** A uniform nomenclature should be used to avoid misinterpretation**.** It states: "The severity of symptoms and functional impairments range between 'mild' and 'severe', i.e. despite only mild symptoms, the symptoms result in a clear functional impairment or, despite only a current presentation of minor impairments in the domains of social, academic or occupational functioning, the symptoms present are clearly in excess of those required for rendering the diagnosis.

When considering pharmacotherapy at school age, it is not the symptoms (which may mainly affect those around the person) but the degree of functional impairment (which is decisive with regard to the developmental restrictions of the affected child) that is decisive for the indication of pharmacotherapy. Due to unpredictable undesirable effects of early medication, it is important to assess on an individual basis whether psychotherapy is initially indicated after completing extensive psychoeducation and an intensive psychosocial intervention.

Steering Committee commentary on the dissenting vote:

If pharmacotherapy is indicated, both the symptom severity and the degree of functional impairment should be taken into account, as severe symptoms, regardless of the functional impairment, are unfavorable as a prognosis for the child's further development. The adverse effects of ADHD medication have been extensively reviewed and can therefore be easily predicted. In moderate symptoms, based on empirical evidence, no clear recommendation for behavioral therapy or pharmacotherapy can be given, so both treatment methods are open.

Dissenting vote 3 to 1.2.2. "How should the treatment be planned?" Point 6, wording:

In severe ADHD, pharmacotherapy should primarily be offered after intensive psychoeducation. Concomitant intensive psychosocial (including psychotherapeutic) interventions can be integrated into pharmacotherapy.

Steering Committee commentary on the dissenting vote:

No reasoning is available for this dissenting vote. Pharmacotherapy combined with previous and ongoing psychoeducation may be sufficient, because a substantial proportion of patients do not have any further functional limitations or relevant ADHD symptoms whatsoever with these measures. In these cases, additional psychotherapy is not necessary. Adjuvant psychotherapy is indicated in other instances where residual ADHD symptoms or functional limitations persist over the course of pharmacotherapy.

Dissenting vote 4 to 1.3.1.2.1. "Which psychosocial (including psychotherapeutic) interventions should be used in preschool children with ADHD (aged approx. three to six years)?" point 1.3.1.2.1.1., wording:

Addendum: Initially, contributing factors in the psychosocial environment should be considered in the differential diagnosis, so that current stress reactions due to problematic environmental conditions are recognized and children's behavior is not pathologized as index patients.

Reasoning:

The diagnosis of ADHD is based on the described symptoms. This additional note should emphasize the fact that it is imperative to rule out reactive symptoms due to stressful environmental factors so that the child is not falsely pathologized. Furthermore, in addition to the initial diagnostic process, the possibility of such a scenario must be considered, as caregivers can intentionally or unintentionally disguise their contribution to the development of symptoms. Long-term symptom reduction can only be achieved with an understanding of how the symptoms develop.

Addendum: If there are intense psychosocial and environmental stresses and signs of pathological family structures, the indication for extensive behavioral therapeutic or psychodynamic psychotherapy should be examined.

Reasoning:

It may be necessary to offer psychotherapy in order to achieve long-term treatment benefits as well.

Steering Committee commentary on the dissenting vote:

It has been already stated in the recommendations (1.1.3) that, in the context of the diagnostic process, amongst others, current and previous framework conditions, resources and burdens as well as coexisting psychological symptoms or disorders should be recorded. Current stress reactions as well as other mental disorders must be differentiated diagnostically. It is also explicitly stated that all diagnostic criteria must be met in order to reach the diagnosis (1.1), as the core symptoms of attention-deficit disorder, motor agitation and increased impulsivity in ADHD can also be based on other disorders. In recommendation (1.2.2.), it is generally emphasized that coexisting symptoms or disorders require appropriate treatment. Psychosocial interventions can be aimed directly at the patient or caregivers or can also include the patient's immediate or wider environment (see definition of psychosocial interventions).

Dissenting vote 5 to 1.3.1.2.5. "Under what conditions should child-centered interventions be delivered in preschool children with ADHD and which child-centered interventions are recommended?", wording:

Psychodynamic-based psychotherapy interventions can also be used. It can be carried out according to the manual for psychoanalytic-psychotherapeutic treatment in children with psychosocial integration problems, especially hyperkinetic disorder/ADHD (Staufenberg 2011) (see Appendix III.5.2.).

Reasoning:

For decades, performance audits within the scope of expert reviews have shown that psychodynamic methods are effective for managing ADHD.

Addendum: In the case of other coexisting disorders, in particular disorders of emotional development, other developmental disorders, traumatic stress and behavioral abnormalities, the indication of a more extensive behavioral therapy or psychodynamic psychotherapy (for coping with new developmental challenges, trauma processing, handling conflicts and relationship disorders) should be examined.

Reasoning behind the addendum:

In preschool age, ADHD cannot be diagnosed with certainty, especially if symptoms are mild due to varying development levels in children. On the other hand, disorders that can mimic ADHD symptoms, and especially more complex disorders, are treated with psychotherapy to prevent chronification.

Steering Committee commentary:

Based on the studies available to date, the Steering Committee classified the evidence for effectiveness of the Staufenberg manual (2011) as "low" (see Appendix III.5.2.).

The reference to coexisting disorders applies to all age groups. For this reason, recommendations II.1.1.10 and II.1.2.2 highlight, in general, that coexisting symptoms or disorders require appropriate (psychotherapeutic or pharmacological) treatment.

Dissenting vote 6 to 1.3.1.3.1. "Which psychosocial (including psychotherapeutic) interventions should be performed in school-aged children and adolescents with ADHD and mild to moderate functional impairment?" Point 1.3.1.3.1.3, wording:

Psychodynamic-based psychotherapy interventions can also be used. They can be carried out according to the manual on psychoanalytic-psychotherapeutic management of children with psychosocial integration problems, especially hyperkinetic disorder/ADHD (Staufenberg, 2011) (see Appendix III.5.2.).

Reasoning for the dissenting vote:

For decades, performance audits within the scope of expert reviews have shown that psychodynamic methods are effective for managing ADHD.

Steering Committee commentary on the dissenting vote:

Based on the studies available to date, the Steering Committee classified the evidence for effectiveness of the Staufenberg manual (2011) as "low" (see Appendix III.5.2.).

Dissenting vote 7 to 1.3.1.3.6. "Which psychosocial (including psychotherapeutic) interventions should be carried out in children and adolescents with ADHD and moderate to severe functional impairments starting at school age?" wording:

Addendum: If psychosocial interventions have not proven to be sufficiently effective or if the overall problem of coexisting disorders or residual associated symptoms after pharmacotherapy has proven to be inadequate, the indication for a more extensive behavioral therapy or psychodynamic psychotherapy should be explicitly examined.

Reasoning:

It must be emphasized that psychotherapeutic treatment in particular is necessary for complex disorders and pronounced functional limitations.

Steering Committee commentary on the dissenting vote:

It has been already stated in the recommendations (1.2.2) that psychosocial (including psychotherapeutic) interventions should be offered to manage residual ADHD symptoms requiring

treatment in patients who have completed pharmacotherapy, while coexisting disorders should be treated in accordance with the practice guidelines.

Dissenting vote 8 to 1.3.1.4.3. "What psychosocial interventions should be used in adults with ADHD?" Point 1.3.1.4.3.2. , wording:

Psychodynamic-based psychotherapy interventions can also be used.

Reasoning for the dissenting vote:

For decades, performance audits within the scope of expert reviews have shown that psychodynamic methods are effective for managing ADHD.

8.4. Dissenting vote by DGPs dated 19 February 2018

Dissenting vote on 1.1.3 "Which diagnostic measures should be deployed routinely", wording:

However, the DGPs points out that important scientific findings on the methodology and *process of data collection* were not taken into account. However, this is meaningful as the rationale for therapeutic decision-making and recommendations relies on diagnoses. Scientific evidence shows that the use of standardized and/or structured surveys (clinical interviews/checklists) based on ICD or DSM significantly increases the reliability of the diagnosis and differential diagnosis. If possible, a structured *clinical* assessment should be included in the diagnostic process.

Rationale for the vote from the DGPs

Reliable and valid diagnostic tests are a prerequisite in order to make responsible treatment decisions for the benefit of the patient. An S3 clinical practice guideline should therefore include evidence-based decisions about the *process* of data collection in the diagnosis of ADHD.

In summary, the use of structured clinical interviews/checklists is justified as follows:

- Structured clinical interviews/checklists carried out by (trained) clinical experts prevent bias in the diagnostic process.
- Structured clinical interviews/checklists show better reliability values than unstructured clinical explorations.
- Structured clinical interviews/checklists are economical and have a high level of acceptance among patients of all ages.
- Structured clinical interviews/checklists ensure that patients from treatment studies are comparable to patients in routine clinical care.

(1) Rosenhan's studies [480] using experimental methods have already shown clearly that people (and diagnosticians) are susceptible to bias. In cognitive psychology, the two cognitive psychologists and Nobel Prize Laureates Kahneman and Tversky have, in their experimental studies, systematically worked through the advantages and disadvantages of data-based vs. heuristic decision making [481, 482]. Some studies even show that experts are particularly susceptible to cognitive bias and prefer heuristic rather than data-based recording of findings [483]. In medical and clinical-psychological settings, however, judgment bias can have serious consequences as it can lead to the erroneous decisions when rendering the diagnosis. In professions such as pilots where the aim is to prevent serious human errors, the use of checklists is therefore an absolute standard and completely independent of the pilot's experience. Clinical studies show that the use of checklists/structured interviews significantly reduces the number of misdiagnoses [484].

(2) Extensive work in the field of diagnosis of mental disorders shows that

(a) An unstructured clinical judgment ("comprehensive exploration") is unreliable [485-488]

(b) A structured *clinical* interview shows good to very good reliability values [489-492]

(c) The agreement between clinical judgment and structured clinical questioning is insufficient [485-487, 493-495]. In a meta-analysis [487] on the agreement between clinical judgment ("comprehensive exploration") and standardized clinical interviews, which are considered the gold standard for research and without which study results are more or less impossible to publish, on average Kappa values of .27 are achieved (38 articles from 1995-2006; n = 15,967; Kappa for internalizing disorders = .28; for externalizing = .29; for ADHD = .49). Kappa values above .75 are considered satisfactory.

(3) Structured clinical interviews ensure the recording of comorbid disorders, the degree of severity and the functional limitations (see commentary on recommendation 1.1.5), so that the factor of test economy is also applied and unnecessary, for example, the use of numerous other questionnaires for recording comorbid problems or other methods for recording the level of severity can be avoided. Furthermore, structured clinical interviews show a high level of acceptance among children, adolescents and adults, and are therefore an efficient and accepted form of diagnostic data collection [496-500].

(4) As a result of this, methodically sound treatment studies only include patients in the study if the primary diagnosis has been confirmed with a structured clinical interview. The transferability of the

treatment study results to routine care requires that the same diagnostic procedures be used in order to ensure the comparability of patient groups.

(5) There are a number of studies on ADHD that spotlight the problem of overdiagnosis of this disorder. A summary of the various studies makes it clear that an overdiagnosis of ADHD must be assumed. An overview of this issue summarizes the current study situation and discusses factors that are responsible for misdiagnoses [501]. Factors such as non-systematic exploration of the symptoms of ADHD [502], insufficient knowledge of the diagnostic criteria or the developmental psychology of the core symptoms seem to play an important role in the overdiagnosis of ADHD.

Steering Committee commentary:

In its dissenting vote, the DGPs recommends that, if possible, a structured assessment should be carried out using standardized/structured clinical interviews or checklists.

The introduction to the recommendations for diagnostics (Section 1.1) refers to a structured assessment and exploration: "In order to reach an ADHD diagnosis, the symptoms of hyperactivity, impulsivity and/or inattention must meet the criteria of ICD-10 or DSM-5." Using structured interviews or checklists (e.g. from DISYPS-III [172]) can be helpful. From the Steering Committee's point of view, the following points, however, speak against the inclusion of a corresponding recommendation of such procedures within the Practice Guideline:

1. Although studies have shown a higher inter-rater reliability of diagnoses based on structured interviews, but usually only after extensive rater training. This cannot be realistically guaranteed in the context of standard care (especially in the area of private practice). A new meta-analysis on the test-retest reliability of structured interviews [503] also questions the usefulness of structured interviews to record mental disorders in children and adolescents.
2. The diagnoses in routine clinical care are oriented towards ICD-10 clinical diagnostic criteria. However, the structured interviews and diagnostic checklists are based on ICD-10 research criteria or DSM-5 criteria, which require clearer and higher cut-offs for making a diagnosis. In this respect, the unquestioned use of structured interviews can also lead to increased misdiagnoses (in the sense of the significantly more flexible clinical-diagnostic criteria based on ICD-10). This can lead to false positive as well as false negative diagnostic assessments. The cited studies [e.g. 484], which are intended to show that the rate of misdiagnoses using structured interviews is lower than without using these tools, are questionable because they use the ICD-10 research criteria, respectively the operationalized DSM-5 criteria, as the gold standard.
3. In addition, the clinical-diagnostic assessment compared to the structured diagnosis, based on interviews designed almost exclusively as layperson interviews for research, enables the integration

of various information sources, the consideration of differential diagnostic aspects and the differentiation of comorbid disorders more effectively.

4. The argument that structured interviews/checklists can be used to make comparisons with therapy studies is not valid because it requires research to be brought closer to clinical practice (e.g. via studies on effectiveness in routine care, see e.g. Walter et al., [504]) and not vice versa, that only patients who meet the criteria of research should be treated.

5. The aforementioned general overdiagnosis of ADHD cannot be explained as the prevalence rates from epidemiological studies are significantly higher than the administrative prevalence rates from health insurance company studies [505].

The methods described can be a helpful in diagnostic add-ons under certain circumstances (especially if one is not familiar with diagnostic criteria). Although set against the backdrop of weak empirical evidence, expected higher costs, the divergence between clinical and research criteria as well as questionable additional benefits, the Steering Committee believes that no general recommendation can be derived from this.

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Versions-Nummer: **version number:**	**5.0**
Erstveröffentlichung: **Initial release:**	**05/2017**
Nächste Überprüfung geplant: **Review planned:**	**05/2022**