ADHD AND MEDICATION

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Attention deficit hyperactivity disorder (ADHD) has become treatable with medication and psychotherapeutic approaches that have become available recently. This article provides a brief overview of some aspects of the medication used for ADHD.

The most widely used group of medication for ADHD comprises the stimulants. Stimulants such as methylphenidate and amphetamine are currently the most common treatment for ADHD. The substance used should fit the particular individual and the particular condition and situation.

Open and transparent communication between clinician and patient is of paramount importance in the case of ADHD for a successful treatment outcome.

Keywords: ADHD, attention deficit hyperactivity disorder, medication, psychiatry

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Introduction

The use of medications to treat attention deficit hyperactivity disorder (ADHD) has increased. Using a common protocol and data from thirteen countries and one SAR, Raman and colleagues show increases over time but large variations in ADHD medication use in multiple regions across the world. (Raman et al., 2018)

While medication is effective, one needs to keep in mind that most mental health conditions, and particularly ADHD, is maintained not only by neurobiology, but also by psychological and environmental and social patterns. Most patients would thus benefit from a combined approach. Safren and colleagues, for example, studied cognitive-behavioral therapy (CBT) for adults with attention-deficit hyperactivity disorder (ADHD) who have been stabilized on medications but still show clinically significant symptoms. The data showed that CBT for adults with ADHD with residual symptoms is a feasible, acceptable, and potentially efficacious next-step treatment approach, worthy of further testing. (Safren et al., 2005)

The most widely used class of medication for ADHD is the group of stimulants, including methylphenidate and other substances. For years, it was assumed that stimulants had paradoxical calming effects in ADHD patients, whereas stimulating 'normal' individuals and producing locomotor activation in rats. It is now known that low doses of stimulants focus attention and improve executive function in both normal and ADHD subjects. Stimulants are frequently used to treat attention deficit-hyperactivity disorder. A stimulant is a drug that stimulates the central nervous system, increasing arousal, attention and endurance. Because the medications can be addictive, patients with a history of drug abuse are typically monitored closely or treated with a non-stimulant. It is argued that the risk of addiction in patients diagnosed with ADHD is much lower.

The Prefrontal Cortex

At low doses that improve prefrontal cortex-dependent cognitive function and that are devoid of locomotor-activating effects, methylphenidate substantially increases norepinephrine and dopamine efflux within the prefrontal cortex. In contrast, outside the prefrontal cortex these doses of methylphenidate have minimal impact on norepinephrine and dopamine efflux. (Berridge et al., 2006) The prefrontal cortex regulates behavior and attention using representational knowledge, and imaging and neuropsychological studies have shown that the prefrontal cortex is weaker in subjects with ADHD. This cortical area is very sensitive to levels of catecholamines: moderate levels engage postsynaptic α2A-adrenoceptors and D1 receptors and improve prefrontal regulation of behavior and attention, while high levels impair prefrontal function via α1-adrenoceptors and excessive D1 receptor stimulation. Administering low doses of

methylphenidate to rats improves the working memory and attentional functions of the prefrontal cortex, while high doses impair working memory and produce a perseverative pattern of errors similar to that seen in patients. The low dose improvement is hiocked by either an α2-adrenoceptor or Dl receptor antagonist, suggesting that both norepinephrine and dopamine contribute to the beneficial actions of stimulant medications. (Arnsten, 2006)

Substance Abuse

Chang and colleagues found no indication of increased risks of substance abuse among individuals prescribed stimulant ADHD medication; if anything, the data suggested a long-term protective effect on substance abuse. Although stimulant ADHD medication does not seem to increase the risk for substance abuse, clinicians should remain alert to the potential problem of stimulant misuse and diversion in ADHD patients. (Chang et al., 2014)

In a survey study by McCabe and colleagues, misusers were more likely than nonmisusers to divert their controlled medications and to abuse other substances. The odds of a positive screening result for drug abuse were substantially higher among medical misusers compared with medical users who used their controlled medications appropriately. The odds of drug abuse did not differ between medical users who used their controlled medications appropriately and nonusers. Conclusions Most adolescents who used controlled medications took their medications appropriately. Substance use and diversion of controlled medications were more prevalent among adolescents who misused their controlled medications. Careful therapeutic monitoring could reduce medical misuse and diversion of controlled medications among adolescents. (McCabe et al., 2011)

In a literature review by Torgersen and colleagues psychopharmacotherapy did not seem to have an effect on substance use disorder. (Torgersen, Gjervan, & Rasmussen, 2008) However, it is also important to keep in mind the risk of untreated ADHD. Empirical data indicates that ADHD is a significant risk factor for the development of SUDs and cigarette smoking in both sexes. (Wilens et al., 2011)

Psychotherapy

Psychotherapy should usually be combined with medication in ADHD. The author has described communication-focused therapy for ADHD elsewhere. (Haverkampf, 2010, 2017c, 2018b)

Social

The social and environmental aspects are often underestimated in the case of ADHD. Pfiffner and colleagues evaluated in their study the efficacy of the Child Life and Attention Skills (CLAS) program, a behavioral psychosocial treatment integrated across home and school, for youth with attention-deficit/hyperactivity disorder-inattentive type (ADHD-I). CLAS resulted in greater improvements in teacher-reported inattention, organizational skills, social skills, and global functioning relative to both PFT and TAU at posttreatment. Parents of children in CLAS reported greater improvement in organizational skills than PFT and greater improvements on all outcomes relative to TAU at posttreatment. Differences between CLAS and TAU were

maintained at follow-up for most parent-reported measures but were not significant for teacher-reported outcomes. Direct involvement of teachers and children in CLAS appears to amplify effects at school and home and underscores the importance of coordinating parent, teacher, and child treatment components for cross-setting effects on symptoms and impairment associated with ADHD-I. (Pfiffner et al., 2014)

There are also several psychological models that have been helpful in the treatment of adults. Solanto and colleagues assessed the effectiveness of a new manualized group Meta-Cognitive Therapy (MCT) for adults with ADHD that extends the principles and practices of cognitive-behavioral therapy to the development of executive self-management skills in thirty patients. General linear modeling revealed a robust significant posttreatment decline on the CAARS DSM-IV Inattentive symptom scale as well as improvement on the Brown ADD Scales. The findings indicated that participants in the MCT program showed marked improvement with respect to core ADHD symptoms of inattention, as well as executive functioning skills, suggesting that this program has promise as a treatment for meta-cognitive deficits in adults with ADHD. (Solanto, Marks, Mitchell, Wasserstein, & Kofman, 2008)

Charach and colleagues in a review of the literature between 1980 and 2010. The available evidence suggested that underlying prevalence of ADHD varies less than rates of diagnosis and treatment. Patterns of diagnosis and treatment appeared to be associated with such factors as locale, time period, and patient or provider characteristics. The strength of evidence for parent behavior training as the first-line intervention for improved behavior among preschoolers at risk for ADHD was high, while the strength of evidence for methylphenidate for improved behavior among preschoolers was low. Evidence regarding long-term outcomes following interventions for ADHD was sparse among persons of all ages, and therefore inconclusive, with one exception. Primary school–age children, mostly boys with ADHD combined type, showed improvements in symptomatic behavior maintained for 12 to 14 months using pharmacological agents, specifically methylphenidate medication management or atomoxetine. (A Charach et al., 2011)

Diagnosis of ADHD

The clinical interview is the most important pillar in the process of diagnosing ADHD. Reflecting on the interaction with the patients and observing the communication patterns used is very helpful in the diagnosis and in the treatment of ADHD.

There is also the overall problem in the case of ADHD that, while the diagnostic criteria in the diagnostic manuals are quite clear, it may sometimes be diagnosed based on the individual heuristic criteria the therapist has developed over time. Since attention deficit can occur in several disorders and is not as pathognomonic as, for example, feeling depressed or anxious for depression and anxiety, respectively, it takes more complex algorithms to formulate a diagnosis. However, there still seem to be problems, which, however, are not uncommon in psychiatric diagnosis. The accuracy itself even seems to depend on the diagnosis. For some diagnoses, especially psychotic categories, administrative data were generally predictive of true diagnosis. For others, such as anxiety disorders, the data were less satisfactory. (Davis, Sudlow, & Hotopf, 2016)

Different Types of ADHD

ADHD is to a certain degree heterogeneous which can have a n efefct of how well a particular treatment modality or even a specific treatment works. Unfortunately, there are not many clear parameters that can help to optimize treatment. However, in speical circumstances there may be information available that can be helpful in designing a treatment plan.

1. ADHD, Predominantly Inattentive Presentation (ADHD-I)

   Patients have difficulty paying attention. They are easily distracted but do not have significant symptoms of impulsivity or hyperactivity. This is sometimes called attention-deficit disorder (or ADD).

2. ADHD, Predominantly Hyperactive-Impulsive Presentation (ADHD-H)

   Patients who have this type of ADHD have symptoms of hyperactivity and feel the need to move constantly. They also struggle with impulse control. Inattention is not a significant issue. This type is seen most often in very young children.

3. ADHD, Combined Presentation (ADHD-C)

   Patients with this type of ADHD show significant problems with both hyperactivity/impulsivity and inattention. Children may gradually have less trouble with hyperactivity/impulsivity as they get into their teen years.

In a study by Mullins and colleagues, children with ADHD varied more in the size and direction of their time reproduction errors than control children. Those with ADHD-C demonstrated more intraindividual variability than did those with ADHD-I in the size of their errors. The data provided support for a relationship between sustained attention and time reproduction.(Mullins, Bellgrove, Gill, & Robertson, 2005)

EEG

Arns and colleagues demonstrated in their study that the EEG phenotypes as described by Johnstone, Gunkelman & Lunt are identifiable EEG patterns with good inter-rater reliability. Furthermore, it was also demonstrated that these EEG phenotypes occurred in both ADHD subjects as well as healthy control subjects. The Frontal Slow and Slowed Alpha Peak Frequency and the Low Voltage EEG phenotype discriminated ADHD subjects best from controls (however the difference was not significant). The Frontal Slow group responded to a stimulant with a clinically relevant decreased number of false negative errors on the CPT. The Frontal Slow and Slowed Alpha Peak Frequency phenotypes have different etiologies as evidenced by the treatment response to stimulants. In previous research Slowed Alpha Peak Frequency has most likely erroneously shown up as a frontal theta sub-group. Furthermore, the divergence from normal of the frequency bands pertaining to the various phenotypes is greater in the clinical group than in the controls. Investigating EEG phenotypes provides a promising new way to approach EEG data, explaining much of the variance in EEGs and thereby potentially leading to more specific prospective treatment outcomes. (ARNS, GUNKELMAN, BRETELER, & SPRONK, 2008)

Diagnosis of ADHD in Children

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder of childhood and can profoundly affect the academic achievement, well-being, and social interactions of children; the American Academy of Pediatrics first published clinical recommendations for the diagnosis and evaluation of ADHD in children in 2000; recommendations for treatment followed in 2001. (American Academy of Pediatrics, 2000)

Bruchmüller and colleagues sent a case vignette to 1,000 child psychologists, psychiatrists, and social workers and asked them to give a diagnosis. The results were that in the non-ADHD vignettes, 16.7% of therapists diagnosed ADHD. In the boy version of these vignettes, therapists diagnosed ADHD around 2 times more than they did with the girl vignettes. Their study suggested that there may be an overdiagnosis of ADHD and that the patient's gender influences diagnosis considerably. (Bruchmüller, Margraf, & Schneider, 2012) It is unclear whether the problem is that therapists do not adhere enough to diagnostic manuals and diagnostic criteria, or if there are other factors, such as issues with the diagnostic criteria or diagnostic algorithms. Another explanation could be that a significant amount of information gets lost in the interaction with the patient. Especially, if the time allowed for the meeting is very limited, there is the risk of both over- and underdiagnosis where maybe several other issues are involved, such as trauma, anxiety or depression, for example.

This guideline has been developed to advise on the treatment and management of attention deficit hyperactivity disorder (ADHD). The guideline recommendations have been developed by a multidisciplinary team of healthcare professionals, service users and carers, and guideline methodologists after careful consideration of the best available evidence. It is intended that the guideline will be useful to clinicians and service commissioners in providing and planning high-quality care for people with ADHD while also emphasizing the importance of the experience of care for them and their carers (see Appendix 1 for more details on the scope of the guideline). Although the evidence base is rapidly expanding, there are a number of major gaps; future revisions of this guideline will incorporate new scientific evidence as it develops. The guideline makes a number of research recommendations specifically to address gaps in the evidence base. In the meantime, it is hoped that the guideline will assist clinicians, people with ADHD and their carers by identifying the merits of particular treatment approaches where the evidence from research and clinical experience exists. ((UK, 2018)

While the disorder continues to be viewed as one of inattention and/or hyperactive-impulsive behavior, theories of ADHD are beginning to focus more on poor inhibition and deficient executive functioning (self-regulation) as being central to the disorder. Clinicians should be aware of these problems and the adjustments that need to be made to them when dealing with special populations that were not represented in the field trials used to develop these criteria. (Barkley, 2003)

Kadesjo and Gillberg examined patterns of comorbid/associated diagnoses and associated problems in a population sample of children with and without DSM-III-R attention-deficit hyperactivity disorder (ADHD). Half (N = 409) of a mainstream school population of Swedish 7-year-olds were clinically examined, and parents and teachers were interviewed and completed questionnaires. The children were followed up 2–4 years later. Eighty-seven per cent of children meeting full criteria for ADHD (N = 15) had one or more—and 67% at least two—comorbid diagnoses. The most common comorbidities were oppositional defiant disorder and developmental coordination disorder. Children with subthreshold ADHD (N = 42) also had very

high rates of comorbid diagnoses (71% and 36%), whereas those without ADHD (N = 352) had much lower rates (17% and 3%). The rate of associated school adjustment, learning, and behavior problems at follow-up was very high in the ADHD groups. We concluded that pure ADHD is rare even in a general population sample. Thus, studies reporting on ADHD cases without comorbidity probably refer to highly atypical samples. By and large, such studies cannot inform rational clinical decisions. (Kadesjö & Gillberg, 2001)

Stability over Time

Children rarely remain in the HT classification over time; rather, they sometimes desist from ADHD but mostly shift to CT in later years. In a study on a sample of 118 4- to 6-year-olds who met DSM-IV criteria for ADHD, Lahey and colleagues showed that the number of children who met criteria for ADHD declined over time, but most persisted. Children who met criteria for the combined subtype (CT, n = 83) met criteria for ADHD in more subsequent assessments than children in the predominantly hyperactive-impulsive subtype (HT, n = 23). Thirty-one (37%) of 83 CT children and 6 (50%) of 12 children in the predominantly inattentive subtype (IT) met criteria for a different subtype at least twice in the next 6 assessments. Children of the HT subtype were even more likely to shift to a different subtype over time, with HT children who persisted in ADHD mostly shifting to CT in later assessments. The subtypes exhibited consistently different mean levels of hyperactive-impulsive symptoms during years 2 through 8 that corresponded with their initial subtype classifications, but initial subtype differences in inattention symptoms diminished in later years. Conclusions In younger children, the CT and IT may be stable enough to segregate groups for research, but they seem too unstable for use in the clinical assessment of individual children. (Lahey, Pelham, Loney, Lee, & Willcutt, 2005) The authors suggested a continuous hyperactivity-impulsivity rating model in the diagnosis.

Adult ADHD

The diagnosis of attention-deficit hyperactivity disorder (ADHD) in adults is a complex procedure which should include retrospective assessment of childhood ADHD symptoms either by patient recall or third party information, diagnostic criteria according to DSM-IV, current adult ADHD psychopathology including symptom severity and pervasiveness, functional impairment, quality of life and comorbidity. The author has discussed the diagnosis of adult ADHD in greater depth elsewhere. (Haverkampf, 2018c)

A valid and reliable assessment should be comprehensive and include the use of symptom rating scales, a clinical interview, neuropsychological testing, and the corroboration of patient reports. Specific diagnostic criteria that are more sensitive and specific to adult functioning are needed. In treatment, pharmacological interventions have the most empirical support, with the stimulants methylphenidate and amphetamine and the antidepressants desipramine and atomoxetine having the highest efficacy rates. Scientific research on psychosocial treatments is lacking, with preliminary evidence supporting the combination of cognitive behavioral therapy and medication. (Davidson, 2008)

The Wender-Utah Rating Scale (WURS) and the Childhood Symptoms Scale by Barkley and Murphy try to make a retrospective assessment of childhood ADHD symptoms. The Connors Adult ADHD Rating Scales (CAARS), the Current Symptoms Scales by Barkley and Murphy (CSS), the Adult Self Report Scale (ASRS) by Adler et al. and Kessler et al. or the Attention Deficit Hyperactivity Disorder—Self Report Scale (ADHD-SR

by Rösler et al.) are self-report rating scales focusing mainly on the DSM-IV criteria. The CAARS and the CSS have other report forms too. The Brown ADD Rating Scale (Brown ADD-RS) and the Attention Deficit Hyperactivity Disorder-Other Report Scale (ADHD-OR by Rösler et al.) are instruments for use by clinicians or significant others. Both self-rating scales and observer report scales quantify the ADHD symptoms by use of a Likert scale mostly ranging from 0 to 3. This makes the instruments useful to follow the course of the disease quantitatively. Comprehensive diagnostic interviews not only evaluate diagnostic criteria, but also assess different psychopathological syndrome scores, functional disability measures, indices of pervasiveness and information about comorbid disorders. The most comprehensive procedures are the Brown ADD Diagnostic Form and the Adult Interview (AI) by Barkley and Murphy. An instrument of particular interest is the Wender Reimherr Interview (WRI) which follows a diagnostic algorithm different from DSM-IV. The interview contains only items delineated from adult psychopathology and not derived from symptoms originally designed for use in children. (Rösler et al., 2006)

Baseline assessment

Before starting medication for ADHD, people with ADHD should have a full assessment, possibly through their GP, which should include also:

- a review to confirm they continue to meet the criteria for ADHD and need treatment
- a review of mental health and social circumstances, including:
    - presence of coexisting mental health and neurodevelopmental conditions
    - current educational or employment circumstances
    - risk assessment for substance misuse and drug diversion
    - care needs

There should also be a review of physical health, including also:

- a medical history, taking into account conditions that may be contraindications for specific medicines
- current medication
- height and weight (measured and recorded against the normal range for age, height and sex)
- baseline pulse and blood pressure (measured with an appropriately sized cuff and compared with the normal range for age)
- a cardiovascular assessment
- an electrocardiogram (ECG) if the treatment may affect the QT interval.

One should refer for a cardiology opinion before starting medication for ADHD in cases including also:

- history of congenital heart disease or previous cardiac surgery
- history of sudden death in a first-degree relative under 40 years suggesting a cardiac disease
- shortness of breath on exertion compared with peers
- fainting on exertion or in response to fright or noise
- palpitations that are rapid, regular and start and stop suddenly (fleeting occasional bumps are usually ectopic and do not need investigation)
- chest pain suggesting cardiac origin

- signs of heart failure
- a murmur heard on cardiac examination
- blood pressure that is classified as hypertensive for adults

Medication

Stimulants are the classic medication which is used in the treatment of ADHD. If it is used correctly and for the correct indication, it can help patients have a significant improvement in their quality of life.

However, treatment success in the individual and treatment success on average in a large group can diverge significantly. A clinician's skills in using the medication can play a significant role. In a large Canadian study, Currie and colleagues found little evidence of improvement in either the medium or the long run. Our results are silent on the effects on optimal use of medication for ADHD, but suggest that expanding medication in a community setting had little positive benefit. (Currie, Stabile, & Jones, 2014)

Long-Term Effect

While methylphenidate (MPH) often ameliorates attention-deficit/hyperactivity disorder (ADHD) behavioral dysfunction, it there is little evidence that methylphenidate (MPH) medication leads to long-term-term academic gains in ADHD. In a study by Hale and colleagues, children aged 6 to 16 with ADHD inattentive type (IT; n = 19) and combined type (n = 33)/hyperactive-impulsive type (n = 4) (CT) participated in double-blind placebo-controlled MPH trials with baseline and randomized placebo, low MPH dose, and high MPH dose conditions. Robust cognitive and behavioral MPH response was achieved for children with significant baseline executive working memory (EWM) / self-regulation (SR) impairment, yet response was poor for those with adequate EWM/SR baseline performance. Even for strong MPH responders, the best dose for neuropsychological functioning was typically lower than the best dose for behavior. (Hale et al., 2011)

There is overall little evidence to suggest that the type of treatment in the present affects the severity of ADHD in the future. A study by Molina and colleagues has shown that or intensity of 14 months of treatment for ADHD in childhood (at age 7.0–9.9 years) does not predict functioning 6 to 8 years later. Rather, early ADHD symptom trajectory regardless of treatment type is prognostic. This finding implies that children with behavioral and sociodemographic advantage, with the best response to any treatment, will have the best long-term prognosis. As a group, however, despite initial symptom improvement during treatment that is largely maintained after treatment, children with combined-type ADHD exhibit significant impairment in adolescence. (Molina et al., 2009)

Anxiety

Compared to parent and teacher reports of anxiety, child reported comorbid anxiety shows foremost the largest associations with the neurocognitive dysfunctions observed in children with ADHD. (Bloemsma et al., 2013) In another study, overall rates of individual anxiety disorders, as well as age of onset and severity

of illness were not significantly different in the presence of comorbid ADHD. School functioning in children with anxiety disorders was negatively impacted by the presence of comorbid ADHD. Frequency of mental health treatment in children with anxiety disorders was significantly increased in the presence of comorbid ADHD. ADHD had a limited impact on the manifestation of anxiety disorder in children suggesting that ADHD and anxiety disorders are independently expressed. (Hammerness et al., 2010)

Tics

Findings in a study by Gadow and Nolan suggest that the co-occurrence of diagnosed ADHD, chronic multiple tick disorder and anxiety represents a particularly troublesome clinical phenotype, at least in the home setting. Comorbid anxiety disorder was not associated with a less favorable response to immediate release methylphenidate in children with ADHD and chronic multiple disorder, but replication with larger samples is warranted before firm conclusions can be drawn about potential group differences. (Gadow & Nolan, 2011)

Emotional Lability

Emotional lability, or sudden strong shifts in emotion, commonly occurs in youth with attention-deficit/hyperactivity disorder. Although these symptoms are impairing and disruptive, relatively little research has addressed their treatment, likely due to the difficulty of reliable and valid assessment. Promising signals for symptom improvement have come from recent studies using stimulants in adults, children and adolescents. Similarly, neuroimaging studies have begun to identify neurobiological mechanisms underlying stimulants' impact on emotion regulation capacities. (Posner, Kass, & Hulvershorn, 2014)

Smoking

Individuals suffering from ADHD have a significantly higher risk of cigarette smoking. Stimulant treatment of ADHD may reduce smoking risk. Schoenfelder and colleagues examined the relationship between stimulant treatment of ADHD and cigarette smoking in a meta-analysis. The study revealed a significant association between stimulant treatment and lower smoking rates. the effect was larger in samples with more severe psychopathology. Implications for further research, treatment of ADHD, and smoking prevention are discussed. (Schoenfelder, Faraone, & Kollins, 2014)

Medication Groups

Common stimulants include:

Methylphenidate (Methylphenidate®, Concerta®), a norepinephrine-dopamine reuptake inhibitor
Dextroamphetamine (Dexedrine®), the dextro-enantiomer of amphetamine
Dexmethylphenidate (Focalin®), the active dextro-enantiomer of methylphenidate
Lisdexamfetamine (Vyvanse®), a prodrug containing the dextro-enantiomer of amphetamine

There are also mixed amphetamine salts, such as Adderall®, a 3:1 mix of dextro/levo-enantiomers of amphetamine.

Atomoxetine (Strattera ®) is a norepinephrine (noradrenaline) reuptake inhibitor which is approved for the treatment of attention deficit hyperactivity disorder (ADHD).

There are also some antidepressants that have mild stimulant effects. Further information can be found in the author's book *An Overview of Psychiatric Medication* (Haverkampf, 2018a)

Methylphenidate

Methylphenidate is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms:

- moderate-to-severe distractibility
- short attention span
- hyperactivity
- emotional lability, an
- impulsivity.

The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Non-localizing neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

Atomoxetine

In pediatric patients with ADHD and comorbid symptoms of depression or anxiety, atomoxetine monotherapy appears to be effective for treating ADHD. (Kratochvil et al., 2005) In the study by Kratochvil and colleagues, anxiety and depressive symptoms also improved, but the absence of a placebo-only arm did not allow the investigators to conclude that these effects are specifically the result of treatment with atomoxetine. Combined atomoxetine and fluoxetine therapy were, however, well tolerated.

Extended Release

When prescribing stimulants for ADHD, one needs to consider modified-release once-daily preparations for the following reasons:

- convenience
- improving adherence
- reducing stigma (because there is no need to take medication at school or in the workplace)
- reducing problems of storing and administering controlled drugs at school
- the risk of stimulant misuse and diversion with immediate-release preparations
- their pharmacokinetic profiles.

Immediate-release preparations may be suitable if more flexible dosing regimens are needed, or during initial titration to determine correct dosing levels.

Sex

ADHD was once thought of as a predominantly male disorder. While this may be true for ADHD in childhood, extant research suggests that the number of women with ADHD may be nearly equal to that of men with the disorder (Faraone et al., 2000). There is accumulating research which clearly indicates subtle but important sex differences exist in the symptom profile, neuropathology and clinical course of ADHD. Compared to males with ADHD, females with ADHD are more prone to have difficulties with inattentive symptoms than hyperactive and impulsive symptoms, and females often receive a diagnosis of ADHD significantly later than do males (Gaub & Carlson, 1997; Gershon, 2002a, 2002b). Emerging evidence suggests differences exist in the neuropathology of ADHD, and there are hormonal factors which may play an important role in understanding ADHD in females. Although research demonstrates females with ADHD differ from males in important ways, little research exists that evaluates differences in treatment response. Given the subtle but important differences in presentation and developmental course of ADHD, it is essential that both clinical practice and research be informed by awareness of these differences in order to better identify and promote improved quality of care to girls and women with ADHD. (Nussbaum, 2012)

Medication for Children

Drug treatment is not indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is generally necessary. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

Methylphenidate should not be used in children under 6 years, since safety and efficacy in this age group have not been established.

Consider offering

1. **Methylphenidate** as the first line pharmacological treatment,
2. **Lisdexamfetamine** for those who have had a 6-week trial of methylphenidate at an adequate dose and not derived enough benefit in terms of reduced ADHD symptoms and associated impairment,
3. **Dexamfetamine** for those whose ADHD symptoms are responding to lisdexamfetamine but who cannot tolerate the longer effect profile,
4. **Atomoxetine** or **Guanfacine** if:
    - they cannot tolerate methylphenidate or lisdexamfetamine or
    - their symptoms have not responded to separate 6-week trials of lisdexamfetamine and methylphenidate, having considered alternative preparations and adequate doses.

Medication for Adults

Consider offering

1. **Lisdexamfetamine** or **Methylphenidate** as first-line pharmacological treatment,
2. **Lisdexamfetamine** for those who have had a 6-week trial of methylphenidate at an adequate dose but have not derived enough benefit in terms of reduced ADHD symptoms and associated impairment,
   Methylphenidate for those who have had a 6-week trial of lisdexamfetamine at an adequate dose but have not derived enough benefit in terms of reduced ADHD symptoms and associated impairment,
3. **Dexamfetamine** for those whose ADHD symptoms are responding to lisdexamfetamine but who cannot tolerate the longer effect profile,
4. **Atomoxetine** if:
   - they cannot tolerate lisdexamfetamine or methylphenidate or
   - their symptoms have not responded to separate 6-week trials of lisdexamfetamine and methylphenidate, having considered alternative preparations and adequate doses.

Do not offer any of the following medication for ADHD without advice from a tertiary ADHD service:

- guanfacine for adults
- clonidine for children with ADHD and sleep disturbance, rages or tics
- atypical antipsychotics in addition to stimulants for people with ADHD and coexisting pervasive aggression, rages or irritability
- other medication than that listed above.

ADHD Type and Medication

Subtype

In a study by Barbaresi and colleagues, there was no association between DSM-IV subtype and likelihood of a favorable response or of side effects. Dextroamphetamine and methylphenidate were equally likely to be associated with a favorable response, but dextroamphetamine was more likely to be associated with side effects. (Barbaresi et al., 2014)

Sleep

Differences in sleep problems seem to be a function of ADHD subtype, comorbidity, and medication. In a study by Mayes and colleagues, children with ADHD-I alone had the fewest sleep problems and did not differ from controls. Children with ADHD-C had more sleep problems than controls and children with ADHD-I. Comorbid anxiety/depression increased sleep problems, whereas ODD did not. Daytime sleepiness was greatest in ADHD-I and was associated with sleeping more (not less) than normal. Medicated children had greater difficulty falling asleep than unmedicated children. (Mayes et al., 2008) Linear regression analyses by Corkum and colleagues showed that (1) dyssomnias were related to confounding factors (i.e., comorbid

oppositional defiant disorder and stimulant medication) rather than ADHD; (2) parasomnias were similar in clinical and nonclinical children; and (3) the DSM-IV combined subtype of ADHD was associated with sleep-related involuntary movements. However, sleep-related involuntary movements were more highly associated with separation anxiety. (CORKUM, MOLDOFSKY, HOGG-JOHNSON, HUMPHRIES, & TANNOCK, 1999)

Anxiety

ADHD co-occurring with internalizing disorders (principally parent-reported anxiety disorders) absent any concurrent disruptive disorder, ADHD co-occurring with ODD/CD (oppositional defiant disorder / conduct disorder) but no anxiety (ADHD + ODD/CD), and ADHD with both anxiety and ODD/CD (ADHD + ANX + ODD/CD) may be sufficiently distinct to warrant classification as ADHD subtypes separate from ADHD without this phenomenology. Jensen and colleagues found evidence of main effects of internalizing and externalizing comorbid disorders. Moderate evidence of interactions of parent-reported anxiety and ODD/CD status were noted on response to treatment, indicating that children with ADHD and anxiety disorders (but no ODD/CD) were likely to respond equally well to behavioral and medication treatments. Children with ADHD-only or ADHD with ODD/CD (but without anxiety disorders) responded best to medication treatments (with or without behavioral treatments), while children with multiple comorbid disorders (anxiety and ODD/CD) responded optimally to combined (medication and behavioral) treatments. (JENSEN et al., 2001)

Genotype

Stein and colleagues studied the relationship between DAT1 3′-untranslated region (3′-UTR) variable number tandem repeats (VNTR) genotypes and dose response to MPH. Children were genotyped for the DAT1 VNTR and evaluated on placebo and three dosage levels of OROS® MPH. Children who were homozygous for the less common, 9-repeat DAT1 3′-UTR genotype displayed a distinct dose–response curve from that of the other genotype groups, with an absence of typical linear improvement when the dose was increased from 18 mg to 36 and 54 mg. (Stein et al., 2005)

In a study by Epstein and colleagues, youths and adults with ADHD showed attenuated activity in fronto-striatal regions. In addition, adults with ADHD appeared to activate non-fronto-striatal regions more than normals. A stimulant medication trial showed that among youths, stimulant medication increased activation in fronto-striatal and cerebellar regions. In adults with ADHD, increases in activation were observed in the striatum and cerebellum, but not in prefrontal regions. Conclusions: This study extends findings of fronto-striatal dysfunction to adults with ADHD and highlights the importance of frontostriatal and frontocerebellar circuitry in this disorder, providing evidence of an endophenotype for examining the genetics of ADHD. (Epstein et al., 2007)

Some medication which is licensed for use in childhood may have to be continued off license in adults if there are no better alternatives and the patient has benefitted from it significantly. Psychotherapy may have to be adjusted to external and internal changes that are part of growing up.

Dose Titration

The dose should be titrated against symptoms and adverse effects in line with guidelines until optimized. This means reduced symptoms, positive behavior changes, improvements in education, employment and relationships, with tolerable adverse effects.

During the titration phase, ADHD symptoms, impairment and adverse effects should be recorded at baseline and at each dose change on standard scales, in children also by parents and teachers, and progress reviewed regularly.

Dose titration should be slower and monitoring more frequent if another condition is present, such as

- neurodevelopmental disorders (for example, autism spectrum disorder, tic disorders, learning disability)
- mental health conditions (for example, anxiety disorders [including obsessive–compulsive disorder], schizophrenia or bipolar disorder, depression, personality disorder, eating disorder, post-traumatic stress disorder, substance misuse)
- physical health conditions (for example, cardiac disease, epilepsy or acquired brain injury).
- Think about using immediate- and modified-release preparations of stimulants to optimize effect (for example, a modified-release preparation of methylphenidate in the morning and an immediate-release preparation of methylphenidate at another time of the day to extend the duration of effect).
- Addictions

Abuse

One needs to be particularly careful about prescribing stimulants for ADHD if there is a risk of addictions and/or diversion for cognitive enhancement or appetite suppression. One should not offer immediate-release stimulants or modified-release stimulants that can be easily injected or insufflated, if this may be an issue.

Coexisting Conditions

In ADHD the comorbidity for other conditions is quite high, which can play a significant role in treatment. The same medication choices can be offered to people with ADHD and anxiety disorder, tic disorder or autism spectrum disorder as other people with ADHD.

Studies indicate that co-occurrence of clinically significant ADHD and autistic symptoms is common, and that some genes may influence both disorders. However, the DSM basically does not allow for the concurrent diagnosis of ADHD and autism.

Children with the combination of ADHD and motor coordination problems are particularly likely to suffer from an autism spectrum disorder. These co-occurrences of symptoms are important since children with

ASD in addition to ADHD symptoms may respond poorly to standard ADHD treatments or have increased side effects. Such children may benefit from additional classes of pharmacologic agents, such as α-agonists, selective serotonin reuptake inhibitors and neuroleptics. They may also benefit from social skills therapy, individual and family psychotherapy, behavioral therapy and other nonpharmacologic interventions. (Reiersen & Todd, 2008)

Caution

Stimulants need to be used with care and caution, and it is important to have as much information about the medical and psychological state of the patient as possible. The following list just gives some examples, but is by no means comprehensive or factually up to date:

- Some contraindications for methylphenidate are marked anxiety, tension, and agitation are contraindications to Methylphenidate, since the drug may aggravate these symptoms. Methylphenidate is contraindicated also in patients known to be hypersensitive to the drug, in patients with glaucoma, and in patients with motor tics or with a family history or diagnosis of Tourette's syndrome.
- Methylphenidate is contraindicated during treatment with monoamine oxidase inhibitors, and within a minimum of 14 days following discontinuation of a monoamine oxidase inhibitor (hypertensive crises may result).
- Because of possible effects on blood pressure, methylphenidate should be used cautiously with pressor agents.
- Methylphenidate may decrease the effectiveness of drugs used to treat hypertension. Human pharmacologic studies have shown that racemic methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g., phenobarbital, phenytoin, primidone), and tricyclic drugs (e.g., imipramine, clomipramine, desipramine). Downward dose adjustments of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentration (or, in case of coumarin, coagulation times), when initiating or discontinuing methylphenidate.

Stimulant medications cause a modest increase in average blood pressure (about 2-4 mmHg) and average heart rate (about 3-6 bpm), and individuals may have larger increases. While the mean changes alone would not be expected to have short-term consequences, all patients should be monitored for larger changes in heart rate and blood pressure. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, such as those with preexisting hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia.

Psychosis

Psychosis is an important, unpredictable side effect of stimulant medication. In the case of acute psychotic or manic episodes, ADHD medication should be stopped because it can exacerbate or even trigger them

under certain conditions. Restarting the ADHD medication after the episode has resolved can be considered, taking into account the individual circumstances, risks and benefits of the ADHD medication. The potential for psychotic side effects are well known, but usually reported as rare. Long acting preparations appear to be a contributory factor to the development of psychotic side effects, while symptoms resolve with discontinuation of treatment. (Shibib & Chalhoub, 2009)

Administration of stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a preexisting psychotic disorder.

Mosholder and colleagues analyzed data from 49 randomized, controlled clinical trials in the pediatric development programs for these products. A total of 11 psychosis/mania adverse events occurred during 743 person-years of double-blind treatment with these drugs, and no comparable adverse events occurred in a total of 420 person-years of placebo exposure in the same trials. The rate per 100 person-years in the pooled active drug group was 1.48. The analysis of spontaneous postmarketing reports yielded >800 reports of adverse events related to psychosis or mania. In about 90% of the cases, there was no reported history of a similar psychiatric condition. Hallucinations involving visual and/or tactile sensations of insects, snakes, or worms were common in cases in children. (Mosholder, Gelperin, Hammad, Phelan, & Johann-Liang, 2009)

Bipolar Disorder

ADHD in combination with bipolar disorder may be associated with more severe symptoms and worse outcomes of both conditions. Prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. The frequent coexistence with alcohol and substance abuse may further complicate treatment management. A hierarchical approach is desirable, with mood stabilization preceding the treatment of ADHD symptoms.

Atomoxetine may be effective in the treatment of ADHD symptoms in patients with bipolar disorder, with a modestly increased risk of (hypo)manic switches and destabilization of the mood disorder when utilized in association with mood stabilizers. (Perugi & Vannucchi, 2015)

Aggression

Aggressive behavior or hostility is often observed in children and adolescents with ADHD and has been reported in clinical trials and the post-marketing experience of some medications indicated for the treatment of ADHD. Patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility.

Seizures

There is some clinical evidence that stimulants may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and, very rarely, in

patients without a history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

Priapism

Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products in both pediatric and adult patients. Priapism usually developed after some time on the drug, often subsequent to an increase in dose. Priapism has also appeared during a period of drug withdrawal (drug holidays or during discontinuation). Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention.

Peripheral Vasculopathy, Including Raynaud's Phenomenon

Stimulants are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild, although less frequently permanent tissue damage can occur. Signs and symptoms often improve after reduction in dose or discontinuation of the drug. Careful observation for digital changes is necessary during treatment with ADHD stimulants.

Visual Disturbance

Difficulties with accommodation and blurring of vision have been reported with stimulant treatment. However, in a study by Martin and colleagues in children, visual acuity increased significantly in the ADHD group after treatment with a stimulant. Also, more ADHD subjects had subnormal visual field results without stimulants, compared with controls, but with stimulants the difference was no longer significant. (Martin, Aring, Landgren, Hellström, & Andersson Grönlund, 2008)

Drug Dependence

Methylphenidate should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use, since severe depression or another underlying condition may surface.

Pregnancy

The number of pregnancies exposed to ADHD medication has increased similarly to the increase in use of ADHD medication among women of childbearing age. Use of ADHD medication in pregnancy was associated with different indicators of maternal disadvantage and with increased risk of induced abortion and miscarriage.

Haervig and colleagues studied data from the Danish national health registries to identify all recorded pregnancies from 1999 to 2010. From 2003 to the first quarter of 2010, use of ADHD medication during pregnancy increased from 5 to 533 per 100 000 person-years. Compared with unexposed, women who used ADHD medication during pregnancy were more often younger, single, lower educated, received social security benefits, and used other psychopharmaca. Exposed pregnancies were more likely to result in induced abortions on maternal request, induced abortions on special indication, and miscarriage compared with unexposed pregnancies. (Haervig, Mortensen, Hansen, & Strandberg-Larsen, 2014)

However, ADHD treatment could put both mother and baby at risk. This has to be balanced against the possible risks to the baby of continuing treatment. Although the data remain inadequate, the risk of the latter appears to be quite small overall, at least for methylphenidate, (Besag, 2014) while there is evidence, that the rates of fetal loss both through abortion and through miscarriage are increased with methylphenidate. Discussions about ADHD treatment with women of childbearing age should be balanced, open and honest, acknowledging the lack of information on the possible risks to the offspring of continuing treatment, while also drawing attention to the possible risks to both mother and child of discontinuing treatment. (Besag, 2014)

Monitoring

Medication is an important element of therapeutic strategies for ADHD. While medications for ADHD are generally well-tolerated, there are common, although less severe, as well as rare but severe adverse events that can occur during treatment with ADHD drugs. Cortese and colleagues reviewed the literature. The review covers monitoring and management strategies of loss of appetite and growth delay, cardiovascular risks, sleep disturbance, tics, substance misuse/abuse, seizures, suicidal thoughts/behaviors and psychotic symptoms. Most AEs during treatment with drugs for ADHD are manageable and most of the times it is not necessary to stop medication, so that patients with ADHD may continue to benefit from the effectiveness of pharmacological treatment. (Cortese et al., 2013)

Behavior

Monitor the behavioral response to medication, and if behavior worsens adjust medication and review the diagnosis.

Height

Growth should be monitored during treatment with stimulants, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

Research on the issue of growth suppression is lacking, mostly owing to insufficient follow-up on patients' final heights. However, it has been argued that the rate of height loss seems relatively small and is likely reversible with withdrawal of treatment. (Goldman, 2010)

Weight

Some young adults are misusing prescription stimulants for weight loss. This behavior is associated with other problematic weight loss strategies. Interventions designed to reduce problematic eating behaviors in young adults may wish to assess the misuse of prescription stimulants. (Jeffers, Benotsch, & Koester, 2013) In the study by Jeffers and colleagues, undergraduates who reported using prescription stimulants for weight loss had greater appearance-related motivations for weight loss, greater emotion and stress-related eating, a more compromised appraisal of their ability to cope, lower self-esteem, and were more likely to report engaging in other unhealthy weight loss and eating disordered behaviors.

Weight should be measured at least once at 3 and 6 months after starting treatment in children over 10 years and young people, and at least once every 6 months thereafter. In adults, weight should be measured at least once every 6 months. Monitoring the BMI of adults is in many cases important.

If a child or young person's height over time is significantly affected by medication (that is, they have not met the height expected for their age), stopping the medication or at least a break in treatment over school holidays to allow 'catch-up' growth may be considered.

Cardiovascular System

Stimulants agents can increase heart rate and blood pressure and cause other cardiovascular symptoms. Since increased BP and HR in general are considered risk factors for cardiovascular morbidity and mortality, heart rate and blood pressure should be monitored closely. Patients who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam to assess for the presence of cardiac disease and should receive further cardiac evaluation if findings suggest such disease (e.g., electrocardiogram and echocardiogram).

Statistically significant pre–post increases of SBP, DBP and HR were associated with amphetamine and atomoxetine treatment in children and adolescents with ADHD, while methamphetamine treatment had a statistically significant effect only on SBP in these patients. These increases may be clinically significant for a significant minority of individuals that experience larger increases. (Hennissen et al., 2017)

Among young and middle-aged adults, current or new use of ADHD medications, compared with nonuse or remote use, does not seem associated with an increased risk of serious cardiovascular events. Habel and colleagues examined whether current use of medications prescribed primarily to treat ADHD is associated with increased risk of serious cardiovascular events in young and middle-aged adults. Participants were adults aged 25 through 64 years with dispensed prescriptions for methylphenidate, amphetamine, or atomoxetine at baseline. The sample size was 443 198 users and nonusers. The multivariable-adjusted rate ratio (RR) of serious cardiovascular events for current use vs nonuse of ADHD medications was 0.83. Among new users of ADHD medications, the adjusted RR was 0.77. The adjusted RR for current use vs remote use was 1.03; for new use vs remote use, the adjusted RR was 1.02. (Habel et al., 2011) In the study including data about 1,200,438 children and young adults between the ages of 2 and 24 years and 2,579,104 person-years of follow-up, including 373,667 person-years of current use of ADHD drugs, Habel et al showed no evidence that current use of an ADHD drug was associated with an increased risk of serious cardiovascular

events, although the upper limit of the 95% confidence interval indicated that a doubling of the risk could not be ruled out. (Habel et al., 2011)

Children and Adolescents

Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug.

Adults

Sudden death, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs.

Tics

If a person taking stimulants develops tics, one should consider whether the tics are related to the stimulant (tics naturally wax and wane) and the impairment associated with the tics outweighs the benefits of ADHD treatment. If tics are stimulant related, one may need to reduce the dose or switch the medication.

Sexual Dysfunction

Erectile and ejaculatory dysfunction are potential adverse effects of atomoxetine.

Seizures

If a person with ADHD develops new seizures or a worsening of existing seizures, their ADHD medication needs to be reviewed and any medication that might be contributing to the seizures stopped.

Patients with ADHD seem to be at a higher risk of seizures. However, ADHD medication was associated with lower risk of seizures within individuals while they were dispensed medication, which is not consistent with the hypothesis that ADHD medication increases risk of seizures. Wiggs and colleagues followed a sample of 801,838 patients with ADHD medication. Patients with ADHD were at higher odds for any seizure compared with non-ADHD controls (odds ratio [OR] = 2.33). In adjusted within-individual comparisons, ADHD medication was associated with lower odds of seizures among patients with (OR = 0.71) and without (OR = 0.71) prior seizures. Long-term within-individual comparisons suggested no evidence of an association between medication use and seizures among individuals with (OR = 0.87) and without (OR = 1.01) a seizure history. (Wiggs et al., 2018) Koneski and colleagues evaluated 24 patients ranging from 7 to 16 years of age

who took MPH for 6 months. Inclusion criteria were at least two epileptic seizures in the previous 6 months and a diagnosis of ADHD based on DSM-IV criteria. There was an overall improvement in ADHD symptoms in 70.8% of patients, and there was no increase in frequency of epileptic seizures in 22 patients (91.6%). (Koneski, Casella, Agertt, & Ferreira, 2011)

Sleep

Changes in sleep pattern should always be asked for, the timing and dose of the medication adjusted. Immediate release methamphetamine should usually not be administered after 4pm.

Compliance

Experiences of adverse effects are a frequent explanation for discontinuation among youth. Despite impaired functioning during adolescence, many discontinue medication treatment. Beliefs and attitudes may differ widely. Some families understand that ADHD is a neurobiological condition and accept that medication is indicated, for others, such treatment is unacceptable. Converging evidence describes negative perceptions of the burden associated with medication use as well as concerns about potential short- and long-term adverse effects. Ways to improve shared decision making among practitioners, parents and youth, and to monitor effectiveness, safety and new onset of concurrent difficulties are likely to optimize outcomes. (Alice Charach & Fernandez, 2013).

Psychotherapy

Psychotherapy should always be part of a comprehensive treatment plan for ADHD. Communication-Focused Therapy® (CFT) as it was developed by the author focuses on internal and external communication patterns which has shown to be helpful in ADHD. (Haverkampf, 2017a, 2017c, 2017b)

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