Attention Deficit Hyperactivity Disorder (ADHD) in Children and Adults

Prohibited Substances: Stimulants

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurobehavioral disorders. ADHD is a chronic disease which begins in childhood with an estimated worldwide prevalence rate of 5% in children and adolescents and 3% in adults.[1-4] The symptoms of ADHD often persist through adolescence into adulthood and until old age.[5-8] This has been confirmed in long-term follow-up studies which have demonstrated the persistence of symptoms in many adults diagnosed with ADHD in childhood.[9-12] A meta-analysis of follow-up ADHD studies reported that 15% of all cases show persistence of full DSM-5 diagnostic criteria into adulthood, whilst almost 75% continue to have significant ADHD related impairments in their adult life.[13-14]

ADHD is characterized by symptoms of inattention and/or hyperactivity-impulsivity that interfere with functioning or development and are present in more than one setting. ADHD may cause difficulties at school, in the workplace, and in the social environment. Children with ADHD may experience significant adaptation problems because their functional level and behavior may not correspond to their chronological age or expected development level.[15] Although the male: female ratio is higher in children, perhaps due to underdiagnosis, the male: female ratio in adults is almost equal.

ADHD sufferers have a high incidence of comorbidities. Studies showed that the most frequent comorbidities in children are learning disorders (47.3%), conduct disorders (28.6%), and oppositional defiant disorder (22.1%).[15-16] Other relevant studies have reported comorbid depressive disorder rates of 5%–47% in children and adolescents with ADHD.[17-18] Evidence from a meta-analysis of prospective studies in children with ADHD suggests that those with ADHD also have a higher risk of developing substance use disorders and cigarette smoking than those without ADHD.[19] Untreated ADHD has also been associated with (morbid) obesity in children and adults.[20-21] These and other comorbidities are also present in the adult population with ADHD.[22-23] Seventy percent of adults with ADHD have a second psychiatric comorbidity.[24] Studies of a large Danish clinical register find increased mortality rate ratios in children, adolescents, and adults with ADHD, even after adjustment for comorbid psychiatric disorders such as oppositional defiant disorder, conduct disorder, and substance use disorder. The increased mortality rates may in part be related to the increased rates of somatic illnesses in ADHD, such as dementia,[25] immune disorders, allergies, asthma, migraine, sleep disorders, epilepsy, cardiovascular disease, obesity, diabetes, hypermobility syndromes, etc.[26]

This increase in mortality is however mainly driven by deaths from unnatural causes such as accidents.[27] Similar studies find that injury prevalence and emergency ward visits in children with ADHD were reduced significantly with appropriate pharmacological treatment.[28] Similarly, when individuals with ADHD are receiving medication, they experience significantly fewer unintentional physical injuries, motor vehicle crashes, substance use disorders, and criminal acts, as well as improved academic functioning, compared with times when they are untreated.[29]

2. Diagnosis

a. Medical history

The diagnosis of ADHD is a clinical one and requires a complete medical evaluation to detect specific symptoms. The presence of symptoms is directly obtained from the patient (child or adult), parents, and other family members or spouses, teachers, and work colleagues. The Diagnostic and Statistical Manual of Mental Disorders, 2022 (DSM-5-TR) criteria for ADHD, as defined by the American Psychiatric Association, are the most widely used criteria and describe three presentation types of ADHD based on the predominant symptom pattern: inattentive presentation, hyperactive-impulsive presentation, and the combined presentation.[30] The International Classification of Diseases (ICD-11) criteria for hyperkinetic disorder (HKD), as defined by the World Health Organization (WHO), are more conservative and define a severe subgroup of people fulfilling the ADHD combined type diagnosis.

The essential feature of attention deficit/hyperactivity disorder is a persistent pattern of inattention and or hyperactivity-impulsivity that interferes with functioning and development. The requirement that several symptoms be present before age 12 years conveys the importance of a substantial clinical presentation during childhood that may maintain a trajectory of symptoms and impairments into adulthood. Manifestations of the disorder must be present in more than one setting (e.g., home, school, work). There is an exclusion that the symptoms should 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).

In most parts of the world, the clinicians involved in the diagnosis and treatment of ADHD are pediatricians, psychiatrists, and clinical psychologists. In recent years, primary care providers in some countries have assumed the responsibility for diagnosis and care of adults with ADHD. It is not unusual in some countries to have the initial evaluation and diagnosis performed by clinical psychologists, in conjunction with a general practitioner. This recognizes the non-availability of psychiatrists for ADHD evaluations, especially for adults, in some countries.

While a comprehensive evaluation for ADHD may be performed by a clinical psychologist, patients with ADHD may have concurrent medical illnesses or prescribed medication that may factor into the differential diagnosis of ADHD. Careful solicitation of such medical information is essential for a conclusive, accurate ADHD diagnosis and appropriate selection of ADHD medication (if recommended as part of the treatment). Therefore, a letter from the prescribing physician documenting their clinical assessment and treatment recommendations needs to accompany any psychologist's evaluation.

b. Diagnosis criteria

i) Evaluation should be performed by a pediatrician, psychiatrist, or physician, with the help of a clinical psychologist when appropriate.

ii) The physician/psychologist should have assessed the athlete's clinical history and examination and may have also interviewed parents or partners and assessed supporting documents in the form of school reports and/or previous medical/paramedical assessments. The findings of this comprehensive assessment must meet the DSM-5-TR criteria (or ICD-11).

Simply stating that the patient meets the DSM-5-TR criteria is not adequate. An accompanying report should provide a concise yet comprehensive account of the assessment process, demonstrating how the criterion was evaluated and explicitly identifying those that were met.

In the diagnostic assessment, there should ideally be a reference to the use of validated diagnostic instruments and scales assessing symptoms and impairment. These could include, but are not limited to:

- Adults: ACDS, CAADID, CAARS, Barkley, ASRS-v1.1, DIVA 5.0 or DIVA 2.0,[21,31] Weiss Functional Impairment Scale[32]
- Children: Vanderbilt, K-SADs, DISC, Conners[33], SNAP, Young DIVA 2, ACE

Note: patient-rated scales are not a diagnostic tool, or substitute for clinical assessment, but are complementary to a comprehensive clinical evaluation.

iii) Description of previous therapies trialed, both pharmacological and non-pharmacological, as well as evidence of symptom return after a break from medication, can assist in supporting the DSM-5-TR diagnosis. However, it is not mandatory to demonstrate that a patient has tried and failed other medications.

c. Primary diagnosis of ADHD as an adult (i.e. after 18 years)

To fulfill the DSM-5-TR criteria, there should be evidence of symptoms during childhood, regardless of the age of the primary diagnosis, i.e., the DSM-5-TR criteria cannot be met unless there were symptoms in childhood. This should ideally be from reliable independent sources, psychologist reports, school reports, etc. However, if there was difficulty in establishing this history, which is not unusual, a second opinion from another independent specialist medical practitioner (usually a psychiatrist) confirming the diagnosis may be requested.

3. Treatment

a. Name of prohibited substances

Sympathomimetic psychostimulants [methylphenidate and amphetamine (amfetamine) derivatives, including the amphetamine prodrug lisdexamfetamine] form the basis of the treatment of ADHD in most countries around the world. Pharmacologic treatment with stimulants usually has the direct effect of reducing overactivity, increasing attention, and reducing impulsiveness, with the effects being evident within a short period of time.[34] It should be noted that the choice of first-line pharmacological treatment in ADHD varies across countries.

Atomoxetine, viloxazine ER, guanfacine ER, and clonidine ER are non-prohibited substances that are also used in the treatment of ADHD and may be considered first line in some countries, but not in others.[33,35-37]

b. Route of administration

Oral

c. Dosage and frequency

Both methylphenidate and amphetamine compounds come in immediate release (active for 2-5 hours) and extended release (6-14 hours) preparations. There are also combinations of immediate and extended-release formulations in single tablets. Combinations of these preparations may be used to achieve the best symptom control throughout the day. Optimal doses vary greatly, and dosages based on body weight are too variable across the world to use as guidelines in this document. Long-lasting, extended-release formulations in general are preferred in the treatment of adults for reasons of adherence to treatment, for the protection against abuse, to avoid rebound symptoms, and to provide coverage throughout the day without the need for multiple dosing.[38]

Optimal doses, however, are best decided on an individual basis whilst adequately monitoring for symptom control and side effects.

It should be noted that there is no need to cease treatment during competition periods. It is now generally considered that cessation of treatment can have a number of negative effects, including an adverse effect on symptom control, which can take time to re-establish. This destabilization of symptom control can also lead athletes to have an increase in risk-taking behaviors and can potentially increase their involvement in conflict situations (e.g., altercations with referees or other athletes).

Patients usually find that their symptoms are best controlled on a regular, stable dose of stimulant medication once their optimal dosing regimen has been achieved. For this reason, intermittent use, including PRN dosing, is not generally recommended.

In newly diagnosed ADHD patients, particularly in young teenage patients who will continue growing, there will be dosage changes until optimal management is achieved. Given this, a range of doses may be appropriate on the approval certificate with a maximal 12-month approval allowing

for the next approval to be granted for a stable dose. This prevents the need for repeat TUE applications in the first year for changes of doses whilst stabilizing the symptoms.

Side effects of stimulants for consideration by treating physicians

Some of the more common side effects reported with the use of psychostimulants include insomnia, reduced appetite, headaches, and jitteriness, but these are usually tolerable.[35] There is evidence that stimulants can increase the blood pressure and heart rate with "relative" contra-indications to use in those with hypertension, arrhythmias, and cardiomyopathies.

There are some studies linking increased cardiac events with the use of stimulants. The studies in the younger population indicate that there is no significant risk in an otherwise healthy population. The studies in adults are more varied but there remains insufficient evidence to advise against the use of stimulants for the treatment of ADHD in an otherwise well young adult. Despite this, it would be advisable to take a thorough cardiovascular history. A cardiac examination may be appropriate in patients with a history of specific cardiac issues and/or symptoms, family cardiac history, and in patients above age 50.

Literature reviews have confirmed that the risk of developing long-term substance abuse whilst taking psychostimulants for the treatment of attention deficit hyperactivity disorder (without comorbidities) is small and appropriate treatment may even decrease the risk and/or use of these substances.[38] There is no evidence that the therapeutic use of stimulants in the treatment of ADHD increases aggressive behavior. There are, however, reviews suggesting that untreated ADHD patients are more likely to become involved in risk-taking behavior and conflict situations, including car accidents, and that treatment with stimulants reduces this risk.[39-40]

d. Recommended duration of treatment

The pharmacological treatment of ADHD is usually over many years.

It is recommended for any athlete on continued therapy with psychostimulants to undergo at least an annual review by their physician.

4. Non-prohibited alternative treatments

Atomoxetine and viloxazine have been identified as non-prohibited alternate treatments for some patients with ADHD. These medications are considered by many to be less effective than stimulant medication and have a different side effect profile. In addition, these medications are not available in all countries. Other medications [e.g., clonidine, guanfacine, and bupropion (off-label for ADHD)][41] have also been shown to have some efficacy in the treatment of ADHD.

In general, the medications listed above are considered second line treatment in many (but not all) countries, and therefore it is not necessary to demonstrate a failed trial of these medications prior to the acceptance of methylphenidate or amphetamine for a TUE.

5. Consequences to health if treatment is withheld

Untreated, ADHD is widely recognized as having detrimental effects on the quality of life and psycho-social development of the patient. Untreated ADHD leads to higher risks of negative consequences such as driving accidents, academic and occupational underachievement, unplanned pregnancies, criminal behavior, impulsive spending and financial debt, divorce, substance use disorders, and concussions, to name a few. Recent evidence also suggests that Comorbid psychiatric conditions are common in adults with ADHD and need to be treated concurrently with the ADHD.

6. Treatment monitoring

Following the initiation of treatment, the patient should be reevaluated until the medication is optimized and the treatment stabilized. Further reviews should occur at a frequency dictated by the circumstances and the treating physician's recommendation.

7. TUE duration

Due to the chronic nature of ADHD, a TUE, in the case of a well-documented diagnosis of ADHD on a stable dose of medication, can be granted for up to four (4) years at a time.

A recent diagnosis with ongoing dose titration could initially be approved for 12 months, with consideration of a dose range to allow for titration. At the next application, if the dose is stable, a 4-year approval could be granted.

A TUE reapplication should include current and appropriate notes from the treating physician documenting symptom response, change in daily functional impairments, tolerability of medication, and general adherence with treatment.

Any change of medication or significant adjustment of the dosage during the approval period should result in a resubmission or advisement to the Anti-Doping Organization granting the TUE.

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