



## 1. Medical Condition

# ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN CHILDREN AND ADULTS

## Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurobehavioral disorders. ADHD is a chronic disease which begins in childhood (estimated prevalence rates vary from 3% to 9.9%), the symptoms of which can persist through adolescence into adulthood and become lifelong.<sup>1-3</sup> 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.<sup>4-8</sup> A meta-analysis of follow-up ADHD studies reported that 15% of all cases show persistence of symptoms beyond childhood, and 40%–50% of patients continue to have a partial diagnostic status and impairment in their adult life.<sup>9-10</sup>

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 work place, 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.<sup>11</sup>

ADHD sufferers have a high incidence of co-morbidities. A recent study showed the most frequent co-morbidities in children to be learning disorders (47.3%), conduct disorders (28.6%), and oppositional defiant disorder (22.1%).<sup>12,13</sup>

Other relevant studies have reported co-morbid depressive disorder rates of 5%–47% in children and adolescents with ADHD.<sup>14-16</sup> Evidence from a meta-analysis of prospective studies in children with ADHD suggests that children with ADHD also have a higher risk of developing substance use disorders and cigarette smoking than those without ADHD.<sup>17</sup>

These co-morbidities are also present in the adult population with ADHD.<sup>18</sup>

## **2. Diagnosis**

### **A. Medical History**

The diagnosis of ADHD is a clinical one and requires a complete medical evaluation to detect specific symptoms that have to be present in consistent contexts and with a persistent level of deterioration.<sup>19</sup>

The presence of symptoms is directly obtained from the patient (child or adult), parents and other family members or spouses, teachers and work colleagues. Multiple scales have been created to identify specific symptoms in order to diagnose ADHD, but the most commonly used diagnostic criteria are those of the DSM-V (Diagnostic and Statistical Manual of Mental Disorders Fifth Edition May 2013).<sup>20</sup>

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. 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)<sup>20</sup>

In most parts of the world, clinicians involved in the diagnosis and treatment of ADHD include pediatricians, psychiatrists and clinical psychologists.

### **B. Diagnostic criteria**

- 1) Evaluation by a pediatrician, psychiatrist or other physician who specializes in the treatment of ADHD/ADD;
- 2) Clinical history and examination findings supporting the diagnosis that must meet the **DSM-V criteria**. (Children must have at least 6 symptoms from either or both the inattentive and hyperactivity sections. Older adolescents and adults (over the age 17 years) must present with 5 symptoms and several of these symptoms should have been present prior to the age of 12 years.<sup>20</sup>

- 3) There should be evidence of the use of a comprehensive validated diagnostic scale assessing symptoms and impairment. These could include but are not limited to:
  - a) Adults: ACDS, CAADID, Barley, DIVA
  - b) Children: Vanderbilt, K-SADs, DISC, Connors<sup>21</sup>, SNAP
- 4) Reports from non-medical personnel, which can include teachers, parents or colleagues, reporting on behavior and symptom impact in realms of life other than sport (i.e. home, school, work) can assist in demonstrating that the impairments occur in multiple settings.
- 5) When ADHD is diagnosed for the first time as an adult (>18 years), a second opinion from an independent specialist medical practitioner (usually psychiatrist) confirming the diagnosis, may be required unless the presence of symptoms in childhood can be confirmed by other reliable independent sources (i.e. psychologists reports, school reports etc.).
- 6) In athletes > age 18 the medical evaluation should particularly consider medical and mental health co-morbidities (e.g. depression) and history of brain injuries, particularly in contact sports.
- 7) Description of the use of behavioral therapy and other forms of non-medication treatments is helpful.

### **3. Medical best practice treatment**

#### **A. Name of prohibited substance**

Sympathomimetic psychostimulants (methylphenidate and amphetamine derivatives) 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 activity and increasing attention, with the effects being evident within a short period of time.<sup>22</sup> It should be noted that the choice of first line pharmacological treatment in ADHD varies across countries and Atomoxetine (Strattera) is a non-prohibited substance that is also used in the treatment of ADHD and is considered first line in some countries.

#### **B. Route**

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 are often used to achieve the best symptom control. Maximal dosages based on body weight are too variable across the world to use as guidelines in this document. Optimal doses are best decided on an individual basis whilst adequately monitoring for symptom control and side effects.

It should be noted that there is no necessity 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 destabilizing of symptom control can also lead athletes to have an increase in risk taking behaviors and can increase their involvement in conflict situations (e.g. altercations with referees).

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 there will be dosage changes until optimal management is achieved. Given this, a range of dose may be appropriate on the approval certificate with a maximal 12 months 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.

Any change of medication or significant adjustment of the dosage should result in a re-submission or advisement to the ADO granting the TUE.

#### **Side effects of stimulants for consideration by treating doctors**

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.<sup>24</sup> 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 complete a thorough cardiovascular history and examination in all patients who are being prescribed stimulants. There are no current recommendations for mandatory pre-screening (specifically ECGs) based solely on concerns of the risk of psychostimulants. 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 co-morbidities) is small and may even decrease with proper treatment.<sup>26</sup>

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. Some treatment review articles indicate lack of control of aggressive behavior can be an indication to increase the dose of psychostimulant medication.

#### C. Recommended duration of treatment

The pharmacological treatment of ADHD is usually long term over many years.

It is highly recommended for any athlete on continued therapy with methylphenidate or dextroamphetamine to undergo an annual review by a specialist in the management of ADHD.

## **4. Other non-prohibited alternative treatments**

Atomoxetine (Strattera) has been identified as a non-prohibited alternate treatment for some patients with ADHD. This medication is considered by many to be less effective than stimulant medication and it has a different side effect profile which includes somnolence, sexual side effects and occasionally liver complications. In addition, this medication is not available in all countries. At this point, Atomoxetine is considered a second line treatment for ADHD in most countries because of its lower efficacy and side effect profile.

As it is generally considered a second line treatment, it is not necessary to demonstrate a failed trial of Atomoxetine prior to the acceptance of methylphenidate or amphetamine for a TUE.

Otherwise, apart from some behavior-modifying techniques, treatments with non-prohibited substances have not been shown to be effective.

## **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. Co-morbid psychiatric conditions may manifest if ADHD is left untreated.

## **6. Treatment monitoring**

Following the initiation of treatment, monitoring should be undertaken to assess the effectiveness of treatment until stabilization has been achieved. This may require 2-3 monthly reviews. Symptom scales can be helpful in these reviews. Once stabilized on a dosage regimen, regular review appointments are recommended and the maximum time between specialist reviews should be 12 months.

## **7. TUE validity and recommended review process**

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

An initial application for a newly diagnosed ADHD patient may be more appropriately approved for 12 months until a stable dose is achieved. Evidence of yearly reviews by the treating clinician must accompany a TUE reapplication.

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