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 for children and adolescents of 5% and 3% in adults.[1-4] The symptoms of ADHD often persist through adolescence into adulthood and until old age .[5-7, 30] 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.[8-10,31] A meta-analysis of follow-up ADHD studies reported that 15% of all cases show persistence of full diagnosis into adulthood, whilst almost 75% continue to have significant ADHD related impairments in their adult life. [11-12]

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.[13]

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%).[13.14] Other relevant studies have reported co-morbid depressive disorder rates of 5%–47% in children and adolescents with ADHD.[15-17]. 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.[18] Untreated ADHD has also been associated with (morbid) obesity in children and adults.[32,33] These and other co-morbidities are also present in the adult population with ADHD.[19, 20] 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.

This increase in mortality is largely driven by deaths from unnatural causes such as accidents.[38] Similar studies find that injury prevalence and emergency ward visits in children with ADHD were reduced significantly with appropriate pharmacological treatment. [39]

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, 2013 (DSM 5) criteria for ADHD as defined by the American Psychiatric Association are the most widely used criteria and describe three subtypes of ADHD based on the predominant symptom pattern: inattentive type, hyperactive-impulsive type and the combined type.[21] The International Classification of Diseases (ICD-10) criteria for hyperkinetic disorder (HKD), as defined by the World Health Organisation (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. 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. It is not unusual in some countries to have the evaluation and diagnosis performed by clinical psychologists, in conjunction with a general practitioner. This recognizes the non-availability of psychiatrists for ADHD evaluations in some countries.

To be clear, it is acceptable to have the evaluation performed by a clinical psychologist although the prescribing physician should write an accompanying letter. A proper evaluation as described below is imperative.

b. Diagnosis Criteria

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

ii) The physician/psychologist should have assessed the patient/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 criteria (or ICD 10).

Simply stating that the patient meets the DSM 5 criteria is not adequate. There should be some description or summary on how the criteria were assessed and which criteria were met.

Additional Information in the assessment of ADHD (these are not mandatory):

In the diagnostic assessment there should ideally be 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, DIVA 5.0 or DIVA 2.0[33,34]
- ⇨ Children: Vanderbilt, K-SADs, DISC, Conners [24], SNAP, Young DIVA 2, ACE

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 diagnosis. However, it is not mandatory to demonstrate that a patient has tried and failed other medication.

c. Primary Diagnosis of ADHD as an Adult (i.e., after 18 years).

To fulfill the DSM 5 criteria, there should be evidence of symptoms during childhood, regardless of the age of the primary diagnosis, i.e., the DSM 5 criteria cannot be met unless there were symptoms in childhood. This should ideally be from reliable independent sources, psychologist's 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 amfetamine [amphetamine] derivatives, including the amfetamine 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 over activity, increasing attention and reducing impulsiveness, with the effects being evident within a short period of time.[22] It should be noted that the choice of first line pharmacological treatment in ADHD varies across countries and atomoxetine (Strattera), guanfacine and clonidine 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.[24,25,2729]

b. Route of Administration

Oral

c. Dosage and Frequency

Both methylphenidate and amfetamine 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. 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[29]. 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 destabilizing 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).

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 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.[24] 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.

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.[26]

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 [28,37].

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 (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 more expansive side effect profile. In addition, this medication is not available in all countries. Other medications (e.g. clonidine, guanfacine, bupropion)[35] 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 amfetamine 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. 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.

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 and 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.

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

References

1. International Consensus Statement on ADHD. Clin Child Fam Psychol Rev. 2002; 5:89–111.

2. Kutchner S, Aman M, Brooks SJ, et al. International consensus statement on attention deficit hyperactivity disorder (ADHD) and disruptive behaviour disorders (DBDs): clinical implications and treatment practice suggestions. Eur Neuropsychopharmacol. 2004;14:11–28.

3. Wilens TE, Faraone SV, Biederman J. Attention-deficit/hyperactivity disorder in adults. JAMA. 2004;292:619–623.

4. Polanczyk, G., de Lima, M. S., Horta, B. L., Biederman, J. & Rohde, L. A. (2007). The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am J Psychiatry 164, 942-8.

5. Fayyad, J., De Graaf, R., Kessler, R., Alonso, J., Angermeyer, M., Demyttenaere, K., De Girolamo, G., Haro, J. M., Karam, E. G., Lara, C., Lepine, J. P., Ormel, J., Posada-Villa, J., Zaslavsky, A. M. & Jin, R. (2007). Cross-national prevalence and correlates of adult attention-deficit hyperactivity disorder. Br J Psychiatry 190, 402-9.

6. Biederman J, Mick E, Faraone SV. Age-dependent decline of symptoms of attention deficit hyperactivity disorder: impact of remission definition and symptom type. Am J Psychiatry. 2000;157:816–818.

7. Weiss G, Hechtman L, Milroy T, Perlman T. Psychiatric status of hyperactives as adults: a controlled prospective 15-year follow-up of 63 hyperactive children. J Am Acad Child Adolesc Psychiatry. 1985;24:211–220.

8. Barkley RA, Fischer M, Smallish L, Fletcher K. Young adult follow-up of hyperactive children: antisocial activities and drug use. J Child Psychol Psychiatry. 2004;45:195–211.

9. Biederman J, Faraone SV, Spencer TJ, Mick E, Monuteaux MC, Aleardi M. Functional impairments in adults with self-reports of diagnosed ADHD: A controlled study of 1001 adults in the community. J Clin Psychiatry. 2006;67:524–540.

10. Mannuzza S, Klein RG, Bonagura N, Malloy P, Giampino TL, Addalli KA. Hyperactive boys almost grown up. V. Replication of psychiatric status. Arch Gen Psychiatry. 1991;48:77–83.

11. Faraone SV, Biederman J, Mick E. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. Psychol Med. 2006;36:159–165.

12. American Academy of Pediatrics Clinical practice guideline: diagnosis and evaluation of the child with attention-deficit/hyperactivity disorder. Pediatrics. 2000;105:1158–1170.

13. Practice Parameter for the Assessment and Treatment of Children and Adolescents With Attention-Deficit/ Hyperactivity DisorderJ. AM. ACAD. CHILD ADOLESC. PSYCHIATRY, 46:7, JULY 2007.

14. Larson K, Russ SA, Kahn RS, Halfon N. Patterns of comorbidity, functioning, and service use for US children with ADHD, 2007. Pediatrics. 2001;127:462–470.

15. Pliszka SR. Comorbidity of attention-deficit/hyperactivity disorder with psychiatric disorder: an overview. J Clin Psychiatry. 1998;59 (Suppl 7):50–58.

16. Spencer T, Biederman J, Wilens T, Greene R. Principals and Practice. New York, NY: Oxford University Press; 2003. Pediatric Psychopharmacology.

17. Wilens TE, Biederman J, Brown S, et al. Psychiatric comorbidity and functioning in clinically referred preschool children and school age youths with ADHD. J Am Acad Child Adolesc Psychiatry. 2002;41:262–268.

18. Wilens TE, Martelon MK, Joshi G, et al. Does ADHD predict substance-use disorders? A 10-year follow-up study of young adults with ADHD. J Am Acad Child Adolesc Psychiatry. 2011;50:543–553.

19. Wilens TE, Biederman J, Brown S, et al. Psychiatric comorbidity and functioning in clinically referred preschool children an school age youths with ADHD. J Am Acad Child Adolesc Psychiatry. 2002;41:262–268.

20. Valdizán JR, Izaguerri-Gracia AC. ADHD in adults. Rev Neurol. 2009;48(Suppl 2):S95–S99.

21. American Psychiatric Association The Diagnostic and Statistical Manual of Mental Disorders, Fifith Edition, Washington, DC: American Psychiatric Association; 2013.

22. Journal of the American Academy of Child & Adolescent Psychiatry. 42(2):193-200, February 2003.

23. Faraone SV, Spencer T, Aleardi M, Pagano C, Biederman J. Meta-analysis of the efficacy of methylphenidate for treating adult attention-deficit/hyperactivity disorder. J Clin Psychopharmacol. 2004;24:24–29.

24. Conners CK, March JS, Frances A, Wells KC, Ross R. The expert consensus guideline series: treatment of attention-deficit/hyperactivity disorder. J Atten Disord. 2001;4(Suppl 1):7–128.

25. Wigal T, Greenhill L, Chuang S, et al. Safety and tolerability of methylphenidate in preschool children with ADHD. J Am Acad Child Adolesc Psychiatry. 2006;45:1294–1303.

26. Lerner M, Wigal T. Long-term safety of stimulant medications used to treat children with ADHD. Pediatr Ann. 2008;37:37–45.

27. Merkel RL, Kuchibhatla A. Safety of stimulant treatment in attention deficit hyperactivity disorder: Part I. Expert Opin Drug Saf. 2009;8:655–668.

28. Turgay, A. Aggression and disruptive behaviour disorders in children and adolescents. Expert Rev Neurother. 2004 Jul;4(4):623-32.

29. Kooij et al. European consensus statement on diagnosis and treatment of adult ADHD. The European network Adult ADHD. BMC Psychiatry. 2010; 10:67.

30. Michielsen M, Semeijn E, Comijs HC, van de Ven P, Beekman AT, Deeg DJ, Kooij JJ. Prevalence of attention-deficit hyperactivity disorder in older adults in The Netherlands. Br J Psychiatry. 2012 Oct;201(4):298-305.

31. Cortese S, Moreira-Maia CR, St Fleur D, Morcillo-Peñalver C, Rohde LA, Faraone SV. Association Between ADHD and Obesity: A Systematic Review and Meta-Analysis. Am J Psychiatry. 2016 Jan;173(1):34-43.

32. Kooij JJ. ADHD and Obesity. Am J Psychiatry. 2016 Jan;173(1):1-2.

33. Ramos-Quiroga JA, Nasillo V, Richarte V, Corrales M, Palma F, Ibáñez P, Michelsen M, Van de Glind G, Casas M, Kooij JJ. Criteria and Concurrent Validity of DIVA 2.0: A Semi-Structured Diagnostic Interview for Adult ADHD. J Atten Disord. 2016 Apr 28.

34. Pettersson R, Söderström S, Nilsson KW. Diagnosing ADHD in Adults: An Examination of the Discriminative Validity of Neuropsychological Tests and Diagnostic Assessment Instruments. J Atten Disord. 2015 Dec 17.

35. Buoli M, Serati M, Cahn W. Alternative pharmacological strategies for adult ADHD treatment: a systematic review. Expert Rev Neurother. 2016;16(2):131-44.

36. Tripp G, Luk SL, Schaughency EA, Singh R: DSM-IV and ICD-10: a comparison of the correlates of ADHD and hyperkinetic disorder. JAmAcadChild AdolescPsychiatry 1999, 38(2):156-164.

37. Barkley RA, Cox D: A review of driving risks and impairments associated with attention-deficit/hyperactivity disorder and the effects of stimulant medication on driving performance. J Safety Res 2007, 38(1):113-128.

38. Dalsgaard S, Østergaard SD, Leckman JF, Mortensen PB, Pedersen MG: Mortality in children, adolescents, and adults with attention deficit hyperactivity disorder: a nationwide cohort study. Lancet 2015, 30;385 (9983):2190-6.

39. Dalsgaard S, Leckman JF, Mortensen PB, Nielsen HS, Simonsen M: Effect of drugs on the risk of injuries in children with attention deficit hyperactivity disorder: a prospective cohort study. Lancet Psychiatry 2015, 2(8):702-9.