ATTENTION-DEFICIT HYPERACTIVITY DISORDER

CHI Formulary Indication Review

مجلس الضمان الصحي
Council of Health Insurance

INDICATION UPDATE

ADDENDUM- January 2024

To the CHI Original Clinical Guidance- Issued ADHD May 2020

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Abbreviations

ADD	Attention Deficit Disorder
ADHD	Attention-Deficit Hyperactivity Disorder
APA	American Psychiatric Association
ATX	Atomoxetine
CADTH	Canadian Agency for Drugs and Technologies in Health
CHI	Council of Health Insurance
CI	Confidence Interval
CPG	Clinical Practice Guideline
DALY	Disability-Adjusted Life Year
DSM	Diagnostic and Statistical Manual of Mental Disorders
ER/XR	Extended Release
GBD	Global Burden of Disease
GXR	Guanfacine Extended Release
HAS	Haute Autorite de Sante
LDX	Lisdexamfetamine
MPH	Methylphenidate
PMDA	Pharmaceuticals and Medical Devices Agency
RCT	Randomized Controlled Trial
SFDA	Saudi Food and Drug Authority
SUD	Substance Use Disorder

Executive Summary

Attention-deficit hyperactivity disorder (ADHD) is a psychiatric condition that has long been recognized as affecting children's ability to function. According to the American Psychiatric Association (APA), ADHD is placed within the manual's chapter "neurodevelopmental disorders". These are characterized by developmental deficits or differences in brain processes that produce impairments of personal, social, academic, or occupational functioning[1,2]. Hence, the definition of ADHD as stated by DSM-5-TR is "a neurodevelopmental disorder defined by impairing levels of inattention, disorganization, and/or hyperactivity-impulsivity"[2].

Individuals suffering from this disorder show patterns of developmentally inappropriate levels of inattentiveness, hyperactivity, or impulsivity. Although there used to be two different diagnoses of attention deficit disorder vs. ADHD. Inattention and disorganization entail inability to stay on task, seeming not to listen, and losing materials necessary for tasks, at levels that are inconsistent with age or developmental level. Hyperactivity-impulsivity entails overactivity, fidgeting, inability to stay seated, intruding into other people's activities, and inability to wait symptoms that are excessive for age or developmental level[2]. Yet, the DSM IV combined this into one disorder with three subtypes: predominantly inattentive, predominantly hyperactive, or combined type[3].

The symptoms begin at a young age and usually include lack of attention, lack of concentration, disorganization, difficulty completing tasks, being forgetful, and losing things. These symptoms should be present before the age of 12, have lasted six months, and interfere with daily life activities to be labeled as ADHD. This must be present in more than one setting (i.e., at home and school, or school and after-school activities). It can have large consequences, including social interactions, increased risky behaviors, loss of jobs, and difficulty achieving in school[3].

ADHD is not a new condition and has been called different names throughout history. It was labeled as 'minimal brain dysfunction' in the 1930s and has ever since changed names to ADD and ADHD, respectively. Its prevalence has increased over time, with a seeming spike in the 1950s as school became more standardized for children[3].

ADHD is a disorder that is diagnosed clinically and does not have any specific laboratory or radiologic tests. Even though the authors of DSM-5-TR themselves explicitly admit, the discoveries that could confirm ADHD as a neurodevelopmental disorder have not yet materialized. As such, no biological marker is diagnostic for ADHD. Moreover, meta-analyses of all neuroimaging studies do not show differences between individuals with ADHD and control subjects[2], thus no form of neuroimaging can be used for diagnosis of ADHD. Hence the disorder should be

diagnosed based upon the history of the patient. The evaluation of the patient with ADHD is usually done with different rating scales and multiple informants who may include the teachers and parents. It is necessary for a clinician to look for other disorders as they may be a cause for the symptoms that a child is exhibiting. It should not be diagnosed in the context of symptoms from another disorder, for example, a psychotic episode or manic episode[3].

Types of ADHD (DSM-5)[3]

1. Predominantly inattentive
2. Predominantly impulsive or hyperactive
3. Combination of the above
    - The onset is usually before age 12.
    - Symptoms present at school, work, or home.
    - The disturbance causes significant impairment in social, occupational, and academic functioning.
    - The disorder is not accounted for by any other behavior disorder.

The etiology of ADHD is related to a variety of factors that include both a genetic and an environmental component. It is one of the most heritable conditions in terms of psychiatric disorders. There is a much greater concordance in monozygotic twins than dizygotic. Siblings have twice the risk of having ADHD than the general population. Similarly, viral infections, smoking during pregnancy, nutritional deficiency, and alcohol exposure in the fetus have also been explored as possible causes of the disorder. The number of dopaminergic receptors has also been implicated in the development of the disorder whereby research has shown that the receptors are decreased in the frontal lobes in individuals with ADHD. There is also evidence for the role of noradrenergic receptor involvement in ADHD[3].

The prevalence of persistent adult ADHD (with a childhood onset) and symptomatic adult ADHD (regardless of a childhood onset) both decreased with advancing age. By adjusting for the global demographic structure in 2020, the prevalence of persistent adult ADHD was 2.58% and that of symptomatic adult ADHD was 6.76%, translating to 139.84 million and 366.33 million affected adults in 2020 globally[4].

The pooled prevalence of ADHD in the Saudi population was 12.4% (95% CI: 5.4%–26%). For ADHD-Inattentive and ADHD-Hyperactive presentations, the prevalence was 2.9% (95% CI: 0.3%–23.3%) and 2.5% (95% CI: 0.2%–20.5%), respectively. Regarding the combined AD and HD, the prevalence was 2.5% (95% CI: 0.2%–20.5%). Children of women with psychological disorders during pregnancy (P = 0.043), insufficient vitamin B during pregnancy (P = 0.006), allergic reactions (P = 0.032), and disabling

symptoms of muscle pain during pregnancy (P = 0.045) were associated with an increased risk of ADHD[5].

ADHD accounted for 0.8% of the global mental disorder disability-adjusted life years (DALYs), with mortality set at zero by the global burden of disease (GBD). From 1990 to 2019 there was a decrease of −8.75% in the global age-standardized prevalence and of −4.77% in the global age-standardized incidence. The largest increase in incidence, prevalence, and burden from 1990 to 2019 was observed in the United States; the largest decrease occurred in Finland. Incidence, prevalence, and DALYs remained approximately 2.5 times higher in males than females from 1990 to 2019. Incidence peaked at age 5–9 years, and prevalence and DALYs at age 10–14 years. Our re-analysis of data prior to 2013 showed a prevalence in children/adolescents two-fold higher (5.41%, 95% CI: 4.67–6.15%) compared to the corresponding GBD estimated prevalence (2.68%, 1.83–3.72%), with no significant differences between low- and middle- and high-income countries[6].

Pharmacological therapy remains the mainstay of treatment for patients who have ADHD. It is divided into two major categories, which fall into stimulants or non-stimulants. Stimulants are further broken into amphetamines and methylphenidates. Both types of stimulants block the reuptake of dopamine in the presynaptic membranes and postsynaptic membranes. Amphetamines also directly release dopamine. Stimulants are the mainstay of treatment for ADHD. They are effective in about 70% of patients[3]. There are multiple formulations of each subtype of stimulants, including immediate-release and extended-release, long-acting, or sustained release. Side effects of stimulants include changes in blood pressure, decreasing appetite and sleep, and risk of dependency. However, there is an increased risk of substance use in patients with ADHD and studies show treating with a stimulant decreases their overall lifetime risk of substance abuse. There is a higher risk of substance use or, misuse with Ritalin immediate release and Adderall in comparison with concerta[7,8]. Because stimulants are controlled substances, providers often are hesitant to use them. However, repeated evidence has shown how imperative it is to try stimulants in ADHD[3]. Atomoxetine, methylphenidate and lisdexamfetamine are stimulant medications available in Saudi Arabia. Controlled medication, including those for ADHD, can only be filled with a local prescription[9].

CHI issued ADHD guidelines in May 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations. Below is a description of sections that need updates.

This report functions as an addendum to the prior CHI ADHD clinical guidance and seeks to offer guidance for the effective management of **ADHD.** It provides an **update on the ADHD Guidelines** for CHI Formulary with the ultimate objective of

updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update are summarized, being **the updated guidelines added to the report such as** Attention deficit hyperactivity disorder (ADHD) in adults: Good practice guidelines Royal College of Psychiatrists in Scotland CR235, January **[2023]** and **the new guidelines added to the report such as** Evidence-based clinical practice guideline for management of attention deficit hyperactivity disorder ADHD in Saudi Arabia **[2020],** Updated European Consensus Statement on diagnosis and treatment of adult ADHD **[2019],** Society for Developmental and Behavioral Pediatrics Clinical Practice Guideline for the Assessment and Treatment of Children and Adolescents with Complex Attention Deficit/Hyperactivity Disorder **[2020].**

After carefully examining clinical guidelines and reviewing the SFDA drug list, there is a new SFDA registered drug to include in the CHI formulary, lisdexamfetamine dimesylate while removing lithium sulfate as it is no longer SFDA-registered.

There have been no changes and updates made to the previously listed drugs in terms of drug information and prescribing edits since May 2020.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in ADHD therapeutic management.

Below is a table summarizing the major changes based on the different ADHD guidelines used to issue this report:

Table 1. General Recommendations for the Management of ADHD

Management of ADHD		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
Methylphenidate is recommended as a first line of treatment for ADHD in adults, as is **lisdexamfetamine**. Methylphenidate should be offered to those who have not had an adequate response to lisdexamfetamine, if this has been the first choice, (at an adequate dose for less than six weeks) as some individuals	Not graded	Royal College of Psychiatrists in Scotland (2023)

may respond better to an alternative stimulant. Primarily a dopamine reuptake inhibitor, with some action on noradrenaline and other catecholamines.		
Stimulants are the treatment of choice for adults with ADHD. Long-lasting, extended-release formulations are preferred for reasons of adherence to treatment, for the protection against abuse, to avoid rebound symptoms, for safer driving, and to provide cover throughout the day without the need for multiple dosing.	Not graded	European Consensus Statement (2019)
Psychoeducation for adults with ADHD and their significant others is recommended as a *first treatment step.*	Not graded	European Consensus Statement (2019)
Atomoxetine (second line) should be considered in adults unresponsive or intolerant to both methylphenidate and lisdexamphetamine.	Not graded	Royal College of Psychiatrists in Scotland (2023)
Guanfacine – an alpha agonist and a non-stimulant treatment. It has a license for ADHD in children for whom stimulants are not suitable, tolerated, or effective. It does not currently have a license for adults but is being increasingly used.	Not graded	Royal College of Psychiatrists in Scotland (2023)
Other treatments – other medications which have less of an evidence base are: • *Bupropion* (dopamine and noradrenaline reuptake inhibitor) • *Modafinil* (indirect dopamine enhancing substance) *Clonidine* (alpha agonist) and Noradrenergic antidepressants such as *duloxetine, reboxetine, imipramine* and *venlafaxine*. Activating antidepressants should not be taken in the evening/at	Not graded	Royal College of Psychiatrists in Scotland (2023)

night, i.e. morning and lunchtime dosing only.		
The *non-stimulant atomoxetine* is recommended as a *second line treatment*. There is limited evidence in adults for *guanfacine*, *bupropion*, tricyclic antidepressants (imipramine) and *reboxetine* in controlled studies.	Not graded	European Consensus Statement (2019)
Stimulants can potentially trigger or exacerbate psychosis, mania, and tics, primarily via their dopaminergic effect. However, atomoxetine may in fact be helpful for anxiety disorders.	Not graded	Royal College of Psychiatrists in Scotland (2023)
In the evaluation of a child or adolescent with complex ADHD, the clinician should verify any previous diagnoses and assess for coexisting conditions employing an evidence-based approach that is developmentally appropriate, culturally sensitive, and inclusive of data from multiple settings and sources (home, school, community). The evaluation should include an appropriate, comprehensive medical history and physical examination, and psychological assessment based on the child's presenting problems and their severity, functional impairments, cognitive/developmental level, and the judgment of the treating clinician	Grade B. Strong recommendation	Society for Developmental and Behavioral Pediatrics (2020)
In patients with ADHD and substance use disorder, to be effective, treatment with stimulants may use higher dosages than normal.	Not graded	European Consensus Statement (2019)
In patients with ADHD and bipolar disorder, the combined approach of a mood stabilizer with a stimulant has been shown to treat both disorders effectively without inducing (hypo)manic states.	Not graded	European Consensus Statement (2019)

During pregnancy stimulants are not advised, though large cohort data showed no increased risk for congenital malformations using stimulants during the first trimester.	Not graded	European Consensus Statement (2019)
In patients with ADHD and sleep problems, in many cases, ADHD in children and adults is associated with a circadian rhythm disorder with delayed sleep onset.	Not graded	European Consensus Statement (2019)
Treatment of complex ADHD should include evidence-based approaches that address ADHD and account for coexisting conditions while respecting family background and preferences. Although behavioral and educational approaches serve as the foundation for intervention, it is often necessary to combine these approaches with pharmacological treatments. Treatment should focus on areas of functional impairment, and not just symptom reduction, by incorporating developmentally appropriate strategies for self-management, skill building, and prevention of adverse outcomes (e.g., substance use, conduct problems, problems of depression/anxiety, suicidal ideation, educational failure).	Grade C to B (may vary by specific coexisting condition). Strength: Recommendation.	Society for Developmental and Behavioral Pediatrics (2020)

At the end of the report, a **key recommendation synthesis section** is added highlighting the latest updates in **the clinical and therapeutic management of ADHD.**

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI ADHD report, and the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

This section contains the **updated versions** of the guidelines mentioned in the May 2020 CHI ADHD Report and the corresponding recommendations:

Table 2. Guidelines Requiring Revision

Guidelines Requiring Revision	
Old Versions	**Updated versions**
Section 1.1 National Institute for Health and care excellence (NICE) guidelines for attention deficit hyperactivity disorder: diagnosis and management **[Updated September 2019]**	N/A*
Section 1.2 American Academy of Pediatrics (AAP) Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents **[2019]**	N/A*
Section 1.3 The Canadian ADHD Practice Guidelines **[2020]**- Canadian ADHD resource alliance (CADDRA)	N/A*
Section 1.4 ADHD in adults: good practice guidelines (Royal College of Psychiatrists in Scotland) **[2017]**	**Section 1.1.1.** Attention deficit hyperactivity disorder (ADHD) in adults: Good practice guidelines Royal College of Psychiatrists in Scotland CR235, January **[2023]**[10]

Section 1.5 Clinical Practice Points on the diagnosis, assessment, AND management OF ATTENTION DEFICIT HYPERACTIVITY disorder in children and adolescents- Australian government **[2012]**	N/A*
Section 1.6 National Health and Medical Research Council (NHMRC) Clinical Practice Points on diagnosis, assessment, and management of ADHD in children and adolescents **[2012]**	N/A*
Section 1.7 The Texas Children's Medication Algorithm Project: Revision of the Algorithm for Pharmacotherapy of Attention-Deficit/Hyperactivity Disorder **[2005]**	N/A*
Section 1.8 International consensus statement on attention-deficit/hyperactivity disorder (ADHD) and disruptive behavior disorders (DBDs): Clinical implications and treatment practice suggestions **[2003]**	N/A*

*: *No updated versions available*

1.1.1 Royal College of Psychiatrists in Scotland Attention Deficit Hyperactivity Disorder (ADHD) in Adults: Good Practice Guidelines (2023)

The 2023 revised edition of the attention deficit hyperactivity disorder (ADHD) in adults good practice guidelines published by the Royal College of Psychiatrists in Scotland introduced a set of recommendations without a grading scheme, outlined as follows[10]:

Management of ADHD

Drug treatments can be classified into stimulants (**methylphenidate**, **lisdexamphetamine**, **dexamfetamine**) and non-stimulants (**atomoxetine**, **guanfacine, imipramine**, and others). Their mechanism of action involves increased availability of synaptic dopamine and/or noradrenaline.

- Stimulants have an immediate action and can therefore be titrated to an effective dose for each patient more quickly.
- Stimulants are usually considered before non-stimulants due to their superior efficacy. Stimulants come in immediate-release or slow/modified-release preparations.
- A combination of modified- and immediate-release preparations can be used to fine-tune symptom control at certain times of day. For example, a slow-release preparation taken in the morning may have little effect by evening time and can be 'topped up' with an immediate-release preparation.
- Stimulants have more potential for diversion/misuse, particularly immediate-release preparations.
- Stimulants have an appreciable positive effect on attention in those without ADHD and a 'therapeutic trial' therefore has no diagnostic value. Stimulants are controlled drugs.
- The non-stimulants have a delayed onset of action like that of antidepressants. They are also gradually titrated but more to counter potential side effects than to reach an effective dose for that individual. Non-stimulants are not controlled drugs.

Licensed medications

Not all treatments licensed for ADHD in children have a license for use with adults.

However, this should not prevent medications being prescribed according to best practice and with reference to local formularies.

In 2017, the Royal College of Psychiatrists has produced a consensus statement for use of licensed medicines for 'off-label' uses.

Before prescribing, the clinician must ensure that the patient knows of the 'off-label' use and understands the potential risks and benefits of the medication, that this is documented clearly and that the patient is able to give fully informed consent.

If prescribing responsibility is to be shared with primary care, the clinician should ensure that the risk assessment and consent issues are communicated to the GP.

Local formularies may specify preferred branded generics of reference products which are subject to change, and prescribers are advised to continuously refer to this.

- First line medications

Methylphenidate (first line)

- Recommended as a first line of treatment for ADHD in adults, as is Lisdexamfetamine (NICE, 2018[11]).
- Methylphenidate should be offered to those who have not had an adequate response to Lisdexamfetamine, if this has been the first choice, (at an adequate dose for less than six weeks) as some individuals may respond better to an alternative stimulant (NICE, 2018[11]).

Dose titration, using immediate- or slow-release preparations, should be done using the smallest available dose increments at fixed intervals (e.g. every fortnight), until an adequate response is achieved, or intolerable side effects are experienced.

- Immediate-release: 5mg, 2–3 times daily, increased every 1–2 weeks by 5mg 2–3 times daily to three times daily, according to response/tolerability, to a maximum of 100mg daily.
- Modified-release: start at lowest dose, e.g. 18mg Concerta XL, increased every 1–2 weeks by minimum available dose, according to response/tolerability.
- Monitor weight, blood pressure and pulse rate.

Lisdexamfetamine (first line)

- Recommended as a first line of treatment for ADHD in adults, as is Methylphenidate (NICE, 2018[11]).
- Should be offered to those who have not had an adequate response to methylphenidate, if this has been the first choice (at an adequate dose for less than six weeks), as some individuals may respond better to an alternative stimulant (NICE, 2018[11]).
- Is a slow-release pro-drug.
- Promotes the release and prevents the reuptake of dopamine and noradrenaline.
- Dose titration follows the same principles as for methylphenidate.
- Lisdexamfetamine can have a long effect into the evening which may cause problems such as insomnia. In adults who cannot tolerate the longer effect profile, dexamphetamine (immediate-release) 2–3 times per day should be considered as an alternative (NICE, 2018[11]).
- Conversely some individuals may notice a rebound of ADHD symptoms in the evening when lisdexamfetamine wears off. Topping up with

dexamphetamine (immediate release) in the evening may be appropriate here but can risk insomnia and tolerance.

- Dexamfetamine is considered to have more misuse/diversion potential than methylphenidate, although there is likely to be less misuse potential with lisdexamfetamine owing to its pharmacokinetic profile. It is placed as a second-line agent in the NICE 2018 guideline and is useful for those with a good symptom response to lisdexamphetamine but not tolerating its side effects (such as insomnia).

Atomoxetine (second line)

- Noradrenaline reuptake inhibitor, non-stimulant treatment: it is not a controlled drug.
- Should be considered in adults unresponsive or intolerant to both methylphenidate and lisdexamphetamine. Or when misuse/diversion of stimulants is a concern. Does not require the same individual fine-tuning of dose that stimulants require and has the advantage of once-daily dosing.
- Side effects are usually avoided by a gradual dose titration, for example starting at 40mg and increasing by 20mg per week.
- Doses above 80mg have not shown any additional benefit. Some individuals are poor metabolizers of atomoxetine and are sensitive to side effects at low doses.
- Acute liver failure and suicidality are rare but there are significant potential side effects. All patients should be advised of symptoms of these adverse events.
- Monitor weight, blood pressure and pulse rate at baseline, after each dose change and long-term every three months, with weight every six months. ·
- Increased risk of ventricular arrhythmias has been described when used with drugs that prolong the QTc interval.

Other pharmacological options

- ***Guanfacine*** – an alpha agonist and a non-stimulant treatment. It has a license for ADHD in children for whom stimulants are not suitable, tolerated, or effective. It does not currently have a license for adults but is being increasingly used.
- Combinations – if there is an inadequate response to monotherapy, then combining a stimulant with a non-stimulant is occasionally done in clinical practice, although there is currently a limited evidence base for this.

- Other treatments – other medications which have less of an evidence base are:
- ***Bupropion*** (dopamine and noradrenaline reuptake inhibitor)
- ***Modafinil*** (indirect dopamine enhancing substance)
- ***Clonidine*** (alpha agonist) and
- Noradrenergic antidepressants such as ***duloxetine, reboxetine, imipramine*** and ***venlafaxine***. Activating antidepressants should not be taken in the evening/at night, i.e. morning and lunchtime dosing only.

Whilst every attempt has been made in this document to ensure that doses are correct, prescribers are encouraged to check doses against relevant reference documents.

In general, prescribers are encouraged to use generic names, however cost implication may mean that specific trades names are recommended by local formulary groups that may change over time. Clinicians should check the equivalency of formulations in these situations.

1.2 Additional Guidelines

This part includes the added guidelines to the previous CHI ADHD report, along with their recommendations.

Table 3. List of Additional Guidelines

Additional Guidelines
Section 1.2.1. Evidence-based clinical practice guideline for management of attention deficit hyperactivity disorder ADHD in Saudi Arabia, 2020[12]
Section 1.2.2. Updated European Consensus Statement on diagnosis and treatment of adult ADHD, 2019[13]
Section 1.2.3 Society for Developmental and Behavioral Pediatrics Clinical Practice Guideline for the Assessment and Treatment of Children and Adolescents with Complex Attention Deficit/Hyperactivity Disorder, 2020[14]

1.2.1 Evidence-Based Clinical Practice Guideline for Management of Attention Deficit Hyperactivity Disorder (ADHD) in Saudi Arabia (2020)

The evidence-based clinical practice guideline for management of attention deficit hyperactivity disorder (ADHD) in Saudi Arabia was published in 2020 and endorsed by the Saudi Health Council, the Saudi Psychiatric Association, the Saudi Pediatric

Neurology Society, the Saudi Pediatric Association, the Saudi Pharmaceutical Society, and the Saudi Society for Professional Psychology. It is intended for use by healthcare professionals to aid in the management of ADHD in children under 5 years, children, and young people (aged 5 to 17 years), and adults aged 18 years or over[12].

Table 4. The Evidence-Based Clinical Practice Guideline for Management of Attention Deficit Hyperactivity Disorder (ADHD) in Saudi Arabia

Strength of Recommendations
Must: Recommendations That Must (or Must Not) Be Followed
The words 'must' or 'must not' are generally only used if there is a legal duty to apply the recommendation. Occasionally the word 'must' (or 'must not') has been used if the consequences of not following the recommendation could be extremely serious or potentially life threatening.
Should: Recommendations That Should (or Should Not) Be Followed – a 'Strong' Recommendation
The word 'offer' (and similar words such as 'refer' or 'advise') has been used when there is a good degree of confidence that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. Similar forms of words (for example, 'Do not offer…') are used when an intervention will not be of benefit for most patients
Could: Recommendations That Could Be Followed
The word 'consider' is used when an intervention will do more good than harm for most patients, and will be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's/caregiver's values and preferences than on the strength of a recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Planning treatment

Healthcare providers should ensure continuity of care for people with ADHD.

Ensure that people with ADHD have a comprehensive, holistic shared treatment plan that addresses psychological, behavioral, and occupational or educational needs. Consider:

- the severity of ADHD symptoms and impairment, and how these affects or may affect everyday life (including sleep)
- their goals
- their resilience and protective factor
- the relative impact of other neurodevelopmental or mental health conditions
- the relative impact or interaction of other general medical conditions and/or their treatments.

Regularly discuss with people with ADHD, and their family members or carers, how they want to be involved in treatment planning and decisions; such discussions should take place at intervals to take account of changes in circumstances (for example, the transition from children to adult services) and developmental level and should not happen only once.

Before starting any treatment for ADHD, discuss the following with the person, and their family or carers as appropriate, encouraging children and young people to give their own account of how they feel:

- the benefits and harms of non-pharmacological and pharmacological treatments (for example, the efficacy of medication compared with no treatment or nonpharmacological treatments, potential adverse effects and non-response rates)
- the benefits of a healthy lifestyle, including exercise
- their preferences and concerns (it is important to understand that a person's/carer's decision to start, change or stop treatment may be influenced by media coverage, teachers, family members, friends, and differing opinion on the validity of a diagnosis of ADHD)
- how other mental health or neurodevelopmental conditions might affect treatment choices
- how nutritional status and/or other general medical conditions or existing medication regimens might affect treatment decisions.
- the importance of adherence to treatment and any factors that may affect this (for example, it may be difficult to take medication at school or work, or to remember appointments).

Record the person's preferences and concerns in their treatment plan.

- Ask young people (over 18 years old) and adults with ADHD if they wish a parent, partner, close friend, or carer to join discussions on treatment and adherence.

- Reassure people with ADHD, and their families or carers as appropriate, that they can revisit decisions about treatments.

Children under 5 years

These recommendations are for healthcare professionals with training and expertise in diagnosing and managing ADHD.

- Offer an ADHD-focused group parent-training program to parents or carers of children under 5 years with ADHD as first-line treatment.
- If after an ADHD-focused group parent-training program, ADHD symptoms across settings are still causing a significant impairment in a child under 5 years after environmental modifications have been implemented and reviewed, obtain advice from a specialist ADHD service with expertise in managing ADHD in young children (ideally a tertiary service).
- Do not offer medication for ADHD for any child under 5 years without a second specialist opinion from an ADHD service with expertise in managing ADHD in young children (ideally a tertiary service).

Children aged 5 years and over and young people

These recommendations are for healthcare professionals with training and expertise in diagnosing and managing ADHD.

- Give information about ADHD and offer additional support to parents and carers of all children aged 5 years and over and young people with ADHD. The support should be ADHD focused, can be group based and as few as 1 or 2 sessions. It should include:
    - education and information on the causes and impact of ADHD
    - advice on parenting strategies
    - with consent, liaison with school, college, or university
    - both parents and carers if feasible.
- If a child aged 5 years or over or young person has ADHD and symptoms of oppositional defiant disorder or conduct disorder, offer parents and carers a parent-training program that focuses on these behaviors, as well as group-based ADHD-focused support.
- Consider individual parent-training programs for parents and carers of children and young people with ADHD and symptoms of oppositional defiant disorder or conduct disorder when:

    - There are difficulties for families in attending group sessions (for example, because of disability, needs related to diversity such as language differences, learning disability [intellectual disability], parental ill-health, problems with transport, or where other factors suggest poor prospects for therapeutic engagement)
    - A family's needs are too complex to be met by group-based parent-training programs.
- Offer medication for children aged 5 years and over and young people only if:
    - Their ADHD symptoms are still causing a persistent significant impairment in at least one domain after environmental modifications have been implemented and reviewed.
    - They and their parents and carers have discussed information about ADHD.
    - A baseline assessment has been carried out See the recommendations on medication.
- Consider a course of cognitive behavioral therapy (CBT) for young people with ADHD who have benefited from medication but whose symptoms are still causing a significant impairment in at least one domain, addressing the following areas:
    - social skills with peers
    - problem-solving
    - self-control
    - active listening skills
    - dealing with and expressing feeling
- There are some low-quality evidence that cognitive-behavioural-based treatments may be beneficial for treating adults with ADHD in the short term (Cochrane, 2018)[15]. Reductions in core symptoms of ADHD have been achieved in addition to some low-quality evidence that cognitive behavioural therapy (CBT) may also improve common secondary disturbances in adults with ADHD, such as depression and anxiety.

<u>Adults</u>

- Offer medication to adults with ADHD if their ADHD symptoms are still causing a significant impairment in at least one domain after environmental modifications have been implemented and reviewed.

- Consider non-pharmacological treatment for adults with ADHD who have:
    - made an informed choice not to have medication
    - difficulty adhering to medication
    - found medication to be ineffective or cannot tolerate it.
- Consider non-pharmacological treatment in combination with medication for adults with ADHD who have benefited from medication but whose symptoms are still causing a significant impairment in at least one domain.
- When non-pharmacological treatment is indicated for adults with ADHD, offer the following as a minimum:
    - a structured supportive psychological intervention focused on ADHD
    - regular follow up either in person or by phone.
- Treatment may involve elements of or a full course of CBT.

Medication choice

Children aged 5 years and over and young people.

- Offer **methylphenidate** (either short or long acting) as the first line pharmacological treatment for children aged 5 years and over and young people with ADHD, taking into consideration that this is an off-label use for children aged between 5 and 6 years.
- Consider switching to **lisdexamfetamine** for children aged 5 years and over and young people who have had a 6-week trial of methylphenidate at an adequate dose and have not derived enough benefit in terms of reduced ADHD symptoms and associated impairment.
- Consider dexamfetamine for children aged 5 years and over and young people whose ADHD symptoms are responding to lisdexamfetamine but who cannot tolerate the longer effect profile.
- Offer atomoxetine or guanfacine to children aged 5 years and over and young people 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.

Adults

- Offer lisdexamfetamine or methylphenidate as first-line pharmacological treatment for adults with ADHD. This is an off-label use of lisdexamfetamine for adults with no ADHD symptoms in childhood. Not all preparations of methylphenidate are licensed for treating symptoms of ADHD in adults.
- Consider switching to lisdexamfetamine for adults 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.
- Consider switching to methylphenidate for adults 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.
- Consider dexamfetamine for adults whose ADHD symptoms are responding to lisdexamfetamine but who cannot tolerate the longer effect profile.
- Offer atomoxetine to adults 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.

Further medication choices

- Obtain a second opinion or refer to a tertiary service (such as specialized hospitals) if ADHD symptoms in a child aged 5 years or over, a young person or adult are unresponsive to one or more stimulants and one non-stimulant.
- Do not offer any of the following medications 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.

People with coexisting conditions

- Offer the same medication choices to people with ADHD and anxiety disorder, tic disorder or autism spectrum disorder as other people with ADHD.
- For children aged 5 years and over, young people and adults with ADHD experiencing an acute psychotic or manic episode:
    - Stop any medication for ADHD.
    - Refer to a tertiary ADHD service or specialized psychiatrist who may consider restarting or starting new ADHD medication after the episode

has resolved, considering the individual circumstances, risks, and benefits of the ADHD medication.

Considerations when prescribing ADHD medications

- When prescribing stimulants for ADHD, think about 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.
- When prescribing stimulants for ADHD, be aware that effect size, duration of effect and adverse effects vary from person to person.
- Think about using immediate- and modified-release preparations combination 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).
- Be cautious about prescribing stimulants for ADHD if there is a risk of diversion for cognitive enhancement or appetite suppression.
- Do not offer immediate-release stimulants or modified-release stimulants that can be easily injected or insufflated if there is a risk of stimulant misuse or diversion.
- Take into consideration the nutritional status of the child (e.g. BMI) because of the risk of weight loss when taking stimulants.

1.2.2 Updated European Consensus Statement on Diagnosis and Treatment of Adult ADHD (2019)

The European Network Adult ADHD (ENAA) was founded in 2003 to help improve the diagnosis and treatment of ADHD in adults in Europe and beyond. ENAA represents mental health care professionals and researchers from 28 countries with expertise on ADHD in adults. Recommendations from the 2019 updated European consensus statement on diagnosis and treatment of adult ADHD are outlined below without a grading scheme. Treatment's key points are listed below[13]:

- The treatment of adults with ADHD should follow a multimodal and multidisciplinary approach, which includes psychoeducation, pharmacotherapy, cognitive behavior therapy (CBT) and coaching for ADHD, which are all discussed in this article. Ideally, the treatment plan also involves the adult's partner, family, or close relationships, and in some cases systemic (family) therapy may be required when gross disruption to family relationships and functioning is present.
- *Psychoeducation* for adults with ADHD and their significant others is recommended as a *first treatment step.*

Pharmacotherapy

In the first European Consensus Statement, psychostimulants (methylphenidate and dexamphetamine) were recommended as the first-line pharmacotherapy for adult ADHD, as they exert moderate-to-high clinical effects, with average effects higher than atomoxetine (ATX) and other non-stimulant medications.

There were, however, no head-to-head studies providing robust comparative analysis of efficacy differences. Across most of Europe, lisdexamfetamine (LDX) has been introduced as a slow-release formulation of dexamphetamine.

The recent systematic review and network meta-analysis on the comparative efficacy and tolerability of medications for ADHD in children, adolescents, and adults by Sam Cortese et al showed, that the first pharmacological choice for ADHD in children and adolescents is methylphenidate, and amphetamines in adult.

In fact, in adults, amphetamines were not only the most efficacious compounds, as rated by clinicians and by self-report, but also as well tolerated as methylphenidate and the only compounds with better acceptability than placebo.

- Stimulants are the treatment of choice for adults with ADHD.
- Long-lasting, extended-release formulations are preferred for reasons of adherence to treatment, for the protection against abuse, to avoid rebound

symptoms, for safer driving, and to provide cover throughout the day without the need for multiple dosing.

- The *non-stimulant* ***atomoxetine*** is recommended as a *second line treatment*. There is limited evidence in adults for ***guanfacine***, ***bupropion***, tricyclic antidepressants and ***reboxetine*** in controlled studies.
- Cognitive Behavior Therapy reduces ADHD-core symptoms, associated symptoms such as emotion dysregulation, anxiety and depression, and functional impairments across different areas of daily living in adults.
- CBT is best used within a multi-modal treatment approach and as an adjunct to medication, as research does not fully support the efficacy of CBT as a sole treatment for adult ADHD.

Atomoxetine (ATX)

ATX may be a good choice with co-occurring anxiety that might be exacerbated by stimulants, as a RCT of adults with comorbid ADHD and social anxiety disorder found improvements in both ADHD and social anxiety. ATX does not appear to be effective in the treatment of comorbid depression in adolescents.

Guanfacine and clonidine

- In Europe, guanfacine extended-release (GXR), an alfa-2 adrenergic agonist, is licensed for the treatment of children and adolescents with ADHD for whom stimulants are not suitable, not tolerated or where shown to be ineffective Notably, there are currently no RCTs in adult patients to support the use of GXR in this age group, only a study using GXR or placebo as an adjunct to stimulant treatment that had insufficient effect. Both treatments did not differ in efficacy
- Extended-release (ER) clonidine is approved in the US for treatment of ADHD in 6–17-year-olds as monotherapy or an adjunct to stimulants. There are RCTs on both ER clonidine and IR clonidine in children and adolescents with ADHD, but no equivalent studies in adults.

Bupropion

- There are conflicting findings for bupropion from a small number of adult studies. Positive results were reported with higher doses (400–450 mg per day). Due to a limited evidence base, bupropion use should be restricted to cases who do not tolerate other ADHD medications.

Other medications

- Selective noradrenaline reuptake inhibitors such as reboxetine may be an alternative to ATX.
- There is limited evidence for tricyclic antidepressants.
- Selective serotonin reuptake inhibitors (SSRIs) are not effective for the treatment of ADHD.
- Modafinil, a wakefulness-promoting agent used in the treatment of narcolepsy, has not been demonstrated as an effective treatment for adult ADHD in a phase 3 trial that had high rates of side effects (86%) and drop-out (47%) possibly resulting from excessive doses (210–510 mg/day).

Combined psychopharmacology

The high rate of psychiatric comorbidity in adult ADHD frequently necessitates combined psychopharmacology. Accordingly, the risk of possible drug-drug interactions when treating adults with ADHD must be considered. These include the following:

- Monoamine oxidase inhibitors are generally contraindicated due to the risk of hypertensive crisis.
- Although methylphenidate (MPH) is mainly metabolized in the liver, drug interactions via CYP enzymes are uncommon. Amphetamines, however, are metabolized primarily via the CYP 2D6 enzyme system making drug interactions possible (with inhibitors or inducers of this enzyme system, e.g. fluoxetine and paroxetine)
- Treatment with medications that act on the noradrenaline system, including certain antidepressants (e.g. duloxetine, venlafaxine), will have an additive effect and may increase the risk of hypertension and other adverse cardiovascular events.
- Due to its metabolism by the CYP 2D6 enzyme system, ATX levels can increase in combination with enzyme-inhibiting SSRIs (e.g. fluoxetine and paroxetine).

Pharmacological treatment of special groups

- In patients with ADHD and substance use disorder, to be effective, treatment with stimulants may use higher dosages than normal.
- In patients with ADHD and bipolar disorder, the combined approach of a mood stabilizer with a stimulant has been shown to treat both disorders effectively without inducing (hypo)manic states.
- During pregnancy stimulants are not advised, though large cohort data showed no increased risk for congenital malformations using stimulants during the first trimester.
- In patients with ADHD and sleep problems, in many cases, ADHD in children and adults is associated with a circadian rhythm disorder with delayed sleep onset.

A meta-analysis of nine studies investigating the effects of stimulant medication on sleep in children and adolescents found that stimulants can lead to longer sleep latency, worse sleep efficiency, and shorter sleep duration. Similar findings have been reported in adults[16].

Careful titration of stimulants and psychoeducation around sleep optimization can improve the quality of sleep, possibly due to improved daytime structure, the maintenance of regular physical activity and improved mood.

In children with ADHD and chronic insomnia, melatonin has been shown to advance the sleep onset, and increase sleep duration.

Treatment of insomnia should always start with sleep hygiene education and optimizing the stimulant or non-stimulant treatment of ADHD. A low dose of IR MPH (usually 5 mg) taken at nighttime can reduce ceaseless mental activity to a degree that allows sleep in some cases.

The risk for cardiac malformations using MPH however was slightly increased, while this was not the case for amphetamines. Research on the wishes of older people with ADHD regarding treatment, and trials on the safety and efficacy of medicines are needed. Based on data from large cohort studies, following treatment, the negative outcomes associated with ADHD significantly diminish, i.e. traffic accidents, mortality, criminality, depression and suicide, and substance abuse.

Long-term safety concerns

- Currently there is no evidence of significant long-term risks using stimulants. Tomography scans find higher striatal dopamine transporter availability in ADHD patients treated with stimulants. The clinical implications of this up-regulation are not clear.

- Potential toxicity on heart valves of medications with an agonist effect on 5-HT2B receptors have been discussed, including MPH and guanfacine.
- Some argue that echocardiography should be routinely performed prior to treatment with potential valvulopathic drugs. This risk is not however established, and we and others do not recommend routine echocardiograms except in older adults (> age 50).

1.2.3 Society for Developmental and Behavioral Pediatrics Clinical Practice Guideline for the Assessment and Treatment of Children and Adolescents with Complex Attention Deficit/Hyperactivity Disorder (2020)

The 2020 recommendations by the Society for Developmental and Behavioral Pediatrics for the assessment and treatment of children and adolescents with complex ADHD are outlined below[14]:

Table 5. Society for Developmental and Behavioral Pediatrics Clinical Practice Guideline for the Assessment and Treatment of Children and Adolescents with Complex Attention Deficit/Hyperactivity Disorder (2020)

Grade	
B	Strong Recommendation
C	Recommendation, if there was a high to moderately high quality of evidence and a preponderance of benefit over harm
Option Level	"Option level" action statements, are supported by lower quality or limited evidence combined with the consensus expert opinion of the Panel. "Option level" action statements should be viewed as guidelines that may be considered by clinicians based on their knowledge of their patient with complex ADHD and their clinical judgment.

The clinician with specialized training or expertise should initiate a comprehensive assessment and develop an interprofessional, multimodal treatment plan for any child or adolescent through age 18 years with suspected or diagnosed complex ADHD with functional impairments upon referral from a primary care clinician. Complex ADHD is defined by any of the following:

- Aged 4 years or 12 years at the time of initial presentation of symptoms or impairment.
- Presence or suspicion of coexisting disorders and complicating factors:

    - Other neurodevelopmental disorders (e.g., global developmental delay, intellectual disability [ID], autism spectrum disorder [ASD], speech and language disorders, tic disorders)
    - Significant problems with the acquisition of academic skills including specific learning disorders (LDs) (i.e., reading, math, written language)
    - Mental health disorders (e.g., depression, anxiety, oppositional defiant disorder, conduct disorder, substance use disorders [SUDs], eating disorders)
    - Chronic medical conditions (e.g., history of extreme prematurity, epilepsy, cancer, traumatic brain injury, motor disabilities, fetal alcohol spectrum disorders)
    - Genetic disorders (e.g., Down syndrome, Fragile X syndrome)
    - Complicated psychosocial factors (e.g., adverse childhood experiences such as trauma, neglect, and poverty; parental mental health disorders)
- Moderate to severe functional impairments in important aspects of daily living (e.g., relationships with family and peers, activities of daily living)
- Diagnostic uncertainty on the part of the primary care clinician
- Inadequate response to treatment (or uncertainty about treatment planning). Aggregate evidence quality: Grade B. Strong recommendation

In the evaluation of a child or adolescent with complex ADHD, the clinician should verify any previous diagnoses and assess for coexisting conditions employing an evidence-based approach that is developmentally appropriate, culturally sensitive, and inclusive of data from multiple settings and sources (home, school, community).

The evaluation should include an appropriate, comprehensive medical history and physical examination, and psychological assessment based on the child's presenting problems and their severity, functional impairments, cognitive/developmental level, and the judgment of the treating clinician. Aggregate evidence quality: Grade B. Strong recommendation.

Psychoeducation about ADHD and its coexisting conditions and evidence-based behavioral and educational interventions are foundational for the treatment of complex ADHD and should be implemented at the outset of treatment whenever possible.

Evidence-based behavioral and educational interventions (e.g., behavioral parent training [BPT], behavioral classroom management [BCM], behavioral peer interventions [BPIs], and, for older children, organizational skills training [OST]) should be provided to all children and adolescents with complex ADHD.

These treatment approaches in home, school, and peer settings address key functional domains (behavioral, educational, social) that are associated with long-term outcomes. Aggregate evidence quality: Grade B. Strong recommendation.

Treatment of complex ADHD should include evidence-based approaches that address ADHD and account for coexisting conditions while respecting family background and preferences. Although behavioral and educational approaches serve as the foundation for intervention, it is often necessary to combine these approaches with pharmacological treatments.

Treatment should focus on areas of functional impairment, and not just symptom reduction, by incorporating developmentally appropriate strategies for self-management, skill building, and prevention of adverse outcomes (e.g., substance use, conduct problems, problems of depression/anxiety, suicidal ideation, educational failure). Aggregate evidence quality: Grade C to B (may vary by specific coexisting condition). Strength: Recommendation.

Given that ADHD is a chronic condition that often persists into adulthood, treatment of complex ADHD should include ongoing, scheduled monitoring of patients throughout the lifespan, commensurate with individual patient's needs and profile with particular emphasis on preparing for key developmental transitions (preschool to school, elementary to middle school, middle to high school, and high school to postsecondary education or employment). Aggregate evidence quality: Grade B. Strong recommendation.

Section 2.0 Drug Therapy in ADHD

This section comprises four subsections: the first contains the newly recommended drugs, the second covers drug modifications, the third outlines the drugs that have been withdrawn from the market, and the fourth details drugs that have been approved by the FDA and/or EMA but are not currently registered by the SFDA.

2.1 Additions

Since May 2020, there have been new drugs for the management of ADHD that have received FDA approval. These include: a non-stimulant, *Qelbree* (***Viloxazine***), *a CNS stimulant, Azstarys* (**serdexmethylphenidate and dexmethylphenidate**) and *Xelstrym* (**dextroamphetamine**). These three agents have not yet been registered by the SFDA and are discussed in section 2.4 below.

In addition, a CNS stimulant, **lisdexamfetamine,** approved in April 2008 for the treatment of ADHD in adults was **registered by the SFDA**. Hence, relevant information pertaining to this drug can be found below.

2.1.1 Lisdexamfetamine

This section includes pertinent information regarding the use of lisdexamfetamine in ADHD[17].

Table 6. Lisdexamfetamine Drug Information

SCIENTIFIC NAME Lisdexamfetamine	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	No
Indication (ICD-10)	F90, F98.8
Drug Class	Central Nervous System Stimulant
Drug Sub-class	-
ATC Code	N06BA12
Pharmacological Class (ASHP)	Central Nervous System Stimulant

DRUG INFORMATION	
Dosage Form	Capsule, hard
Route of Administration	Oral use
Dose (Adult) [DDD]*	30 mg once daily in the morning; may increase in increments of 10 mg or 20 mg at weekly intervals until optimal response is obtained; maximum: 70 mg/day. **Note:** Individualize dosage based on patient need and response to therapy. Administer at the lowest effective dose.
Maximum Daily Dose Adults*	70 mg/day
Dose (pediatrics)	Children ≥6 years and Adolescents: Capsules, chewable tablets: Oral: Initial: 20 to 30 mg once daily in the morning; may increase in increments of 10 mg/day or 20 mg/day at 3- to 7-day intervals until optimal response is obtained; maximum daily dose: 70 mg/day
Maximum Daily Dose Pediatrics*	70 mg/day
Adjustment	**Dosing: Altered Kidney Function**: Adult GFR ≥30 mL/minute/1.73 m2: There are no dosage adjustments provided in the manufacturer's labeling. GFR 15 to <30 mL/minute/1.73 m2: Maximum dose: 50 mg/day. GFR <15 mL/minute/1.73 m2: Maximum dose: 30 mg/day. ESRD requiring hemodialysis: Maximum dose: 30 mg/day; lisdexamfetamine and dextroamphetamine are not dialyzable. **Dosing: Hepatic Impairment: Adult** There are no dosage adjustments provided in the manufacturer's labeling. **Dosing: Altered Kidney Function: Pediatric** Children ≥6 years and Adolescents:

	GFR ≥30 mL/minute/1.73 m^2: There are no dosage adjustments provided in the manufacturer's labeling. GFR 15 to <30 mL/minute/1.73 m^2: Maximum daily dose: 50 mg/day. GFR <15 mL/minute/1.73 m^2: Maximum daily dose: 30 mg/day. ESRD requires hemodialysis: Maximum daily dose: 30 mg/day; lisdexamfetamine and dextroamphetamine are not dialyzable. **Dosing: Hepatic Impairment: Pediatric** There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	**AGE, MD, PA**
AGE (Age Edit): Treatment of attention-deficit/hyperactivity disorder (ADHD) in adults and pediatric patients ≥ 6 years of age.	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Lisdexamfetamine is a schedule 2 controlled drug and is subject to legal prescription requirements. It has the potential for misuse and diversion. Lisdexamfetamine should be prescribed by a neurologist, psychiatrist and/or a paediatrician.	
PA (Prior Authorization): Lisdexamfetamine should be given for the treatment of attention-deficit/hyperactivity disorder (ADHD) in adults and pediatric patients ≥6 years of age. For adults, at a dose of 30 mg once daily in the morning; may increase in increments of 10 mg or 20 mg at weekly intervals until optimal response is obtained; maximum: 70 mg/day. Dosage should be individualized based on patient need and response to therapy and administered at the lowest effective dose. Lisdexamfetamine should be prescribed by a neurologist, psychiatrist experienced in the diagnosis and treatment of ADHD.	
QL (Quantity Limit: N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**<u>Most common:</u>**

	• Gastrointestinal: Decreased appetite (children and adolescents: 34% to 39%; adults 8% to 27%), upper abdominal pain (children: 12%; adults: 2%), xerostomia (children and adolescents: 4% to 5%; adults: 26% to 36%) • Nervous system: Insomnia (13% to 27%) **Most serious:** • **Cardiovascular events** • **Growth suppression** • **Psychiatric/behavioral effects** • **Serotonin syndrome**
Drug Interactions	**Category X** **X**Acebrophylline **X**Iobenguane I 123 **X**Iobenguane I 131 **X**Isocarboxazid **X**Kratom **X**Linezolid **X**Methylene Blue **X**Moclobemide **X**Phenelzine **X**Rasagiline **X**Safinamide **X**Selegiline **X**Tranylcypromine **Category D** **D**Cocaine (Topical) **D**Iohexol *Depends on Route* **D**Iomeprol *Depends on Route* **D**Iopamidol *Depends on Route* **D**Potassium Citrate **D**Ringer's Injection (Lactated) **D**Sodium Bicarbonate (Systemic) **D**Sodium Citrate **D**Sodium Lactate

	DTromethamine
Special Population	Older adult: Use caution in this age group due to CNS stimulant adverse effects **Pediatric Considerations** Prior to treatment with medications for attention-deficit/hyperactivity disorder (ADHD), the American Heart Association and the American Academy of Pediatrics recommend that all children and adolescents diagnosed with ADHD have a thorough cardiovascular assessment, including patient and family health histories, determination of all medications used (prescribed and over the counter), and a physical examination focused on cardiovascular disease risk factors. An ECG is not mandatory but is reasonable to consider prior to stimulant medication therapy. Prompt evaluation and appropriate referral and testing, if warranted, should occur if any cardiac symptoms present.
Pregnancy	Lisdexamfetamine is converted to dextroamphetamine. The majority of human data is based on illicit amphetamine/methamphetamine exposure and not from therapeutic maternal use. Use of amphetamines during pregnancy may lead to an increased risk of premature birth and low birth weight; newborns may experience symptoms of withdrawal. Behavioral problems may also occur later in childhood.
Lactation	The majority of human data is based on illicit amphetamine/methamphetamine exposure and not from therapeutic maternal use. Amphetamines are excreted into breast milk and use may

	decrease milk production. Increased irritability, agitation, and crying have been reported in nursing infants. Due to the potential for adverse reactions in a nursing infant, breast-feeding is not recommended by the manufacturer.
Contraindications	Hypersensitivity to amphetamine products or any component of the formulation; concurrent use of monoamine oxidase (MAO) inhibitor (including linezolid or IV methylene blue), or within 14 days of the last MAO inhibitor dose. Significant drug interactions exist, requiring dose/frequency adjustment or avoidance. Consult drug interactions database for more information. *Canadian labeling:* Additional contraindications (not in US labeling): Known hypersensitivity or idiosyncrasy to sympathomimetic amines; advanced arteriosclerosis; symptomatic cardiovascular disease; moderate-to-severe hypertension; hyperthyroidism; glaucoma; agitated states; history of drug abuse
Monitoring Requirements	Cardiac evaluation (including medical or family history of sudden death or ventricular arrhythmia; ECG as indicated) should be completed at baseline and on any patient who develops exertional chest pain, unexplained syncope, and any symptom of cardiac disease during treatment with stimulants. Monitor blood pressure and heart rate (baseline, following dose increases and periodically during treatment); growth rate (height and weight) and appetite in children; weight in adults; signs of

	peripheral vasculopathy (e.g., digital changes); sleep and behavioral changes; assess family history and evaluate for tics or Tourette syndrome prior to initiation of therapy; assess for new signs or worsening of tics or Tourette syndrome during treatment. Assess for risk of abuse prior to prescribing and signs of misuse, abuse, or substance use disorder throughout treatment). Screen for bipolar disorder and risk factors for developing a manic episode prior to treatment; monitor for psychotic or manic symptoms (e.g., delusional thinking, hallucinations, mania) or suicide-related behavior; monitor for development or worsening of aggressive behavior or hostility.
Precautions	**CNS effects:** Amphetamines may impair the ability to engage in potentially hazardous activities; patients must be cautioned about performing tasks which require mental alertness (e.g., operating machinery or driving). **Peripheral vasculopathy:** Stimulants are associated with peripheral vasculopathy, including Raynaud phenomenon; signs/symptoms are usually mild and intermittent, and generally improve with dose reduction or discontinuation. Peripheral vasculopathy effects have been observed at different times, at therapeutic doses, and in all age groups. Digital ulceration and/or soft tissue breakdown have been observed; further evaluation (e.g., rheumatology) may be necessary in patients developing signs and symptoms of peripheral vasculopathy.

	Visual disturbance: Difficulty in accommodation and blurred vision has been reported with the use of stimulants.
Black Box Warning	**N/A**
REMS	**N/A**

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of ADHD treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable.

Table 7. Lisdexamfetamine HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Lisdexamfetamine	NICE[18]	**14 March 2018;** Consider switching to lisdexamfetamine for children aged 5 years and over and young people 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. Offer lisdexamfetamine or methylphenidate as first-line pharmacological treatment for adults with ADHD. Consider switching to lisdexamfetamine for adults 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.
	CADTH[19]	**18 December 2009;** The Canadian Expert Drug Advisory Committee (CEDAC) recommends that lisdexamfetamine not be listed. Reason for the Recommendation: There is insufficient evidence that lisdexamfetamine offers a therapeutic advantage compared with less expensive alternatives.

	HAS[20]	N/A
	IQWIG[21]	N/A
	PBS[22]	N/A

Conclusion Statement – Lisdexamfetamine

Lisdexamfetamine is mentioned in most of the guidelines including the Saudi guidelines. Its favorable use is only backed up by NICE HTA body in the indications mentioned below:

For children aged 5 years and over and young people, consider switching to lisdexamfetamine 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.

For adults with ADHD, offer lisdexamfetamine or methylphenidate as first-line pharmacological treatment. Consider switching to lisdexamfetamine for adults 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.

2.2 Modifications

No modifications have been made since May 2020.

2.3 Delisting

The medications below are no longer SFDA registered[23], therefore, it is advisable to delist the following drugs from CHI formulary. *Please refer to* ***Drugs in the disease - section 2*** *of CHI ADHD original clinical guidance:*

- Lithium Sulfate

Lithium citrate and lithium carbonate remain registered by the SFDA.

2.4 Other Drugs

Qelbree (Viloxazine) is a non-stimulant approved for the treatment of ADHD in children and adults in 2021 and 2022, respectively.

- **May 2, 2022;** The FDA has approved viloxazine extended-release capsules (Qelbree; Supernus Pharmaceuticals) for the treatment of attention-deficit hyperactivity disorder (ADHD) in patients 18 years of age and older. Viloxazine

extended-release capsules are indicated as a once-daily, flexible-dose nonstimulant drug.[24]

- A randomized, double-blind, placebo-controlled phase 3 trial showed that patients treated with viloxazine achieved the primary endpoint of a statistically significantly reduced change from baseline in Adult ADHD Investigator Symptom Rating Scale (AISRS) total score compared with placebo (*P* = .004). The data also showed a significant improvement in AISRS subscale scores for inattention and hyperactivity/impulsivity symptoms among treated patients. Further, adult patients administered viloxazine achieved the key secondary efficacy endpoint of change in Clinical Global Impression—Severity of Illness (CGI-S) scale from baseline to week 6 (*P* = .0023).[24]

Azstarys (serdexmethylphenidate and dexmethylphenidate) is a once-daily central nervous system (CNS) stimulant approved for the treatment of ADHD in patients ages six or older in 2021.

- **Mar 3, 2021;** BOSTON, March 3, 2021 /PRNewswire/ -- Corium, Inc., a commercial-stage biopharmaceutical company leading the development and commercialization of novel central nervous system (CNS) therapies, announced today the U.S. Food and Drug Administration (FDA) approval of once-daily oral capsule AZSTARYS (serdexmethylphenidate [SDX] and dexmethylphenidate [d-MPH]), the first and only product containing a d-MPH oral prodrug for the treatment of attention deficit hyperactivity disorder (ADHD) symptoms in patients aged 6 years and older.[25]
- AZSTARYS was evaluated in a multicenter, double-blind, randomized, placebo-controlled, laboratory classroom phase 3 study in 150 children aged 6 to 12 years diagnosed with ADHD (NCT03292952). The results of this study were presented in January 2021 at the American Professional Society of ADHD and Related Disorders Annual Meeting. In this study, AZSTARYS significantly improved ADHD symptoms with a single dose, as measured by the primary endpoint, the change from baseline in Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale – Combined (SKAMP-C) scores averaged over a 13-hour laboratory classroom day. As ADHD symptoms improve, SKAMP-C scores decline. In the study, the improvements significantly differed for children treated with AZSTARYS compared to those receiving a placebo, with an average SKAMP-C score reduction of -5.4 points more in the AZSTARYS group [95% CI: (-7.1, -3.7)]. Adverse events (AEs) occurring more frequently in the AZSTARYS group (in 2 percent or more of the participants) compared to the placebo group were headache (5.4 vs. 1.3 percent, AZSTARYS and placebo respectively), upper abdominal pain (4.1 vs. 1.3 percent), insomnia (2.7 vs. 1.3 percent), and pharyngitis (sore throat) (2.7 vs. 0 percent). No serious AEs were reported in this study.[25]

Xelstrym (dextroamphetamine) was approved by the FDA in March 2022. It is a once-daily transdermal amphetamine patch used to treat ADHD in adults and children ages six and older.

- **March 23, 2022**, Noven Therapeutics announced the FDA approval of Xelstrym (dextroamphetamine), for the treatment of attention deficit hyperactivity disorder (ADHD) in adults and pediatric patients 6 years and older. — Limitation of use: Pediatric patients younger than 6 years of age experienced more long-term weight loss than patients 6 years and older. — Xelstrym is a Schedule II controlled substance.
- Xelstrym is the first transdermal patch formulation of amphetamine.
- The efficacy of Xelstrym was established in a randomized, double-blind, placebo-controlled, crossover design, modified analog classroom study in 110 pediatric patients 6 to 17 years with ADHD. Efficacy was assessed using the Swanson, Kotkin, Agler, M.Flynn, and Pelham (SKAMP) total score, a validated 13-item rating scale assessing manifestations of ADHD in a classroom setting. Efficacy was solely based on data from the first week of the two-week double-blind, placebo controlled, crossover treatment phase of the study.
  - The least-squares mean SKAMP total score (averaged over classroom day) was 12.4 and 17.1 with Xelstrym and placebo, respectively (placebo-subtracted difference -4.7, 95% CI: - 8.0, -1.4).
- In addition to the study above, the efficacy of Xelstrym was also established based on adequate and well-controlled studies of lisdexamfetamine in pediatric and adult patients.

Section 3.0 Key Recommendations Synthesis

Drug treatments can be classified into stimulants (**methylphenidate**, **lisdexamphetamine**, **dexamfetamine**) and non-stimulants (**atomoxetine**, **guanfacine** etc.). Their mechanism of action involves increased availability of synaptic dopamine and/or noradrenaline.[10]

Stimulants have an immediate action and can therefore be titrated to an effective dose for each patient more quickly. Stimulants are usually considered before non-stimulants due to their superior efficacy. Stimulants come in immediate-release or slow/modified-release preparations. A combination of modified- and immediate-release preparations can be used to fine-tune symptom control at certain times of day. For example, a slow-release preparation taken in the morning may have little effect by evening time and can be 'topped up' with an immediate-release preparation. Stimulants have more potential for diversion/misuse, particularly immediate-release preparations. Stimulants have an appreciable positive effect on attention in those without ADHD and a 'therapeutic trial' therefore has no diagnostic value. Stimulants are controlled drugs.[10]

The non-stimulants have a delayed onset of action like that of antidepressants. They are also gradually titrated but more to counter potential side effects than to reach an effective dose for that individual. Non-stimulants are not controlled drugs.[10]

Methylphenidate (first line)

Recommended as a first line of treatment for ADHD in adults, as is Lisdexamfetamine. Methylphenidate should be offered to those who have not had an adequate response to Lisdexamfetamine, if this has been the first choice, (at an adequate dose for less than six weeks) as some individuals may respond better to an alternative stimulant.[10]

Lisdexamfetamine (first line)

Recommended as a first line of treatment for ADHD in adults, as is Methylphenidate.

Should be offered to those who have not had an adequate response to methylphenidate, if this has been the first choice (at an adequate dose for less than six weeks), as some individuals may respond better to an alternative stimulant.[10]

Atomoxetine (second line)

Should be considered in adults unresponsive or intolerant to both methylphenidate and lisdexamphetamine.

Also used when misuse/diversion of stimulants is a concern.[10]

There is limited evidence in adults for **guanfacine**, **bupropion**, tricyclic antidepressants and **reboxetine** in controlled studies.[13]

Cognitive Behavior Therapy reduces ADHD-core symptoms, associated symptoms such as emotion dysregulation, anxiety and depression, and functional impairments across different areas of daily living in adults.[13]

CBT is best used within a multi-modal treatment approach and as an adjunct to medication, as research does not fully support the efficacy of CBT as a sole treatment for adult ADHD.[13]

Other medications

Selective noradrenaline reuptake inhibitors such as reboxetine may be an alternative to ATX. [13]

There is limited evidence for tricyclic antidepressants.[13]

Selective serotonin reuptake inhibitors (SSRIs) are not effective for the treatment of ADHD.[13]

Modafinil, a wakefulness-promoting agent used in the treatment of narcolepsy, has not been demonstrated as an effective treatment for adult ADHD in a phase 3 trial that had high rates of side effects (86%) and drop-out (47%) possibly resulting from excessive doses (210–510 mg/day).[13]

Pharmacological treatment of special groups

In patients with ADHD and substance use disorder, to be effective, treatment with stimulants may use higher dosages than normal.[13]

In patients with ADHD and bipolar disorder, the combined approach of a mood stabilizer with a stimulant has been shown to treat both disorders effectively without inducing (hypo)manic states. [13]

During pregnancy stimulants are not advised, though large cohort data showed no increased risk for congenital malformations using stimulants during the first trimester.[13]

In patients with ADHD and sleep problems, in many cases, ADHD in children and adults is associated with a circadian rhythm disorder with delayed sleep onset. [13]

In children with ADHD and chronic insomnia, melatonin has been shown to advance the sleep onset, and increase sleep duration. A trial targeting insomnia in adults with ADHD is ongoing, and clinical experience points in the same direction of possible efficacy of treatment with melatonin at night, and of light therapy in the morning. Treatment of insomnia should always start with sleep hygiene education and optimizing the stimulant or non-stimulant treatment of ADHD. A low dose of IR MPH

(usually 5 mg) taken at nighttime can reduce ceaseless mental activity to a degree that allows sleep in some cases.[13]

The risk for cardiac malformations using MPH however was slightly increased, while this was not the case for amphetamines. Research on the wishes of older people with ADHD regarding treatment, and trials on the safety and efficacy of medicines are needed. Based on data from large cohort studies, following treatment, the negative outcomes associated with ADHD significantly diminish, i.e. traffic accidents, mortality, criminality, depression and suicide, and substance abuse.[13]

Treatment of complex ADHD should include evidence-based approaches that address ADHD and account for coexisting conditions while respecting family background and preferences. Although behavioral and educational approaches serve as the foundation for intervention, it is often necessary to combine these approaches with pharmacological treatments. Treatment should focus on areas of functional impairment, and not just symptom reduction, by incorporating developmentally appropriate strategies for self-management, skill building, and prevention of adverse outcomes (e.g., substance use, conduct problems, problems of depression/anxiety, suicidal ideation, educational failure). Aggregate evidence quality: Grade C to B (may vary by specific coexisting condition). Strength: Recommendation.[14]

Given that ADHD is a chronic condition that often persists into adulthood, treatment of complex ADHD should include ongoing, scheduled monitoring of patients throughout the lifespan, commensurate with individual patient's needs and profile with particular emphasis on preparing for key developmental transitions (preschool to school, elementary to middle school, middle to high school, and high school to postsecondary education or employment). Aggregate evidence quality: Grade B. Strong recommendation.[14]

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI ADHD report** and aims to provide recommendations to aid in the management of ADHD. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with ADHD. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing Edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses, and sequence of therapy

Appendix B. ADHD Scope

Section	Rationale/updates
Section 1.1 National Institute for Health and care excellence (NICE) guidelines for attention deficit hyperactivity disorder: diagnosis and management **[Updated September 2019]**	**N/A**
Section 1.2 American Academy of Pediatrics (AAP) Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents **[2019]**	**N/A**
Section 1.3 The Canadian ADHD Practice Guidelines, 4th Edition **[2018]**- Canadian ADHD resource alliance (CADDRA)	**N/A**
Section 1.4 ADHD in adults: good practice	**Section 1.1.1.** Attention deficit hyperactivity disorder (ADHD) in adults: Good practice guidelines Royal College of Psychiatrists in Scotland CR235, January **[2023]** [10]

guidelines (Royal College of Psychiatrists in Scotland) **[2017]**	*Management of ADHD* • Drug treatments can be classified into stimulants (methylphenidate, lisdexamphetamine, dexamfetamine) and non-stimulants (atomoxetine, guanfacine etc.). Their mechanism of action involves increased availability of synaptic dopamine and/or noradrenaline. Stimulants have an immediate action and can therefore be titrated to an effective dose for each patient more quickly. Stimulants are usually considered before non-stimulants due to their superior efficacy. Stimulants come in immediate-release or slow/modified-release preparations. A combination of modified- and immediate-release preparations can be used to fine-tune symptom control at certain times of day. For example, a slow-release preparation taken in the morning may have little effect by evening time and can be 'topped up' with an immediate-release preparation. Stimulants have more potential for diversion/misuse, particularly immediate-release preparations. Stimulants have an appreciable positive effect on attention in those without ADHD and a 'therapeutic trial' therefore has no diagnostic value. Stimulants are controlled drugs. • The non-stimulants have a delayed onset of action like that of antidepressants. They are also gradually titrated but more to counter potential side effects than to reach an effective dose for that individual. Non-stimulants are not controlled drugs. ***Methylphenidate (joint first line)*** • Recommended as a first line of treatment for ADHD in adults, as is Lisdexamfetamine. • Methylphenidate should be offered to those who have not had an adequate response to Lisdexamfetamine, if this has been the first choice, (at an adequate dose for less than six weeks) as some individuals may respond better to an alternative stimulant. ***Lisdexamfetamine (joint first line)*** • Recommended as a first line of treatment for ADHD in adults, as is

	Methylphenidate.
	Atomoxetine (second line)
	• Non-stimulant treatment.
	• Should be considered in adults unresponsive or intolerant to both methylphenidate and lisdexamphetamine.
	• Also used when misuse/diversion of stimulants is a concern.
	Other pharmacological options
	• Guanfacine – an alpha agonist and a non-stimulant treatment. It has a license for ADHD in children for whom stimulants are not suitable, tolerated, or effective. It does not currently have a license for adults but is being increasingly used.
	• Combinations – if there is an inadequate response to monotherapy, then combining a stimulant with a non-stimulant is occasionally done in clinical practice, although there is currently a limited evidence base for this.
	• Other treatments – other medications which have less of an evidence base are:
	  • Bupropion (dopamine and noradrenaline reuptake inhibitor)
	  • Modafinil (indirect dopamine enhancing substance)
	  • Clonidine (alpha agonist) and
	  • Noradrenergic antidepressants such as duloxetine, reboxetine, imipramine and venlafaxine. Activating antidepressants should not be taken in the evening/at night, i.e. morning and lunchtime dosing only.
	Whilst every attempt has been made in this document to ensure that doses are correct, prescribers are encouraged to check doses against relevant reference documents.
	In general, prescribers are encouraged to use generic names, however cost implication may mean that specific trades names are recommended by local formulary groups that may change over time. Clinicians should check the equivalency of formulations in these situations.

Section 1.5 Clinical Practice Points on the diagnosis, assessment, AND management OF ATTENTION DEFICIT HYPERACTIVITY disorder in children and adolescents- Australian government **[2012]**	**N/A**
Section 1.6 National Health and Medical Research Council (NHMRC) Clinical Practice Points on diagnosis, assessment, and management of ADHD in children and adolescents **[2012**]	**N/A**
Section 1.7 The Texas Children's Medication Algorithm Project: Revision of the Algorithm for Pharmacotherapy of Attention-Deficit/Hyperactivity Disorder **[2005]**	**N/A**
Section 1.8 International consensus statement on	**N/A**

attention-deficit/hyperactivity disorder (ADHD) and disruptive behavior disorders (DBDs): Clinical implications and treatment practice suggestions **[2003]**	
N/A	**Section 1.2.1.** Evidence-based clinical practice guideline for management of attention deficit hyperactivity disorder ADHD in Saudi Arabia, **[2020]** **Recommendations for healthcare professionals with training and expertise in diagnosing and managing Children under 5 years and for Children aged 5 years and over and young people with ADHD** **Adults** • Offer medication to adults with ADHD if their ADHD symptoms are still causing a significant impairment in at least one domain after environmental modifications have been implemented and reviewed. • Consider non-pharmacological treatment for adults with ADHD who have: • made an informed choice not to have medication • difficulty adhering to medication • found medication to be ineffective or cannot tolerate it. • Consider non-pharmacological treatment in combination with medication for adults with ADHD who have benefited from medication but whose symptoms are still causing a significant impairment in at least one domain. • When non-pharmacological treatment is indicated for adults with ADHD, offer the following as a minimum: • a structured supportive psychological intervention focused on ADHD • regular follow up either in person or by phone. Treatment may involve elements of or a full course of CBT. **Medication choice for Children aged 5 years and over and young people, adults.**

	and people with coexisting conditions **Further medication choices** • Obtain a second opinion or refer to a tertiary service if ADHD symptoms in a child aged 5 years or over, a young person or adult are unresponsive to one or more stimulants and one non-stimulant. • Do not offer any of the following medications 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. **Considerations when prescribing ADHD medication** • When prescribing stimulants for ADHD, think about 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. • When prescribing stimulants for ADHD, be aware that effect size, duration of effect and adverse effects vary from person to person. • 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). • Be cautious about prescribing stimulants for ADHD if there is a risk of diversion for cognitive enhancement or appetite suppression. • Do not offer immediate-release stimulants or modified-release stimulants that can be easily injected or insufflated if there is a risk of stimulant misuse or diversion.

	• Prescribers should be familiar with the requirements of controlled drug legislation governing the prescription and supply of stimulants.
N/A	**Section 1.2.2.** Updated European Consensus Statement on diagnosis and treatment of adult ADHD, **[2019]** ➢ *Pharmacotherapy* • Stimulants are the treatment of choice for adults with ADHD. Long-lasting, extended-release formulations are preferred for reasons of adherence to treatment, for the protection against abuse, to avoid rebound symptoms, for safer driving, and to provide cover throughout the day without the need for multiple dosing. Licensing of stimulants for adult ADHD is urgently needed in European countries and beyond. • The *non-stimulant* ***atomoxetine*** is recommended as a *second line treatment*. There is limited evidence in adults for ***guanfacine***, ***bupropion***, tricyclic antidepressants and ***reboxetine*** in controlled studies. • Cognitive Behavior Therapy reduces ADHD-core symptoms, associated symptoms such as emotion dysregulation, anxiety and depression, and functional impairments across different areas of daily living in adults. • CBT is best used within a multi-modal treatment approach and as an adjunct to medication, as research does not fully support the efficacy of CBT as a sole treatment for adult ADHD. Recommendations on: Atomoxetine (ATX), Guanfacine and clonidine, Bupropion and other medications ➢ *Combined psychopharmacology* The high rate of psychiatric comorbidity in adult ADHD frequently necessitates combined psychopharmacology. Accordingly, the risk of possible drug-drug interactions when treating adults with ADHD must be considered. These include the following: Monoamine oxidase inhibitors are generally contraindicated due to the risk of

	hypertensive crisis. Although MPH is mainly metabolized in the liver, drug interactions via CYP enzymes are uncommon. Amphetamines, however, are metabolized primarily via the CYP 2D6 enzyme system making drug interactions possible (with inhibitors or inducers of this enzyme system, e.g. fluoxetine and paroxetine) Treatment with medications that act on the noradrenaline system, including certain antidepressants (e.g. duloxetine, venlafaxine), will have an additive effect and may increase the risk of hypertension and other adverse cardiovascular events. Due to its metabolism by the CYP 2D6 enzyme system, ATX levels can increase in combination with enzyme-inhibiting SSRIs (e.g. fluoxetine and paroxetine). ➢ *Recommendations on the Pharmacological treatment of special groups* ➢ *Long-term safety concerns* Currently there is no evidence of significant long-term risks using stimulants. Tomography scans find higher striatal dopamine transporter availability in ADHD patients treated with stimulants. The clinical implications of this up-regulation are not clear. Potential toxicity on heart valves of medications with an agonist effect on 5-HT2B receptors have been discussed, including MPH and guanfacine. Some argue that echocardiography should be routinely performed prior to treatment with potential valvulopathic drugs. This risk is not however established, and we and others do not recommend routine echocardiograms except in older adults (> age 50).
N/A	**Section 1.2.3** Society for Developmental and Behavioral Pediatrics Clinical Practice Guideline for the Assessment and Treatment of Children and Adolescents with Complex Attention Deficit/Hyperactivity Disorder, **[2020]** • The clinician with specialized training or expertise should initiate a comprehensive assessment and develop an interprofessional, multimodal treatment plan for any child or adolescent through age 18 years with suspected or diagnosed complex ADHD with functional impairments upon referral from a primary care clinician. Complex ADHD is defined by any of the following:

	• Aged 4 years or 12 years at the time of initial presentation of symptoms or impairment. - Presence or suspicion of coexisting disorders and complicating factors: o Other neurodevelopmental disorders (e.g., global developmental delay, intellectual disability [ID], autism spectrum disorder [ASD], speech and language disorders, tic disorders) o Significant problems with the acquisition of academic skills including specific learning disorders (LDs) (i.e., reading, math, written language) o Mental health disorders (e.g., depression, anxiety, oppositional defiant disorder, conduct disorder, substance use disorders [SUDs], eating disorders) o Chronic medical conditions (e.g., history of extreme prematurity, epilepsy, cancer, traumatic brain injury, motor disabilities, fetal alcohol spectrum disorders) o Genetic disorders (e.g., Down syndrome, Fragile X syndrome) o Complicated psychosocial factors (e.g., adverse childhood experiences such as trauma, neglect, and poverty; parental mental health disorders) ➢ Moderate to severe functional impairments in important aspects of daily living (e.g., relationships with family and peers, activities of daily living) ➢ Diagnostic uncertainty on the part of the primary care clinician ➢ Inadequate response to treatment (or uncertainty about treatment planning). Aggregate evidence quality: Grade B. Strong recommendation • In the evaluation of a child or adolescent with complex ADHD, the clinician should verify any previous diagnoses and assess for coexisting conditions employing an evidence-based approach that is developmentally appropriate, culturally sensitive, and inclusive of data from multiple settings and sources (home, school, community). The evaluation should include an appropriate, comprehensive medical history and physical examination, and psychological assessment based on the child's presenting problems and their severity,

	functional impairments, cognitive/developmental level, and the judgment of the treating clinician. Aggregate evidence quality: Grade B. Strong recommendation. • Psychoeducation about ADHD and its coexisting conditions and evidence-based behavioral and educational interventions are foundational for the treatment of complex ADHD and should be implemented at the outset of treatment whenever possible. Evidence-based behavioral and educational interventions (e.g., behavioral parent training [BPT], behavioral classroom management [BCM], behavioral peer interventions [BPIs], and, for older children, organizational skills training [OST]) should be provided to all children and adolescents with complex ADHD. These treatment approaches in home, school, and peer settings address key functional domains (behavioral, educational, social) that are associated with long-term outcomes. Evidence quality: Grade B. Strong recommendation. • Treatment of complex ADHD should include evidence-based approaches that address ADHD and account for coexisting conditions while respecting family background and preferences. Although behavioral and educational approaches serve as the foundation for intervention, it is often necessary to combine these approaches with pharmacological treatments. Treatment should focus on areas of functional impairment, and not just symptom reduction, by incorporating developmentally appropriate strategies for self-management, skill building, and prevention of adverse outcomes (e.g., substance use, conduct problems, problems of depression/anxiety, suicidal ideation, educational failure). Aggregate evidence quality: Grade C to B (may vary by specific coexisting condition). Strength: Recommendation. • Given that ADHD is a chronic condition that often persists into adulthood, treatment of complex ADHD should include ongoing, scheduled monitoring of patients throughout the lifespan, commensurate with individual patient's

	needs and profile with particular emphasis on preparing for key developmental transitions (preschool to school, elementary to middle school, middle to high school, and high school to postsecondary education or employment). Aggregate evidence quality: Grade B. Strong recommendation

Appendix C. MeSH Terms PubMed

C.1 PubMed Search for ADHD:

Query	Filters	Search Details	Results
((((((((((((((((((((Attention Deficit Disorder with Hyperactivity[MeSH Terms]) AND (Attention Deficit Disorder with Hyperactivity[Title/Abstract])) OR (Attention Deficit Disorders with Hyperactivity[Title/Abstract])) OR (ADHD[Title/Abstract])) OR (Attention Deficit Hyperactivity Disorder[Title/Abstract])) OR (Hyperkinetic Syndrome[Title/Abstract])) OR (Syndromes, Hyperkinetic[Title/Abstract])) OR (Attention Deficit-Hyperactivity Disorder[Title/Abstract])) OR (Attention Deficit-Hyperactivity Disorders[Title/Abstract])) OR (Deficit-Hyperactivity Disorder,	Guideline, in the last 5 years	(("attention deficit disorder with hyperactivity"[MeSH Terms] AND "attention deficit disorder with hyperactivity"[Title/Abstract]) OR "attention deficit disorders with hyperactivity"[Title/Abstract] OR "ADHD"[Title/Abstract] OR "attention deficit hyperactivity disorder"[Title/Abstract] OR "hyperkinetic syndrome"[Title/Abstract] OR (("syndrom"[All Fields] OR "syndromal"[All Fields] OR "syndromally"[All Fields] OR "Syndrome"[MeSH Terms] OR "Syndrome"[All Fields] OR "syndromes"[All Fields] OR "syndrome s"[All Fields] OR	7

Attention[Title/Abstract])) OR (Deficit-Hyperactivity Disorders, Attention[Title/Abstract])) OR (Disorder, Attention Deficit-Hyperactivity[Title/Abstract])) OR (Disorders, Attention Deficit-Hyperactivity[Title/Abstract])) OR (ADDH[Title/Abstract])) OR (Attention Deficit Hyperactivity Disorders[Title/Abstract])) OR (Attention Deficit Disorder[Title/Abstract])) OR (Attention Deficit Disorders[Title/Abstract])) OR (Deficit Disorder, Attention[Title/Abstract])) OR (Deficit Disorders, Attention[Title/Abstract])) OR (Disorder, Attention Deficit[Title/Abstract])) OR (Disorders, Attention Deficit[Title/Abstract])) OR (Brain Dysfunction,		"syndromic"[All Fields] OR "syndroms"[All Fields]) AND "Hyperkinetic"[Title/Abstract]) OR "attention deficit hyperactivity disorder"[Title/Abstract] OR "attention deficit hyperactivity disorders"[Title/Abstract] OR "deficit hyperactivity disorder attention"[Title/Abstract] OR "deficit hyperactivity disorders attention"[Title/Abstract] OR "disorder attention deficit hyperactivity"[Title/Abstract] OR "disorders attention deficit hyperactivity"[Title/Abstract] OR "ADDH"[Title/Abstract] OR "attention deficit hyperactivity disorders"[Title/Abstract] OR "attention deficit disorder"[Title/Abstract] OR "attention deficit	

Minimal[Title/Abstract])) OR (Dysfunction, Minimal Brain[Title/Abstract])) OR (Minimal Brain Dysfunction[Title/Abstract])		disorders"[Title/Abstract] OR "deficit disorder attention"[Title/Abstract] OR "deficit disorders attention"[Title/Abstract] OR "disorder attention deficit"[Title/Abstract] OR "disorders attention deficit"[Title/Abstract] OR "brain dysfunction minimal"[Title/Abstract] OR (("dysfunctional"[All Fields] OR "dysfunctionals"[All Fields] OR "dysfunctioning"[All Fields] OR "dysfunctions"[All Fields] OR "physiopathology"[MeSH Subheading] OR "physiopathology"[All Fields] OR "Dysfunction"[All Fields]) AND "minimal brain"[Title/Abstract]) OR "minimal brain dysfunction"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	

Appendix D. Treatment Algorithm

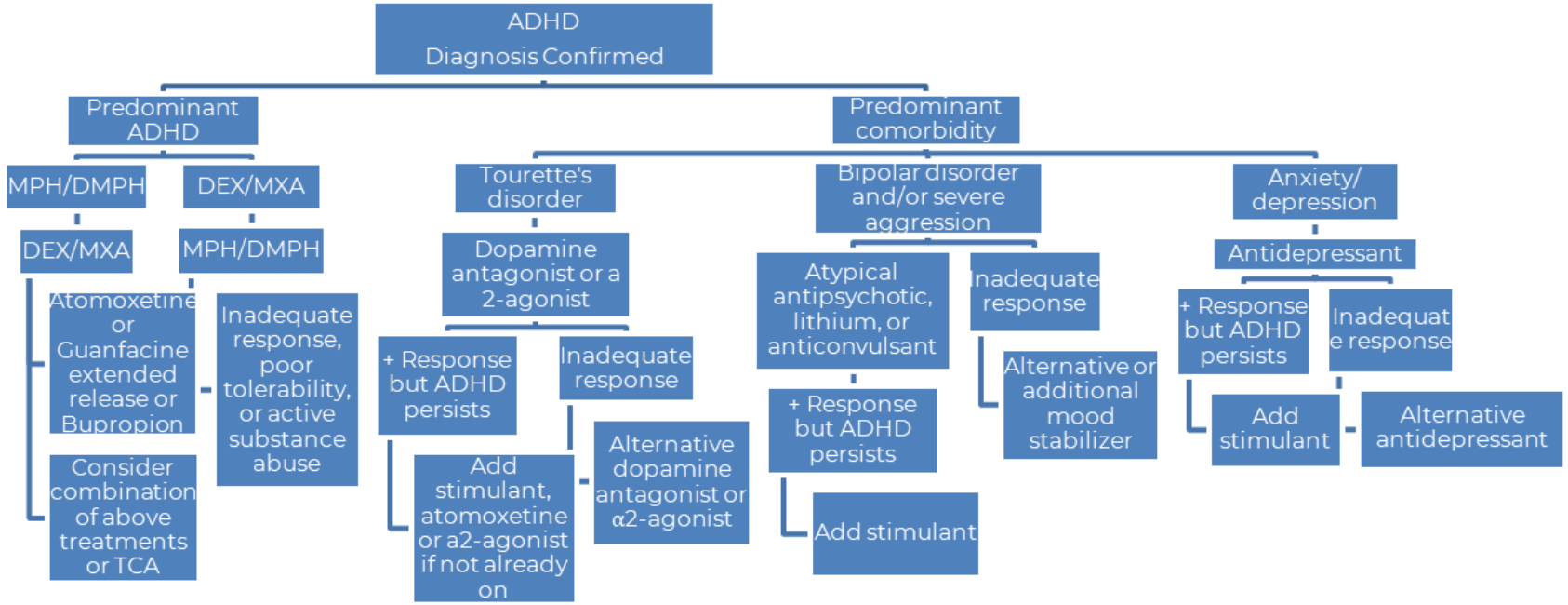

Figure 1. *Algorithm for drug selection in the treatment of ADHD*

Treat predominant disorder first, reassess, and consider alternative or adjunct medications for optimal symptom control. (DEX, dextroamphetamine; DMPH, dexmethylphenidate; MPH, methylphenidate; MXA, mixed amphetamine salts; TCA, tricyclic antidepressant.)