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Pharmacotherapy for ADHD in children and adolescents: A summary and overview of different European guidelines

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Abstract

Attention deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by a persistent pattern of inattention, hyperactivity, and impulsivity. It is the most common neurodevelopmental disorder presenting to pediatric services, and pediatricians are often involved in the early assessment, diagnosis, and treatment of children with ADHD. The treatment of ADHD typically involves a multimodal approach that encompasses a combination of psychoeducation, parent/teacher training, psychosocial/psychotherapeutic interventions, and pharmacotherapy. Concerning pharmacotherapy, guidelines vary in drug choice and sequencing, with psychostimulants, such as methylphenidate and (lis)dexamfetamine, generally being the favored initial treatment. Alternatives include atomoxetine and guanfacine. Pharmacotherapy has been proven effective, but close follow-up focusing on physical growth, cardiovascular monitoring, and the surveillance of potential side effects including tics, mood fluctuations, and psychotic symptoms, is essential. This paper presents an overview of current pharmacological treatment options for ADHD and explores disparities in treatment guidelines across different European countries.

Conclusion: Pharmacological treatment options for ADHD in children and adolescents are effective and generally well-tolerated. Pharmacotherapy for ADHD is always part of a multimodal approach. While there is a considerable consensus among European guidelines on pharmacotherapy for ADHD, notable differences exist, particularly concerning the selection and sequencing of various medications.

What is Known:

- There is a significant base of evidence for pharmacological treatment for ADHD in children and adolescents.
- Pediatricians are often involved in assessment, diagnosis and management of children with ADHD.

What is New:

- Our overview of different European guidelines reveals significant agreement in the context of pharmacotherapy for ADHD in children and adolescents.
- Discrepancies exist primarily in terms of selection and sequencing of different medications.

Keywords Attention deficit hyperactivity disorder · Pharmacotherapy · Guideline · Intervention

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Introduction

Attention deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder defined by a persistent pattern of inattention, hyperactivity and impulsivity that is apparent across different settings and leads to functional impairment [1]. ADHD is prevalent globally, affecting approximately 5.9% of children and adolescents, according to meta-analyses. No significant differences in prevalence between Europe and other continents have been found [2]. Isolated ADHD in children is the exception rather than the rule as up to two-thirds of

children with ADHD have coexisting psychiatric disorders, including but not limited to depression, bipolar disorder, autism spectrum disorders, anxiety disorders, oppositional defiant disorder, conduct disorder, eating disorders, and substance use disorders [3]. Moreover, ADHD has been found to be associated with various negative life outcomes and poses a significant burden on individuals, their families, and society in general [4]. Consequences of untreated ADHD include poorer educational outcomes [5], an increased risk for accidents, and premature mortality [6, 7].

In Europe, the role of pediatricians in the treatment of ADHD varies depending on the specific country and health-care system in place. However, pediatricians frequently play a key role in the early assessment, diagnosis, and treatment of ADHD in children. They often serve as the primary contact for parents who express concerns about their child's behavior and academic performance. Treatment of ADHD in children typically involves a multimodal approach, with pediatricians frequently being responsible for the initiation and management of pharmacotherapy in children affected. This paper aims to provide an update on current pharmacological treatment options for ADHD. Furthermore, it aims to explore disparities in treatment guidelines different European countries.

European treatment guidelines: The role of pharmacotherapy

Several national guidelines provide recommendations for the management of ADHD [8–13]. Our review of recently published guidelines from Belgium, Denmark, Germany, the Netherlands, Spain, and the UK reveals both similarities and variations in their approaches. In general, the different guidelines demonstrate significant overlap, indicating reasonable consensus regarding treatment decision trees and guidelines for medication. For children below 6 years old (5 years according to the UK guidelines), psychoeducation and parent/teacher trainings are recommended. Pharmacological treatment is generally not advised in this age group, with referral to a specialist in case necessary. For children and adolescents aged 6–18, most guidelines recommend a stepwise approach [8–13]. The initial step involves psychoeducation, followed by additional interventions such as parent/teacher trainings, other psychosocial approaches and/or pharmacotherapy. In Belgian, Dutch, and German guidelines, the choice of treatment strategies is guided by the severity of ADHD, with pharmacotherapy typically reserved for moderate to severe cases. Moreover, the Belgian and Dutch guidelines also consider the presence of behavioral problems as a criterion for treatment selection [8, 9]. Most guidelines emphasize the importance of shared decision-making, allowing patient preference to sometimes overrule specific steps in the treatment process. Overall,

the guidelines prioritize comprehensive and individualized treatments, incorporating a combination of interventions as necessary. Most guidelines acknowledge the importance of addressing comorbidities; however, the interventions for these coexisting disorders usually do not hinder the implementation of ADHD treatment according to the guidelines [8–13]. However, the Belgian and Dutch guidelines prioritize treating severe mood disorders before addressing ADHD. Notably, the Belgian and Dutch guidelines specifically emphasize implementing psychotherapy (cognitive behavioral therapy and parent/teacher training) even in more severe cases of ADHD, if there are comorbid conditions like oppositional defiant disorder (ODD) or conduct disorder (CD) [8, 9]. For a more comprehensive overview of the role of pharmacotherapy in different guidelines, we refer to Table 1.

Psychostimulants

Stimulants, which are comprised of methylphenidate and amphetamines, are considered the first-line pharmacotherapy in most international guidelines [8–13]. Stimulant drugs work on the dopaminergic and the noradrenergic neurotransmission. At clinically approved doses, methylphenidate non-competitively blocks the dopamine transporter (DAT) and noradrenaline (NAT), thus upregulating noradrenergic and dopaminergic neurotransmission. Meta-analyses have shown that methylphenidate has moderate to high effect on core ADHD symptoms, with effect sizes ranging from 0.62 for parent-reported symptoms [14], 0.78 for clinician reports [15], and from 0.74 to 0.82 for teacher reports [14, 15]. Amphetamines work on DAT and NAT as well; however, they competitively bind these transporters. At higher doses, amphetamines also displace dopamine from the presynaptic vesicles and thus heighten the concentration in the synaptic cleft. In Europe, amphetamines are represented by dexamfetamine and by the dexamfetamine prodrug lisdexamfetamine. The meta-analysis by Cortese et al. showed amphetamines to have an effect size of about 1; however, tolerability of amphetamines was worse than the tolerability of methylphenidate as shown by the rate of treatment discontinuation [15].

Most children with ADHD respond to methylphenidate and/or amphetamine if both options are explored. However, some patients exhibit a better response to methylphenidate, while others respond better to amphetamine. A review looking at the different methylphenidate vs amphetamine cross-over studies showed that about 41% of children responded to both medications, 16% responded well to methylphenidate only, 28% responded to amphetamine only, and 13% did not respond to either. Response was defined by the individual source studies and includes a wide range of different outcomes [16].

Table 1 Treatment ladders

Belgium, 2021 Hoge Gezondheidsraad	Denmark, 2021 Sundhedsstyrelsen	The Netherlands, 2019 GGZ Standaarden	UK, 2018 The National Institute for Health and Care Excellence	Spain, 2017 Clinical practice guidelines in the Spanish national health-care system	Germany, 2017 Association of the Scientific Medical Societies
<p><6 years old: 1st psychoeducation (parents/teachers) 2nd parent/teacher training 3rd referral to specialist Pharmacological treatment not recommended</p>	<p><6 years old: Age group not covered in this guideline 1st psychoeducation (parents/teachers) 2nd parent/teacher training 3rd referral to specialist Pharmacological treatment not recommended</p>	<p><6 years old: 1st psychoeducation (parents/teachers) 2nd parent/teacher training 3rd referral to specialist Pharmacological treatment not recommended</p>	<p><5 years old: 1st group parent-training program 2nd referral to specialist Pharmacological treatment not recommended</p>	<p><6 years old: Psychological and/or pedagogical interventions Pharmacological treatment not recommended</p>	<p><3 years old: Pharmacological treatment not recommended 3–6 years old: 1st psychoeducation (patient/parents/educators) 2nd psychosocial interventions 3rd pharmacotherapy only by a physician with specialized knowledge in behavioral disorders in this age group</p>
<p>6–12 years old: 1st psychoeducation (parents/teachers) 2nd <i>Without</i> behavioral problems - Mild: parent training - Moderate/severe: monotherapy; pharmacological treatment <i>With</i> behavioral problems - Mild/moderate: parent/teacher training - Severe: combination therapy 3rd combination therapy</p>	<p>6–18 years old: 1st psychological and/or educational interventions 2nd pharmacological treatment - Mild: parent and/or teacher training - Moderate/severe: monotherapy; parent/teacher training OR pharmacotherapy <i>With</i> behavioral problems - Mild/moderate: parent and/or teacher training - Severe: combination therapy 3rd switch agent or combination therapy</p>	<p>6–12 years old: 1st psychoeducation (parents/teachers) 2nd <i>Without</i> behavioral problems - Mild: parent and/or teacher training - Moderate/severe: monotherapy; parent/teacher training OR pharmacotherapy <i>With</i> behavioral problems - Mild/moderate: parent and/or teacher training - Severe: combination therapy 3rd switch agent or combination therapy</p>	<p>>5 years old: No sequencing specified: - Psychoeducation (patient/parents/carers), advice on parenting strategies, liaison with school - Parent-training programs - Pharmacological treatment: when environmental modifications are insufficient - 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</p>	<p>6–18 years old: 1st psychological and/or psychopedagogical interventions 2nd pharmacological treatment (when above-mentioned interventions have not given results or in severe cases)</p>	<p>6–18 years old: Mild: 1st psychoeducation (patient/parents/educators) 2nd psychosocial interventions based on behavioral therapy 3rd switch to psychosocial interventions, pharmacological treatment, or combination therapy Moderate: 1st psychoeducation 2nd psychosocial interventions based on behavioral therapy OR pharmacological treatment (with counseling/accompanying psychosocial interventions) 3rd combination treatment Severe: 1st psychoeducation (patient/parents/educators) 2nd pharmacological treatment (with accompanying counseling/psychosocial interventions) 3rd combination treatment</p>
<p>12–18 years old: 1st psychoeducation (patient/parents/teachers) 2nd - Mild: CBT with involvement of parents/teachers - Moderate/severe: monotherapy; pharmacotherapy OR CBT 3rd switching to CBT, pharmacological treatment, or combination therapy</p>	<p>12–18 years old: 1st psychoeducation (patient/parents/teachers) 2nd - Mild: CBT with involvement of parents/teachers - Moderate/severe: Monotherapy; CBT with or without parent/teacher training OR pharmacotherapy 3rd switching to another pharmacological agent or combination therapy</p>	<p>12–18 years old: 1st psychoeducation (patient/parents/teachers) 2nd - Mild: CBT with involvement of parents/teachers - Moderate/severe: Monotherapy; CBT with or without parent/teacher training OR pharmacotherapy 3rd switching to another pharmacological agent or combination therapy</p>	<p>12–18 years old: 1st psychoeducation (patient/parents/teachers) 2nd - Mild: CBT with involvement of parents/teachers - Moderate/severe: Monotherapy; CBT with or without parent/teacher training OR pharmacotherapy 3rd switching to another pharmacological agent or combination therapy</p>	<p>12–18 years old: 1st psychoeducation (patient/parents/educators) 2nd psychosocial interventions based on behavioral therapy OR pharmacological treatment (with counseling/accompanying psychosocial interventions) 3rd combination treatment Severe: 1st psychoeducation (patient/parents/educators) 2nd pharmacological treatment (with accompanying counseling/psychosocial interventions) 3rd combination treatment</p>	<p>12–18 years old: 1st psychoeducation (patient/parents/educators) 2nd psychosocial interventions based on behavioral therapy OR pharmacological treatment (with counseling/accompanying psychosocial interventions) 3rd combination treatment Severe: 1st psychoeducation (patient/parents/educators) 2nd pharmacological treatment (with accompanying counseling/psychosocial interventions) 3rd combination treatment</p>

Side effects

Growth

Meta-analysis has indicated that over the first 2 years of treatment, methylphenidate leads to an average decrease in growth gain of approximately 1.25 cm and 1.43 kg for a 10-year-old boy and 1.65 cm and 2.6 kg for a 14-year-old boy [17]. Another study comparing height velocity during 4 years of treatment found a significant ($p < 0.01$) difference between height velocity during the first year of treatment and height velocity during 2–4 years of treatment, arguing that the growth inhibition of stimulants is most significant during the first year of treatment, and the extent of inhibition is less and less distinctive thereafter [18]. Moreover, a recent, prospective study involving over 1400 children, 756 of whom were prescribed methylphenidate, showed no significant impact of methylphenidate on height velocity over a period of 2 years. Additionally, there was only a limited effect on weight in the first 6 months, emphasizing that any effect is likely to be temporary and not of clinical concern [19]. However, a clinically significant and meaningful impact on growth and/or weight can be possible on an individual level. In that case, Belgian, UK and Dutch guidelines recommend a planned break, for example, during school holidays, allowing for “catch-up” growth [8, 9, 11]. In a recent literature review that identified 22 studies published from 1972 to 2013 mapping the experience of drug holidays from ADHD medication, evidence for a positive impact on child growth with longer breaks (for example, during summer holidays) was found [20].

Cardiovascular function

In a meta-analysis, stimulants were shown to be associated with a significant mean small increase of systolic blood pressure (standard mean difference (SMD) 0.25, 95% confidence interval (CI) 0.08–0.42 for methylphenidate, SMD 0.09, 95% CI 0.03–0.15 for amphetamines) after an average duration of 28.7 weeks. Additionally, amphetamines were associated with a small increase in diastolic blood pressure (SMD 0.16, CI 0.03–0.29) and heart rate (SMD 0.37, CI 0.13–0.60) [21]. Meta-analytically, in a median follow-up time frame ranging from 0.25 to 9.5 years, no significant association between psychostimulants and the risk of cardiovascular problems (including cardiac arrest and arrhythmias, cerebrovascular diseases, and myocardial infarction) was found, neither for children and adolescents nor for adults. However, a modest increased risk cannot be entirely ruled out due to the low incidence of the events under study [21]. One retrospective chart review on stimulant safety in 831 patients with pre-existing heart disease found an incidence of serious cardiac events of 0.21%, similar to that of serious

cardiac arrhythmias in the general population [22]. Another retrospective cohort study in 151 children with congenital heart disease (CHD) did not find any clinically significant changes in cardiovascular parameters in children with CHD and ADHD treated with stimulants compared with CHD-matched controls. These data suggest that stimulant use is safe in this population. However, data on this subject are scarce and need further investigation [23].

Psychiatric side effects

Multiple studies suggest that methylphenidate does not worsen tics [14, 19], while a single study on dexamfetamine treatment in boys aged 6–13 years showed a significant increase in tics at relatively high doses (0.6–1.2 mg/kg per day) early in treatment ($p < 0.05$) [24]. However, evidence is limited, and stimulants may worsen tics in individual cases. With methylphenidate, mood and irritability generally do not seem to be adversely affected. On the contrary, a large, naturalistic long-term study showed that mood improved significantly more in the methylphenidate group than in the no-methylphenidate group after 24 months of treatment [19, 25]. Similarly, meta-analysis indicated a significantly decreased risk of irritability with methylphenidate compared to placebo (risk ratio 0.89 [95% CI, 0.82 to 0.96], $p = 0.004$) whereas an increased risk of irritability was described with amphetamines compared to placebo (risk ratio = 2.90 [95% CI, 1.26 to 6.71], $p < 0.01$) [25]. While suicidality and psychosis are typically considered contraindications for stimulant treatment, recent register studies have failed to find an effect of stimulants on the risk of suicide attempts or psychotic events [26, 27]. However, the treatment of children and adolescents with these clinical features should be the remit of specialized mental health professionals.

A meta-analysis found that stimulants are associated with shorter sleep duration, longer sleep latency, and reduced sleep efficiency [28]. An increased number of daily doses as well as long-acting formulations have been found to be associated with increased sleeping problems [28, 29]. Some children and adolescents may experience rebound, a transient deterioration of behavior as stimulant medications wear off [30]. Stimulants possess abuse potential and can be used recreationally at higher doses or intranasally [31]. Moreover, stimulant prescriptions can be diverted for use as cognitive enhancers in non-diagnosed individuals [32]. However, there is no evidence to suggest that treatment with stimulants contributes to the development of substance abuse disorders. In fact, treating ADHD patients with methylphenidate may even reduce their risk, probably due to the improvement of ADHD symptomatology [33, 34].

It is important to note that while the above studies provide valuable information, individual responses to medications can vary. There may be cases where certain individuals

experience unique side effects or reactions that are not observed or predicted by group-level data.

Long-acting formulations

Due to the limited duration of action of immediate-release stimulants, typically ranging from 4 h for methylphenidate to 6–8 h for dexamfetamine, multiple doses a day are usually necessary. Meanwhile, several long-acting formulations of methylphenidate have been developed with a duration of action from 8 to 12 h. Effect sizes for long-acting stimulants are generally comparable to effect sizes reported for short-acting stimulants [35, 36]. However, long-acting stimulants have been found to be associated with better medication adherence. This may be due to factors such as convenience (i.e., no need to bring medication to school), reduced risk of forgetting a dose, and decreased stigma associated with medication use, as children do need to take medications at school [37]. Moreover, controlled-release formulations have been suggested to lower the abuse potential, due to fact that a slower absorption is linked to less drug-induced euphoria [38]. However, it is worth noting that many long-acting stimulants can still be modified to allow for rapid intranasal absorption [39].

In Europe, for methylphenidate, both controlled-release and osmotic release preparations are available. Controlled-release preparations combine immediate-release and delayed-release forms of methylphenidate, with different preparations offering varying ratios of immediate- versus delayed-release methylphenidate. Controlled-release preparations generally have a duration of action of up to 8 h. The osmotic release variant uses osmotic pressure to regulate the gradual release of the drug over time, with a duration of action of 8 to 12 h.

For dexamfetamine, the prodrug lisdexamfetamine dimesylate is available. Lisdexamfetamine dimesylate itself is inactive but is converted to active dexamfetamine in the body by peptidases. Its duration of action is about 12 h [40].

Pharmacokinetic considerations

Methylphenidate is metabolized by a carboxylesterase to an inactive metabolite [41]. The enzymes involved in amphetamine metabolism have not been clearly defined, though CYP2D6 is known to be involved. Thirty to 40% of amphetamines are excreted renally without metabolism. Substances that acidify the gastrointestinal tract (ascorbic acid, fruit juices, etc.) decrease the absorption, and acids may increase excretion of amphetamines. Clonidine can prolong the duration of action of amphetamines. Dexamfetamine can reduce the antihypertensive effect

of clonidine. Simultaneous use of β -blockers can lead to severe hypertension. Dexamfetamine can counteract the sedative effect of antihistamines, counteract the (respiratory) depressive effects of opioids, enhance the analgesic effect of morphine, and reduce the effects of methyl dopa. Sympathomimetics and presumably tricyclic antidepressants can potentiate the blood pressure-raising effect of amphetamines. Drug interactions are similar for methylphenidate and amphetamines.

Noradrenaline reuptake inhibitor

Atomoxetine is a noradrenaline reuptake inhibitor; it works by binding NAT thus increasing noradrenaline levels in the synaptic cleft. In addition, atomoxetine also inhibits the reuptake of dopamine in regions such as the prefrontal cortex, where DAT is minimal and reuptake of dopamine is handled by the noradrenaline transporter [42]. Meta-analysis has shown a moderate effect size (0.56 parent rated) for atomoxetine in the treatment of ADHD in children and adolescents [15].

Side effects

In clinical trials in children and adolescents, atomoxetine has been linked to gastrointestinal adverse events such as nausea, vomiting, decreased appetite, and abdominal pain. The Food and Drug Administration (FDA) issued a black-box warning concerning suicidal ideation in 2005. A meta-analysis of clinical trials revealed a higher incidence of recorded suicidal ideation among children and adolescents treated with atomoxetine compared to those on placebo (5/1357 versus 0/851) with a number needed to harm of 227 [43]. Subsequent studies on suicidal ideation associated with atomoxetine yielded mixed results [43]. Overall, the evidence suggests a small risk for suicidal ideations associated with atomoxetine treatment. Therefore, patients should be carefully monitored during treatment, in particular at the beginning and after a dose increase [44]. There are some rare, spontaneous reports of liver injury, manifested by changes in hepatic enzymes and bilirubin with jaundice, and even liver failure [45]. The FDA label states that routine laboratory tests are not required, upon the first symptom of liver dysfunction (e.g., pruritus, dark urine, jaundice, right upper quadrant tenderness, or unexplained “flu like” symptoms), a lab test to determine liver enzymes should be performed, and both the European Summary of Product Characteristics (SmPC) and FDA label state that atomoxetine should be immediately discontinued in case liver injury. There are some data from a pooled analysis reporting on sexual and genitourinary adverse events of atomoxetine in adolescent and adult males, with erectile

dysfunction (8%) being the most common [46]. German guidelines specifically recommend monitoring sexual side effects when administering atomoxetine [13].

Pharmacokinetic considerations

Atomoxetine is primarily metabolized by the CYP2D6 enzyme of the P450 system. Poor metabolizers of CYP2D6 have a tenfold higher exposure to atomoxetine and a five-fold higher peak concentration to a given dose compared with extensive metabolizers which is considered the norm. CYP2D6 metabolizer status can be determined from either blood or saliva. A similarly increased exposure is seen when atomoxetine is coadministered with potent CYP2D6 inhibitors (e.g., paroxetine and fluoxetine). These higher plasma levels may lead to a higher rate of some adverse effects of atomoxetine. Simultaneous use with other QT-prolonging agents, thiazide diuretics, and CYP2D6 inhibitors increases the risk of a prolonged QT interval.

Alpha-2 adrenergic agonists

Guanfacine and clonidine have an agonistic effect on alpha-2 adrenergic receptors; this leads to a stimulation of noradrenergic neurotransmission in the prefrontal cortex. Guanfacine has been described to be more selective than clonidine, which also binds to several other receptors [47], which may lead to guanfacine being less sedative. Guanfacine is administered in a single dose, either in the morning or in the evening. In the USA, clonidine is available in a long-acting formulation, whereas in Europe, only short-acting forms are accessible. Clonidine administration is divided into three doses a day. Meta-analyses showed similar effect sizes for guanfacine and clonidine (0.63 to 0.71) [48]. In some European countries, guanfacine is approved when stimulants are not suitable, not tolerated or have been shown to be ineffective [8–13]. Clonidine is not approved for the treatment of ADHD (European Medicines Agency, 2020). Among the European guidelines we reviewed, only the Belgian and Dutch guidelines mention the use of clonidine, and then, only as a fourth-line drug, reserved for prescription by specialists [8, 9]. Guanfacine is available as an extended-release formulation, whereas clonidine is only available as an immediate-release formulation.

Side effects

Adverse effects of clonidine and guanfacine are comparable including somnolence, fatigue, irritability, insomnia, headache, hypotension, and bradycardia. Care should be taken when discontinuing guanfacine or clonidine to avoid

rebound hypertension. For the discontinuation of guanfacine ER, the manufacturer advises tapering the dose.

Pharmacokinetic considerations

Clonidine is primarily metabolized via CYP2D6; in addition, 40–60% is excreted unmetabolized. Guanfacine is metabolized by CYP3A4 and CYP3A5. It is sensitive to interactions with medium and potent CYP3A4 and CYP3A5 inhibitors (e.g., grape fruit juice) leading to increased exposure to guanfacine and increased risk of side effects. Interaction with CYP3A4-CYP3A5-inducers (e.g., rifampicin, carbamazepine, phenytoin, St John's wort, and efavirenz) reduces the plasma concentration, rate, and extent of exposure to guanfacine. Caution is warranted when using concurrently with antihypertensives or other medications that may lower blood pressure or heart rate, increasing the risk of syncope or prolonging the QT interval.

Drug choice

The guidelines uniformly discourage the use of medication in children under the age of six (or five according to UK guidelines), unless specifically prescribed by a specialist for severe symptoms [8–13]. For children aged 6–18, guidelines vary in their recommendations for drug choices. In most guidelines, the primary medication of choice is psychostimulants and in particular methylphenidate [8–11, 13]. While most guidelines do not favor either short-acting or long-acting forms, Belgian and Dutch guidelines prioritize long-acting forms of methylphenidate due to its positive impact on treatment adherence, thereby enhancing effectiveness, and lowering the risk of abuse [8, 9]. The UK guidelines specify that if ADHD symptoms and associated functional impairment do not sufficiently improve after 6 weeks of treatment with an appropriate dose of methylphenidate, switching to an alternative treatment should be considered [11]. This recommendation has been adopted by the Belgian and Dutch guidelines [8, 9]. Potential alternatives to methylphenidate include lisdexamfetamine, dexamfetamine, atomoxetine, and guanfacine, except in the UK, where the use of guanfacine is not included in the guideline [8–13]. A treatment hierarchy approach is proposed by Belgian, Dutch, and UK guidelines, with (lis) dexamfetamine as a second-line option, followed by atomoxetine or guanfacine as the third step [8, 9, 11]. Spain, on the other hand, does not specify a preferred order of medication [12]. Similarly, the Danish guidelines found insufficient evidence to favour methylphenidate, lisdexamfetamine, or atomoxetine as first-line treatment options. Nevertheless, the Danish guidelines do recommend considering atomoxetine or guanfacine preferably in cases where stimulants are not

Table 2 Sequencing of medication

Belgium, 2021 Hoge Gezondheidsraad	Denmark, 2021 Sundhedsstyrelsen	The Netherlands, 2019 GGZ Standaarden	UK, 2018 The National Institute for Health and Care Excellence	Spain, 2017 Clinical practice guidelines in the Spanish national healthcare system	Germany, 2017 Association of the Scientific Medical Societies
<p>< 6 years old: Pharmacological interventions not recommended, unless - On the advice of a competent and experienced specialist in the 2nd line</p> <p>- In case of very severe symptoms where non-pharmacological treatments have insufficient effect</p> <p>6–18 years old: 1st methylphenidate (either short or long acting) or lisdexamfetamine/dexamfetamine or atomoxetine 2nd guanfacine or atomoxetine, when central stimulants are not tolerated, not suitable or have been shown to be ineffective</p> <p>In case of comorbidities: No specific recommendations regarding drug choice. All drugs can be used</p> <p>6–18 years old: 1st methylphenidate, preferably long-acting agents 2nd lisdexamfetamine or dexamfetamine 3rd atomoxetine or guanfacine 4th other drugs such as clonidine or nortriptyline (reserved for specialists)</p> <p>In case of comorbidities: Mood disorders, tics, anxiety, ASD, and substance misuse: all drugs can be used. Medication should be stopped in case of psychosis or mania and extra caution is warranted when deciding to restart</p>	<p>< 6 years old: Pharmacological interventions not recommended, unless - Prescribed by an experienced specialist</p> <p>- In case of severe ADHD when non-pharmacological interventions have insufficient effect</p> <p>> 5 years old: 1st methylphenidate (either short or long acting) 2nd lisdexamfetamine, only dexamfetamine when responding to but not tolerating lisdexamfetamine 3rd atomoxetine or guanfacine 4th other drugs such as clonidine or nortriptyline (reserved for specialists)</p> <p>In case of comorbidities: Mood disorders, tics, anxiety, ASD, and substance misuse: all drugs can be used. Medication should be stopped in case of psychosis or mania and extra caution is warranted when deciding to restart</p>	<p>< 6 years old: Pharmacological treatment not recommended. In situations where the severity of symptoms necessitates it, treatment should start with the lowest possible therapeutic dose, considering the higher likelihood and severity of side effects in this population</p> <p>6–18 years old: No 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)</p> <p>> 5 years old: 1st methylphenidate (either short or long acting) 2nd lisdexamfetamine, only dexamfetamine when responding to but not tolerating lisdexamfetamine 3rd atomoxetine or guanfacine In case of comorbidities: Mood disorders, tics, anxiety, ASD, and substance misuse: all drugs can be used. Medication should be stopped in case of psychosis or mania and extra caution is warranted when deciding to restart</p>	<p>< 6 years old: Pharmacological treatment not recommended. In situations where the severity of symptoms necessitates it, treatment should start with the lowest possible therapeutic dose, considering the higher likelihood and severity of side effects in this population</p> <p>6–18 years old: No specific order: Methylphenidate (either short or long acting) Lisdexamfetamine Atomoxetine Guanfacine In case of comorbidities: No specific recommendations regarding drug choice</p>	<p>6–18 years old: 1st stimulants 2nd atomoxetine or guanfacine In case of comorbidities: ADHD + conduct disorder: 1st stimulants 2nd atomoxetine or guanfacine ADHD + anxiety: Stimulants or atomoxetine ADHD + substance misuse: Long-acting stimulants or atomoxetine or guanfacine ADHD + tics: stimulants or atomoxetine or guanfacine</p>	

well tolerated, are considered unsuitable, or have demonstrated ineffectiveness [10]. The German guidelines provide specific drug recommendations tailored to individual comorbidities, whereas other guidelines either lack specific advice or suggest that all medications can be used for ADHD and any comorbidities without differentiation based on specific conditions [13]. Notably, only the Dutch and Belgian guidelines mention clonidine and nortriptyline as a fourth-choice medication, reserved for specialists [8, 9]. For an overview of recommendations on the sequencing of medication across guidelines, we refer to Table 2.

Monitoring

Prior to initiating medication, it is recommended to evaluate children and adolescents for cardiac disease or related risk. All guidelines, except for the Danish and Spanish guidelines, recommend similar specific cardiovascular precautions [8, 9, 11, 13]. A comprehensive evaluation, including a medical and family history screening for risk factors, alongside a clinical examination, is recommended. Specific risk factors such as a family history of premature sudden death, personal symptoms like syncope, palpitations, chest pain, and unexplained dizziness (especially during exertion) are highlighted. Additional factors to consider include a history of congenital heart disease or prior cardiac surgery, exertional shortness of breath, exertional or stress-related fainting, sudden onset and cessation of palpitations, probable cardiac chest pain, signs of heart failure, and consistently elevated blood pressure above the 95th percentile for children and young individuals. Electrocardiogram and referral to a pediatrician or cardiologist are recommended only when the above screening shows positive results. General ADHD medication monitoring guidelines encompass multiple important aspects. Prior to starting any ADHD medication, it is recommended to assess blood pressure, heart rate, weight, and height. During the dose titration phase and with each dose adjustment, it is essential to follow-up with an evaluation of efficacy and tolerability is recommended. Once an adequate dose is achieved, guidelines differ on the frequency of check-ups: annually in Belgium and every 6 months in the Netherlands, the UK, Denmark, and Germany [8–11, 13]. Spanish guidelines do not specify follow-up frequency [12]. During check-ups, in addition to evaluating of the medication's effect, height, weight, and BMI should be measured and their respective percentiles calculated based on local growth charts. Cardiovascular monitoring includes measuring the child's pulse and blood pressure. Monitoring of side effects, including tics, mood changes, and psychotic symptoms, is recommended. Follow-up of mood changes should include irritability, dysphoria, and suicidality. Should

severe mood symptoms, psychotic or manic features, or suicidality occur, an urgent referral to a mental health specialist is recommended. The guidelines emphasize the importance of preventing stimulant diversion and supporting treatment adherence. German guidelines particularly address monitoring sexual dysfunctions and dysmenorrhea with atomoxetine, as well as closely monitoring pulse, blood pressure, and somnolence with guanfacine [13]. Gradual discontinuation of guanfacine is advised to avoid adverse reactions. All guidelines except for the Spanish guideline recommend considering medication breaks [8–11, 13]. These drug-free periods can facilitate a re-evaluation of the need for continued pharmacological treatment. When specified, these breaks are typically on a yearly basis for a duration of 1–2 weeks.

Conclusion

Various pharmacological treatment options are available for the treatment of ADHD in children and adolescents. Most medications have moderate to high effect sizes and are well-tolerated. Systematic monitoring of cardiovascular parameters and physical measurements, as well as a frequent evaluation of benefits and possible adverse effects, is crucial. Prescribers of medication for ADHD need specific knowledge regarding evidence-based recommendations. While our overview of European guidelines reveals significant agreement in the context of pharmacotherapy for ADHD, there are also relevant discrepancies among them, primarily in terms of selection and sequencing of different medications.

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Declarations

Competing interests The authors declare no competing interests.

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