Pharmacology & Therapeutics 230 (2022) 107940

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Evidence-based pharmacological treatment options for ADHD in children and adolescents

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ARTICLE INFO

Available online 23 June 2021

Keywords:
Attention-deficit hyperactivity disorder
Psychopharmacology
Methylphenidate
Amphetamines
Atomoxetine
Guanfacine
Clonidine

ABSTRACT

Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by inattention, hyperactivity, and impulsivity, causing functional impairment. Its prevalence lies at approximately 5% in children and adolescents and at approximately 2.5% in adults. The disorder follows a multifactorial etiology and shows a high heritability. Patients show a high interindividual and intraindividual variability of symptoms, with executive deficits in several cognitive domains. Overall, ADHD is associated with high rates of psychiatric comorbidities, and insufficient treatment is linked to adverse long-term outcomes. Current clinical guidelines recommend an individualized multimodal treatment approach including psychoeducation, pharmacological interventions, and non-pharmacological interventions. Available medications include stimulants (methylphenidate, amphetamines) and non-stimulants (atomoxetine, guanfacine, clonidine). While available pharmacological treatment options for ADHD show relatively large effect sizes (in short-term trials) and overall good tolerability, there is still a need for improvement of current pharmacotherapeutic strategies and for the development of novel medications.

This review summarizes available pharmacological treatment options for ADHD in children and adolescents, identifies current issues in research and evidence gaps, and provides an overview of ongoing efforts to develop new medications for the treatment of ADHD in children and adolescents by means of a systematic cross-sectional analysis of the clinical trials registry *www.clinicaltrials.gov*.

Contents

1. Introduction

Inattention, hyperactivity, and impulsivity by themselves are population traits, which – if present to an extreme degree – lead to functional impairment and represent the cardinal symptoms of attention-deficit hyperactivity disorder (ADHD). The prevalence of ADHD in children and adolescents has been estimated at approximately 5%, with no significant differences between countries worldwide (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007; Polanczyk, Willcutt, Salum, Kieling,

Abbreviations: ADHD, Attention-Deficit Hyperactivity Disorder; FDA, United States Food and Drug Administration.

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https://doi.org/10.1016/j.pharmthera.2021.107940

& Rohde, 2014). Moreover, ADHD is not limited to childhood or adolescence, but rather shows a high persistence into adulthood, with an estimated prevalence of 2.5% in adults (Faraone et al., 2015). Extensive research efforts have so far revealed a multifactorial etiology with a complex but high heritability (Faraone & Larsson, 2018).

Patients with ADHD show executive deficits in several cognitive domains, e.g., visuospatial and verbal working memory, inhibitory control, vigilance, planning and reward regulation (Faraone et al., 2015; Sergeant, 2005; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). These deficits are substantiated by abnormal findings from structural and functional brain imaging studies, predominantly in larger-scale brain networks such as frontostriatal, frontoparietal and ventral attention networks (Faraone et al., 2015). In line with the heterogeneity of research findings, ADHD symptoms likewise show a high variability on the interindividual and intraindividual level and need to be viewed within the context of a chronic neurodevelopmental disorder.

Core symptoms of ADHD are frequently associated with additional symptoms (e.g., sleep problems, depressed mood or oppositional behavior), which further reduce psychosocial functioning (Cortese, Faraone, Konofal, & Lecendreux, 2009; Faraone et al., 2015). Overall, ADHD is associated with high rates of psychiatric (e.g., conduct disorder) and somatic (e.g., obesity) comorbidities (Cortese, 2019; Faraone et al., 2015; Fliers et al., 2013; Reale et al., 2017).

Due to the described characteristics of ADHD, making a diagnosis is challenging. The diagnostic process is aided by assessment tools (rating scales, semi-/structured interviews) and guided by classification systems (e.g., DSM-5 or ICD-10), but relies mainly on the classical skills of psychiatrists: a careful and comprehensive clinical interview and behavioral observation of the patient and respective family members/caregivers as well as an observation of their interactions.

As (insufficiently treated) ADHD negatively affects many long-term outcomes (e.g., academic achievement, employment status, traffic accidents), timely and adequate treatment is crucial (Arnold, Hodgkins, Kahle, Madhoo, & Kewley, 2020; Faraone et al., 2015; Harpin, Mazzone, Raynaud, Kahle, & Hodgkins, 2016; Vaa, 2014). Current clinical guidelines recommend an individualized multimodal and multidisciplinary treatment approach. On the basis of extensive psychoeducation, a framework of pharmacological and/or non-pharmacological interventions should be established, which takes into account the age, the severity of symptoms and the individual needs of the patient. In adult ADHD, treatment generally follows the same multimodal and multidisciplinary approach while ideally involving the patient's partner, family or close relationships (de Crescenzo, Cortese, Adamo, & Janiri, 2017; Kooij et al., 2019).

The aims of this review are (i) to summarize available pharmacological treatment options for ADHD in children and adolescents, (ii) to identify current issues in research and evidence gaps, and (iii) to provide an overview of ongoing efforts to develop new medications for the treatment of ADHD in children and adolescents.

2. Approved medications

2.1. Stimulants

Psychostimulants including methylphenidate and amphetamine are first-line pharmacotherapies for patients with ADHD (National Institute for Health and Care Excellence, 2018). Amphetamine actions include the inhibition of dopamine and norepinephrine transporter, vesicular monoamine transporter 2, and monoamine oxidase activity. Methylphenidate actions include dopamine and norepinephrine transporter inhibition, agonist activity at the serotonin type 1A receptor, and redistribution of the vesicular monoamine transporter 2 (Faraone, 2018). By enhancing the impact of dopamine and norepinephrine, psychostimulants increase the efficiency of prefrontal cortex activity and optimize executive and attentional function in patients suffering from ADHD (Arnsten, 2011; Arnsten & Pliszka, 2011).

Psychostimulants are available in short-acting and long-acting formulations, with the latter encompassing different controlled-release stimulant formulations (typically including a combination of immediate-release and delayed-release beads), osmotic-release oral system methylphenidate, and the prodrug lisdexamfetamine dimesylate (López & Leroux, 2013). Research has shown that long-acting formulations are associated with better medication adherence and probably a lower risk of rebound effects, while short-acting formulations allow for more flexibility with the dosing frequency and titration (Hodgkins, Shaw, Coghill, & Hechtman, 2012; Wilens & Spencer, 2000). The last two decades have seen a strong increase in the number of available stimulant formulations, including several novel delivery systems such as chewable tablets, liquid formulations or transdermal patches (for an overview see Steingard, Taskiran, Connor, Markowitz, & Stein, 2019). Long-acting stimulant formulations differ regarding their pharmacokinetic profiles, particularly with respect to the rate at which peak levels are attained and decline. Physicians should take these differences into account in order to choose a formulation that is appropriate for the symptom profile of the patient and his or her individual needs (Coghill et al., 2013; Maldonado, 2013; Steingard et al., 2019).

Both methylphenidate and amphetamine are associated with a range of adverse effects, which are generally acceptable as they are predominantly mild and/or temporary (Graham & Coghill, 2008; Hodgkins et al., 2012). Common adverse effects include decreased appetite, sleep disturbances, increased blood pressure and pulse, headaches, irritability, and stomach pain. Moreover, it is still controversially debated whether stimulant medication might increase the risk of serious adverse events such as sudden death or suicidality. Taking into account data from large registry studies, many authors conclude that a causal relationship between stimulant medication and such serious adverse events is unlikely, although such a risk cannot be completely excluded (Graham & Coghill, 2008). However, with regard to suicidality recent evidence rather suggests that psychostimulant medication decreases the risk of suicidal events in patients suffering from ADHD (Chen et al., 2014; Man et al., 2017).

Stimulant medications are associated with statistically significant increases in blood pressure and heart rate. While these effects are small on the group level, they may be clinically relevant for a small subgroup of patients, especially those with preexisting cardiovascular diseases (Hennissen et al., 2017; Liang et al., 2018; Stiefel & Besag, 2010; Vetter et al., 2008). Therefore, clinical guidelines generally recommend monitoring of pulse and blood pressure when prescribing psychostimulant medication (Cortese et al., 2013; National Institute for Health and Care Excellence, 2018; Vetter et al., 2008).

Findings from longitudinal studies indicate that treatment with psychostimulants is associated with a statistically significant reduction in height and weight gain (Cortese et al., 2018; Faraone, Biederman, Morley, & Spencer, 2008; Greenhill et al., 2020; Swanson et al., 2017). These effects are usually minor, but again, can be clinically relevant in subgroups and generally require careful monitoring. It appears that the effects are dose-related and similar for both methylphenidate and amphetamine (Hodgkins et al., 2012; Pliszka, Matthews, Braslow, & Watson, 2006). To date, it remains unclear whether effects on height should be considered as reversible (Faraone et al., 2008; Greenhill et al., 2020). Reduced appetite, as a highly frequent side effect of stimulant treatment, certainly plays a major role in this regard. However, other possible mechanisms contributing to reduced weight and height, such as hormonal dysregulation, require further investigation.

2.1.1. Comparative efficacy of stimulants

There is substantial evidence for the efficacy of psychostimulants in reducing ADHD core symptoms in children and adolescents. A recent network meta-analysis of double-blind randomized controlled trials including data of more than 10,000 children and adolescents revealed large effect sizes for psychostimulants in reducing ADHD core symptoms as rated by clinicians (Cortese et al., 2018). Other studies found

that psychostimulants were effective not only in reducing ADHD core symptoms but also in improving overall quality of life and reducing functional impairment (Banaschewski et al., 2014; Coghill, 2010). Moreover, there are studies suggesting that psychostimulants also reduce the risk of emergency admission to hospital for trauma (Man et al., 2017), suicidal events (Chen et al., 2014), substance abuse (Chang et al., 2013), criminality (Lichtenstein et al., 2012), and unintentional injuries (Ghirardi et al., 2020; Ruiz-Goikoetxea et al., 2018).

For clinicians, it is important to note that on an individual level, patients with ADHD may respond to either amphetamine or methylphenidate with an overall very high response rate when both psychostimulants (amphetamine and methylphenidate) are tried (Arnold, 2000; Hodgkins et al., 2012).

Whereas the short-term efficacy of psychostimulants is well established, longer-term effects have been less well investigated. Follow-up observations from the Multimodal Treatment of ADHD (MTA) study suggest that children with ADHD who continued psychostimulants for more than 10 years fared no better in terms of symptom reduction than those who had discontinued their medication (MTA Cooperative Group, 1999; Swanson et al., 2017). Such observational findings, although methodologically insufficient to allow clear conclusions, raise questions about whether long-term treatment with psychostimulants continues to be beneficial. As long-term placebo-controlled trials are not feasible due to ethical considerations, different methodological approaches are needed. In this vein, in a seven-week randomized placebo-controlled methylphenidate-(dis)continuation study, Matthijssen et al. investigated the change in ADHD symptoms for children and adolescents who had previously been treated with methylphenidate in regular care for more than two years (Matthijssen et al., 2019). The authors reported a significant between-group difference in change over time in favor of the group that continued methylphenidate treatment. Such data support clinical guideline recommendations that patients with ADHD should be periodically assessed, potentially including a medication-free interval, to determine whether there is a continued need for psychostimulant treatment (National Institute for Health and Care Excellence, 2018; Pliszka et al., 2000; Wolraich et al., 2019).

2.2. Non-stimulants

2.2.1. Atomoxetine

Atomoxetine increases synaptic noradrenaline by binding to the norepinephrine transporter and is therefore classified as a norepinephrine reuptake inhibitor. In the prefrontal cortex, norepinephrine transporters are also responsible for regulation of dopamine reuptake, as dopamine transporters are scarce in this region. Consequently, atomoxetine increases both noradrenaline and dopamine in the synapses within the prefrontal cortex (Bymaster, 2002).

Atomoxetine is orally administered and primarily metabolized through the cytochrome P450 2D6 (CYP2D6) pathway. This should be taken into account, as some selective serotonin reuptake inhibitors can elevate serum atomoxetine levels (Eli Lilly and Company, 2020).

Atomoxetine is currently approved in many countries, including the United States and Europe, to treat ADHD in children and adolescents as well as in adults (Eli Lilly and Company, 2020; Therapeutic Goods Administration, 2020; US Food and Drug Administration, 2009). It is manufactured in capsules containing 10, 18, 25, 40, 60, 80, or 100 mg of atomoxetine hydrochloride as well as in an oral solution (4 mg/ml). Titration follows a sequential, weight-based approach, with a maximum recommended dosage of 1.4 mg/kg/day or 100 mg/day, whichever is lower (Eli Lilly and Company, 2020).

Analyses of twelve placebo-controlled trials in children and adolescents showed a greater risk of suicidal ideation during treatment in those participants receiving atomoxetine, which has led to special warnings by federal agencies and regulatory bodies, e.g., in the United States and Australia (Eli Lilly and Company, 2020; Therapeutic Goods Administration, 2020). It is stated that all children being treated with atomoxetine should be monitored closely for suicidality, clinical worsening, and unusual changes of behavior, especially during the first few months of treatment or at times of dose change (Eli Lilly and Company, 2020; Therapeutic Goods Administration, 2020). Analyses of similar trials in adults did not yield such an observation (Therapeutic Goods Administration, 2020). Warnings also exist for preexisting cardiovascular diseases/significant cardiac abnormalities, emergent psychotic or manic symptoms, bipolar disorder, aggressive behavior or hostility, possible allergic reactions, effects on urine outflow and growth, and priapism in children, adolescents and adults (Eli Lilly and Company, 2020; Therapeutic Goods Administration, 2020).

The most common adverse effects of atomoxetine in child and adolescent clinical trials were nausea, vomiting, fatigue, decreased appetite, abdominal pain, and somnolence (Eli Lilly and Company, 2020; Therapeutic Goods Administration, 2020). Seven percent of the population have been estimated to be poor metabolizers of atomoxetine, with significantly higher plasma levels and longer half-lives. This may lead to an increase in adverse effects (US Food and Drug Administration, 2009).

2.2.2. Clonidine and guanfacine

Clonidine and guanfacine are pharmacologically very similar, and their main mechanism of action is an agonistic effect at alpha-2 adrenergic receptors throughout the brain. In the brain stem, alpha-2 agonists lead to a reduction in peripheral vascular resistance and consequently lower blood pressure. This has been the traditional therapeutic use of alpha-2 agonists.

In the prefrontal cortex, postsynaptic alpha-2 agonism leads to enhanced noradrenergic neurotransmission. This, in turn, strengthens the regulatory role of the prefrontal cortex, which is responsible for top-down guidance of attention, thought and working memory (Arnsten & Pliszka, 2011; Cinnamon Bidwell, Dew, & Kollins, 2010; Sallee, Connor, & Newcorn, 2013; Wang et al., 2007). The literature describes further theoretical constructs and hypotheses which may further explain the beneficial effects of alpha-2 agonists (Faraone, McBurnett, Sallee, Steeber, & López, 2013) in ADHD and which are omitted here for reasons of conciseness (Hu, Vidovic, Chen, Lu, & Song, 2008; Huss, Chen, & Ludolph, 2016; Ren, Liu, & Li, 2012; Song, Abou-Zeid, & Fang, 2004).

While sharing the same mechanism of action, clonidine and guanfacine differ regarding their potency, with guanfacine being approximately ten times less potent than clonidine (Giovannitti, Thoms, & Crawford, 2015). The documented higher specificity of guanfacine to alpha-2A receptors may mediate differences between the two agents regarding the adverse effects profile, e.g., less sedative effects of guanfacine (Giovannitti et al., 2015; López, 2006; Newcorn et al., 1998). The two agents also differ in respect to metabolization, with clonidine being primarily metabolized via CYP2D6 and excreted renally and hepatically in equal shares, and guanfacine being primarily metabolized via CYP3A4 and excreted predominantly renally (Boellner, Pennick, Fiske, Lyne, & Shojaei, 2007; Shire Pharmaceuticals, 2019; US Food and Drug Administration, 2010).

Clonidine and guanfacine are approved as extended-release formulations for the treatment of ADHD as a monotherapy or as an adjunctive therapy to stimulants in various countries, with certain differences with respect to approval details. In Europe, guanfacine is only approved for therapeutic use when stimulants are not suitable, not tolerated or have been shown to be ineffective while clonidine is not approved for the treatment of ADHD (Dittmann, Häge, Pedraza, & Newcorn, 2018; Elbe & Reddy, 2014; European Medicines Agency, 2020; Shire Pharmaceuticals, 2019).

Clonidine is available in tablet form with dosages of 0.1 and 0.2 mg. The recommended starting dose is 0.1 mg tablet at bedtime, which can then be increased to a twice-daily administration and subsequent careful uptitration. Doses higher than 0.4 mg/day are not recommended. A

transdermal therapeutic patch is also available, with dosages of 0.1, 0.2 and 0.3 mg (US Food and Drug Administration, 2010).

Guanfacine is available in tablet form, with doses of 1, 2, 3, and 4 mg, and it is recommended that the dosing regimen is adjusted to body weight, with once-daily administration (0.1 mg/kg as a rule of thumb) (European Medicines Agency, 2020; Shire Pharmaceuticals, 2019).

Adverse effects of clonidine and guanfacine are generally considered very similar (cf. mechanism of action), and are most commonly somnolence, fatigue, irritability, insomnia, and nightmares. For clonidine, dry mouth, sedation, bradycardia, and syncope have also been reported. Warnings also exist in the approvals/labels of both clonidine and guanfacine and refer to hypotension/bradycardia, somnolence/sedation, discontinuation, and allergic reactions, and cardiac conduction abnormalities (Faraone et al., 2013; Huss et al., 2016; Ruggiero et al., 2014; US Food and Drug Administration, 2010; Wilson et al., 1986).

2.2.3. Comparative efficacy of non-stimulants

The non-stimulants atomoxetine, clonidine and guanfacine have been shown to be efficacious in treating ADHD, but their effect sizes compared to placebo are generally in the medium range and smaller than those of stimulants (Cortese et al., 2018). This is supported by the results of several clinical trials comparing stimulant and non-stimulant treatment "head-to-head" (Dittmann et al., 2013; Newcorn et al., 2008; Wigal et al., 2005).

Beyond their effects on core ADHD symptomatology, atomoxetine and guanfacine have both been shown to be associated with improved functional impairment and quality of life (Childress, 2016; Hervas et al., 2014). Longer-term maintenance of treatment effects is documented for atomoxetine and guanfacine, while it has not yet been systematically evaluated for clonidine (Dittmann et al., 2018; Newcorn et al., 2016; Song et al., 2004; US Food and Drug Administration, 2010).

Due to their relatively smaller effect sizes, current guidelines for the treatment of ADHD generally recommend non-stimulant medication as a second-line treatment with stimulant medication as the first-line treatment (Hughes et al., 2007; Mahajan et al., 2012; National Institute for Health and Care Excellence, 2018; Pliszka, 2007; Taylor et al., 2004; Wolraich et al., 2019). Nevertheless, there are further limitations and benefits of non-stimulant medication to consider in the treatment of ADHD. It is important to note that the treatment effects are not usually observed until several weeks after initiation of treatment with atomoxetine (6–12 weeks), clonidine and guanfacine (2–4 weeks) (Childress, 2016; Dickson et al., 2011; Sallee, Kollins, & Wigal, 2012). This differs significantly from stimulants, which have a much more rapid onset of treatment effects.

Potential benefits of non-stimulants – in comparison to stimulants – include their non-controlled status and their "around-the-clock" effects. In order to reduce adverse effects, the daily dose of atomoxetine can be split into two equal doses administered in the morning and evening. If needed, atomoxetine can also be administered in the evening only (Banaschewski, Roessner, Dittmann, Santosh, & Rothenberger, 2004; US Food and Drug Administration, 2009).

With clonidine and guanfacine, administration in the evening is generally preferable due to the relatively frequent occurrence of somnolence/fatigue as an adverse effect, although no significant difference between administration in the morning vs. evening was found within a study setting (Newcorn et al., 2013).

While atomoxetine seems to have similar cardiovascular effects to stimulants (= few), evidence suggests that it shows lower effects regarding decreased appetite and, consequently, fewer growth/height problems (McCarthy et al., 2018; Savill et al., 2015; Wernicke et al., 2003). Within the non-stimulants, adverse effects of atomoxetine are considered to be less frequent and less pronounced compared to clonidine and guanfacine (Dittmann et al., 2018).

In the USA, guanfacine and clonidine have both been approved "as adjunctive therapy to stimulant medications", which presents either an increase in treatment effects and/or a decrease in adverse effects of stimulants, predominantly sleep disturbances and cardiovascular effects (elevated blood pressure and heart rate) (European Medicines Agency, 2020; Kollins et al., 2011; Sallee, Lyne, Wigal, & McGough, 2009; Shire Pharmaceuticals, 2019; US Food and Drug Administration, 2010).

Given these potential benefits, non-stimulants play an important role in the treatment of patients with ADHD *and* certain comorbidities. They may be considered as first-line treatment options in disruptive behavior disorders, tic disorder, Tourette's syndrome and – in particular – substance use disorders (where stimulants may be regarded as an unviable treatment option due to their dopaminergic activity in the nucleus accumbens and striatum) (Association of the Scientific Medical Societies in Germany, 2017; Biederman et al., 2007; Dittmann et al., 2011; Geller et al., 2007; Ghanizadeh, 2013; Thurstone, Riggs, Salomonsen-Sautel, & Mikulich-Gilbertson, 2010). When sleep disturbances are present, clonidine and guanfacine may be considered (Banaschewski et al., 2004). Clinical trials found that tics did not worsen under treatment with atomoxetine (Allen et al., 2005; Spencer et al., 2008). Guanfacine may reduce tics, but evidence regarding its beneficial effects on tics (comorbid to ADHD) remains inconclusive (Chappell et al., 1995; Cummings, Singer, Krieger, Miller, & Mahone, 2002; Murphy et al., 2017; Scahill et al., 2001).

There is some evidence supporting the use of atomoxetine in ADHD with comorbid anxiety or autism spectrum disorder (Arnold et al., 2006; Geller et al., 2007; Ghanizadeh, 2013). Despite the initial efforts to develop atomoxetine as an antidepressant, evidence so far does not support efficacy in this symptom domain (Bangs et al., 2007).

For an overview of available medications for treatment of ADHD (See Table 1).

3. Treatment strategies

First and foremost, it needs to be emphasized that pharmacological treatment of ADHD should always be part of an individualized multimodal treatment approach. This underlying principle is reflected in the recent major clinical guidelines on the treatment of ADHD (Association of the Scientific Medical Societies in Germany, 2017; National Institute for Health and Care Excellence, 2018).

Such a multimodal treatment approach generally includes psychoeducation, pharmacological treatment as well as psychotherapeutic and psychosocial interventions. Pharmacological treatment therefore represents only one piece of the puzzle, albeit a sizeable one due to the relatively large effect sizes (more pronounced in stimulants versus non-stimulants as described above) which have so far not been matched by non-pharmacological treatments (Sonuga-Barke et al., 2013).

The main factor in deciding whether to initiate pharmacological treatment in school children and adolescents is severity of ADHD symptoms, as emphasized by clinical guidelines: Cases with low and moderate severity "can" while severe cases "should" be offered pharmacological treatment. However, personal factors (e.g., level of suffering), situation of the patient's family, comorbidities, and global psychosocial functioning should also be taken into account.

As with all other treatment decisions, this process should follow the shared decision-making model, involving parents/caregivers and the child/young person (in a manner adjusted to developmental age) (Association of the Scientific Medical Societies in Germany, 2017; National Institute for Health and Care Excellence, 2018; Wolraich et al., 2019).

Pharmacological treatment should be provided in parallel with other interventions, e.g., behavioral therapy, as deemed appropriate according to remaining symptoms and deficits in psychosocial functioning (Association of the Scientific Medical Societies in Germany, 2017).

In preschool children, ADHD should primarily be treated by psychosocial and behavioral interventions (e.g., parent training in behavior management). In this age group, pharmacological treatment has been

Table 1
Overview of available medications for treatment of ADHD.

	Substance	(Likely) mode of action	Major adverse effects	Parameters to be monitored under therapy	Potential advantages	Potential disadvantages
Stimulants	Methlyphenidate, lisdexamfetamine	Reuptake inhibition (plus release in amphetamines) of dopamine and norepinephrine	Decreased appetite Sleep disturbances Increased blood pressure and pulse Headaches Irritability Stomach pain	Height Weight Pulse Blood pressure	Large effect sizes for reducing ADHD core symptoms Rapid onset of treatment effects Available in short-acting and various long-acting formulations Chewable tablets, liquid formulations and transdermal patches available Positive effects on conduct disorder and oppositional defiant disorder	Limited daily duration of effects Partial potential for rebound of symptoms when effect wears off in the afternoon/evening Controlled substance
Non-stimulants	Atomoxetine	Norepinephrine reuptake inhibition	Decreased appetite Headache Stomach pain Nausea Vomiting Sleep disturbances Increased blood pressure and pulse	Suicidality Clinical worsening Unusual changes of behavior Especially during the first few months of treatment or at times of dose change Pulse Blood pressure	"Around-the-clock" effects Uncontrolled substance Possible first-line option in comorbid substance use disorders, disruptive behavior disorders, tic/Tourette's disorder Augmentation of stimulant treatment possible	Smaller effect size in comparison to stimulants 6–12 weeks until effects are observed
	Clonidine, guanfacine	Agonism at alpha-2 adrenergic receptors (leading to enhanced noradrenergic neurotransmission)	Somnolence/sedation Fatigue Hypotension Bradycardia Irritability Insomnia	Pulse Blood pressure	"Around-the-clock" effects Uncontrolled substance Possible first-line option in comorbid sleep disorder, substance use disorder, disruptive behavior disorders, tic/ Tourette's disorder Augmentation of treatment with stimulants possible Clonidine: transdermal patch available	Smaller effect size in comparison to stimulants 2–4 weeks until effects are observed Somnolence/sedation frequent adverse effect (administration in the evening preferable) Clonidine: twice daily dosing necessary

shown to be less efficacious and associated with higher rates of adverse events than in school-age populations (Greenhill et al., 2006). It should therefore be approached with more restraint and careful consideration than in school children with ADHD and should only be reserved for cases with very high severity (Wolraich et al., 2019).

After making the decision to initiate pharmacological treatment, one of the several approved medications for the treatment of ADHD needs to be selected. In general, it is recommended to use stimulants as first-line therapy and non-stimulants as second-line therapy. However, the approval statuses of individual medications do vary slightly between different countries and need to be considered. For example, lisdexamfetamine and atomoxetine are approved as first-line therapies in the United States, but as second-line therapies in many European countries.

The complex construct of ADHD itself – a disorder affecting different age groups and with significant heterogeneity regarding etiology, underlying risk factors, course of disease as well as presence and severity of symptoms and comorbidities – already implies that a "one-size-fits-all" approach cannot be adequate and helpful in guiding the decision for a medication in all cases (Association of the Scientific Medical Societies in Germany, 2017). All relevant factors, such as severity of symptoms, presence of comorbidities, for what periods of the day symptom relief is needed, and patients' preferences, need to be considered (Faraone et al., 2015). In the case of methylphenidate, different extended-release formulations allow for an individualization of pharmacological treatment (Association of the Scientific Medical Societies in Germany, 2017; National Institute for Health and Care Excellence, 2018; Wolraich et al., 2019). Adjustment and changes of the pharmacological treatment regimen are the rule and not the exception. This may be due to changes in symptomatology or the psychosocial situation of the patient, but also due to normal development, e.g., increased weight (Association of the Scientific Medical Societies in Germany, 2017).

For example, if no desired benefit is observed after adequate treatment (dosage and duration) with methylphenidate, lisdexamfetamine should be preferred as the next option over non-stimulants (National Institute for Health and Care Excellence, 2018).

Healthcare systems vary notably in general, and also specifically with regard to the legal framework of how medication prices are set and paid for (e.g., copayments for prescription medication). Consequently, the respective framework and the situation of the patient's family (e.g., conditions of health insurance policy) may also need to be considered during the process of deciding on a medication. While this does not reflect an ideal situation, it is common day-to-day practice for psychiatrists and physicians in general in many countries and should therefore mandate further improvement by the respective legislative bodies.

Medication adherence is a common problem in ADHD treatment (MTA Cooperative Group, 2004; Osterberg & Blaschke, 2005). Lack of adherence may lead to reduced effectiveness, increased adverse events and other consequent problems, hampering the course of pharmacological treatment (Hack & Chow, 2001; Häge et al., 2018; Mechler & Häge, 2019).

During the course of treatment, medication adherence should be regularly assessed and potential issues in adherence openly discussed. To increase medication adherence as early as possible, relevant factors should be evaluated – and improved if possible — before the initiation of pharmacological treatment and should influence decision making. Such factors include attitudes of patients and parents toward pharmacological treatment, a trustful physician-patient relationship, family support, and knowledge about the disorder and the intended medication (Ferrin et al., 2012; Niemeyer et al., 2018; Wolraich et al., 2019). Apart from the choice of a medication, the dosing regimen can also affect medication adherence. Once-daily dosing should generally be preferred over twice-daily dosing (e.g., q.d. extended-release

methylphenidate over b.i.d. short-acting methylphenidate) (Osterberg & Blaschke, 2005).

4. Current issues in research and evidence gaps

Despite extensive research efforts over the last decades (a search for "(ADHD[MeSH Terms]) AND (pharmacotherapy[MeSH Terms])" on PubMed yielded 1601 entries as of August 17th 2020), there are still evidence gaps and unanswered questions in the context of pharmacological treatment of ADHD.

While short-term efficacy and safety of both stimulants and non-stimulants have been soundly demonstrated in various clinical trials (Banaschewski et al., 2006; Cortese et al., 2018; Faraone & Buitelaar, 2009; Padilha, Virtuoso, Tonin, Borba, & Pontarolo, 2018; Reed et al., 2016; Savill et al., 2015), a comparable extent of systematic assessments for longer-term outcomes is not yet available. Nevertheless, important progress has been made in this regard over the last years (Arnold et al., 2020; Carucci et al., 2021; Chang, D'Onofrio, Quinn, Lichtenstein, & Larsson, 2016; Hollis et al., 2019; Inglis et al., 2016; Krinzinger et al., 2019; Mazza et al., 2013; McCarthy et al., 2018; van Tebartz Elst et al., 2016), but needs to be followed up by further studies in the future.

Clinical trials comparing ADHD medications head-to-head as well as in combination are also needed. Such treatment approaches are common in clinical practice, which does not reflect the conditions of a placebo-controlled randomized trial design because it follows a multimodal treatment approach as recommended by clinical guidelines (Wong et al., 2019). First randomized withdrawal trials have been performed (Buitelaar et al., 2007; Coghill et al., 2014).

Currently, the decision on an ADHD medication is based on clinical factors only. Pharmacogenomic markers could inform this decision in the future by predicting likelihoods of treatment response and adverse effects, while therapeutic drug monitoring could improve pharmacovigilance (Gerlach et al., 2016; Wehry, Ramsey, Dulemba, Mossman, & Strawn, 2018). Relatively large numbers of studies have shown statistically significant associations between the effectiveness of stimulant treatment and DNA variants including single nucleotide polymorphisms (e.g., in dopamine related candidate genes) and DNA repeat variants (Myer, Boland, & Faraone, 2018; Pagerols et al., 2017). Even though no reliable genetic predictors for pharmacological treatment choices in ADHD have been identified yet, these findings appear promising and warrant further research in this area.

Age- and gender-specific differences with regard to pharmacological treatment are still underrepresented in ADHD research. However, there are findings supporting the hypothesis that sex differences are relevant in terms of response to ADHD medication. For instance, girls with ADHD have been found to show a superior response at 2.5 h post-dosing with stimulant medication and an inferior response after 12 h compared to boys with ADHD, suggesting that females may benefit from a different treatment regime (Sonuga-Barke et al., 2007).

Interventions to improve medication adherence in children and adolescents with ADHD need to be developed and scientifically evaluated in order to address this common issue (Association of the Scientific Medical Societies in Germany, 2017; Mechler & Häge, 2019).

Medications also need to be systematically compared to non-pharmacological treatment options (e.g., behavioral therapies, neurofeedback) as well as combined in order to reach conclusive recommendations for individualized treatment of ADHD (Sherrill, 2016). Research efforts in this regard are increasing after first trials have investigated or are currently investigating multimodal treatments and adaptive interventions for treatment of ADHD (Döpfner et al., 2004; Döpfner et al., 2015; Döpfner et al., 2017; Pelham et al., 2016). For the purpose of developing evidence-based treatment algorithms, Sequential Multiple Assignment Randomized Trials (SMARTs) are of particular value since they allow randomization of participants into sequences of interventions according to predefined rules (Almirall, Nahum-Shani, Wang, & Kasari, 2018; DuPaul, Evans, Mautone, Owens, & Power, 2020).

Study populations in clinical trials are also often highly selected, and their representativeness may be rightfully questioned (Kennedy-Martin, Curtis, Faries, Robinson, & Johnston, 2015; Lally et al., 2018). Trials which focus on "real-life" conditions with adaptive treatment approaches according to clinical guidelines and patient-centered outcomes are needed, but such trials are costly, require elaborate designs and lie outside of the conventional research areas of pharmaceutical companies aiming for regulatory approval of substances (Döpfner et al., 2017; Langley et al., 2010; Setyawan et al., 2013). Wong et al. have addressed these issues and suggested key methodological approaches for future research (Wong et al., 2019).

Beyond these aspects, there is also a need for new medications with novel mechanisms of action, because a significant proportion of patients treated with currently approved medications show a non-response and/or unsatisfactory effectiveness (Cortese et al., 2018; Hegvik et al., 2019; Mattingly & Anderson, 2016; Nageye & Cortese, 2019). Such endeavors face strong headwinds as the pharmaceutical industry has substantially reduced research and development efforts in disorders of the central nervous system over the last decade (Wegener & Rujescu, 2013).

5. Novel medications

In order to provide an overview of ongoing efforts to develop novel medications for the treatment of ADHD, we conducted a succinct cross-sectional analysis of the United States National Institute of Health's clinical trials registry accessible at *www.clinicaltrials.gov*. The database was queried for ongoing interventional clinical trials in children and/or adults by using the search terms "ADHD" and its synonyms "attention deficit", "hyperactivity disorder", "disorder hyperactivity", "hyperkinetic disorder", and "hyperkinetic syndrome". Filters were applied in order to only identify trials with at least one of the following statuses: "active", "not yet recruiting", "recruiting", "enrolling by invitation", and "recently suspended". Out of a total of 185 identified clinical trials, we omitted those which investigated an already approved substance, adjunctive treatments (e.g., vitamins, minerals, probiotic supplements, homeopathy), web-based tools, mobile health apps, therapeutic video games, neurofeedback, brain stimulation, or behavioral training programs.

The results of this search were then complemented by findings from a recent work with a similar purpose (Nageye & Cortese, 2019) and an open internet search via Google (www.google.com) and Google Scholar (www.scholar.google.com) using the search term [("novel" OR "new") "treatment" "ADHD"].

As of September 1st, 2020, we identified $n = 14$ novel substances which are currently or have been recently under development for the treatment of ADHD. These include $n = 4$ substances with no intended development for pediatric ADHD or only targeting comorbidities (delta-9-tetrahydrocannabinol plus cannabidiol, memantine, oxytocin, tolcapone) and $n = 5$ substances, which recently failed pivotal trials resulting in a halt of further development as announced by the respective companies (dasotraline, fasoracetam, metadoxine, molindone, vortioxetine). Therefore, these are not further discussed here. In the following, the remaining n = 5 substances are briefly described, and the current evidence summarized in alphabetical order:

5.1. Centanafadine

Centanafadine has been reported to be a novel reuptake inhibitor of serotonin, norepinephrine and dopamine, leading to a stimulation of norepinephrine and dopamine and therefore potentially of benefit in the treatment of ADHD (Bymaster, Golembiowska, Kowalska, Choi, & Tarazi, 2012). This potential was confirmed in animal models of ADHD, and a clinical development program was subsequently initiated (Bymaster et al., 2012). The current manufacturer Otsuka Pharmaceutical Co., Ltd. recently announced (June 2020) that two phase III trials of

centanafadine in adults with ADHD showed positive results demonstrating its efficacy, safety and tolerability (Otsuka Pharmaceutical Co., Ltd., 2020).

At the time of completing this manuscript – with these results remaining to be published in scientific, peer-reviewed journals – it is not possible to estimate what future role centanafadine might play within the management of ADHD. Furthermore, no evidence from pediatric populations is available at this time, but Otsuka Pharmaceutical Co., Ltd. also announced plans to investigate the effects of centanafadine in pediatric patients with ADHD (Otsuka Pharmaceutical Co., Ltd., 2020).

5.2. Mazindol

Mazindol represents a so-called "repurposed" medication, meaning that it has been, or was previously approved for another indication. In this case, the FDA approved mazindol for the treatment of obesity in adults in 1973. In 2000, the manufacturer withdrew it from United States and European Union markets, but it is reportedly still marketed in Mexico/Central America, Japan, and Argentina and still available in the European Union for compassionate use in narcolepsy and idiopathic hypersomnia (Nittur et al., 2013).

Mazindol is an imidazo isoindole agent with chemical similarity to amphetamine. It has been reported to inhibit reuptake of norepinephrine, dopamine and serotonin and to be a weak dopamine releasing agent (Abad & Guilleminault, 2017; Aggarwal & Mortensen, 2017). Based on these findings, mazindol has been classified as a central nervous stimulant with properties similar to those of amphetamine (Aronson, 2016) and, more recently, as an atypical stimulant (Nageye & Cortese, 2019). The novelty of its mechanism of action is therefore highly debatable. Nevertheless, mazindol is currently being developed for the treatment of ADHD (and narcolepsy) (Adare Pharmaceuticals, 2020). Overall positive results regarding efficacy and tolerability, comparable to approved stimulants, have been reported from a phase II study in $n = 85$ adults with ADHD, a phase II study in $n = 21$ children with ADHD, and a preceding open-label trial in $n = 24$ children with ADHD (Konofal et al., 2011; Konofal et al., 2014; Wigal et al., 2018). The status of further development efforts following these trials remained unclear at the time of completing this manuscript.

5.3. Serdexmethylphenidate

Serdexmethylphenidate is a prodrug of *d*-methylphenidate and considered a new molecular entity by the FDA. A New Drug Application was submitted to the FDA in May 2020, with a decision expected to be released on March 2nd 2021 (KemPharm Inc, 2020a). The product in question (KP415) contains a combination of serdexmethylphenidate and immediate-release d-MPH (KemPharm Inc, 2020b). The manufacturer claims that this leads to an earlier onset of action, longer durations of therapy, fewer adverse events due to the absence of spikes in methylphenidate concentrations, as well as a lower abuse potential due to the prodrug mechanism (Braeckman et al., 2018). No publications detailing results from clinical trials could be identified in the process of this review. Consequently, it can only be assumed that the prodrug serdexmethylphenidate will show similar core properties regarding efficacy and tolerability to the pharmacologically active methylphenidate.

5.4. Tipepidine hibenzate

Tipepidine is a non-opioid antitussive which has been used in Japanese children for decades. Its main mechanism of action seems to be the inhibition of G-protein-coupled inwardly rectifying potassium channels. In animal models, this was shown to lead to changes in monoamine levels in the brain (Kawaura et al., 2009; Kawaura et al., 2012; Kawaura, Honda, Soeda, Shirasaki, & Takahama, 2010). Therefore, tipepidine may be of use in psychiatric disorders with imbalances in monoamine levels and impairment of related neural circuits. It has been investigated in adolescent depression in a 4-week open-label preliminary study with a beneficial effect reported for six out of ten participants (Sasaki et al., 2014a). Investigating the potential therapeutic effect in ADHD, a pilot study and a first randomized controlled trial (as an add-on to methylphenidate treatment in 53 children with ADHD) showed encouraging results (Dehbozorghi et al., 2019; Hashimoto & Sasaki, 2015; Sasaki et al., 2014b). Further research in pivotal clinical trials is required in order to demonstrate efficacy and tolerability.

5.5. Viloxazine

A recent study by Yu and colleagues has found that viloxazine increases serotonin levels in the prefrontal cortex, exhibits moderate inhibitory effects on the norepinephrine transporter and elicits moderate activity at noradrenergic and dopaminergic systems (Yu, Garcia-Olivares, Candler, Schwabe, & Maletic, 2020). Yu et al. suggest classifying viloxazine as a serotonin norepinephrine modulating agent and regard its serotonin modulating activity as "an important (if not the predominant) component of its mechanism of action". Since its development in the 1970s, it was used as an antidepressant, until it was withdrawn from the markets in 2002 (Pinder, Brogden, Speight, & Avery, 1977; Vignatelli, D'Alessandro, & Candelise, 2008; Yu et al., 2020).

It has now been repurposed and is in development for treatment in ADHD, with several pivotal clinical trials completed in children reporting favorable efficacy and tolerability (Johnson et al., 2020; Nasser et al., 2020; Nasser et al., 2020a, 2020b). A New Drug Application was submitted to the FDA in late 2019. At the time of completing this manuscript manuscript manu, no decision had been made by the FDA.

6. Conclusions

ADHD is a heterogeneous disorder in virtually all aspects. It is a chronic neurodevelopmental disorder with high persistence into adulthood. ADHD has a relatively high prevalence in childhood and adolescence, which combined with causing substantial functional impairment, leads to a serious societal burden. Extensive research efforts have revealed underlying pathomechanisms and investigated various therapeutic approaches, most prominently pharmacological treatment. Available medications include stimulants (methylphenidate, amphetamines) and non-stimulants (atomoxetine, guanfacine, clonidine).

While available pharmacological treatment options for ADHD show relatively large effect sizes (in short-term trials) and overall good tolerability, there is still a need for improvement of current pharmacotherapeutic strategies as well as for the development of novel medications. Future research should investigate longer-term medication effects, compare medications head-to-head and in combination, and address the limited representativeness of study populations.

Regarding novel medications, a prodrug of methylphenidate and a repurposed antidepressant (viloxazine) are closest to a potential FDA approval/marketing authorization for the treatment of ADHD. These two medications can barely be termed "novel" due to their mechanism and background, respectively. Although several other medications are in development, it is too early to judge their potential for the future pharmacological treatment of ADHD.

Declaration of Competing Interest

Konstantin Mechler was involved as investigator in clinical trials by Shire, Otsuka, Sunovion, Servier, Lundbeck, Takeda, Nuvelution, Gedeon Richter, and Emalex.

Tobias Banaschewski served in an advisory or consultancy role for Lundbeck, Medice, Neurim Pharmaceuticals, Oberberg GmbH, Takeda, and Infectopharm. He received conference support or speaker's fees by Lilly, Medice, and Takeda. He received royalties from Hogrefe, Kohlhammer, CIP Medien, Oxford University Press.

Sarah Hohmann was involved as investigator in a clinical trial by Servier.

Alexander Häge received conference support, speaker's fees and/or served in an advisory role for Shire/Takeda and Lily. He was involved as investigator in clinical trials by Shire, Takeda, Janssen-Cilag, Otsuka, Sunovion, Servier, Lundbeck, Nuvelution, Gedeon Richter, and Emalex.

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