Current pharmacological treatments for ADHD

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Abstract Attention-Deficit Hyperactivity Disorder (ADHD) is a prevalent neurodevelopmental condition associated with impaired function and increased risk of poor outcomes in children, young people and adults with the condition. Currently approved pharmacological treatments for ADHD include a range of stimulant (methylphenidate, amphetamine) and nonstimulant (atomoxetine, guanfacine, clonidine) medications. All have been shown to be effective in treating the symptoms of ADHD and improving other functional outcomes including quality of life, academic performance, rates of accidents and injuries, and do not appear to be associated with significant adverse outcomes or side-effects. In this chapter, we review medications for ADHD by summarising the mechanisms of action of each of the two main classes of compounds (stimulants and nonstimulants), the formulations of the most commonly prescribed medications within each class, their efficacy in treating ADHD symptoms and other outcomes, and other factors that influence treatment decisions including side effects and tolerability, comorbidities and medical history. We conclude with a summary of the treatment decisions made by clinicians and suggest some next steps for research. Further research is needed to understand the mechanisms of action of these medications and how exactly they improve symptoms, and to examine their effects on commonly occurring comorbidities.

Keywords: ADHD ● amphetamine ● clonidine ● comorbidity ● efficacy ● guanfacine ● functional outcomes ● methylphenidate ● nonstimulant ● stimulant ● tolerability ● treatment

Abbreviations

ADHD	Attention-Deficit Hyperactivity Disorder
AMP	Amphetamine
ASD	Autism Spectrum Disorder
ATX	Atomoxetine
BP	Blood Pressure
CD	Conduct Disorder
CLON	Clonidine

CNS	Central Nervous System
CNV	Copy Number Variation
DA	Dopamine
DAT	Dopamine Transporter
EF	Executive Functions
FDA	Food and Drug Administration (U.S.A)
GXR	Guanfacine – extended release
HR	Heart Rate
HRQoL	Health-related Quality of Life
LC	Locus Coeruleus
LDX	Lisdexamfetamine
MAO	Monoamine Oxidase
MPH	Methylphenidate
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
NE	Norepinephrine
NET	Norepinephrine Transporter
NICE	National Institute for Health and Care Excellence (U.K.)
ODD	Oppositional Defiant Disorder
PFC	Pre-frontal Cortex
QoL:	Quality of Life
RCT	Randomised Controlled Trial
RTV	Reaction Time Variability
SNP	Single Nucleotide Polymorphism

SUD	Substance Use Disorder
WHO	World Health Organisation
WM	Working Memory

1. Introduction

ADHD is associated with significant adverse outcomes in mental and physical health, and increased risk of criminality, substance misuse and long-term unemployment (Daley et al. 2019). The costs to healthcare and society are significant (Swensen et al. 2003; Gustavsson et al. 2011; Sciberras et al. 2020). Effective intervention can reduce the risks of these negative outcomes (Boland et al. 2020) and can therefore increase the potential for people with ADHD to live productive and satisfying lives.

Medication is recommended as a core component of treatment for ADHD in evidence-based national guidelines in a number of countries worldwide (see Table 1) and has been shown to be cost-effective (Jensen et al. 2005; Wu et al. 2012). The emphasis in these guidelines is on first-line treatment with medication in moderate to severe cases of ADHD aged 6 years and over, with psychosocial or behavioural therapies offered as an adjunct or as first-line treatment in those whose symptoms are mild or who are too young for medication.

[insert Table 1 here]

Psychostimulant medications (methylphenidate (MPH) and amphetamines (AMP)), and the nonstimulant, atomoxetine (ATX), are now licensed for the treatment of ADHD in many countries throughout the world, including the UK, USA, Canada, Europe, Australia, India, Saudi Arabia and parts of Africa. Increasingly, medications licensed to treat children and adolescents (aged 6 to 17 years) are now also licensed for treatment of adults with ADHD. More recently, α_2-adrenergic nonstimulant treatments (clonidine and guanfacine) have been made available in some countries, although they are less frequently licensed than MPH, AMP and ATX. As shown in Table 1 stimulants are recommended as first-line medication in all the included guidelines, although some guidelines recommend offering a choice between MPH or AMP or the nonstimulant ATX. Medications for ADHD all influence central nervous system (CNS) function (Arnsten and Dudley 2005; Berridge and Arnsten 2013; Chandler et al. 2014; Arnsten 2020) and have been shown to reduce core symptoms of ADHD (inattention, hyperactivity, impulsivity) with varying degrees of efficacy (Cortese et al. 2018). All are also associated with side-effects and there are some

contraindications to their use, including medical history and risk of substance misuse (Cortese et al. 2018; Cortese 2020). These factors, coupled with the preferences of the parent, child/young person, or adult with ADHD, must be brought together to develop an appropriate treatment plan for each individual case.

2 Medications for ADHD and their mechanism of action

2.1 Stimulant medications

Stimulant medications include MPH and AMP. As shown in Table 1, national guidelines in several countries advocate the use of MPH and AMP as first-line treatments for moderate to severe ADHD symptoms in children and adolescents aged 6 years and over, and adults. Stimulants increase extracellular dopamine (DA) in the striatum and to a lesser degree, norepinephrine (NE) in the prefrontal cortex (PFC) (reviewed in: Faraone 2018). It is thought that these pharmacological effects are responsible for the clinically therapeutic effects of stimulant medications in treating ADHD symptoms, although the specific relationship between modulation of DA and NE transmission and ADHD symptoms has yet to be established (Childress et al. 2019).

2.1.1 Methylphenidate

MPH is a racemic mixture with a 50:50 ratio of *d*-threo-MPH and *l*-threo-MPH; the *d*-threo enantiomer affects extracellular concentration of DA in striatum, whereas the effects of *l*-MPH are not specific to the CNS and binding to the DAT is comparatively low (Markowitz and Patrick 2008; Childress et al. 2019). Plasma concentrations of *d*-threo-MPH correlate with the proportion of DAT blockade in the striatum in a dose-dependent manner. In seminal PET imaging studies in humans, Volkow et al. (1998) reported that peak DAT blockade is reached 60-90 minutes after oral administration and suggested that it is the time taken to reach this peak in plasma that likely explains why there is not usually a ‘high’ associated with

these stimulant medications, unlike substances such as cocaine, which have a much more rapid effect (reviewed in: Swanson and Volkow 2002).

There are subtle (but potentially clinically important) differences in the ways that MPH and AMP influence DA and NE transmission. The primary action of MPH is to block DA transporters (DAT) in the striatum (Swanson and Volkow 2002; Martinez et al. 2020) where the largest concentration of DA receptors in the brain is located, thereby increasing extracellular dopamine in the striatum and activation of its afferent targets, including PFC. It should be noted that evidence is inconsistent as to whether these effects are primarily in ventral or dorsal striatum (see: Faraone 2018 for a review). Transporter blockade reduces reuptake of the neurotransmitter presynaptically thereby prolonging the effect of the neurotransmitter on the postsynaptic receptors (Swanson and Volkow 2002). MPH also blocks NE transporters (NET) in the PFC (Childress et al. 2019) with evidence of high affinity of MPH for NET (Hannestad et al. 2010). It has been suggested that increases in both DA and NE following MPH administration occur because NE and DA compete to bind with the NET, which are significantly more abundant in PFC than DAT, resulting in increases in extracellular levels of both catecholamines in the PFC (Arnsten and Dudley 2005; Spencer et al. 2015). [See Chapters 4 and 5 for a comprehensive overview of biological/pharmacological action of MPH.]

2.1.2 Amphetamine

AMP also increases extracellular levels of DA in the striatum and NE in the PFC but the mechanisms are slightly different to those of MPH. AMP reduces reuptake of DA and NE but, at higher doses, also interacts with vesicular monoamine transporter-2 (VMAT2) presynaptically to increase release of DA from synaptic vesicles and reverse DAT uptake (Faraone 2009; Hodgkins et al. 2012; Heal et al. 2013). These effects on presynaptic release occur at high doses and are unlikely to explain the clinically therapeutic effects on ADHD but they are associated with a drug ‘high’ and therefore with abuse potential, as well as impairing effects on cognition (Spencer et al. 2015). AMP also weakly inhibits monoamine oxidase (MAO), which is responsible for intraneuronal metabolism of DA and NE, thereby further increasing indirectly their availability at the postsynaptic receptor.

Similarities and differences in the way that MPH and AMP influence extracellular concentrations of DA and NE might partly account for a proportion of the inter-individual variability in treatment response between these two types of stimulant medication. Notably, Volkow et al. (2002a) suggested that individual differences in the amount of DA released into the synaptic space may then influence the rate of DAT blockade: those with lower amounts of DA release will be influenced more strongly by DAT blockade than those with higher rates of DA release. Similar to MPH, further research is needed to understand individual differences in DA and NE transmission following clinically therapeutic doses of AMP, to determine whether these differences are relevant for predicting treatment response.

Further research is also needed to establish the relative roles of DA and NE transmission in the therapeutic effects of stimulant medications for ADHD. In particular, individual differences in DAT and NET availability and distribution, mediated by genetic polymorphisms on the DAT and NET genes (Hahn et al. 2011; Sigurdardottir et al. 2016), might contribute to individual differences in response to MPH. Radioligands that are effective in competing for NET have been developed in recent years and indicate reduced NET availability in ADHD (Sigurdardottir et al. 2016; Ulke et al. 2019) (although see: Vanicek et al. (2014) who reported no significant difference between adults with ADHD and a typical control group). This means that knowledge of the effects of MPH and AMP on NET will increase and give a more accurate picture of the balance between DAT and NET, given that research to date has predominantly focused on the role of DA in understanding the effects of these medications. It has also been suggested that individual differences in DA release, as well as DAT availability, may be crucial to understanding the effects of MPH on ADHD symptomatology (Volkow et al. 2002b). Furthermore, there is a need to map the effects of MPH and AMP on DA and NE in different brain regions and link these more systematically to cognitive and functional impairments in this population to better understand the mechanisms of action at the level of brain networks (Swanson et al. 2011). Gaining greater insight into individual differences in treatment response is an important aim for future research given the often slow, trial-and-error approach to identifying the right medication for each individual child or adult affected by ADHD.

2.2 Nonstimulants

As outlined above, stimulants are recommended as first-line treatments for ADHD, in those aged 6 years and over, in clinical guidelines. However, a substantial proportion of children with ADHD (up to 30%) do not respond to stimulant medication (Spencer et al. 1996; Bates 2009) and there are others who cannot tolerate the side-effects which include loss of appetite, weight loss and disrupted sleep (Cortese et al. 2013; Connolly et al. 2015). Although the proportion of non-responders is small relative to the numbers of responders, in real terms this represents a significant number of children, adolescents and adults with ADHD worldwide who do not benefit from stimulant medication. In addition, where there is risk of misuse or diversion of stimulant medication, or where there are medical factors or other comorbidities that contraindicate stimulant use, an alternative treatment is needed. These alternative, nonstimulant therapies currently comprise atomoxetine and NE receptor agonists, guanfacine and clonidine. Others are available but are not yet commonly recommended in national guidelines so in this chapter we will consider only these three nonstimulant medications.

2.2.1 Atomoxetine

ATX is a selective NE reuptake inhibitor recommended for children and adolescents with ADHD who do not respond well to stimulants or who have comorbidities that preclude the use of stimulants (Hutchison et al. 2016). It was the first nonstimulant medication to be approved by the Federal Drug Administration (FDA (USA)) and recommended by national guidelines in several countries. Randomised Controlled Trials (RCTs) and meta-analyses indicate that the efficacy of ATX is lower than MPH or AMP (see Section 5), but it can be particularly useful when stimulant medications are contraindicated. ATX inhibits reuptake of NE by blocking presynaptic NET, thereby increasing synaptic concentrations of NE and stimulating postsynaptic α_2-adrenoceptors (Clemow and Bushe 2015). Relative to stimulant medications, ATX has a much higher affinity and selectivity for NE than DA transporters but it should be noted that it also inhibits DA reuptake in the PFC indirectly through its blockade of NET (Clemow and Bushe 2015) .

2.2.2 Guanfacine & Clonidine

The extended-release versions of guanfacine (GXR) and clonidine (CLON) are nonstimulant medications approved for use as monotherapy and adjunctive therapy (most commonly as adjuncts to stimulant medications) to treat children and adolescents in the UK, USA and Canada (see Table 1). Both are NE receptor agonists; unlike ATX, they stimulate postsynaptic receptors directly rather than by blocking reuptake of NE from the synaptic cleft (Huss et al. 2016). GXR is highly selective for the α_{2A}-adrenoceptor subtype, while CLON stimulates all α-adrenoceptor subtypes (α_{2A}, α_{2B} and α_{2C}) (Hirota 2014). Alpha$_{2A}$- and α_{2C}-adrenoceptors are found throughout the brain (although the PFC contains mostly the α_{2A} subtype) whereas the α_{2B}-subtype is most prevalent in thalamus (Huss et al. 2016).

In keeping with its properties as an α_{2A}-adrenoceptor specific agonist, guanfacine was initially designed to enhance PFC-dependent executive functions (EFs) including working memory (Wang et al. 2007). Evidence suggests that the cognitive-promoting benefits of guanfacine arise from stimulation of α_{2A}-adrenoceptors, predominantly located on the dendritic spines of PFC pyramidal neurons, where they stimulate intracellular communication by closing voltage-dependent hyperpolarization-activated and cyclic nucleotide-gated (HCN) channels, thereby strengthening pre-frontal cortical networks (Arnsten 2009; Huss et al. 2016; Arnsten 2020). This increase in functional connectivity supports EFs and may also be fundamental to the positive effects of these medications on ADHD symptoms (Berridge and Arnsten 2013; Arnsten 2020). Antagonistic, but complimentary, roles of these medications on NE and DA signaling have been proposed by Arnsten (2020): specifically, stimulation of prefrontal D1 receptors (a sub-type of DA receptors and the most abundant in the brain) stimulates voltage-dependent HCN channels causing them to open, leading to reduced network connectivity and thereby reducing 'noise', while NE receptor stimulation closes these channels and retains the integrity of task-specific functional networks, enhancing the 'signal' and supporting focused attention. Together, these two actions of NE and D1 receptor stimulation are proposed to enhance the 'signal to noise' ratio of stimulus processing during cognitive tasks (Chandler et al. 2014).

Further research is needed to understand the mechanisms through which ADHD medications ameliorate the clinical and cognitive impairments associated with the condition. The NE receptor agonists are a prime example of drug development driven by experimental work to first understand the mechanisms of action of specific compounds. Swanson et al. (2011) suggest that fuller examination of cognitive profiles of strengths and difficulties in ADHD may facilitate better understanding of the mechanisms of action of currently available

medications but may also lead to new developments that target cognitive functions and their neural substrates more precisely. Similarly, Connolly et al. (2015) propose that the identification of functionally relevant copy number variations (CNVs) may drive forwards pharmacogenetic approaches that are driven by an understanding of the effects of specific single nucleotide polymorphisms (SNPs) on neuronal signalling, rather than focusing on genes involved in DA and NE transmission, such as DAT and DRD4 which have offered limited success in understanding the mechanisms of medications for ADHD. In the next section, we briefly describe ways in which the design of specific medications can influence their mechanisms of action.

3 Pharmacokinetics of ADHD medications

The speed of onset and duration of the effects of medications for ADHD differ depending on their precise formulation and drug design; these differences offer a significant amount of flexibility in selecting the right treatment for individuals. Table 2 summarises the main FDA-approved medications for ADHD, including their formulation, drug delivery mode and approximate duration of response. A fuller review of these different drug designs is beyond the scope of this chapter; the interested reader is referred to (Brown et al. 2018; Childress et al. 2019; Cortese 2020) for further information on this topic. [See also: Chapters 3 and 4]

[Insert Table 2 here]

Initially, MPH and AMP were available only as immediate release formulations, which reach peak plasma concentrations rapidly (within 1-3 h). These are effective in reducing symptoms (Moreira Maia et al. 2017) but extended-release preparations are now often preferred and outnumber immediate release options (see Table 2). The majority of extended-release preparations are designed to release the drug bi-phasically, mimicking the multi-dosing regimen of immediate-release formulations but without the disadvantages that arise from sustained exposure over long periods of time (Childress et al. 2019). To achieve this, they combine immediate- and extended-release components in varying ratios resulting in

longer lasting effects (generally up to 9-12 h), whilst requiring only one daily dose, and thereby negating the difficulties of trying to adhere to multiple dosing during the school or working day. They also have lower abuse potential because of their slower action, although nonstimulants are still preferable for those deemed to be at significant risk of abuse or diversion (Martinez-Raga et al. 2017) (see Section 7 for further discussion).

The preparations of MPH (see Table 2) differ in the way they release the drug. For example, 'Osmotic-release oral system methylphenidate' (OROS-MPH) releases MPH via an osmotic pump that expands as water permeates the membrane. This drug delivery platform releases 22% of MPH immediately and the remainder is released gradually over the course of several hours. In contrast, the 'Controlled Delivery' formulations deliver approximately 30% immediately and the 'Spheroidal Oral Drug Absorption System' (SODAS) platform releases 50% immediately, with the remainder released over an extended time-period.

Similarly, AMP formulations comprise different drug delivery platforms such as 'extended release orally disintegrating tablet' (XR-ODT), which delivers AMP via an orally disintegrating tablet combining a 50:50 ratio of immediate to extended-release delivery. These drug delivery modes result in different peak plasma times and different response durations, which may be better suited to individual patients, depending on the time of day when they need to gain the most benefit. It is worth noting that lisdexamfetamine (LDX), an amphetamine-based medication, has different pharmacokinetic properties from other amphetamines. Specifically, LDX is a prodrug, whereby the core component (*d*-amphetamine) is inactive until the lys-moiety is cleaved by metabolism resulting in *in vivo* transformation of lisdexamfetamine into *d*-amphetamine (Heal et al. 2013). This mode of delivery reduces the abuse potential of this drug and also promotes longer acting effects on symptoms (up to 13 h, as well as avoiding inter-individual effects in gut metabolism, which can influence the onset and duration of medication effects but are difficult to predict *a priori* in individual patients (Goodman 2010).

Nonstimulant medications take longer to reach a clinically therapeutic effect, although peak plasma effects can be just as rapid as stimulant medications. For instance, ATX reaches peak plasma levels after 1-2 h with a half-life of around 5 h in most people, although this can be up to 20 h in some (Barton 2005). Based on RCTs and open-label design studies, there appear to be sub-groups of non-responders, partial responders and maximal responders, with the latter group showing a response after just 1 week, but the other two groups potentially

taking over 12 weeks to reach a therapeutic response (reviewed in: Clemow and Bushe 2015). Indeed, there is evidence that the magnitude of the therapeutic response of ATX increases during RCTs and that the maintenance of response after treatment withdrawal is longer for ATX than for stimulant medications (Buitelaar et al. 2015). This may explain why once-daily dosing is sufficient for this medication, resulting in symptom reduction which persists into the evening (Clemow and Bushe 2015), despite a 5 h half-life for most people. This pattern of effects also raises the interesting question of whether the typical 12-week follow-up period in RTCs is sufficient to gain an accurate measure of the efficacy of ATX.

Immediate-release versions of GXR and CLON are considered unsuitable for treatment of ADHD because, as described by Huss et al. (2016), the rapid ascension to peak plasma levels results in unpleasant sedative effects such as fatigue and somnolence and the short half-life necessitates multiple dosing throughout the day. The extended-release formulations are slower, reaching peak plasma levels around 5 h after oral administration, with a half-life up to 17 h, resulting in a gradual and sustained effect on receptor activation. However, it can take up to 2 weeks before clinically therapeutic effects are seen on ADHD symptoms.

In the next section we present evidence relating to the neural mechanisms proposed to give rise to ADHD and how ADHD medications may target these mechanisms.

4 ADHD medications and the cognitive neuroscience of ADHD

ADHD is associated with atypical function in a range of cognitive domains. These cognitive impairments and the brain systems underpinning them provide important insights into the aetiology of ADHD and further our understanding of the mechanisms of action of ADHD medications. Cognitive functions most frequently affected in ADHD include attention and the executive functions including response inhibition, task-switching, selective and divided attention and working memory (Rommelse et al. 2011). These functions depend upon the PFC and its connectivity with other cortical and sub-cortical brain regions including the basal ganglia, anterior cingulate cortex, cerebellum, thalamus, and the temporal, parietal and occipital association cortices (Duncan and Owen 2000; Miller and Cohen 2001). Atypicalities in these brain regions in ADHD have been reported in many functional and structural MRI

studies (for reviews see: Konrad and Eickhoff 2010; Cortese and Castellanos 2012; Rubia 2018). Furthermore, stimulant and nonstimulant medications have been shown to enhance cognition and normalise activity in the brain networks that support cognitive function (Groom et al. 2010; Liddle et al. 2011; Rubia et al. 2014; Hawk et al. 2018).

Catecholamine signalling is strongly implicated in the cognitive processes commonly found to be impaired in ADHD (Chandler et al. 2014). Both DA and NE show an inverted U-shaped relationship with cognitive performance: too much or too little of either neurotransmitter is associated with poorer performance (Arnsten 2009). Moderate levels of NE stimulate post-synaptic α_{2A} receptors in the PFC and are associated with good performance on tasks of working memory, response inhibition and attention in animal studies, whereas low levels are associated with a drowsy, inattentive state (Aston-Jones and Cohen 2005). High levels, for instance under conditions of stress, stimulate the lower affinity α_{2B} receptors, leading to distractibility and poorer cognitive performance (Arnsten 2009). Dopaminergic effects on cognition are thought to arise from stimulation of D1 receptors such that moderate rates of stimulation lead to optimal performance but higher rates are associated with suppressed firing and are linked to poorer cognitive function (reviewed in: Berridge and Arnsten 2013). This evidence, coupled with evidence of atypical DAT and NET levels in ADHD (Dougherty et al. 1999; Jucaite et al. 2005), suggests that DA and NE transmission is atypical in ADHD and that ADHD medications exert their effects by enhancing catecholamine signalling in cortico-striatal brain regions.

As well as direct effects on PFC function, NE exerts effects on cognition via modulation of arousal states in response to environmental context and task demands (Aston-Jones and Cohen 2005; Berridge and Arnsten 2013). NE signalling in ADHD has not been thoroughly investigated but more broadly, there is evidence implicating arousal dysregulation in ADHD. For instance, autonomic and electrophysiological markers suggest hypoarousal (Geissler et al. 2014; Strauß et al. 2018; Bellato et al. 2020), which may contribute to some of the cognitive deficits commonly reported in ADHD, including difficulties with response conflict/inhibitory processing (Borger and van der Meere 2000; Bellato et al. 2021) and increased response time variability (RTV) (Kuntsi and Klein 2012; Karalunas et al. 2014). Furthermore, both MPH and ATX reduce RTV (Ni et al. 2016), implicating NE and DA-mediated effects on arousal in the mechanisms of action of these medications.

In summary, there is a range of evidence demonstrating a clear role for DA and NE in the cognitive and neural differences that have been described in ADHD. These findings provide further context to the mechanisms of action of the main ADHD medications and suggest that they promote cognition, and alleviate symptoms, partly via their effects on frontally mediated brain circuits that rely on DA and NE signalling. The relatively low level of precision afforded by current neuroimaging brain methods precludes a firmer understanding of the roles of DA and NE in cognition in ADHD but, with the growth in techniques such as MR spectroscopy, the increase in high-field strength MRI capable of imaging small regions such as the LC, and the refinement of functional imaging methods, significant advances in knowledge in this area seem likely in the near future.

5 Efficacy & tolerability: comparison between medications

The individual treatments included in this chapter are efficacious in reducing ADHD symptoms over the short, medium and longer term, provided treatment is maintained (Cortese et al. 2018). The evidence attesting to their efficacy forms the basis of the clinical guidelines that specify how they should be selected and, in combination with prescribing guidelines in each country, how they should be titrated and monitored. For the sake of brevity, we will not review the efficacy and tolerability of each individual treatment. Instead, in this section, we compare the treatments with one another.

A recent systematic review and network meta-analysis (Cortese et al. 2018) compared the efficacy and tolerability of all the primary current pharmacological treatments for ADHD (MPH, AMP (including LDX), ATX, CLON and GXR, in addition to bupropion and modafinil, which, in some countries, are used ‘off-licence’ for ADHD). The authors calculated (from published and unpublished double-blind RCTs) the standardised mean difference of each treatment against placebo. They also compared treatments with one another by conducting a network meta-analysis, an approach which adjusts for between-study variability and therefore gives a more robust estimate of the differences in efficacy between treatments. The results were calculated separately for children and adolescents (6-17 years) and adults (18+ years). The primary outcome was ADHD symptom change reported by clinicians and, in children and adolescents, teacher-reported symptoms. Secondary outcomes included tolerability (measured as the proportion of participants who left the trial early).

Mean differences from baseline were computed at timepoints closest to 12 weeks, 26 weeks and 52 weeks, where available. Of 133 RCTs, 81 reported data from children and adolescents (aged >5 to <18 years), 51 reported data from adults (aged 18+) and 1 reported data from children, adolescents and adults.

The network meta-analysis showed significant effects at the 12-week time-point for all drugs (compared with placebo) on clinician-rated symptoms in children and adolescents. The effects were more variable for teacher-rated symptom improvement with only MPH and modafinil superior to placebo. The pattern of results was similar in adults, but modafinil was not superior to placebo, and there were no data available for CLON or GXR in accordance with the fact that these medications are not yet licensed for use in adults.

In line with previous meta-analyses (Faraone 2009; Faraone and Buitelaar 2010; Hodgkins et al. 2012; Joseph et al. 2017), AMP was superior to MPH and ATX in all the age groups included in the meta-analysis. In addition, AMP was superior to GXR and MPH was superior to ATX in children and adolescents while, in adults, MPH, ATX and bupropion were superior to modafinil. This is partially in line with a previous meta-analysis showing superiority of short- and long-acting stimulants over nonstimulants in adolescents (Faraone 2009) and evidence favouring LDX over other stimulant and nonstimulant medications in children and adolescents (Joseph et al. 2017). Further research is needed to provide estimates of efficacy of guanfacine in adults.

Previous RCTs have also measured the effects of medication withdrawal, including the duration of maintenance of treatment effects after withdrawal. ATX has been shown to have a substantially longer maintenance phase (post-medication withdrawal) relative to stimulant medications. Specifically, there are positive effects on ADHD symptoms for up to 6 months after ATX withdrawal (Michelson et al. 2004; Buitelaar et al. 2007), albeit at 50% of the maximum clinical effect, whereas stimulant withdrawal leads to a rapid return of symptoms within 1-2 weeks in children (Coghill et al. 2014) and adults (Brams et al. 2012).

With regards to tolerability, the most commonly reported side-effects of stimulant and nonstimulant medications are loss of appetite, dry mouth, insomnia, fatigue, headache, nausea, abdominal pain/discomfort and irritability. These side-effects are recorded within RCTs and are used to give insights into the side-effect profile of the medication. Tolerability is also assessed by measuring the numbers of participants who leave a trial early due to side-effects. The network meta-analysis of Cortese et al. (2018) reported that, in children and

adolescents, GXR and AMP were inferior to placebo in terms of their adverse events profile while, in adults, all medications included in the analysis, namely ATX, MPH, AMP and modafinil, were inferior to placebo. The authors also assessed change in weight and blood pressure during the trial. AMP, MPH, ATX were all associated with a significant decrease in weight compared with placebo in children, adolescents and adults; in addition, modafinil led to decreased weight in children and adolescents. Systolic blood pressure increased in children and adolescents treated with MPH, ATX and AMP and in adults treated with MPH and ATX.

Further analyses were conducted on LDX separately from other amphetamines due to the unique pharmacokinetics of LDX. The authors found that LDX was less well-tolerated than placebo in children and adolescents whereas the other amphetamines were tolerated slightly better than placebo, suggesting that the initial tolerability analysis reported above was influenced by the inclusion of LDX in the amphetamine category. This is an important finding because, as described above, LDX has been shown in some studies to have superior efficacy to other stimulant medications, but this may come at the cost of inferior tolerability in some individuals. The tolerability profile for LDX seems to be dependent on age, however, as tolerability was found to be superior to other amphetamines in adults.

In another meta-analysis focusing exclusively on the α_{2A}-adrenoceptor agonists, Hirota (2014) identified issues with tolerability for GXR and CLON. Although neither compound was associated with greater all-cause discontinuation, or discontinuation due to non-efficacy, than placebo across RCTs, all α_{2A}-adrenoceptor agonists were associated with somnolence and fatigue in addition to reduced systolic and diastolic blood pressure and heart rate (see Section 7 for further discussion of these effects). This is consistent with Joseph et al. (2017) who reported tolerability that was higher for ATX than GXR, although both were lower than MPH. The α_{2A}-adrenoceptor agonist medications appear to have a slightly different side-effect profile from stimulants and ATX with a greater incidence of somnolence and sedation. This is an important consideration because some individuals may be more sensitive to these effects, and it is difficult to predict *a priori* who will be adversely affected. Careful monitoring in the initial phase of titration is needed.

In summary, evidence supports the use of MPH and AMP as first-line medications for ADHD where pharmacological treatment is warranted, as specified in international guidelines (see Table 1). Importantly, although evidence on efficacy and tolerability is weaker for nonstimulant medications, there is sufficient evidence of efficacy to support their use in

patients who do not respond to MPH or ATX or cannot tolerate side-effects. Identifying adverse events and minimising their persistence is an essential part of treatment titration during the early initiation phase of medication. If titrated properly, as part of regular monitoring, adverse events are less likely to emerge, and therapeutic effects are higher (Martinez-Raga et al. 2017; Huss et al. 2017). This is a particularly important consideration because treatment discontinuation increases the risk of poor long-term outcomes in individuals with ADHD.

Finally, it is important to note concerns about the quality of some research in this field. In separate published Cochrane reviews of the efficacy of MPH (Immediate Release formulations) and ATX in adults (Cunill et al. 2013; Epstein et al. 2014), studies were rated as low quality, with some classed as very low, indicating that caution is needed when interpreting findings on efficacy in adults. Large standard deviations were found when assessing efficacy and tolerability of the newer (and therefore less well-researched) compounds, GXR and CLON, in the network meta-analysis of Cortese et al, indicating that further research is needed to establish more reliable estimates of the efficacy and tolerability of these medications.

6 Effects of ADHD medications on other outcomes and comorbidities

Although symptom reduction is often the primary outcome when assessing treatment response, evidence indicates that this may not always be the most important outcome to those with ADHD. Research has highlighted the importance of other outcomes including quality of life (QoL), social function, academic attainment and risks of accidents and injuries. The effects of medication on psychiatric outcomes, either by exacerbating known comorbidities, or increasing the risk of poor mental health outcomes, are also important areas of research. In this section we will consider research that has assessed the effect of ADHD medications on these other outcomes.

QoL is becoming an important outcome of ADHD treatment in recognition that the impact of ADHD extends beyond the symptoms of the condition to other aspects of the

person's life (Adamo et al. 2015). Health-related Quality of Life (HR-QoL) is defined by the World Health Organisation (WHO) as "individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (The World Health Organisation Quality of Life [WHOQOL], no date). It is typically measured using standardised rating-scales completed either by proxy (usually parents in studies of children and adolescents with ADHD) or self-report (Adamo et al. 2015).

Adamo et al. (2015) reviewed the current evidence of HRQoL in ADHD and reported that there are reductions in HRQoL ratings in ADHD that are at least as large as those for physical health conditions, such as asthma. These authors highlight the importance of HRQoL as an outcome measure in ADHD, both in clinical practice and when investigating treatment effects in RCTs. Coghill et al. (2017) conducted a meta-analysis of RCTs of pharmacotherapy for ADHD and investigated their efficacy on HRQoL in children, adolescents and adults with ADHD. The data were not subjected to meta-analysis but the authors present the statistical results from each study and effect-sizes for the comparison of medication against placebo. Of 12 studies that investigated HRQoL in children and adolescents (all parent-ratings), 10 reported a significant effect of medication on at least one HRQoL domain and of these, 7 were associated with an effect-size greater than 0.5 (favouring medication over placebo). The most reliable effects were on measures of achievement, risk-taking behaviour and interpersonal relationships and, on these indices, effect-sizes were larger for stimulants (effect size range .54 – 1.28) than non-stimulants (effect size range .29-.87). To facilitate a comparison between effects of medication on symptoms and HRQoL, Coghill et al. provided the effect-sizes for symptom ratings on the studies they included in their review. In children and adolescents, the effect-sizes for symptom ratings range from .8 to 1.8 for stimulants and .43 to 1.2 for nonstimulants, compared with the HRQoL effect-size ranges provided above, revealing that effect-sizes for HRQoL are smaller than for symptoms, and also follow the same pattern of larger effect-sizes for stimulants than nonstimulants reported by (Cortese et al. 2018). The effects of medications on HRQoL were smaller overall in adults than children and adolescents, ranging from .21-.93 from 7 studies, with only one study identifying an effect-size greater than .5 on one measure of HRQoL, 'life productivity'.

As the data in this review were not appropriate for meta-analysis, and multiple outcome measures and scales were reported, it is difficult to establish an overall effect of

medications on HRQoL. The authors also highlight that there are difficulties with measuring QoL, mostly around whether the instrument is specific to ADHD (measures tended to be centred on ADHD in adult studies but were more likely to be general health QoL measures in children and adolescents) and whether the rating is conducted by proxy or by children and adolescents themselves. It has been found that self-ratings of HRQoL tend to be lower than proxy ratings (Adamo et al. 2015). Considering that the adult studies included in the review used self-reports of HRQoL, whereas the child/adolescent studies were all parent-rated reports, this may contribute to the finding of smaller effects of medication on HRQoL in adults.

More broadly, differences in the instruments used to assess HRQoL, including whether they are rated by self or proxy, may explain the high degree of variability between studies in the effect of medication on QoL and modest correlations with symptom improvements (Adamo et al. 2015). These measurement issues require further research to develop more effective and accurate measures of these important outcomes in ADHD. In particular, it is essential to develop ADHD-specific measures that are reliable across different raters and that capture aspects of QoL that are deemed important to those with ADHD, preferably by involving those with ADHD, or their advocates, in the design.

Boland et al. (2020) conducted a narrative review and meta-analysis of the effects of ADHD medications on functional outcomes and identified 40 studies that had examined the risk of comorbid mood disorders (depression and bipolar disorder), Substance Use Disorder (SUD), criminality, suicidality, traumatic brain injury, motor vehicle accidents, accidents and injuries, and academic attainment. The narrative synthesis reported that stimulant medications were associated with reduced risk of criminality, motor vehicle accidents, injuries and with enhanced academic outcomes (performance on tests, school attendance and reading). Many of these effects did not reach statistical significance in meta-analysis, but this is likely due to the small number of studies on each outcome and associated heterogeneity. Importantly, where possible, the authors examined the outcomes in relation to within-individual differences in medication adherence and reported that outcomes were better during periods of medication-adherence than non-adherence.

Similarly, in a systematic review and meta-analysis of studies adopting a within-individual design, Chang et al. (2019) reported no significant increase in suicidality in relation to ADHD medication use, with some evidence of a protective effect of medication in

reducing incidents of self-harm and suicide. Similarly, the review identified a decrease in hospital visits due to depression and decreased rates of SUD and criminality in ADHD patients when on than off ADHD medication. The authors also reviewed evidence on accidents and injuries and reported reduced injury and trauma, reduced driving accidents and enhanced academic achievement during periods of medication adherence. Overall, the general pattern is for ADHD medication to improve these other outcomes, or at least not to exacerbate them.

In a similar vein, Krinzinger et al. (2019) presented an evidence map of research that has measured the long-term outcomes of treatment with MPH for at least twelve months. The findings indicated that MPH is associated with improvements on some neuropsychiatric outcomes, notably depression, SUD and suicidality, and the authors described the evidence on these outcomes as strong. The authors highlighted some evidence of increased tics and psychotic symptoms in their evidence map but also reported evidence that these outcomes are rare and appear to be negated once MPH is withdrawn. In support of this, a recent Cochrane systematic review (Osland et al. 2018) reported no adverse effects of any ADHD medications (including stimulant treatments) on tics in children with comorbid ADHD and tic disorder, and significant improvements in tics following treatment with MPH, GXR and CLON, suggesting that initial concerns over treatment with stimulant medications may not be warranted. As the data reviewed by Krinzinger et al. (2019) were not submitted to a meta-analysis, firm conclusions cannot be drawn, but it is useful to note that the findings of Boland et al. (2020), Chang et al. (2019) and Krinzinger et al. (2019) are broadly congruent and indicate overall potential protective effects ADHD medications on these other outcomes

As well as studies that have been conducted to examine the effects of ADHD medications on the emergence of mental health difficulties, others have focused on whether medications exacerbate, or improve, the symptoms of current comorbidities. Common ADHD comorbidities include autism spectrum disorder (ASD), oppositional defiant disorder (ODD), conduct disorder (CD), tic disorders and mood disorders (Jensen and Steinhausen 2015). There has been some concern that stimulants may exacerbate comorbidities, particularly tics, psychosis and ASD, and this led clinicians to favour nonstimulants when treating ADHD in the presence of comorbid symptoms.

Two questions arise from this: 1) do nonstimulants treat ADHD symptoms effectively when there are comorbidities present; and 2) do nonstimulants exacerbate or improve

comorbid symptoms? In response to the first question, evidence obtained from recent systematic reviews suggests that the efficacy of ATX in treating ADHD symptoms is not diminished by the presence of comorbidities including anxiety, tics, ASD, mood disorder, and ODD/CD in children (Hutchison et al. 2016) or adults (Clemow et al. 2017). However, in response to the second question, according to these reviews, only anxiety symptoms and ODD/CD improved under treatment with ATX; other comorbidities were neither exacerbated nor ameliorated, indicating that additional treatment targeting the comorbid symptoms is necessary.

The precise role of ADHD medications in improving comorbid symptoms remains to be established: do these medications improve some comorbid symptoms through their effect on ADHD symptoms, or do they have a direct effect on the comorbid symptoms themselves? Further research is needed in this area, particularly as patients with comorbidities have historically tended to be excluded from RCTs; we therefore have limited understanding of the efficacy of ADHD medications in treating ADHD symptoms, and/or comorbidities, in these individuals (Chang et al. 2019). This is a significant limitation considering that in one large population study (Jensen and Steinhausen 2015), 52% of children, adolescents and adults with ADHD had at least one comorbidity, and 26% had more than one. There are also widely reported difficulties with devising effective treatment plans for children with ADHD with comorbidities (see Davis and Kollins 2012; Antshel and Russo 2019), partly because of the paucity of data on the efficacy of ADHD medications in the context of comorbidities.

Remarkably few studies have been conducted to evaluate the effects of ADHD medication on social function, an area of significant impairment in ADHD (Nijmeijer et al. 2008; Davis and Kollins 2012). A small number of studies suggest that medication may decrease the rates of negative peer interactions but without a concomitant increase in pro-social behaviors (McQuade and Hoza 2008). There is a need for further research in this area to compare different types of ADHD mediations on a range of social outcomes in ADHD and to determine whether such impairments (and their potential amelioration by medication) arise from comorbidity with autism spectrum conditions and oppositional defiant/conduct disorder, or whether they reflect a core impairment in ADHD.

7 Factors to consider when choosing treatments

When selecting treatments, clinicians are guided by the evidence and clinical guidelines which advocate stimulant medications (MPH, AMP or LDX) in the first instance, unless there is a clear reason why these medications would not be suitable (see Table 1). This is supported by evidence indicating that MPH and AMP are superior in efficacy to other medications in children, adolescents and adults (Cortese et al. 2018). As outlined in Section 3 above, there are a number of medication preparations to choose from, particularly MPH and AMP-based preparations, each with different pharmacokinetic properties These features lead to differences in the onset and duration of response to medication, meaning that some medications are more effective early in the day, while others peak later. Furthermore, these factors interact with age, as described by Coghill et al. (2013) in their systematic review of head-to-head studies of long-acting MPH formulations.

As shown in Table 2, medications are also available in different preparations, including tablets, capsules, oral suspensions and transdermal patch. This flexibility in drug preparation provides greater choice to patients; in particular, younger children may find it difficult to swallow tablets and capsules whole and several of the medications can be crushed or chewed specifically to overcome this problem. Discussions with the patient and their parent/carer are crucial to finding the right balance between the timing of maximum drug effects, with due consideration of the effects of the dosing regime on sleep onset, duration and quality, appetite and functional outcomes during the day (e.g., school or work).

In addition to considerations about the timing and duration of the drug effects, it is important to take a full medical history to establish whether there are any physical health factors, co-occurring neurodevelopmental or mental health diagnoses/symptoms, or other medications, that may influence treatment decisions. Height and weight should be monitored regularly as evidence indicates that MPH is associated with reduced growth (height and weight) in children (Carucci et al. 2021). Although the deviation from normal growth is small and resolves after medication withdrawal, significant changes in these parameters indicate a possible need for adjustments in dosing schedule/level or medication breaks.

Secondly, there is consistent evidence of small but statistically significant changes in systolic and diastolic blood pressure (BP) indices and heart rate (HR) in response to ADHD medications. Specifically, there are increases in HR and BP with stimulants and decreases with α-adrenoceptor agonists (Hirota 2014; Hennissen et al. 2017; Cortese et al. 2018; Fay

and Alpert 2019), which may be more pronounced when medication is first started (Martinez-Raga et al. 2017). Despite these changes, the odds of serious cardiovascular events are not significantly increased in those prescribed stimulants or ATX (Liu et al. 2019; Houghton et al. 2020) although it is important to bear in mind that the confidence intervals around the effects reported in some studies do not rule out moderately increased risk on some measures (Liu et al. 2019). Careful monitoring of HR, BP and weight and height are therefore important components of treatment titration and longer-term monitoring, as well as establishing family history of cardiac illness prior to treatment initiation. Furthermore, medications for other mental health conditions, should be checked as part of a thorough investigation of medical history prior to initiating ADHD medication (Faraone 2018). In particular, monoamine oxidase inhibitors, prescribed for the treatment of mood disorder may lead to significant risk of hypertension and should not be co-administered with any ADHD medications described in this chapter.

It is also important to ensure that medications prescribed to treat ADHD do not exacerbate comorbidities or increase risk for the emergence of other psychiatric outcomes. As described in Section 6, the research conducted so far suggests some caution is needed when prescribing stimulant medication to those with tics or history/risk of psychosis, but in general, the risks of exacerbating (latent or diagnosed) comorbidities, seems low overall. Indeed, the NICE (UK) guidelines (National Institute of Health and Care Excellence 2018) recommend offering the same treatment to individuals with ADHD with comorbid conditions as those without comorbid conditions, but to withdraw medication from anyone experiencing a psychotic or manic episode. Treatment of ADHD symptoms seems to be effective when comorbidities are present (see Section 6), although there is little evidence that these comorbidities are effectively treated by ADHD medications. A multi-modal treatment approach is therefore likely to be needed in these more complex cases. Cortese (2020) presents clinical recommendations for assessing, monitoring and responding to a range of possible adverse events, including appetite loss (and associated height and weight changes), increased blood pressure or heart rate, sleep disturbance, tics, seizures and psychotic symptoms.

Age is a key consideration when discussing medication choices with the patient and their family/carers primarily because some medications are not yet licensed for adults (GXR, CLON) and some cannot be used in children aged under 5 years. The network meta-analysis of Cortese et al. (2018) revealed that efficacy and tolerability differed between children and

adolescents (aged 6 to 17 years) and adults (aged 18+) for several of the medications included in the review, and GXR and CLON are not yet licensed for use in adults.

In relation to age, it is also important to consider the risk of misuse (taking the medication at higher doses than prescribed) or diversion (selling or giving away) of stimulant medications which is likely to be of particular concern in young men aged 18-25 (Faraone et al. 2020). This is often motivated by a desire to experiment with drugs or to enhance cognitive or academic performance but carries with it the risks of adverse events and side-effects described above. In cases where there is significant concern over the potential for misuse or diversion, nonstimulant medications are the preferred option. Changes in weight and height with age also necessitate regular, effective monitoring of treatment effects to ensure the dosing regimen remains optimal.

8 Conclusions

In conclusion, this chapter has provided a review of current pharmacological treatments for ADHD, focusing specifically on those medications that are FDA-approved at the time of writing, and those that are recommended in treatment guidelines published in several countries including the UK, USA and Canada. The evidence reveals advances in understanding the mechanisms of action of the main treatments for ADHD and increasingly sophisticated drug formulations and drug delivery modes. The range of medications available provides clinicians and patients with choice when selecting the optimum treatment for each individual.

The evidence of efficacy from several studies has informed the development of treatment guidelines and has also found these medications to be generally well-tolerated and safe. Despite these advances, treatment is still reliant on a trial-and-error approach, sometimes lasting several months. In the life of an individual with ADHD this is a significant amount of time and many decide not to continue, choosing other means to manage their symptoms such as exercise, strategies to aid organisation and time management, and practising good sleep hygiene. There is a need for significant investment in research to develop prognostic markers of treatment response that can accurately predict non-response to a given treatment and/or the likelihood of intolerable side effects. This will lead to more rapid improvements in symptoms and other functional outcomes and enhance medication adherence. Further research is also

needed to explore the interactions between ADHD medications and common comorbidities with ADHD to determine whether they remain effective in treating ADHD symptoms without exacerbating comorbid conditions.

References

Adamo N, Seth S, Coghill D (2015) Pharmacological treatment of attention-deficit/hyperactivity disorder: assessing outcomes. Expert Rev Clin Pharmacol 8(4):383–397. https://doi.org/10.1586/17512433.2015.1050379ADHD Institute ADHD Guidelines - ADHD Institute.com. In: ADHD Institute. https://adhd-institute.com/disease-management/guidelines/. Accessed 9 Jul 2021

Alda JA, Cardo ME, Díaz del Campo P, García A, Gurrea A, Izaguirre J (2017) Guía de Práctica Clínica sobre las intervenciones terapéuticas en el Trastorno por Déficit de Atención con Hiperactividad (TDAH), 1st edn. GuíaSalud

Antshel KM, Russo N (2019) Autism Spectrum Disorders and ADHD: Overlapping Phenomenology, Diagnostic Issues, and Treatment Considerations. Curr Psychiatry Rep 21(5):34. https://doi.org/10.1007/s11920-019-1020-5

Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, (AWMF) [Association of the Scientific Medical Societies in Germany] (2017) Long version of the interdisciplinary, evidence- and consensus-based (S3) guidelines “Attention Deficit Hyperactivity Disorder (ADHD) in children, adolescents and adults” (AWMF-Regiisternummmer 028-045). In: https://www.awmf.org/uploads/tx_szleitlinien/028-045l_S3_ADHS_2018-06.pdf

Arnsten AF, Dudley AG (2005) Methylphenidate improves prefrontal cortical cognitive function through alpha2 adrenoceptor and dopamine D1 receptor actions: Relevance to therapeutic effects in Attention Deficit Hyperactivity Disorder. Behav Brain Funct 1(1):2

Arnsten AFT (2020) Guanfacine’s mechanism of action in treating prefrontal cortical disorders: Successful translation across species. Neurobiology of Learning and Memory 176:107327. https://doi.org/10.1016/j.nlm.2020.107327

Arnsten AFT (2009) Toward a New Understanding of Attention-Deficit Hyperactivity Disorder Pathophysiology An Important Role for Prefrontal Cortex Dysfunction. CNS Drugs 23:33–41

Aston-Jones G, Cohen JD (2005) An integrative theory of locus coeruleus-norepinephrine function: Adaptive gain and optimal performance. Annu Rev Neurosci 28:403–450. https://doi.org/10.1146/annurev.neuro.28.061604.135709

Australian Government National Health and Medical Research Council (2012) Clinical Practice Points - ADHD in children and adolescents | NHMRC.

https://www.nhmrc.gov.au/about-us/publications/clinical-practice-points-adhd-children-and-adolescents. Accessed 9 Jul 2021

Barton J (2005) Atomoxetine: a new pharmacotherapeutic approach in the management of attention deficit/hyperactivity disorder. Archives of Disease in Childhood 90(suppl 1):i26–i29. https://doi.org/10.1136/adc.2004.059386

Bashiri FA, Albatti TH, Hamad MH, Al-Joudi HF, Daghash HF, Al-Salehi SM, Varnham JL, Alhaidar F, Almodayfer O, Alhossein A, Aldhalaan H, Ad-Dab'bagh YA, Al Backer N, Altwaijri W, Alburikan K, Buraik MW, Ghaziuddin M, Nester MJ, Wahabi HA, Alhabib S, Jamal AA, Amer YS (2021) Adapting evidence-based clinical practice guidelines for people with attention deficit hyperactivity disorder in Saudi Arabia: process and outputs of a national initiative. Child and Adolescent Psychiatry and Mental Health 15(1):6. https://doi.org/10.1186/s13034-020-00351-5

Bates G (2009) Drug treatments for attention-deficit hyperactivity disorder in young people. Advances in Psychiatric Treatment 15(3):162–171. https://doi.org/10.1192/apt.bp.108.005561

Bellato A, Arora I, Hollis C, Groom MJ (2020) Is autonomic nervous system function atypical in attention deficit hyperactivity disorder (ADHD)? A systematic review of the evidence. Neuroscience and Biobehavioral Reviews 108:182–206. https://doi.org/10.1016/j.neubiorev.2019.11.001

Bellato A, Arora I, Kochhar P, Hollis C, Groom MJ (2021) Indices of Heart Rate Variability and Performance During a Response-Conflict Task Are Differently Associated With ADHD and Autism. J Atten Disord :1087054720972793. https://doi.org/10.1177/1087054720972793

Berridge CW, Arnsten AFT (2013) Psychostimulants and motivated behavior: Arousal and cognition. Neurosci Biobehav Rev 37(9):1976–1984. https://doi.org/10.1016/j.neubiorev.2012.11.005

Boland H, DiSalvo M, Fried R, Woodworth KY, Wilens T, Faraone SV, Biederman J (2020) A literature review and meta-analysis on the effects of ADHD medications on functional outcomes. J Psychiatr Res 123:21–30. https://doi.org/10.1016/j.jpsychires.2020.01.006

Borger N, van der Meere J (2000) Motor control and state regulation in children with ADHD: a cardiac response study. Biol Psychol 51(2–3):247–67

Brams M, Weisler R, Findling RL, Gasior M, Hamdani M, Ferreira-Cornwell MC, Squires L (2012) Maintenance of Efficacy of Lisdexamfetamine Dimesylate in Adults With

Attention-Deficit/Hyperactivity Disorder: Randomized Withdrawal Design. J Clin Psychiatry 73(7):977–983. https://doi.org/10.4088/JCP.11m07430

Brown KA, Samuel S, Patel DR (2018) Pharmacologic management of attention deficit hyperactivity disorder in children and adolescents: a review for practitioners. Transl Pediatr 7(1):36–47. https://doi.org/10.21037/tp.2017.08.02

Buitelaar J, Asherson P, Soutullo C, Colla M, Adams DH, Tanaka Y, Haynes VS, Escobar R, Upadhyaya H (2015) Differences in maintenance of response upon discontinuation across medication treatments in attention-deficit/hyperactivity disorder. Eur Neuropsychopharmacol 25(10):1611–1621. https://doi.org/10.1016/j.euroneuro.2015.06.003

Buitelaar JK, Michelson D, Danckaerts M, Gillberg C, Spencer TJ, Zuddas A, Faries DE, Zhang S, Biederman J (2007) A randomized, double-blind study of continuation treatment for attention-deficit/hyperactivity disorder after 1 year. Biol Psychiatry 61(5):694–699. https://doi.org/10.1016/j.biopsych.2006.03.066

Canadian ADHD Resource Alliance (2018) Canadian ADHD Guidelines 4th Edition. https://www.caddra.ca/wp-content/uploads/CADDRA-Guidelines-4th-Edition_-Feb2018.pdf

Carucci S, Balia C, Gagliano A, Lampis A, Buitelaar JK, Danckaerts M, Dittmann RW, Garas P, Hollis C, Inglis S, Konrad K, Kovshoff H, Liddle EB, McCarthy S, Nagy P, Panei P, Romaniello R, Usala T, Wong ICK, Banaschewski T, Sonuga-Barke E, Coghill D, Zuddas A, ADDUCE Consortium (2021) Long term methylphenidate exposure and growth in children and adolescents with ADHD. A systematic review and meta-analysis. Neurosci Biobehav Rev 120:509–525. https://doi.org/10.1016/j.neubiorev.2020.09.031

CHADD (nd) CHADD - Improving the lives of people affected by ADHD. In: CHADD. https://chadd.org/wp-content/uploads/2020/02/ADHD-Medications-Approved-by-US-FDA.pdf/. Accessed 15 Jul 2021

Chandler DJ, Waterhouse BD, Gao W-J (2014) New perspectives on catecholaminergic regulation of executive circuits: evidence for independent modulation of prefrontal functions by midbrain dopaminergic and noradrenergic neurons. Front Neural Circuits 8. https://doi.org/10.3389/fncir.2014.00053

Chang Z, Ghirardi L, Quinn PD, Asherson P, D'Onofrio BM, Larsson H (2019) Risks and benefits of ADHD medication on behavioral and neuropsychiatric outcomes: a qualitative review of pharmacoepidemiology studies using linked prescription

databases. Biological psychiatry 86(5):335. https://doi.org/10.1016/j.biopsych.2019.04.009

Childress AC, Komolova M, Sallee FR (2019) An update on the pharmacokinetic considerations in the treatment of ADHD with long-acting methylphenidate and amphetamine formulations. Expert Opin Drug Metab Toxicol 15(11):937–974. https://doi.org/10.1080/17425255.2019.1675636

Clemow DB, Bushe C, Mancini M, Ossipov MH, Upadhyaya H (2017) A review of the efficacy of atomoxetine in the treatment of attention-deficit hyperactivity disorder in children and adult patients with common comorbidities. Neuropsychiatr Dis Treat 13:357–371. https://doi.org/10.2147/NDT.S115707

Clemow DB, Bushe CJ (2015) Atomoxetine in patients with ADHD: A clinical and pharmacological review of the onset, trajectory, duration of response and implications for patients. J Psychopharmacol 29(12):1221–1230. https://doi.org/10.1177/0269881115602489

Coghill D, Banaschewski T, Zuddas A, Pelaz A, Gagliano A, Doepfner M (2013) Long-acting methylphenidate formulations in the treatment of attention-deficit/hyperactivity disorder: a systematic review of head-to-head studies. BMC Psychiatry 13(1):237. https://doi.org/10.1186/1471-244X-13-237

Coghill DR, Banaschewski T, Lecendreux M, Johnson M, Zuddas A, Anderson CS, Civil R, Dauphin M, Higgins N, Lyne A, Gasior M, Squires LA (2014) Maintenance of efficacy of lisdexamfetamine dimesylate in children and adolescents with attention-deficit/hyperactivity disorder: randomized-withdrawal study design. J Am Acad Child Adolesc Psychiatry 53(6):647-657.e1. https://doi.org/10.1016/j.jaac.2014.01.017

Coghill DR, Banaschewski T, Soutullo C, Cottingham MG, Zuddas A (2017) Systematic review of quality of life and functional outcomes in randomized placebo-controlled studies of medications for attention-deficit/hyperactivity disorder. Eur Child Adolesc Psych 26(11):1283–1307. https://doi.org/10.1007/s00787-017-0986-y

Connolly J, Glessner J, Elia J, Hakonarson H (2015) ADHD & Pharmacotherapy: Past, Present and Future. Ther Innov Regul Sci 49(5):632–642. https://doi.org/10.1177/2168479015599811

Cortese S (2020) Pharmacologic Treatment of Attention Deficit-Hyperactivity Disorder. N Engl J Med 383(11):1050–1056. https://doi.org/10.1056/NEJMra1917069

Cortese S, Adamo N, Del Giovane C, Mohr-Jensen C, Hayes AJ, Carucci S, Atkinson LZ, Tessari L, Banaschewski T, Coghill D, Hollis C, Simonoff E, Zuddas A, Barbui C,

Purgato M, Steinhausen H-C, Shokraneh F, Xia J, Cipriani A (2018) Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. Lancet Psychiatry 5(9):727–738. https://doi.org/10.1016/S2215-0366(18)30269-4

Cortese S, Castellanos FX (2012) Neuroimaging of Attention-Deficit/Hyperactivity Disorder: Current Neuroscience-Informed Perspectives for Clinicians. Curr Psychiatry Rep 14(5). https://doi.org/10.1007/s11920-012-0310-y

Cortese S, Holtmann M, Banaschewski T, Buitelaar J, Coghill D, Danckaerts M, Dittmann RW, Graham J, Taylor E, Sergeant J (2013) Practitioner Review: Current best practice in the management of adverse events during treatment with ADHD medications in children and adolescents. Journal of Child Psychology and Psychiatry 54(3):227–246. https://doi.org/10.1111/jcpp.12036

Cunill R, Castells X, Tobias A, Capellà D (2013) Atomoxetine for attention deficit hyperactivity disorder in the adulthood: a meta-analysis and meta-regression. Pharmacoepidemiology and Drug Safety 22(9):961–969. https://doi.org/10.1002/pds.3473

Daley D, Jacobsen RH, Lange A-M, Sørensen A, Walldorf J (2019) The economic burden of adult attention deficit hyperactivity disorder: A sibling comparison cost analysis. Eur Psychiatry 61:41–48. https://doi.org/10.1016/j.eurpsy.2019.06.011

Davis NO, Kollins SH (2012) Treatment for Co-Occurring Attention Deficit/Hyperactivity Disorder and Autism Spectrum Disorder. Neurotherapeutics 9(3):518–530. https://doi.org/10.1007/s13311-012-0126-9

Dougherty DD, Bonab AA, Spencer TJ, Rauch SL, Madras BK, Fischman AJ (1999) Dopamine transporter density in patients with attention deficit hyperactivity disorder. Lancet 354(9196):2132–2133. https://doi.org/10.1016/S0140-6736(99)04030-1

Duncan J, Owen AM (2000) Common regions of the human frontal lobe recruited by diverse cognitive demands. Trends in Neurosciences 23(10):475–483. https://doi.org/10.1016/S0166-2236(00)01633-7

Epstein T, Patsopoulos NA, Weiser M (2014) Immediate-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults. Cochrane Database of Systematic Reviews. https://doi.org/10.1002/14651858.CD005041.pub2

Faraone SV (2018) The pharmacology of amphetamine and methylphenidate: Relevance to the neurobiology of attention-deficit/hyperactivity disorder and other psychiatric

comorbidities. Neurosci Biobehav Rev 87:255–270. https://doi.org/10.1016/j.neubiorev.2018.02.001

Faraone SV (2009) Using Meta-analysis to Compare the Efficacy of Medications for Attention-Deficit/Hyperactivity Disorder in Youths. P T 34(12):678–694

Faraone SV, Buitelaar J (2010) Comparing the efficacy of stimulants for ADHD in children and adolescents using meta-analysis. Eur Child Adolesc Psychiatry 19(4):353–364. https://doi.org/10.1007/s00787-009-0054-3

Faraone SV, Rostain AL, Montano CB, Mason O, Antshel KM, Newcorn JH (2020) Systematic Review: Nonmedical Use of Prescription Stimulants: Risk Factors, Outcomes, and Risk Reduction Strategies. Journal of the American Academy of Child & Adolescent Psychiatry 59(1):100–112. https://doi.org/10.1016/j.jaac.2019.06.012

Fay TB, Alpert MA (2019) Cardiovascular Effects of Drugs Used to Treat Attention-Deficit/Hyperactivity Disorder Part 2 Impact on Cardiovascular Events and Recommendations for Evaluation and Monitoring. Cardiol Rev 27(4):173–178. https://doi.org/10.1097/CRD.0000000000000234

Flisher AJ, Hawkridge S (2013) Attention deficit hyperactivity disorder in children and adolescents. South African Journal of Psychiatry 19(3):5. https://doi.org/10.4102/sajpsychiatry.v19i3.943

Geissler J, Romanos M, Hegerl U, Hensch T (2014) Hyperactivity and sensation seeking as autoregulatory attempts to stabilize brain arousal in ADHD and mania? Atten Defic Hyperact Disord 6(3):159–173. https://doi.org/10.1007/s12402-014-0144-z

Goodman DW (2010) Lisdexamfetamine Dimesylate (Vyvanse), A Prodrug Stimulant for Attention-Deficit/Hyperactivity Disorder. P T 35(5):273–287

Groom MJ, Scerif G, Liddle PF, Batty MJ, Liddle EB, Roberts KL, Cahill JD, Liotti M, Hollis C (2010) Effects of Motivation and Medication on Electrophysiological Markers of Response Inhibition in Children with Attention-Deficit/Hyperactivity Disorder. Biol Psychiat 67(7):624–631. https://doi.org/10.1016/j.biopsych.2009.09.029

Gustavsson A, Svensson M, Jacobi F, Allgulander C, Alonso J, Beghi E, Dodel R, Ekman M, Faravelli C, Fratiglioni L, Gannon B, Jones DH, Jennum P, Jordanova A, Jönsson L, Karampampa K, Knapp M, Kobelt G, Kurth T, Lieb R, Linde M, Ljungcrantz C, Maercker A, Melin B, Moscarelli M, Musayev A, Norwood F, Preisig M, Pugliatti M, Rehm J, Salvador-Carulla L, Schlehofer B, Simon R, Steinhausen H-C, Stovner LJ, Vallat J-M, den Bergh PV, van Os J, Vos P, Xu W, Wittchen H-U, Jönsson B, Olesen

J (2011) Cost of disorders of the brain in Europe 2010. European Neuropsychopharmacology 21(10):718–779. https://doi.org/10.1016/j.euroneuro.2011.08.008

Hahn T, Heinzel S, Dresler T, Plichta MM, Renner TJ, Markulin F, Jakob PM, Lesch KP, Fallgatter AJ (2011) Association between reward-related activation in the ventral striatum and trait reward sensitivity is moderated by dopamine transporter genotype. Hum Brain Mapp 32(10):1557–65. https://doi.org/10.1002/hbm.21127

Hannestad J, Gallezot J-D, Planeta-Wilson B, Lin S-F, Williams WA, van Dyck CH, Malison RT, Carson RE, Ding Y-S (2010) Clinically relevant doses of methylphenidate significantly occupy norepinephrine transporters in humans in vivo. Biol Psychiatry 68(9):854–860. https://doi.org/10.1016/j.biopsych.2010.06.017

Hawk LW, Fosco WD, Colder CR, Waxmonsky JG, Pelham WE, Rosch KS (2018) How do stimulant treatments for ADHD work? Evidence for mediation by improved cognition. J Child Psychol Psychiatry 59(12):1271–1281. https://doi.org/10.1111/jcpp.12917

Heal DJ, Smith SL, Gosden J, Nutt DJ (2013) Amphetamine, past and present – a pharmacological and clinical perspective. J Psychopharmacol 27(6):479–496. https://doi.org/10.1177/0269881113482532

Hennissen L, Bakker MJ, Banaschewski T, Carucci S, Coghill D, Danckaerts M, Dittmann RW, Hollis C, Kovshoff H, McCarthy S, Nagy P, Sonuga-Barke E, Wong ICK, Zuddas A, Rosenthal E, Buitelaar JK (2017) Cardiovascular Effects of Stimulant and Non-Stimulant Medication for Children and Adolescents with ADHD: A Systematic Review and Meta-Analysis of Trials of Methylphenidate, Amphetamines and Atomoxetine. CNS Drugs 31(3):199–215. https://doi.org/10.1007/s40263-017-0410-7

Hirota T (2014) Alpha-2 Agonists for Attention-Deficit/Hyperactivity Disorder in Youth: A Systematic Review and Meta-Analysis of Monotherapy and Add-On Trials to Stimulant Therapy. ADOLESCENT PSYCHIATRY 53(2):21

Hodgkins P, Shaw M, Coghill D, Hechtman L (2012) Amfetamine and methylphenidate medications for attention-deficit/hyperactivity disorder: complementary treatment options. Eur Child Adolesc Psychiatry 21(9):477–492. https://doi.org/10.1007/s00787-012-0286-5

Houghton R, de Vries F, Loss G (2020) Psychostimulants/Atomoxetine and Serious Cardiovascular Events in Children with ADHD or Autism Spectrum Disorder. CNS Drugs 34(1):93–101. https://doi.org/10.1007/s40263-019-00686-4

Huss M, Chen W, Ludolph AG (2016) Guanfacine Extended Release: A New Pharmacological Treatment Option in Europe. Clin Drug Investig 36:1–25. https://doi.org/10.1007/s40261-015-0336-0

Huss M, Duhan P, Gandhi P, Chen C-W, Spannhuth C, Kumar V (2017) Methylphenidate dose optimization for ADHD treatment: review of safety, efficacy, and clinical necessity. Neuropsychiatr Dis Treat 13:1741–1751. https://doi.org/10.2147/NDT.S130444

Hutchison SL, Ghuman JK, Ghuman HS, Karpov I, Schuster JM (2016) Efficacy of atomoxetine in the treatment of attention-deficit hyperactivity disorder in patients with common comorbidities in children, adolescents and adults: a review. Ther Adv Psychopharm 6(5):317–334. https://doi.org/10.1177/2045125316647686

Jensen CM, Steinhausen H-C (2015) Comorbid mental disorders in children and adolescents with attention-deficit/hyperactivity disorder in a large nationwide study. Atten Defic Hyperact Disord 7(1):27–38. https://doi.org/10.1007/s12402-014-0142-1

Jensen PS, Garcia JA, Glied S, Crowe M, Foster M, Schlander M, Hinshaw S, Vitiello B, Arnold LE, Elliott G, Hechtman L, Newcorn JH, Pelham WE, Swanson J, Wells K (2005) Cost-effectiveness of ADHD treatments: findings from the multimodal treatment study of children with ADHD. Am J Psychiatry 162(9):1628–36

Joseph A, Ayyagari R, Xie M, Cai S, Xie J, Huss M, Sikirica V (2017) Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison. Eur Child Adolesc Psych 26(8):875–897. https://doi.org/10.1007/s00787-017-0962-6

Jucaite A, Fernell E, Halldin C, Forssberg H, Farde L (2005) Reduced midbrain dopamine transporter binding in male adolescents with attention-deficit/hyperactivity disorder: association between striatal dopamine markers and motor hyperactivity. Biol Psychiatry 57(3):229–238. https://doi.org/10.1016/j.biopsych.2004.11.009

Karalunas SL, Geurts HM, Konrad K, Bender S, Nigg JT (2014) Annual Research Review: Reaction time variability in ADHD and autism spectrum disorders: measurement and mechanisms of a proposed trans-diagnostic phenotype. J Child Psychol Psychiatry 55(6):685–710. https://doi.org/10.1111/jcpp.12217

Konrad K, Eickhoff SB (2010) Is the ADHD brain wired differently? A review on structural and functional connectivity in attention deficit hyperactivity disorder. Hum Brain Mapp 31(6):904–916. https://doi.org/10.1002/hbm.21058

Krinzinger H, Hall CL, Groom MJ, Ansari MT, Banaschewski T, Buitelaar JK, Carucci S, Coghill D, Danckaerts M, Dittmann RW, Falissard B, Garas P, Inglis SK, Kovshoff H, Kochhar P, McCarthy S, Nagy P, Neubert A, Roberts S, Sayal K, Sonuga-Barke E, Wong ICK, Xia J, Zuddas A, Hollis C, Konrad K, Liddle EB (2019) Neurological and psychiatric adverse effects of long-term methylphenidate treatment in ADHD: A map of the current evidence. Neurosci Biobehav Rev 107:945–968. https://doi.org/10.1016/j.neubiorev.2019.09.023

Kuntsi J, Klein C (2012) Intraindividual variability in ADHD and its implications for research of causal links. Curr Top Behav Neurosci 9:67–91. https://doi.org/10.1007/7854_2011_145

Liddle EB, Hollis C, Batty MJ, Groom MJ, Totman JJ, Liotti M, Scerif G, Liddle PF (2011) Task-related default mode network modulation and inhibitory control in ADHD: effects of motivation and methylphenidate. J Child Psychol Psychiatry 52(7):761–71. https://doi.org/10.1111/j.1469-7610.2010.02333.x

Liu H, Feng W, Zhang D (2019) Association of ADHD medications with the risk of cardiovascular diseases: a meta-analysis. Eur Child Adolesc Psych 28(10):1283–1293. https://doi.org/10.1007/s00787-018-1217-x

Markowitz JS, Patrick KS (2008) Differential Pharmacokinetics and Pharmacodynamics of Methylphenidate Enantiomers: Does Chirality Matter? Journal of Clinical Psychopharmacology 28(3):S54. https://doi.org/10.1097/JCP.0b013e3181733560

Martinez E, Pasquereau B, Drui G, Saga Y, Météreau É, Tremblay L (2020) Ventral striatum supports Methylphenidate therapeutic effects on impulsive choices expressed in temporal discounting task. Sci Rep 10(1):716. https://doi.org/10.1038/s41598-020-57595-6

Martinez-Raga J, Ferreros A, Knecht C, de Alvaro R, Carabal E (2017) Attention-deficit hyperactivity disorder medication use: factors involved in prescribing, safety aspects and outcomes. Ther Adv Drug Saf 8(3):87–99. https://doi.org/10.1177/2042098616679636

McQuade JD, Hoza B (2008) Peer problems in Attention Deficit Hyperactivity Disorder: Current status and future directions. Dev Disabil Res Revs 14(4):320–324. https://doi.org/10.1002/ddrr.35

Michelson D, Buitelaar JK, Danckaerts M, Gillberg C, Spencer TJ, Zuddas A, Faries DE, Zhang S, Biederman J (2004) Relapse prevention in pediatric patients with ADHD treated with atomoxetine: a randomized, double-blind, placebo-controlled study. J Am

Acad Child Adolesc Psychiatry 43(7):896–904. https://doi.org/10.1097/01.chi.0000125089.35109.81

Miller EK, Cohen JD (2001) An Integrative Theory of Prefrontal Cortex Function. Annual Review of Neuroscience 24(1):167–202. https://doi.org/10.1146/annurev.neuro.24.1.167

Moreira Maia CR, Cortese S, Caye A, Deakin TK, Polanczyk GV, Polanczyk CA, Paim Rohde LA (2017) Long-Term Efficacy of Methylphenidate Immediate-Release for the Treatment of Childhood ADHD: A Systematic Review and Meta-Analysis. J Atten Disord 21(1):3–13. https://doi.org/10.1177/1087054714559643

National Institute of Health and Care Excellence (2018) Overview | Attention deficit hyperactivity disorder: diagnosis and management | Guidance | NICE. https://www.nice.org.uk/guidance/ng87. Accessed 9 Jul 2021

Ni H-C, Gu S-LH, Lin H-Y, Lin Y-J, Yang L-K, Huang H-C, Gau SS-F (2016) Atomoxetine could improve intra-individual variability in drug-naive adults with attention-deficit/hyperactivity disorder comparably with methylphenidate: A head-to-head randomized clinical trial. J Psychopharmacol 30(5):459–467. https://doi.org/10.1177/0269881116632377

Nijmeijer JS, Minderaa RB, Buitelaar JK, Mulligan A, Hartman CA, Hoekstra PJ (2008) Attention-deficit/hyperactivity disorder and social dysfunctioning. Clinical Psychology Review 28(4):692–708. https://doi.org/10.1016/j.cpr.2007.10.003

Osland ST, Steeves TDL, Pringsheim T (2018) Pharmacological treatment for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders. Cochrane Database Syst Rev (6):CD007990. https://doi.org/10.1002/14651858.CD007990.pub3

Rommelse NNJ, Geurts HM, Franke B, Buitelaar JK, Hartman CA (2011) A review on cognitive and brain endophenotypes that may be common in autism spectrum disorder and attention-deficit/hyperactivity disorder and facilitate the search for pleiotropic genes. Neurosci Biobehav Rev 35(6):1363–1396. https://doi.org/10.1016/j.neubiorev.2011.02.015

Rubia K (2018) Cognitive Neuroscience of Attention Deficit Hyperactivity Disorder (ADHD) and Its Clinical Translation. Front Hum Neurosci 12:100. https://doi.org/10.3389/fnhum.2018.00100

Rubia K, Alegria AA, Cubillo AI, Smith AB, Brammer MJ, Radua J (2014) Effects of Stimulants on Brain Function in Attention-Deficit/Hyperactivity Disorder: A

Systematic Review and Meta-Analysis. Biol Psychiatry 76(8):616–628. https://doi.org/10.1016/j.biopsych.2013.10.016

Schoeman R, Liebenberg R (2017) The South African Society of Psychiatrists/Psychiatry Management Group management guidelines for adult attention-deficit/hyperactivity disorder. SAJP 23:a1060. https://doi.org/10.4102/sajpsychiatry.v23i0.1060

Sciberras E, Streatfeild J, Ceccato T, Pezzullo L, Scott JG, Middeldorp CM, Hutchins P, Paterson R, Bellgrove MA, Coghill D (2020) Social and Economic Costs of Attention-Deficit/Hyperactivity Disorder Across the Lifespan. J Atten Disord :1087054720961828. https://doi.org/10.1177/1087054720961828

Shah R, Grover S, Avasthi A (2019) Clinical Practice Guidelines for the Assessment and Management of Attention-Deficit/Hyperactivity Disorder. Indian J Psychiatry 61(Suppl 2):176–193. https://doi.org/10.4103/psychiatry.IndianJPsychiatry_543_18

Sigurdardottir HL, Kranz GS, Rami-Mark C, James GM, Vanicek T, Gryglewski G, Kautzky A, Hienert M, Traub-Weidinger T, Mitterhauser M, Wadsak W, Hacker M, Rujescu D, Kasper S, Lanzenberger R (2016) Effects of norepinephrine transporter gene variants on NET binding in ADHD and healthy controls investigated by PET. Hum Brain Mapp 37(3):884–895. https://doi.org/10.1002/hbm.23071

Spencer RC, Devilbiss DM, Berridge CW (2015) The Cognition-Enhancing Effects of Psychostimulants Involve Direct Action in the Prefrontal Cortex. Biol Psychiatry 77(11):940–950. https://doi.org/10.1016/j.biopsych.2014.09.013

Spencer T, Biederman J, Wilens T, Harding M, O'Donnell D, Griffin S (1996) Pharmacotherapy of attention-deficit hyperactivity disorder across the life cycle. J Am Acad Child Adolesc Psychiatry 35(4):409–432. https://doi.org/10.1097/00004583-199604000-00008

Strauß M, Ulke C, Paucke M, Huang J, Mauche N, Sander C, Stark T, Hegerl U (2018) Brain arousal regulation in adults with attention-deficit/hyperactivity disorder (ADHD). Psychiatry Research 261:102–108. https://doi.org/10.1016/j.psychres.2017.12.043

Swanson J, Baler RD, Volkow ND (2011) Understanding the effects of stimulant medications on cognition in individuals with attention-deficit hyperactivity disorder: a decade of progress. Neuropsychopharmacology 36(1):207–26. https://doi.org/10.1038/npp.2010.160

Swanson JM, Volkow ND (2002) Pharmacokinetic and pharmacodynamic properties of stimulants: implications for the design of new treatments for ADHD. Behav Brain Res 130(1–2):73–8

Swensen AR, Birnbaum HG, Secnik K, Marynchenko M, Greenberg P, Claxton A (2003) Attention-deficit/hyperactivity disorder: increased costs for patients and their families. J Am Acad Child Adolesc Psychiatry 42(12):1415–23. https://doi.org/10.1097/01.chi.0000093323.86599.44

Ulke C, Rullmann M, Huang J, Luthardt J, Becker G-A, Patt M, Meyer PM, Tiepolt S, Hesse S, Sabri O, Strauß M (2019) Adult attention-deficit/hyperactivity disorder is associated with reduced norepinephrine transporter availability in right attention networks: a (S,S)-O-[11 C]methylreboxetine positron emission tomography study. Transl Psychiatry 9(1):1–10. https://doi.org/10.1038/s41398-019-0619-y

Vanicek T, Spies M, Rami-Mark C, Savli M, Höflich A, Kranz GS, Hahn A, Kutzelnigg A, Traub-Weidinger T, Mitterhauser M, Wadsak W, Hacker M, Volkow ND, Kasper S, Lanzenberger R (2014) The Norepinephrine Transporter in Attention-Deficit/Hyperactivity Disorder Investigated With Positron Emission Tomography. JAMA Psychiatry 71(12):1340–1349. https://doi.org/10.1001/jamapsychiatry.2014.1226

Volkow ND, Fowler JS, Wang GJ, Ding YS, Gatley SJ (2002a) Role of dopamine in the therapeutic and reinforcing effects of methylphenidate in humans: results from imaging studies. Eur Neuropsychopharmacol 12(6):557–66

Volkow ND, Wang Gene-J, Fowler JS, Gatley SJ, Logan J, Ding Y-S, Hitzemann R, Pappas N (1998) Dopamine Transporter Occupancies in the Human Brain Induced by Therapeutic Doses of Oral Methylphenidate. AJP 155(10):1325–1331. https://doi.org/10.1176/ajp.155.10.1325

Volkow ND, Wang G-J, Fowler JS, Logan J, Franceschi D, Maynard L, Ding Y-S, Gatley SJ, Gifford A, Zhu W, Swanson JM (2002b) Relationship between blockade of dopamine transporters by oral methylphenidate and the increases in extracellular dopamine: Therapeutic implications. Synapse 43(3):181–187. https://doi.org/10.1002/syn.10038

Wang M, Ramos BP, Paspalas CD, Shu Y, Simen A, Duque A, Vijayraghavan S, Brennan A, Dudley A, Nou E, Mazer JA, McCormick DA, Arnsten AFT (2007) Alpha2A-adrenoceptors strengthen working memory networks by inhibiting cAMP-HCN channel signaling in prefrontal cortex. Cell 129(2):397–410. https://doi.org/10.1016/j.cell.2007.03.015

Wolraich ML, Hagan JF, Allan C, Chan E, Davison D, Earls M, Evans SW, Flinn SK, Froehlich T, Frost J, Holbrook JR, Lehmann CU, Lessin HR, Okechukwu K, Pierce KL, Winner JD, Zurhellen W (2019) Clinical Practice Guideline for the Diagnosis,

Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. Pediatrics 144(4). https://doi.org/10.1542/peds.2019-2528

World Health Organisation The World Health Organization Quality of Life (WHOQOL). https://www.who.int/publications-detail-redierct/WHO-HIS-HSI-Rev.2012.03. Accessed 24 May 2021.

Wu EQ, Hodgkins P, Ben-Hamadi R, Setyawan J, Xie J, Sikirica V, Du EX, Yan SY, Erder MH (2012) Cost effectiveness of pharmacotherapies for attention-deficit hyperactivity disorder: a systematic literature review. CNS Drugs 26(7):581–600. https://doi.org/10.2165/11633900-000000000-00000

Table 1 Treatment guidelines for ADHD in several countries**.** The table provides a representative overview of guidelines in different geographical regions of the world and the similarities and differences between them but is not an exhaustive list of all ADHD guidelines worldwide

MPH=Methylphenidate; AMP=Amphetamine; LDX=Lisdexamphetamine; DEX=dexamphetamine; ATX=Atomoxetine; GXR=Guanfacine-extended release; CLON=Clonidine; MAS = Mixed Amphetamine Salts; CBT=Cognitive Behavioural Therapy,

[a] MPH has not yet received FDA approval for treatment of children aged less than 6 years and use is therefore off-label

[b] Summaries of the guidelines were retrieved from the website of the ADHD Institute (ADHD Institute n.d.)

Country	Organisation	Publication	Specification
UK	National Institute for Health and Care Excellence (NICE)	(National Institute of Health and Care Excellence, 2018)	Children aged less than 5 years: Offer parent training. Only offer medication with advice from a specialist ADHD service. Children and young people aged 5 years and over: Offer psychoeducation and parent-training. If symptoms persist, offer MPH first for 6 weeks. If no response, switch to LDX after 6 weeks or DEX if cannot tolerate LDX Offer ATX or GXR if no benefit from MPH or LDX/DEX

			Consider CBT for young people who have some benefit from medication but whose symptoms are still causing significant impairment in at least one domain. Adults (>17 years): Offer medication to adults if environmental modifications have been tried but symptoms are still causing significant impairment. Offer MPH or LDX first for 6 weeks (switch from LDX to MPH or vice versa if no benefit). Offer DEX to adults whose symptoms are responding to LDX but cannot tolerate the longer effect profile. Offer ATX if no response or cannot tolerate MPH or LDX after 6-week trials.
USA	American Academy of Pediatrics	Wolraich et al. (2019)	Children aged 4-5 years: Consider MPH in children with moderate to severe symptoms for whom parent training/behaviour modification has not been successful[a]. Children aged 6-11 years and adolescents aged 12-17: Prescribe an FDA-approved medication in conjunction with parent-training and classroom interventions. Try MPH or AMP first. If no response or families are concerned about abuse/diversion potential, offer nonstimulant. Combine stimulant and nonstimulant in those who show partial response to stimulants. Adults: No recommendations.
Canada	Canadian ADHD Resource Alliance (CADDRA)	(Canadian ADHD Resource Alliance, 2018)	All age groups: Psychoeducation and psychological interventions that are appropriate to the individual's developmental stage and circumstances are advocated. First-line treatments: Long-acting stimulants (LDX, MPH, MAS) with an adequate trial to measure response before considering second-line treatment.

			Second-line treatments: ATX, GXR and short/intermediate acting stimulants (MPH, DEX), or long-acting non-stimulants (GXR or ATX in children aged 6-17 years, GXR in adults aged 18 and over) in patients who experience significant side effects/no response to first-line medications. Combine these with first-line medications in sub-optimal responders. Third-line treatments: Bupropion, CLON, imipramine, modafinil (reserved for treatment-resistant cases and require specialise input).
Australia	National Health & Medical Research Council	(Australian Government National Health and Medical Research Council, 2012)	Children aged less than 7 years and aged 6 to 12 years: Behaviour modification, family therapy, CBT recommended first. Only offer medication if these are ineffective. Adolescents: CBT recommended. Only if psychosocial interventions are ineffective, offer stimulant medication (MPH or DEX) for 1 month. Clinicians are referred to other sources, including NICE guidelines, for decisions around non-stimulant medication prescribing. Adults: No recommendations.
Spain[b]	Ministry of Health, Social Services and Equality	Alda et al. (2017)	Children aged less than 6 years: Pharmacological therapy not recommended. Children aged over 6 years: Offer psychoeducational and/or psychological therapies first. When symptoms are severe, or if these interventions are not effective, offer MPH, LDX, GXR or ATX.

			Adults: If symptoms are mild, offer non-pharmacological treatments. Pharmacological recommended for moderate to severe symptoms. If LDX and OROS-MPH were prescribed in childhood, continue these medications into adulthood. Otherwise, ATX.
Germany[b]	Association of the Scientific Medical Societies in Germany	(Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, (AWMF) [Association of the Scientific Medical Societies in Germany], 2017)	Children aged 6 years and over: If symptoms are mild, offer psychosocial treatment and psychotherapy with supplementary pharmacotherapy only in isolated cases to treat residual symptoms. For moderate symptoms offer intensified psychosocial intervention/psychotherapy or pharmacological treatment. Severe symptoms: Intensive psychoeducation followed by pharmacotherapy with psychosocial therapy. In all cases, medication structure is stimulants first choice (MPH then DEX or LDX if inadequate response), Non-stimulants (ATX or GXR) as second choice if stimulants not suitable/tolerated. Adults: Start with psychoeducation/psychotherapy and offer pharmacotherapy only for more severe symptoms or as an adjunct to non-pharmacological therapies. When medication is offered, offer MPH (delayed or extended release) or DEX or LDX as first-line and then offer ATX if stimulants are not sufficiently effective or tolerated.
India	Indian Psychiatric Society	Shah et al. (2019)	Children aged less than 6 years: Offer psychosocial interventions. Only offer medication if significant impairment persists Children aged 6+ years: Offer environmental modifications first then parent training if symptoms are not severe. If symptoms are severe or do not respond to these

			interventions, offer MPH for 6 weeks. If poor response, offer ATX or CLON, with preference for ATX. Adults: No recommendations.
Saudi Arabia	Saudi ADHD Society	Bashiri et al. (2021)	Children<5 years: Offer psychosocial interventions. Do not offer medication without specialist advice. Children 5 years and older: Offer group-based psychoeducation first, then CBT. Offer pharmacotherapy if symptoms persist. First-line: MPH. Second-line: LDX or DEX. Third-line: ATX or GXR Adults: Offer psychosocial therapies first. If symptoms persist, offer pharmacotherapy. First-line: MPH or LDX. Second-line: DEX or ATX.
South Africa	South African Society of Psychiatrists	Child guidelines: Flisher and Hawkridge (2013) Adult guidelines: Schoeman and Liebenberg (2017)	Children: if symptoms are mild/moderate with minimal impairment or family do not want medication, use behavioural interventions as first-line If symptoms are severe or behavioural treatment is not effective, offer medication trial. Offer MPH or ATX first. Switch to other one if no or limited response. If still no response, check diagnosis is correct then offer CLON or tricyclic antidepressants Adults: Multimodal treatment is advocated, combining non-pharmacological and pharmacological therapies. Based on guidelines in other countries (e.g. NICE, APA, CADDRA), extended-release stimulants are recommended, in combination with immediate release stimulants to 'top up' if the ER dose starts to wear off. ATX recommended as second-line. The alpha-adrenoceptor agonists are not available.

Table 2 Pharmacodynamics of extended-release stimulant medications and nonstimulant medications for ADHD

IR=Immediate Release, ER=Extended Release; MAS=mixed amphetamine salts (amphetamine and dextroamphetamine); OROS-MPH=Osmotic-release oral system methylphenidate; MPH-CD=methylphenidate-Controlled Delivery; SODAS=Spheroidal Oral Drug Absorption System; XR-ODT=extended release orally disintegrating tablet; MAS-ER – Mixed amphetamine salts extended release; N/A=Not applicable; NR=Not reported

[a] Information obtained from the website of chadd.org (CHADD, n.d.)

[b] Capsule/tablet can be chewed or sprinkled on food or swallowed whole

Medication Class	Preparation	Drug delivery platform (IR:ER %)	Form	Approx Duration of Response (h)[a]
Stimulants				
	Methylphenidate	OROS-MPH (22:78)	Tablet	10-12
	Methylphenidate	MPH-CD (30:70)	Tablet[b]	8
	Methylphenidate	SODAS (50:50)	Capsule[b]	8
	Methylphenidate	Transdermal patch (N/A)	Transdermal patch	9
	Methylphenidate	LiquiXR (20:80)	Liquid suspension	8-12
	Dexmethylphenidate	SODAS (50:50)	Capsule[b]	9-12
	Mixed amphetamine salts	SODAS (50:50)	Capsule	8-12
	Lisdexamfetamine	Prodrug (N/A)	Capsule[b]	10-12
	Dexamphetamine sulfate	Bead capsule (50:50)	Capsule[b]	6-9
	Amphetamine	LiquiXR (NR)	Liquid suspension	8-12
	Amphetamine	XR-ODT (50:50)	Tablet	9-12
	Mixed amphetamine salts	Triple-bead MAS-ER (NR)	Capsule[b]	16
Nonstimulants				
	Atomoxetine	N/A	Capsule	24
	Guanfacine-ER	N/A	Tablet	12-24
	Clonidine-ER	N/A	Tablet	12-24