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EXPERT REVIEW

Treatment strategies for ADHD: an evidence-based guide to select optimal treatment

Arthur Caye[1] · James M. Swanson[2] · David Coghill[3,4,5] · Luis Augusto Rohde[1,6]

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a common and impairing disorder affecting children, adolescents, and adults. Several treatment strategies are available that can successfully ameliorate symptoms, ranging from pharmacological to dietary interventions. Due to the increasing range of available options, an informed selection or prioritization of treatments is becoming harder for clinicians. This review aims to provide an evidence-based appraisal of the literature on ADHD treatment, supplemented by expert opinion on plausibility. We outline proposed mechanisms of action of established pharmacologic and non-pharmacologic treatments, and we review targets of novel treatments. The most relevant evidence supporting efficacy and safety of each treatment strategy is discussed. We review the individualized features of the patient that should guide the selection of treatments in a shared decision-making continuum. We provide guidance for optimizing initiation of treatment and follow-up of patients in clinical settings.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is characterized by pervasive and impairing symptoms of inattention, hyperactivity, and impulsivity [1]. The disorder affects around 5% of children and adolescents [2] and 2.5% of adults [3] worldwide. Decades of research consistently report strong links between ADHD and adverse life outcomes [4–6]. Children with ADHD show an increased risk of accidental injuries [7], poor relationship with peers [8] and parents [9], worse quality of life [10], and impaired school performance [11]. Adolescents with ADHD show more school refusal and grade retention [11], earlier and more frequent use of marijuana, tobacco, and other drugs [12, 13], earlier sexual engagement [14], and more frequent teenage pregnancy [15, 16]. Prospective studies of adults with child-onset show that individuals with persistent ADHD (but not remitting ADHD) have lower education attainment, reduced job performance, and increased emotional problems [17–19], and studies of adult onset ADHD show increased risk of traffic accidents [20], criminality [21], unemployment [22], and substance abuse [23]. A common denominator throughout the life cycle is increased mortality by external and accidental causes [24]. Overall, the economic burden caused by ADHD ranges from $143 to $266 only in the United States [25].

The evidence documenting the individual and social impact of ADHD is the most important justification for treatment. Accordingly, there is an agreement between clinical guidelines from Pediatrics, Psychiatry, and Primary Care bodies that health professionals should be identifying, diagnosing, and treating individuals with ADHD [26–30]. Furthermore, numerous meta-analyses published in the last few years have assessed the efficacy of pharmacological, non-pharmacological, and combined treatment for managing ADHD [31–42]. The evidence clearly supports short-term efficacy of pharmacological treatments, but evidence for long-term efficacy is less clear. Non-pharmacological interventions such as cognitive training and neurofeedback

✉ Arthur Caye
arthurcaye@gmail.com

1 Department of Psychiatry, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

2 Department of Pediatrics, University of California, Irvine, USA

3 Department of Paediatrics, University of Melbourne, Melbourne, Australia

4 Department of Psychiatry, University of Melbourne, Melbourne, Australia

5 Murdoch Children's Research Institute, Melbourne, Australia

6 National Institute of Developmental Psychiatry for Children and Adolescents, São Paulo, Brazil

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are probably not efficacious, and more research is needed to support or refute the role of behavioral therapies on ADHD treatment. Interestingly, health professionals are often given differing and sometimes contradictory advice about how to best interpret this evidence and prioritize the various treatment approaches for their patients. In this review, we examine the evidence of efficacy, safety, and tolerance of available interventions, and propose a balanced hierarchical approach to treatment selection and optimization.

Pharmacological treatment

Pharmacological treatment remains the mainstay of ADHD treatment in most clinical settings and guidelines [26–30]. In some settings, around 90% of children with ADHD eventually receive medication as treatment [43]. The most widely used medications are two psychostimulants, methylphenidate (MPH) and the amphetamines (AMP). Second-line medications include atomoxetine (ATX), guanfacine (GFC), and clonidine (CLO), usually prescribed after lack of response, intolerance, or contraindication to the psychostimulants. Other unlicensed medication options include bupropion, modafinil, and tricyclic antidepressants (TCAs).

Mechanisms of action of medications for ADHD treatment

A comprehensive discussion on the mechanism of action of all drugs used for ADHD treatment is beyond the scope of this paper; however, most medications for ADHD are thought to act primarily on catecholamine pathways [44] (Fig. 1). At the synaptic level, these drugs seem to be catecholamine agonists, increasing the availability of dopamine or norepinephrine (e.g., by blocking reuptake). However, there is controversy about the density of dopamine transporters in individuals with ADHD and the impact of this on catecholamine levels. Some studies suggest increased transporter density with rapid recycling of synaptic dopamine resulting in a dopamine deficit [45–47]. Others [48, 49] suggest a dopamine deficit associated with low dopamine release, which in untreated cases is associated with low transporter density. Recent PET imaging studies indicate that transporter density increases and becomes high after chronic treatment with stimulants [50, 51].

There are differences in the specific mechanism of action for each medication. The psychostimulants (MPH and AMP) inhibit dopamine and norepinephrine transporters. They work as reuptake inhibitors increasing neurotransmission, primarily in the striatum and prefrontal cortex [52]. ATX inhibits the norepinephrine transporter 1 (NET 1). It prevents the reuptake and therefore increases neurotransmission of norepinephrine in all regions of the brain [53] and of dopamine specifically in the prefrontal cortex, where there are very few dopamine transporters [53]. The alpha-2 receptor agonists (CLO and GFC) stimulate alpha-2 noradrenaline receptors in the central nervous system. The mechanism of action in ADHD symptoms is mediated by the increased noradrenergic tone in the prefrontal cortex and an indirect input of noradrenaline from the locus coeruleus [54]. Bupropion is converted into two main metabolites (hydroxybupropion and threohydrobupropion) that are potent norepinephrine enhancers by transporter inhibition [55]. TCAs primarily act by blockade of the serotonin and norepinephrine transporters, which enhances neurotransmission [56]. There is little effect on dopamine transporters [52]. Modafinil has been shown to induce an atypical conformational change in the DAT compared to traditional psychostimulants [57].

The simplified mechanisms of action described are useful for an initial discussion of the expected therapeutic and adverse effects of these medications. Nonetheless, we acknowledge that this is a reductionist and incomplete perspective. For example, although these medications may have different mechanisms of action, the ultimate effects may be similar, since they all appear to increase the availability of dopamine and/or noradrenaline. This in turn modulates neurotransmission of a wide range of brain circuits (primarily GABAergic and glutamatergic) that control a range of cognitive functions including executive functioning, response to reward, memory, and timing [58–61] (Fig. 1—inferior left panel). These immediate effects on dopaminergic and noradrenergic neurotransmission do not fully explain other aspects of treatment, such as differences in the latency for onset and offset in efficacy, which are short (hours to days) for stimulants and longer (weeks to months) for non-stimulants [62–65]. One plausible albeit speculative hypothesis is that some ADHD medications may promote long-term alterations in the brain through the regulation of genes and proteins involved in neurite outgrowth and configuration of receptors and transporters of neurotransmitters [66–68] (Fig. 1—inferior right panel). If this hypothesis is correct, long-term stimulant treatment could even normalize the trajectory of cortical development and other structural brain changes [69]. However, these changes are also consistent with the development of long-term tolerance through up-regulation of monoamine transporters [70].

Pharmacogenomics of medication for ADHD

Although pharmacological treatment with psychostimulants for ADHD are among the most effective interventions available in Psychiatry [71], a considerable proportion of patients—roughly a third—do not respond adequately to

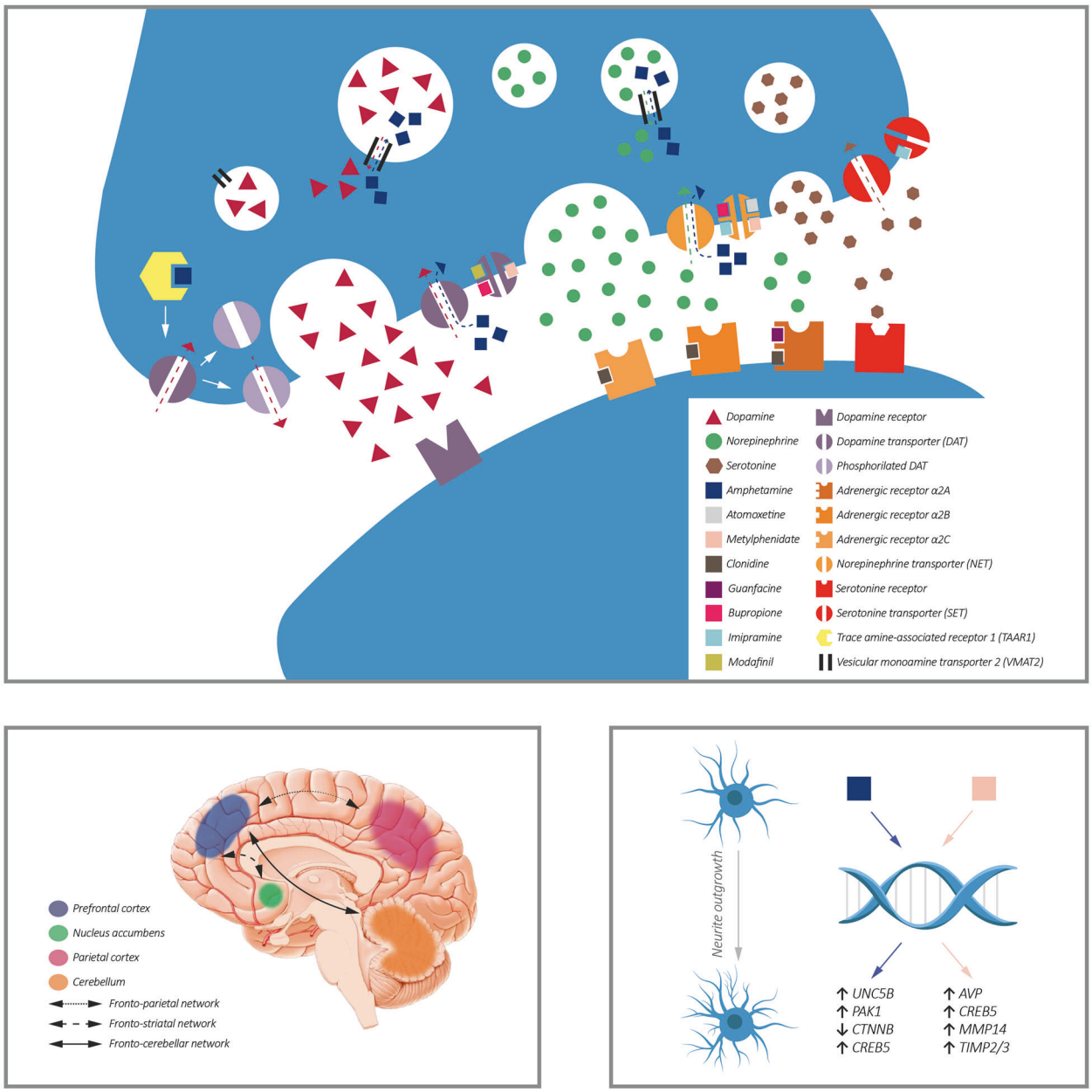

Fig. 1 Proposed mechanisms of action for the medications commonly used to treat ADHD. *Pharmacodynamics (superior panel)*: **Amphetamines** have at least three mechanisms of action: (1) they are transported by the monoamine transporters DAT and NET, thus competing with those neurotransmitters and decreasing their reuptake in the synapse; (2) They also cause trace amine-associated receptor 1 (TAAR1) to phosphorylate DAT. The phosphorylated DAT is either internalized into the presynaptic neuron and ceases transport or inverses the efflux of dopamine; (3) they enter the presynaptic monoamine vesicle and cause efflux of neurotransmitters off the vesicle, which in turn augments the efflux towards the synapse. These mechanisms are more studied and established for dopamine neurotransmission, but are thought to occur similarly for norepinephrine. **Atomoxetine** binds to NET, inhibiting the reuptake of norepinephrine. In the prefrontal cortex, where there is much less expression of DAT, dopamine reuptake by NET is also inhibited by the action of atomoxetine. **Methylphenidate** binds to NET and DAT, inhibiting the reuptake of norepinephrine and dopamine. **Clonidine** binds to and activates alpha-2 adrenergic receptors. **Guanfacine** binds to and activates specifically alpha-2A adrenergic receptors. **Bupropion** inhibits DAT and NET weakly. **Imipramine** inhibits NET and SET. **Modafinil** inhibits DAT to a weaker extent than other psychostimulants. *Brain network activation (left inferior panel)*: Pharmacological treatment acutely enhances activation and normalize brain networks involved in attention, cognitive control and working memory in children with ADHD. *Neurodevelopmental signal (right inferior panel)*: ADHD medications regulate the expression of genes involved in neurite outgrowth. In the panel, for illustration, we provide mechanisms for methylphenidate and amphetamines (color figure online)

Table 1 Efficacy and tolerability of treatments approved for ADHD

	Efficacy		Tolerability	
	Magnitude	# Trials	Magnitude	# Trials
Methylphenidate	++++	40	+++	55
Amphetamine derivatives	++++	9	++++	8
Atomoxetine	+++	27	++++	37
Clonidine	+++	4	++	6
Guanfacine	+++	10	++++	9
Modafinil	++++	5	+++	6
Bupropion	++	1	+++	3
Behavioral therapies	+++	15	+++	25
Cognitive training	+/−	2	++++	10
Neurofeedback	++/−	4	+++	10
Poly-unsaturated fatty acids	++/−	3	++++	9
Stimulants + behavioral	++++	8	+++	13
Non-stimulants + behavioral	++++	4	++++	3
Stimulants + non-stimulants	++++	4	+++	7

+ up to 0.2; ++ 0.2–0.5; +++ 0.5–0.8; ++++ more than 0.8; and /− non-significant

Efficacy and tolerability estimates were extracted from a recent network meta-analysis [32]. Odds ratio against placebo were converted to Cohen's d effect sizes. The higher the number of +, higher are efficacy and tolerability. Tolerability expressed as the number of patients discontinuing the protocol

Please note that the strength of the evidence is not considered (there is large heterogeneity in the overall number of trials available for each intervention). # trials represent the number of high-quality trials (as judged by the authors of the meta-analysis) used to compute the effect estimates

Estimated effects for non-pharmacological interventions stem from studies using unblinded raters

and/or tolerate stimulant treatment [72, 73]. This heterogeneity in individual response and adverse events could be due to genetic factors, which has been investigated in dozens of ADHD pharmacogenomic studies in the last decades, with most studies focusing on MPH [74].

Most reports describe candidate-gene approaches with catecholamine receptor genes. A recent meta-analysis reviewed all pharmacogenomic studies with MPH and suggested associations of single nucleotide polymorphisms (SNPs) at ADRA2A, COMT, SLC6A2, and variable number of tandem repeats (VNTRs) in DRD4 and SLC6A3 [75] with response to treatment. Authors suggested that future studies might propose a multivariable approach to combine small effects of individual genes into one valuable clinical tool, but current clinical use is not yet recommended.

Another promising field of research in ADHD pharmacogenomics relates to genes involved in the metabolism of the medications. Studies investigating the role of the human carboxylesterase 1 gene (CES1), which encodes an enzyme that metabolizes MPH [76], have shown that CES1 variants are associated with the total dose needed and the effect side profile in children medicated with MPH [77, 78]. Likewise, different alleles of the cytochrome p450 2D6 (CYP2D6) gene confer to individuals the feature of poor to extensive metabolizers of ATX, which has been shown to significantly affect clinical response and effect side profile [79, 80].

Lately, more sophisticated designs have been applied to the study of ADHD pharmacogenomics. Two genome-wide studies have been conducted, failing to find specific genetic variants associated with response to treatment or adverse effects [81, 82]. A study which combined GWAS, functional annotation, pathway enrichment analyses, and expression quantitative trait loci strategies, provided promising evidence for potential gene candidates that mediate MPH response in adult patients. A meta-analysis conducted within this study identified 15 positive signals. The phosphatidylethanolamine binding protein 4 (PEBP4), which is involved in cell proliferation and survival, was the top hit [83]. The underlying mechanisms that mediate these findings through clinical effects are yet to be clarified.

Several companies offer extensive genetic testing with a promise of optimizing pharmacological selection for ADHD [84–86]. We reviewed the information on the websites, which we find to be insufficient for the claims made. We and others do not believe that routinely use of these genetic tests to guide ADHD treatment is currently supported by evidence and that they should not be recommended [74, 87]. However, special cases, such as patients with clear indication to ATX but refractory to treatment, might benefit from dose adjustments based on their classification between slow and fast metabolizers through CYP2D6 genotyping.

Evidence of efficacy

Psychostimulants

Psychostimulants are the most studied medications used for ADHD. Hundreds of randomized clinical trials have been conducted to study short-term efficacy and safety of psychostimulants for the treatment of ADHD in children, adolescents, and adults and have been summarized in many meta-analyses [32, 33, 38, 39, 88–106]. The overall conclusion is that psychostimulants are the most effective available treatment for ADHD, at least in the short-term [88, 90, 107], with clear acute benefits (typically within an hour after an adequate dose) that continue until the drug is metabolized (which depends on pharmacokinetic properties

of the drug and method of drug delivery used). If medication is continued, these acute benefits persist for at least a year (although dose increases may be necessary to maintain full efficacy). The evidence also suggests that stimulants are safe and well-tolerated [37, 108].

A recent Cochrane review and meta-analysis questioned the quality of available data on the efficacy of MPH [33]. Authors confirmed the previously observed substantial effect sizes for symptom reduction and the absence of major adverse effects in randomized clinical trials of MPH for children and adolescents with ADHD. However, they classified all 185 included trials as being at high risk of bias. This review has been criticized by experts in the field due to methodological choices of bias assessment [109–111]. For instance, randomized clinical trials funded by government or independent funding agencies were labeled as biased if any one of multiple authors had disclosed a financial connection to the pharmaceutical industry.

A network meta-analysis including 190 randomized clinical trials of ADHD treatments supported psychostimulants as the most efficacious treatment available for ADHD considering pharmacological and non-pharmacological options [32]. This review also found no differences in acceptability between psychostimulants and other pharmacological options. Summarized estimates of efficacy and tolerability reported in this meta-analysis are presented in Table 1. However, the overall quality of the studies ranged from low to very low according to the GRADE system. A second network meta-analysis of pharmacological treatments including 73 studies and 15,025 participants used a ranking strategy to stratify medications according to efficacy and tolerability [112]. Authors concluded that lisdexamfetamine and MPH had the best overall ranking scores. It is important to note that some methodological aspects in these meta-analyses like the heterogeneity among studies, the different number of studies included for each comparison, and the quality of some studies included provide results that need to be checked in future studies.

Atomoxetine

ATX is considered an important pharmacological treatment for ADHD in clinical guidelines [26–30], particularly when psychostimulants are contraindicated or not tolerated. In addition, it might be considered in some special situations, e.g., when ADHD is comorbid with bipolar disorder and the risk of mood destabilization is high with stimulants, substance abuse/dependence, or Tourette syndrome [26–30].

Randomized clinical trials and several meta-analyses have consistently suggested that ATX has acceptable efficacy and tolerability, but the observed effect size is smaller than that for psychostimulants [32, 38, 88]. Importantly, clinical trials have been conducted in children and adults with common comorbidities, like anxiety disorders. In these patients, ATX was effective in reducing ADHD symptoms while not exacerbating and in some cases reducing symptoms of comorbid disorders [113–116].

Alpha-2 agonists

The effectiveness of immediate-release CLO was demonstrated in several early randomized clinical trials [117]. An early meta-analysis reported a moderate effect size for the reduction of ADHD symptoms, particularly hyperactivity [118], although not as big as that for stimulants. However, due to a short duration of action and adverse effects such as somnolence and hypotension [119–121], it is relatively infrequently prescribed as a standalone treatment. In some countries, it is used as an add-on treatment with psychostimulants [26–28, 32]. An extended-release formulation of CLO has been approved for ADHD in some countries.

GFC is a more selective alpha 2 agonist with less sedating and cardiovascular effects. An extended-release preparation of GFC was approved by the FDA for the treatment of ADHD in 2010. Seven randomized clinical trials in children and adolescents, support efficacy compared to placebo. Meta-analyses suggest that the effect size is lower than for psychostimulants and comparable to ATX [32, 88, 117]. While one small clinical trial in adults reported a large effect [122], the actual effect size is still uncertain. There is evidence that GFC is useful as an adjunctive treatment to psychostimulants, being more effective than placebo when both are compared as an add-on treatment [123–125].

Antidepressants

The effectiveness of bupropion as a treatment for ADHD has been studied in six clinical trials for children and adolescents and six clinical trials for adults. Results were summarized recently in two systematic reviews both of which concluded that the overall effect is small to moderate and quality of the evidence is poor [126, 127]. Comparative evidence seems to suggest that bupropion efficacy is inferior to that of psychostimulants and probably similar or inferior to that of ATX [128, 129].

Tricyclics, and in particular desipramine, have been studied in six randomized clinical trials for children and adolescents including 216 participants summarized in a Cochrane meta-analysis [130]. There are even fewer studies in adults and no meta-analysis is available [122, 131, 132]. The evidence seems to support the efficacy of these medications in reducing ADHD symptoms. However, tricyclics are usually considered a third or fourth-line option in the treatment of ADHD [26–30], because of the small number of studies and the overall

low quality of evidence, as well as their adverse effect profiles.

Modafinil

Evidence describing the efficacy of modafinil for ADHD symptom reduction is still emerging. The results of five short-term randomized clinical trials in children and adolescents have been summarized in a meta-analysis [133]. Modafinil appeared to have a moderate effect in reducing ADHD symptoms and a dropout rate due to side effects similar to placebo. Prominent adverse effects were insomnia and decreased appetite. Studies on adults are less conclusive with contradictory results [122]. Clinical trials and post-surveillance reports have associated modafinil with serious skin reactions, which led to FDA's request of more data for the approval of the drug for ADHD [134, 135].

New drugs on the ADHD portfolio

Nearly all of drugs in development for ADHD continue to focus on enhancing dopamine and norepinephrine (e.g., HLD200, Dasotraline, Viloxazine, and Mazindol) [136–139]. These drugs are being successfully tested in phase II and III trials and are likely to enter the market soon. However, because of the very similar mechanisms of action, their side effect profile and counter indications are likely to overlap with the drugs already available.

Nevertheless, clinical trials registers and patent applications indicate that novel targets are being considered in preclinical studies. Amiloride is a sodium channel blocker used as an adjunctive treatment for high blood pressure. There is one ongoing clinical trial investigating its role in ADHD [140]. Fasoracetam is a metabotropic glutamate agonist that is approved for stroke and vascular dementia. Phase II and III trials have been completed with adolescents, but no results have been published so far [141]. Metadoxine is a GABA modulator approved for acute alcohol intoxication. It was being tested for ADHD, but it failed phase III trials and the company halted its development [142]. Molindone, an antipsychotic drug that antagonizes dopamine receptors, is being tested as an add-on treatment for aggressive behavior in children and adolescents with ADHD [143]. Vortioxetine is an atypical antidepressant that inhibits the reuptake of serotonin, and is being tested in a phase II trial with adults with ADHD [144]. While these have very different mechanisms of action to current ADHD medications, it should be noted that they are likely to be acting on the same brain circuits but downstream of the dopamine and noradrenaline modulation.

In summary, the field should not expect significant revolutions in drug resources for ADHD in the next few years. Most of the new developments are focused on changing the mechanisms of drug delivery, especially by increasing their half-lives to cover wider intervals of the day.

Nonpharmacological treatments

Behavioral and psychosocial treatments

Behavior parent training and social skills training are the primary recommended alternatives to medication management of ADHD [26–28]. They are usually regarded as first-line treatments for very young children or those with mild to moderate ADHD [26–28]. They are also the standard add-on to medication treatment for severe presentations at any age [26–28]. In summary, most guidelines recommend behavioral interventions for ADHD in any situation, either alone or in combination with medication treatment [26–28] and these are the most frequently used nonpharmacological treatment among children and adolescents [43].

However, the evidence is mixed and complex, making a definitive interpretation difficult. A seminal study was the Multimodal Treatment study for ADHD (MTA) [145]. In this 14-month randomized clinical trial, children were randomized to receive MPH plus behavioral treatment (a combination of previously suggested strategies of parent-training, child-focused, and school-based behavioral therapies), medication only, behavioral treatment only, or referred to usual care within a community setting. The authors and others have noted [146] that there was no statistical difference between combined treatment and medication alone at the end of the treatment-by-protocol (primary analyses). This led to the conclusion that intensive behavioral treatment did not add to the efficacy of well-managed treatment with medication.

Subsequent to the MTA, additional studies have provided evidence of efficiency for behavioral treatments. For example, (a) Charach and colleagues reviewed the efficacy of behavioral and pharmacological treatment for preschool children with ADHD [95]. For this age group, the evidence for benefits of behavioral treatment was strong, but the evidence for pharmacological treatment was not, and (b) sequencing of behavioral and pharmacological treatment revealed that starting with behavioral treatment and adding medication resulted in better outcome (at a lower dose) than starting with medication and adding behavioral treatment [147].

Current appraisals of the available evidence do not agree on whether the balance of evidence supports or refutes the efficacy of psychosocial treatments for ADHD. One meta-analysis concluded that behavioral treatments were highly effective for ADHD [148], and a review for the Agency for Health Care Research and Quality concluded that the

evidence for positive effects of behavioral treatment on preschool children was strong enough to guide clinical practice [95]. However, a Cochrane systematic review and meta-analysis of randomized trials concluded that while BPT may have a positive effect on the behavior of children and adolescents with ADHD, the evidence is not strong enough to guide clinical practice [41]. A separate Cochrane meta-analysis concluded that the evidence was insufficient to support social skills training for adolescents [42]. Several clinical guidelines have recommended both BPT and social skills as behavioral treatments [26–28]. Some of these discrepancies may be explained by the type of rater considered by reviews. Two recent meta-analyses identified a moderate and statistically significant pooled effect size for behavioral therapies on ADHD symptoms when all probably unblinded raters were included but that this effect was not maintained when considering only probably blinded raters [36, 149]. The same group did however confirm that behavioral therapies were effective in improving positive parenting and conduct problems of children with ADHD, even on blinded ratings.

The evidence for psychological therapies in adults is also conflicting. A carefully conducted randomized clinical trial compared the effect of adding a highly structured cognitive behavioral therapy (CBT) or relaxation with educational support to standard medication treatment. The main finding was a greater improvement in ADHD symptoms in the CBT group [150]. Another important study compared group CBT with individual clinical management either in combination with MPH or placebo, finding no difference in core symptom reduction but better outcomes in the Clinical Global Impression Scale [151]. Meta-analyses conclude that the overall effect of cognitive-behavioral therapies is small to moderate compared to active control groups for adults with ADHD [152, 153].

In summary, the evidence for behavioral interventions is difficult to integrate and summarize. Several different protocols are available and it is likely that not all patients are suitable for receiving each of the behavioral interventions. This may explain some of the controversial findings in the literature. Meanwhile, behavioral interventions are supposedly free from adverse effects and are strongly preferred over medication by some patients and caregivers [154–156]. Considering the evidence from blinded studies, we conclude that we need more high-quality studies before we can support the effectiveness of behavioral interventions on core ADHD symptoms. For now, well-controlled studies suggest that they are effective at improving parenting, parent–child relationships and oppositional behaviors that are common in children with ADHD and their families. Positive effects are more likely to be seen in favorable clinical settings where patient and/or caregiver are willing to engage in therapy, and a suitable protocol is readily available. Also, the combination of behavioral intervention with medication may result in a clinical dose that is lower than for treatment with medication alone. However, more studies are needed to unequivocally prove or refute the effectiveness of behavioral interventions in either reducing symptoms or improve the overall functioning of patients with ADHD.

Cognitive training

Cognitive training strategies aim to reduce ADHD symptoms by improving performance in specific neuropsychological functions associated with ADHD (e.g., attention, inhibitory control, and working memory) [31, 157]. Cognitive training programs are usually delivered through electronic interfaces such as computers or mobile phones, and are designed to be appealing to the user (i.e., resembling videogames). Performance is continually reassessed so that training is adaptive [158–160].

A recent meta-analysis evaluated the effects, across 16 randomized clinical trials, for probably blinded and potentially unblinded raters separately [35]. The conclusions match those of previous meta-analyses [40, 149], indicating moderate efficacy in improving the neuropsychological functions targeted by the intervention but a less clear effect on symptoms. The effect size for total ADHD symptoms and inattentive symptoms was moderate and significant when rated by a potentially un-blinded rater. The estimates decreased when outcomes were rated by a probably blinded rater. Of note, the effect size was much larger for programs that included multiple process training (i.e., targeting more than one executive functioning) compared to those that focused on just on cognitive process. However, for the multiple process studies only potentially unblinded ratings were available. In summary, evidence so far available suggests that cognitive training has no effect on core ADHD symptoms or other functional outcomes for ADHD patients.

Neurofeedback

In neurofeedback, the patient is trained to improve self-control over brain activity patterns, which is most often monitored through simultaneously collected electroencephalogram (EEG) data [161, 162]. Its use in ADHD stems from the knowledge that patients with ADHD exhibit distinct EEG patterns compared to their non-affected peers [163, 164]. Current neurofeedback protocols focus predominantly on decreasing *theta* waves (low-frequency waves related to decreased vigilance) and/or increasing *beta* waves (high-frequency waves related to concentration and neuronal excitability). This is achieved by measuring EEG activity while the patient is engaged in a task, often a simple computer game, and modulates performance and reward according to specific changes in EEG pattern. It is estimated

that in the US around 10% of children and adolescents with ADHD have received neurofeedback interventions [43].

While preliminary evidence from open-label trials suggested moderate to large effect for ADHD symptoms [165, 166], the latest meta-analyses concluded that the effects are moderate to large when proximal, potentially unblinded, raters were considered, but reduced by half and lost statistical significance when pooling estimates from probably blinded raters [34, 149]. However, the aggregated measures included both trials with standard and non-standard protocols. An exploratory analysis revealed that, considering only three trials with both probably blinded raters and a standard protocol, the effect was moderate and significant, albeit with a large confidence interval.

Although neurofeedback may have few adverse effects, it is a specialized intervention which usually requires 20–40 sessions, and as a consequence it is often expensive for the end user. Future research may identify more effective methods for using neurofeedback in ADHD. For instance, new protocols are using simultaneous functional magnetic resonance imaging as the therapy target of the intervention (i.e., the parameter that patients are induced to improve) [167, 168]. On the other hand, feasibility also requires less expensive and complex equipment requirements. The evidence available indicates that neurofeedback is not effective for core ADHD symptoms and more high-quality studies should be performed before we can support the effectiveness of neurofeedback on core ADHD symptoms. Future trials should focus on standard protocols and effectively blinded raters.

Dietary modifications

The hypothesis that dietary factors might play a role in the etiology of ADHD was first proposed over 40 years ago, and it remains a controversial topic until the present day. The main restrictive strategies are to remove artificial food colors (AFC) from diet continuously or to restrict several foods in a rapid course of 9–28 days—the "few foods approach" (FFD). Supplementation with poly-unsaturated fatty acids (PUFAs) is also a commonly proposed strategy, based on the possible neuroprotective effect of those substances.

The observed effect of dietary modification strategies for ADHD varies considerably depending on methodological aspects, including whether assessments are made by blinded or unblinded raters. A recent systematic reviewed data from 6 out of 14 available meta-analyses on this subject and concluded that the estimated effect size of PUFAs for ADHD is too small to be considered a tangible contribution [169]. The estimated effect of AFC exceeds that of PUFAs, but, while it is not so small to dismiss, neither is it large enough nor secure enough to make conclusive recommendations for implementation. The effect sizes for FFD were medium to large, and authors consider that the results might justify its administration in children with ADHD. However, they also note that the complete implementation of this treatment, which encompasses several courses of intense food restriction to identify the individual ideal scheme, might be unfeasible in many cases. Authors of the trials with the largest effect sizes have not made the protocols for their interventions public and it is therefore not yet possible to implement these outside of the original research setting. An overall appraisal of the evidence seems to suggest that the FFD and AFC diets have significant, although clinically small, effects on ADHD symptoms while having few adverse effects.

Other promising nonpharmacological therapies

New nonpharmacological options and strategies are being developed and tested for ADHD. Coaching programs designed to help an individual cope with the demands of the environment usually focus on improving executive functions such as time management, prioritization, and effort sustainment over time. Initial empirical studies have shown promising results [170, 171], but these trials are small naturalistic studies that need to be confirmed by randomized clinical trials. The Supporting Teens' Autonomy Daily (STAND) program targets adolescents with ADHD and uses motivational interviewing to enhance adherence. A randomized clinical trial showed promising acute and long-term (6 months after treatment ceased) effects on ADHD symptoms, parental stress, and executive functioning skills [172]. Mindfulness is the act of self-regulating attention towards the current moment and the self. Mindful-based therapies are rooted in ancient Buddhist practices, and have recently gained popularity in western cultures to promote general well being and treat psychiatric disorders [173]. Some investigators suggest that mindfulness therapies are especially well suited to address the deficits associated with ADHD, as it involves intensive training of attentional and emotional regulation. A recent systematic suggested that the observed effect is moderate to large for children with ADHD, but the overall quality of the studies is very low [174]. The only randomized clinical trial reported negative results, as did two out of only three trials that had a control group. At the moment, more well-designed studies are needed.

Impact of treatment in real-life outcomes

The extent to which reduction of ADHD symptoms leads to better real-life outcomes is studied. A systematic review of long-term clinical studies suggested that patients with

Table 2 Major clinical aspects implicated in the selection of treatment strategies for ADHD

Aspect	Recommendation	Rationale
Patient's age	–Start with behavioral treatment when possible in preschool children –Prefer pharmacological treatment in adults	–Less evidence supporting safety and efficacy and lower benefit: risk ratio for medication in preschool children –Lower efficacy of nonpharmacological interventions
ADHD severity	–Monotherapy with nonpharmacological treatment for mild disorder –Combination treatment for severe disorder	–Expected efficacy of treatment lies within a continuum: nonpharmacological < non-stimulants < stimulants < combination therapy
Comorbidities	–Tic disorders: non-stimulants might be an option in cases where methylphenidate increases tics –Disruptive disorders: prefer stimulants –Substance use disorders: non-stimulants might be an option –Mood and psychotic disorders: prioritize comorbidity treatment	–Psychostimulants might exacerbate symptoms of tic disorders in some cases –Psychostimulants reduce ODD/CD symptoms with large effect sizes –Theoretical potential for abuse of this class of medication –Comorbid conditions may cause or exacerbate ADHD symptoms; their core features are not likely treated with ADHD medication

ADHD who received treatment (by any modality) had better long-term outcomes than their non-treated counterparts across most studied domains, and the effect was higher for combined pharmacological and nonpharmacological treatment than for either of those alone [175]. Evidence from randomized clinical trials supports the conclusion that treatment for ADHD improves the quality of life of patients [176–179].

Medical registries from large-scale observational studies have been used to investigate outcomes within the same individuals by comparing periods on and off medication. Those studies showed that medication periods were associated with improved performance on higher education test exams [180], reduced vehicle motor crashes [181], reduced criminality [21], reduced emergency room admission related to substance abuse [23], and reduced risk of trauma and brain injuries [182–184]. Some limitations of these studies need to be highlighted. The within-subject design controls for between-subject and time-independent within-subject factors but not for time-dependent factors that might influence on patient's decision to start or stop medication. Furthermore, the nature of this design (based on frequent starting and stopping of medication) evaluates effects over short periods of time, limiting the evaluation of long-term effects of medication.

In line with this reasoning, prospective follow-up studies of childhood-onset ADHD have documented clear beneficial effects of starting medication, but have not detected long-term benefits in adulthood associated with typical long-term patterns of treatment (either residual effects of inconsistent treatment associated with stopping medication in childhood or adolescence or consistent treatment into adulthood that occurs in less than 10% of the cases) [185–187]. An important complicating factor might be the age-related decrease in symptom-severity and remission of ADHD in many affected children, which is associated with improved real-life outcomes, regardless of treatment.

Overall, the evidence suggests that treating ADHD can improve several important functional outcomes. Likewise, cost-effectiveness studies consistently show that treatment benefits significantly outweigh its costs [188–190]. The critical question for clinicians is how to prioritize among available treatments for individual patients.

Selection of treatment

Among the available efficacious treatments for ADHD, the main differences relate to modality (i.e., pharmacological and nonpharmacological), age of the patient, financial cost, patient and caregiver time demand, expected effectiveness on symptom reduction, adverse effects, safety, and tolerability. Selection should be a shared decision-making process with input from the clinician and the patient and their caregivers. To engage in this process, patients and their families need to be adequately and accurately informed about the evidence and the choices [191]. The first major decision will be to consider whether pharmacological and/or non-pharmacological interventions will be used, and if both how they will be sequenced.

The clinician input

The clinician's input is a technical appraisal of the patient's characteristics that takes evidence into account to favor some treatment options above others. Major considerations include: (1) age of the patient; (2) severity of the disorder; and (3) comorbidities (Table 2).

Age is a major factor in the recommendations of ADHD clinical guidelines. For instance, most guidelines do not usually recommend pharmacological therapy for preschool children (under age 6 years) [26–28]. Although this partially relates to the fact that these medications are generally not licensed for use in those under 6 years of age, it is also true

that the efficacy and safety of medication treatments is much less studied in this age range [192]. When studied, the benefits are smaller and the side effects are greater than in older children [193]. Behavioral therapy has more evidence of efficacy than medication for preschoolers [95]. Furthermore, the targets of treatment may be different since the academic demands are less for preschool than school-aged children. With increasing patient's age, there will be a tendency to favor medication due to increased evidence for efficacy and safety and as increasing academic and social demands are less likely to be met with nonpharmacological interventions alone. For school-aged children, pharmacological treatment is usually the first choice. Likewise, the technical appraisal of evidence is balanced towards pharmacological treatment for adult patients, as effectiveness is less clear for nonpharmacological interventions [194]. In adulthood, findings on the effectiveness of combined treatments (i.e., CBT interventions + stimulants) [150, 151] are more controversial.

The severity is another important clinical consideration. As addressed here and elsewhere [32, 88, 107], the effectiveness of ADHD treatments are on a continuum beginning with nonpharmacological treatment showing small to moderate effect sizes; non-stimulant pharmacological treatment with moderate to large effect sizes; and stimulant treatment with large to very large effect sizes. Combined treatments (medication plus CBT or stimulant plus non-stimulant) has often been assumed to be the most effective strategy, although the evidence supporting superiority to psychostimulants alone remains controversial. We recommend that severity should be matched with the expected effectiveness of the treatment: (a) for low severity, non-pharmacological interventions; (b) for moderate severity, pharmacological interventions; and (c) for high severity, combined intervention.

Simple and uncomplicated ADHD is not common. In most cases, ADHD co-occurs with other psychiatric and developmental disorders, and these comorbidities also have implications for the treatment required (see Table 2). For example, oppositional defiant disorder and conduct disorder are the most common co-occurring disorders, and only pharmacological treatment has been shown to reduce these comorbid symptoms with large effect sizes [39]. Tics or tic disorders also co-occur with ADHD, and although psychostimulants might not exacerbate these comorbid symptoms in general [195], tic worsening might occur in some patients [196]. Co-occurrence with substance use disorders (SUDs) is also common in adolescence and adulthood. In patients who have both ADHD and SUDs [197], the evidence suggests that psychostimulants are effective in reducing ADHD symptoms, but not in improving substance abstinence. Also, many clinicians are apprehensive to prescribe these medications for these comorbid cases because of their potential for abuse, although available evidence does not fully support this view [198]. Thus, non-stimulants like ATX and the alpha 2 agonists, which have a much lower liability of abuse than the stimulants, or non-pharmacological treatment might be preferred for treatment of some ADHD patients with comorbid SUDs [199]. If stimulants are recommended, MPH and extended-release formulations (which may have less abuse potential) should be preferred over AMP derivatives and immediate-release formulations [200]. It was usually believed that ATX was the preferred option when ADHD was comorbid with anxiety disorders, due to its positive effect in anxiety symptoms, while psychostimulants might have a negative effect [115, 201]. Particular co-occurring disorders might cause or exacerbate ADHD symptoms while being hierarchically prioritized in the treatment decision. These include mood disorders such as depression and bipolar disorder, and psychotic disorders in the schizophrenia spectrum. Even if the clinician judges that the criterion E of the DSM is met (i.e., symptoms are not explained by the co-occurring disorder), we recommend prioritizing treatment of the comorbid disorder. The clinical assessment of ADHD to select treatment should focus on symptoms that remain after stabilization of a major mood or psychotic disorder.

The patient/caregiver input

The patient/caregiver input involves an analysis of personal aspects that, considering the clinician's recommendations, will give more or less weight to a given set of suggested treatment options. This is highly variable and depends on complex sociocultural aspects and their interactions. The most important aspects are: (1) preferences around treatment modality; (2) expectations of efficacy; (3) feasibility considering financial and time demands; and (4) age of the patient.

Among the most important individual aspect to consider is the acceptance of the proposed treatment by the patient/caregiver. Studies suggest that the likelihood of preferring medication treatment as a first-line approach for ADHD is somewhat idiosyncratic but highly dependent on social and cultural characteristics [154, 155]. For instance, parents with higher education more frequently conceptualize ADHD as a biomedical illness, which in turn increases their likelihood of accepting medication [185, 202]. However, these preconceived conceptualizations should not be considered a closed topic and an adequate understanding of the disorder by patients and parents should be one of the goals of the therapeutic process. Furthermore, discrepancies between child and parent preferences are common. A trial on medication is usually sought by the parent, and children are frequently reluctant to or refuse to take medication due to complex factors such as social stigma, side effects, or

Table 3 Factors implied in the selection of the first medication treatment for ADHD

Factor	Evidence	Recommendation
Effectiveness	Stimulants are the most effective class	Prefer stimulants for moderate to severe cases
Adverse effects	Non-stimulants (especially ATX and GFC) have different profile of adverse effects	Prefer non-stimulants in case of intolerance to stimulants or when specific adverse effects are a special concern
Duration of action	Extended-release formulations of stimulants last for around 12 h; ATX and extended-release GFC last for the entire day	Prefer these when the effect is desired for more than one segment of the day
Abuse potential	Stimulants have theoretical abuse liability	Non-stimulants might be an option when abuse is a relevant concern
Time to onset of effect	Stimulants have immediate onset/offset of action	Prefer stimulants when immediate onset/predicted offset is needed
Patient and parental preferences	Patients and parents might have personal opinions on existing options	Consider patient and parent preferences, provide evidence-based information

simply not appreciating the benefits of treatment [203, 204]. In those cases, particular characteristics of the family such as the extent of autonomy that parents give to the child play an important role in treatment choice. In summary, patient and caregivers usually exhibit preconceived treatment preferences closely related to their sociocultural context.

They also have different expectations about treatment effectiveness. These expectations should be carefully assessed by the clinician, as they should be matched with actual treatment efficacy/safety. Unrealistic expectations should be discussed and patients properly informed. A young adult attending college with severe ADHD causing failure to thrive academically probably expects more from the treatment than another young adult with less attentional demand and a milder disorder. The former would have his/her expectations frustrated by treatments with small to moderate effect sizes; the latter may not find the benefit to risk and cost ratios of the most effective treatments favorable. Accordingly, the degree of symptom control was the most important factor taken into account by parents who selected stimulant treatment in a study of six European countries [155].

Finally, the gap between the ideal world and clinical practice also impacts the final decision on treatment selection for ADHD. Effective nonpharmacological strategies such as behavioral therapies, neurofeedback, or cognitive training are more expensive, time-consuming, and less available outside central urban areas of developed countries than pharmacological alternatives. There are also differences in the cost of medications that need to be considered in countries where patients pay with out of the pocket money.

Selection of the first medication

Many cases that present to clinical practice will require and ADHD medication. Several factors need to be considered for the selection of the first medication, mainly to decide between stimulants versus non-stimulants. These are summarized in Table 3.

Monitoring, follow up, and continued care

There is evidence that monitoring patient improvement through the use of rating symptom scales in each visit increases positive clinical outcomes and chance of remission in Psychiatry [205]. There is also now emerging evidence that implementing a carefully constructed medication protocol with a routine measure of standardized outcomes can result in significant improvements in clinical outcomes and that these can be sustained over long periods of time [206]. We recommend assessing the intensity of ADHD

symptoms before and after treatment at each appointment using validated rating scales [207, 208] and adjusting treatment in order to optimize outcomes (see the MTA medication algorithm [209] and the Dundee ADHD Clinical Care Pathway protocol [206] for possible strategies). Alongside symptom monitoring, clinicians should also assess real-life measurable parameters of functional benefits accompanying from symptom control. They need to combine their subjective impressions with such objective measures to guide dosage adjustments, treatment switch, or add-on therapy. Likewise, adverse effects should be actively asked about in a "review of systems" manner and in the physical exam, focusing on the most likely adverse effects of each medication. After stabilization of symptoms, clinicians should reassess treatment response and adherence, vital signs and adverse effects at least once a year [26].

The question "how long should a patient be treated?" is an incompletely answered question. ADHD is regarded as a chronic disorder: in long-term clinical follow-up studies (i.e., 6 years or more), about 50% of the child-onset cases are reported to have persisting ADHD impairing symptoms [210, 211]. Adverse outcomes also continue to occur more frequently in those with ADHD for many years after the initial diagnosis, even for those who symptoms remit [212]. Although some meta-analyses suggest that treatment improves the majority of long-term ADHD outcomes and combined treatment seems to be associated with larger effects sizes for these improvements [175], long-term benefits of ADHD treatment is yet a controversial area. After treatment cessation, the associated benefits tend to reduce until they are no longer discernable.

This suggests that in routine clinical practice patients and caregivers should be informed about the heterogeneous course of ADHD symptoms throughout life, and that desistance is seen in many childhood-onset cases. Several childhood factors increase the risk of long-term syndrome persistence. These include increased ADHD severity and comorbidity with disruptive disorders and major depression [213]. Also, self-selection will result in stopping medication in many cases from whom ADHD is recognized and treatment is initiated in childhood. In some cases, shared treatment decisions will result in carefully medication tapering (or to reduce the intensity of non-pharmacological treatments gradually) over time as an individual matures. This may be used to evaluate syndrome remission, preferably in a period of stable relatively lower demands from the environment. Alternatively, in some cases, the symptoms may emerge when some individuals encounter higher demands in adolescence or adulthood [214], and previously treated cases may require re-starting medication (or previous unrecognized and untreated cases may require a trial on medication).

Conclusions

Patients with ADHD benefit from a wide variety of available efficacious treatments that target and alleviate the disorder symptoms, impairment, and poor functioning. They encompass different classes of medication, several protocols of therapy, computerized training, dietary modification, and their combinations. New strategies, such as coaching and mindfulness, are being developed and tested. Facing this wealth of options, the clinician may find it hard to hierarchize treatments in an effective, evidence-based manner.

We conclude that all ADHD medications, while differing in their synaptic mechanisms, eventually act on broader neuro-cognitive networks in the short-term. Psychostimulants are highly effective, when compared to other psychiatric medications. Non-stimulants while less effective options should be considered in special situations. Psychosocial interventions are especially useful for very young children or mild disorders, or as an add-on treatment to medication to improve efficacy or reduce required dosage. Treatment selection should rely on a shared decision-making process between the clinician and his or her patient. The main aspects to be considered by the clinician are age of the patient, severity of the disorder, and comorbidities. Patients should be routinely followed to assess response to treatment and adverse events, as well as disorder persistence or remission.

Compliance with ethical standards

Conflict of interest Dr. Caye declares no conflicts of interest. Prof. Coghill reports grants from The European Union FP7 Programme and Shire; honoraria from Shire, Eli-Lilly, Novartis, and Janssen-Cilag; acted as an advisor to Shire and Lundbeck; and received royalties from Oxford University Press. Prof. Coghill was a member of British Association for Psychopharmacology ADHD, Depression and Bipolar Disorder Guideline groups. Prof. Swanson was a member of the advisory board and/or acted as a consultant for Medice and NLS Pharma in 2017. Prof. Rohde has been a member of the speakers' bureau/advisory board and/or acted as a consultant for Eli-Lilly, Janssen-Cilag, Medice, Novartis, and Shire in the last 3 years. He receives authorship royalties from Oxford Press and ArtMed. The ADHD and Juvenile Bipolar Disorder Outpatient Programs chaired by him received unrestricted educational and research support from the following pharmaceutical companies in the last 3 years: Eli-Lilly, Janssen-Cilag, Novartis, and Shire. He also received travel awards from Novartis and Shire to attend the 2015 WFADHD and the 2016 AACAP meetings.

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