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THERAPY IN PRACTICE

A Practical, Evidence-informed Approach to Managing Stimulant-Refractory Attention Deficit Hyperactivity Disorder (ADHD)

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Abstract

Stimulants (methylphenidate or amphetamines) are the recommended first-line option for the pharmacological treatment of individuals with attention deficit hyperactivity disorder (ADHD). However, some patients with ADHD will not respond optimally to stimulants. Here, we discuss strategies to manage stimulant-refractory ADHD, based on the recommendations advanced in clinical guidelines, knowledge of expert practice in the field, and our own clinical recommendations, informed by a comprehensive literature search in PubMed, PsycInfo, EMBASE + EMBASE classic, OVID Medline, and Web of Science (up to 30 March 2021). We first highlight the importance of stimulant optimization as an effective strategy to increase response. We then discuss a series of factors that should be considered before using alternative pharmacological strategies for ADHD, including poor adherence, time action properties of stimulants (and wearing-off of effects), poor tolerability (that prevents the use of higher, more effective doses), excessive focus on or confounding from presence of comorbid non-ADHD symptoms, and tolerance. Finally, we consider the role of non-stimulants and combined pharmacological approaches. While the choice of medication for ADHD is still to a large extent based on a trial-and-error process, there are reasonably accepted data and guidelines to aid in clinical decision-making. It is hoped that advances in precision psychiatry in the years ahead will further guide prescribers to tailor medication choice to the specific characteristics of the patient.

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1 Introduction

Pharmacological interventions are an important component of the multimodal treatment plan for attention deficit hyperactivity disorder (ADHD), both in children/adolescents and adults. Medications for ADHD include stimulant (i.e. methylphenidate and amphetamines) and non-stimulant compounds. Stimulants are generally recommended as first-line pharmacological options for ADHD [1]. However, a subgroup of individuals with ADHD do not respond or cannot tolerate stimulant medications. An early comparative review of six cross-over trials concluded that ~ 41% of children treated with immediate-release stimulants responded equally well to amphetamines or methylphenidate, 28% responded better to amphetamines, 16% had a better response to methylphenidate, with 15% not responding to either medication [2], though adequacy and/or comparability of dosing may have contributed to the findings. A more recent review concluded that ~ 91% of those with ADHD respond to either or both class of stimulants [3]. This figure is in line with the results of a single-subject analysis of a cross-over trial in

Key Points

Most patients with attention deficit hyperactivity disorder (ADHD) will respond to properly optimized stimulants.

In patients who appear to have not responded, before switching to non-stimulants or combinations of stimulants and non-stimulants, several clinical factors should be considered; these include poor adherence to current treatment, pharmacokinetic and pharmacodynamic properties of stimulants (and wearing-off of effects), whether adverse effects prevent the use of higher, more effective doses, excessive focus on or confounding from comorbid non-ADHD symptoms and conditions, and the possibility of tolerance.

Currently, it is not possible to predict the response to ADHD medications.

36 children with ADHD, showing that 19 children (53%) responded to both stimulant classes, while 14 children (39%) responded to only one type of stimulant, with cases equally distributed between methylphenidate and dextroamphetamine. The response rate increased to 92% after both stimulants had been tried sequentially in each child. No response to either stimulant was found in 8% of these children [4]. Evidence does not support the notion that specific core symptoms of ADHD (i.e. inattention, hyperactivity, and impulsivity) respond (or do not respond) differently to the different stimulant classes and formulations. For instance, a double-blind crossover trial of methylphenidate did not provide any support for differential response according to ADHD subtype (now termed presentation) [5]. However, there is evidence that the efficacy of ADHD medications is generally higher for core compared to non-core ADHD symptoms (such as emotional dysregulation). While stimulants are in general highly effective in decreasing the severity of ADHD core symptoms, efficacy on frequently associated symptoms such as aggressiveness and irritability tends to be lower. A meta-analysis of six randomized controlled trials (RCTs) of stimulants found a standardized mean difference (SMD) of 0.98 (95% confidence interval [CI] 0.44–1.51) on ADHD core symptoms and an SMD of 0.57 (0.34–0.80) on symptoms of emotional lability in adults with ADHD [6]. Another meta-analysis of RCTs with ADHD medications found an SMD of 0.30 (95% CI 0.18–0.42) for methylphenidate (nine parallel-group RCTs) and an SMD of 0.50 (95% CI 0.21–0.80) for lisdexamfetamine (two parallel-group RCTs) when focusing on emotional dysregulation as an outcome [7]. Therefore, regardless of the exact percentage of individuals with ADHD who do and do not respond to stimulants, practitioners are likely to be faced with patients who are refractory to one or more stimulants when considering the effects on core symptoms, as well as effects on important related symptoms and other associated or comorbid conditions. We note here that, to our knowledge, there is no established, agreed definition of "refractory", so this may refer to failure to remit, minimal improvement, partial response but with persistence of impairments, or no benefit of any sort. The term may also refer to cases where some ADHD core symptoms decrease significantly in terms of intensity and others do not, even though we are not aware of any robust evidence pointing to differential effects of stimulants on inattention, hyperactivity, or impulsivity within the same individual.

The present paper aims to provide evidence-based and expert-informed practical guidance on the management of individuals with ADHD who are refractory to stimulant treatment. We will first provide an overview of the relevant literature; we will then summarize recommendations from current national/international guidelines/guidance documents; finally, we will provide a series of practical recommendations for the management of stimulant-refractory cases. Even though non-pharmacological strategies may offer an important alternative or complementary option in the management of these patients, the current paper focuses on pharmacological strategies only. The interested reader is referred to recent publications on the combination of pharmacological and non-pharmacological strategies, e.g. [8–10].

2 Literature Review

We performed a comprehensive search of the literature to retrieve empirical studies pertinent to the present article. Our reason for doing this was to ground the practical suggestions made here in the available data—highlighting the extent to which clinically based recommendations are supported by research or extend beyond it.

We first discuss evidence on the optimization of stimulants, as before considering second- or third-line options after stimulants, it is crucial to make sure the treatment with stimulants has been properly optimized in terms of dose and coverage throughout the day.

We then provide an overview of the evidence from RCTs on the efficacy, tolerability, and acceptability of non-stimulant agents reported in recent meta-analyses. As, under certain methodological assumptions, network meta-analyses (NMAs) are considered to provide more precise estimates compared to pairwise meta-analyses, we draw mainly on evidence from NMAs, when available. We identified relevant NMAs via a recent meta-review of NMAs in child and adolescent psychiatry [11], which we updated to find any additional NMA

on ADHD medications in children/young people or adults. Among the available NMAs, we selected those based not only on published but also unpublished data, as the inclusion of unpublished data arguably provides more precise estimates of the effects. Ultimately, this led to the inclusion of two NMAs (Cortese et al. [12] and Catalá-López et al. [10]).

Finally, to retrieve evidence specifically on agents used for patients refractory to stimulants, as monotherapy or augmenting/combined agents, we searched PubMed, PsycInfo, EMBASE + EMBASE classic, OVID Medline, Web of Science (Science citation index expanded, Biological abstracts, Biosis, Food science and technology abstracts) up to 30 March 2021 (please see the electronic supplemental material for the search terms). We selected relevant peer-reviewed RCTs, excluding case reports or case series, conference proceedings, editorials, and commentaries. We present in the next subsections evidence from RCTs relevant to the management of patients with ADHD refractory to stimulants, alongside other non-randomized studies of relevance.

2.1 Optimization of Stimulants for Attention Deficit Hyperactivity Disorder (ADHD) Core Symptoms

Coghill and Seth adapted the approach used in the Multimodal Treatment of Attention Deficit Hyperactivity Disorder (MTA) study in terms of optimization of medication dose to a community-based, "real-world" clinic. Their clinical pathway has been fully described previously [13]. Their approach to treatment initiation included an initial structured titration and dose optimization using a measurement-based care approach that assessed ADHD symptoms at each visit through semi-structured interviews. This initial phase of treatment focussed on balancing maximal symptom reduction whilst minimizing adverse effects. Stimulants were the first- and second-line treatments in almost all cases. Dosing was guided by UK licensing and recommendations. In general, if there was no response at the maximum licensed doses for the first stimulant, treatment was switched to the other stimulant class. However, there was no formal maximum dose, and for those patients with a partial response and no significant issues with tolerability, higher doses were prescribed. There was a deliberate effort to make use of the pharmacokinetic and pharmacodynamic properties of the various stimulant formulations to optimize treatment response across the day using the Dundee Difficult Times of Day Scale [13]. They continued to adopt a measurement-based care approach to continuing care with additional, mainly non-pharmacological, treatment added as required for non-core ADHD difficulties. In an observational study of day-to-day clinical practice using their protocol, they were able to report that careful titration of stimulants, which in some patients resulted in using higher doses than before the implementation of the protocol, alongside intensive clinical monitoring with adjustments of the dose as needed, led to an increase in the rate of responders from 44 to 67% [14]. This result is highly relevant as it has been reported that clinicians are often satisfied with *some* degree of improvement in the severity of ADHD symptoms rather than trying to achieve *optimal response* across the day [15]. Pragmatic RCTs are needed to further strengthen the evidence supporting an optimization approach such as the one proposed by Coghill and Seth, and test guidelines for implementation in clinical practice.

Optimization of stimulants is key also to address problems that are associated with ADHD but are not part of the defining core symptoms, in particular, aggressive behaviours [16]. Blader et al. [7] conducted a double-blind RCT assessing the comparative efficacy and tolerability of adjunctive risperidone, sodium valproate, or placebo for aggressive behaviours in children, aged 6–12 years, with ADHD and comorbid oppositional defiant disorder or conduct disorder (CD). Notably, all participants were either receiving ongoing stimulant treatment or had a history of previous stimulant treatment (a minimum daily total dose equivalent of 30 mg of immediate-release methylphenidate for at least 30 days). Upon entry into the study, children had their stimulant re-titrated and, in the case of non-response, had a second titration with the other stimulant class. The following algorithm was used: patients were started on 18 mg/day of methylphenidate Osmotic Release Oral System (OROS), with titration in 18-mg increments until a maximum dose (72 mg/day) was reached; however, clinicians could choose to titrate up to 90 mg/day if this dose was indicated and well tolerated. When adverse effects probably related to the long duration of OROS-methylphenidate occurred, a biphasic methylphenidate preparation, up to 60 mg/day, was used. Mixed amphetamine salts, up to 35 mg/day, were the second-line option when methylphenidate was not efficacious or not well tolerated. Children with aggressive symptoms persisting after this open-label optimization of stimulant medication entered the 8-week randomized phase. Of note, 63.6% of those completing the optimization phase met the study criteria for remission (i.e. 3 consecutive weeks with subthreshold scores on the Retrospective Modified Overt Aggression Scale)—meaning that most children originally thought to be non-responders to stimulant monotherapy achieved full response when the stimulant dose was optimized.

2.2 Alternative Monotherapies for ADHD Core Symptoms

A variety of non-stimulant medications are available for use when stimulants are not tolerated or yield suboptimal response

Table 1 Summary of effect sizes for efficacy, tolerability, and acceptability vs. placebo for medications approved by the FDA as reported in the NMAs by Cortese et al. [12] and Catalá-López et al. [10] (viloxazine, approved by the FDA in April 2021, was not included in these NMAs)

	Cortese et al. [12]	Catalá-López et al. [10]
Atomoxetine		
Children/young people	Efficacy rated by clinicians: **SMD = 0.56 (95% CI 0.45 to 0.66)**[a]	Response: **OR = 3.63 (2.81-4.73)**[a]
	Efficacy rated by teachers: SMD = 0.32 (95% CI −0.18 to 0.32)	Acceptability: OR = 0.85 (0.68 to 1.07)
	Efficacy rated by parents: **SMD = 0.60 (95% CI 0.50 to 0.71)**[a]	
	Tolerability: OR = 1.49 (95% CI 0.84 to 2.64)	
	Acceptability: OR = 0.85 (95% CI 0.61 to 1.18)	
Adults	Efficacy rated by clinicians: **SMD = 0.45 (95% CI 0.32 to 0.58)**[a]	Not applicable (focus on children/young people)
	Efficacy self-rated efficacy: **SMD = 0.37 (95% CI 0.27 to 0.47)**[a]	
	Tolerability: **OR = 2.33 (95% CI 1.28 to 4.25)**[b]	
	Acceptability: OR = 1.28 (95% CI 0.97 to 1.70)	
Clonidine[c]		
Children/young people (no RCTs included in adults)	Efficacy rated by clinicians: **SMD = 0.71 (95% CI 0.24 to 1.17)**[a]	Response: **OR = 3.96 (1.89-8.41)**[a]
	Tolerability: OR = 4.52 (95% CI 0.75 to 27.03)	Acceptability: **OR = 0.40 (0.20-0.78)**[a]
	Acceptability: OR = 0.60 (95% CI 0.26 to 1.37)	
Guanfacine[c]		
Children/young people (no RCTs included in adults)	Efficacy rated by clinicians: **SMD = 0.67 (95% CI 0.50 to 0.85)**[a]	Response: **OR= 3.29 (2.27-4.82)**[a]
	Efficacy rated by teachers: SMD = 0.63 (95% CI −0.35 to 1.62)	Acceptability: OR= 0.79 (0.54–1.14)
	Efficacy rated by parents: SMD: 0.23 (95% CI −0.45 to 0.90)	
	Tolerability: **OR = 2.64 (95% CI 1.20 to 5.81)**[b]	
	Acceptability: OR = 0.81 (95% CI 0.54 to 1.23)	

Significant differences between active medication and placebo are bolded

CI confidence interval, *FDA* Food and Drug Administration, *NMAs* network meta-analyses, *OR* odds ratio, *SMD* standardized mean difference, *RCT* randomized controlled trial

[a]Active medication better than placebo

[b]Active medication worse than placebo

[c]Pooling data for immediate and extended-release formulations

2.2.1 Food and Drug Administration (FDA)-Approved Non-stimulants

Non-stimulants approved by the Food and Drug Administration (FDA) and other regulatory agencies and recommended in current clinical guidelines include atomoxetine, clonidine extended-release (ER), guanfacine ER, and viloxazine (FDA and US only at present). Overall, it can be concluded that the effect sizes for the efficacy of these agents are in a range considered "moderate", and while they are lower than those for stimulants in children, they are comparable to those found for methylphenidate in adults and higher than many other commonly prescribed psychiatric medications [17]. It should also be noted that the body of evidence from RCTs for atomoxetine is larger compared with that for guanfacine and clonidine. For instance, in the analysis of efficacy in children rated by clinicians, Cortese et al. [12] were able to include 21 RCTs of atomoxetine versus placebo compared to six RCTs for guanfacine and only one RCT for clonidine versus placebo. We note also that the overall moderate degree of efficacy includes the full distribution of response, and that response in selected individuals may be more robust; at the same time, there also may be non-responders [18].

The effect sizes for efficacy for different raters (as available), tolerability (defined as drop-outs due to side effects), and acceptability (drop out due to any cause) from the NMAs by Cortese et al. [12] and Catalá-López et al. [10] are summarized in Table 1.

Viloxazine is an unscheduled selective noradrenaline reuptake inhibitor with antagonistic activity at 5-HT_{2B} and agonistic activity at 5-HT_{2C} receptors [19]. It may also upregulate the levels of GABA-B receptors, and it has some affinity for the noradrenaline transporter [20]. Initially approved in the UK and other European countries as an antidepressant, viloxazine has been reformulated as an XR preparation and repurposed for use in ADHD and has been recently approved by the FDA (April 2021). Effect sizes for efficacy are in the moderate range (e.g. 0.55–0.62 in a phase 2 study in children 6–12 years old) [21]. These results were substantially replicated in subsequent phase 3 studies [22], albeit the efficacy of the highest dose (400 mg) was not significantly different from that of placebo [23]. Significantly higher efficacy compared to placebo was noted by 2 weeks, and response at 2 weeks was found to predict end-of-treatment outcome at 6 weeks [24].

2.2.2 Non-FDA-Approved Agents

2.2.2.1 Tricyclic Antidepressants Historically, noradrenergic tricyclic antidepressants have constituted the major non-stimulant alternative for the treatment of ADHD. Evidence on tricyclic antidepressants has been summarized in a Cochrane systematic review/meta-analysis of six RCTs [25], five of which included the comparison between desipramine and placebo, and one focused on nortriptyline versus placebo. When considering treatment response expressed as the proportion of participants achieving a predefined improvement in the severity of ADHD core symptoms, tricyclic antidepressants were significantly better than placebo (odds ratio [OR] 18.50, 95% CI 6.29–54.39, three RCTs). As for the effects on ADHD core symptoms severity measured with continuous outcome, desipramine was significantly better than placebo, with large mean effect sizes—but also large CIs—according to ratings by parents (SMD −1.42, 95% CI −1.99 to −0.85, two RCTs) and teachers (SMD −0.97, 95% CI −1.66 to −0.28, two RCTs). While tricyclic antidepressants are mentioned in the Canadian ADHD Resource Alliance (CADDRA) guidelines (see above), they are not recommended in other guidelines (e.g. see Table 1), likely due to concerns regarding cardiovascular effects.

2.2.2.2 Bupropion Bupropion is an approved antidepressant that is also an alternative non-FDA-approved non-stimulant option for ADHD. There are multi-site studies in both children [26] and adults [27] with ADHD; therefore, there is a reasonably supportive evidence base. In the Cortese et al. [12] NMA, a high effect size was reported for efficacy rated by clinicians (SMD 0.96, 95% CI 0.22–1.69), but there was a large 95% CI due to the fact that only one RCT was included. Effects sizes for efficacy rated by teachers and parents were smaller and non-significant (SMD −0.32, 95% CI −1.07 to 0.43, and SMD 0.24, 95% CI −0.44 to 0.92, respectively). No significant differences, compared to placebo, were found for tolerability (OR 1.51, 95% CI 0.17–13.27) and acceptability (OR 0.89, 95% CI 0.21–3.74). In the Catalá-López et al. NMA [10], efficacy (treatment response: OR 2.41, 95% CI 0.48–11.63) and acceptability (OR 1.54, 95% CI 0.39–7.76) results were not significantly different to those reported for comparison to placebo. The large CIs reflect the poor precision of the estimate due to the inclusion of a limited number of small studies (three RCTs in total) and the variability in outcome between these trials.

2.2.2.3 Modafinil Modafinil is a wake-promoting agent licensed in many countries for the treatment of narcolepsy and as an adjunctive treatment for obstructive sleep apnoea/hypopnoea syndrome. Modafinil is considered to be an atypical stimulant with lower potential for abuse (Schedule IV controlled substances according to the US FDA; in contrast, methylphenidate and the amphetamines are Schedule II). In addition to this agent's approved use treating excessive somnolence, a recent systematic review [28] concluded that modafinil appears to consistently improve attention, executive functions, and learning, and may act as a cognitive enhancer in healthy, non-sleep- deprived adults. A clinical development programme investigating the efficacy

and tolerability of a long-acting preparation of modafinil reported positive effects on ADHD symptoms [29]. However, the formulation was not approved by the FDA due to concerns over a possible association with an increased risk for Stevens-Johnson syndrome in the child and adolescent study [30], whilst an RCT in adults failed to differentiate modafinil from placebo [31]. Further investigation is therefore required to determine whether modafinil is a safe and effective treatment for ADHD.

2.2.2.4 Other Non-approved Medications A variety of other medications—including other selective norepinephrine reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and buspirone, among others—have been used to treat ADHD, mainly owing to their known effects on norepinephrine, dopamine, or serotonin. The evidence base for these medications is, however, meagre, and there are few if any systematic controlled studies.

2.2.2.5 Investigational Compounds Several novel non-stimulant compounds have been trialled in RCTs over the last decade. Nageye and Cortese [32] systematically reviewed RCTs of investigational drugs registered in ClinicalTrials.gov in the period between 1 January 2014 and 24 May 2019, supplemented by searches in PubMed, Web of Science, and drug manufacturers websites to find evidence on novel (or repurposed) non-stimulant ADHD medications. With the exception viloxazine, none of the compounds identified in this review have been so far approved by the FDA.

2.3 Combination Pharmacological Treatments for ADHD Core Symptoms

Table 2 summarizes the findings from RCTs including a comparison of stimulants versus stimulants + adjunctive compounds in individuals with ADHD. While the atomoxetine [33], guanfacine XR [34], and clonidine XR studies [35] focussed specifically on participants for whom there was an insufficient response to stimulants, this was not a requirement for the other included RCTs.

2.3.1 Atomoxetine

We did not find any RCT comparing stimulants + placebo versus stimulants + atomoxetine; however, we identified one small RCT ($n = 25$) [33] in which children with ADHD with an insufficient response to a stimulant trial were initially switched to atomoxetine + placebo for 4 weeks. Responders were continued on atomoxetine + placebo. Non-responders were randomized to atomoxetine + methylphenidate or atomoxetine + placebo for 6 weeks. After 1 week of combined treatment, scores of ADHD core symptoms (ADHD Rating Scale-IV [ADHD-RS-IV]-Parent: Inv total) were significantly lower in the atomoxetine + stimulants arm compared to the atomoxetine + placebo arm; however, no significant differences between the two groups were found at week 10. No statistically significant differences within patients or between groups in changes in blood pressure or pulse rate were reported.

2.3.2 Guanfacine Extended-Release

In some countries (e.g. the USA and Australia), guanfacine XR is approved both as monotherapy and as an adjunct treatment to stimulants. One large RCT ($n = 461$) in children/adolescents showed the superiority of guanfacine XR added to stimulants over stimulants alone in decreasing ADHD symptoms severity [34]. In another smaller RCT in children/adolescents [36], d-methylphenidate ER added to guanfacine immediate-release was better than guanfacine alone, but not better than d-methylphenidate ER, in reducing ADHD core symptoms severity ($n = 207$) and improving working memory ($n = 182$) [37]. Of note, discontinuation at any time due to treatment-emergent adverse events was not significantly different across study arms (1.5% for guanfacine, 1.5% for d-methylphenidate, and 2.9% for the combined treatment). Another interesting finding from this study was that during acute titration, guanfacine immediate-release decreased heart rate, as well as systolic and diastolic blood pressures, while d-methylphenidate ER increased heart rate as well as systolic and diastolic blood pressures. Combined treatment increased diastolic blood pressure, but had no effects on heart rate or systolic blood pressure. During maintenance, guanfacine immediate-release-associated decreases in heart rate and d-methylphenidate-ER-associated increases in systolic blood pressure returned to baseline values [38].

2.3.3 Clonidine

Similarly to guanfacine, we found one RCT ($n = 198$) in children/adolescents showing that clonidine XR added to stimulants was superior to stimulants + placebo in decreasing the severity of ADHD core symptoms [39] and another smaller RCT ($n = 67$) of clonidine immediate-release in children/adolescents [35] showing no benefit on ADHD core symptoms but significant effects on conduct symptoms (see below) in adding clonidine immediate-release to stimulants, even though clonidine dose was not optimized. Of note, these trials showed an overall good tolerability of the combination stimulants + clonidine, and no major issues in terms of safety, contrary to early concerns [40].

2.3.4 Bupropion

We found no evidence in the literature to support combined use of bupropion with stimulants. However, we mention it

Table 2 RCTs including a comparison of stimulants vs. a combination of stimulants and another compound for ADHD core symptoms

Compound	Registration ID (reference)	*N* randomized	Age (years)	Arm (dose)	Duration (weeks)	Key findings (efficacy)
Guan	NCT00429273 [36]	207	7–14	Guan (1–3 mg/day) DMPH XR (5–20 mg/day)	8	Participants treated with COMB had significantly greater reductions in ADHD symptoms severity (ADHD-RS-IV total score) compared to those treated with Guan ($P = 0.049$), but not vs. those treated with DMPH. Considering ADHD-RS-IV Inattentive subscale scores, COMB was superior to Guan ($P = 0.02$) as it showed a trend of greater improvement vs. DMPH ($P = 0.05$) COMB was superior to Guan, but not to DMPH, on measures of working memory
Guan-XR	NCT00734578 [34]	461	6–17	Stimulant + Guan-XR a.m. (average: 3.3 ± 1 mg/day) Stimulant + Guan-XR p.m. (average: 3.2 ± 1 mg/day) Stimulant + placebo	9	At endpoint, Guan-XR showed significantly greater improvement in ADHD core symptoms severity (ADHD-RS-IV total scores) in the two Guan-XR arms compared to stimulants + placebo. Both Guan-XR arms showed greater improvement in the morning (Guan-XR a.m. $P = 0.019$; Guan-XR p.m. $P < 0.001$) and evening symptoms (Guan-XR a.m. $P = 0.002$; Guan-XR p.m. $P < 0.001$) of ADHD
Clon	Not provided [35]	67	6–14	Stimulants + Clon (0.1–0.2 mg/day) Stimulants + placebo	6	35% in the stimulants + Clon arm and 17% in the placebo arm met criteria for improvement on the Hyperactive Index of the Conners' Parent Report checklist (not significant difference)
Clon-XR	NCT00641329 [39]	198	6–17	Stimulants + Clon-XR Stimulants + placebo	5	Participants treated with stimulants + Clon-XR had significantly greater reductions in ADHD symptoms severity ADHD-RS-IV total score ($P = 0.009$), ADHD-RS-IV hyperactivity and inattention subscale scores ($P = 0.014$ and $P = 0.017$, respectively), Conners' Parent Rating Scale scores ($P = 0.062$), Clinical Global Impression of Severity ($P = 0.021$), Clinical Global Impression of Improvement ($P = 0.006$), and Parent Global Assessment ($P = 0.001$) compared to those treated with stimulants + placebo
l-Carnosine	Not provided [56]	56	6–17	MPH + l-carnosine MPH + placebo	8	Significantly higher reduction of ADHD core symptoms severity in the MPH + l-carnosine vs. MPH + placebo arm according to parents' but not teachers' ratings

Table 2 (continued)

Compound	Registration ID (reference)	*N* randomized	Age (years)	Arm (dose)	Duration (weeks)	Key findings (efficacy)
ALC	NCT01099072 [57]	40	7–13	ALC (500–1500 mg/day) + MPH MPH + placebo	6	No significant differences between the two arms on ADHD core symptoms [Parent and Teacher Rating Scale scores ($P = 0.74$ and $P = 0.63$, respectively)]
Dextromethorphan	NCT01787136 [58]	44	6–12	MPH + dextromethorphan MPH alone	8	No significant difference between the two arms on the ADHD core symptoms (SNAP-IV total scores) with significantly lower scores on the Inattentive ($P = 0.002$) and Hyperactive ($P = 0.004$) scales of the SNAP-IV in the MPH-only arms
Omega-3/6 fatty acids	Not provided [59]	90	6–12	Omega-3/6 fatty acids	52	No significant differences between omega-3/6 and MPH + omega-3/6 on ADHD total score ($P < 0.696$), Inattention ($P < 0.429$), or Hyperactivity-Impulsivity ($P < 0.824$) of the ADHD-RS
Propericiazine	Not applicable [60]	15	5–11	MPH + propericiazine MPH + placebo		Significantly higher reduction of ADHD core symptoms severity in the MPH + propericiazine vs. MPH + placebo arm according to teachers' but not parents' ratings (Conners' rating scales)
Tipepidine	RCT20090117001556N108 [61]	53	6–12	MPH + tipepidine (15–30 mg/day) MPH + placebo	8	Significantly greater reduction in the ADHD core symptoms severity (Parent ADHD-RS-IV) in the total and Hyperactivity-Impulsivity subscale scores in the MPH + tipepidine vs. MPH + placebo arm ($P < 0.05$)
Pramipexole	Not provided [62]	30	8.47 ± 2.08	MPH + pramipexole MPH + placebo	12	Significantly greater reduction in the ADHD core symptoms severity (Conners' score total) in the MPH + pramipexole vs. MPH + placebo arm ($P < 0.05$)
Vit D	IRCT201404222394N10 [63]	62	5–12	MPH + vit D (2000 IU) MPH + placebo	8	No significant differences between the two study arms in ADHD core symptoms (Conners' Parents Rating Scale and ADHD-RS) but significantly lower scores in the MPH + vit D arm on the WPREMB scale
Zinc	IRCT2016050716077N5 [64]	60	7–12	MPH + zinc (10 mg/day) MPH + placebo	6	No significant differences on the total and Hyperactive score, but significantly lower scores in the MPH + zinc arm on the Inattentive scale of the Conners' parent rating questionnaire
Zinc	Not provided [65]	52	6–14	Relevant for the present review: AMPH + zinc (15 mg/day) AMPH + placebo	5 (phases 2 and 3)	No significant difference between the two arms in terms of ADHD core symptoms severity at endpoint

Table 2 (continued)

Compound	Registration ID (reference)	*N* randomized	Age (years)	Arm (dose)	Duration (weeks)	Key findings (efficacy)
HX106 [a]	KCT0005285 [66]	27	6–23	MPH + HX106 MPH + placebo	4	Significantly greater reduction in the severity of ADHD core symptoms (K-ARS score) in the HX106 group compared to the placebo group

ADHD attention deficit hyperactivity disorder, *ADHD-RS-IV* ADHD Rating Scale-IV, *ALC* acetyl-L-carnitine, *AMPH* amphetamines, *Clon* clonidine, *Clon-XR* clonidine XR, *COMB* combined, *DMPH* d-methylphenidate, *Guan* guanfacine IR, *Guan-XR* guanfacine XR, *IR* immediate-release, *K-ARS* Korean ADHD Rating Scale, *MPH* methylphenidate, *RCT* randomized controlled trial, *SNAP-IV* Swanson, Nolan and Pelham Teacher and Parent Rating Scale-IV, *vit D* vitamin D, *WPREMB* Weekly Parent Ratings of Evening and Morning Behavior, *XR* extended-release

[a]Mixed herbal extract of *Gastrodia elata* Blume, *Liriope platyphylla* Wang et Tang, *Salvia miltiorrhiza* Bunge, and *Dimocarpus longan* Lour.

here because there is an evidence base for ADHD, and the XR formulation offers a pharmacokinetic profile that may translate into activity that covers the entire day. Bupropion is also likely to be used in combination with stimulants because of the relatively high comorbidity of ADHD and depression across the lifespan, though it is important to assess for cardiovascular adverse effects.

2.3.5 Other Compounds

Other RCTs reported in Table 2 [48–58] are small trials, have not been replicated, and refer to compounds which are generally not available or investigational. As such, these compounds should not be considered in clinical practice.

2.4 Management of Aggression/Oppositional Behaviours Refractory to Stimulants in Individuals with ADHD

RCTs on the management of ADHD patients with aggressiveness/oppositional behaviours refractory to stimulants are summarized in Table 3.

In the previously mentioned RCT ($n = 175$) by Blader et al. [7], children with aggressiveness refractory to optimized stimulant treatment presented with a significantly greater reduction in the severity of aggression when treated with stimulants + risperidone or (with a slightly smaller effect size) with stimulants + divalproex sodium compared to stimulants versus placebo. These results extend those from a previous RCT [41] by the same group showing a significant reduction in aggressive symptom severity in children treated with optimized stimulants + divalproex sodium versus optimized stimulants + placebo. Another small RCT [42] of risperidone augmentation provided mixed findings, with positive results according to scores of aggressive behaviours rated by parents but not by teachers. In a secondary analysis of the RCT by Wilens et al. [34], guanfacine XR was found to be an efficacious augmentation strategy for oppositional behaviours in children with ADHD [43]. Regarding clonidine, while the previously mentioned RCT by Hazell and Stuart [35] failed to find any significant difference between stimulant + clonidine versus stimulant + placebo on ADHD core symptoms, it did find a significantly higher reduction in the severity of CD symptoms in the stimulants + clonidine arm.

3 Recommendations in Guidelines

Table 4 shows a selection of recent national/international guidelines [44–48] on the management of ADHD. In general, currently available guidelines indicate stimulants as the first-line treatment. Some guidelines provide a specific

Table 3 RCTs on the management of aggressiveness/oppositional behaviours refractory to stimulants in individuals with ADHD

Compound	Registration ID (references)	*N* randomized	Age (years)	Arms (dose)	Duration (week)	Key findings (efficacy)
RISP DVPX	NCT00794625 [7]	45 (refractory to stimulant optimization)	6–12	Stimulants + RISP Stimulants + DVPX Stimulants + placebo	8	Greater reduction in ratings of aggression (scores on the Retrospective Modified Overt Aggression Scale rated by parents) in the stimulants + RISP (least squares means difference ES = 1.32) and stimulants + DVPX arms (ES = 0.91) vs. stimulants + placebo arm
DVPX	NCT00228046 [41]	30	6–13	Stimulants + DVPX Stimulants + placebo	8	Significantly higher proportion of remitters (for aggressive behaviour) in the stimulants + DVPX arm [57.14%] vs. stimulants + placebo arm [15.38%] ($P < 0.05$)
RISP	NCT00297739 [42]	25	7–12	Stimulants + RISP Stimulants + placebo	4	100% of the participants in the stimulants + RISP arm improved by more than 30% on the Children's Aggression Scale-Parent vs. 77% of those in the stimulants + placebo arm. No significant differences on the Children's Aggression Scale-Teachers
GXR	NCT00734578 [43]	274	6–17	Stimulant + GXR a.m. Stimulant + GXR p.m. Stimulant + placebo	8	Significantly greater reduction on the oppositional subscale of the Conners' Parent Rating Scale–R:L in the stimulant + GXR arms vs. the stimulant + placebo arm (GXR a.m. $P = 0.001$; GXR p.m. $P = 0.003$) in the entire sample and in the subgroup with significant baseline oppositional symptoms (GXR a.m. $P = 0.001$; GXR p.m. $P = 0.013$)
CLON	Not provided [35]	67	6–14	Stimulants + CLON (0.1–0.2 mg/day) Stimulants + placebo	6	56% in the stimulants + CLON arm vs. 20% in the placebo arm met criteria for improvement on the Conduct scale of the Conners' Parent Report checklist ($P < 0.01$)
CLON	Not provided [67]	24	Not provided	MPH CLON MPH + CLON		No significant differences across arms on symptoms of oppositional defiant disorder and conduct disorder

ADHD attention deficit hyperactivity disorder, *CLON* clonidine, *DVPX* divalproex sodium, *ES* effect size, *GXR* guanfacine extended-release, *MPH* methylphenidate, *RCT* randomized controlled trial, *RISP* risperidone, *R:L* revised long form

Table 4 Recommendations on the management of ADHD from a selection of recent national/international guidelines (in alphabetical order)

AAP (2019) [44]	CADDRA (2018) [45]	German guidelines (2018) [46]	NICE (2018) [47]	Spanish guidelines (2017) [48]
Preschool children (4–6 years) First line: Parent training and/or behavioural classroom interventions Second line: Methylphenidate (off-label) **Children 6–11 years** *Medications in the following order: (1) stimulants; (2) atomoxetine; (3) extended-release guanfacine; (4) extended-release clonidine* and parent training and/or behavioural classroom interventions (preferably both) **Adolescents 12–18 years** FDA-approved medications. Training and/or behavioural interventions when available	**Pre-schoolers** Psychosocial interventions **Children/adolescents and adults** *Medications, in the following order: (1) long-acting stimulants; (2) atomoxetine, guanfacine extended-release and short/intermediate-acting psychostimulants; (3) bupropion, clonidine, imipramine, and modafinil* Psychosocial treatments	**Children < 6 years** First line: ADHD-focused group or individual parent or teacher training. Medication if needed only after specialist advice for children > 3 years **Children ≥ 6 years and young people** Psychoeducation. Then: ***Mild to moderate ADHD:*** First line: Parent-training/family-based interventions; when appropriate, patient- and school/workplace-based interventions. *Second line: Medication, in the following order: (1) stimulants; (2) atomoxetine or guanfacine* ***Moderate to severe ADHD:*** *First line: Medication, in the following order: (1) stimulants; (2) atomoxetine or guanfacine.* Second line: Parent training or family-based interventions; when appropriate: patient- and school/workplace-based interventions **Adults** Psychoeducation. Then: Medication. Non-pharmacological treatment if patient choice, or if medication ineffective or not tolerated	**Children < 5 years** First line: ADHD-focused group parent training programme. Medication to be considered only after second specialist opinion **Children ≥ 5 years and adolescents** If ADHD symptoms persist in at least one area of functioning after environmental modification and ADHD-focused support: *Medication, in the following order: (1) methylphenidate; (2) lisdexamfetamine (or dexamphetamine if lisdexamfetamine not tolerated); (3) atomoxetine or guanfacine.* If symptoms of ODD or CD: Parent training. CBT for young people if symptoms still impairing in at least one area of functioning after pharmacological interventions. **Adults** If ADHD symptoms persist in at least one domain of functioning after environmental modification: *Medication, in the following order: (1) methylphenidate or lisdexamfetamine (or dexamphetamine if lisdexamfetamine not tolerated); (2) atomoxetine.* Psychological intervention if medication ineffective or not tolerated	**Pre-schoolers** Psychosocial interventions; medications not recommended **School-aged children and adolescents:** Psychological or pedagogical support Medication only recommended if psychological/pedagogical support not effective, or in severe cases. *Pharmacological options (with no order specified): methylphenidate, lisdexamfetamine, guanfacine, and atomoxetine* **Adults** First-line pharmacological treatment in moderate-to-severe cases. Psychosocial interventions or medications in mild cases

Recommendations on the hierarchy in the choice of medication are italicized

AAP American Academy of Pediatrics, *ADHD* attention deficit hyperactivity disorder, *CADDRA* Canadian ADHD Alliance Resource, *CBT* cognitive behavioural therapy; *CD* conduct disorder, *FDA* Food and Drug Administration, *NICE* National Institute for Health and Care Excellence, *ODD* oppositional defiant disorder

hierarchy in the selection of the medication at the patient-group level, which reflects interpretations of the empirical evidence on efficacy/effectiveness and tolerability/safety and, in some cases, takes into account other factors, including cost-effectiveness analyses and the availability/licence of the product. For instance, the 2018 National Institute for Health and Care Excellence (NICE) UK guidelines [47] recommend methylphenidate, followed by lisdexamfetamine (or dexamphetamine in the case of relevant side effects with lisdexamfetamine that cannot be managed), followed by atomoxetine or guanfacine in children/adolescents. They also recommend methylphenidate or lisdexamfetamine (or dexamphetamine if lisdexamfetamine is associated with an unacceptable side effect profile), followed by atomoxetine in adults. (We note that in the UK mixed amphetamine salts and clonidine XR are not available and, hence, have not been recommended by NICE.) Other guidelines, while generally recommending stimulants as the first-line option (without specifying the hierarchy of the type of stimulant), provide a suggested ranking for the choice of alternatives to stimulants. For instance, the guidelines from the American Academy of Pediatrics [44] recommend atomoxetine, followed by guanfacine, followed, in turn, by clonidine when stimulants are not effective/not tolerated. Of note, none of the guidelines currently available include viloxazine [49], as this compound has only recently been approved by the FDA and, at the time of writing, only in the USA as a non-stimulant alternative for the treatment of ADHD.

The hierarchy of medication choice suggested in these guidelines is in general consistent with recent meta-analytic evidence from RCTs summarized above and in Table 1. Overall, the NMA of Cortese et al. [12] concluded that, in children, methylphenidate should be preferred over amphetamines as first-line choice as, even though it is slightly less efficacious, it is better tolerated than amphetamines. We note that the Cortese et al. NMA [12] is not a guideline, but a synthesis of the evidence and its conclusions should be interpreted and used considering a series of factors that often vary from country to country. Additionally, the NMA by Cortese et al. [12] suggested that, in adults, amphetamines should be the first choice, as they are the most efficacious agents and their tolerability is not significantly different compared to methylphenidate. Similarly, the NMA by Catalá-López et al., including both pharmacological and non-pharmacological interventions in children/adolescents [10], found that amphetamines and methylphenidate were significantly better than atomoxetine and guanfacine. Whilst current guidelines such as NICE are informed by the interpretation of meta-analyses of aggregate-level data from RCTs, which are helpful to provide general indications, there are not yet guidelines informed by sequential trials that can determine more accurately effective treatment sequencing.

Moreover, whilst current guidelines recommend a hierarchy of common/licensed medications, they do not, in general, provide more fine-grained guidance on medication optimization or additional alternatives to common second- or third-line medications when these are not effective. One notable exception is the guideline of the CADDRA [45], which is based mainly on expert consensus rather than a systematic review of the literature and meta-analytic evidence. CADDRA recommends a trial of long-acting stimulants (either class) as the first-line pharmacological option. Acknowledging that individual patients may respond to or tolerate one class of stimulants better than the other, CADDRA recommends an adequate trial of both classes of long-acting psychostimulants (methylphenidate or amphetamines) before moving to second-line medications (i.e. atomoxetine, guanfacine XR, and short/intermediate-acting stimulants). CADDRA also highlights that non-stimulants may also be used in combination with first-line stimulant compounds to augment response when there is suboptimal response to stimulant monotherapy. In this regard, the guidelines note that only guanfacine XR has been approved by Health Canada as an adjunctive treatment in combination with long-acting stimulants, even though other combinations (e.g. atomoxetine, clonidine, and immediate-release or short-acting stimulants) are used in clinical practice by some clinicians. The CADDRA guidelines mention bupropion, clonidine, imipramine, and modafinil as third-line options, highlighting that their use may require specialized care. Finally, exceeding the recommended maximum dosages of licensed medications is another third-line strategy listed in the CADDRA guidelines. In terms of titration, the CADDRA recommendations are as follows: "A general rule is to start low and go slow but continue to increase the dose until the desired goals of treatment have been reached or side effects preclude dose increases or when maximum recommended dosage is reached. Optimal dose is the dose above which there is no further improvement. Optimal treatment means that the symptoms have decreased and that there is improvement in functioning". We add here that, in our view, optimal treatment is a more complex construct that refers to the overall treatment and support package and implies not only optimization of symptoms and response, but also maximal improvement in overall functioning as well as tolerability.

4 Practical Suggestions

We provide here practical suggestions based on knowledge of expert practice in the field and our own clinical expertise. These are summarized in Table 5. Before discussing possible specific options, it is important to highlight three

Table 5 Management of patients with ADHD non responsive to stimulants (adapted from [68])

Questions to ask before switching to non-stimulants or adding augmenting strategies:
1. Have I titrated properly?
2. Is the patient at the maximum dose?
3. Is this drug/preparation working well at any times during the day and do I need to change the dose or preparation to get a more balanced effect?
4. Am I targeting the right symptoms?
5. Is there a behavioural explanation for the drug "wearing off" or is the patient becoming tolerant to this medication?
6. What else is going on in patient's life/family life, and are there non-pharmacological reasons for poor response?
7. Have I missed any comorbidity?
Consider second-line medications (atomoxetine, guanfacine, clonidine)
Consider augmenting agents (guanfacine or clonidine extended-release)
Consider other agents under specialistic advice/supervision

ADHD attention deficit hyperactivity disorder

principles of good practice in clinical (psycho)pharmacology. First, change one medication at a time, to avoid misleading interpretation of efficacy or tolerability. Second, gather appropriate evidence to document response and, when present, clarify that an adverse event is indeed a side effect of the medication. For instance, some patients may present with irritability during the initial phase of the treatment, which decreases with an increased dose of medication; in this case, stopping or reducing the dose of the medication would prevent patients from receiving optimized doses of the medication. Third, re-titrating after a patient has reported experiencing possible side effects may be beneficial, since the presumed side effects may have been related to other contemporaneous factors and not exposure to the drug.

When facing a non-response to stimulants in a child, young person, or adult with ADHD, practitioners should consider a series of options.

- First, they should check if they have given an adequate trial of medication that has been titrated properly and reached the maximum recommended and tolerated dose of the first and, if relevant (if inadequate response to the first) also of the second stimulant (methylphenidate and amphetamines or vice versa). We are unaware of any single accepted definition of an "adequate trial". We believe, however, that most experts would agree that this would include a trial of at least several weeks duration, with multiple doses tested, and in ranges that are considered to offer therapeutic benefit, unless limited by adverse effects. Some researchers have reported that there is no evidence-based rationale for the maximum doses in RCTs [50] and labels of ADHD medications. Furthermore, as there is, in general, only a modest correlation between dose and blood levels, it is possible that a dose that is considered high translates in blood levels within the accepted range in some individuals; however, measuring blood levels for ADHD medications is not often implemented in clinical practice [51]. We suggest that if there has been no clinical response at the recommended/licensed dose, it is important to consider the alternative class of stimulant before increasing the dose further. Whilst we do not recommend it as standard practice, we do think that the dose of stimulant can be reasonably increased beyond the maximum recommended dose when there has been a partial response and there is also some degree of improvement at the maximum recommended dose, tolerability is good, and the prescriber is aiming to optimize the response. For instance, bearing in mind that one should use the immediate-release component of each formulation as the reference and try to adjust for this when switching between formulations of methylphenidate, the dose of OROS methylphenidate equivalent to an XR formulation of methylphenidate delivering 20 mg in the morning would be 90 mg, which exceeds the maximum recommended dose of methylphenidate (60 mg/day). Going beyond the recommended dose may be needed in particular with adult patients.
- Another aspect to consider is whether patient/parent-reported non-response to the stimulant is indeed confirmed by more formal assessment of symptoms. Here, we emphasise the benefits of measurement-based care approaches such as those described by Coghill and Seth [13]. This enables an accurate determination of symptoms across different domains in a time efficient manner and can be used as the basis for discussions with families about management. One particular example of this is to determine whether a lack of response to the stimulant is observable throughout the entire day or just at particular times (e.g. later in the day and reported by parents but not teachers, or during late morning and the end of the school day and reported by teachers for children on immediate-release preparations). In this case, rather than

a true non-response, the issue is likely to be about the wearing-off effect of the medication. An increase in dose or additional dose of immediate-release stimulant in the afternoon for those on twice-daily dosing, or a switch to an XR formulation or changing time of administration should be considered. With OROS methylphenidate, the issue may be of underdosing during the morning, as highlighted in the example above. For lisdexamfetamine, the longer time to onset of action can be problematic for some patients.

- There are of course limits to what aspects of behaviour can be expected to respond to ADHD medications, and it is important to consider whether apparent "non-response" is in relation to ADHD core symptoms, other non-core but common symptoms such as emotional lability, or other aspects of functioning often experienced as a complication or consequence of ADHD. In clinical practice, it is not uncommon for parents or patients themselves to complain about a lack of efficacy regarding stimulants and symptoms/aspects (e.g. oppositional behaviour, emotional lability, irritability, academic functioning) that require targeted and specific management in their own right. It is always important when one meets treatment non-response to consider the potential impact of concomitant life events (e.g. stressors, traumatic events) that may impact attention and behaviour and hamper the response to stimulants. When present, the consequences of co-occurring life events could benefit from appropriate supportive and psychosocial interventions, rather than additional medications for ADHD.
- Additionally, the role of possible comorbidities in mimicking or exacerbating ADHD symptoms should not be overlooked. For instance, individuals with comorbid learning disabilities (LD) may present with apparent attenuated response, mainly attributable to the LD rather than the ADHD, and those with anxiety disorders may have symptoms that can mimic ADHD symptoms, such as procrastination (which can be due to anticipatory anxiety as well as ADHD).
- It is also possible that some patients may develop tolerance to stimulants, as suggested by evidence from a positron emission tomography (PET) study [52], even though the extent and frequency of this is not well understood. In this case, short drug holidays, e.g. during the weekend or for brief periods of time (e.g. over a vacation), could be considered. Indeed, to simply keep on increasing the dose in the face of tolerance may provide a temporary solution, but after a period of time, tolerance would probably manifest again. However, it is also possible that some patients simply outgrow a dose that was effective earlier on, due to increase in body weight, in which case an increased dose may be beneficial.
- If none of these factors is considered a possible explanation for the lack of response to stimulants, then second-line and, if needed, third-line agents recommended in currently available guidelines/licensed should be considered. With atomoxetine, there is evidence showing that early response (2–4 weeks) predicted optimal response at 6 weeks defined as 40% or more change from baseline [18]. Therefore, patients who show no improvement at all during the first 4 weeks are unlikely to respond later on. However, some expert clinicians/researchers believe that full response may not be reached for 2–3 months [53]. This has led them to recommend waiting for up to 12 weeks before determining non-response and moving to another line of treatment.
- The role of other medications mentioned in this article is still unclear, and therefore, these should not be considered routinely.
- As a general principle, combination of two pharmacological agents may be advantageous when the two agents have different pharmacokinetic profiles and different mechanisms of actions, to more efficiently tackle the multiple dysfunctions underpinning the disorder and cover the day more thoroughly. As shown by our literature review (see above), with the exception of guanfacine XR and clonidine XR, evidence on the efficacy of a number of agents as an augmenting strategy is lacking or weak at best. As such, while augmentation with guanfacine XR or clonidine XR is an option when monotherapy is not effective, we do not generally endorse augmentation strategies with other compounds. Caution should be used when combining stimulants and atomoxetine. Of note, combined use of atomoxetine together with drugs such as fluoxetine and paroxetine, which are also dependent on cytochrome P450 2D6 (CYP2D6) for their metabolism, can greatly increase the half-life of atomoxetine, raising the effective dose [54], and there are some data to suggest that this may be associated with improved response [55]. However, monitoring for the occurrence of adverse effects at higher blood levels is essential. Augmentation with α2-agonists (clonidine and guanfacine), neuroleptics such as risperidone or aripiprazole, or divalproex for the management of aggressive/oppositional behaviour unresponsive to stimulants and augmentation with α2-agonists (clonidine and guanfacine) and neuroleptics for severe tics can be considered, but once again the key is first to optimize the dose of stimulants, which could avoid the need for additional agents in a substantial proportion of patients.

5 Conclusions

With appropriate optimization strategies, the vast majority of patients with ADHD will have a significant reduction in the severity of ADHD with stimulants (methylphenidate and, if no response, amphetamines or vice versa). After checking that the lack of response is not due to alternative explanations (inadequate dosing, poor adherence, wearing-off of effects across the day, poor tolerability that prevents the use of higher doses [but can be managed], focus on non-ADHD symptoms that are not expected to be the target of ADHD medications, comorbidity, the development of tolerance, a wrong diagnosis/formulation), augmenting with guanfacine XR or clonidine XR and, if this is not successful, moving to second- or third-line pharmacological options should be considered. Whilst the focus on non-pharmacological options was beyond the scope of this paper, combining pharmacological and non-pharmacological/supportive strategies and accommodations should also be considered early in treatment, especially to target problems that occur at a specific time of the day or when medication effects wear off. Currently, there are no clinical, genetic, or biological indicators that can reliably predict which stimulant class any individual will respond best to or, if needed, which non-stimulant agent will be best for each patient at the individual level. While the choice of medications is currently based on a trial-and-error process, it is hoped that advances in precision psychiatry will allow more personalized, tailored, and efficient management of patients with ADHD.

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